Title
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Journal
Advances in Radiation Biology, Vol. 16 - Low-Level Radiation Effects, 16

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Publication Date
1992

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To be published as a chapter in *Advances in Radiation Biology,*
Oddvar R. Nygaard and Warren K. Sinclair, Eds., Vol. 16,
Academic Press, Inc., San Diego, CA, 1992

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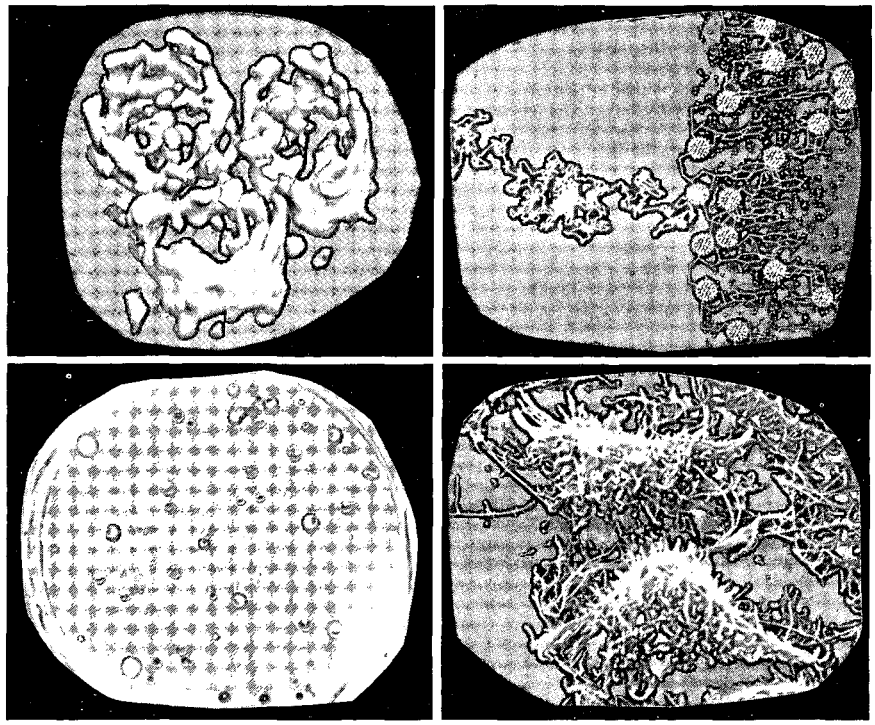

Prepared for the U.S. Department of Energy under Contract Number DE-AC03-76SF00098

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LBL-31684

DOSE-TIME-RESPONSE MODELS FOR RADIATION CARCINOGENESIS

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This work has been supported in part by the National Aeronautics and Space Administration under Order No. T-9310R and by the Director, Office of Energy Research, Office of Health and Environmental Research, Radiological and Chemical Physics and Radiation Dosimetry Division, of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

I. INTRODUCTION

One of the major tasks of radiation risk assessment is to determine the variation of a given response (e.g., the incidence above background of a particular type of cancer) with the amount of radiation dose an individual or a group of individuals has received. Such a functional dependence of incidence on absorbed dose is referred to as a *dose-response relation.* Because the doses of interest in most cases are very small and the incidence has a low probability, it is impossible to determine the shape of the curve at low doses with high statistical precision.

This chapter will first review the current practice of how dose-response relations are determined for various types of radiation and various types of cancer from epidemiological evidence. Emphasis will be placed on the role of time-related modifiers, such as age at exposure, time since exposure, attained age, and duration of exposure (or equivalently, dose rate). All affect in some way the probability of the emergence of cancer.

In addition, the shapes of such dose-time-response relationships are strongly affected by the "linear energy transfer" (LET) of the radiation. This refers to the rate of energy deposition per unit distance along the tracks of the charged particles that are depositing the energy: high-LET radiation, such as alpha particles, deposits large amounts of energy per unit particle track length by creating closely spaced electrons along the track in the absorbing medium, and low-LET radiation, such as X or gamma rays, deposits only a small amount of energy per unit electron track length by creating isolated electrons in the absorbing medium. Both the form of the dose-response relationships and the modifying effects of time-related variables, such as duration of exposure, differ for low- and high-LET radiation. One of the goals of this chapter is to review these differences and their mechanistic bases.

Two types of dose-time-response models are considered: descriptive and mechanistic. Section II summarizes the data from epidemiologic studies analyzed by regression models that simply

describe the observed rates in terms of a minimal set of variables. These descriptive models are useful for risk assessment purposes but no pretense is made that they are based on biological mechanisms. Section III presents a broad overview of the radiobiological principles that have emerged from a considerable amount of cellular and animal experimentation with both highly and sparsely ionizing radiations and are considered to be relevant to risk assessment modeling at low doses. Section IV reviews several mathematical models that have been proposed to describe the carcinogenic process. Finally, Section V concludes with some comments on directions that research may take in the field of low dose modeling of radiation carcinogensis.

II. DESCRIPTIVE MODELS

In this section, the sources of epidemiologic data are briefly reviewed and then the descriptive findings on dose-response relationships and selected modifying effects are summarized for selected cancers and types of radiation. Several comprehensive reviews have recently been completed by various national and international advisory committees [the BEIR Committees of the National Academy of Sciences (NAS, 1988, 1990) and the UNSCEAR Committee of the United Nations (UNSCEAR, 1988)], to which the reader is referred for details. The aim here is simply to provide the general foundations on which the mathematical models discussed below are based. The section concludes with a few comments about the evidence from various low-dose studies about the adequacy of risk estimates derived from high-dose studies.

A. Sources of Data

By far the most important human data on the carcinogenic effects of radiation exposure come from the Japanese atomic bomb survivors, specifically the series of reports from the "Life Span Study (LSS)". This is a cohort mortality study, in which 120,128 survivors who were known to be alive on Sept 1, 1950 are being followed, with periodic updating of their vital status using

the local family registration offices; ascertainment of deaths is thought to be virtually complete. The most recent results (Shimizu *et al.*, 1988) are based on follow-up through December 31, 1985. Dose estimates for each subject are based on their location at the time of the bombing (ATB), including information on shielding. Recently revised dose estimates based on the new dosimetry system (DS86) are available for 75,991 members of the cohort, or about 83.3% of those exposed (Preston and Pierce, 1988). Most analyses of these data are based on a fine cross-tabulation of the numbers of deaths from various causes and the numbers of person-years at risk by dose, attained age, age ATB, time since bombing, gender, and city. The importance of these data derives from the large number of subjects, the wide range of doses, and the long period of follow-up, all of which contribute to estimates of dose-response relationships having considerable statistical precision.

A number of cohorts of patients with medical exposures, usually at rather high doses, have also been followed to observe their cancer experience. These include patients with cervical cancer (Boice *et al*, 1987), ankylosing spondylitis (Darby *et al*, 1987), and post-partum mastitis (Shore *et al*, 1986) who received radiotherapy for their conditions, and patients with tuberculosis who received multiple fluoroscopies (Boice *et al*, 1981; Miller *et al*, 1989). One advantage of these studies is that the doses received are often known quite precisely, but there may be concern about whether any cancer excesses are attributable to the radiation exposure or to the disease for which the radiation was given. These studies are generally smaller than the atomic bomb survivor series and the dose ranges are narrower, so that their dose-response relations are less precise.

B. The Generalized Relative and Absolute Risk Models

Of the various recent reviews of these data, the ones by the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation [BEIR IV (NAS, 1988) and BEIR V (NAS, 1990)] are particularly useful for our purposes, because they include reanalyses of the available data from several studies in a consistent manner. The BEIR IV report was concerned with the effects of internal emitters of high-LET radiation (alpha particles), particularly from radon and its progeny, while the BEIR V report was concerned with low-LET radiation (X and gamma rays) as well as with high-LET radiation (neutrons). As the review of the descriptive observations of dose-response relations for various cancers given below will be based heavily on these analyses, it would be helpful to describe first the basic form of these models. In the BEIR formulations, the death rate r from a specific cause C is modeled as a function of attained age A *, dose D, and various modifiers such as gender G (0 for males, 1 for females), age at exposure E, or time since exposure T, in terms of what might be called a "generalized relative risk model". This is a product of a "baseline rate" r_{0C} in the unexposed population, depending on A and G (and perhaps E and T to allow for secular trends and birth cohort effects), multiplied by a relative risk RR that depends on dose and possibly some of these modifiers. The excess relative risk (RR-1) in turn is modeled as a product of a term f(D) that depends only on dose and a term g(A,G,E,T,...) that depends on the modifiers. In its general form, then, the model can be written as

$$r_C(A,G,D,E,T) = r_{0C}(A,G,E,T) \, [\, 1 + f(D) \, g(A,G,E,T) \,] \, . \qquad (1)$$

A "generalized absolute risk model" could be defined in a similar way as

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* For future reference in this chapter:

A = attained age, E = age at exposure, T = time since exposure, G = gender, D = absorded dose.

$$r_C(A,D,G,E,T) = r_{0C}(A,G,E,T) + f(D)\, g(A,G,E,T)\,. \qquad (2)$$

Models of the latter form were also considered by the BEIR V committee, but found to require more modifying variables in the function g and greater variation in g across the range of these modifiers to obtain a comparable fit to the Japanese data. In short, the generalized relative risk model was found to provide a more economical description of the data and the absolute risk models were abandoned.

Usually, f is taken to be a linear-quadratic function of dose,

$$f(D) = \alpha_1 D + \alpha_2 D^2\,. \qquad (3)$$

At high doses, cancer rates may decline due to cell killing effects. Such effects are usually described by multiplying the entire expression by a term of the form $\exp(- \alpha_3 D - \alpha_4 D^2)$. The Japanese data show a reduction in slope beginning about 3 Gy, but the interpretation is confounded by possible systematic overestimation of the highest doses (Pierce and Vaeth, 1989). Rather than address these complexities, the BEIR V committee chose to restrict their analyses to those survivors who received less than 4 Gy, a point at which any bias caused by cell killing was virtually eliminated without loss of much information.

The modifying factor g was taken to be an exponential function of the various modifiers, e.g.,

$$g(A,G,E,T) = exp\,[\beta_1 ln(A/50) + \beta_2 G + \beta_3 ln(E/30) + \beta_4 ln(T/20) + \beta_5 ln^2(T/20) + \beta_6 ln(E/30)\, ln(T/20) + \ldots]\,. \qquad (4)$$

The choice of an exponential form is simply one of mathematical convenience, in order to avoid negative rates, but the particular modifying factors and their specific functional forms were

chosen empirically for each cancer. The coefficients α_1 and α_2 are the slope of the linear and quadratic components of the dose-response relation at the "centered" values of the modifying variables (in the above expression, males aged 30 at exposure, 20 years after exposure) and the coefficients β measure how these slopes vary away from the centered values of each modifier. For example, $\exp(\beta_2)$ is the amount by which the slope of the dose-response for females is higher than for males, $\exp(\beta_3)$ is the change in slope per year of age at exposure, and $\exp(\beta_6)$ tests whether the dependence of slope on time since exposure varies with age at exposure.

