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The Effects of High vs. Low-Level Radiation Exposure

V. P. Bond

I. Introduction

In order to appreciate adequately the various possible effects of radiation, particularly from high-level vs. low-level radiation exposure (HLRE, vs. LLRE), it is necessary to understand the substantial differences between a) "exposure" as used in exposure-incidence curves, which are always initially "linear and without threshold", and b) "dose" as used in dose-response curves, which always have a threshold, above which the function is curvilinear with increasing slope. The differences are discussed first in terms of generally familiar non-radiation situations involving dose vs. exposure, and then specifically in terms of exposure to radiation, vs. a dose of radiation. Examples are given of relevant biomedical findings illustrating that, while dose can be used with HLRE, it is inappropriate and misleading with LLRE where exposure is the conceptually correct measure of the amount of radiation involved.

II. Dose-Response vs. Exposure-Incidence Functions

Dose-response curves are seen only under conditions in which the purpose of an endeavor involving an agent* is to alter the health status of an individual(s), an objective that is to be realized by the administration of the agent to that individual(s).

* An agent is a chemical or biological entity or substance that, when administered to biological systems (e.g., a cell, cell population, organ), causes a biological reaction or "effect". With ionizing radiation, the agent is energy.

Accordingly, a specific agent is transferred from an identified agent source and administered to the specific individual(s) to be treated, in an amount (dose*) estimated, by reference to an appropriate dose-response function, to produce the type and severity of health alteration planned. The emphasis is on the individual, and the type and dose of agent is tailored to each individual circumstance so that the expected biomedical result will be seen in each case. The only uncertainty or element of chance arises from the normal range of individual variation in response to a given dose, and from the rare instances of marked hyper- or hypo-sensitivity to the agent. The above-described circumstances involving dose-response functions are those that pertain in medicine, pharmacology and toxicology.

In Fig. 1 is shown schematically a function for dose vs. the amount of organ injury (curve A) and a function for dose vs. the fraction of organs responding quantally** (curve B). Organ injury, or non-quantal or "subeffective" damage, increases continuously as the dose increases (e.g., organ output of hormones, antibodies, new cells, enzymes). The initial part of curve A is dotted to indicate that a given small dose may cause no detectable effect, although more refined measurements usually uncover effects at still lower doses. Above some threshold level of injury (I_t) and corresponding dose (D_t), organs in the lower range of normal sensitivity may show a quantal response.** The fraction of organs showing a quantal response (i.e., number of equally-dosed and responding organs, over the total given that dose) increases with dose,

* Although the amount or "dose" of an agent administered is frequently quantified for practical purposes in terms of mass, weight, or volume, the dose for dose-response curves is usually quantified in terms of the mass concentration of the agent itself, frequently in the organ principally affected.

** A quantal effect or response (1) is a discrete change in an organ (or cell), which occurs only above a specific amount of non-quantal or "subeffective" injury, is "all-or-none" or go-no-go in character (i.e., it is scorable as either present or not), and in general is not spontaneously reversible. Examples of organ quantal effects are clinically-characterized gross lesions or functional failure which may be scored indirectly in terms of specific illness in, or death of the host. A non-quantal response is one of severity insufficient to cause a quantal response.

but saturates at 1.0 where essentially all dosed organs have shown the response. An important characteristic of functions A and B, Fig. 1, of importance in contrasting dose-response with exposure incidence curves, is that all organs at a specific dose level have received nominally the identical dose, so that the effects and responses shown are unique to that dose (i.e., the variance of the dose to the individuals in a dose group is small).

Curve B' is the derivative of curve B, and represents the distribution of normal organ sensitivities, which cannot be observed or measured directly. Thus curves B and B' are the functions in terms of which the absolute and relative sensitivities of organs from different groups of individuals can be compared quantitatively.

Exposure-incidence curves, in contrast, are seen only under circumstances in which the endeavor involves containers (sources, carriers) of sizeable amounts of agent, located in the vicinity of an individual(s), and periodically or continuously in motion relative to the individual(s). Examples are vehicles carrying the agent energy; lightning bolts; containers of combustible or potentially toxic liquids or gases; animal, insect or human disease carriers[2]. Because the purpose of the carriers is far removed from altering the health status of any individual by means of agent transfer, normally the agents are completely contained. Therefore agent transfer and consequent injury can occur only under the rare circumstances in which, as a result of some predisposing event (e.g., equipment or human failure), there is a

random or stochastic encounter or collision between an individual(s) and an agent source, with consequent release of agent, transfer of some amount of agent to the few individual(s) involved, and consequent harm to the individual(s) involved, the severity of which is a function of the amount of agent transferred, or "hit size".* It is only under these circumstances that exposure**-incidence functions, such as those shown in Fig. 2, are encountered (i.e., in the public health disciplines, including accidents[2]). Clearly the focus is on a "normal" population exposed, very few of whom are hit and injured. Of the injured, only a small fraction is seriously or lethally injured (i.e., the incidence, equal to the number hit and injured, over total number of "normal" individuals exposed, is small).

First with respect to curve C in Fig. 2, for hit and injured individuals without regard to hit size or severity of injury, the curve is initially linear because, since the collisions are random or stochastic, and thus the average number of hits per unit exposure or exposure time must be constant. Also, essentially no individual receives more than one hit (i.e., if many received more than one hit, the curve would be linear initially, but with decreasing slope as the exposure increases). The curve is without threshold because the hits are stochastic in time, and therefore "no matter how small the exposure to moving agent sources, there is a finite probability of a collision and consequent injury".

* "Hit size" is the analogue, for stochastically-delivered agent, of "dose" for agent delivered in a planned and ordered fashion. Although conceptually similar, the distribution of agent and therefore the variance with hit size is likely to be gr -- than with dose. "Dose" in quotes is sometimes used here to indicate "hit size".

** The exposure defines the number concentration of agent sources in the environment of the individual(s), times the mean distance $\bar{s}$ traveled by the agent source relative to the individual(s) during the exposure time t_E, or the number of agent sources/unit area "seen by" or "presented to" the individual during an exposure. Although difficult to quantify for most "macro" accident situations, exposure so defined is precisely quantifiable for radiation (see below) as the charged particle fluence [i.e., $(P/cm^3)(\bar{s}/t)(t_E) = P/cm^2$, where P is the number of agent sources, charged particles).

With respect to curve D in Fig. 2, the function for the incidence of quantally responding individuals is also linear and without threshold simply because, under a given set of conditions, a constant fraction of those hit and non-quantally injured will show a quantal response. The reasons for this can be seen in Fig. 3. There it is shown schematically that, for any exposure such as E_1 in Fig. 2, and since the hit size is determined by stochastic processes, there must result a wide distribution of hit sizes, or "doses". With increasing exposure, since "single hit kinetics" pertain, the spectrum does not change with exposure (i.e., curve F, with increasing exposure becomes curve F', with greater area reflecting the larger exposure, but no change in spectrum). For a given exposure, the hit size and therefore the severity of injury, can vary from near zero where both a hit and "injury" are difficult to define, and where the hit size is too small to inflict serious injury, to an upper limit, determined by the amount of agent per carrier and other characteristics of the carrier, the individual and the circumstances, capable of causing substantial injury.

By reference to Fig. 1, and noting that hit size and "dose" are conceptually similar, one would expect quantal effects only above some threshold hit size, H_t. Since the fraction of hit sizes above H_t does not change with exposure, the fraction of quantally-responding individuals remains constant (i.e., in Fig. 3, because the spectrum does not change with increasing exposure, neither does the relative number of hits above the threshold H_t). Thus the quantal response curve is a

constant times the curve for incidence of hit cells, and must therefore also be linear and without threshold.

Fig. 3 also explains why "any amount of exposure or exposure time can be lethal." In the rare event of an accident, which can occur as soon as exposure begins or any time later, the hit size may well be above the threshold so that there is a non-zero chance of a hit and a lethal quantal response, no matter how small the exposure or exposure time. Thus, even though a very small exposure may result in a lethal quantal effect, that effect always results from a large, above-threshold hit size or "dose" delivered stochastically during that exposure. Fig. 3 also explains a key difference between a pharmaco-toxicological dose-response curve and an exposure-quantal response curve seen in public health accident situations. With the former, all individuals at a given dose have nominally the identical organ concentration of the agent itself, or dose. Thus below the threshold dose there can be no chance of a lethal quantal response. With the latter, any amount of exposure in terms of the concentration of agent sources can equate to collisions, with a wide range of consequent hit sizes, from no hit at all (zero size hit), a sub-threshold hit size or "dose", or an above-threshold and therefore a potentially lethal quantal effect.

A convenient example of exposure and exposure-incidence functions is vehicle accidents, particularly since the agent is energy. Approximately 200 million persons are exposed essentially continuously to the risk of a collision involving a vehicle, of which approximately

5 million per year are involved or "hit" in a collision[2], and of which about 50,000 die per year. The hit sizes or "doses" range from virtually zero to very large, as does the severity of the resulting injury. Essentially a constant fraction of hit sizes is above the threshold for a lethal quantal response, and thus the number of killed per year is a small fraction of the total hit and injured, and remains essentially constant at about 50,000/yr. If one then plots the accumulated incidence of hit and injured persons (i.e., hit over exposed persons) against the exposure time in years (as a surrogate for exposure which, although difficult to quantify, can be assumed to remain essentially the same from year to year), the resulting curve (i.e., curve C, Fig. 2) will be linear and without threshold, with a slope of $5 \times 10^6/200 \times 10^6$, or 2.5% per year. The curve for the accumulated mortality vs. exposure time will similarly be linear and without threshold, with a slope of $50 \times 10^3/200 \times 10^6$, or 0.025% per year (i.e., curve D, Fig. 2).

With gross accidents, victims are removed from the hazardous environment where they remain until they either succumb to the injury or are essentially fully recovered. Were this not done, then more "multihit" injuries and deaths would be seen (i.e., an initial non-quantal hit followed by a second in quick order could be fatal, where neither alone could be). Such multihit phenomena would eventually increase the slope of the curve (e.g., curve D', Fig. 2).

III. Exposure to vs. a Dose of Radiation

Low-level radiation exposures yield the linear, no threshold exposure-incidence relationships described above for the public health-accident situation, and high-level exposures yield the threshold dose-response functions of pharmacology-toxicology. However, some key differences between radiation exposure and other more familiar exposures must be pointed out to show why this is so. With radiation exposure, the primary actions take place in the "microenvironment" of cells in a "field" of principally charged particles. Thus the carriers of the agent energy are charged energetic particles (e.g., electrons, protons, alpha rays), and it is only stochastic interactions or "collisions" between a charged particle and a cell (CV) that can cause injury or a quantal effect. Thus it is injury to the individual cell, the smallest semi autonomous living unit of the body, that must be of primary concern with LLRE.

Thus to expose cells means to place them in a charged particle field of a strength defined in terms of the number of charged particles per unit area per unit time, termed the "fluence rate", ϕ (see footnote immediately above). Exposure for a time t_E results in an accumulated fluence $\phi t_E = \Phi$ of particles having passed in the vicinity of a cell(s), and an associated probability that the cell will have interacted with a charged particle, with a consequent transfer of energy to the critical volume of that cell.

"Exposure" is defined as the amount of radiation or number of particles "seen" by a cell(s) during an exposure time of length t_E, namely Φ. This definition is conceptually similar to those provided by the ICRU[3] in that it describes the amount of radiation in the field (i.e., the amount in the vicinity of, and not absorbed in, any given cell). It differs from the ICRU second or alternative definition of exposure, in that it is particle and not energy fluence.

The cell critical volume (CV) is a non-anatomical volume within the cell, the apparent mean diameter or "cross section" σ of which can be calculated, and within which the macromolecular sensitive target(s) must reside. The CV must be "hit" by a charged particle and the hit must be of a minimum size* in order for the chance of an all-or-none alteration of the cell (a quantal response) to be other than zero.

"Non-quantal" or "subeffective" damage to the cell, as with the organ, is injury, the seriousness of which increases continuously and monotonically as a function of the amount of agent received (e.g., numbers of DNA strand breaks; perhaps membrane damage). A quantal effect or response is a discrete change in a cell or organ, which occurs only at or above a specific amount of non-quantal damage and therefore of the corresponding amount of agent; is "all-or-none" or "go-no-go" in character (i.e., it can be reproducibly scored as either present or not present); and in general is not reversible spontaneously. Examples of radiation-induced quantal effects for cells are chromosome abnormalities, other cytologically-definable changes, mutagenic or carcinogenic transformation and cell death.

