

A Model for Dose Rate and Duration of Exposure Effects in Radiation Carcinogenesis

by Duncan C. Thomas*

Multistage models have been used to describe various features of the incidence of cancer including the shape of the age-incidence curve; the influence of age at, duration of, and time since exposure; and the synergistic effect of exposure to multiple carcinogens. However, the models require from five to seven distinct transformations that must occur in a particular sequence. The lack of experimental support for so many events suggests a simpler model involving only two mutational events with a proliferative advantage for intermediate-stage cells. Neither model easily explains the paradoxical phenomenon that protraction of low linear energy transfer (LET) radiation leads to lower risks per unit of total exposure, whereas the reverse occurs for high-LET radiation. In this paper, a three-stage model is considered that consists of two mutations at homologous sites, either or both of which might be induced by radiation, followed by activation of the transformed oncogene, which is not induced by radiation. Single-stranded lesions are potentially repairable, whereas double-stranded lesions may increase the proliferation rate. For low-LET radiation, these two mutations are more likely to occur as the result of independent transversals of a cell by separate quanta of radiation, whereas for high-LET radiation, they are more likely to occur simultaneously as the result of a single particle. The predictions of the model are illustrated for various patterns of exposure and choices of model parameters. Various tests of the proposed model are discussed.

Introduction

There are abundant epidemiological and experimental data establishing the carcinogenic effect of radiation and the dependence of cancer rates on dose and temporal factors (age at exposure, time since exposure, attained age, duration of exposure, etc.). In general, the excess rate of cancer appears to be a linear or linear-quadratic function of dose at low doses, and excess rates increase with both age at exposure and time since exposure. However, several characteristics of the exposure-time-response relation differ between types of radiation with high and low linear energy transfer (LET).[†] High-LET radiation appears to produce nearly linear dose-response relations, whereas low-LET radiation often produces linear quadratic relations. The effects of dose rate and duration of exposure also depend on the LET: for low-LET radiation, a long exposure at low dose rates generally produces lower risks than a short, intense exposure for the same total dose, whereas for high-LET

radiation the reverse may be the case. These various phenomena have been reviewed in the series of reports from the National Academy of Science's Committee on the Biological Effects of Ionizing Radiation (BEIR) (1-3).

These descriptive observations have potential significance for understanding the mechanisms of radiation carcinogenesis. Although the previously discussed material is in many ways an oversimplification—different patterns are observed for different cancers, types of radiation, species, and studies—the general patterns previously discussed are sufficiently common to merit trying to develop a general explanation for them. We will restrict attention to the solid tumors, because leukemia shows a very different dependence on dose and temporal factors. For illustration, data on the category of all cancers, other than leukemia, from the atomic bomb survivors will be used. This choice of grouping is motivated by a need for sufficient numbers of cases for adequate statistical power and by the general similarity of the dose and time-dependence of the individual cancer sites within this category. Some important differences are of course obscured by this grouping, but it has been found to be useful for descriptive purposes. The development of a general model that would incorporate leukemia remains a major challenge.

The next section introduces some notation and points

*Department of Preventive Medicine, University of Southern California, 1420 Son Pablo Street, Los Angeles, CA, 90033.

[†]Linear energy transfer is defined as the rate at which radiation deposits energy as it traverses matter. Low-LET radiation (e.g., X-rays and gamma rays) loses energy slowly and thus is able to penetrate deeply; high-LET radiation (e.g., alpha particles and neutrons) deposits large amounts of energy over a relatively short distance.

out the need to control the confounding effects of other temporal variables. In the third section some of the classical mathematical theories of carcinogenesis are reviewed, and their abilities to explain the above phenomena are discussed. The section "The Proposed Three-Stage Model" develops a more general model that incorporates features from each of the classical models and describes some of the predictions of the model in special cases; the aim of this section is to show how the general model is capable of explaining all of the basic phenomena with a minimum number of parameters. The last section discusses possible tests of the model using available data.

The Need to Control for Other Temporal Variables

For the purposes of this discussion, attention will be confined to the case of instantaneous exposures or extended exposures at constant dose rates. It will be convenient to introduce some notation. For an extended exposure, let t_0 = age at first exposure, t_1 = age at last exposure, $L = t_1 - t_0$ = length of exposure, T = attained age, $F = T - t_1$ = length of follow-up after last exposure, R = dose rate, and $C = L \times R$ = cumulative dose.

For an instantaneous exposure, let $t = t_0 = t_1$ = age at exposure. Although R goes to infinity as L goes to zero, it will simplify notation to assume $L = 1$ and $R = C$. Finally let $\lambda_0(T)$ denote the age-specific cancer rate in the absence of exposure (the baseline rate) and $\lambda[T, R(t)]$ the corresponding cancer rate given an exposure history $R(t)$. Then, let $ER = \lambda[T, R(t)] - \lambda_0(T)$ = excess risk, and $RR = \lambda[T, R(t)]/\lambda_0(T)$ = relative risk.

A major point of confusion in the literature on dose rate and duration effects is the failure to clarify what other variables are being controlled. Throughout this paper, all statements about R and L are conditional on C ; i.e., C will be held fixed and R varied inversely with L . Most of the literature on the predictions of the multistage model (4) also shows conditions on t_0 and F , but this implies that T varies with L . Because λ_0 also varies with T , L will have different effects on ER and RR . To avoid this complexity, T will be held fixed in all comparisons, but this still leaves one free variable to control. Because $\lambda[T, R(t)]$ varies with both t and F , any statements about the effect of L are easily confounded by these factors. An attractive choice is to hold the average age at exposure $\bar{t} = (t_0 + t_1)/2$ fixed, say at $T/2$, thereby also fixing the average time since exposure. However, most of the experimental studies have instead fixed t_0 and varied L by varying t_1 .