For modeling instantaneous exposures, such as to an atomic bomb blast, exploration of the effects of time-related modifiers is fairly straight-forward because the variables A and E are well-defined. The main difficulty is the multicolinearity in the relation A=E+T; thus, any two of these three factors suffice to describe the linear effects of all three, but if the relationships are nonlinear it may be difficult to find the best combination of variables. Modeling the effects of extended exposures is more complex, owing to the problem that there is not a single point from which to define E or T. Rather one must integrate the effects of these variables over all instants at which exposure occurred, weighted by the dose rate, D'(t), at that instant, i.e.,

$$r_C(A,G,\{D'(t),\, t\le A\}) = r_{0C}(A,G)\,\{1 + \int_0^A f[D'(t)]\, g(A,G,t)\, dt\} \qquad (5)$$

(Thomas, 1988). This approach is based on the assumption that each increment of exposure acts additively on the total risk, rather than enhancing damage caused by earlier exposures. This additivity hypothesis seems plausible, because the alternative would tend to produce exponential dependencies of risk on total dose, which are not observed (Thomas, 1990). However, it does appear that in many cases (discussed below), extended exposures do not produce the same quantitative effects as instantaneous exposures. This problem can be addressed by multiplying the integrand in equation (5) by a "Dose Rate Effectiveness Factor (DREF)" which must also be estimated from the data or assumed by other means. In principle,

the DREF might itself depend on radiation quality, dose, age, duration of exposure, or other factors, but presently available data are inadequate to describe such dependencies.

C. Applications to Specific Cancer Sites

In the following, we present examples of how the relative risk model has been applied to analyze available epidemiological data for several cancer sites.

1. Leukemia

The BEIR V model for leukemia was based entirely on the atomic bomb survivor data. Although both the ankylosing spondylitis and cervical cancer patient series showed dose-related excesses of leukemia, the raw data from these studies were not available to the committee at the time.

The dose-response function for leukemia induction in the atomic-bomb survivor data has both linear and quadratic components, with a "cross-over dose" (the dose at which linear and quadratic components contribute equally) of about 1 Gy (Figure 1a). Earlier analyses failed to show a strong quadratic component over the entire dose range because of a marked down-turn in the risk at doses over about 4 Gy. This down-turn might be due to cell killing effects, but a strong case has been made that it reflects some overestimation of the doses in these subjects (Pierce and Vaeth, 1989). A pure linear dose-response model was also considered, but found not to fit the data as well.

There are strong modifying effects of age at exposure, time since exposure, and an interaction between the two. Several ways of describing the modifying effects of age at and time since exposure were considered by the BEIR V committee. The relative risk clearly declined with increasing age at exposure and with increasing time since exposure, but the rate of decline with time was significantly faster in those under age 20 than in those over age 20 (Figure 2a).

Analysis of time-since-exposure effects in the atomic bomb survivor data are complicated by the absence of any data in the first five years after exposure, where most of the leukemia effect was concentrated in both the ankylosing spondylitis and cervical irradiation patients.

A commonly suggested hypothesis is that the latent period is shorter in individuals receiving higher doses. Unfortunately, the evidence that is usually offered to support this hypothesis consists of the distribution of cases by time-since-exposure and dose, without taking account of the different numbers at risk over time in the different dose groups (Guess and Hoel, 1977). The hypothesis was tested by the BEIR committee by adding dose-latency interaction terms to the risk models described above and no evidence that latency was shorter in the higher dose groups was found.

Data from the cohort of cervical cancer patients has been analysed by comparing their risks with those of the general population (Day and Boice, 1983) and by comparing the doses of the leukemia cases in the cohort with those of matched "controls" drawn from cohort members who outlived the cases (Boice *et al*, 1987). Both approaches showed associations between leukemia risk and radiation exposure, confined mainly to the first five years after exposure. However, the cohort analyses could not establish a dose-response relationship because information on dose was not available for all the members of the cohort. The case-control comparisons examined the dose-response relationship in considerable detail, by estimating the dose to each of 14 components of the bone marrow for each subject. Because the doses to some components were in the tens of Gy, where cell killing effects are substantial, the leukemia risk cannot be described by a function of just the average bone marrow dose. Instead, the investigators fitted a model to each component separately and then took a weighted average of the predicted leukemia risks, i.e.,

$$r(D) = \sum_{k=1}^{14} [\,(1 + \alpha_1 D_k + \alpha_2 D_k^{\,2}) \exp(-\alpha_3 D_k)\,]\, w_k \qquad (6)$$

where w_k is the proportion of the bone marrow located in component k (Boice *et al*, 1987). A number of restricted models, setting particular coefficients to zero, were also tested (Figure 1b). Paradoxically, despite the considerable excess of leukemia in the early time period in the cohort comparisons, none of the dose-response models significantly rejected the null hypothesis, nor were there any significant differences in fit between the alternative models considered. Part of the reason for this is the failure to include any time-related modifiers in the dose-response model and part of the reason is the restricted range of doses among the irradiated group (Day, 1991). To remedy these problems, Thomas *et al.* (1991) extended this model to include effects of age at exposure and time since exposure, and also combined the case-control comparisons with the comparisons of the cohort as a whole against the external rates. This joint analysis had considerably greater statistical power for distinguishing alternative models. Inclusion of both age at and time since exposure significantly improved the fit of the model, but the interaction between the two found in the atomic bomb survivor data was not apparent (there being no patients under age 20, Figure 2b). With age, latency, and cell-killing terms in the model, either a linear (α_2=0) or a quadratic (α_1=0) model fitted equally well, although the best estimate of α_1 in the full model was zero.

The ankylosing spondylitis data have so far been reported only in terms of an overall comparison of leukemia rates in the entire cohort relative to external rates. These comparisons show a "wave-like" pattern of excess risk over time since exposure, peaking 3-4 years after exposure (Figure 2c), and a decline in excess RRs with age at exposure similar to that seen in the other two studies. The best fitting model involves linear-quadratic dependencies on both E and T, but no interaction between the two. A case-control comparison similar to that done for

the cervical irradiation patients is currently in progress, with the controls being an unmatched 15% random sample of all the non-cancers in the cohort. To date, no results from this analysis have been published.

None of these studies allow any test of the modifying effect of dose-rate or duration of exposure. Although some of the individuals in the two medical cohorts received multiple courses of radiotherapy, all the analyses reported to date have been restricted to the effects of initial therapy. Preliminary comparisons seem to indicate that the multiply irradiated patients in both medical cohorts experienced lower excess risks per unit dose, but whether this is due to dose rate, cell killing, characteristics of the populations, or other differences cannot be determined from such between-study comparisons. However, the BEIR V committee treated the linear-quadratic dose-response function as containing an implicit DREF, because the quadratic component becomes trivial at low dose-rates.

2. Cancers Other Than Leukemia

In this section, the other cancers are discussed first as a group and then individually for selected sites. The justification for treating them as a group is that they tend to show fairly similar dose-time-response relationships (and rather different ones from leukemia) and that greater statistical power results from the larger sample sizes.

a. All nonleukemias. As a group, the nonleukemias are characterized by generally linear dose-response relations (Figure 3), long minimum latent periods (typically about 10 years), and an excess risk that remains elevated for the 40 years the atomic bomb survivor cohort has so far been studied. On an absolute risk scale, that excess is still growing (Figure 4a), although not as fast as the baseline rates, so that the relative risk does not increase as rapidly (Figure 4b). The exact behavior of that excess over time is crucial to predicting lifetime risk, but it is now clear that considering either the absolute or the relative risk as a constant is incorrect.

The BEIR V analysis described both absolute and relative risks in terms of using only pairs of the variables A, E, and T. For absolute risk, the best fit was obtained using E and T, whereas for relative risk, the best fit was obtained using A and T. Although the fit to the data was about the same for either of these two situations, the magnitude of the variation in risks across levels of each of the time-related variables was much lower for the relative risk model. Thus, for risk assessment the relative risk model is preferable because this measure is more stable over time and it seems reasonable to assume that this might continue into the future. Because data were available only for acute exposures, it was again not possible to test a modifying effect of dose-rate or duration of exposure. Furthermore, the apparent linearity of the dose-response relation precluded treating the ratio of linear components in pure linear and linear-quadratic models as an implicit DREF, as was done for leukemia. The committee therefore summarized a range of factors that had been derived from the experimental literature (between 2 and 10) and recommended that some number in that range be applied to their risk estimates. This range of 2 to 10 has also been suggested for DREF in an extensive earlier review of experimental animal and cell data (NCRP, 1980).

Individual sites departed somewhat from these general patterns. The BEIR V report describes separate analyses for the categories of respiratory, digestive, breast, and all other cancers. For the purposes of this chapter, lung, breast, and bone cancer are singled out as they illustrate a number of unique features.

b. Lung cancer. The category of respiratory cancer is interesting because of the comparisons that can be made with high-LET exposure (specifically alpha-particle radiation from radon daughters) in the BEIR IV report. For both low- and high-LET radiation, the dose-response relation appears to be linear, with no indication of a quadratic component. The minimum latent period appears to be about ten years for low-LET radiation and about five years

for radon exposure, although this difference is not well established. For both low- and high-LET radiation, the relative risk declines more rapidly with time since exposure for lung cancer than for other sites. For low-LET radiation, the BEIR V model includes a continuous power function dependence on T with an exponent of -1.44 per year; the statistical significance of this term was only marginal but it was included because of its large magnitude, its presence for most other sites and the rapid decline seen for this site in the ankylosing spondylitis data. For high-LET radiation, the BEIR IV report adopted a step-function for the time intervals 5-9, 10-14, and 15+ years after exposure; the first two intervals showed little difference and the 15+ interval was assigned a weight of 50% relative to the period 5-14. In BEIR V, the low-LET model has no dependence on A or E, but the BEIR IV model for radon includes a declining step function with attained age having discontinuities at ages 55 and 65.

The BEIR IV committee noted a greater effectiveness per unit dose for long than for short exposures in two of the four data sets they considered (but significant in only one of these); in view of the inconsistency of the data on this point, the effect was not included in their final model. It is important to note that if it is true, such an effect would go in the opposite direction from that generally accepted to hold for low-LET radiation. A similar "inverse dose-rate effect" has been noted in humans for ^{224}Ra exposure (Spiess and Mays, 1973) and for radon exposure in several other epidemiological and experimental cell and animal studies (see for review, Curtis, 1989, and Darby and Doll, 1990). It has been pointed out, however, that the risk coefficent derived from the miner data may not be applicable to the much lower exposure rates found in the domestic radon exposure situation (Curtis, 1989). If two-hit kinetics apply in the miner case to cause the inverse dose-rate effect and if the dose rates relevant in the domestic situation are so low that only single-hit kinetics apply, the risk coefficient might be considerably lower in the domestic case than the one applicable to the miners. A similar conclusion has been drawn by Brenner and Hall in this volume.

