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A Different Approach to Evaluating Health Effects from Radiation Exposure*

V. P. Bond[1], C. A. Sondhaus[2], and L. E. Feinendegen[3]

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1 Brookhaven National Laboratory
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2 Army Chemical School, Radiation Laboratory, Fort McClellan, Alabama
3 Laboratory for Nuclear Research (KFA), Juelich, FRG

ABSTRACT

Absorbed dose D is shown to be a composite variable, the product of the fraction of cells hit (I_H) and the mean "dose" (hit size) $\bar{z}$ to those cells. D is suitable for use with high level (HLE) to radiation and its resulting acute organ effects because, since I_H = 1.0, D approximates closely enough the mean energy density in the cell as well as in the organ. However, with low-level exposure (LLE) to radiation and its consequent probability of cancer induction from a single cell, stochastic delivery of energy to cells results in a wide distribution of hit sizes z, and the expected mean value, $\bar{z}$, is constant with exposure. Thus, with LLE, only I_H varies with D so that the apparent proportionality between "dose" and the fraction of cells transformed is misleading. This proportionality therefore does not mean that any (cell) dose, no matter how small, can be lethal. Rather, it means that, in the exposure of a population of individual organisms consisting of the constituent relevant cells, there is a small probability of particle-cell interactions which transfer energy. The probability of a cell transforming and initiating a cancer can only be greater than zero if the hit size ("dose of energy") to the cell is large enough. Otherwise stated, if the "dose" is defined at the proper level of biological organization, namely, the cell and not the organ, only a large dose z to that cell is effective. The above precepts are utilized to develop a drastically different approach to evaluation of risk from LLE, that holds promise of obviating any requirement for the components of the present system: absorbed organ dose, LET, a standard radiation, REB(Q), dose equivalent and rem.

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INTRODUCTION

Radiation is one of the few, if not the only agent of interest in the health sciences that spans the entire range from constituting an ubiquitous environmental agent of concern, to being an effective therapeutic agent for the control of cancer. These characteristics place the former in the realm of public health including epidemiology (Ph); the latter in the discipline of pharmacology, toxicology, and medicine (Md). The same characteristics divide low-level exposure (LLE) to radiation, from high-level exposure (HLE).

The basic radiation quantities and units in current use and defined by the ICRU (1) were developed during that era in which essentially the sole focus was on diagnostic and therapeutic uses, and largely on the early acute effects on an organ or a tumor: clearly in the Md realm. Thus, the description and quantification of these effects of HLE could, and still can be comfortably accommodated by those quantities and units adopted early during this period. These consisted mainly of organ or tumor exposure, proportional to absorbed dose, on which depends the fraction of organs or tumors responding quantally (i.e., an all-or-nothing change of state, from functional, to essentially permanent or lethal dysfunction).

However, the above happy state of affairs was not achieved without considerable discussion and disagreements about how the "amount" or quantity of radiation was to be defined. In the physicist's eye, this quantity was the total energy flow from a source, per unit area, i.e., the energy fluence times the exposure time. On the other hand, from the physician's standpoint, the amount of radiation in the ambient field was regarded as irrelevant: what mattered was considered to be that which was actually absorbed in tissue. In fact, the "skin erythema dose" unit of radiation "amount" had already been invented and used, which by-passed any physical measurement beyond the amount of time spent in a radiation field celebrated with such a "biological dosimeter".

The two views were eventually resolved, but only after the second meeting of the ICRU in 1928 (1). At this gathering the "quantity" of x-radiation was defined as the Roentgen, equal, with additional detailed specifications, to one electrostatic unit of charge in one cc of air. It seems evident that the word "quantity" was to be interpreted in the physical sense, i.e., as a measure of the energy fluence. However, due in part to ambiguity among the words "amount", "quantity", and "dose", and in part to the fact that air and tissue have close to the same electron density, the physicist's "quantity" of radiation was equal-, or proportional to the physician's "amount", i.e., dose. Thus almost immediately the Roentgen was widely described as the unit of x-ray "dose". The ICRU in time endorsed this preemptive move, as evidenced by the later adoption of the "rep" and then the rad as the unit of absorbed dose. With improved instrumentation and the use of phantoms for measurement in depth, this system has continued to work well for HLE, even when high-LET radiations, necessitating the use of the concept of relative biological effectiveness (RBE), were introduced into the radiotherapy of tumors. The basic principle involved in the above problem can be stated as follows: For a physician (or anyone) to estimate the probability of a serious or labeled consequence of stochastic agent transfer, preferred is an evaluation of the severity of injury sustained by the casualty. Lacking this, an estimate of the dose is the next fall-back position. Exposure is of little or no help in this regard. That is to say, needed for prognosis evaluation in an object-oriented quantity, measured in or for the individual of concern.

Low-Level Radiation Exposure

It was observed quite early that cancer could result from HLE. However, only much later was it widely appreciated that the "single cell-originating" effects, cancer and heritable effects, must also be taken seriously, even at very low doses, or larger doses at very low dose rates, i.e., following LLE. It was also apparent that the basic phenomena involved fell into the category of Ph, particularly its subdisciplines of epidemiology and accident statistics. However, no effort was made to adjust the basic quantities and units as demanded by this different

discipline. It apparently was tacitly assumed, since the expression of a tumor is observed in an organ or organs, that the relevant parameter for cancer initiation should also be the absorbed dose to the organ. This practice was adopted. Absorbed dose also continued to be used for studies using "simple cell systems" for which a defined population could be regarded as a "system" to which an "organ dose" could be applied.

However, serious conceptual and operational difficulties were encountered. While a number of these problems will be detailed later in this communication, the initial objective is simply to indicate the basic reason for the difficulties associated with this attempt to use the old concepts and quantities appropriate for HLE, for LLE that requires Ph concepts. A new approach to the evaluation of risk from LLE, and how it can be applied to the evaluation of risk from LLE, is then presented, following which the method of application is described. This is then followed by a more detailed and technical description of the underlying concepts and methodologies.

