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EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?[1]

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Introduction

This paper is concerned with what has and has not been learned from animal experiments about external radiation carcinogenesis. The intent is not to be encyclopedic, and therefore, I will omit reference to many experiments that have produced valuable information. Also, I will not refer to the body of work devoted to internal emitters, an area of research vital to the understanding of the special problems of dose-distribution posed by radionuclides.

Radiation provides a very useful and an underutilized tool in the study of mechanisms of carcinogenesis. However, because cancer is the somatic risk of most concern in establishing standards for radiation protection there has been a greater investment in studies of the aspects of radiation induction of tumors that can help in guiding the sensible selection of standards than in unraveling the mysteries of mechanisms. While protection standards for genetic effects have been based on data obtained from experimental systems (1) those for cancer are based on the human experience. That does not mean that the results from animal experiments have had no role in the selection of protection standards. There are various reasons that results from animal experiments have been used less in the area of somatic effects than genetic effects. First, of course is the fact that there is substantial, though inadequate, data about the risk of cancer in man after exposure to radiation. Secondly, suitable quantitative data for the dose-responses over appropriate

dose-ranges from animal experiments have not been available until very recently. This lack of information is not due to sloth but to the magnitude of the problem of executing the necessary experiments.

The role of animal experiments:

The existing human data cannot, by itself, possibly provide estimates of risk of exposures to very low doses and the fact that some model for the dose-response relationships must be used, make it imperative to design animal experiments in order to test the models.

The results and appropriate analysis of the large scale animal experiments that were designed to examine the effects of dose-rate fractionation, and radiation quality are now accumulating. From these experiments a better understanding of time-dose relationships and the relative biological effectiveness (RBE) of different radiation qualities is being realized. Such knowlege can be used profitably. It is assumed, and partially substantiated, that the effects of factors such as dose-rate and radiation quality can be extrapolated to man in a qualitative way and that generalizations about certain aspects of radiation effects can be made. It has been held that results from such experiments can only be applied to the problem of human risks in a general manner and that quantitative risk estimates cannot be extrapolated from experimental animals to man. The possibility of quantitative extrapolation has been considered to a much lesser extent than the establishment of general principles, but more about that later.

In both man and experimental animals, age is the strongest determinant of cancer. The increasing incidence with age that is found

for most tumors (Fig. 1) poses a fundamental problem for our understanding of mechanisms and even for the analysis of the responses to radiation. Another interrelated problem is that the most extensive studies have been carried out on tumors that occur with relatively high frequency. The combination of these two facts leads to the problem, illustrated in Fig. 2, of determining whether the increase in incidence at times after exposure is due to induction of tumors or purely to the advancement of time of appearance of tumors that would have occurred naturally. Despite the fact that the distinction between these two types of response is often considered unimportant from an acturial viewpoint, the matter is not trivial if our interest is in mechanisms. For example, it seems reasonable to believe that either the type or number of events required for advancement might be different from that required for induction. It can be seen from the curves on the left of Fig. 2 that if a complete life-time study is not carried out, and with the rationalization of economy, animals are killed at some time earlier than the time of natural death, the comparative incidences may suggest a marked effect. It is true there is a marked effect but only on the time of appearance. It is also obvious that quantitatively the result that is obtained in such a system depends on when the observation is made not just that the observation is made. Lung tumors in $B6CF_1$ mice appear to be an example of the radiation-induced advancement of time of appearance. In the female of this hybrid the prevalence of lung tumors rises slowly over the first half of the life span and more rapidly between 600 and 1000 days when the prevalence plateaus at about 45 percent (2). In lifetime studies only 18 percent of deaths among

F-1

F-2

mice with lung tumors are due to lung tumors. In other words most of the tumors are incidental to the cause of death. After irradiation, it can be seen (Fig. 3) that lethal lung tumors kill the mice at an earlier age than in the controls. The age-specific mortality curves are shifted to the left but show no significant change in slope. The results are consistent with the contention that in the case of this tumor in the $B6CF_1$ female, irradiation results in an advancement of time of death from this specific cause without any evidence of an increase in incidence. The importance of the difference in lethal and incidental tumors in the choice of method of analysis has been appreciated for some time (3). Recently, analysis of the incidence of mammary neoplasms in the Sprague-Dawley rats after exposure to radiation has been made in terms of an advancement of time of appearance (4). This is important because results from experiments in the Sprague-Dawley rat have been used as evidence to support certain models based on the assumption that tumors were induced.

F-3

Dose-response curves

The question of whether the so-called linear-quadratic dose-response is more appropriate than the non-threshold linear dose-response for the description of data for radiation-induced cancer and the estimate of risk in man has exercised the minds and patience of those on committees that deal with this matter, not to mention their critics. Although the various arguments for and against the use of one particular dose-response curve have used scientific facts in the attempt to package such a complex and multi-faceted response as cancer induction into one

dose-response curve tbe approach is more simplistic than scientific. In some experimental tumors none of the simple models are appropriate (5).

It can be seen from Fig. 4 that from the present experimental (F-4) evidence there is every reason to believe that the form of the dose-response curves covers the gambit of probable shapes. It is quite reasonable that it should be so. In the mouse, the evidence is that the induction of tumors can involve not only a direct effect on the target cell but also abscopal effects. For example, destruction of the highly sensitive oocytes disturbs the hypophyseal-ovarian axis with altered probabilities of certain tumors that are influenced by hormone levels. In short, the mechanism of radiation-induced cancer varies between organs and cell systems, and yet it is conventional to plot the incidence of tumors as a function of dose. The formulation of the current models is based on the factors involved in initiation, for example, mutation. Neither the role of the many factors influencing the expression nor the manner in which they alter the shape of the dose-response curve is usually taken into account although recently, Marshall and Groer put forward a more comprehensive model for bone tumors (6).

The importance of the factors influencing expression is easily illustrated by results obtained with ultraviolet radiation (UVR) shown in Fig. 5. The curve on the right, which represents the incidence of (F-5) skin cancer as a function of dose of UVR in mice photosensitized with 8-methoxypsoralen appears sigmoid in shape with an apparent threshold. With reduced total doses but with the exposure regime followed by promotion with a phorbol ester, (TPA) the shape of the dose-response curve appears more linear and without a threshold (7). One might

conclude from these results that plots of incidence of cancer as a function of dose are not good representations of the dose-response relationships for the induction or initial events of transformation. Irrespective of whether or not one- or two-track events are involved in initiation, it is clear that, at least in some tumors, the appearance of tumors induced by those events depends on further and possibly multiple changes. The shapes of the tumor dose-response curve reflects the influence of all of these events. There is nothing new in these remarks; the same concepts have been stated from the time of the first International Radiation Research Congress by Kohn in 1959 (8) to Upton's paper at the Society's Symposium on Radiobiological Response Relationships at Low Doses in 1976 (9). However, for whatever reason, many of the discussions about dose-response, and more importantly, the interpretations still seem to ignore the facts that there are a number of very different forms of dose-response relationships and that the shape of the curves depends on the mechanisms. It is likely that most of the differences and complexities of the mechanisms lie mainly in the factors influencing expression, and the understanding of those factors is incomplete. We need other techniques to allow us to discern the radiation-induced initial events from the exogenous and endogenous factors that influence the final tumor incidence and different experimental systems in order to examine separately the shape and slopes of dose-responses for initiation and expression.