In epidemiological studies, it is not possible to fix any of these variables by design, so the effects of the various temporal variables must be studied by multivariate analysis. This is complicated by the multicollinearity of their effects (4), so that a full multivariate analysis is seldom reported. Indeed, most studies report only the

marginal effects of t_0 , L , or F , adjusted only for T . These can be quite difficult to interpret.

Some Standard Stochastic Models of Carcinogenesis

The Kellere-Rossi Theory of Dual Radiation Action

The linear-quadratic dependence of risk on dose has been widely interpreted in terms of the theory of dual-radiation action (5), which postulates that radiation can cause lesions in either a single strand (SS) of DNA or in both strands (DS) simultaneously. The linear component is thus attributable either to DS lesions, induced by a single quantum of radiation, or to SS lesions, induced by radiation where the homologous lesion occurs spontaneously (either before or after). The quadratic component is attributable to a pair of SS lesions at the same locus caused by two separate quanta of radiation. Microdosimetry theory suggests that simultaneous DS lesions would be rare for low-LET radiation but common for high-LET radiation.

The reduced effect of protracted low-LET radiation is interpreted in this theory as the result of repair of SS lesions: the longer the duration of exposure, the higher the probability that the first lesion has been repaired before the next mutation at the same locus occurs. For high-LET radiation, this phenomenon would not occur, since most lesions would be DS. The increased effect of protracted doses of high-LET radiation cannot be explained by this mechanism, but it is natural to inquire whether it could be due to a promoting effect of extended exposures, i.e., an effect on the rate of proliferation of transformed cells. The implications of this possibility are explored in the subsection entitled The Moolgavkar-Knudson Two-Stage Model.

The theory of dual radiation action does not attempt to explain the dependence of cancer rates on t , F or T . For these phenomena, the more general stochastic models of carcinogenesis described in the next two sections are needed.

The Armitage-Doll Multistage Model

Probably the most widely discussed model of carcinogenesis is the multistage model (6). This model postulates that cancer results from a single cell undergoing a sequence of k distinct heritable transitions in a particular sequence and that the instantaneous hazard rate for any of these transitions might be influenced by the current dose of carcinogen at that point in time. The simplest prediction of the model is that the background incidence of cancer (i.e., in the absence of a major carcinogenic exposure) should be proportional to the $k-1$ power of attained age. This fits the population age-incidence curves for many cancers if k is approximately 5 to 7.

In preliminary analyses for the BEIR V Committee,

this model was fitted to the data on all cancers, other than leukemia, among the atomic bomb survivors using DS86 dosimetry. The data provided to the BEIR Committee by the Radiation Effects Research Foundation (RERF) was the same as that used in the most recent reports from RERF (7). The data consisted of the numbers of observed cases by site of cancer, person-years, and mean gamma and neutron doses for 3399 cells of a tabulation by city, sex, dose, age at exposure, and time since exposure. The data were fitted using Poisson regression techniques as implemented in the program AMFIT (8). For this purpose, the relative biological effectiveness (RBE) of neutrons was fixed at 20, organ doses were calculated for a weighted average of various internal organs, and observations with doses greater than 4 Sv were excluded. The entire time period from 1950 to 1985 was used, and all ages were included. The background rates were taken to be proportional to a power of attained age multiplied by a loglinear function of sex, birth cohort, and calendar year. Further details of the methods can be found in the BEIR V report (3).

The maximum likelihood estimate of k was 5.07 with a standard error of 0.43, so k was fixed at 5 in all subsequent analyses. It is worth noting, however, that there was a significant departure from the simple power function model and significant differences in the exponents between the sexes. Such differences would be inconsistent with the multistage model if the background causes of cancer were constant in time, but may be explainable by age, sex, and year-related trends in these factors.

Another prediction of this model is that the dose-response relationship will be a polynomial function of dose rate, with order equal to the number of transitions that are dose related. Thus, the observation that the dose response is generally linear or linear quadratic would imply that, at most, one or two transitions would be related to radiation. Whittemore (9) has shown that if a single transition rate i is linearly related to the current dose rate $R(t)$ with $\mu_i(t) = \mu_{i0} [1 + \beta_i R(t)]$, then the ER at age T resulting from an instantaneous exposure at age t is proportional to

$$\beta_i R t^{i-1} F^{k-i-1}. \quad (1)$$

For an extended exposure, the ER is the integral of Eq. (1) from t_0 to t_1 .

Thus, if only the first transition is affected, the ER would be independent of t and would increase with F ; whereas if only the penultimate transition is affected, ER would be independent of F and would increase with t (9-11). The observation that the ER increases with both t and F in the RERF and many other data sets therefore rules out a model in which $i = 1$ or $i = k - 1$ alone. One possibility that would fit the data (assuming a linear dose response) is an intermediate stage ($i = 2, \dots, k - 2$) effect. Upon fitting these models to the RERF data, the best fit was obtained with $i = 2$, all other values of i being strongly rejected (Table 1).