The Problem and the New Approach

A fact central to the need for a new approach to LLE risk evaluation will at this point simply be stated, and then later demonstrated. This is that the absorbed dose D to an organ is conceptually the quantity exposure of that organ, expressible in terms of the physical quantity fluence. That is, it is conceptually the number of primary and secondary particles per unit area, which is a parameter of the radiation source, and field of the radiation in which the cell population of an organ or other cell population of interest is exposed. Thus, in the typical organ dose-cell response curves shown in Fig. 1, the absorbed dose shown on the abscissa should be regarded conceptually although not numerically, as the exposure in terms of particle fluence, to which the cell population of an organ or other cell population of interest is exposed. Thus the basic problem appears to be conceptually identical to that encountered by the early physicians who wished to know the dose to the organ. The radiobiologist concerned with the study of single cell-initiated effects must be interested in the amount of energy deposited in the cells--not that which may be in the environment of the cells.

The solution to this problem must be in the same approach used by the physycians, who had no direct way of determining what the tumor or normal tissues were receiving from a given exposure. That is to say, one must use a "cell phantom" if one wishes to estimate the dose to a living cell. Thus we must outline the requirements and necessary characteristics of such a cell phantom. However, in so doing we must be ever mindful that, unlike the early (and present) physicians who operated in an Md mode and required only the dose to the individual organ or tumor of interest, we must approach the problem from the Ph, i.e., epidemiological and accident statistics standpoints. This is, of course, because any transfer of radiation energy to tissues takes place only as a result of stochastic (i.e., due to random processes) encounters or collisions between a charged particle and a target-containing volume (TCV) within the cell. Thus we first need, with LLE, the (fractional) number of cells hit. Also, because energy is deposited in the TCV in separate, discrete amounts, we need also the amount of energy deposited, i.e., the "hit size" or "cell dose". The magnitude of the cell dose varies greatly from cell to cell, and ranges from zero to the maximum amount of kinetic energy carried by the particle. Thus the dose, to be relevant, must be registered in individuals at the level of biological organization at which the initation of the response of interest occurs. The important conclusion is that, while with HLE only the one physical quantity organ dose is required for risk evaluation, with LLE *at least two independent quantities are required.*

The first requirement, to be able to register the number of cells hit and dosed during any given exposure period requires that the phantom be electronic. It can then have the short recovery time needed in order that many hits per cell can be recorded (i.e., if a number of phantom cells register a total of x hits during an exposure time t, then a single rapidly recovering cell will also register x hits during a time xt). This property of the phantom will, with use of the appropriate scaling factor, provide us with the first of at least two probabilities[1] needed in principle for epidemiological evaluation, namely, the number of hits per cell, equal numerically to the probability that a cell will be hit, dosed, and injured.

[1]The number in a group expected to respond quantally after a given exposure provides the numerical probability that such a response will occur. Thus, the term probability will be used interchangeably with the terms "fraction" or "proportion" of equally dosed quantal responders and the term "risk" will be used interchangeably with the proportion or incidence of stochastically, and thus unequally-dosed quantal responders.

Next, the phantom must record separately for every discrete hit on the phantom cell, the magnitude of the energy deposited. That is to say, it must provide the distribution of the magnitudes of the energy deposits in the cell TCV's, or the cell doses. This distribution of cell doses must be obtainable for any given exposure to a single type of radiation, or any mixture.

THe electronic phantom can be made to arrange the stochastic cell doses neatly in order of increasing magnitude. Thus we have the exact analogue of what is commonly used in pharmacology and toxicology--a graded series of cell doses, which in principle permits us to develop a function for the (fractional) number of hit cells that will respond quantally, at each value of cell dose. This is the cell analogue of the "organ dose-organ response" curve. This fraction is equal to the conditional probability that, if hit, and with a dose of a given magnitude, a cell will respond quantally. Such curves are now available, for several cellular end points. We thus have three probabilities to be evaluated, 1) the probability that an exposed cell will be hit, 2) that the hit cell will be of a given range with a given size, and 3) will respond quantally. It is these probabilities that permit us to determine, for a given exposure, the fraction of those exposed that will respond quantally.

An example will help to clarify the above statements. In Fig. 2 are shown schematically three distributions of cell doses from stochastic particle collisions, one for each of three exposures, and all for a radiation of a single quality. Note that as the exposure increases, neither the mean nor the maximum of the distributions changes--it is only the area under the distributions, i.e., the number of exposed cells that are hit, that increases. Note that these distributions represent a graded series of doses. Also shown is the S-shaped curve, an HSEF (hit-size effectiveness function), a relationship that provides the probability of a quantal response as a function of the cell dose. If the cell dose distribution is multiplied by the HSEF, the result will be the correspondingly-marked smaller distribution, under the larger one. The area under the smaller distribution provides the single and determining end point in quantitative epidemiology or risk assessment, i.e., the fraction of those exposed during a given exposure, that will respond quantally.

As will be expanded on later, what has been termed above a "cell phantom", is much more than the analogue of an organ phantom. It, rather than simply determine a dose to a single organ or organism, provides not

only the risk that a cell will be dosed and that dose will be of a given size, but also, with the HSEF, the probability that that dose will result in a quantal response. Thus the phantom should be called a "cell risk meter", rather than just a cell phantom.

Now that the basic outlines of the approach have been laid out, the necessary more detailed information on each element of the overall approach can be provided.

Organ Dose: Conceptual Exposure

In order to explain and extend the above statements, it is useful first to demonstrate the relationship between the absorbed dose to the organ and that to the cellular elements of the system. This can be done as follows:

$$D = \left(\frac{z_{1a} + z_{1b}\text{---}}{N_E}\right) = \left(\frac{z_{1a} + z_{1b}\text{---}}{N_H}\right) \cdot \frac{N_H}{N_E} = \bar{z}P_H, \quad (1)$$

in which z is a single energy deposition in the target-containing volume (TCV) of the cell, i.e., the "cell dose"; N_H and N_E are the number of hit and exposed cells, respectively, and P_H is the simple probability of a cell TCV receiving an energy deposit during exposure E, equal numerically to N_H/N_E.