In the recent past the information on dose-response relationships for a spectrum of tumors in mice has accumulated, and has helped to establish the range of the forms of the dose-response curves (10, 11),

but many of the tumors involved are influenced by hormones, in particular ovarian hormones. In experiments on female mice, whole body irradiation results in sterilization even at low total doses. The subsequent hormonal imbalance raises the question of independence of the various tumor types. A lack of independence of certain tumor types is suggested by the increase in multiplicity of tumor types in female mice after whole body exposure to radiation (2). The predominance of data from whole-body irradiation rather than partial body or local irradiation is unfortunate and tumor dose-response curves for local irradiation of certain organs are needed.

Low dose and low dose rate effects

The use of linear interpolation from data obtained at high dose-levels for estimating the risk of radiation-induced cancer in humans has been considered a cautious approach for low LET-radiation and a reasonable method for high LET-radiation (Fig. 6). The lack of certainty stimulates discussion and it has been suggested that even in the case of low LET-radiation interpolation could underestimate the effects (12). (F-6)

The question of the effect of reducing the dose rate on the incidence of tumors is a suitable one to answer by animal experiments. It is unlikely that the data for humans will ever be adequate to determine the influence of dose rate. As a result of series of experiments at Oak Ridge National Laboratory, the effects of dose rate on murine tumors are now well documented (11, 13). An example from these experiments is shown in Fig. 7. It can be seen that there is a (F-7)

marked effect of dose-rate on this tumor. To illustrate how dependent the effect of dose-rate is on the specific tumor, I have made a comparison of linear regressions of the data for dose-responses for a number of different tumor types obtained after exposure to gamma radiation at high and low dose-rates (Fig. 8). The solid lines indicate the range of slopes obtained from linear fits for the responses of the selected tumors after exposure to radiation at a high dose-rate. Similar fits to the data for the responses of the same tumor types after exposure to low dose-rate irradiation are shown individually. It is clear that all of the responses to exposures at low dose-rates are less than the range of responses to irradiation at high dose-rates; however, it is evident that the degree of the effect of lowering the dose-rate varies considerably for the different tumor types. The two sets of data for myeloid leukemia shown in Fig. 8 illustrate the complexity of the factors that influence cancer. The experiments of Upton et al. (13), and Ullrich and Storer (11) were both carried out on the RFM strain but the mice of the latter workers were maintained in a specific-pathogen free facility. It is not clear why the difference in the microbial environment influenced the incidence of radiation-induced leukemia, but it is possible that either the number of myeloid stem cells at risk or their proliferative rate was different in the two experimental series. It has been shown that the reduced risk of myeloid leukemia in germ-free RFM mice is offset by an increased susceptibility to thymic lymphoma (14). It is this type of influencing factor that will not be revealed easily by <u>in vitro</u> experiments. The results are

(F-8)

also salutary for those willing to interpret dose-response curves purely from biophysical principles.

NCRP committee 40 has spent a long time examining dose-rate effects for every biological endpoint that had been investigated in a systematic manner. The number of tumors that have been studied sufficiently to make conclusions about dose rate effects is limited. Unfortunately many of the tumors studied are influenced by the same hormones and therefore one must be concerned about independence. The NCRP committee concluded that the "dose-rate effectiveness factor" (effect at high dose rate/effect at low dose rate) varied from about 2 - 10. These estimates are deliberately cautious and examination of Fig. 6 will reveal the reason. If the dose-rate effectiveness was determined from data from only below 100 rad (which would be very reasonable) the factor would be very large. The committee chose to include the data over the complete dose-response range.

In the case of high-LET radiation, if interpolation is used to estimate risks of low doses (below 5 rad) from data for higher doses, the result could be an underestimate of the risk (Fig. 6). The reason for a possible underestimation is that results consistently show that the dose-response curve for tumor incidence after exposure to neutron radiation bends over at relatively low doses (7, 13, 15, 16). A similar form of dose-response has been obtained for life shortening in the two major studies of fission neutron effects at Argonne and Oak Ridge National Laboratories (17, 18, 19). The curvilinear (concave downward) form is seen in the three sets of data (Fig. 9). The radiation-induced life shortening is significantly less in the male hybrid B6CF$_1$ than in

the females from specific strains. Since tumors are the major cause of death in the irradiated mice, the shape of the dose-response for life shortening probably reflects the similar shape found for individual tumor systems.

In Fig. 10, life shortening is used again to illustrate the difference in the responses to low and high LET-radiations. The response to gamma radiation appears linear in contrast to the curve for fission neutron that has a much greater initial slope but bends over. When the exposures to gamma radiation are fractionated or protracted the effect is less than after a single exposure but it is just the contrary with fractionated exposures to neutrons (20). A greater tumor response after fractionated or protracted high LET-radiation has also been noted in both man and mouse (15, 21, 22-24). No satisfactory explanation has been offered for the finding that fractionation and protraction of high LET-exposures increase the effect.

F-10

In order to estimate the risk of cancer as a result of exposure to low doses of high LET-radiation it must be either possible to interpolate from incidences obtained at higher dose-levels or directly determine the low-level effect. We have used the Harderian gland of mice to investigate factors that influence the dose-response for high LET-radiation carcinogenesis. This tumor system has proven useful because it occurs naturally at a low incidence, is reasonably susceptible and the radiation initiation can be promoted by pituitary hormones (assumed to be prolactin) that can be provided conveniently by pituitary isografts. In Fig. 11, it can be seen that there is a steep initial rise in the radiation-induced incidence of the tumors but the