Finally, because of the importance of smoking for lung cancer, the joint effect of radiation and smoking is of particular interest. No smoking data were available for the entire LSS cohort, so this effect could not be included in the BEIR V model, but the BEIR IV report reviewed the available data for both low- and high-LET radiation. Two models are of particular interest because of their simplicity: the additive relative risk model, $r(A,D,S) = r_0(A)\,(1 + \beta_1 D + \beta_2 S)$, where S denotes smoking, and the multiplicative relative risk model, $r(A,D,S)=r_0(A)(1+\beta_1 D)(1+ \beta_2 S)$. The observational data are equivocal, some appearing more consistent with an additive, some with a multiplicative model, but overall the committee preferred a multiplicative model. Although the atomic bomb survivor data were among those that supported an additive model, these data could not reject a multiplicative model; thus, whether the form of the interaction between smoking and radiation is different for low- and high-LET radiation remains unresolved.

c. Breast cancer. This site is particularly interesting because of the strong dependence on age at exposure, which is probably related to hormonal status. The BEIR V model, which is based on several cohorts of medical patients as well as the atomic bomb survivors, involves a particularly high relative risk for exposures up to age 15, an abrupt drop at age 15, and a continuous decline thereafter. The rationale for this discontinuity is that the major difference seen in the data may be due to a biological change occurring after menarche. (The choice of age 15 for this purpose was dictated by the fact that the data available were already grouped in five-year age intervals.) An earlier report (Tokunaga *et al.*, 1987) had suggested that the relative risk was highest for exposure at ages 0-9, but there are so few deaths in this category that the confidence limits for this group include those for age 10-14 (the highest risk) and 50+ (the lowest).

An appealing way of thinking about the effects of menarche and other hormonal events has been suggested by Pike *et al.* (1983), who proposed a "breast tissue aging model". They proposed

that breast cancer might result from several spontaneous changes (mutations, etc.) occurring to a single cell, and that the rate of these changes depends upon the rate at which breast tissue is proliferating, which in turn is determined by hormonal events. Thus, if radiation acts by causing mutations, its effectiveness should be highest at the times when breast tissue is proliferating most rapidly - in their model, from menarche to first full-term pregnancy and during the first pregnancy. This would imply that the period from age 0-9 would have relatively low radiosensitivity; only the atomic bomb survivor data have any subjects exposed at that age, and as already noted, the data are inconclusive on this point, at least until this subcohort enters the age at which breast cancer is common. None of the studies had any data on those exposed during pregnancy, so the prediction that the breast should be highly radiosensitive during first pregnancy cannot be tested.

Breast cancer appears to have a somewhat longer latent period than some other cancers. The BEIR V model involves a 15 year minimum latent period and a declining effect with time since exposure thereafter. Most of the data sets showed a pure linear dose-response relation. The exception was the Canadian fluoroscopy series (Miller *et al.*, 1989), but the quadratic component observed here seems to be due to a difference in risk between Nova Scotia and the rest of the country, which might be explained by the fact that these women were X-rayed in a different position. When the data were stratified on exposure position, the quadratic component became nonsignificant. Although it was not possible to examine an effect of dose rate or fractionation within any of the cohorts, the general similarity of the relative risk estimates between cohorts, some of whom had single and some of whom had highly fractionated doses, suggests that dose rate effects are not important for breast cancer.

d. Bone Cancer. Bone cancer due to alpha-particle radiation from radium exposure is a final site for which extensive human dose-response data are available. The most interesting contrast here is between the radium dial painters, who were exposed mainly to the long-lived

^{226}Ra and ^{228}Ra, and the medical patients, who were exposed mainly to the short-lived ^{224}Ra. For the dial painters, the dose-response seems to include a strong quadratic component and a long latency period, whereas the medical patients experienced a more linear dose-response and shorter latent periods (Figure 5). It has been suggested that the differences in latency can be explained by differences in the way the dose was delivered over time (Mays and Spiess, 1984), i.e., that both studies would be consistent with the same latency function g in equation (5) if D'(t) were taken to be the dose-rate for the particular type of radiation, but so far the hypothesis has not been rigorously tested.

E. Summary of the Epidemiologic Evidence

From the above discussion, it should be clear that it is an oversimplification to talk about dose-response relations on either an absolute or relative risk scale, without considering the powerful age and time-related modifiers. The widespread practice of quoting a single risk coefficient (slope per unit dose) is therefore potentially misleading, as estimates of such parameters derived from epidemiologic studies depend strongly on the length of follow-up and age distribution of the study populations and could vary between studies in ways that would not reflect real differences in risk. There appears to be an emerging consensus that the relative risk is the more stable of the two estimators, but it should be recognized that a relative risk coefficient is simply a weighted average of a quantity that varies by gender, age and time.

Some intriguing differences between low- and high-LET radiation have been noted, as well as some differences between chronic low dose-rate and acute high dose-rate exposures. However, LET and dose-rate are confounded in the epidemiologic data, as there are few examples of chronic low-LET or acute high-LET exposures. Unscrambling the relations between these factors must therefore rely on data from the laboratory.

Before closing this section, it would be appropriate to say a few words about the evidence of cancer risks from certain "low-dose" studies. All of the dose-time-response relations that have been discussed so far are based on studies comprising substantial numbers of subjects with doses over 1 Gy, and these subjects are the most influential in determining the form of the dose-response relations. There have, however, been numerous studies of groups exposed to very low doses, often in the range of 0-0.1 Gy, including diagnostic X-rays, occupational exposures, fallout from nuclear weapons testing, the environment near nuclear facilities, and areas with high natural background. A detailed review of these data is beyond the scope of this paper; the interested reader is referred to the BEIR V report for the details. Suffice it to say that these studies have produced a variety of results, in part because of the wide statistical variability that is to be expected from small sample sizes and small expected excess risks, in part because of various methodological problems, and in part because of the problem of "publication bias", i.e., the tendency for authors and journals to prefer to publish positive results. Individually or collectively, these data are therefore not strong enough to allow direct estimation of risks at low doses, but they do provide an important check on whether the estimates of low-dose risks obtained by extrapolation from the high-dose studies are substantially in error. Stevens *et al.* (1990) recently reviewed these data in the context of a study of leukemia in residents of Utah downwind of the Nevada Test Site, in which some evidence of associations with low-LET fallout dose (in the range 0-0.02 Gy) was found in the subgroups expected to be at highest risk. Comparisons with the risk estimates from the atomic bomb survivors indicated that the Utah risk estimates were perhaps 2-3 times higher than the Japanese estimates, but the confidence limits on the Utah estimates were wide and easily included the Japanese estimates. They concluded that there was no convincing evidence, either from the Utah studies or from the other low-dose studies, that the low-dose risk estimates derived from the high-dose studies were substantially in error.

III. RADIOBIOLOGICAL PRINCIPLES

This section addresses the major concepts in radiobiology that may play important roles in determining the emergence of a radiation-induced malignant cell and the subsequent expression of a tumor. Because effects from low- and high-LET radiations are quantitatively and qualitatively different, they will be treated separately.

A. Low-LET Radiation

In general, low-LET radiation fields are characterized by small energy depositions caused by tracks of high and low energy electrons scattered randomly throughout the irradiated volume. The reader is referred to the chapter on microdosimetry by Goodhead in this volume for a detailed discussion of the distributions of energy depositions in the small sites deemed most critical in the cell: the DNA molecule. A large fraction of low-LET damage ultimately leading to most molecular and cellular end points is potentially repairable with time. For many end points, there is a distinct dose-rate effect; that is, for a given total dose, the effect is more pronounced at high than at low dose-rates. There is also less effect if the dose is delivered in several fractions rather than in a single exposure. These effects are considered to be due to cellular recovery taking place during the irradiation in the case of low dose-rate, or between the irradiations in the case of fractionation.

The end point of cell killing is usually described by plotting the logarithm of the measured surviving fraction of cells against the absorbed dose. This, of course, is one minus the fraction of cells killed. The initial slope of this curve is generally found to be nonzero. A nonzero slope is also found for neoplastic cell transformation, mutation induction and in some tumor induction studies in animals. These and other data have been presented as evidence that low doses of low-LET radiation produce effects that are linear with dose and that recovery processes (presumably repair of damage to the DNA) operate at the very low dose-rates relevant to

radiation risk assessment, thus requiring the determination of a DREF for application to risk coefficients deduced from high dose-rate experiments.

It is important to realize, however, that at extremely low doses, the probability of a volume the size of a typical cell nucleus (with diameter of, say, 8 μm) receiving more than one electron track can be quite small. For an absorbed dose of 0.2 mGy of gamma rays, for example, the conditional probability that a cell nucleus that is struck by one electron will be struck by at least one more is less than 10% (Goodhead, 1984). The chapter by Goodhead in this volume should be referred to for more quantiative information on the microdosimetric considerations involved.

B. High-LET Radiation

For high-LET (i.e., highly ionizing) radiation such as neutrons, low-energy alpha particles, and the heavy component of the galactic cosmic rays (HZE particles (Grahn, 1973)), energy deposition patterns at the level of the presumed molecular targets (e.g., the DNA molecule) are drastically different from those caused by electrons. Low energy neutrons, although not producing ionization directly, in hydrogenous materials create "knock-on" protons of short range (and therefore high ionization density) as well as even shorter range and more heavily ionizing nuclear recoils. At higher energy, they also produce alpha particles, which are heavily ionizing as well. The spatial pattern of ionizations produced by charged particles is referred to as their *track structure*. The track structure of the various charged particles plays a crucial role in determining the initial yield of chemical and biological lesions that lead to various end points considered to be important in neoplastic transformation of a cell. In contrast with low-LET radiation, these highly ionizing particles deposit large amounts of energy locally and in a strongly correlated linear array along the particle trajectory. In addition, some of the energy is deposited in regions away from the trajectory by electrons knocked out of the atoms of the material through which the particles pass. The reader is again referred to the chapter by Goodhead in this volume for a more detailed discussion of track structure and its importance.

It has been adequately documented that (1) high-LET radiation causes more damage per Gy of absorbed dose than does low-LET radiation and (2) the damage caused is less repairable. It is generally accepted that, at the physical level, these two experimental observations are due to the different track structures of the particles as they pass through biological material. The much higher density of ionizations caused by high-LET radiation in turn creates more local damage in the DNA, thus leading to more complex and thus presumably less repairable damage. This results in a decreased dose-rate effect as well as less repair observed between fractions in fractionated dose schedules. In fact, some experimental evidence suggests an "inverse dose-rate" effect (i.e., a larger effect at a given dose for a fractionated or low dose-rate schedule than for a single high dose-rate administration) for the end points of cell survival (Ngo *et al.*, 1981), neoplastic cell transformation (Hill *et al.*, 1984, 1985, Yang *et al.*, 1986), tumorigenesis in hamsters (Little *et al.*, 1985) and mice (Ullrich, 1984), reciprocal translocations in mouse spermatogonial stem cells (Grahn *et al.*, 1986), and life shortening in mice (Thomson *et al.*, 1982). An hypothesis that the inverse dose-rate effect is due to a large change in radiosensitivity through the cell cycle has been made (Rossi and Kellerer, 1986) and recently expanded upon (Brenner and Hall, 1990, also, Brenner and Hall , this volume). It is important, however, to distinguish those experiments that provide evidence that the *initial* slope of the dose-response curve increases with decreasing dose-rate from those that suggest a low dose-rate enhancement only at higher doses. The latter are understandable if the single-dose response curve shows "saturation" of effect at high doses. The former are important in risk assessment considerations because of the implication that at very low doses the "risk per Gy" might be greater for very low dose-rate situations than for the higher dose-rate situations for which experimental data are available, i.e., that, perhaps, a DREF less than unity should be applied to the risk coefficients for high LET radiation.