However, it is well known from physics that,

$$P_H = \phi t_E \sigma = \int \sigma, \quad (2)$$

in which ϕ is the field strength measured as fluence rate (units of particles cm^{-2} t^{-1}), which express the rate of exposure (of cells) to the energy-conveying charged particles; t_E is the exposure time; $\int$ is the fluence to which the total exposure is numerically equal; and σ is the "cross section", or constant of proportionality. Thus, substituting in Eq. (1), from Eq. (2),

$$D = \bar{z}\phi_E \sigma = k \int \sigma = k'\phi$$

in which $z = k$ because, with stochastic energy deposition, and LLE, the expectation value of the mean cell dose is invariant with exposure.

Eq. (1) confirms that D to the organ system is not a dose at all, when its equivalent is provided for the level of biological organization appropriate to the "late single-cell initiated effects" of LLE, mutagenesis and carcinogenesis. Rather, it is the exposure of the cell population, expressed as $\bar{\phi}$. This is proportional to the risk of a cell being dosed, equal numerically to the expectation value of N_H/N_E. This "object-oriented quantity" is proportional to the primary independent "field-oriented" variable exposure E, expressed as $\bar{\phi}$ (see Eq. 3).

With D becoming E, a rational basis for the "linear-non-threshold" relationship is provided, i.e., although a purported linear relationship between dose and the probability of a quantal response tends to defy credulity, such a relationship between exposure E and the number of (stochastically) dosed individuals, or of those showing a quantal response is quite plausible. The fact that D is exposure and not dose also provides a significant statement of what is the basic problem when one attempts, as is done in Fig. 1, to express the biological response in terms of a single variable, i.e., as E, or the proportional parameter D. This is depicted in Fig. 3, the lower panel of which shows conceptually any one of the curves shown in Fig. 1. In the upper panel is a three-dimensional schematic, on the exposure-N_H/N_E axes which is depicted the same curve and labeled points shown in the lower panel. On the N_H/N_E-cell dose axes are the cell dose distributions, i.e., the relative numbers of cells dosed, as a function of the cell dose, z.

It then becomes additionally clear that each point in the linear curve does not represent a single value of cell dose, with all dosed individuals having received nominally the same value, as is implied in the term "dose-response" curve. Rather, each point equates to an entire distribution representing groups of cells with different doses. Such distributions are implied in Eq. (1) showing that $D = \bar{z}P_H$, in that obviously, to have a $\bar{z}$, there must exist a corresponding distribution. The number of dosed cells at each value of $\bar{z}$ represents a graded series of cell doses, identical in concept to such a series used in Md to determine the probability of an organ response curve as a function of dose.

A Cell Risk Meter: Microdosimetry

"Microdosimetry", although originally applied only in the context of the techniques devised by Rossi et al. (2-4) to measure the number of hits per cell and their magnitude, has now been extended to include both instrumental and calculational approaches to determining the same quantities.[1] It is perhaps most illuminating to describe the instrument approach.

A microdosimeter is simply a proportional counter containing tissue equivalent gas. Although the counter may be centimeters in diameter, partial evacuation and suitable scaling permits ready simulation of subcellular volumes of several microns in diameter. Each time a particle impinges on or traverses the instrument, a single "hit" is registered, and the size of the resulting "event", measured in terms of the size of the ion cascade, is taken as the magnitude of the hit, the "hit size".

Thus the instrument can be regarded as a "cell phantom", in the sense that it registers the size of the "cell dose" delivered. However, it differs in several quite significant respects from the usual macro-phantoms used in the dosimetry of organs or other tissue volumes. The recovery time of the instrument is extremely rapid, so that, with low-to-modest exposure rates, each hit is registered separately. Thus, one obtains not only the spectrum of the stochastically delivered hit sizes, but also the total

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[1]The idea of discrete, stochastic high-density energy depositions resulting from radiation exposure probably originated early with Dessauer's "point heat" theory and was certainly well appreciated by Lea (5). However, these ideas were not formally developed until the "microdosimeter" was invented by Rossi (2-4). Its use has been more in the context of a substitute for the quantity LET, to describe energy definition within a non-anatomically defined "gross sensitive volume" within the cell. The idea of a "cell dose" was probably applied first by Bond and Feinendegen (10), and developed in NCRP Report No. 63 (11). The idea of a microdosimeter being conceptually a cell phantom with which cell dose could be determined with stochastic dose delivery is relatively recent (Bond et al., Feinendegen et al., Refs. 6 and 12).

number of discrete hits for the given amount of exposure. Since the instrument represents a single cell, the readout is in terms of hits/exposed. The microdosimeter registers essentially all impinging charged particles. However, with scaling factors as large as 10^8, and with extremely small exposures, it provides hits/(hits plus unhit cells), i.e., the fraction of exposed cells hit at least once. It thus quantifies "interperspersed"partial body radiation, in which some contiguous cells are hit and others are not.

An additional important characteristic of stochastic cell particle encounters is time rate. This can be varied at will. Thus a single cell TCV can be subjected to from none up to a very large number of encounters, in an arbitrarily short period of time. Thus the instrument is much more than a dosimeter or a "microdosimeter". Rather, it provides the two basic ingredients necessary for determination of the overall risk of exposure of a population of cells, or any other organized system of elements. That is to say, it determines the number of individuals hit and affected at all, and the hit size which permits prediction of the fraction of hit cells that will respond quantally. Thus, it provides both the probability that a cell will be hit and dosed, and the means of determining, through the hit size, the conditional probability that a hit cell with a given hit size will respond quantally. (In the macro accident analogy, these two factors are referred to as the "probability" and the "severity".) Thus the approach might better be termed "cell risk methodology" and the instrument "a cell risk meter".

Examples of microdosimetric distributions, for radiations of 3 LET's are shown in Figure 4. The amount of energy deposited has been designated the "specific energy" (3,4), with dimensions the same as those of absorbed dose, namely, energy/mass. However, because of the need to use the noun additionally as both an adjective and adverb, and for brevity, it has commonly been called a "nit". Also, with the diameter of the TCV specified as a nucleus of 8 microns in diameter, the term "elementary dose" (4), and often simply "cell dose" have been employed. "Hit", "hit-size", and "cell dose" will be used here interchangeably.

Although it is also useful to distinguish between stochastically delivered as opposed to planned doses, this is to avoid confusion and not a substantive requirement. In other words, all else being equal, an organism has no physiological means of determining whether a given agent transfer has occurred stochastically or by plan.