F-11

curve plateaus at a relatively low dose. These results and other dose-response curves indicate that estimation of the initial slope of the dose-response curve for fission neutron radiation will entail obtaining data at very low doses. It is popular to attribute the "bending" or "plateauing" of the dose-response curves to cell killing (16, 25, 26). When the dose-response represents the tumor incidence as a function of dose the interpretation of the curve is complex. The results shown in Fig. 12 for the incidence of tumors in irradiated animals with pituitary isografts are interestingly different to those for the animals that received only radiation. The effect of the pituitary isograft suggests that in the animals that received only irradiation there were many more initiated cells with the potential for expression that were in fact expressed as frank tumors. This finding does not contradict the importance of cell killing but it does warn against simplistic interpretations. The shape of the dose-response curve shown in Fig. 12 also underlines the disparity between the observed form of the dose-response curve for neutron radiation and what current models suggest, namely, that the linear term predominates over a wider dose range than with low LET-radiation. We do not have a realistic model or mathematical description that is applicable to high LET-radiations. It is not clear why the apparent plateau is reached between 30-40 rad and whether this involves a saturation effect. Presumably, such factors as dose-distribution, transformation rate, and cell killing will influence the dose-level at which the plateauing is observed. Rossi (27) has pointed out that at very low doses (1 rad) of neutrons most of the exposed cells are not traversed by neutron

secondaries and the number of cells traversed is proportional to dose. At doses of about 30 rad there will be at least one traversal per cell. The incidence of tumors at which the plateau occurs must be influenced by biological factors, such as susceptibility, since the "plateau" occurs at different incidence levels for different tumors and possibly independent of the radiation quality.

It is now well established for numerous tissues and for different species that the RBE varies with: (1) LET, (2) total dose, (3) dose-rate, (4) dose fractionation, and (5) the target tissue. The dependence of RBE on dose and LET is illustrated in Fig. 12. In the schematic Figure 13 it is seen that the inverse relationship of RBE to dose or dose rate is due to the fact that the effectiveness of low LET radiation decreases with dose until dose-levels at which dose-rate independence is reached. Similarly, the marked variation in RBE values (Table 1) for different tissues is largely due to the form of the dose-response to low LET-radiation.

F-12
F-13
T-1

Susceptibility and natural incidence

For both the understanding of mechanisms and the appropriate analysis of data for risk estimates, it is important to determine whether or not susceptibility is correlated to the natural incidence of a specific tumor. If this relationship does hold then relative risk is the appropriate method for risk estimates. The question of the relationship between susceptibility to radiation-induced cancer and natural incidence is one that is suitable for experimental solution. Unfortunately, the appropriate data are scanty but the results shown in

Table 2 and other studies (28), do support the contention that susceptibility is related to the natural incidence.

There have been few examinations of the possibility of the quantitative extrapolation of estimates of risk of radiation effects from experimental animals to man (29, 30). Perhaps now is the time for such a task to be undertaken since there are risk estimates for a number of tumors in both man and mice, and methods of extrapolation could be tested; at least the problems in extrapolation across species could be identified and tackled. We have noted that when the excess risk of radiation induced cancer is expressed as a percentage of the natural incidence the risks are of similar order in mouse and man (29). An obvious problem that is raised is whether a tumor type, for example myeloid leukemia, in man and mouse is analogous. Our estimate for the per cent increase per rad for all cancers in man is about 0.03 and 0.024 in the one mouse strain for which there are suitable data. Fortuitous, you may say, and perhaps correctly so, but such comparisons that we have made are encouraging.

Summary

What have we learned about radiation carcinogenesis? Perhaps the most important aspect of what has been learned is that now there is a better realization of what is not known. The variation in dose-response curves for different tumors is a reflection of the differences in mechanisms that are involved, and it is reasonable to believe that just as marked variation in responses will be found in humans. It appears that the probability of inducing potential tumor cells is considerably

greater than the probability of tumors, at least in some tissues and it is important to establish for what tissues this holds. It is possible that the species-dependent differences in susceptibility are due largely to the differences in expression (or suppression) of the initiated cells. Reduction in dose-rate results in lower incidences of radiation-induced tumors but the degree of reduction is dependent on the specific tissue tumor system.

While it is known that there are factors, such as dose-distribution, that influence the shape of the dose response curves for low and high LET-radiation the understanding of the factors that determine the shape of dose-response curves for tumors induced by high LET-radiation is not sufficient to allow a precise description of the curves. It might even be questioned whether the current concepts of dose are appropriate for understanding tumor induction by high LET-radiation. The results from animal experiments show that RBE values can show a marked variation and that high RBE values are due to a correspondingly small effect of the low LET radiation. The variation in RBE values does not argue for the use of a single quality factor for protection standards for neutron radiation.

The increasing information on the incidences of radiation-induced cancer for both man and experimental animals should make it possible to extend the tests of methods of extrapolation. Certainly it should be possible to establish the relationship of susceptibility to natural incidence for a number of tumors in a few strains of mice.

Animal experiments on radiation carcinogenesis have provided information at a frustratingly slow rate but they have provided insights important for the understanding of carcinogenesis in general that cannot be obtained as yet, in other ways. Animal experiments continue to be vital for 1) the study of mechanisms, 2) the establishment of generalizations, 3) the elucidation of dose-response and time-dose relationships, and 4) the determination of dose-distributions and their consequences, particularly in the use of radionuclides.

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References

1. W. L. Russell. Mutation frequencies in female mice and the estimation of genetic hazards of radiation in women. Proc. Natl. Acad. Sci. USA 74, 3523-3527, (1973).

2. R. J. M. Fry, E. Staffeldt and S. A. Tyler. Some problems arising in analysis of large-scale animal irradiation experiments. Environmental International 1, 361-366, (1972).

3. D. G. Hoel and H. E. Walburg. Statistical analysis of survival experiments. J. Natl. Cancer Inst. 49, 361-372, (1972).

4. C. J. Shellabarger, D. Chmelevsky and A. M. Kellerer. Induction of mammary neoplasms in the Sprague-Dawley rat by 430 keV neutrons and x-rays. J. Natl. Cancer Inst. 64, 821-833, (1980).

5. R. L. Ullrich. Carcinogenesis in mice after low doses and dose rates. In: Radiation Biology in Cancer Research (eds. R. E. Meyn and H. R. Withers), pp 309-319, Raven Press, New York, 1980.

6. J. H. Marshall and P. G. Groer. A theory of the induction of bone cancer by alpha radiation. Radiat. Res. 71, 149-192, (1977).

7. R. J. M. Fry, J. B. Storer and R. L. Ullrich. Radiation Toxicology: Carcinogenesis in the Scientific Basis of Toxicity Assessment (ed. H. Witschi), pp 291-304, Elsevier/North Holland Biomedical Press, Amsterdam, 1980.

8. H. I. Kohn. Late effects of ionizing radiation: Some general problems of experimental design. Radiat. Res. Suppl. 1: 235-242, (1959).

9. A. C. Upton. Radiobiological effects of low doses, implication, for radiological protection. Radiat. Res. 71, 51-74, (1977).

10. R. L. Ullrich and J. B. Storer. Influences of γ irradiation on the development of neoplastic diseases in mice. II. Solid tumors. Radiat. Res. 80, 317-324, (1979a).