Alternatively, if two transition rates i and j are dose related, then the ER is given by (11),

Table 1. Fit of the Armitage-Doll multistage model to mortality from all cancers other than leukemia among the atomic bomb survivors.*

Transition(s) affected by radiation exposure		Estimates (SE) of beta		Deviance (d.f.)
i	j	β_i	β_j	
1		2.27 (0.34)		2577.17 (3023)
2		7.71 (0.99)		2553.41 (3023)
3		9.04 (1.21)		2569.81 (3023)
4		4.24 (0.72)		2601.06 (3023)
1	2	0.43 (0.38)	6.69 (1.32)	2552.22 (3022)
1	3	1.32 (0.33)	6.49 (1.29)	2547.81 (3022)
1	4	1.88 (0.33)	3.22 (0.71)	2550.28 (3022)
2	3	6.11 (1.69)	2.41 (2.05)	2551.71 (3022)
2	4	6.56 (1.10)	1.69 (0.76)	2547.28 (3022)
3	4	10.23 (2.06)	-0.84 (1.16)	2569.23 (3022)

* Assuming number of stages $k = 5$, RBE (neutrons) = 20, computing tissue dose under DS86 as an average of doses to various organs weighted by the frequency of cancer in those organs, excluding total doses > 4 Sv, adjusting the background rate for sex, year of birth, and year of death, and including all times from 1950-85.

$$\begin{aligned} \beta_i R \int_{t_0}^{t_1} t^{i-1} (T-t)^{k-i-1} dt \\ + \beta_j R \int_{t_0}^{t_1} t^{j-1} (T-t)^{k-j-1} dt \\ + \beta_i \beta_j R^2 \int_{t_0}^{t_1} \int_t^{t_0} t^{i-1} (s-t)^{j-i-1} (T-s)^{k-j-1} ds dt. \end{aligned}$$

For an instantaneous exposure, the double integral term vanishes unless $j = i + 1$ and the dose response remains basically linear in form. (The quadratic term in the case $j = i + 1$ takes the form $\beta_i \beta_j R^2 t^{i-1} F^{k-i-2}$, which makes a trivial contribution to the rate except for high doses; in the RERF data, its contribution was negligible.) Thus, a model with $i = 1$ and $j = k-1$ would be compatible with ER increasing with both t and F . This choice fitted significantly better than the best fitting single-stage model, the combinations $i = 1, j = 3$ and $i = 2, j = 4$ being indistinguishable (Table 1).

The predictions of this model for the effect of L are more complex, because the effects of t , F , and T must also be considered, depending on which variables are being controlled. The effect of L conditional on t_0 and F (allowing T to vary) is discussed by Thomas (4). In this case, ER increases as a $k-2$ order polynomial of L (varying R inversely), irrespective of the stage of action. Relative risks decrease with L if a single transition is affected but increase and then decrease if two transitions are affected.

Figure 1 shows the predicted effects of varying L holding C , T and either t or t_0 fixed. These plots are based on the fitted RERF models given in Table 1; the arrows indicate the best fitting models, but recall that the fit is determined solely by the t_0 and F effects because there are no extended exposures in these data. Increasing, decreasing, or mixed patterns can occur, depending on the stage(s) at which radiation acts, basically reflecting the effects of t and F . For example, if