C. Cell Proliferation

It is well established that the variation of radiosensitivity of cells through the cell cycle is more pronounced for low- than for high-LET radiation. One suggestion for the low-LET variation is to hypothesize "fixation" points though the cell cycle at which those repairable lesions not yet repaired will become "fixed" (i.e., rendered irreparable). Thus, the amount of damage repaired after low-LET radiation depends on the time available for repair before a "fixation" point is reached. Such points in the cell cycle have been suggested at the G_1/S border and late in the G_2 phase of the cell cycle (or at mitotis) for the cell survival endpoint. Since high-LET damage is less repairable, there is less dependence of survival on the position in the cycle when the cell received the radiation.

Low doses of radiation can produce several effects on a cell population that could modify cell transformation and presumably the probability of tumorigenesis. For low-LET radiation, lesions that were nonlethal but "fixed" at some point in the cell cycle could be produced in proliferating cells. These nonlethal lesions could then be inherited by the daughter cells at mitosis and the subsequent "initiated" cell population could continue to proliferate until another event (not related to radiation) would move the cell (or cells) closer to the transformed phenotype. This would produce a linear term in the dose-response relation. If a second radiation event occurred in the nucleus to cause a second lesion which subsequently "interacted" with the first (e.g., two chromosome breaks leading to a reciprocal translocation), this would produce a quadratic dependence of the dose-response function. For high-LET radiation, these mechanisms could also occur. But since high-LET damage is less repairable by the cell, any damage to a surviving cell is likely to remain either in proliferating cells and their progeny or in nonproliferating (G_0) cells. The latter might be induced into proliferation by the damage (or by some subsequent stress introduced into its environment), thus effectively increasing the number of "initiated" cells. If a subsequent radiation event of importance occurred within one of these cells, this could produce a quadratic term in the dose-response function. If, however, radiation were not involved in subsequent alterations, the resulting response function would have only a

linear term. Thus, we conclude that a quadratic term in the dose-response function does not necessarily imply that cell "recovery" occurs. In addition, one theory of cell killing (Curtis, 1986) predicts that initial slopes of survival curves, in general, depend on the product of the mean repair rate and the time available for repair. Therefore, for proliferating cells, for which the available time for repair is finite, the initial slope depends on the mean repair rate. This is an example of an initial slope of a dose-response function which depends on the rate at which damage is repaired as well as on the amount of irreparable damage.

Finally, numerous studies of neoplastic transformation *in vitro* have implied that proliferation is an important event in the progression toward neoplasia and it has been hypothesized that the probability of one vital step in the transformation process is proportional to the number of times the progeny of the initiated cell undergo mitosis.

IV. MECHANISTIC MODELS

In this section, we consider several of the mathematical models that have been suggested to try to account for some of the epidemiological and laboratory data in terms of recognized radiobiological principles. We begin by reviewing three relatively simple models - an "initiation-latency" model, the multistage model, and a two-stage model with proliferation or removal of intermediate ("initiated") cells - and discuss some of their limitations. We then discuss an extension of the two-stage model that might overcome some of these limitations. We end with a discussion of a three-stage theory of carcinogenesis of osteosarcoma that has been applied to data in humans and dogs.

A. An Initiation-Latency Model for Leukemia

The wave-like behavior of leukemia incidence rates following an instantaneous exposure to radiation suggests a simple "black box" model in which radiation acts by "initiating" one or more cells, which then remain in a "latent" state for a period of time T. The probability of emerging from the latent into the malignant state is given by a probability density function g(T). "Spontaneous" background cancers would be initiated continuously over time in response to exposures to background radiation and other agents; lacking any data on the time variation of such exposures, one might reasonably assume that the initiation of background cancers was uniformly distributed as a function of age. The expected incidence rate at age A resulting from an instantaneous exposure at age E would then be

$$r(A,E,D) = \alpha \int_0^A g(A-T)\, dT + \beta D\, g(A-E)\,. \qquad (7)$$

The linear-quadratic dependence of the logarithm of leukemia rates on *ln*(T) as expressed in equation (4) suggests that a log-normal distribution might be an appropriate choice for the latency distribution g. A variant of this model considered by the BEIR V committee was of the form

$$r(A,E,D) = r_0(A,E)\,[\,1 + f(D)\, g(A-E \mid \mu,\sigma)\,] \qquad (8)$$

where r_0 was estimated nonparametrically by fine stratification on age, sex, and calendar year, f(D) was the usual linear-quadratic dose-response model, and g was a lognormal density function with median μ and geometric standard deviation σ to be estimated together with the coefficients of f. Furthermore, as a test of the hypothesis that the distribution of latent periods was influenced by dose or age at exposure, μ was modeled as $\exp(\gamma_0+\gamma_1 D+\gamma_2 E)$. The term for the modifying effect of dose on the latent period was completely nonsignificant, but a significant modifying effect for age at exposure was found.

Another question to ask is whether the effects of age at and time since exposure differ for the linear and quadratic and for the gamma and neutron components, as might be expected if these components caused different types of lesions. For the atomic bomb survivor data, Thomas (1990a) found significant differences in the effect of age at exposure for leukemia and in time since exposure effects for nonleukemias, when the neutron and quadratic gamma components were combined. Interpreting these findings in mechanistic terms, however, is presently unclear.

In summary, the initiation-latency model seems to provide a good description of the observed data for leukemia, but no mechanistic explanation of the latency distribution is provided - it is described merely as a "black box".

B. The Multistage Model for Nonleukemias

In contrast to leukemia, the nonleukemias have background rates that increase roughly as a power function of age and excess rates that increase with both age at and time since exposure. To explain these observations with the simple initiation-latency model, the median latency would have to be at least 70 years. A more satisfying explanation is provided by the multistage model of Armitage and Doll (1961), who proposed that cancer is caused by a single cell undergoing a sequence of k changes in a particular sequence, one or more of which might be related to exposure to carcinogens. It then follows that (1) background rates would vary as the k-1 power of age; (2) the dose-response would be linear or linear-quadratic if one or two of the transition rates were dose-dependent, respectively; (3) the dose-response would be modified by age at and/or time since exposure depending on which stage(s) were dose-dependent. Specifically, if a single stage i were dose-dependent, then

$$r(A,E,D) = \beta_0 A^{k-1} + \beta_1 D\, E^{i-1} T^{k-i-1} \qquad (10a)$$

or if two stages i and j were dose-dependent, then

$$r(A,E,D) = \beta_0 A^{k-1} + \beta_1 D\, E^{i-1} T^{k-i-1} + \beta_2 D\, E^{j-1} T^{k-j-1} + \beta_1 \beta_2 D^2\, E^{i-1} T^{k-j-1}, \quad \text{for } j=i+1; \qquad (10b)$$

$$r(A,E,D) = \beta_0 A^{k-1} + \beta_1 D\, E^{i-1} T^{k-i-1} + \beta_2 D\, E^{j-1} T^{k-j-1}. \quad \text{for } j>i+1. \qquad (10c)$$

The time from appearance of the first malignant cell to cancer diagnosis or death is usually assumed to be short in comparison with the time from exposure to malignancy and can be ignored without any noticible change in fit. The basic multistage model described above takes no account of repair, proliferation, or immune surveillance.

Thomas (1990b) has described the fit of this model to the atomic bomb survivor data for the category of all cancers other than leukemia. The best fit to the background rates was obtained for k=5. Among the models with only a single dose-dependent stage, the best fit was for i=2, all of the others being overwhelmingly rejected ($P<0.001$) because of the strong dependence of excess rates on both E and T. Among the models with two dose-dependent stages, the cases i=1, j=3 and i=2, j=4 produced virtually the same likelihoods and fitted significantly better than the best single dose-dependent stage model ($p=0.013$). The models with j=i+1 did not fit as well because of the quadratic component which appears to be virtually zero in the descriptive analyses.

Although the multistage model seems to provide an adequate description of the pattern of excess rates, it does not fit the overall data as well as the descriptive models because the background rates do not conform very well to the predicted k-1 power dependence on age. There is also a sex difference in the slope of the age-dependence of background rates. These deviations are

likely due to birth cohort, age, and sex differences in exposure to various background carcinogens that cannot be modeled with the data available. In view of the limitations of the available data, this lack of fit should not necessarily disqualify the model from further consideration. However, there are a number of phenomena that are not well accounted for by the model. These include (1) leukemias, childhood cancers, and certain other sites that do not follow the power function dependence on age assumed by the model, (2) the genetics of cancer, (3) dose-rate effects and repair mechanisms. Furthermore, the need for as many as five distinct changes has been questioned by experimental biologists. Many of these problems are accounted for in the models described in the next sections.

C. The Marshall-Groer Theory of Osteosarcoma Induction by Alpha Particles

In 1977, Marshall and Groer published a detailed theory of the induction of osteosarcoma in humans and dogs by alpha particles emitted in the decay of ^{226}Ra and ^{228}Ra which accumulate near bone surfaces (Marshall and Groer, 1977). The model is a three stage model -- two initiation steps plus one promotion step. The initiation steps are hypothesized as being provided by one or two alpha-particle traversals of a cell-at-risk (a resting endosteal cell within 10 μm of a bone surface). The promotion step is not considered to be radiation-dependent, but is a normal signal to the doubly initiated cell to start dividing. It is assumed that the daughter cells have been rendered incapable by the two initiation events of turning off their proliferative process. Thus, the promotion step is, in fact, the natural process of bone remodeling, and the rate of promotion is then proportional to the bone remodeling rate. Cell killing is specifically considered in the model and it is assumed that killed cells are replaced by stem cells at a constant rate. A diagram of the model is given in Figure 6.

The theory appears to be successful in describing various patterns in the dose and time dependence of alpha-particle induced osteosarcomas in humans and dogs. Figure 7 shows a

least squares fit of the model to 474 human cases with radioactivity intakes greater than 0.1 μCi/kg body weight. The values for the parameters for this fit were:

Endosteal cell replacement rate = 0.1 d^{-1}

Cell killing probability (reciprocal of the D_0) per unit dose = 1 Gy^{-1}

Number of cells at risk = 10^{11}

First and second step initiation probability per unit dose = 4.7×10^{-6} Gy^{-1}

Rate of promotion to malignant state = 0.01 y^{-1}

Tumor growth time = 6 y

Conversion constant from radium intake activity to dose rate = 1.5 (Gy/y)/(μCi/kg body weight)

The model provides an explanation for the following phenomena observed in the epidemiological data on humans:

1. The dose-response curve appears to be quadratic at low doses, although a small linear component caused by one alpha particle traversing both critical targets is not ruled out.