11. R. L. Ullrich and J. B. Storer. Influence of γ irradiation on the development of neoplastic disease in mice. III. Dose-rate effects. Radiat. Res. 80, 325-342, (1979b).

12. J. W. Baum. Population heterogeneity hypothesis on radiation-induced cancer. Health Phys. 25, 97-104, (1973).

13. A. C. Upton, M. L. Randolph and J. W. Conklin. Late effects of fast neutrons and gamma rays in mice as influenced by the dose-rate of irradiation: Induction of neoplasia. Radiat. Res. 41, 467-491, (1970).

14. H. E. Walburg, Jr., G. E. Cosgrove and A. C. Upton. Influence of microbial environment on development of myeloid leukemia in x-irradiated RF mice. Int. J. Cancer 3, 150-154, (1968).

15. R. L. Ullrich, M. C. Jernigan, G. E. Cosgrove, L. C. Satterfield, N. D. Bowles and J. B. Storer. The influence of dose and dose rate on the incidence of neoplastic disease in RFM mice after neutron irradiation. Radiation Res. 68: 115-131, (1976).

16. R. H. Mole. Ionizing radiation as a carcinogen: practical questions and academic pursuits. Brit. J. Radiol. 48, 157-169, (1975).

17. J. F. Thomson, F. S. Williamson, D. Grahn and E. J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. I. Single and short-term fractionated exposures. Radiat. Res. (in press) (1981).

18. J. F. Thomson, F. S. Williamson, D. Grahn and E. J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. II. Duration of life and long-term fractioned exposures. Radiat. Res. (in press) (1981).

19. J. B. Storer, L. J. Serrano, E. B. Darden, Jr., M. C. Jernigan and R. L. Ullrich. Life shortening in RFM and BALB/c mice as a function of radiation quality, dose, and dose-rate. Radiat. Res. 78, 122-161, (1979).

20. E. J. Ainsworth, R. J. M. Fry, P. C. Brennan, S. P. Stearner, J. M. Rust and F. S. Williamson. Life-shortening, neoplastic and systemic injuries in mice after single or fractionated doses of neutron or gamma irradiation. In: Biological Effects of Low-Level Radiation Pertinent to Protection of Man and His Environment. Vol. 1, pp 77-92, IAEA, Vienna, 1975.

21. M. Spiess and C. W. Mays. Protraction effect on bone sarcoma induction ^{224}Ra in children and adults. In: Radionuclide Carcinogenesis (eds. C. L. Sanders, R. H. Bush, J. E. Ballou and D. D. Mahlum. AEC Symposium Series No. 29, Cont. 720505 National Technical Information Services, Springfield, VA, 1973.

22. A. Luz, W. A. Muller, W. Gossner and O. Hug. Estimation of tumor risk at low dose from experimental results after incorporation of short-lived bone-seeking alpha emitters ^{224}Ra and ^{227}Th in mice. In: Biological and Environmental Effects of Low-Level Radiation, pp 171-181, IAEA, Vienna, 1976.

23. R. L. Ullrich, M. C. Jernigan and J. B. Storer. Neutron carcinogenesis: dose and dose rate effects in BALB/c mice. Radiat. Res. 72, 487-498, (1977).

24. R. J. M. Fry. Radiation Carcinogenesis. Int. J. Radiation Oncology Biol. Phys. 3, 219-226, (1977).

25. L. H. Gray. Radiation Biology and Cancer. In: Cellular Radiation Biology, pp 7-20, Williams and Wilkins, Baltimore, 1965.

26. A. Han, C. K. Hill and M. M. Elkind. Repair of cell killing and neoplastic transformation at reduced dose rates of ^{60}Co γ-rays. Cancer Res. 40, 3328-3332, (1980).

27. H. Rossi. The Role of Microdosimetry in radiobiology. Radiat. Environ. Biophys. 17, 29-40, (1979).

28. D. Grahn, G. A. Sacher, R. A. Lea, R. J. M. Fry and J. H. Rust. Analytical approaches to and interpretations of data on time, rate and cause of death of mice exposed to external gamma irradiation. In: Late Effects of Ionizing Radiation, Vol. 2, pp 43-58, IAEA, Vienna, 1978.

29. D. Grahn. Biological effects of protracted low dose radiation exposure of man and animals. In: Late Effects of Radiation (eds. R. J. M. Fry, D. Grahn, M. L. Griem, and J. H. Rust), pp 101-136, Taylor and Francis, London, 1970.

30. O. G. Raabe, S. A. Book and N. J. Parks. Bone cancer from radium. Canine dose response explains data for mice and humans. Science 203, 61-63, (1980).

31. R. J. M. Fry. Extrapolation from experimental systems to man: A review of the problems and the possibilities. In: The Proceedings of a Federal Radiation Research Agency, Issue Paper No. 3, Vol. I, (in press), 1981.

32. C. J. Shellabarger, V. P. Bond, E. P. Cronkite and G. E. Aponte. Relationship of dose of total body ^{60}Co radiation to incidence of mammary neoplasia in female rats in radiation-induced cancer, pp 161-172, IAEA, Vienna, 1969.

33. G. A. Sacher. Dose, dose rate, radiation quality and host factors for radiation-induced life shortening. In Aging, Carcinogenesis and Radiation Biology (ed. K. C. Smith), pp 493-517, Plenum Press, New York, 1975.

34. R. L. Ullrich, M. C. Jernigan and L. M. Adams. Induction of lung tumors in RFM mice after localized exposures to x rays or neutrons. Radiat. Res. 80, 464-473, (1979).

35. I. R. Major and R. H. Mole. Myeloid leukemia in x-ray irradiated CBA mice. Nature 272, 455-456, (1978).

36. P. Maldague. Comparative study of experimentally induced cancer office kidney in mice and rats with x-rays. In: Radiation Induced Cancer, pp 439-458, IAEA, Vienna, 1969.

37. R. E. Albert, F. J. Burns and P. Bennett. Radiation-induced hair-follicle damage and tumor formation in mouse and rat skin. J. Natl. Cancer Inst. 49, 1131-1137, (1972).

Table 1

RBE Values

Estimates are based on the ratio of the slopes of the initial part of the dose response curves for fission neutrons (25 rad/min) and the slope of the dose response (α) for 137 C_s gamma radiation (8.3 rad/day). Data from refs. 15, 38.