It is only because of the above-outlined capabilities of microdosimetric methods that the enormous advantages of using the element dose approach can be realized. The instrument is "completely blind" to the type or energy of the radiation particle responsible for the given energy deposition. Thus the number of hits and the hit sizes are completely "object-oriented" quantities, on which the extent and severity of effect resulting from radiation exposure depends directly. In other words, in principle, it is unnecessary to know anything about the nature of the field in which the biological material is exposed. The large advantage of this lies not only in that it usually is quite difficult practically, even for the most "pure" of radiations, to determine the field strength in terms of the fluences and energies of the different types of particles. In mixed fields, it is essentially impossible to define adequately these variables. Even if defined, they are too remote from the biological effect to make them useful for quantitative prediction purposes. Microdosimetry in principle obviates any requirement to measure these quantities.

The companion advantage of using microdosimetric methods is that, in permitting measurements to be made at the time of stochastic events, they in effect turn the abstract risk of being dosed and of cell doses into concrete values for these quantities. Even though it is usually not possible to designate which living cell is hit, or to attribute any particular hit size to any particular cell, it is possible to state accurately the relative numbers that were hit at any given value of z, for any given exposure. Thus one has essentially all the information that one has in pharmacology and toxicology, in which the number of individuals at any given dose level is known precisely, and from which the (fractional) number of quantal responders can be determined.

With the above digression, we can now return to Fig. 3. It is clear from the figure that it is not appropriate, and is misleading, to present the data in terms of a "linear-no-threshold" relationship. Rather, as shown also in Fig. 3, the data should be presented as distributions of hit cells, the area of the distribution representing the total amount of exposure.

As noted above, the distributions in Figs. 2 and 3 provide a graded series of cell doses, exactly as is done in determining an organ dose-response curve, in Md (the numbers of animals subjects to graded doses in Md are frequently of essentially the same size). It then becomes clear that what is needed to evaluate the number of hit cells that will respond quantally is the cell equivalent of an organ-dose response curve, i.,e., a relationship that will provide the probability of a cell quantal response, as a function of increasing cell dose. Such a function, termed a hit-size effectiveness function (HSEF), has been developed (6-9). One such curve is shown schematically as the S-shaped curve in Fig. 2. An actual curve for chromosome abnormalities, derived from the data in Fig. 1, is shown in Fig. 7. The use of these curves is now discussed, following which their derivation is summarized.

Use of the HSEF

The use of the HSEF is shown schematically in Fig. 2. For any one, or all of the cell hit size distributions shown, one simply multiplies the distribution by the HSEF, i.e., the number of hit cells at each hit size is multiplied by the corresponding point on the HSEF. The resulting products, the fraction of hit cells responding quantally at each cell point on the distribution, are shown as the much smaller distributions within the larger ones. The area under each of the smaller distributions yields the total fraction of exposed cells responding quantally, for each of the exposures marked E-1, E-2, and E-3. It is this fraction, of exposed cells responding quantally for a given amount of exposure, that is the end product of the risk evaluation. It is the total risk to the cellular system, i.e., the excess incidence, in that system, of the end point, for exposure E, of the risk assessment. Thus such a value can be readily obtained for any amount of exposure to a radiation of any LET, or mixture, without any requirement

to utilize the"linear, non-threshold" function required in the currently used approach.

However, it may be useful, to show how the proposed approach can be tied into, but differs from the present system. This is illustrated in Fig. 5. The linear curve in the left hand panel permits one to determine the number of hit cells, or the risk of a cell being hit, for a given exposure X (the open circle on the curve marked R_H). This single curve is for any LET radiation, or mixture. The hit size distributions for the given radiation are provided in the upper right hand corner. This distribution, as opposed to those in Figs. 2 and 3, is normalized to 1.0. If this distribution is then multipled by the HSEF, shown in the center right panel, the product will represent the distribution of quantally responding cells, shown in the right lower panel. The areas under this distribution represent the number of hit cells in the upper normalized distribution that responds quantally--multiplying this value by the number of exposed cells given by the open circle in linear curve P_H in the left panel yields the total risk for exposure E, shown as the open circle on curve R_q.

It is emphasized that the "normalized distributions" approach depicted in Fig. 5 is for illustrative purposes only. Neither "linear, non-threshold" relationship, nor distributions for different LET's need be referred to or used in practice (it is superfluous to provide a curve for the risk of a hit versus exposure--the distribution of hit sizes suffices). That is to say, for any given exposure, whatever the LET or mixtures of LET's, only a single distribution would be recorded by the microdosimeter. Direct application of the HSEF would yield the required "risk coefficient". Thus, in practice, the cell dose approach could obviate the need for multiple "dose response" curves (Fig. 1), and it could replace the concept of LET entirely. That is to say, the "T" in LET does not mean the mean of the energy depositions in tissue. It means the amount deposited in the cell TCV--the cell dose.

Derivation of the HSEF

The derivation of the HSEF is described in detail elsewhere (1,2). The basic input information consists of quite accurately determined cell response data, for a series of radiations covering a wide span of qualities. In addition, it is necessary to have quite accurately determined microdosimetric data, that will provide both the numbers of cell hits and the hit-size distributions. These distributions overlap, as can be seen in Figure 5. It is reasonable to assume that, in and close to the regions of overlap, hits of a given size will have the same effectiveness, independent of the hit size distribution of origin. The effectiveness of the different distributions can then be obtained, and the regions of overlap provide independent information on the effectiveness of the individual hit sizes. It is then possible, by an iterative deconvolution process, to arrive ultimately at an HSEF that most accurately fits the input data.

This derivation is purely empirical, i.e., it is completely independent of assumptions or theories in respect to molecular or other subcellular mechanisms of action of the radiations. In other words, most if not all of available radiobiological action theories, begin with assumptions about mechanisms, e.g., that single or double strand breaks may be responsible for some or all of the cell transformations observed. In deriving the HSEF, on the other hand, only observed quantal responses are used.