* Either of the microdosimetric quantitates lineal energy y, or the specific energy z could have been used instead of the less-committal "hit size". Although the number or incidence of hit cells for a given exposure cannot be measured directly in living cells, this value can be determined by microdosimetric techniques in which a proportional counter is designed to simulate the cell CV4-10.

"Single cell" effects are those quantal effects that arise from a single cell, such that the cell either dies within a short time, is capable of proliferation for a limited number of divisions only, or is capable of carrying the quantal alteration through an indefinite number of divisions in the individual in question to cause a cancer or other proliferative disease, or, if a reproductive cell is involved even into the offspring to produce an abnormal individual. Single cell quantal responses of principal interest with respect to health effects in the human being exposed to low-level radiation are malignant cell transformation, and heritable change in reproductive cells which could become manifest as biochemical or morphological defects in the offspring.

Organ radiation effects are quantal responses in an organ seen only with large exposures and due to extensive anatomical or functional changes throughout the organ, such that the overall functional efficiency of the organ is impaired, e.g., acute organ hypoplasia or aplasia, severe skin lesions, vision-impairing cataracts, sterility. Such effects from radiation derive primarily from severe damage to or death of a large fraction of functional cells in the organ, which constitutes serious non-quantal injury to the organ[11]. Vascular and supporting structure damage may be involved directly with very large and particularly chronic exposure delivered to restricted regions of the body. Quantal organ effects are not observed below a large "threshold" amount of radiation exposure to essentially the entire organ (i.e., they are not seen with LLRE).

Thus low-level radiation exposure can be defined as exposures small enough so that only a fraction of the exposed normal cells are hit at all (i.e., the "micro analogue" of the public health-accident situation described above for "macro accidents"). In contrast, high-level radiation exposure can be defined as exposure of a cell population or organ in a strong field in which essentially all cells are hit at least once. Any further increase in exposure can then result only in additional (multiple) hits per cell and a consequent increase in the average amount of energy deposited in, and therefore harm and risk of serious consequence to, each cell and the organ. Under these circumstances, the concentrations of energy, even though the result of repeated discrete increments of energy transferred stochastically, becomes sufficiently uniform so that it is reasonable to speak of "absorbed dose" (energy per unit mass) as the independent variable. Further, it is then possible to "give" a dose to radiation in an ordered fashion to one or a number of organs, with reasonable assurance that each organ, and each cell in those organs, has received nominally the same amount of agent. Thus one is operating in the realm of pharmacology-toxicology (e.g., in radiotherapy of tumors), where dose response functions are obtained.

IV. Exposure-Incidence vs. Dose-Response Functions

In Fig. 4 is shown the cell analogue of the exposure-incidence curves, described above and shown in Fig. 2 for the "macro" situation

involving organs, namely the incidence of hit cells, I_H,* vs. the exposure, Φ. Note that the initial part of the curve is essentially linear, which is expected from the well known expression in particle and nuclear physics,

$$I_H = \Phi t_E \bar{\sigma}_p = \bar{\sigma}_p, \qquad (1)$$

where $\bar{\sigma}_p$ is the mean cross section of the cell CV, or the average probability per unit Φ that a charged particle will interact with the CV of a cell. That the initial curve must be linear and without threshold can also be seen intuitively as follows: With LLRE, the number of charged particles per exposure is initially so few in number that no more than a small fraction of relevant cells (i.e., cells capable of being transformed, showing a quantal effect and proliferating indefinitely) is hit at all. Further, essentially all such hit cells are involved in no more than one encounter. As a result, with increasing exposure, it is only the number or incidence of hit cells that can increase, and not the amount of agent per cell. Also, because cell-particle collisions are stochastic in both time and space, the increase in the number or incidence of hit cells per unit exposure is constant.

Shown in Fig. 4, in addition to the curve for I_H, are the curves for the incidence of quantally-responding cells, I_q, for radiations of different "quality" or "linear energy transfer" (LET). Note that while

* The number of hit cells, without regard to hit size, over the number of exposed cells. The denominator, with LLRE, includes many unhit (zero hit size) cells.

a single curve suffices for I_H, for radiations of any LET, the slopes of I_q for different LET radiations differ because of different hit size spectra. The linearity of the initial part of the functions for I_q follows because, with single hit kinetics, the hit size spectra must remain constant with increasing ϕ. Thus I_q/I_H must also remain constant. The functions shown in the figure,

$$I_q = \phi \bar{\sigma}_p \bar{P}_q, \tag{2}$$

where $\bar{P}_q$ is the mean probability for a given LET that a hit cell will respond quantally, indicates similarly that I_q/ϕ is simply the product of the mean probability that the cell will be hit ($\bar{\sigma}_p$), and the mean probability per hit cell of a quantal response ($\bar{P}_q$).

That I_q vs. the amount of radiation (in rads, as a mathematically-correct but conceptually inappropriate surrogate for ϕ) is in fact initially linear in many if not all eukaryotic cellular systems is shown in Figs. 5[12] and 6[13], for a wide range of LET values. Fig. 6 is shown to emphasize that even with very low-LET radiation, the initial slope can be shown to be linear in single cell systems, provided that a sufficient number of cells is observed.

In Fig. 7 is shown the transition from LLRE where only ϕ, I_H and I_q for single cell effects is appropriate, to HLRE where either ϕ or absorbed dose, and organ effects are appropriate (although single cell effects are of course also observed with HLRE). Curve A is an entire

curve for exposure vs. incidence of inactivated or killed cells, illustrating the initial linear single hit portion on which is superimposed the multihit or "quadratic" portion commonly represented by

$$I_q = \alpha D + \beta D^2, \tag{3}$$

a surrogate for,

$$I_q = \alpha'\Phi + \beta'\Phi^2, \tag{4}$$

where α and β are constants. Although curve A is a "cellular response" curve viewed from the cell population standpoint, the same curve A is also an organ injury curve viewed from the standpoint of organ failure and organ quantal responses (e.g., organ failure, with acute illness or death of the animal). Above an absorbed dose threshold D_t, f_q, the fraction of quantally-responding organs (curve B)increases monotonically with absorbed dose. Thus it is in terms of dose-f_q curves, and not exposure-I_q curves, that the radiation sensitivity of organs is to be measured.

In curves in Figs. 4-6, the cell population exposure Φ vs. I_q, I_q was determined empirically by observations in cellular systems. Considering the organ dose-organ f_q curves shown in Figs. 1 and 7, and that cell "hit size" is the cell analogue of organ dose, one might then expect the existence of a cell hit size-cell f_q function that might

resemble in general organ dose-f_q curves B, shown in Figs. 1 and 7, respectively. If such a function could be developed, then, in Fig. 4, I_q could be obtained analytically from I_H, rather than empirically, simply by weighting each individual hit size for any given I_H (such as E_1, Fig. 4) by the probability of a quantal response for that hit size. That such a function for cells does exist has been shown,[6-10] where its derivation, use, and implications in radiobiology and radiation protection have been discussed.

V. Mammalian and Human Radiobiology

In what follows "absorbed dose" will be used for LLRE as well as HLRE, as a mathematically correct but conceptually inappropriate surrogate for the fluence Φ, simply because fluence, though recognized as appropriate[14], has not been in common use. That dose is inappropriate for LLRE has been emphasized by Kellerer[4], "absorbed dose is a meaningful concept only if it is sufficiently high in value", and "microdosimetry (which is a measure of hit cells and therefore of Φ) is the extension of classic dosimetry to those situations (i.e., LLRE) for which the concept of absorbed dose is not applicable". The same ideas are expressed by Rossi[5].

In any situation in which there may be release of relatively large amount of radiation, such as nuclear warfare or a serious reactor incident or accident, the potential exists for human beings to be exposed over the entire range, from zero to very large and lethal amounts. Thus early effects on man of large amounts of radiation

delivered in a short time, as well as "late effects" (i.e., carcinogenesis and mutagenesis), are now described.

Early effects of large exposures.

Early effects of radiation (cellular or organ changes, illness and even death within hours, days or a few weeks of exposure) assume clinical significance only at doses to the whole body in excess of about 150 rads[15-17]. The principal site of action is on dividing cells in the proliferative organ systems, consequent organ malfunction, and serious illness and possible death in the heavily exposed. The most important cellular site of action is at the stem cell level so that the source of supply of mature functional cells is temporarily reduced severely, with resultant impaired function of that organ and of the individual. If the individual can survive the period of severe cellular depletion, with or without treatment, then the damaged organ will spontaneously regenerate the normal complement of cells and the individual will survive. If therapeutic efforts are inadequate or regeneration cannot occur soon enough, then the individual may succumb because of the failure of the organ system.

Cellular depletion in organs can be detected at doses as low as 40 rads or less in the bone marrow, in the lymphopoietic organs and in the circulating lymphocyte count, and at much lower doses in the testis and mouse ovaries. With whole-body irradiation of man at doses in roughly the 200-400 rad range, severe bone marrow depletion leads in time to symptoms related primarily to depletion of neutrophiles and platelets in

the blood. The consequent signs and symptoms are those that would be expected, i.e., infection in a variety of body locations and severe bleeding into any of a number of organs and possibly death. Death occurs mainly between 20 and 40 days after exposure. Effective treatment consists of "reverse isolation", neutrophile transfusions and large doses of antibiotics to control infection, and fresh platelet transfusions to control bleeding. With very high doses, replacement of stem cells by bone marrow transfusions may be indicated.

At doses in excess of about 1,000 rads, the "gastrointestinal syndrome" is seen, with the "central nervous system" syndrome appearing at doses in excess of about 1500 rads. Extensive descriptions of early effects may be found in several references[11,15-19].

With the exception of large scale accidents involving the exposure of large numbers of people to LLR, such as that in which the Marshallese were exposed to large doses of fallout radiation[17], the accident rate involving early effects is extremely small. Since the beginning of large scale operations involving nuclear energy in the 40's, there have been no more than about 20 deaths ascribable to accidental HLR exposure[18].

Late Effects

Although a variety of late somatic effect can occur in survivors of exposure to high doses of radiation (particularly following partial body exposure in which the localized damage permits survival at very high doses), a potential increase in cancer is the principal and most serious

late effect. There is no question that radiation does cause an increase in cancer in man at doses of the order of 100 rads or more (of low-LET radiation). At lower doses, it is difficult or impossible to demonstrate such an increase even in large exposed populations. Hence indirect means (interpolation or extrapolation with human data; use of animal data models) must be employed to provide estimates of possible effects at low doses and dose rates.

Central to estimating the incidence (risk) of carcinogenic and genetic effects in man are incidence (risk) vs. exposure relationships, and their variation with exposure rate. In Fig. 8, incidence is plotted against exposure (or dose) and typical data available on the human being (e.g., for human cancer from x- or gamma ray exposure) are represented as the hypothetical data points at relatively high doses, e.g., 100 or more rads. Of principal interest in the context of radiation protection is the very low dose and/or dose rate region, in which no excess incidence is detectable. Estimation of excess incidence at these low doses and dose rates thus must be obtained indirectly, and linear interpolation between background dose and incidence, and the data points at high doses and dose rates (curve B, slope α_L in Fig. 8) is frequently used for the purpose. This relationship is referred to as "linear, no threshold", and is to be contrasted with the curvilinear (curve A) relationship also shown in Fig. 8. Obviously, the linear relationship predicts a greater degree of excess incidence at low doses, than does the curvilinear function.

The low-dose part of curve A in Fig. 8 in principle has the slope "α" in the formulation shown above as Eq. 3. As shown below, this function appears to represent well a large amount of relevant data in "simple" cellular systems. Curve C approximates the slope obtained experimentally at low dose rates, i.e., if the doses represented by the three solid-circle "data points" were delivered at lower and lower dose rates, the data points would move downward and approach curve C. The limiting effect of lowering the dose rate would in principle be the superposition of curve C and curve D in the extension of the low-dose α_1 slope of curve A. Thus to a very large degree, the effect of lowering the dose or the dose rate is the same, and the two are often regarded as being interchangeable. The factor by which the linear, no threshold function may overestimate the incidence a low doses and dose rates is the ratio of the slopes of curve B, to curve C (or ultimately, curve D).