MOUSE STRAIN	SEX	TISSUE-TUMOR	TERM VALUES + S.E.		RBE
RFM	♀	Thymic lymphoma	0.56 ± 0.004	0.039 ± 0.03	14 - ∞
		Pituitary	0.41 ± 0.21	0.007 ± 0.005	59
		Harderian gland	0.54 ± 0.03	0.015 ± 0.004	36
		Lung tumors	1.7 ± 0.15	-0.29 ± 0.151	283-∞
BALB/c	♀	Lung adenocarcinoma	2.6 ± 0.14	0.043 ± 0.003	60
		Mammary adenocarcinoma	1.14 ± 1.0	0.035 ± 0.01	33
		Ovarian tumors	0.67 ± 0.11	0.083 ± 0.09	8

Table 1

Relationship of Natural Incidence and Susceptibility

Tumor Type	Mouse Strain	Natural Incidence (Per cent)	Response to Radiation Increase in Tumor Incidence Per Rad (Per cent)
Ovarian	RFM	2.4	0.39
Ovarian	BALB/c	6.4	1.2
Mammary Gland	BALB/c	7.5	0.067
Mammary Gland	$B6CF_1/Anl$	1.2	0.01
Myeloid Leukemia	RFM ♂	4.0	0.14
Myeloid Leukemia	RFM ♀	3.0	0.09

Figure Legends

Figure 1. Tumor prevalence and survival as a function of age in female $B6CF_1$/Anl mice reproduced from (2) with the kind permission of Pergamon Press.

Figure 2. Schematic of the relationship of tumor incidence as a function in time of a tumor with a high natural incidence. The effect of exposure to radiation is indicated by the curve representing the advancement of time of appearance of the tumors.

Figure 3. Age-specific mortality rates for lethal lung tumors in female $B6CF_1$/Anl mice exposed to JANUS Reactor fission spectrum neutrons reproduced from (2) with the kind permission of Pergamon Press.

Figure 4. Three dose-response curves for low LET-radiation that may describe many of the experimental tumor systems. The curves shown represent the response over a relatively restricted dose-range and the effects of cell killing on the shape of the curves is not considered. In some tumors a dose-squared response cannot be excluded or readily distinguished from a non-linear no threshold curve. Since a substantial fraction of the excess mortality after exposure to radiation is due to tumors life shortening is included.

Left Panel: Linear-no threshold Rat: Mammary Tumors (31) Mouse: female BALB/c, Mammary tumors, Pulmonary adenocarcinomas (10) Mouse: Life shortening male RFM (19) male and female $B6CF_1$ (17). The question of a quadratic dependence is discussed by Sacher (32).

Middle Panel: Non-linear no threshold including the so-called linear quadratic shown in the figure and dose-squared responses. Examples mouse, male, RFM, myeloid leukemia (5) (a dose-squared response cannot be excluded), Female RFM lung adenoma (15 ,34), Male CBA, myeloid leukemia, (best fit $\alpha D^2 e^{-bd}$) (35).

Right Panel: Non-linear threshold Rat: renal tumors (36) skin (37), Mouse: female RFM, thymic lymphoma, ovarian tumors (10) skin (37).

Figure 5. The percent of mice with squamous cell carcinomas as a function of total dose of 320-400 nm UVR given in various numbers of fractions plus 8-methoxypsoralen ○—○ and similar exposures but followed at the end of the fractionation regime by treatment with 5 μg of TPA 3/week.

Figure 6. Schematic dose-response curves for tumor incidence after exposure to high: (▲—▲) and low LET-radiation: (△—△) with linear interpolations through selected points on the curves.

Figure 7. Incidence of thymic lymphoma in RFM mice as a function of dose after 45 rad/min:(●—●) or 8.3 rad/day: (○—○). See ref. (11).

Figure 8. Plot of the slopes (linear regressions of tumor incidences as a function of dose, assuming no threshold, for exposures to high dose-rate irradiation. The minimum and maximum slopes for all the tumors examined are indicated by the solid lines and those for exposures to low dose-rate irradiation are indicated individually by tumor type.

Figure 9. Life-shortening in days a fraction of dose after single exposures to fission neutrons, HP RR ORNL, RFM female mice: (●—●) and BALB/c female mice: (○—○) JANUS reactor Argonne National Laboratory male $B6CF_1$ mice: (▲—▲) (data was taken from refs. 17, 18, 19.

Figure 10. Life shortening as a fraction of dose after single and fractionated exposures of life to JANUS fission neutrons and ^{60}Co-gamma radiation. Data is from refs. 17, 18.

Figure 11. The incidence of Harderian gland tumors as a function of dose of JANUS reactor fission neutrons in $B6CF_1$ female mice with pituitary isografts before: (●—●) and after (○) irradiation, and in mice without pituitary isografts: (△—△).

Figure 12. The incidence of Harderian gland tumors as a function of dose by JANUS reactor fission neutrons (■—■), (□) Fermi Lab neutron facility neutrons (●—●) (○), and ^{60}Co gamma radiation (◆—◆) in B6CF$_1$ female mice with pituitary isografts.

Figure 13. Schematic diagram of the effect per unit dose as a function of doses of low and high LET-radiation.

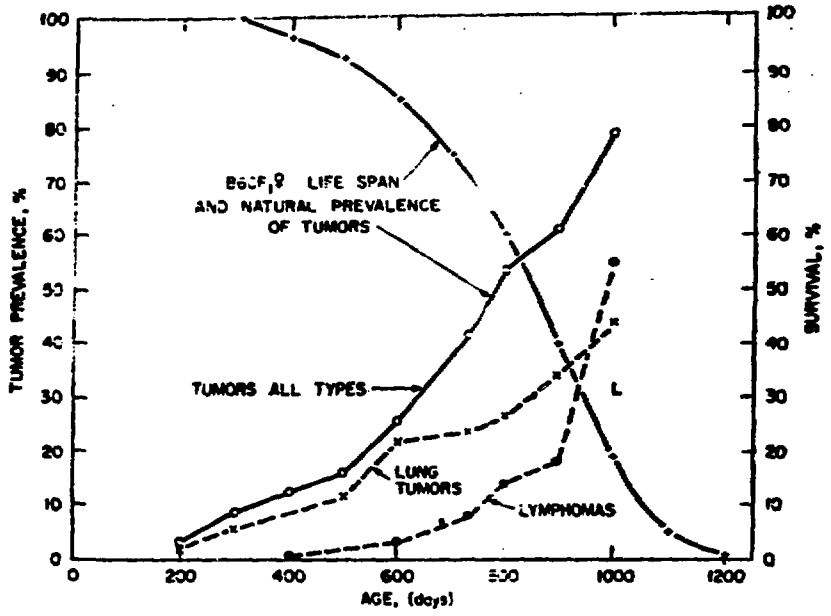

TUMOR PREVALENCE, %
SURVIVAL, %
AGE, (days)
B6CF1♀ LIFE SPAN AND NATURAL PREVALENCE OF TUMORS
TUMORS ALL TYPES
LUNG TUMORS
LYMPHOMAS
L
0
10
20
30
40
50
60
70
80
90
100
200
400
600
800
1000
1200