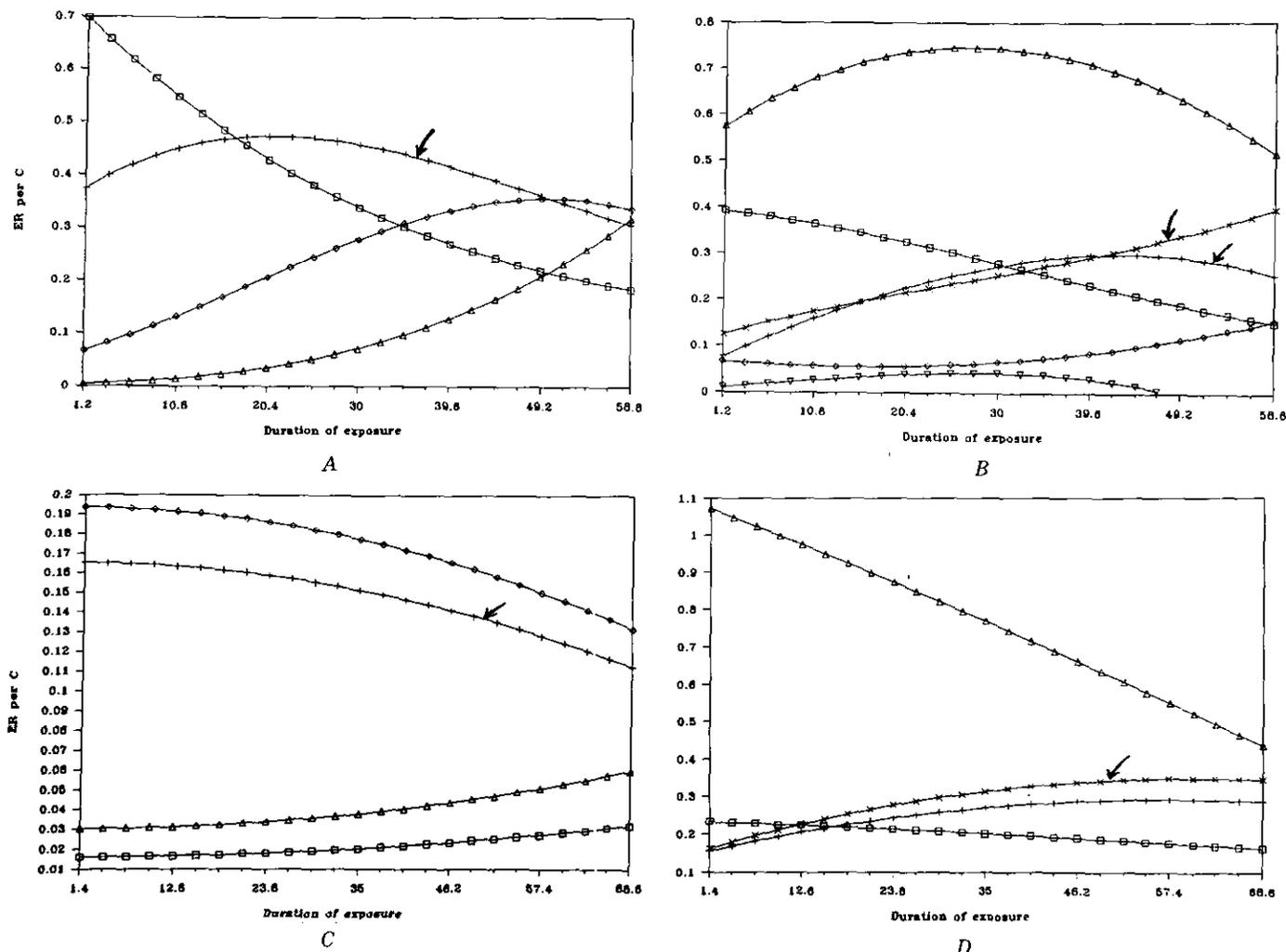


FIGURE 1. Predictions of the multistage model for effect of duration of exposure (L) on excess risk (ER), conditional on cumulative dose (C). Fitted models are based on RERF data. Attained age is fixed at 70 years, cumulative dose at 1 Gy, and the number of stages (k) at 5 in all panels. (A,B) Age at first exposure is fixed at 10 years; (C,D) average age at exposure is fixed at 35 years. A and C are for a single stage radiosensitive (\square) $i = 1$; (+) $i = 2$, (\diamond) $i = 3$; (Δ) $i = 4$; B and D are for two stages radiosensitive (\square) $i = 1/j = 2$; (+) $i = 1/j = 3$; (\diamond) $i = 1/j = 4$; (Δ) $i = 2/j = 3$; (X) $i = 2/j = 4$; (\triangle) $i = 3/j = 4$. The arrows indicate the best fitting model(s) in each panel.

$i = 1$, then the ER is proportional to $[(T - t_0)^{k-1} - (T - t_1)^{k-1}]/L$, which is determined mainly by $T - t_0$. If t is fixed, the ER becomes proportional to $[(T + L)^{k-1} - (T - L)^{k-1}]/L$, which is a polynomial in L with all coefficients positive; thus long low-intensity exposures are more hazardous than short, high-intensity exposures, essentially because $T - t_0$ is larger. (The same pattern occurs if $i = k - 1$.) On the other hand, if t_0 is fixed, ER becomes proportional to $[(T - t_0)^{k-1} - (T - t_0 - L)^{k-1}]/L$, which is a polynomial in L with alternating signs, the linear term being negative; thus, short intense exposures are the more hazardous, essentially because the average value of $T - t$ is smaller. (This pattern is reversed if $i = k - 1$.) For an intermediate stage or multiple stages of action, no simple expressions are possible, but the figure illustrates some of the possibilities. In particular, the best fitting models from the

RERF data are less sensitive to L than purely early or purely late stage models; the stage two only model shows a gentle increasing then decreasing pattern if t_0 is fixed or a gradual decline if t is fixed. The models with two stages affected are essentially mixtures of their component single-stage models.

The Moolgavkar-Knudson Two-Stage Model

The need for as many as five or more transitions has been questioned by experimental biologists who have found experimental support for only two or three stages in carcinogenesis. This has prompted Moolgavkar and Knudson (12) to propose a model involving only two mutational events and allowing the intermediate stage cells to have a proliferative advantage or disadvantage

relative to normal cells. Their model incorporates a number of additional features including a variable number of stem cells at risk by age and the possibility that the first mutation was inherited. For the purpose of this discussion, these features are not essential and will be omitted. The predicted rate of cancer at age T under this model is then approximately proportional to

$$\mu_2[R(T)] \int_0^T \mu_1[R(t)] \exp \left\{ \int_t^T \rho[R(s)] ds \right\} dt \quad (2)$$

where μ_1 and μ_2 are the rate of the first and second mutations respectively, and ρ is the net growth minus death rate of intermediate stage cells. One or more of the rates μ_1 , μ_2 , and ρ are assumed to be linearly related to $R(t)$. Assuming that the time from appearance of the first malignant cell to diagnosis or death is relatively short, a major effect of radiation on μ_2 would be implausible because it would imply an immediate change in the ER on starting or stopping exposure. Thus, it is sufficient to consider the effects of exposure on μ_1 and ρ . If ρ is constant and $\mu_1(t) = \mu_{10} + \mu_{11}R(t)$, then the ER is approximately proportional to

$$\mu_{11} C \exp[(T - t_0)\rho] [1 - \exp(-L\rho)]/L\rho, \quad (3)$$

which reduces to $\mu_{11}C$ at $\rho = 0$. Again the behavior of this function depends on what is held fixed. If t_0 is fixed and $\rho > 0$, then the ER is dominated by the earliest exposure, later ones having less and less effect owing to their shorter time for proliferation; thus Eq. (3) is proportional to C for short exposures, but thereafter it declines and eventually becomes proportional to R alone. Conversely, if $\rho < 0$ then the ER is dominated by the most recent exposures, earlier ones having less and less effect owing to their longer time for removal; thus, Eq. (3) is an exponentially increasing function of L .