Relationships among dose and dose rate can be evaluated most quantitatively in "simple" cellular systems, in which the influence of both variables can be studied in detail. For this purpose, Tradescantia data[20-22] are shown in Fig. 6, in which the incidence of pink mutant events scored in cells comprising the stamen hairs is plotted against dose. A log-log plot is used to make clear the extent and nature of the data at very low doses, i.e., below 10 rads. The data (Fig. 6) indicate clearly the proportionality of dose and incidence at low doses, and the lack of a threshold for incidence of effect. The frequency of events is extremely low. The data up to about 100 or more rads can be represented

well by the function $I_q = \alpha D + \beta D^2$ (the flattening of the curve due to "cell killing", obviously important at higher doses, is not considered here).

The effect of dose rate is seen in Fig. 9 in which are shown on arithmetic coordinates (upper curve) essentially the same data shown in Fig. 6. The two central curves with data points represent lower dose rates than used for the uppermost curve. The lower curve marked "α_X" represents the extension of the "αD" part of the low-dose curve in Fig. 2, corresponding to curve C (and D) in Fig. 8. The lowermost curve marked "α_γ" is analogous to the "α_X" curve in Fig. 8 and is obtained experimentally if γ- instead of x-rays are used to determine the lower part of the curve in Fig. 6.

The influence of average dose rate (or exposure time) is seen in more detail in Fig. 10[13]. A dose of about 80 rads was delivered at progressively lower dose rates. The incidence/80 rads is seen to decrease progressively as the dose rate is lowered (exposure time lengthened), and the slope (incidence/80 rads) is seen to approach asymptotically the (gamma) incidence/rad at low doses, as seen in Figs. 8 and 9. One can thus see that the lower limit of the incidence per rad (slope) at very low doses, seen in the context of a full exposure-incidence curve (Figs. 8 and 9) involving high doses and dose rates, is the same as the lower limit of the incidence/rad (slope) using high doses delivered at low dose rates.

The linear and quadratic components of incidence (Figs. 8 and 9) are thus separable equally well, by lowering either the dose or the dose rate. The two components are shown separately in Fig. 11. The "sub-effect" damage of the quadratic component can be repaired completely at at low dose rate is repaired completely before it can contribute to a visible lesion. The linear component is without threshold and shows a definite increase in incidence at small (fraction of a rad) or large doses, independent of dose rate.*

These same dose-dose rate relationships appear to represent adequately a large amount of data in "higher" systems, including carcinogenesis and mutagenesis in the mammal (Figs. 12 and 13) and man[13,18,23-25]. This does not mean necessarily that the model applies literally ("models are to be used, not believed"), and certainly radiation-induced changes in cancer inhibiting or "promoting" factors can play a substantial role in determining the probability that a transformed or "initiated" cell will be able to proliferate and become manifest as an overt malignancy. Thus, for some types of cancer, the excess incidence could well be zero with LLRE. The relationship does, however, provide a logical, operational framework in which to consider mutagenesis and carcinogenesis, and a conservative framework in which to consider exposure limits for radiation protection purposes.

The following points, based on the above model, are key to an adequate understanding of the risk of potential late effects of "low-level"** radiation exposure in man:

* Oversimplified, the radiation beam and the dose received from it, may be regarded as being composed of two separate components, one of high and one of low-linear energy transfer, or LET.

** "Low-level" radiation exposures can also be defined arbitrarily as single exposures of about 10 rads or less, or larger exposures delivered over periods of hours, days or more (low "dose rates"). "High-level" exposures are in the range of 25-100 or more rads, delivered within minutes to at most hours.

1) High doses of radiation are known to cause a small increase in the background cancer rate among those exposed, and are believed to increase slightly the normal incidence of "genetic defects" in subsequent generations. Radiation carcinogenesis has been recognized since about the year 1900; genetic effects since 1927. The extent of radiation carcinogenesis became fully appreciated when the results of large scale epidemiological studies began to appear in the late 40s and in the 50s. In the Hiroshima and Nagasaki studies, from a total of 285,000 registrants (survivors) exposed at all dose levels, 70,000 deaths from natural causes had occurred by 1974. No more than 500 of these deaths (about 0.7%) had resulted from radiation-induced cancer of any kind. No increase in genetic effects has been found to date in the first generation offspring of those exposed.

2) Radiation carcinogenesis and mutagenesis involve randomly-induced cell injury, and the diseases induced are indistinguishable from those occurring "naturally" or from other carcinogenic/ mutagenic agents. Thus cause and effect can be related only inferentially and statistically, and not on an individual case basis. This situation contrasts with the circumstances characteristic of other common, largely by chance (random, "stochastic", or "accidental") injuries and deaths (e.g., auto accidents, electrical shock deaths, severe and/or lethal drug reactions, falls, drownings, etc.). Here, cause and effect on an individual basis is immediately evident. With carcinogenesis, however, no individual case of cancer can

at present be identified, other than on a probabilistic basis, with any radiation exposure regardless of dose.

3) Radiogenic cancer is difficult to demonstrate at high doses, and essentially impossible to observe or quantify at low doses even with very large populations. The normal or background incidence of cancer is very large (about 400,000 cancer deaths/yr in the United States). Thus, although a large amount of data has been accumulated on human populations exposed to low doses of radiation, these data are all "negative" in the sense that no detectable increase in incidence has been observed. The incidence is too small at low doses to allow one to differentiate any possible increase from the large background incidence. The "signal to noise ratio" is simply too small.

4) From radiobiological experience in lower biological systems (see foregoing) and from theory it can be postulated reasonably that there is "no threshold" for genetic effects, and for a number of induced cancers. Thus the oft-heard warning, "any amount of radiation, no matter how small, has some probability of producing harm in a population." (The phrase, "has some probability of producing" often is erroneously translated "will cause some harm".) The first statement would be equally accurate if reversed and expressed positively, i.e., "the odds are heavily in one's favor that with any given low dose of radiation, there is almost no chance at all of inducing harm of any kind in an exposed individual or in a population".

5) To estimate the potential for a given effect at low doses, it is necessary to interpolate (often mislabeled "extrapolate") over the low dose region. The estimated incidence of effects at low doses is of course dependent upon the shape of the curve used.

6) A major constituent of the "radiation controversy" is disagreement over the shape of the line (or curve) to be drawn to connect the data point at high doses, with zero incidence and dose. Extensive radiobiological experience with lower systems, including mutagenesis and carcinogenesis in experimental mammalian animals, indicates that the correct curve has a shape similar to that of curve A in Fig. 8. The "linear hypothesis" is illustrated by the straight line no-threshold relationship depicted as curve B, Figure 8. This relationship, although held by a few scientists to be the correct function, is considered by most scientists to represent an upper limit or "worst case" situation. A very small group of scientists feel that even the linear hypothesis is not conservative. The data used to support this position fails to hold up under close scrutiny in almost every case.

7) Radiobiological data suggest strongly that a curvilinear relationship is much more likely than is the linear hypothesis. (See studies described above, using "simple" cellular systems.)

8) The carcinogenic effects of low-dose rate exposure, as with low doses, cannot be determined adequately from human data. The data simply are insufficient to permit statistically-valid conclusions to be drawn

and hence one must rely on information from lower systems to address this question.

9) An enormous literature on dose rate effects exists. An effect of dose rate is found to be ubiquitous, both for different biological endpoints, and in different biological species and systems. Virtually without exception in eukaryotic systems and for a large number of endpoints (e.g., cell killing, chromosome abnormalities, acute effects such as skin eryghema, mutagenesis, carcinogenesis), there is a substantial dose rate effect. If a given total dose of radiation is delivered at a low rate, when compared to the same dose delivered at a high dose rate there will be a substantially lower effect. The ultimate of this process as the dose rate becomes very small is the limiting slope of the "αD" or linear component, i.e., the slope of this limiting low dose rate curve D (Fig. 8) is the same as the low-dose slope α_1 of curve A.

10) High doses delivered at low-dose rates, or in small (< 5 rad) increments, are expected to have a similar low effect per rad as does a single dose (< 5 rads) exposure. Thus most exposures incurred through diagnositc x-ray, nuclear medicine techniques or occupational exposure (small increments of exposure, separated by hours or days) can be regarded, in terms of risk/rad, as constituting low-dose rate exposure.

11) The absolute values of radiation risks are small. For all types of cancer, the effect or risk of that effect, per rad of low-LET radiation (termed variously the "risk coefficient", the slope of the

dose-effect curve, or the "damage function") for all types of induced cancer, is usually taken, as an absolute upper limit, to be no more than 100 per million persons exposed to a single dose of 1 rad[13,18,23-25]. That is to say, in a large population exposed to 1 rad, one would expect an upper limit of an additional 100 cancers per million people, for all time after that exposure (a risk of one in 10,000). This additional risk of the single one-rad exposure, in terms of risk per year is roughly 8 per million individuals exposed to 1 rad, for about 25 years following the exposure (an absolute risk of about 1 in 125,000 per year). If an additional dose rate factor were introduced, the absolute risk values would be less by a factor of 2 to 10 depending on cancer type[13]. The risks at any dose level other than 1 rad would of course be proportionally higher or lower.

12) A comparison of exposures actually sustained by American populations from different radiation sources is shown in Table I. Note that, compared to natural background which is ubiquitous and cannot be escaped entirely, actual exposures now sustained are not large. In Table II is shown the average annual risk actually experienced by American populations, from a number of familiar sources. The average annual risk of exposure of occupational workers resulting from the upper limit value of 5 rems (average of less than 0.5 rem) per year, is small compared to the risk from other familiar sources. The risk from background radiation or from diagnostic x-rays would be substantially less than this value.

13) The risks of radiation exposure are low, compared to other risks commonly encountered (see Table II). Although the fact of public exposure to one risk does not of course justify additional exposure to other risks, a comparison of doses of radiation from different sources, or of absolute radiation risks compared to other risks commonly encountered, serves to calibrate the quantitative values of either the dose or of absolute risk in terms that are more familiar and thus meaningful. Also, comparative risks have very direct and justifiable applications, in providing an objective and defensible basis for choosing among various alternative approaches to obtaining the same benefit for either the individual or for society in general (e.g., different modes of transportation, of energy production and distribution, and of obtaining diagnostic information on patients).

References

1. Finney, D. J.: Probit Analysis, 2nd Edition. Cambridge University Press, 1964.

2. Accident Facts. National Safety Council, Chicago, IL. Published Annually.

3. ICRU Report 33, Radiation quantities and units. International Commission on Radiation Units and Measurements, Bethesda, MD, 1980.

4. Kellerer, A. M.: Microdosimetry and its implication for the primary processes in radiation carcinogenesis. Biology of Radiation Carcinogenesis edited by J. M. Yuhas, R. W. Tennant and J. D. Regan. Raven Press, NY, 1976.

5. Rossi, H. H.: The role of microdosimetry in radiobiology. Radiat. Environ. Physics 17:29-40, 1979.

6. Bond, V. P.: The conceptual basis for evaluating risk from low-level radiation exposure. "Critical Issues in Setting Radiation Protection Dose Limits". Proceedings, 17th Annual Meeting, NCRP, 8-9 April 1981.

7. Bond, V. P.: A stochastic approach to explaining radiation quality and temporal influences. Chapter of book, Radiation Carcinogenesis. A. C. Upton, R. E. Albert, F. Burns, and R. Shore, eds. Elsevier-North Holland, 1982.

8. Bond, V. P.: A stochastic basis for curve shape, RBE and temporal dependence. Proceedings, Radiation Carcinogenesis Conference. NIH, Bethesda, MD. 1982.

9. Bond, V. P. and Varma, M. N.: The threshold-microdosimetric approach in radiation. Abstract presented at Radiation Research Meeting, Minneapolis, Minn., 1981.

10. Bond, V. P. and Varma, M. N.: A stochastic, weighted hit size theory of cellular radiobiological action. To be published in the proceedings of the Eighth Symposium on Microdosimetry, Jülich, Germany, September 1982.

11. Bond, V. P.: A basis for estimating the risks of low-level radiation. Medical Physics Monograph No. 5, Biological Risks of Medical Irradiations. Edited by G. D. Fullerton, American Institute of Physics, 1980.