Anomalies in the Present System

Several anomalies in the set of typical cell "dose response" curve, shown in Fig. 1, can be pointed out immediately. For instance, although the response is of individual cells, the "dose" is to the entire organ. It is taken to be axiomatic that the stimulus to an individual, be it a cell or an organ, must be measured at the same level as the initial biological response. Although the effective agent is purported to be energy, myriad "dose response" curves are drawn for that same agent. Also, as seen with lithium ions, the same particle but with different energies results in markedly different curve slopes. In fact, more and more curves can readily be added to the set, simply by using different particles of different energies, until the roughly triangular area represented by the curves is

filled in completely and constitutes an area (Fig. 6). This shows the fallacy and futility of the present dose response curve- RBE system, i.e., one needs in principle a separate, empirically determined "curve", for agent carriers (particles) of every conceivable type and energy so that any generality of the RBE concept is illusory. Thus severe compromises must be made in order for the system to be workable at all.

The fact that the curves can fill an area also indicates that an additional variable is involved as well as an unexpressed continuous function. That is to say, the three-dimensional plot in Fig. 3 is required. This missing variable has been thought to be LET, expressed as keV μm^{-1} in tissues. Such a continuous function, represented by a group of separated points on the curve representing the mean of a segment of the curve, is presented in Fig. 3a. The separated points represent the RBE, or, in radiation protection, assigned values of Q. However, it has long been well appreciated that LET is not adequate for the purpose. It is clear from the above discussion that this missing function is not LET, in the sense of transfer of energy to tissues. Rather, the transfer is quite specific—to the cell TCV, to constitute cell dose. Thus high- and low-LET radiations are in fact large- and small cell dose radiations.

High-Level Exposure

In the above discussion, exposure to low-LET radiation only was discussed. The differences between low- and high-LET radiations are shown in Figure 7, for a low-LET radiation only. Plotted on the abscissa is the exposure, expressed in units of N_H/N_E, or R_H. On the left ordinate is the mean hit size, corresponding to the heavy curved line shown in the figure. On the right ordinate is the number of discrete hits per cell, corresponding to the straight diagonal line, part of which overlaps the curve for the mean hit size.

Where the curves become congruent, at the upper high-exposure part of the curve, each cell has received a large number of hits. If one calls the summation of energy densities from these multiple hits the "cell dose", then it is clear that even though the individual hits constituting that "dose" vary greatly in size, the variance of the mean will become smaller and smaller. There is then no reason to evaluate separately the risk for each discrete hit. It is adequate, for practical reasons, simply to use the summed energy density as the mean dose. In other words, in these high-exposure regions, the cell dose and the organ dose are, for all practical purposes, identical. Then, and most importantly, one can characterize and predict the probability of a biological response in the cell population, or in the organ itself, in terms of a single parameter, the absorbed dose D to the organ.

However, as one goes lower in exposure, it is seen that the exposure splits into independent components, $\bar{z}$ and R_H. Note that the expectation value of $\bar{z}$, even though the variance is large, remains constant, so that the only cellular parameter that can increase with increasing exposure is the R_H or the number of hit sizes per exposed cell. Thus, with HLE, the dose to cells and organs alike can increase because of multiple hits, and the one variable, D, is adequate to predict a response in the individual. However, with LLE, neither the dose to the cells nor the mean dose increases; it is only the number of cells dosed that can increase.

Note that while LLE has its counterpart in macro accidents, and that only a small fraction of the exposed population is hit with increasing exposure, there is no analogue, with macro accidents, of HLE exposure. The reasons for this is that, for practical and ethical reasons, if the accident rate in given population increases above a very small fraction per year, even drastic action is likely to be taken. With radiation, on the other hand, the accident rate can be increased at will, so that any given cell can readily be exposed to dozens or more severe accidents, in the course of minutes, seconds, or less. It is only because of this fact, which may permit interactions between the hits, that the "quadratic" term, seen only with high-level exposure of cells to ionizing radiation, exists.

The transition from low- to high-level radiation exposure is depicted in Figure 8. This is for cell lethality only. Note the initial linear increase in the quantal response as a function of D, in the LLE region. Because of multiple hits and interactive processes, the curve rises rather steeply beginning in the transition zone, so that a large fraction of organ cells have been killed as one enters the HLE region. At this point, some of the organs, and therefore, the organisms, at a given value of D, will fail and die, and the fraction will increase to unity as D increases. This plot demonstrates clearly how a single agent, the energy carried by ionizing radiations, can span the entire gamut, ranging from the accident statistics of Ph in the LLE region, into the HLE region in which Md methodology applies. Again, the largest difference between the two regions is that with HLE the focus is on the individual, and the single parameter D is adequate to evaluate the probability of the quantal response at any given dose D. With LLE, on the other hand, each point on the curve shown represents an entire population of cells, and the interest focuses on how many in that population will be seriously injured or killed. Here three variables, the number of cells hit, the distribution of hit sizes, and an HSEF, are required.

DISCUSSION

The above-presented cell dose approach to radiation risk evaluation differs drastically from that presently used. Cell populations and the energy deposited in each cell replace the organ and organ dose concepts. A Ph and statistical mechanics approach to evaluate cell-charged particle interactions, replaces the Md approach currently used. Mean values of LET in tissues is abandoned in favor of use of the HSEF to evaluate risk to the single cell. Object-oriented physical quantities that are closely related to cell damage replace the more remote field quantities. Thus distributions of cells, the HSEF and the associated distribution of quantally responding cells replace "linear, non-threshold" relationships. The approach, in principle, appears to be far more coherent, internally consistent and logical than is the present system that must employ various factors and various versions of "dose equivalent" to permit it to be operable at all.

The present system could in principle obviate the need for radiation quality and LET; field quantities; a "standard radiation", linear "dose effect" and "dose response" relationship; risk coefficients; RBE; dose equivalent and rem. The problem of obtaining measurements that represent accurately the radiation field in tissues and cell populations is of course difficult, whether one uses the current SE or the proposed ED approaches.

A rather far-reaching conclusion is possible with the proposed approach. Each relevant organ system in the body contains enormous numbers of cell elements. With the proposed approach embracing the HSEF, it is possible, with any exposure, to estimate the (fractional) number of transformed cells in the individual. Assuming all exposed normal individuals have approximately the same number of relevant cells, we then can have, in principle, for a given exposure, a population of individuals with known and equal numbers of transformed cells. With a graded series of exposures, these numbers can then be correlated with cancer incidence, which can be evaluated only long after the exposure, in animals or in human beings. The result would be a function for cancer risk as a function of the number of transformed cells in the individual, to replace the current organ dose-cancer incidence function.