Fig. 1

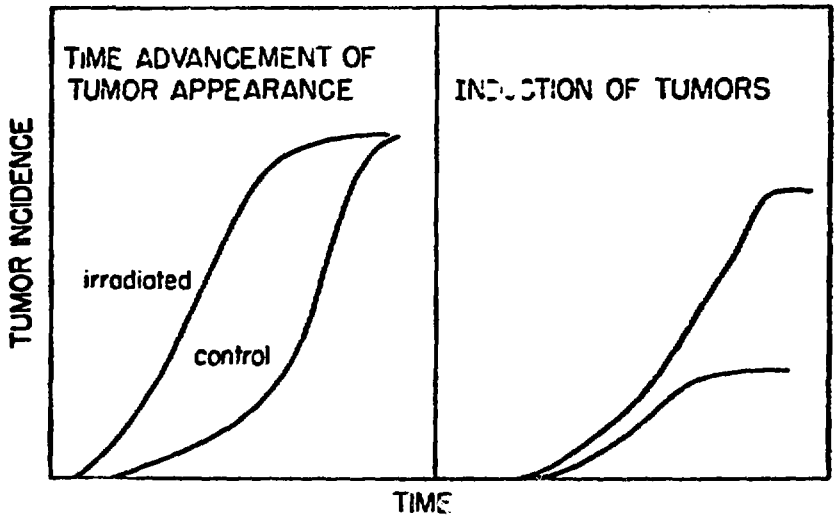
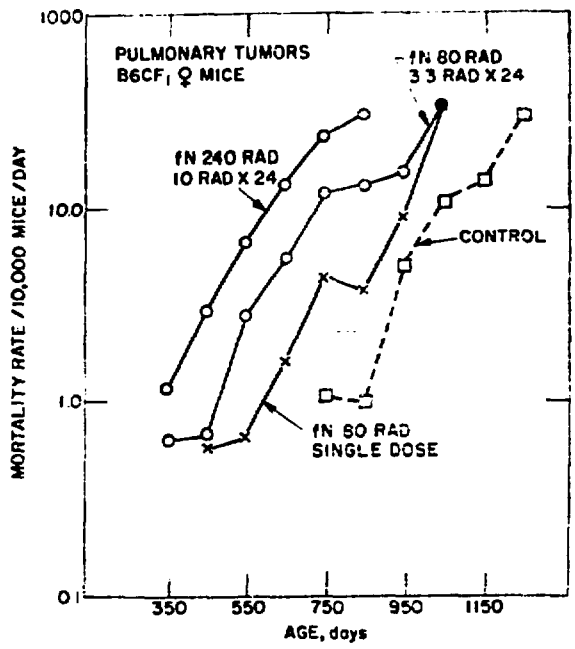
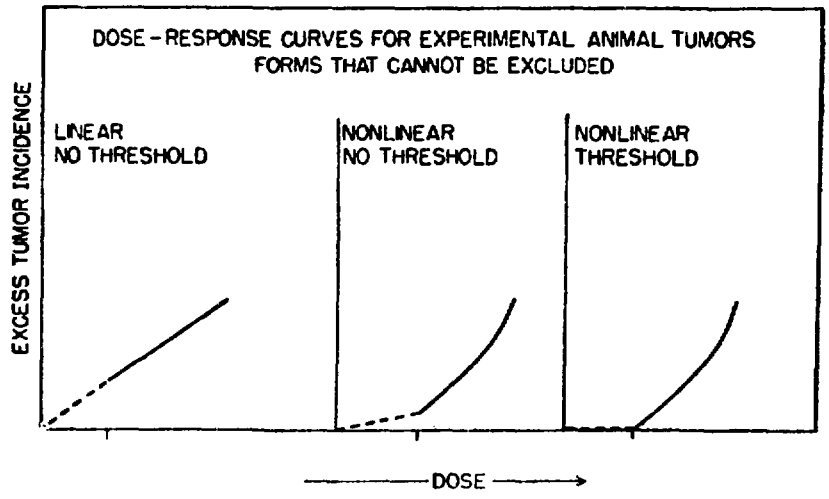
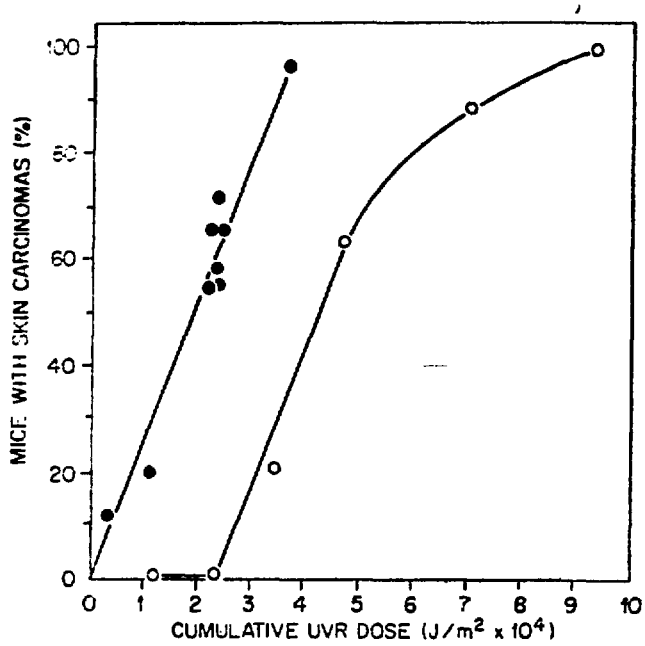
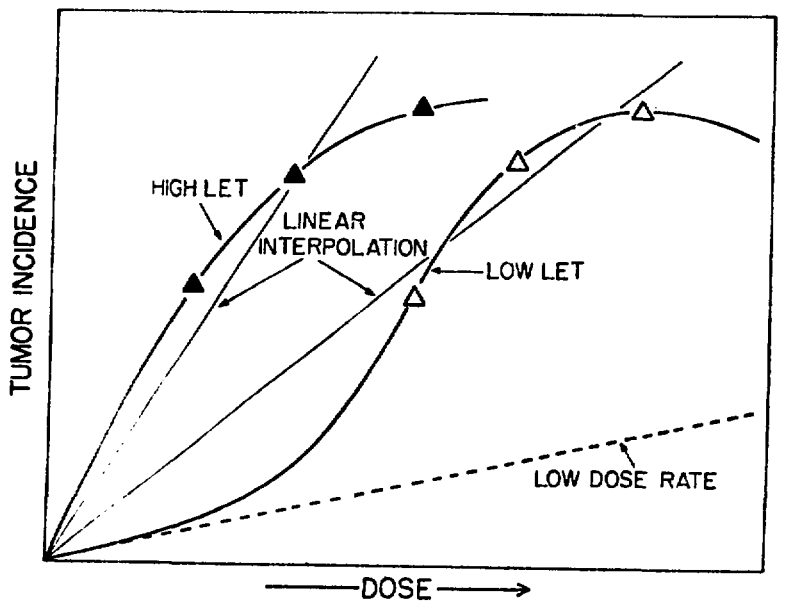