12. Skarsgard, L. D., Kihlman, B. A., Parker, L., Pujara, C. M., and Richardson, S.: Survival, chromosome abnormalities and recovery in heavy ion and x-irradiated cells. Radiat. Res. Supp. 7:208-221, 1967.

13. NCRP Report 64, Influence of dose and its distribution in time on dose-response relationships for low-LET radiations. National Council on Radiation Protection and Measurements, Washington, DC, 1980).

14. Booz, J.: Mapping of fast neutron radiation quality. Proceedings, Third Symposium on Neutron Dosimetry in Biology and Medicine, Munich, Germany, 1977.

15. Bond, V. P., Fliedner, T. M. and Archambeau, J. O.: Mammalian Radiation Lethality Monograph, Academic Press, New York, 1965.

16. Bond, V. P. and Sugahara, T.: Comparative Cellular and Species Radiosensitivity. Ikagu Shoin Ltd. Tokyo.

17. Conard, R. A., et al.: Review of Medical Findings in a Marshallese Population Twenty-Six Years After Accidental Exposure to Radioactive Fallout. Brookhaven National Laboratory, New York. BNL Report 51261, 1980.

18. Reactor Safety Study (The "Rasmussen Report"). Appendix VI; Calculations of reactor accident consequences. Nuclear Regulatory Commission, Washington, D.C., 1975.

19. Hübner, K. F. and Fry, S. A.: The medical basis for radiation accident preparedness. Elsevier/North Holland, 1980.

20. Sparrow, A., Underbrink, A., Rossi, H.: Mutations induced in Tradescantia by small doses of X-rays and neutrons: Analysis of dose-response curves. Science 176:916-921, 1972.

21. Underbrink, A., Kellerer, A., Mills, R., Sparrow, A.: Comparison of X-ray and gamma ray dose-response curves for pink somatic mutations in Tradescantia clones 02. Rad. Environ. Biophys. 13:195-303, 1976.

22. Nauman, C., Underbrink, A. G., Sparrow, A. A.: Influence of radiation dose rate on somatic mutation induction in Tradescantia stamen hairs. Radiat. Res. 62, 79-96, 1975.

23. United Nations Scientific Committee on Effects of Atomic Radiations, "UNSCEAR" reports; 1972 and 1977 reports. Available from United Nations, New York.

24. National Academy of Sciences. The "BEIR" Committee Report. Biological Effects of Ionizing Radiation. NAS/NRC, 1972 ("BEIR I"). Revised in 1980 ("BEIR III" report), 1979.

25. Upton, A. C.: The biological effects of low-level ionizing radiation. Scientific American 246:41-56, 1982.

26. Ullrich, R. L., Jernigan, M. C., Storer, J. B.; Neutron carcinogenesis; dose and dose rate effects in BALB/c mice. Radiat. Res. 72:487-499, 1977.

27. Ullrich, R. L., Storer, J. B.: The influence of dose-dose rate and radiation quality on radiation carcinogenesis and life shortening in RFM and BALB/E mice. I.A.E.A. paper, I.A.E.A.-SM-224/204. Vienna 13-17 March 1978.

Figure Captions

Fig. 1. Typical pharmacological curves for the severity of organ injury, curve A, and the probability of an organ quantal response, curve B. Curve A is also that for the incidence of killed cells, causing the organ damage. Curve B' is the derivative of curve B and represents the normal distribution of organ sensitivities that cannot be observed directly (i.e., other than by differentiating the observed integral curve B.

Fig. 2. Curves showing the incidence of hit and injured organs (I_H), and those organs responding quantally (I_q), vs. exposure (see text).

Fig. 3. The spectrum of hit sizes for a given exposure such as E_1 in Fig. 1. The incidence of hit individuals is plotted against the size of hit.

Fig. 4. Schematic exposure-incidence curves for the incidence of hit cells I_H, and for those cells responding quantally, I_q, for radiations of different LET. The curves are sithout threshold because, no matter how small the exposure of a cell(s) in a field of charged particles, there is always a non-zero chance that, a) a cell will be involved in an encounter with a charged particle (curve I_H), and b) the amount of energy transferred will be large enough to cause a transformation or quantal response in the cell (all curves for I_q).

Fig. 5. Example of "dose-response" curves for quantal effects in cells. Note that the initial part of all curves, for even the lowest-LET radiation are linear and without threshold[12].

Fig. 6. A plot of the same type of cell response curve shown in Fig. 5, but plotted on log-log coordinates to show that, when enough cells are scored, the expected initial linearity is in fact seen. The biological system used in pink mutations in the stamen hairs of Tradescantia, of which only the distal 2 or 3 cells are mutable[13].

Fig. 7. Transition from LLRE to HLRE. Curve A is both an exposure-incidence curve for the population of relevant cells of an organ, and a dose-injury or "dose effect" curve for the organ. Curve B is a dose-quantal response curve for the organ, for organ failure due to cell population depletion. The zones in which Φ and dose are appropriate are shown on the abscissa.

Fig. 8. Schematic curves of incidence vs. absorbed dose. The curved solid line for high absorbed doses and high dose rates (curve A) is the "true" curve. The linear, no threshold dashed line (curve B) was fitted to the three indicated experimental points and the origin. Slope α_1 indicates the essentially-linear portion of curve A at low doses. The dashed curve C, marked "low-dose rate", slope α_{Ex}, represents experimental high-dose data obtained at low dose rates. This experimental low dose rate curve may in principle, at very low dose rates, approach or become indistinguishable from the extension of the solid curve of slope α_1, or the dashed curve D labeled "limiting slope (α_1).

Fig. 9. Dose-response curves for pink mutant events/hair after X-irradiation at 0.05 and 0.5 rad/min (combined in one line), 5 and 30 rad/min. The dashed lines represent the alpha terms in Eq. 1, for x-rays and gamma rays.

Fig.10. Effect of dose rate on the effectiveness of a single large dose of about 80 rad, for induction of pink mutations in Tradescantia. The horizontal line represents the expected limiting low dose rate value for 80 rad (i.e., from the linear term of Eq. 1, the value would be $2.1 \times 10^{-4} \times 80 = 0.017$). Note that the effect per 80 rad decreases appreciably as the exposure time is increased, and that the effect/80 rad at the lowest dose rates approaches asymtotically the limiting "αD" value for gamma radiation.

Fig. 11. The linear-quadratic dose response curve for Tradescantia, with the linear and squared components plotted separately (a "cell killing" factor would be needed to describe the high dose region of the curve marked "$\alpha_1 D + \beta D^2$").

Fig. 12. Incidence of myeloid leukemia in RF male mice. Shaded symbols denote results obtained with fast neutron irradiation; open symbols denote results obtained with X-rays. Solid lines denote results obtained with acute (single) exposures; dashed lines denote results obtained with chronic (23-h, daily) exposures.

Fig. 13. Incidence of Harderian gland tumors in RFM mice after ^{137}Cs gamma ray irradiation, following exposure at high vs. low dose rates.

Table I. U. S. Population Exposure

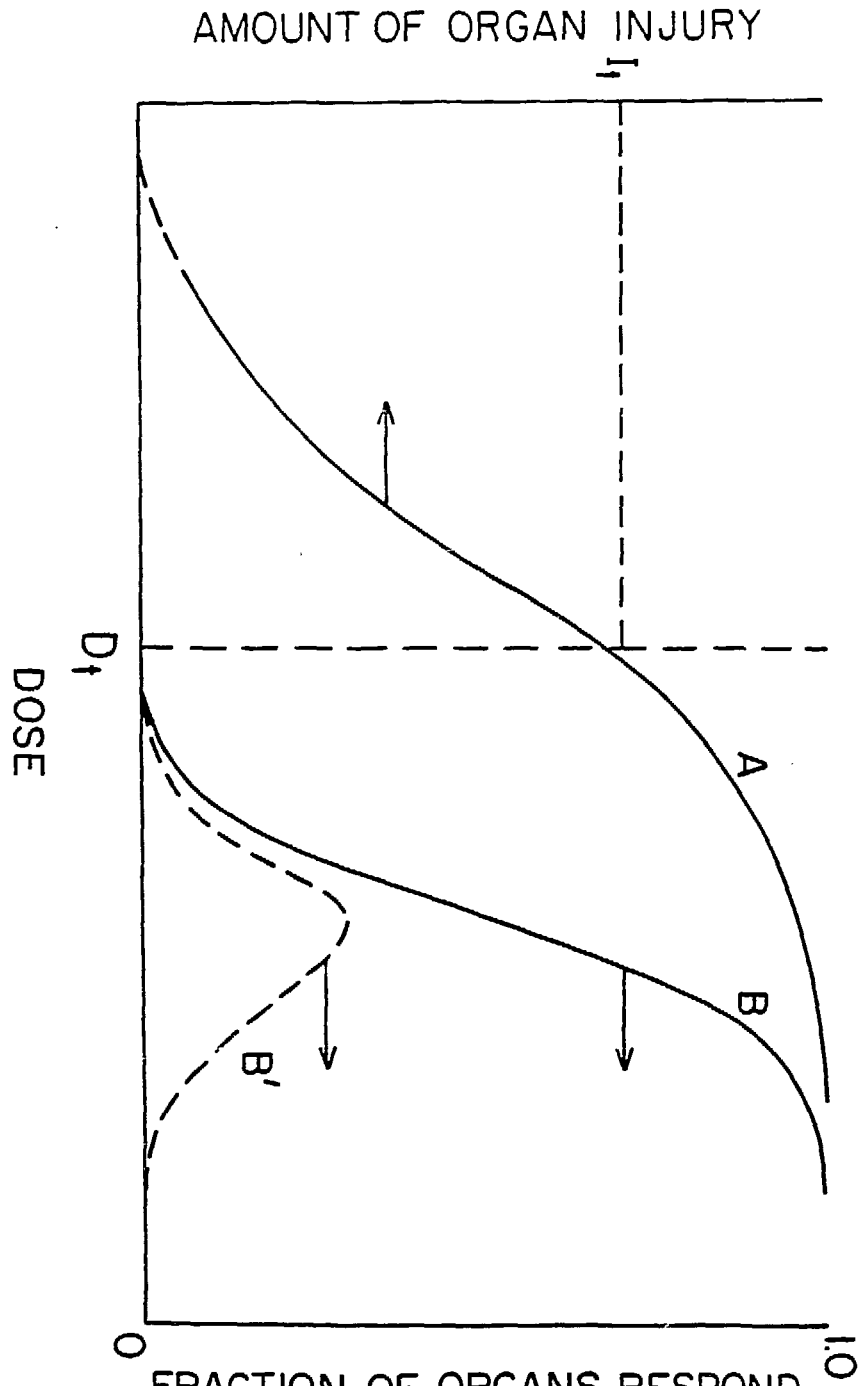
	Avg. Dose mrem/yr.
Natural background	100-150
Diagnostic X-ray	50-150
The "Standards"	170
weapons testing	3
jet travel, watches, color TV, etc.	1
Nuclear power plants	less than 0.001

Annual radiation doses from some of the sources to which the U.S. population is exposed. These are presented as a "calibration scale" to allow one to put a given annual exposure rate into perspective. (The "Standards" refers to the average dose for the general public.) If exposure to the lungs from radon gas from sources such as masonry construction materials are included, the natural background rate would be nearly double the figure given in the table.