The significance of the above is perhaps substantial. In the present system, one can derive only a quite uncertain estimate of the risk of cancer from a physical quantity, and one must use the collective dose equivalent in very large populations to evaluate the risk of cancer in the individual. On the other hand, with the proposed system, one has a measure of actual effect, i.e., the fraction of quantally responding cells, in the individual, from which the cancer risk tailored to that individual can be obtained. In other words, the function for the probability of an effect vs. the amount of exposure may in principle be by-passed completely. Thus one has in principle removed the evaluation of risk from the realm of Ph in which the focus is officially limited to the health of the population or society, and placed it in the Md category, in which the focus is on the health of the individual person. This may have many implications, not only in radiation biology and protection, but in the medical, social and legal spheres as well. With respect to the probability of causation ( ), it

could strengthen substantially the value of this approach in insuring equitable resolution of legal claims involving an allegation that a specific earlier exposure is causally related to a particular, extant cancer.

Note that HSEF's for macro accidents, although obtained in experiments in which stochastic energy transfer is simulated, are not used or even referred to operationally. The obvious reason is because a quantal response that may result can be readily observed, so that neither a dose concept nor dose-response relationships are required for risk evaluation. Similarly, quantal responses of cells, can in most laboratory experiments using "single cell systems", be observed promptly. Thus it is only for severely delayed responses, such as cancer or heritable defects, that early observations are precluded. A complete approach to risk assessment at the time of exposure must then involve the HSEF for cells.

Since the HSEF replaces LET conceptually, this may be of significance to those interested in the detailed significance of "track structure" with radiations of different "quality". Much of what has been ascribed to LET and track structure differences, may well be simply due to a difference in dose to the cells. With most, particularly stochastic agent transfers, it has been more or less generally accepted that a larger dose will be more effective per unit dose than a smaller one, apparently with little or no necessary requirement being perceived to investigate why.

The proposed approach has relevance in the "extrapolation" currently used to estimate cancer risk from low-LET radiation at very low "doses". Clearly, one is not extrapolating high- to low doses of the agent energy. Rather, one is extrapolating to the lower reaches of a curve representing the probability of an expressed cancer, as a function of the number of malignantly transformed cells in the organ or organs of interest.

The interpretation of a "linear, non-threshold" curve (for exposure and not dose) also changes. What is meant is that, with any amount of exposure, there can be stochastic interaction with health consequences. It is true that "any amount", i.e., as little as a single encounter, could be lethal. However, the conditions are 1) one must first have experienced such an encounter, and 2) it must be a large one so that the dose

transferred is large enough to have some tangible probability of causing a quantal response.

Finally, it must be recognized that, with stochastic encounters, the density of energy transfer, a parameter of ion pair density, may well not be the most relevant quantity in terms of causing traumatic injury. Other candidate quantities include momemtum transfer, rate of deceleration, particularly of one part of an organ relative to another part, and impulse.