TIME ADVANCEMENT OF TUMOR APPEARANCE
INDUCTION OF TUMORS
TUMOR INCIDENCE
irradiated
control
TIME

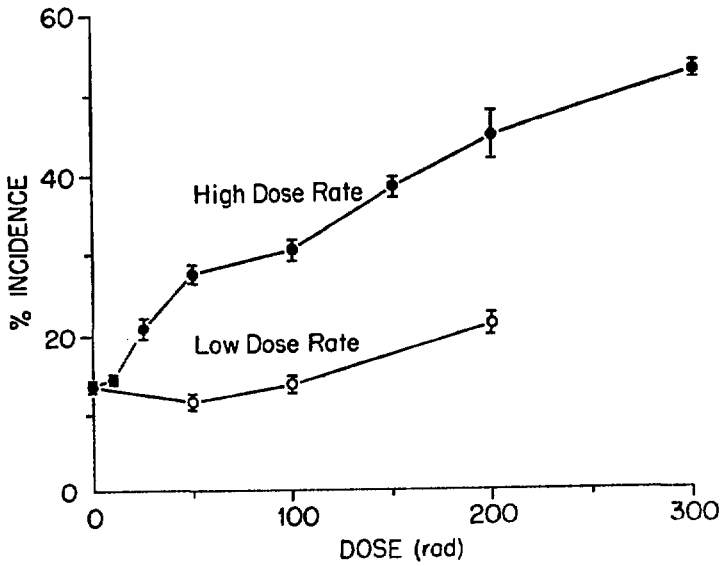
Fig. 2

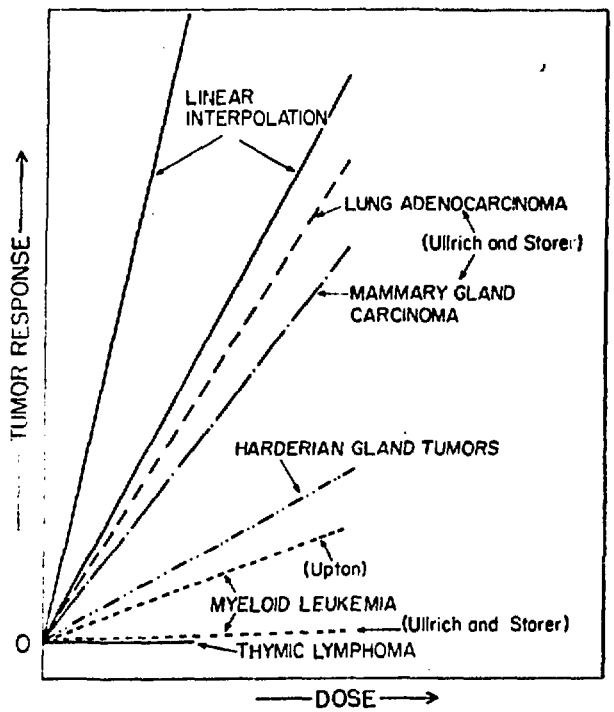

PULMONARY TUMORS
B6CF1 ♀ MICE
fN 80 RAD
3 3 RAD X 24
fN 240 RAD
10 RAD X 24
CONTROL
fN 80 RAD
SINGLE DOSE
MORTALITY RATE /10,000 MICE/DAY
1000
10.0
1.0
0.1
350
550
750
950
1150
AGE, days

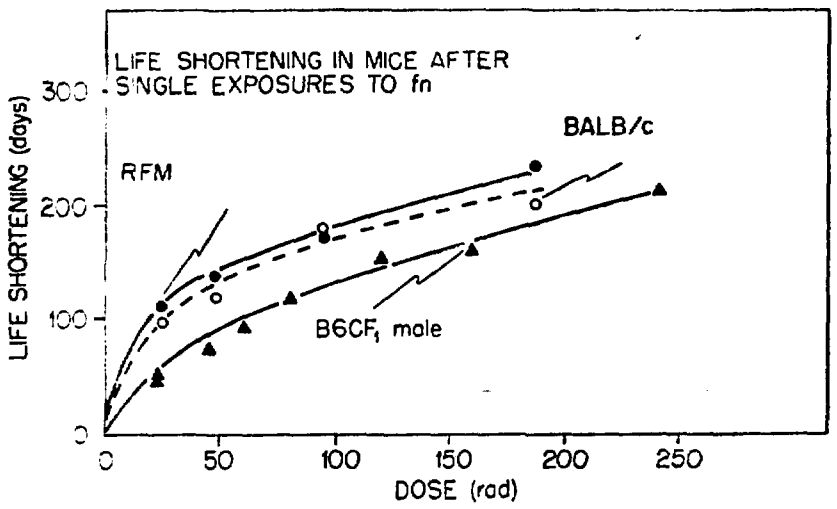

DOSE-RESPONSE CURVES FOR EXPERIMENTAL ANIMAL TUMORS
FORMS THAT CANNOT BE EXCLUDED
LINEAR
NO THRESHOLD
NONLINEAR
NO THRESHOLD
NONLINEAR
THRESHOLD
EXCESS TUMOR INCIDENCE
DOSE


MICE WITH SKIN CARCINOMAS (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10
CUMULATIVE UVR DOSE (J/m² x 10⁴)

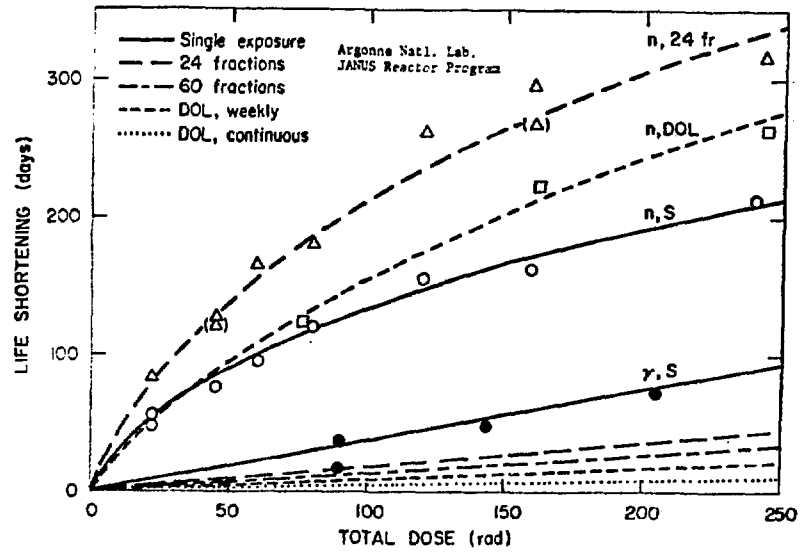

TUMOR INCIDENCE
HIGH LET
LINEAR
INTERPOLATION
LOW LET
LOW DOSE RATE
DOSE


60
40
20
0
% INCIDENCE
High Dose Rate
Low Dose Rate
0
100
200
300
DOSE (rad)