Now suppose that ρ is also dose related, so that $\rho = \rho_0 + \rho_1R(t)$. Note first that if radiation increases ρ but has no effect on the rate of second mutations per cell division, then it should also increase the rate of second mutations per unit time (i.e., μ_2) proportionally; on the other hand, an effect on repair rates would have no effect on μ_2 . As noted earlier, however, an effect of dose-dependent μ_2 disappears as soon as exposure ceases, and thus it can be ignored for the purposes of this discussion. The general expression for ER is complex, owing to the effect of increased proliferation rates on both radiation-induced and background mutations. Assuming that the rate of background mutations is low, the ER is approximately

$$\mu_{11} R \{ \exp(\rho_1 C) - \exp(-\rho_0 L) \} \frac{\exp[(T - t_0)\rho_0]}{(\rho_0 + \rho_1 R)}. \quad (4)$$

In particular, if $\rho_0 = 0$ then this is simply an exponential function of C with no dependence on R or L . Even with $\rho_0 \neq 0$ or $\mu_{10} \neq 0$, the additional effect due to dose-dependent proliferation is still simply an exponential function of C . Thus, dose-dependent proliferation can-

not explain the increasing effect of duration seen with high-LET radiation. Furthermore, as ERs do not appear to be exponentially dependent on L , R , or C , the hypothesis that radiation exerts a promoting effect seems implausible.

Moolgavkar et al. (13) point out that Eq. (2) and its special cases previously discussed are valid only if the lifetime probability of cancer is small. They also provide complex expressions for the exact solution. Although the approximate expression should be adequate for human data, the exponential behavior noted in Eqs. (3) and (4) is considerably attenuated in the exact solution. Upon fitting both the approximate and exact expressions to data on lung tumors in dogs exposed to radon, they found that both models indicated strong effects on μ_1 and ρ . However, their model postulates a power function dependence of these rates on $R(t)$ with fitted exponents considerably less than unity. There does not seem to be any biological basis for such a dependence, and it is possible that the fitted effects on both μ_1 and ρ may represent an attempt by the fitting procedure to compensate for the sublinearity of the power functions.

For now, suffice to say that the standard form of the model has three limitations that render it unsuitable for radiation carcinogenesis. The first is that a linear quadratic dose response cannot be obtained except by having both mutations dose dependent, which seems implausible for reasons discussed previously. The second is that the growth rate of intermediate cells is a function of the difference of proliferation and repair rates; to adequately explain the observed patterns, it may be helpful to allow these two processes to act at different stages. The third is that a modifying effect of age at first exposure would require variation in the number of stem cells with age; although this is foreseen in the general model, it is modeled deterministically and not as an integral part of the carcinogenic process.

The Proposed Three-Stage Model

Each of the models discussed in the previous section offers features that are desirable to include in a general model. The idea that radiation can cause both SS and DS lesions is probably necessary to explain the linear-quadratic dependence of ER on dose. Repair of SS lesions is the simplest explanation of the dose-rate effect for low-LET and its absence for high-LET, and enhanced proliferation of initiated cells is thought to be the primary mechanism of promotion. The existence of multiple stages or exponential proliferation is needed to explain the age dependence of background rates. The possibility that radiation acts at an intermediate stage or a combination of early and late stages would account for the dependence of ER on t_0 and F . And finally, the appeal of the two-stage model lies in its simplicity.

We are thus led to consider the model illustrated in Figure 2. The principal features of the proposed model are the following:

a) The first mutation is replaced by two events corresponding to transitions from normal (N) to single-

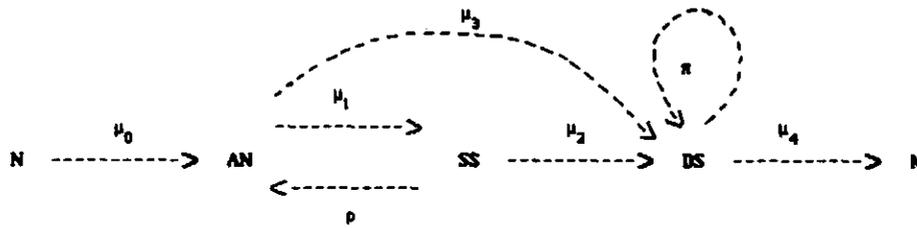


FIGURE 2. Proposed three stage model. N = normal cell; AN = activated normal cell; SS = single-stranded lesion; DS = double stranded lesion; M = malignant cell. Arrows represent transitions between states, with parameters indicated.

stranded (SS) lesions and from SS to double-stranded (DS) lesions.

b) Normal cells can be transformed directly from N to DS by a single particle.

c) SS and DS cells might either proliferate or die, but the predicted risk is a function only of the net proliferation minus death rate. For our purposes, it is sufficient to assume that the repair process dominates the outcome of SS cells and that the proliferation process dominates the outcome of DS cells.

d) Either the repair rate or the proliferation rate might be dose-dependent, although this possibility will not be considered further for reasons discussed in the previous section.

e) In order to avoid an immediate increase in cancer rates after exposure, the final event is assumed to be independent of dose and may correspond to activation of a transformed oncogene by a mutation to some other gene or the action of promoters.

f) Alternatively, an activation step might occur prior to the transformation of the oncogene itself. Evidence in support of this mechanism includes the increase in ER with t_0 in many epidemiologic studies and the observation that certain classes of promoters, such as TPA, appear to activate cells prior to application of initiating agents (14).