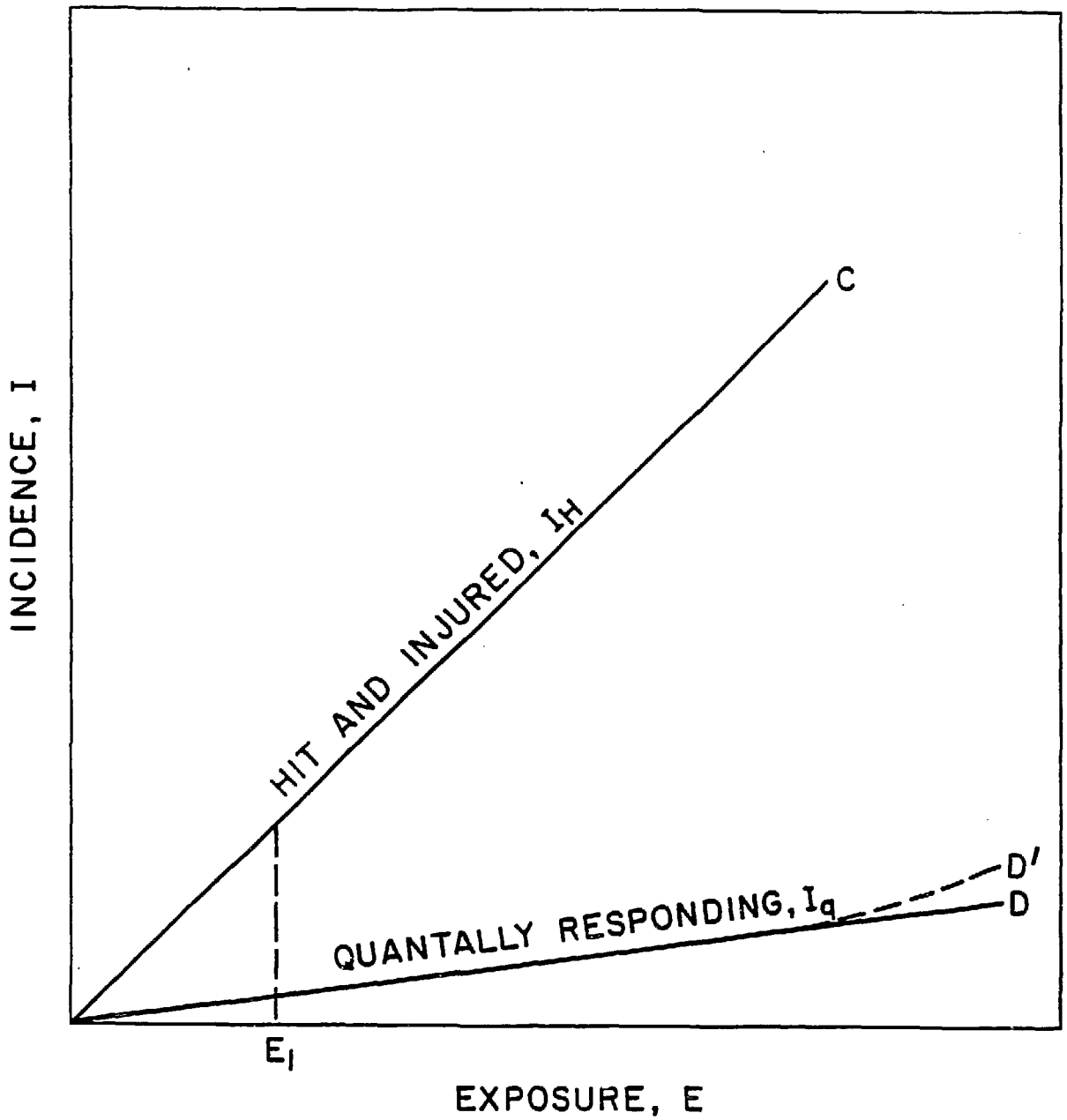
Table II. Chance of Serious Injury or Death-Per Year

Auto accident (disability)	1	chance in	100
Cancer, all types and causes	1	" "	700
Cancer from smoking	1	" "	2,000
Auto death	1	" "	4,000
Fire death	1	" "	25,000
The "Pill" death	1	" "	25,000
Drowning	1	" "	30,000
Electrocution	1	" "	200,000
Airplane trip, New York City-San Francisco and return	1	" "	1,000.000
Reactor Emanations; site boundary (5 to 10 mrem/yr.)	Less than 1	" "	1,000,000
Average for population within 50 miles of reactor	Less than 1	" "	10,000,000

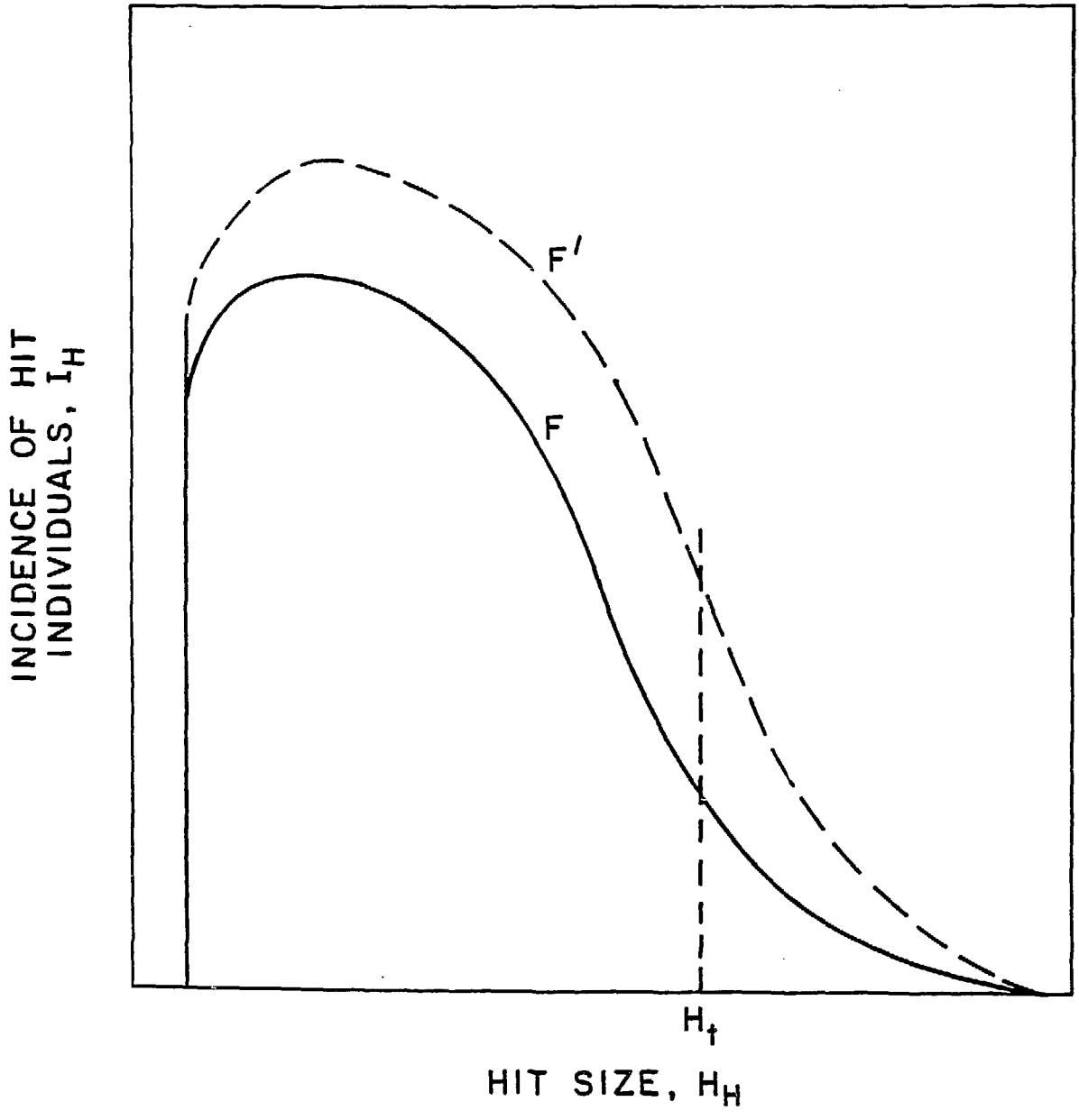
Annual risk rates in the U.S. population from various activities.


AMOUNT OF ORGAN INJURY
1
DOSE
$D_{\frac{1}{2}}$
A
B
B'
0
1.0
FRACTION OF ORGANS RESPONDING QUANTALLY (CURVE B), OR DISTRIBUTION OF SENSITIVITIES OF NORMAL ORGANS (CURVE B')