2. The induction of tumors plateaus at high doses. (A plateau at a higher incidence in the dog studies than in the human studies is explained by assuming canine endosteal cells are an order of magnitude more sensitive than human cells to each of the two initiation events).

3. The tumors have an extended latent period before appearing. This is caused by the very slow promotion rate ($0.01 y^{-1}$).

4. The mean time of tumor appearance increases with decreasing level of uptake. The expected mean time of tumor appearance approaches a constant of two thirds of the lifespan

remaining after the first radium intake. The absence of tumors at low doses is not due to a latent period which exceeds the lifespan, but to the improbability of the initiation of a significant number of endosteal cells.

5. The ^{224}Ra data show a two-fold enhancement of tumor induction when dose is protracted from two months to two years (Spiess and Mays, 1973). This is caused by the higher dose-rate creating a decrease by a factor of two in the number of cells-at-risk, since the endosteal cell replacement rate (0.1 d^{-1}) is not rapid enough to keep up with the cell killing, thus resulting in fewer viable cells at risk.

D. The Moolgavkar-Knudson Two-Stage Model

In a series of papers, Moolgavkar, Knudson and associates (1980, 1981, 1986, 1988, 1989) have formulated a general theory of carcinogenesis and have applied it to a number of cancer sites. Only one application of the theory relates specifically to radiation exposure, an analysis of lung tumors in rats exposed to radon (Moolgavkar *et al.*, 1990). However, many of the features of their model are potentially relevant, so it is worth reviewing in some generality.

The basic model postulates that cancer results from a single cell line undergoing two mutational events at homologous loci [from "normal" to "intermediate" (heterozygous) and from "intermediate" to "malignant" (homozygous)] and that heterozygous cells can either multiply or be removed from the population by differentiation, death or repair. Either or both of the mutation rates and the net proliferation-minus-removal rate of heterozygous cells might be related to carcinogenic exposures. To explain the genetics of cancer, it is also postulated that heterozygotes for the cancer gene begin life with all their cells in the intermediate state. Denoting the mutation rates at time t by $\mu_1(t)$ and $\mu_2(t)$ respectively, the net proliferation-minus-removal rate of heterozygous cells by g(t), the number of normal cells at time t by N(t), and the

probability of inheriting the cancer gene by h, then if all these rates are small enough, the rate of appearance of the first malignant cell is approximately

$$r(A, E,D) = (1-h)\,\mu_2(A) \int_0^A N(t)\,\mu_1(t)\,exp\,\{ \int_t^A g(u)\,du\}\,dt$$

$$+ h\,\mu_2(A)\,N(0)\,exp\,\{ \int_0^A g(u)\,du\}. \qquad (11)$$

(As in the multistage model, the time from appearance of the first malignant cell to cancer diagnosis or death is assumed to be relatively constant, and short in comparison with the period from exposure to malignancy.) This approximate expression is thought to be adequate for modeling human exposures. For animal carcinogenesis experiments, however, where the doses are very high and the various rates cannot be assumed to be small, exact expressions have been derived by Moolgavkar and Luebeck (1989). In their earlier applications, the model was fitted to age-specific rates for retinoblastoma, breast and lung cancer without reference to data on particular exposures. In more recent applications, the rates μ_1, μ_2, and g are modeled as functions of the intensity of exposure to the relevant carcinogen at time t. For example, in a reanalysis of data on lung cancer in British physicians, Moolgavkar *et al.* (1989) concluded that smoking acted primarily on the first mutation, with only a small effect on the second mutation and none on the net growth rate g. For breast cancer, Krailo *et al.* (1987) examined the effects of age at menarche, age at first pregnancy, abortion, oral contraceptive use, benign breast disease, and family history and found them to be consistent with a variety of possible explanations, although in most cases not an effect on the second mutation rate.

In the analysis of the experimental data on lung cancer from radon inhalation by rats, Moolgavkar *et al.* (1990) found a strong dependence of $\mu_1(t)$ and g(t) on the dose of radiation at

time t. However, their model assumed a power function for these dependencies with fitted exponents considerably less than one (i.e., a strongly convex dose-response). There does not seem to be any biological basis for such a model, and it is possible that the fitted effects on both μ_1 and g may be the result of the models trying to compensate for the convexity of the assumed functions in fitting data that are more nearly linear.

Attractive features of the model are that the two mutations are clearly identified as lesions at homologous loci (consistent with standard radiobiologic theory) and that repair can be accomodated in the function g(t). The model also appears to explain the inverse dose-rate effect for high-LET radiation, although part of the predicted effect may be due to differences in the ages over which the radiation is delivered in the high and low dose-rate groups. The three-stage model described in the next section attempts to explain this phenomenon while controlling for such age differences.

E. A three-stage model

Thomas (1990b) proposed an extension of the Moolgavkar-Knudson two-stage model in an attempt to explain the different dose-rate effects for low- and high-LET radiation with a single model. Essentially, the modifications include the following:

1. Mutational events could lead to potentially transforming but repairable lesions or to non-modifiable lesions. In the original presentation, these two types were identified as single-stranded (SS) or double-stranded (DS) lesions, respectively, although the concepts are more general. For notational convenience, the SS/DS shorthand is retained here, although it is acknowledged that single stranded lesions may not be etiologically important.

2. Low-LET radiation is assumed to cause primarily SS lesions while high-LET radiation is assumed to cause primarily DS lesions.

3. Cells with SS and DS lesions either proliferate or repair the lesions; however, it is assumed that the repair process dominates for cells with SS lesions and the proliferation process dominates for cells with DS lesions.

4. An "activation" event that is not related to radiation exposure must also occur, either before or after the mutational events.

Denoting the rate of SS lesion-induction by μ_1, DS lesions by μ_2, activation events by μ_3, repair rate of SS lesions by ρ, and proliferation rate of cells with DS lesions by g, the resulting cancer rate can be shown to be

$$r(A, E, D) = \mu_3 \int_0^T \{ [\mu_1(t) \int_0^t u \, \mu_1(u) \, e^{-(t-u)\rho} \, du] + t \, \mu_2(t) \} \, e^{(A-t)g} \, dt. \qquad (12)$$

By plotting this function for various reasonable choices for the values of the parameters, it was shown that the model could explain observed normal and inverse dose-rate effects for low- and high-LET radiation, respectively. The possibility that repair and/or proliferation rates might also be dose-dependent was considered, but was shown to lead to exponential dependencies on total dose or duration of exposure. As such relations are not observed, this mechanism seems unlikely.

The distinction between SS and DS lesions is recognized to be somewhat naive, but is not crucial to the predictions. Similar results would be obtained, for example, if the two lesions occurred at separate loci but had to evolve further in some sense to produce a malignant cell (as

in oncogene activation or reciprocal translocation). Although there is some experimental basis for postulating an activation step that is unrelated to radiation exposure, the need for this additional feature in the model remains somewhat speculative. Again, the assumption that DS lesions are not repairable is not essential; relaxing that assumption would simply produce intermediate results. To date, no attempt has been made to fit the model to data, as an extensive set of experimental data encompassing acute and chronic, low- and high-LET exposures would be needed to test the model adequately.

V. DIRECTIONS OF FUTURE RESEARCH

There will be a continuing need to update descriptive models for all cancer sites for risk assessment purposes. Efforts to use knowledge of dose-time-response relations for understanding and modeling mechanistic principles, however, will be most usefully directed at those cancers which show the strongest radiosensitivity. In human populations, these include leukemia, radon-induced lung cancer, radium-induced bone cancer, and breast cancer. On a relative risk basis, leukemia is clearly the most radiosensitive end point, and the one with the strongest modification by age and latency. No single study adequately covers the entire range of ages and latencies, so combined analyses of several studies would be helpful. Analysis of the interaction between radon daughter inhalation and smoking in causing lung cancer would be improved by greater attention to time-related modifiers, with appropriate attention paid to the possible importance of such phenomena as the inverse dose-rate effect. A unified description of bone cancer risk for different isotopes of radium could also shed light on dose-rate and latency effects. Analysis of the joint effects of radiation and hormonal events on breast cancer could help understand the role of cell proliferation rates in determining radiation sensitivity.

A fertile new field for improving low dose risk assessment is developing. As more is learned about the basic molecular mechanisms of radiation-induced cancer on a site-by-site basis, it will

become important to incorporate these mechanistic concepts into the structure of statistical models and to fit the models to experimental and epidemiologic data. It will be increasingly valuable for the molecular biologists, the radiation biophysicists and modelers, and the cancer epidemiologists and biostatisticians to bridge the presently rather large gap between their interests in order to provide what will surely become a significant contribution in the area of low dose and dose-rate radiation risk asessment.

The two-stage model of Moolgavkar and Knudson has the appeal of being solidly grounded in our current understanding of the molecular biology of cancer and has been quite successful in fitting epidemiologic data for a number of cancers. Although not specifically based on radiobiologic principles, it has been successful in fitting animal experimental data on lung cancer caused by radon daughter inhalation. This class of models is particularly promising as a vehicle for unifying radiobiological principles with the statistical approach. Areas of future development might include a unified model for dose-rate effects for high and low-LET radiation, incorporation of exposure to other carcinogens (e.g., cigarette smoke) and factors that modify the proliferation of normal or intermediate cells (e.g., hormones) along with the emerging knowledge on genetic susceptibility.

Although broad patterns of risk variation predicted by various mechanistic models have been compared, there have been very few attempts to fit such models directly to epidemiologic data. Direct model fitting would be most rewarding for experimental and epidemiological data sets that show strong dose-response relationships with strong modifying effects of temporal variables. Epidemiologic studies tend to show more natural variability in temporal patterns of exposure than experimental studies, the latter often being restricted to instantaneous exposures or extended exposures at constant dose rates. On the other hand, experimental studies provide better opportunities to compare different types of radiation in a controlled fashion.

Finally, a largely unexplored area is the field of hereditary cancer susceptibilty and its impact on radiation sensitivity to cancer induction. Many of the radiogenic cancers show strong genetic variation as well. Whether such variation is primarily in terms of baseline risks, on which radiation acts simply additively or multiplicatively, or whether there is also intrinsic genetic variation in radiosensitivity (i.e., in the initial slopes of the dose-response relationships) is unknown. Litter-matched animal experiments in which selected genetic components are controlled would be worth conducting and analyzing in terms of mechanistic models.

VI. CONCLUSIONS

The most important message from this chapter is that any dose-response relationship for cancer that ignores gender, age and time effects is a serious oversimplification. All cancer sites seem to have important time-related modifiers, on either an absolute or a relative risk scale, that vary from cancer site to site (NAS, 1990). These modifiers are crucial for describing the risks for regulatory purposes and must be taken into consideration when building biologically plausible mechanistic models. For descriptive purposes, we have relied heavily on the models developed and used by the BEIR V committee, which has carried out extensive reanalyses of epidemiological data from all major available high-dose studies. These descriptive models seem to provide the best description presently available of the risks of leukemia, respiratory, breast, digestive, thyroid, and all other cancers combined resulting from low-LET radiation exposure. Similar analyses for high-LET radiation reported by the BEIR IV committee (NAS, 1988) complete the present picture.