Proceeding as before, the predicted rate of cancer is then proportional to

$$\begin{aligned} & \mu_0 \mu_4 \int_0^T \int_0^t t \{ \mu_1 [R(t)] e^{-(s-t)\rho} \mu_2 [R(s)] + \mu_3 [R(t)] \\ & \times \exp \left\{ \int_t^T \pi [R(u)] du \right\} dt ds. \end{aligned} \quad (5)$$

where μ_0 is the rate of activation of N cells prior to initiation, μ_1 the mutation rate from N to SS, μ_2 the rate from SS to DS, μ_3 the rate from N to DS, μ_4 the rate of activation of DS to fully malignant cells (M), ρ the rate of repair of SS cells, and π the rate of proliferation of DS cells. As before, the rates μ_1 , μ_2 , and μ_3 are assumed to be linear functions of dose rate. The only fundamental difference between this expression and Eq. (2) is the addition of the term t in the integrand, representing the linear accumulation of spontaneously activated normal cells with age. Although analytic expressions are possible for this integral in the case where the dose rate is constant between t_0 and t_1 , they are sufficiently complex so as to be unenlightening. We therefore present the predictions for various choices of

parameters and exposure patterns obtained by numerical integration of this expression.

Figure 3 illustrates the effect of protraction for high-LET radiation for various choices of proliferation rates. For this purpose, the transitions from N to SS and from SS to DS are omitted, with the radiation being assumed to produce N to DS transitions only. Here, the increasing effect of L is generated by the influence of t in the integrand, but is offset by the proliferation process. Thus, if π were zero, ER per unit C would increase linearly with duration. The plotted curves decline from that for the same reason explained in the discussion of Eq. (3): fixing t_0 , longer durations imply shorter average time for proliferation. If instead, \bar{t} were fixed, the effect of age at exposure would disappear, but the proliferation process would introduce an exponential dependence on duration of exposure, as previously discussed.

Figure 4 illustrates the predicted effect of protraction for low-LET radiation for several choices of the repair rate. For this purpose, the direct transitions from N to DS lesions are omitted, and the proliferation rate of DS cells is fixed at 0.01/y. (Adding back in the direct transitions from N to DS simply dilutes this effect, because these direct transitions are not subject to repair in this model.) Some of the curves show an initial rise, owing to the confounding effect of age at exposure, which is partially offset by the proliferation effect as seen in Figure 3. This does not occur if \bar{t} is fixed instead; in this case, a smooth family of negative exponential curves is produced, with the higher r producing steeper dependence on L , as expected.

Thus it appears that the model is capable of explaining both the decreasing effect of protraction for low-LET and the increasing effect for high-LET radiation, without having to change any of the model parameters other than the relative frequency of SS lesions being produced. The model is also consistent with the observed patterns of dose-response relations and the modifying effects of age at and time since exposure. However, the increasing effects occur only with relatively long protraction (on the scale of years). To obtain effects with shorter protraction would appear to require promotion effects that would produce the problems of exponential dependencies discussed previously.

Possible Tests of the Model

Very little human data exist on comparable populations exposed to the same kind of radiation at both short

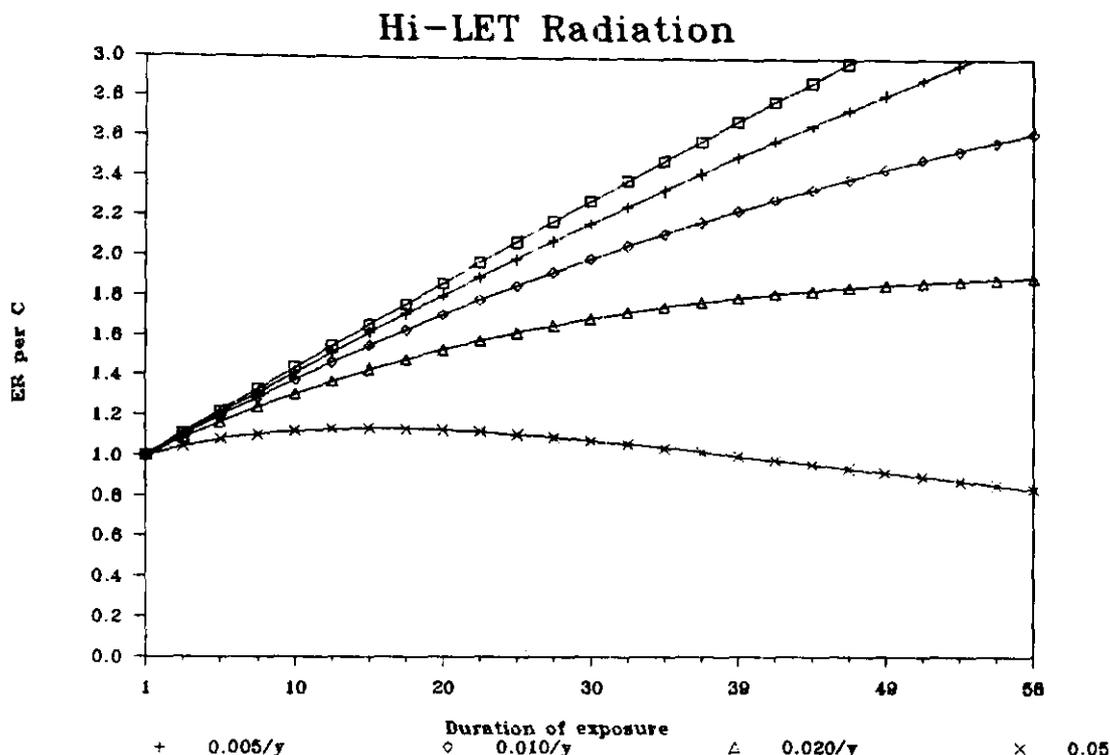


FIGURE 3. Predictions of the three-stage model for the effect of duration of exposure on excess risk due to high-LET radiation at various proliferation rates: (\square) $\pi = 0.0002/y$, (+) $\pi = 0.005/y$, (\diamond) $\pi = 0.010/y$, (\triangle) $\pi = 0.020/y$, (\times) $\pi = 0.050/y$. Transition rates μ_1 and μ_2 assumed to be zero. Exposure conditions as in Figure 1, panels A and B.