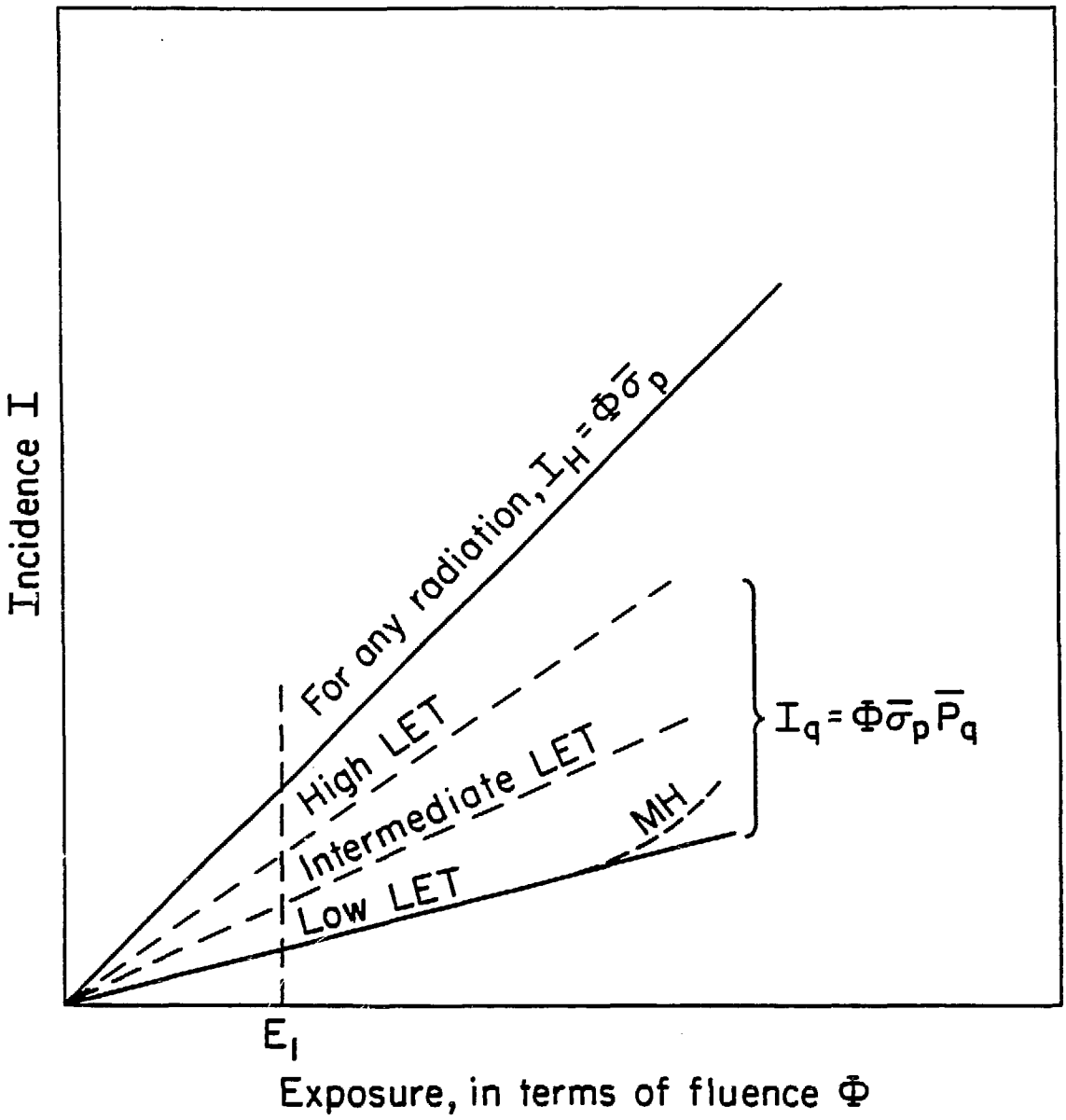
3-1068-83


INCIDENCE, I
C
HIT AND INJURED, I_H
D'
QUANTALLY RESPONDING, I_q
D
E_1
EXPOSURE, E

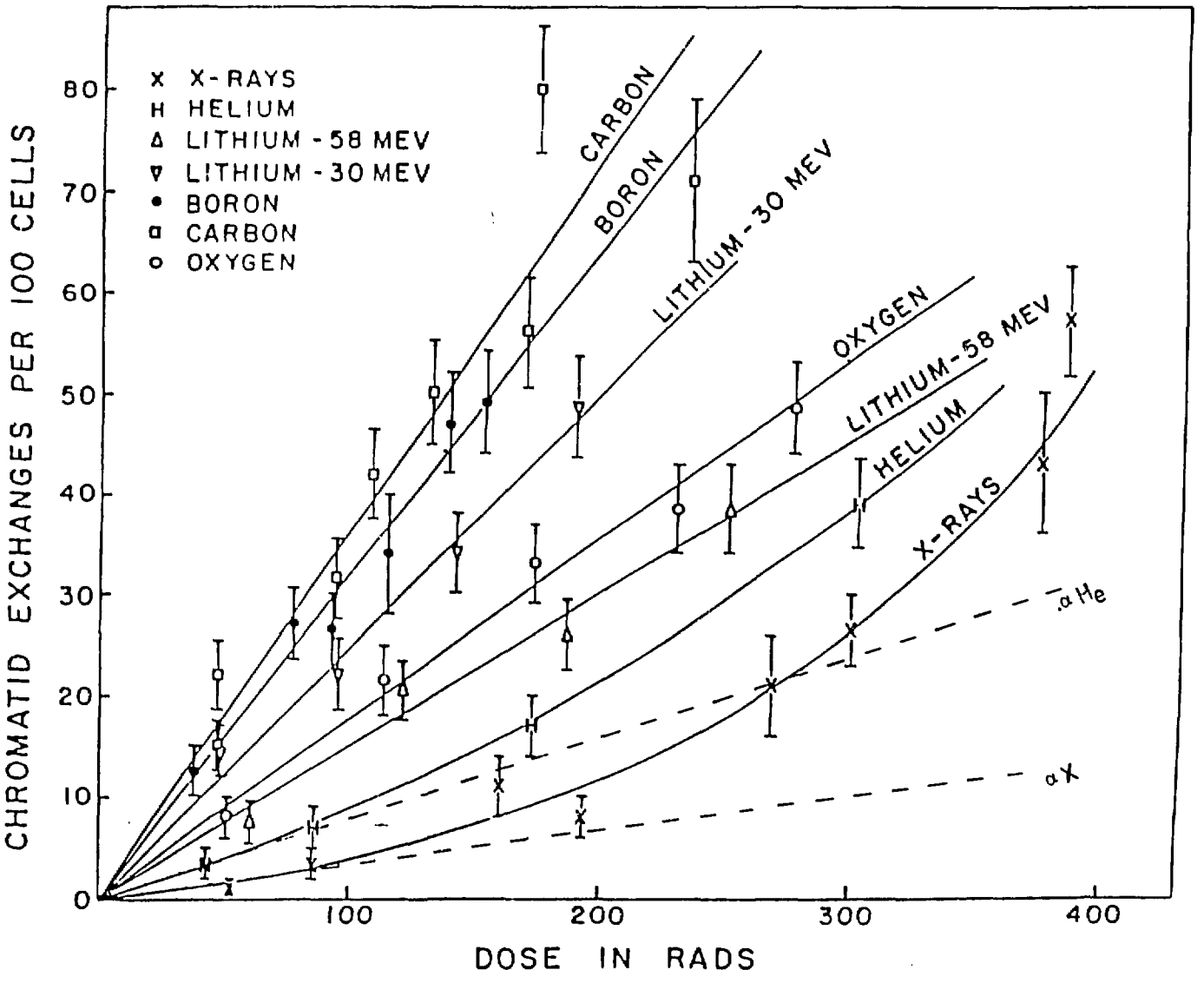
3-919-83



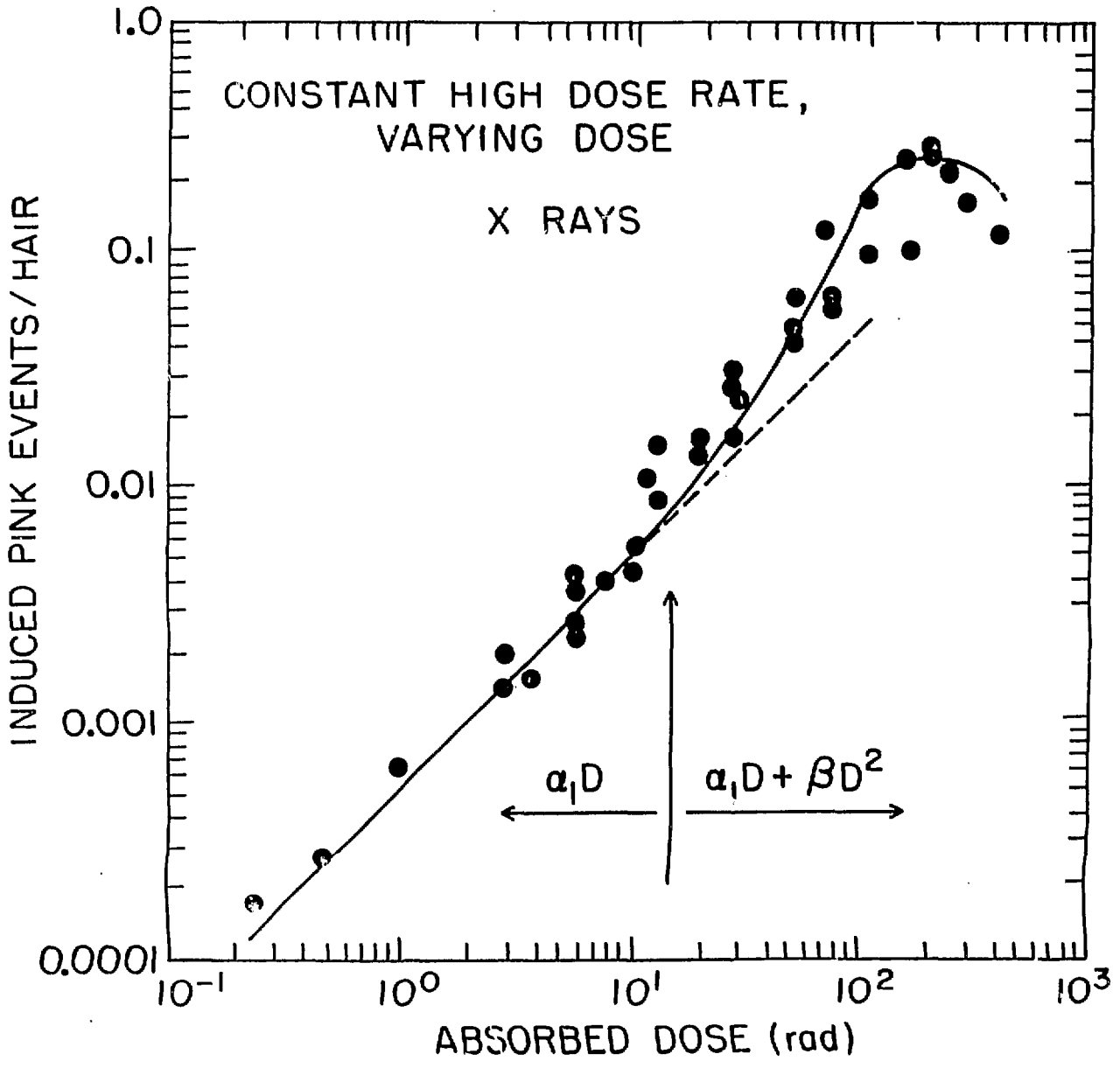
3-918-83


Incidence I
For any radiation, $I_H = \Phi\bar{\sigma}_p$
High LET
Intermediate LET
Low LET
MH
$I_q = \Phi\bar{\sigma}_p\bar{P}_q$
E_1
Exposure, in terms of fluence Φ

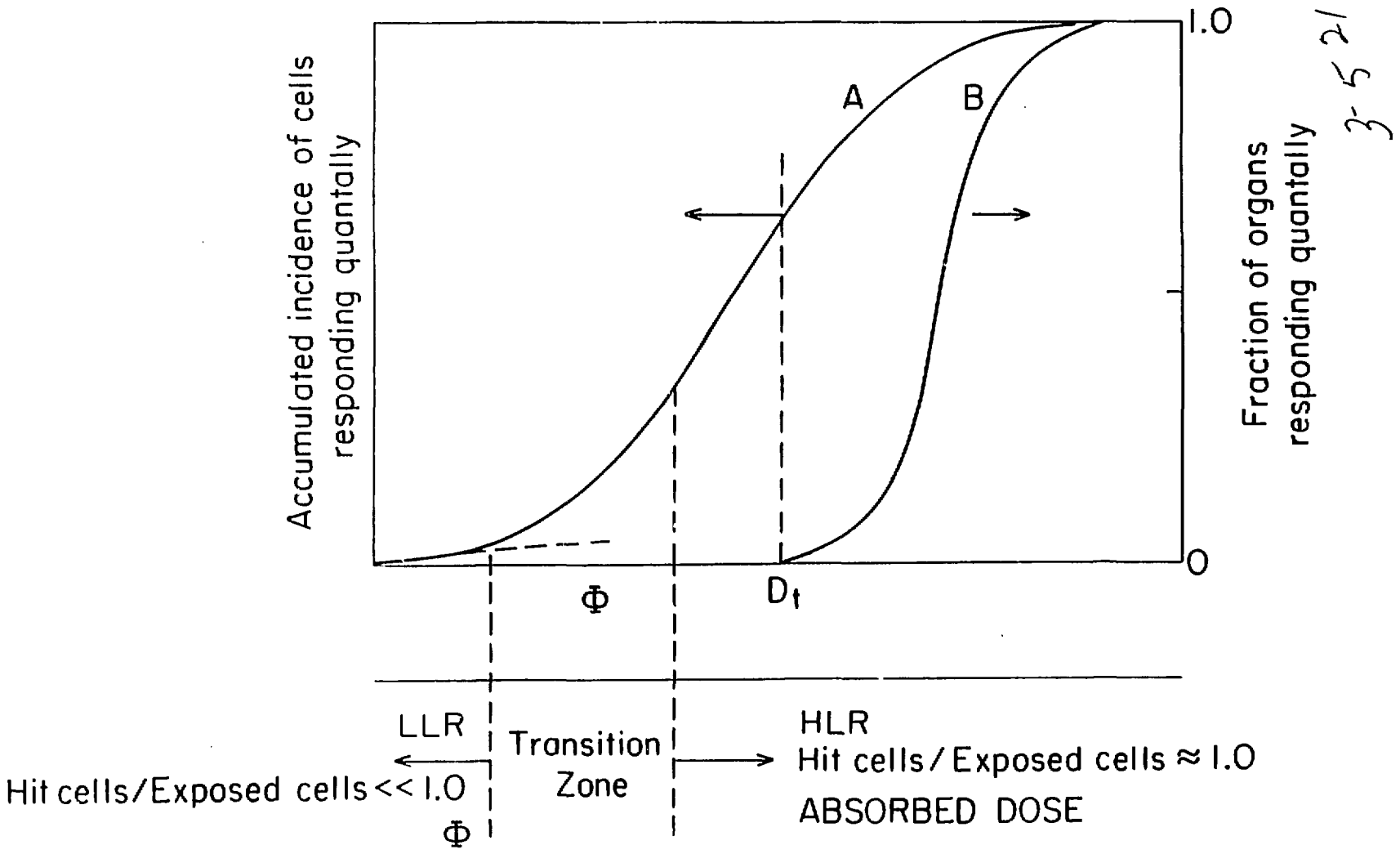
3-917-83


X X-RAYS
H HELIUM
Δ LITHIUM - 58 MEV
▽ LITHIUM - 30 MEV
• BORON
□ CARBON
○ OXYGEN
CARBON
BORON
LITHIUM - 30 MEV
OXYGEN
LITHIUM - 58 MEV
HELIUM
X-RAYS
αHe
αX
CHROMATID EXCHANGES PER 100 CELLS
DOSE IN RADS
0
10
20
30
40
50
60
70
80
100
200
300
400