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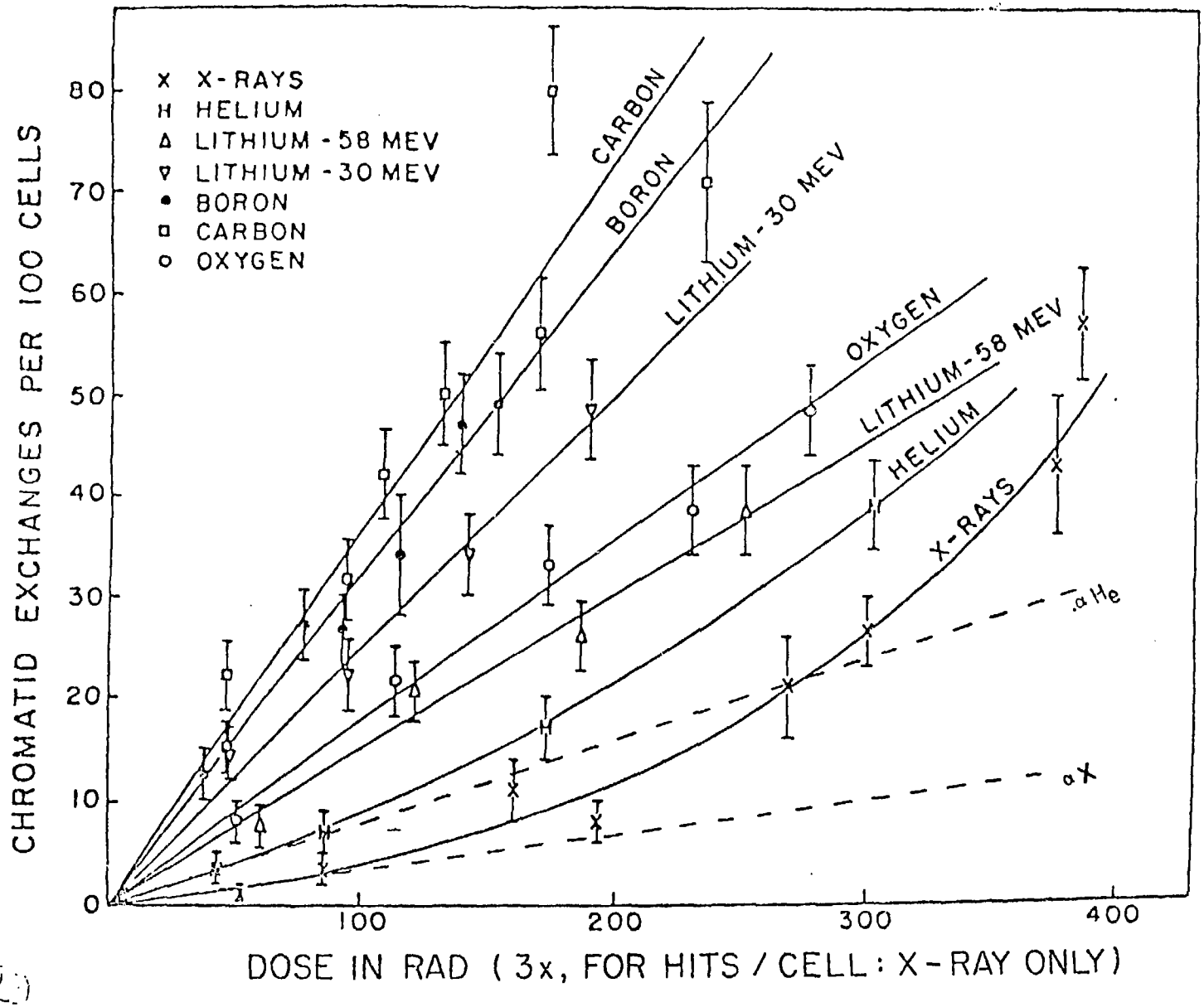
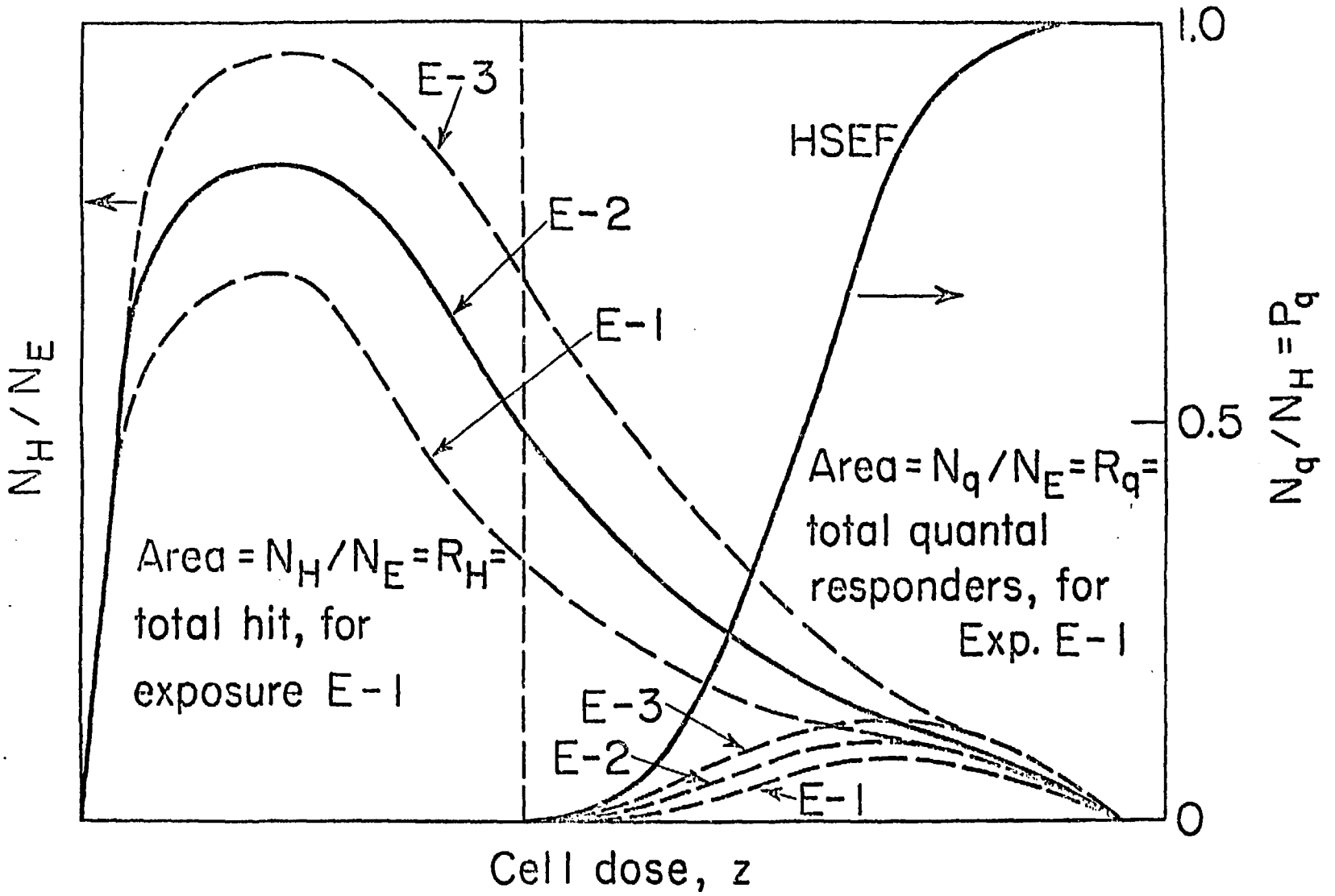
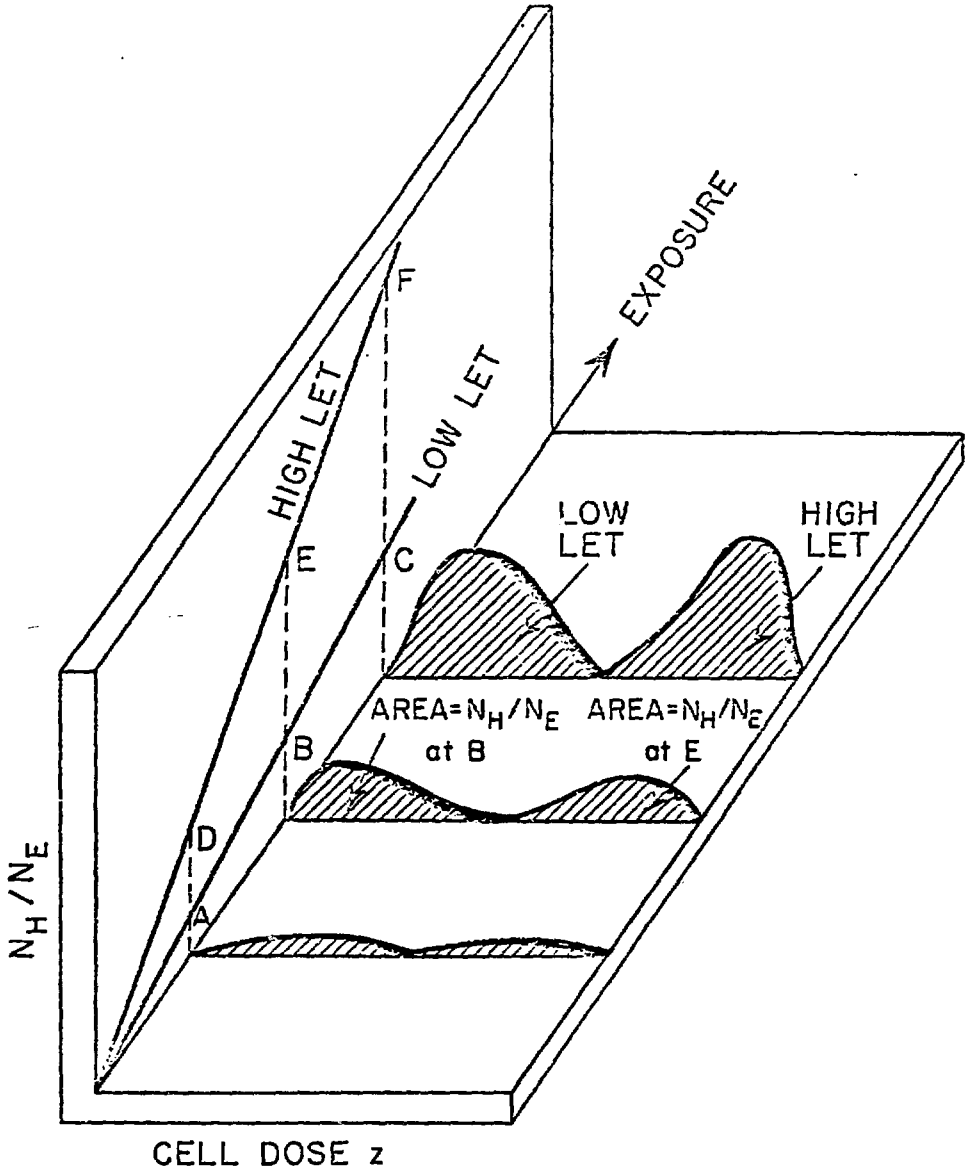
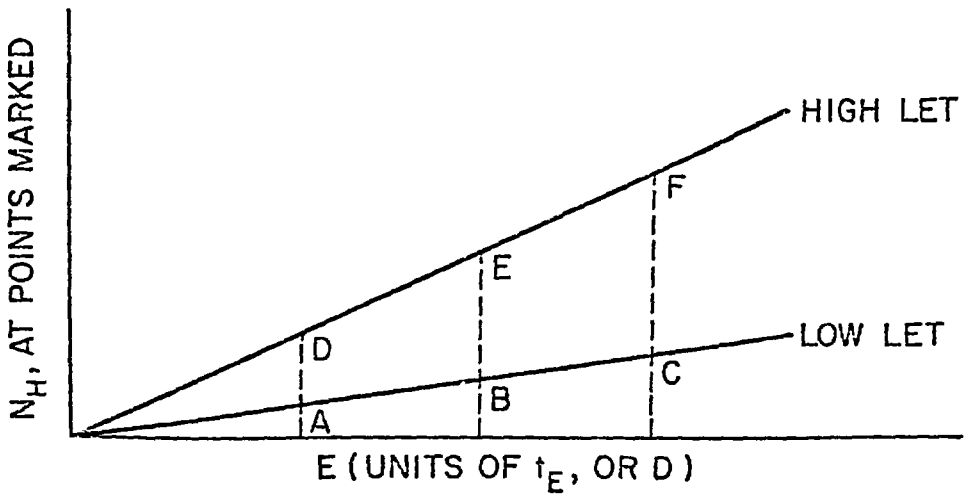