durations with high dose rates and long durations with low dose rates. The atomic bomb survivors provide the best data on short-duration exposures at high dose rates (7). These data have provided great insight into the form of the dose-response relationship and the modifying effects of age at exposure and time since exposure, but obviously no data on the effect of duration of exposure. Although some of the patients treated for ankylosing spondylitis received several courses of treatment, analyses that have been published to date have been restricted to those receiving a single course (15). Comparison of breast cancer rates in women exposed to a single instantaneous exposure (RERF), a small number of therapeutic doses (post-partum mastitis patients), or many small diagnostic exposures (fluoroscopy patients) show little differences in risk per unit dose; if anything, it appears that fractionated doses are slightly more hazardous than single doses (16)—the reverse of what has been found for low-LET radiation in a large number of animal experiments. The U.S. uranium miners show a tendency for long exposures to be more hazardous than short exposures, but this pattern is only marginally significant and not consistently observed in other radon-exposed cohorts (2). A similar pattern is observed in the patients injected with radium (17), but the variability in duration is not very large.

Within any of these studies, it would be important to control for the strong effects of total exposure, age at exposure, and time since exposure before examining the effects of dose rate and duration of exposure. Unfor-

tunately, conditional on these variables, there is seldom enough variation in dose rate and duration to allow for meaningful analyses. To expand this variability one might consider making comparisons between studies (e.g., atomic bomb survivors for acute exposures versus various occupational and medical cohorts for fractionated exposures), but such comparisons are highly susceptible to confounding by differences in source populations, reasons for exposure, types of exposures, periods of follow-up, and numerous methodological artifacts. In short, there are very little data on protracted low-LET exposures or instantaneous high-LET exposures. Although analyses within some of these cohorts may be helpful, they are unlikely to provide very powerful tests of the model.

There are, however, a large number of animal experiments that have addressed the effect of dose-rate and duration for both low- and high-LET radiation (18–20). The advantage of these data is that several dose rate and duration schedules have been used at each of several levels of cumulative dose for both low- and high-LET radiation, all starting at the same age at first exposure. The factorial nature of the design thus ensures sufficient variation in dose rate/duration within category of total dose to allow the two effects to be separated, without having to worry about the confounding effects of age at exposure and time since exposure. The use of the same protocols for low- and high-LET radiation is an additional bonus for testing whether a model can be developed that explains both phenomena with a

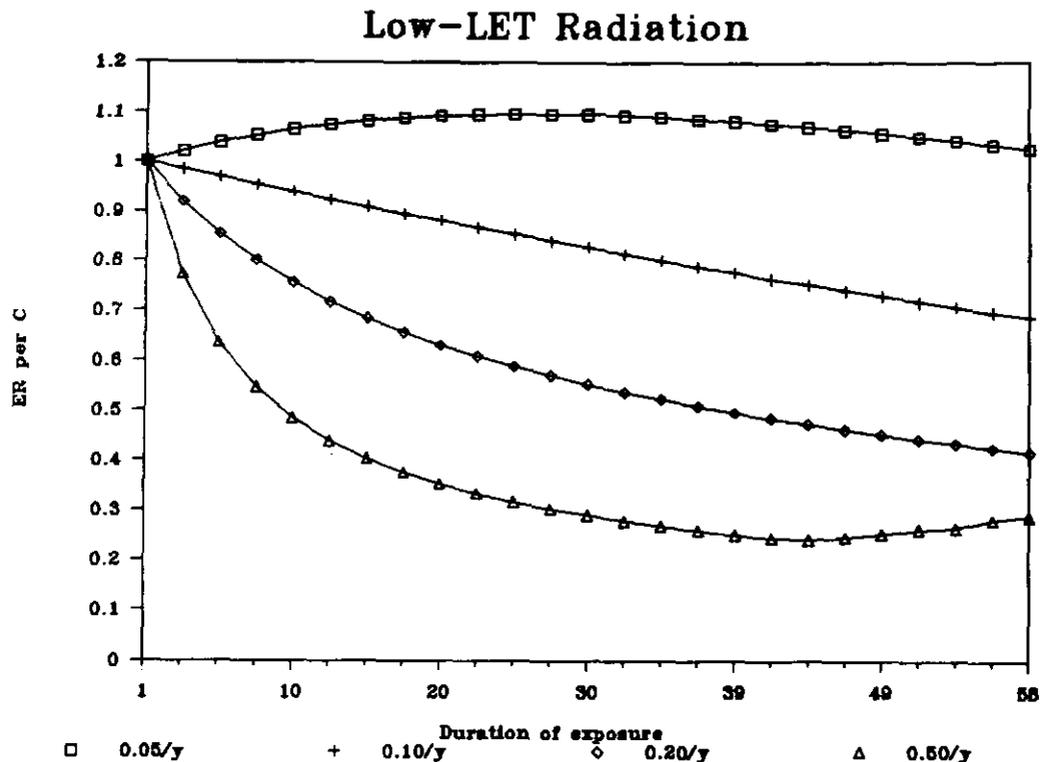


FIGURE 4. Predictions of the three-stage model for the effect of duration of exposure on excess risk due to low-LET radiation at various repair rates: (\square) $\rho = 0.05/y$, ($+$) $\rho = 0.10/y$, (\blacklozenge) $\rho = 0.20/y$, (\triangle) $\rho = 0.50/y$. Proliferation rate fixed at $\rho = 0.01/y$ and transition rate μ_3 assumed to be zero. Exposure conditions as in Figure 1, panels A and B.

minimum number of differences for the different forms of radiation. Analyses that have been reported to date have been primarily descriptive in nature. It is hoped that by fitting mechanistic models of this type to such data some insight into the basic processes might be gained.