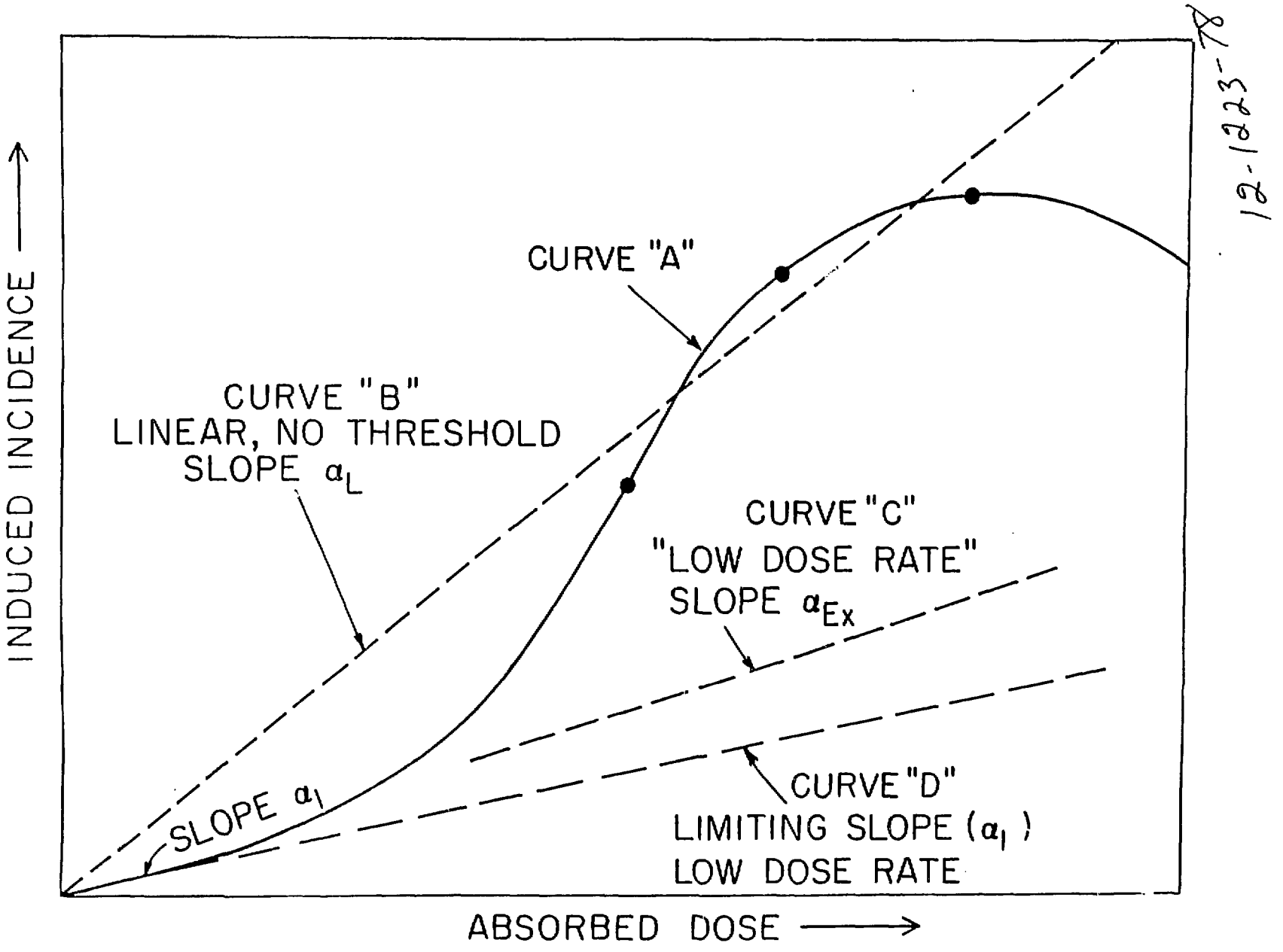
8-31-81

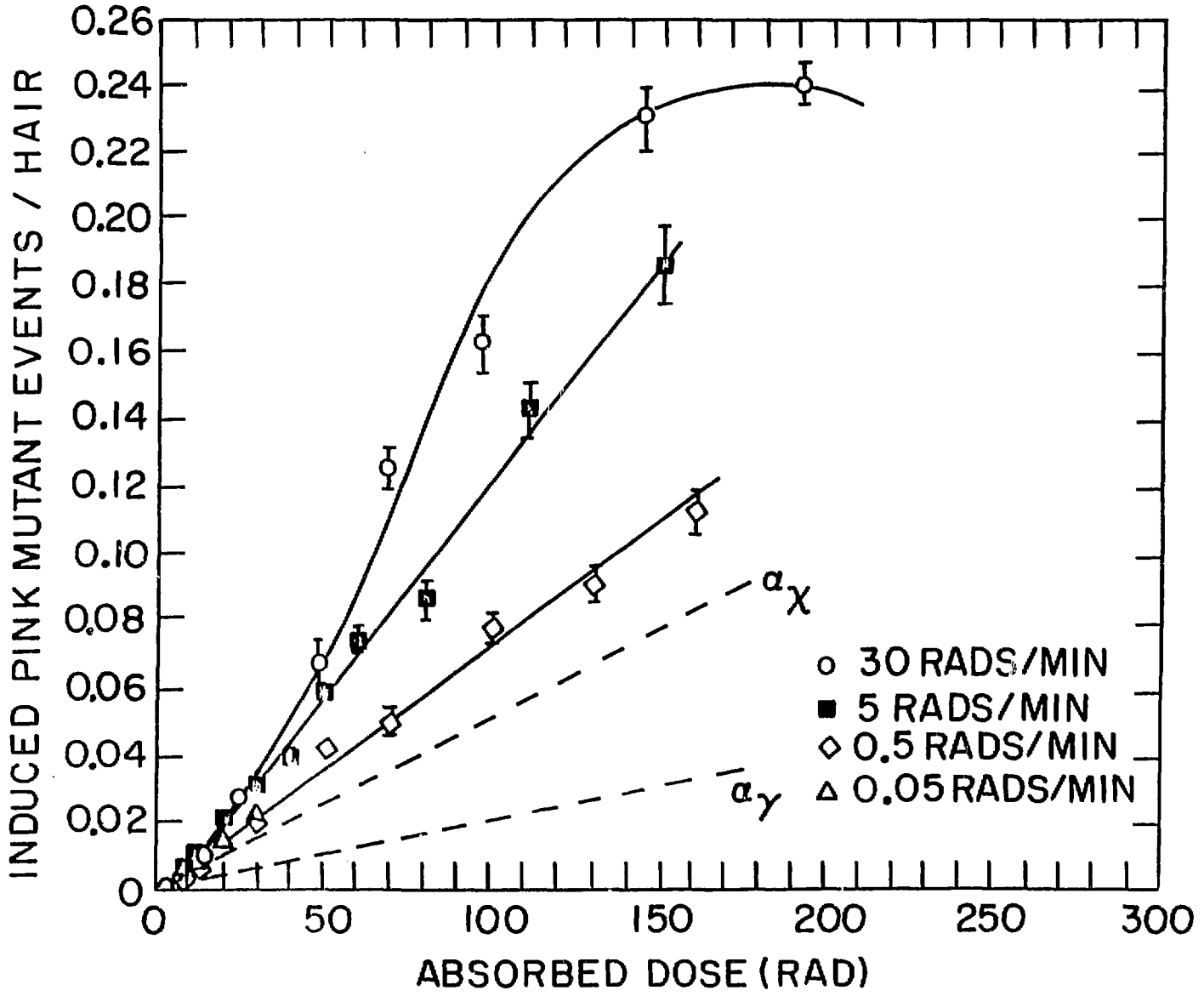

CONSTANT HIGH DOSE RATE,
VARYING DOSE
X RAYS
INDUCED PINK EVENTS / HAIR
1.0
0.1
0.01
0.001
0.0001
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
ABSORBED DOSE (rad)
$\alpha_1 D$
$\alpha_1 D + \beta D^2$

10-35-78

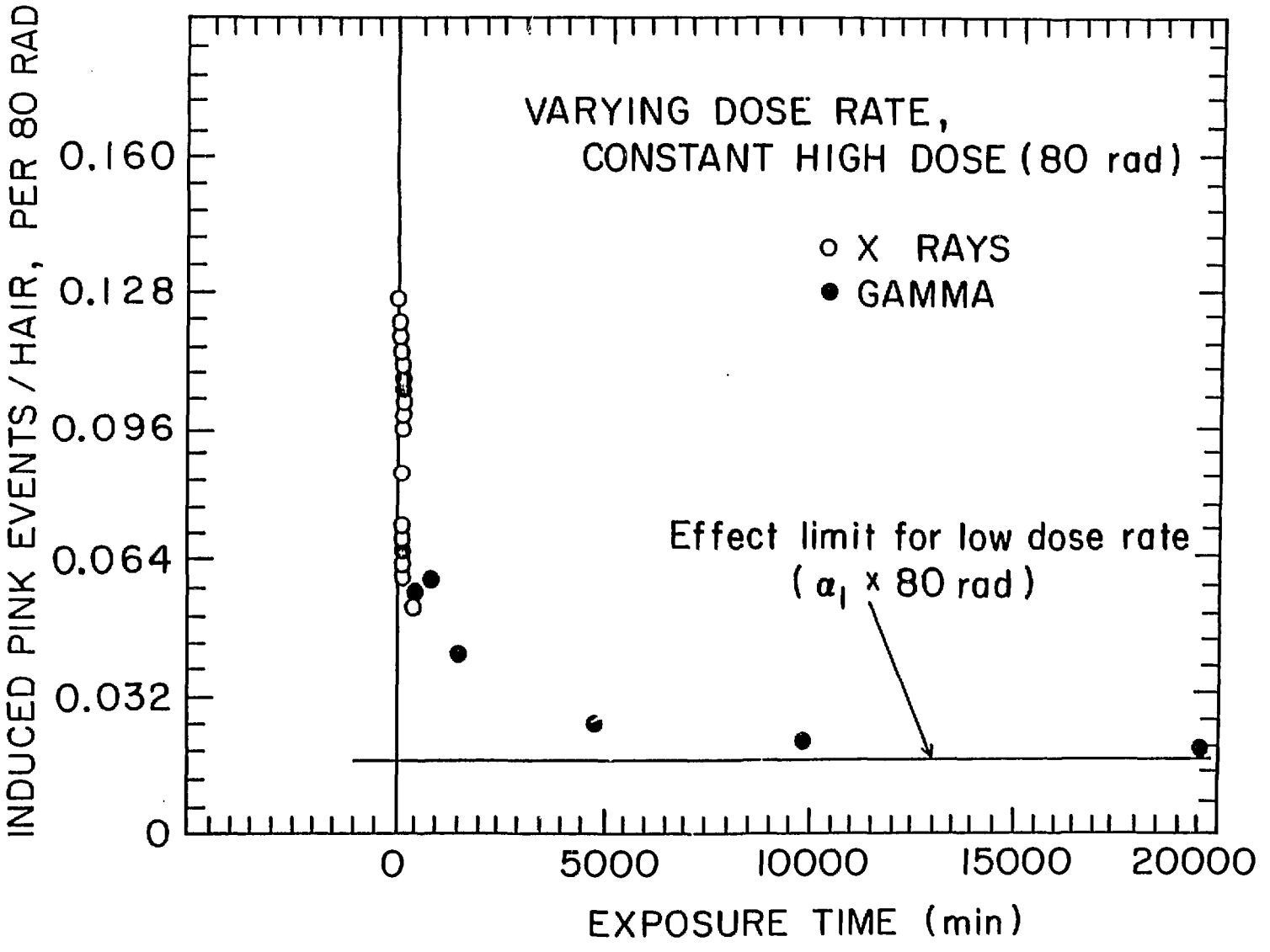

Accumulated incidence of cells responding quantally
Fraction of organs responding quantally
1.0
0
A
B
Φ
D_t
LLR
Hit cells/Exposed cells << 1.0
Φ
Transition Zone
HLR
Hit cells/Exposed cells ≈ 1.0
ABSORBED DOSE