We have also reviewed four biologically-motivated (mechanistic) models of the carcinogenic process. Some of these have been fitted to the atomic bomb survivor or experimental animal data, with mixed results. So far, none of the models appears to provide a comprehensive and biologically plausible explanation for all the relevant observations, but nevertheless, this seems

to be a promising approach that merits further development and testing. One should be clear about the aims of such analyses, however. All of these models are sufficiently general that it is unlikely that one can choose between them on purely statistical grounds. As a class, none of the models is readily falsifiable, nor would a good fit establish the truth of the model. Rather, interest is in the types of comparisons that can be made within the context of a particular model - whether radiation acts at an early or late stage in the multistage model, whether it acts on mutation or growth rates in the two-stage model, for example. The value of a mechanistic model therefore lies in its ability to organize a complex set of hypotheses into a unified framework and to allow tests of submodels within that framework. The long term goal of incorporating mechanistic molecular processes into models of human radiation carcinogenesis is to provide a more reliable extrapolation of risk into the low dose and dose-rate region applicable to radiation risk assessment and protection.

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FIGURE LEGENDS

1. Forms of dose-response relationships for leukemia: a. atomic bomb survivors (adapted from Pierce and Vaeth, 1989); b. cervical irradiation patients (adapted from Boice et al, 1987).

2. Excess relative risk per Gy for leukemia as a function of age at exposure and time since exposure; a. atomic bomb survivors (adapted from BEIR V report); b. cervical irradiation patients (adapted from Thomas et al, 1991); c. ankylosing spondylitic patients (adapted from Darby et al, 1987).

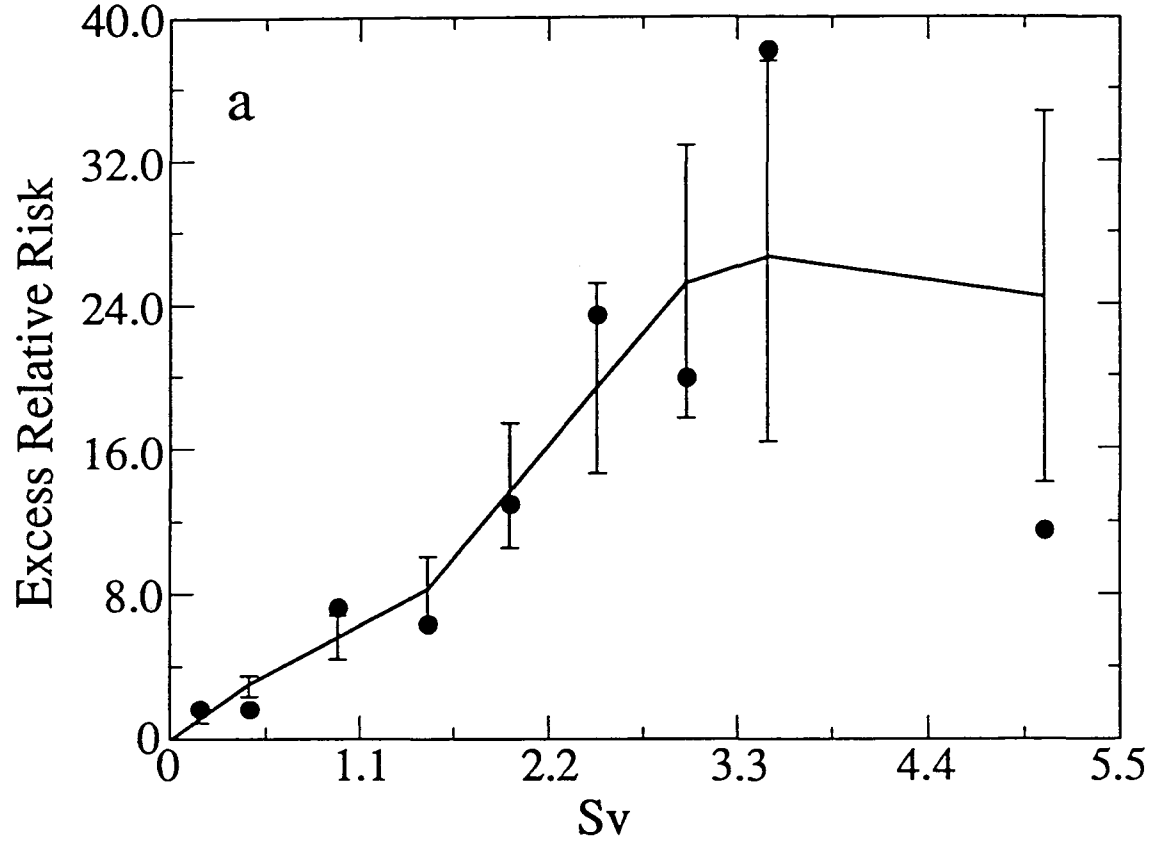
3. Form of dose-response relationship for all nonleukemias and selected cancers in atomic bomb survivors (adapted from Pierce and Vaeth, 1989).

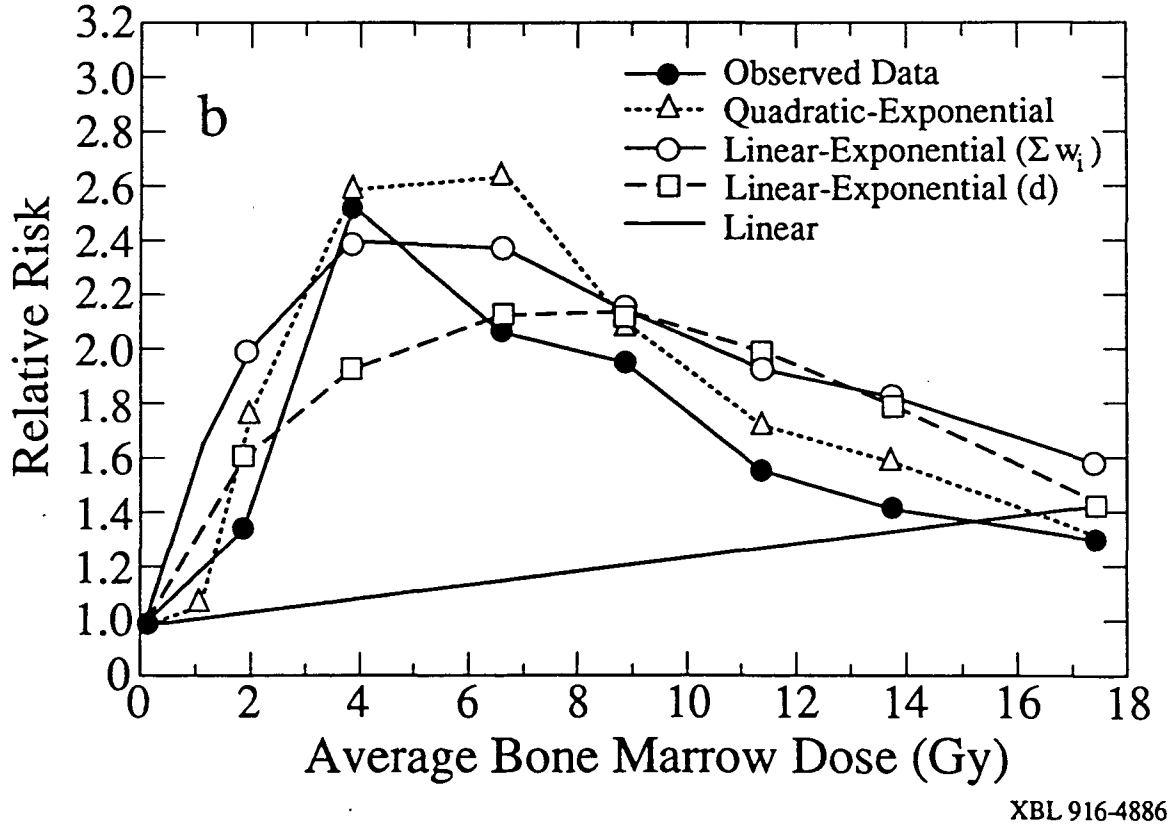
4. Excess absolute (a) and excess relative (b) risk per Gy for all nonleukemias in the atomic bomb survivors, as a function of age at exposure and time since exposure (adapted from Shimizu et al, 1987).

5. Bone sarcoma appearance times after exposure to ^{224}Ra (half-life, 3.6 days) and to ^{226}Ra (half-life, 1600 yr) and ^{228}Ra (half-life, 5.8 yr) (adapted from Mays and Spiess, 1984).

6. Schematic diagram of the Marshall and Groer model. An original endosteal cell is initiated twice and promoted to become an osteosarcoma cell. Cells killed at any stage are replaced by stem cells. F is the endosteal dose rate. The rates of replacement ρ and of promotion λ do not depend upon radiation (adapted from Marshall and Groer, 1977).

7. The cumulative incidence of osteosarcomas in man vs. the total intake of ^{226}Ra plus ^{228}Ra. The two solid points combine data for the eight lowest and the two highest levels of intake. The standard errors are calculated from the data. The error bar on the solid point at low intake corresponds to 1 tumor (adapted from Marshall and Groer, 1977).