A word of caution is in order however. All of these models are sufficiently general that they will probably provide an adequate fit for some choice of parameters. Thus, none is falsifiable as a class, and a good fit does not establish the truth of the model. 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.

This work was supported in part by NIH grants CA 42949 and CA 14089. I am grateful to the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan, for making available the data from the Life Span Study for this purpose. RERF is a private foundation that is funded equally by the Japanese Ministry of Health and Welfare and the U.S. Department of Energy through the U.S. National Academy of Sciences. The conclusions reached in this report are those of the author and do not necessarily reflect the scientific judgment of RERF or its funding agencies.

REFERENCES

1. Committee on the Biological Effects of Ionizing Radiation. *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*. National Academy Press, Washington, DC, 1980.
2. Committee on the Biological Effects of Ionizing Radiations. *Health Risks of Radon and Other Internally Deposited Alpha-Emitters (BEIR IV)*. National Academy Press, Washington, DC, 1988.
3. Committee on the Biological Effects of Ionizing Radiations. *Health Effect of Exposure to Low Levels of Ionizing Radiation (BEIR V)*. National Academy Press, Washington, DC, 1990.
4. Thomas, D. C. Models for exposure-time-response relationships with applications to cancer epidemiology. *Ann. Rev. Publ. Health* 9: 451-482 (1988).
5. Kellerer, A. M., and Rossi, H. H. The theory of dual radiation action. *Curr. Top. Radiat. Res. Q.* 8: 85-158 (1972).
6. Armitage, P., and Doll, R. *Stochastic models of carcinogenesis*. In: *Proceedings of the 4th Berkeley Symposium on Mathematical Statistics and Probability* (J. Neyman, Ed.), University of California Press, Berkeley, CA, 1961, pp. 18-38.
7. Shimizu, Y., Kato, H., and Schull, W. J. Life Span Study Report 11: Part II: Cancer Mortality in the Years 1950-85 Based on the Recently Revised Doses (DS86). Radiation Effects Research Foundation, Hiroshima, Japan, 1988.
8. Preston, D. L., and Pierce, D. A. AMFIT: A Program for Parameter Estimation in Additive and Multiplicative Rate Models Grouped Survival Data: Methods, Models, and Examples. Radiation Effects Research Foundation, Hiroshima, Japan, 1987.
9. Whittemore, A. S. The age distribution of human cancers for carcinogenic exposures of varying intensity. *Am. J. Epidemiol.* 106: 418-432 (1977).
10. Day, N. E., and Brown, C. C. Multistage models and primary prevention of cancer. *J. Natl. Cancer Inst.* 64: 977-989 (1980).
11. Thomas, D. C. Temporal effects and interactions in cancer: implications of carcinogenic models. In: *Environmental Epidemiology: Risk Assessment* (R. Prentice and A. S. Whittemore, Eds.), Society for Industry and Applied Mathematics, Philadelphia, PA, 1982, pp. 107-121.
12. Moolgavkar, S. H., and Knudson, A. G., Jr. *Mutation and cancer: a model for human carcinogenesis*. *J. Natl. Cancer Inst.* 66: 1037-1052 (1981).

13. Moolgavkar, S. H., Cross, F. T., Luebeck, G., and Dagle, G. E. A two-mutation model for radon-induced lung tumors in rats. *Radiat. Res.* 121: 28-37 (1990).
14. Yamasaki, H. Multistage carcinogenesis: implications for risk estimation. *Cancer Metastasis Rev.* 7: 5-18 (1988).
15. Darby, S. C., Doll, R., Gill, S. K., and Smith, P. G. Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. *Br. J. Cancer* 55: 179-190 (1987).
16. Land, D. E., Boice, J. D., Shore, R. E., et al. Breast cancer risk from low-dose exposures to ionizing radiation: results of parallel analysis of three exposed populations of women. *J. Natl. Cancer Inst.* 65: 353-365 (1980).
17. Spiess, H., and Mays, C. W. Protraction effect on bone sarcoma induction of ^{224}Ra in children and adults. In: *Radionuclides Carcinogenesis*, CONF-720505 (C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, Eds.), NTIS, Springfield, VA, 1973, pp. 437-450.
18. Broerse, J. J. The influence of physical factors on carcinogenesis in experimental animals. In: *Low Dose Radiation: Biological Bases of Risk Assessment*. 14th L. H. Gray Conference (K. F. Baverstock and J. W. Stather, Eds.), Taylor and Francis, London, 1989, pp. 181-194.
19. Fry, R. J. M., and Carnes, B. A. Age, sex, and other factors in radiation carcinogenesis. In: *Low Dose Radiation—Biological Bases of Risk Assessment* (K. F. Baverstock and J. W. Stather, Eds.), 14th L. H. Gray Conference, Taylor and Francis, London, 1989, pp. 195-206.
20. Burns, F. J., Sawey, M. J., Hosselet, S., and Garte, S. Risk assessment and multiple stages in radiation carcinogenesis. In: *Low Dose Radiation: Biological Bases of Risk Assessment*. 14th L. H. Gray Conference (K. F. Baverstock and J. W. Stather, Eds.), Taylor and Francis, 1989, pp. 571-582.