3-5-21-8-3

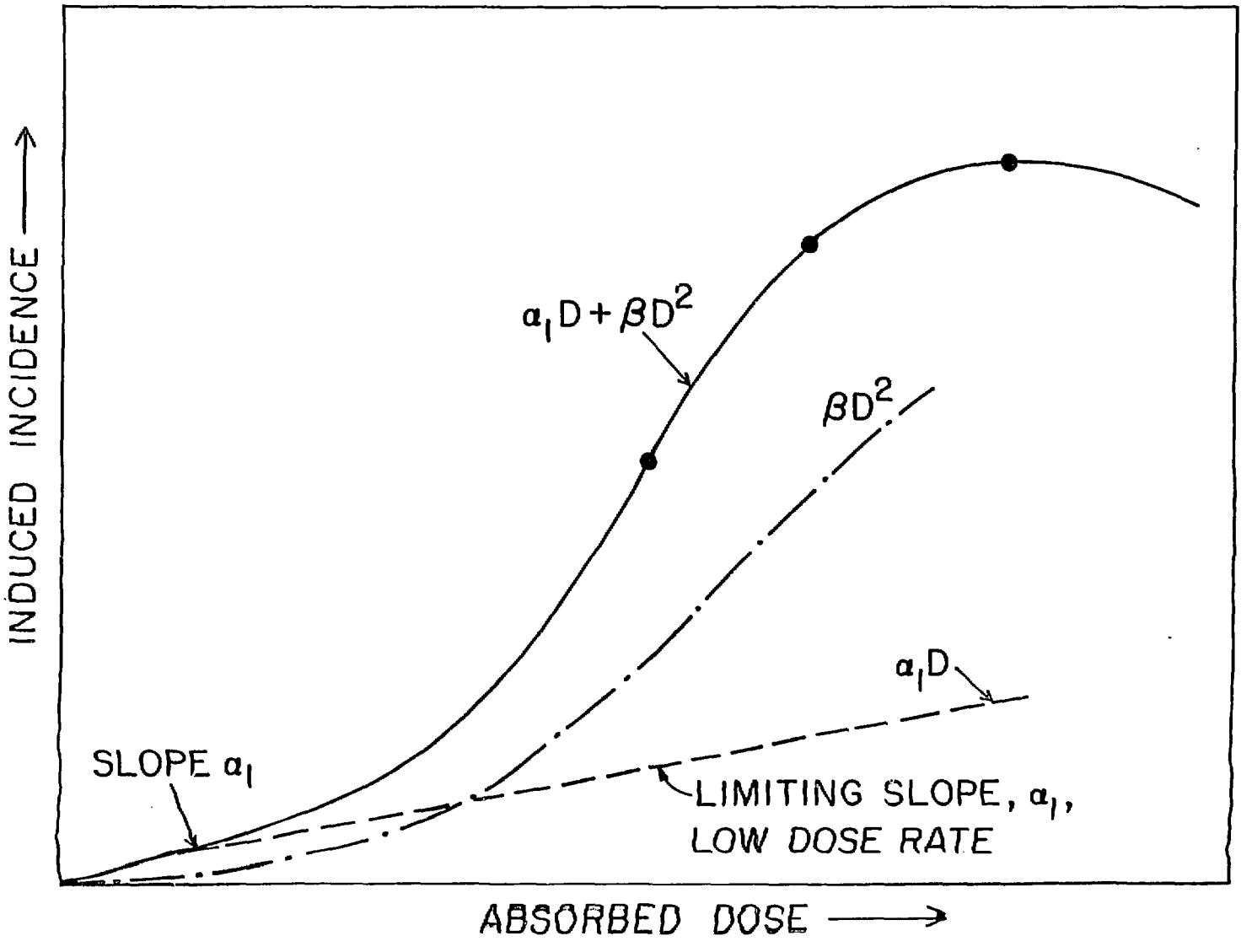

INDUCED INCIDENCE
ABSORBED DOSE
CURVE "A"
CURVE "B"
LINEAR, NO THRESHOLD
SLOPE α_L
CURVE "C"
"LOW DOSE RATE"
SLOPE α_{Ex}
CURVE "D"
LIMITING SLOPE (α_1)
LOW DOSE RATE
SLOPE α_1
12-1223-A


INDUCED PINK MUTANT EVENTS / HAIR
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
ABSORBED DOSE (RAD)
α_χ
α_γ
o 30 RADS/MIN
■ 5 RADS/MIN
◇ 0.5 RADS/MIN
△ 0.05 RADS/MIN

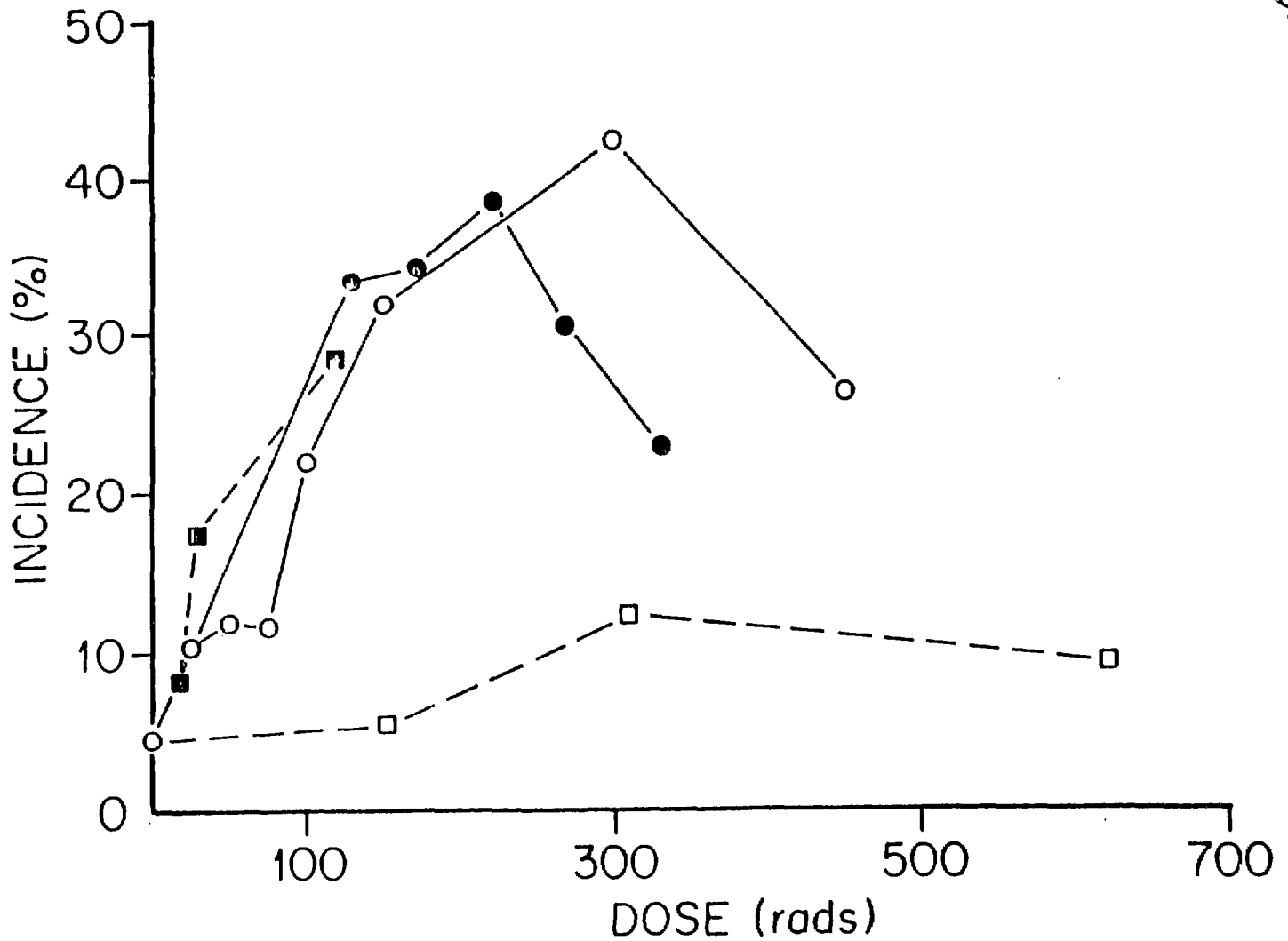
12-12 19-78


VARYING DOSE RATE,
CONSTANT HIGH DOSE (80 rad)
o X RAYS
● GAMMA
Effect limit for low dose rate
(α_1 x 80 rad)
INDUCED PINK EVENTS / HAIR, PER 80 RAD
0.160
0.128
0.096
0.064
0.032
0
0
5000
10000
15000
20000
EXPOSURE TIME (min)

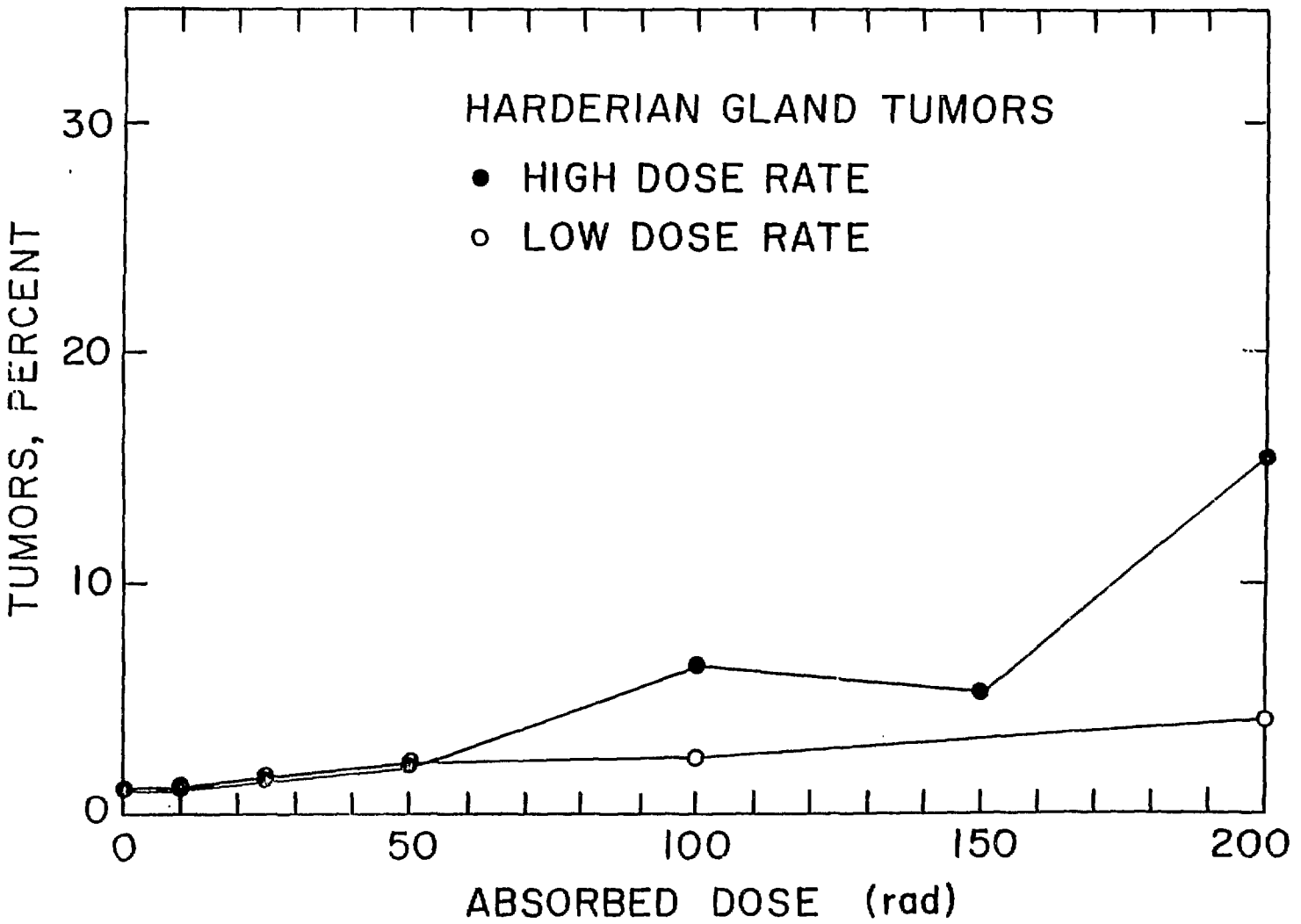
87-94-01


INDUCED INCIDENCE
$\alpha_1 D + \beta D^2$
βD^2
$\alpha_1 D$
SLOPE α_1
LIMITING SLOPE, α_1,
LOW DOSE RATE
ABSORBED DOSE

10-36-78



12,799-78


HARDERIAN GLAND TUMORS
HIGH DOSE RATE
LOW DOSE RATE
TUMORS, PERCENT
30
20
10
0
0
50
100
150
200
ABSORBED DOSE (rad)

4-1367-78