XBL 916-4886

Figure 1

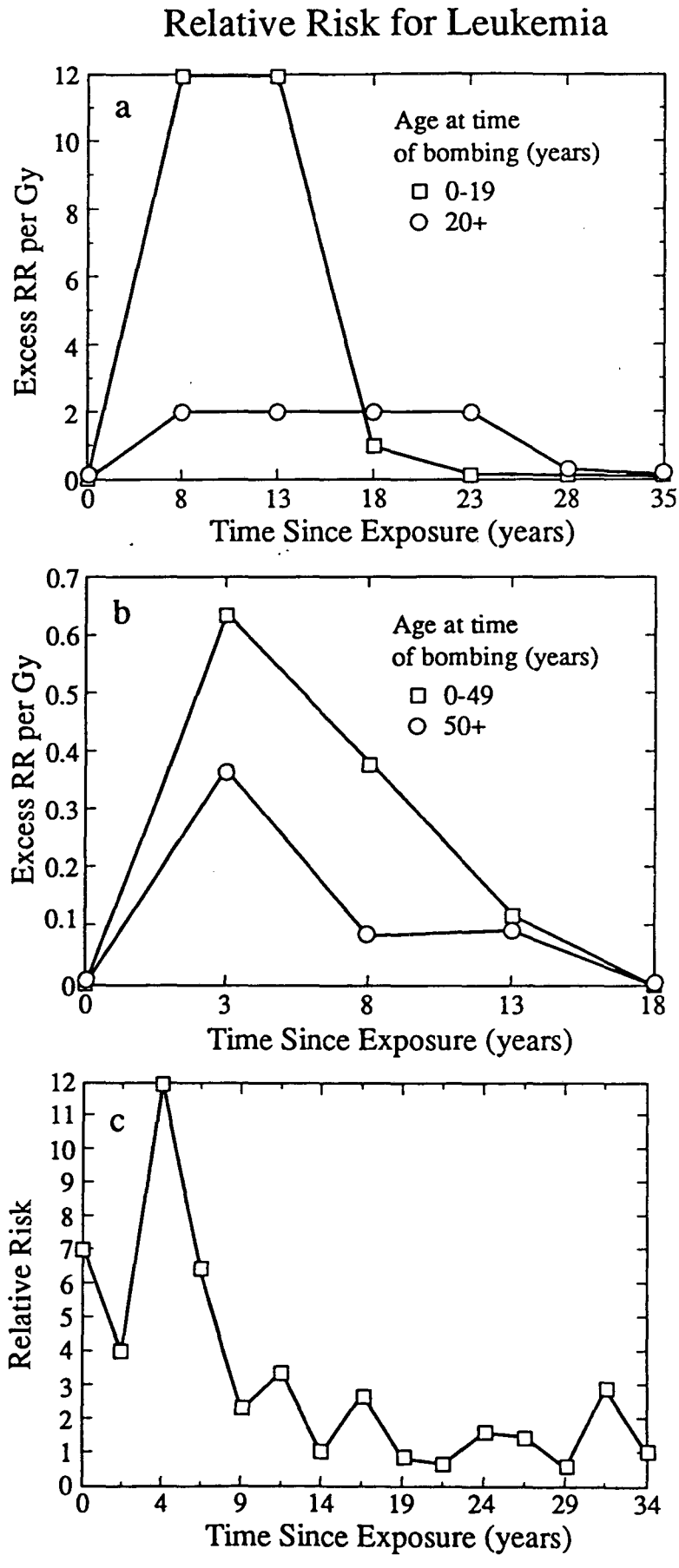

Relative Risk for Leukemia
a
Age at time
of bombing (years)
0-19
20+
Excess RR per Gy
Time Since Exposure (years)
b
Age at time
of bombing (years)
0-49
50+
Excess RR per Gy
Time Since Exposure (years)
c
Relative Risk
Time Since Exposure (years)
XBL 916-4887

Figure 2

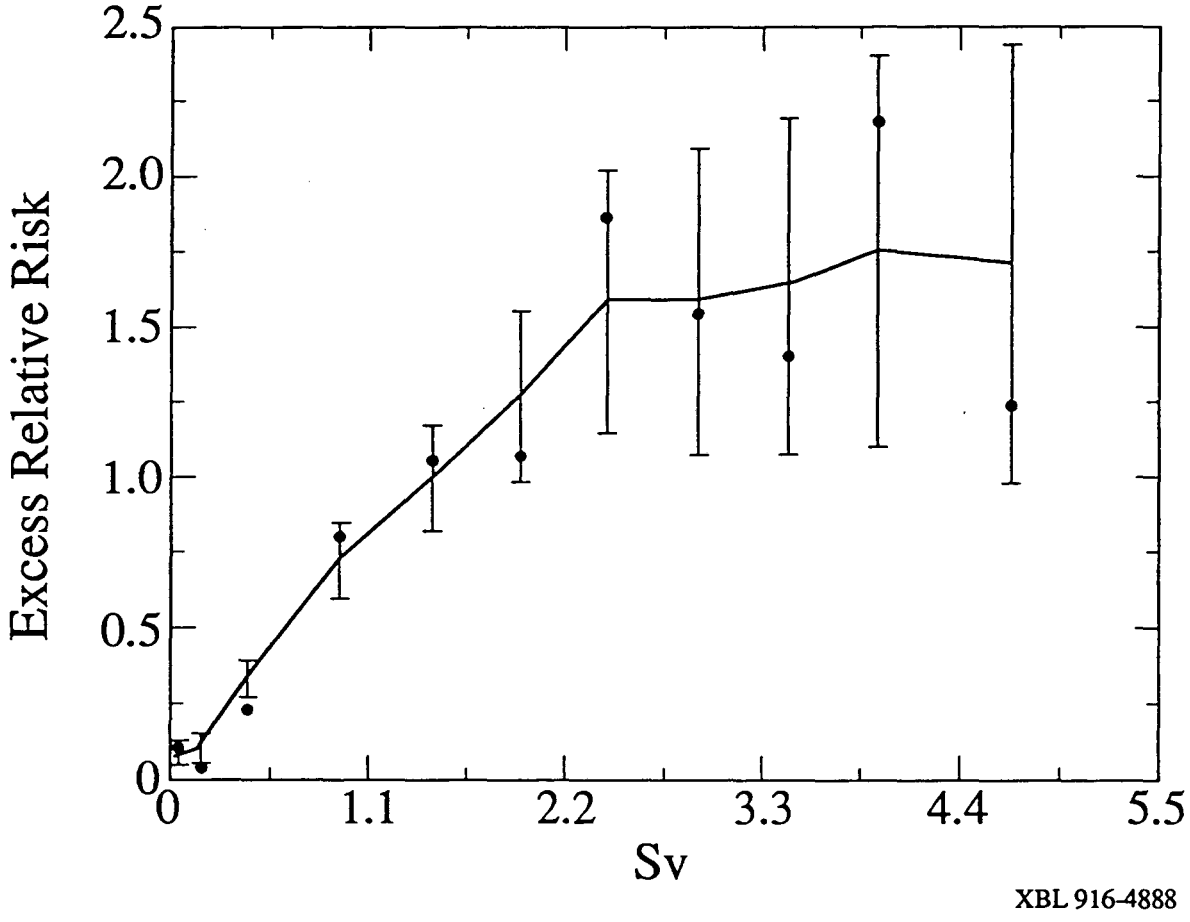

Excess Relative Risk
2.5
2.0
1.5
1.0
0.5
0
0
1.1
2.2
3.3
4.4
5.5
Sv
XBL 916-4888

Figure 3

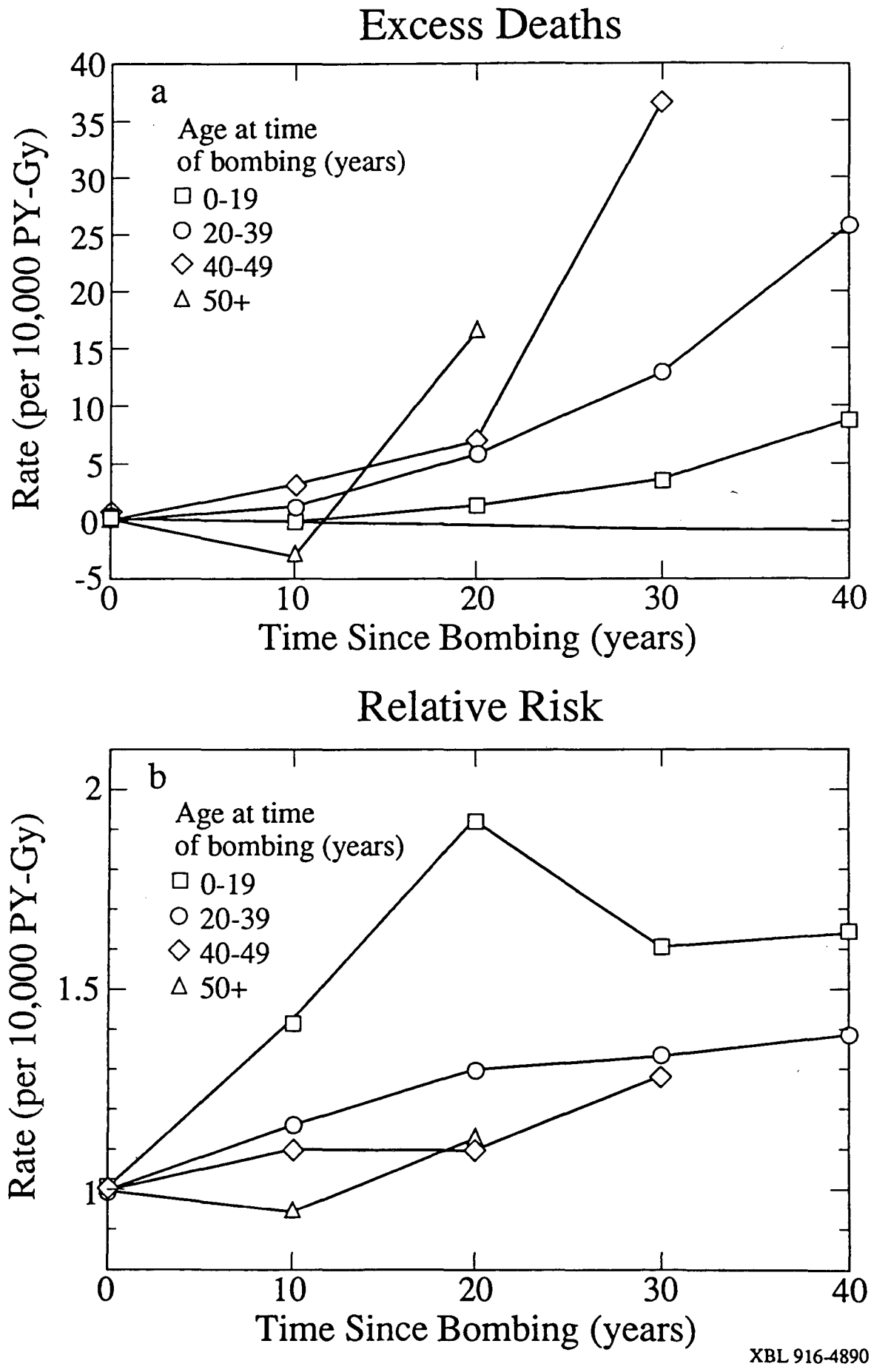
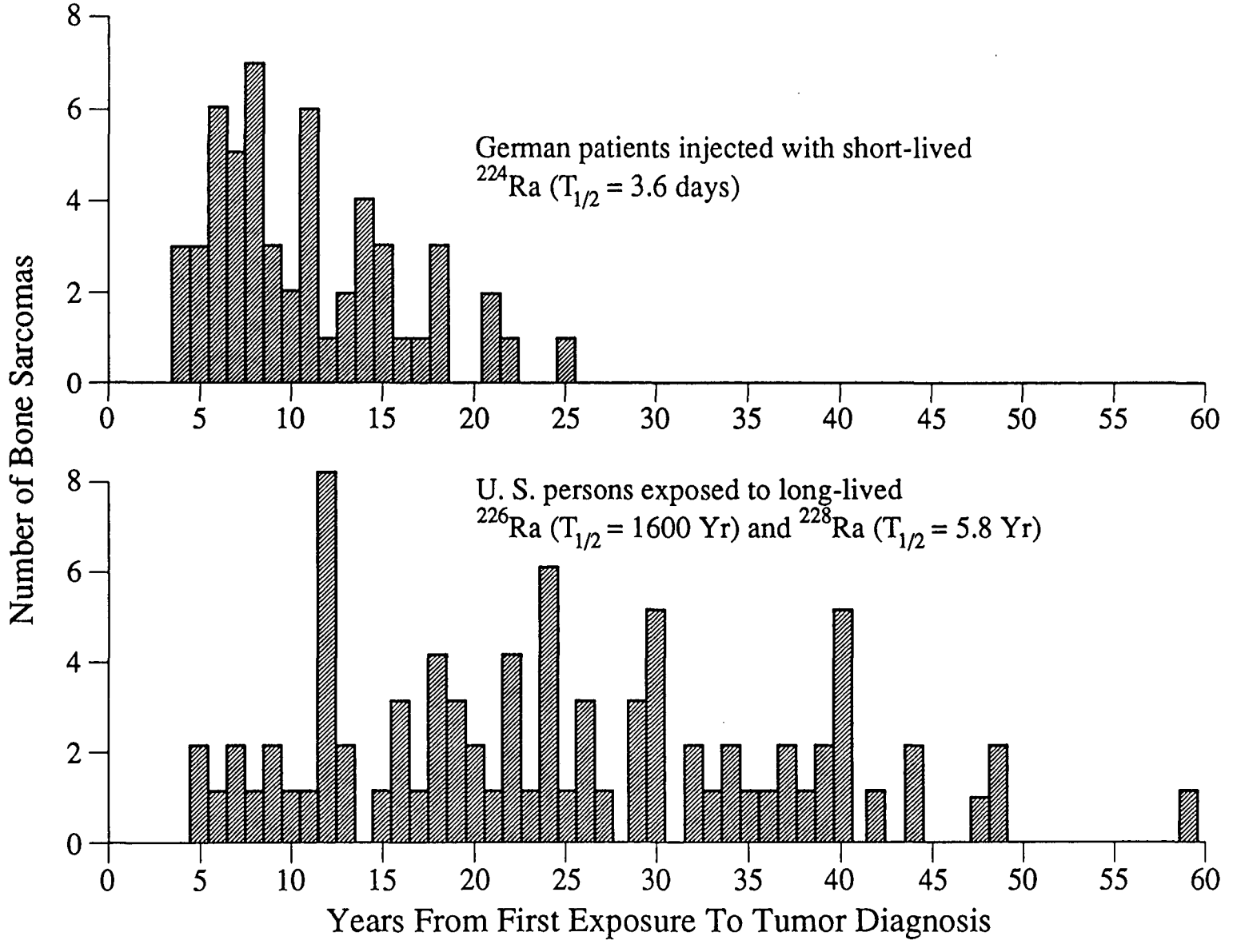