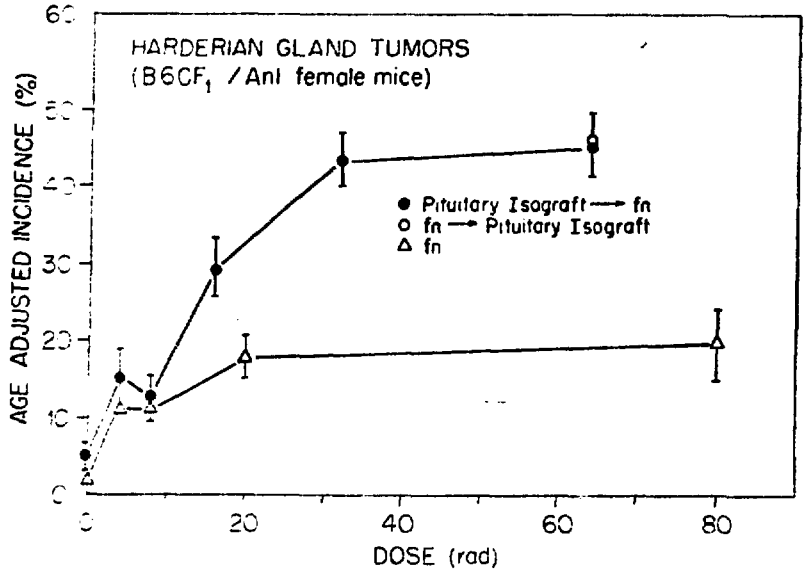

LINEAR
INTERPOLATION
LUNG ADENOCARCINOMA
(Ullrich and Storer)
MAMMARY GLAND
CARCINOMA
HARDERIAN GLAND TUMORS
(Upton)
MYELOID LEUKEMIA
(Ullrich and Storer)
THYMIC LYMPHOMA
TUMOR RESPONSE
0
DOSE

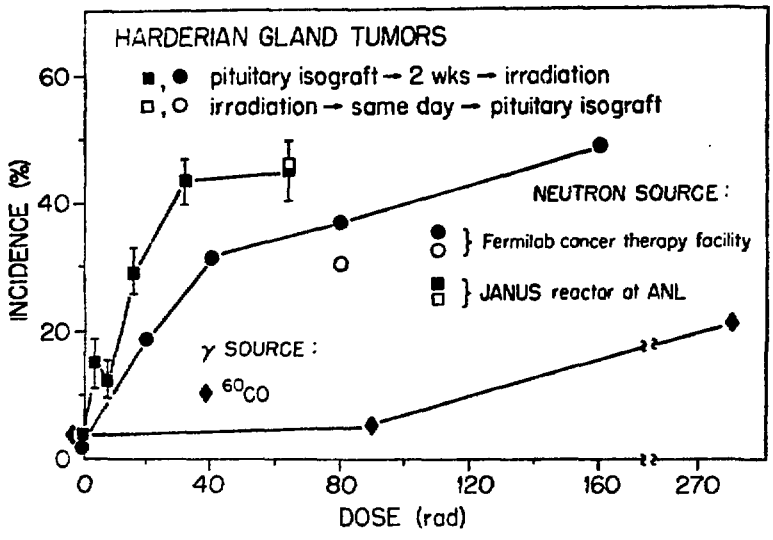

LIFE SHORTENING IN MICE AFTER
SINGLE EXPOSURES TO fn
BALB/c
RFM
B6CF1 male
LIFE SHORTENING (days)
300
200
100
0
0
50
100
150
200
250
DOSE (rad)

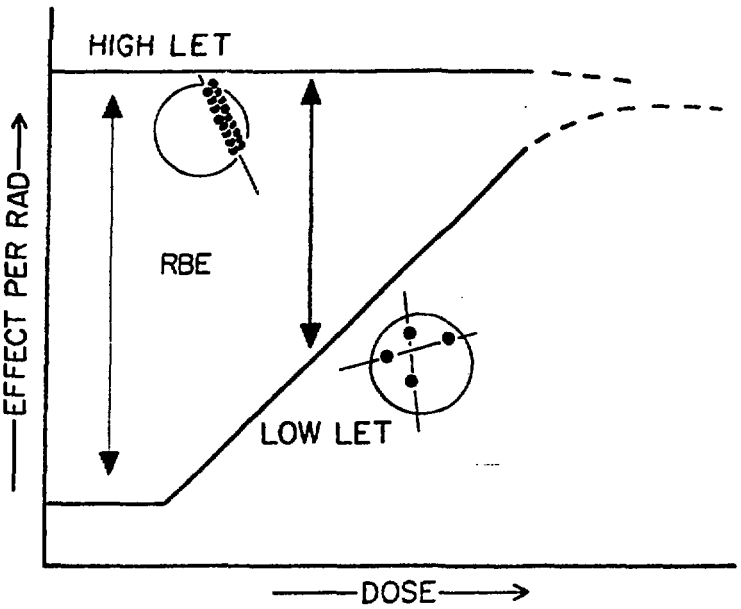
9


Single exposure
24 fractions
60 fractions
DOL, weekly
DOL, continuous
Argonne Natl. Lab.
JANUS Reactor Program
n, 24 fr
n,DOL
n,S
γ,S
LIFE SHORTENING (days)
300
200
100
0
0
50
100
150
200
250
TOTAL DOSE (rad)

D


HARDERIAN GLAND TUMORS
(B6CF1 / Anl female mice)
AGE ADJUSTED INCIDENCE (%)
Pituitary Isograft → fn
fn → Pituitary Isograft
fn
0
20
40
60
80
DOSE (rad)


HARDERIAN GLAND TUMORS
pituitary isograft – 2 wks – irradiation
irradiation – same day – pituitary isograft
INCIDENCE (%)
NEUTRON SOURCE :
Fermilab cancer therapy facility
JANUS reactor at ANL
γ SOURCE :
60Co
0
20
40
60
0
40
80
120
160
270
DOSE (rad)



T 3