Excess Deaths
a
Age at time
of bombing (years)
0-19
20-39
40-49
50+
Rate (per 10,000 PY-Gy)
40
35
30
25
20
15
10
5
0
-5
0
10
20
30
40
Time Since Bombing (years)
Relative Risk
b
Age at time
of bombing (years)
0-19
20-39
40-49
50+
Rate (per 10,000 PY-Gy)
2
1.5
1
0
10
20
30
40
Time Since Bombing (years)
XBL 916-4890

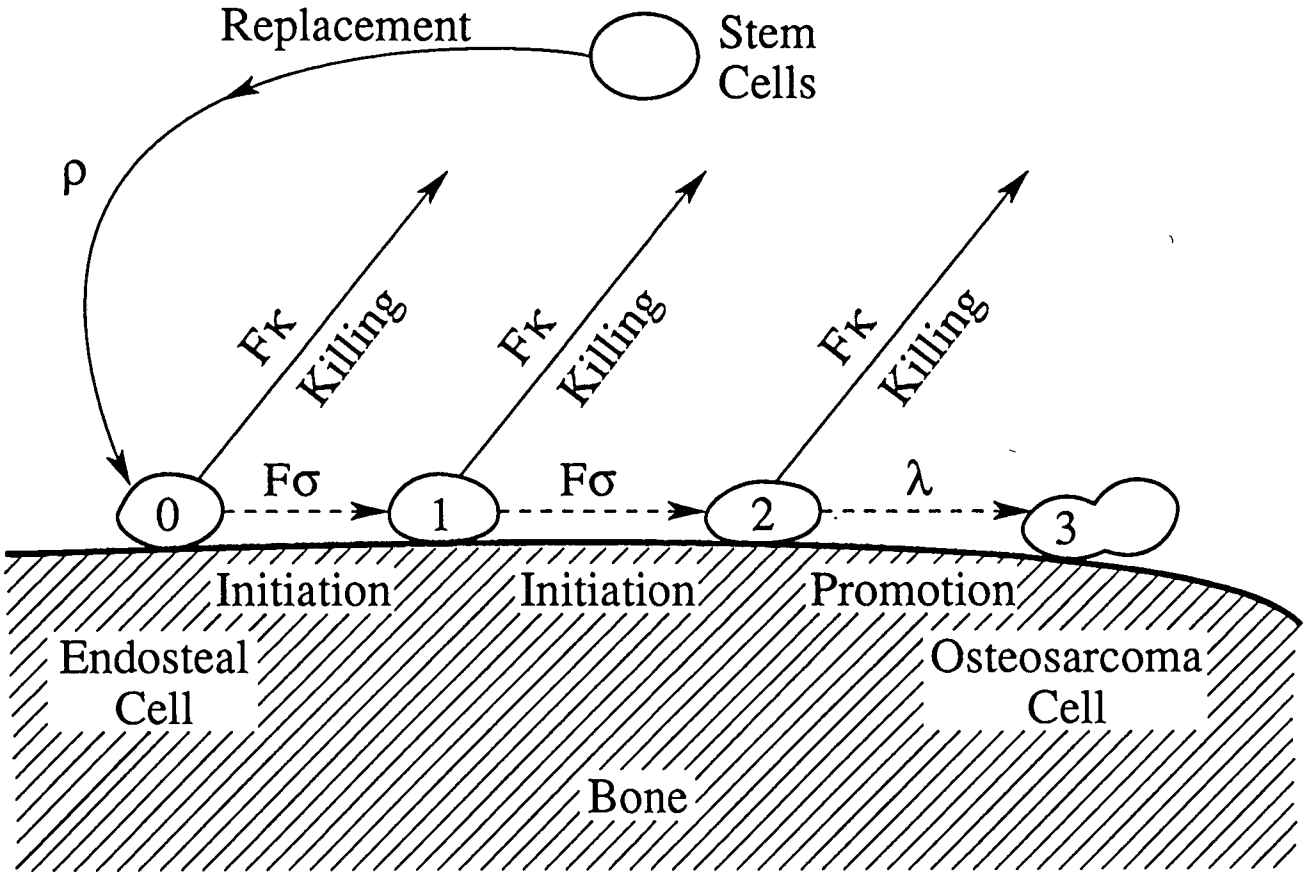
Figure 4



XBL 916-4892

Figure 5

Induction of Osteosarcoma by Alpha Particle Radiation



XBL 916-4893

Figure 6

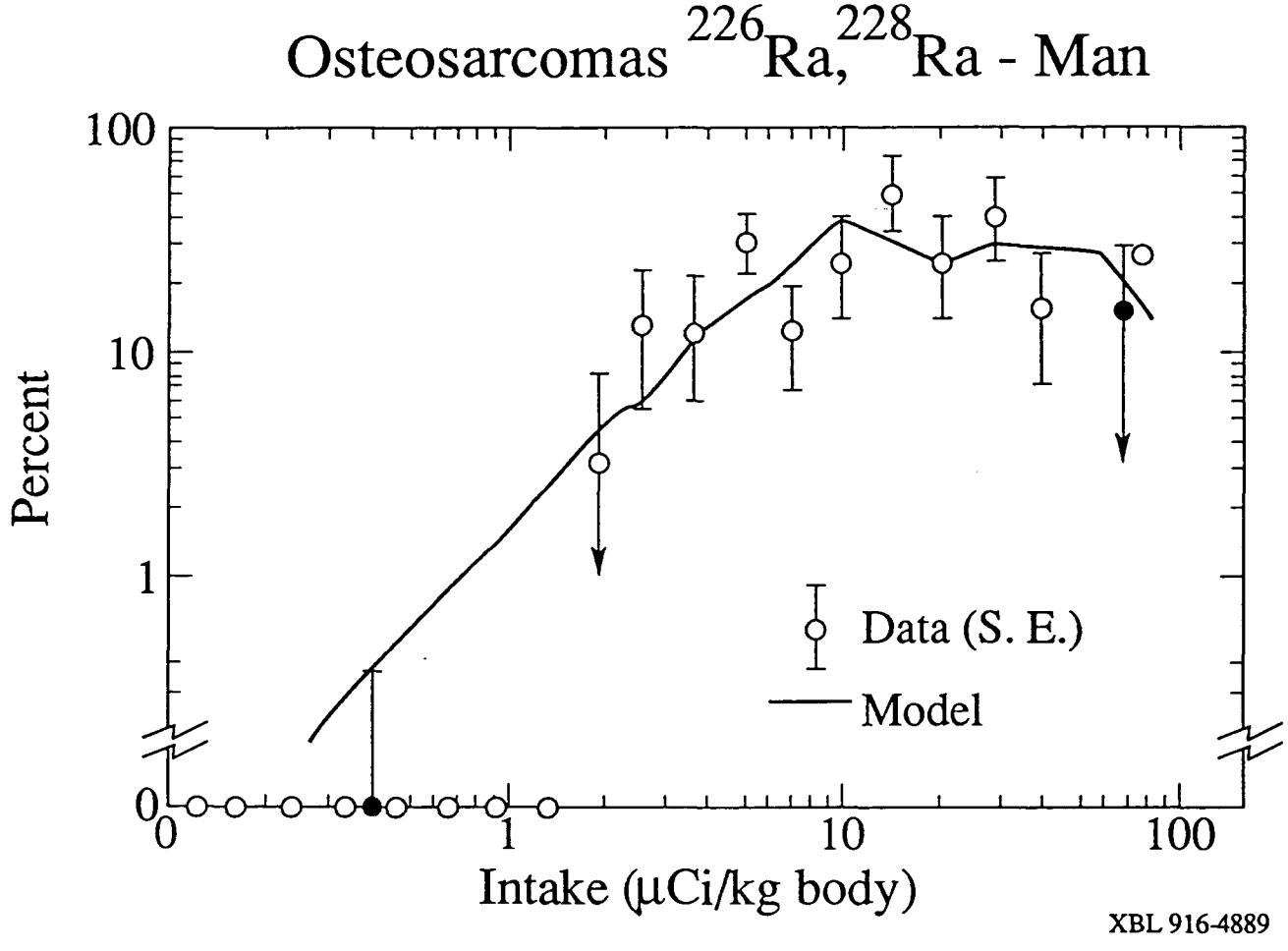

Osteosarcomas ^{226}Ra, ^{228}Ra - Man
Percent
100
10
1
0
0
1
10
100
Intake (μCi/kg body)
Data (S. E.)
Model
XBL 916-4889

Figure 7

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