X X-RAYS
H HELIUM
Δ LITHIUM - 58 MEV
▽ LITHIUM - 30 MEV
• BORON
□ CARBON
○ OXYGEN
CARBON
BORON
LITHIUM - 30 MEV
OXYGEN
LITHIUM - 58 MEV
HELIUM
X-RAYS
αHe
αX
CHROMATID EXCHANGES PER 100 CELLS
0
10
20
30
40
50
60
70
80
100
200
300
400
DOSE IN RAD (3x, FOR HITS / CELL : X-RAY ONLY)

Fig.-2


E-3
E-2
E-1
HSEF
1.0
0.5
0
N_H / N_E
$N_q / N_H = P_q$
Area = $N_H / N_E = R_H$ = total hit, for exposure E-1
Area = $N_q / N_E = R_q$ = total quantal responders, for Exp. E-1
E-3
E-2
E-1
Cell dose, z


EXPOSURE
HIGH LET
LOW LET
F
E
C
LOW LET
HIGH LET
AREA=N_H/N_E at B
AREA=N_H/N_E at E
B
D
A
N_H/N_E
CELL DOSE z


HIGH LET
LOW LET
F
E
D
C
B
A
N_H, AT POINTS MARKED
E (UNITS OF t_E, OR D)

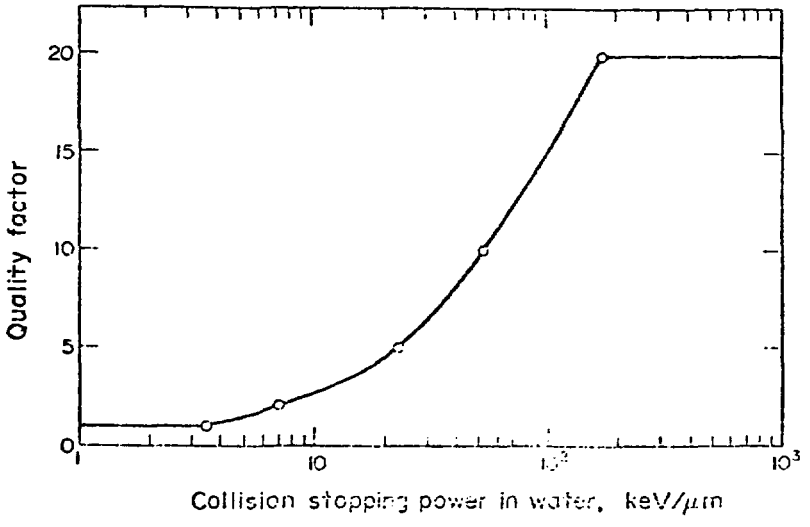
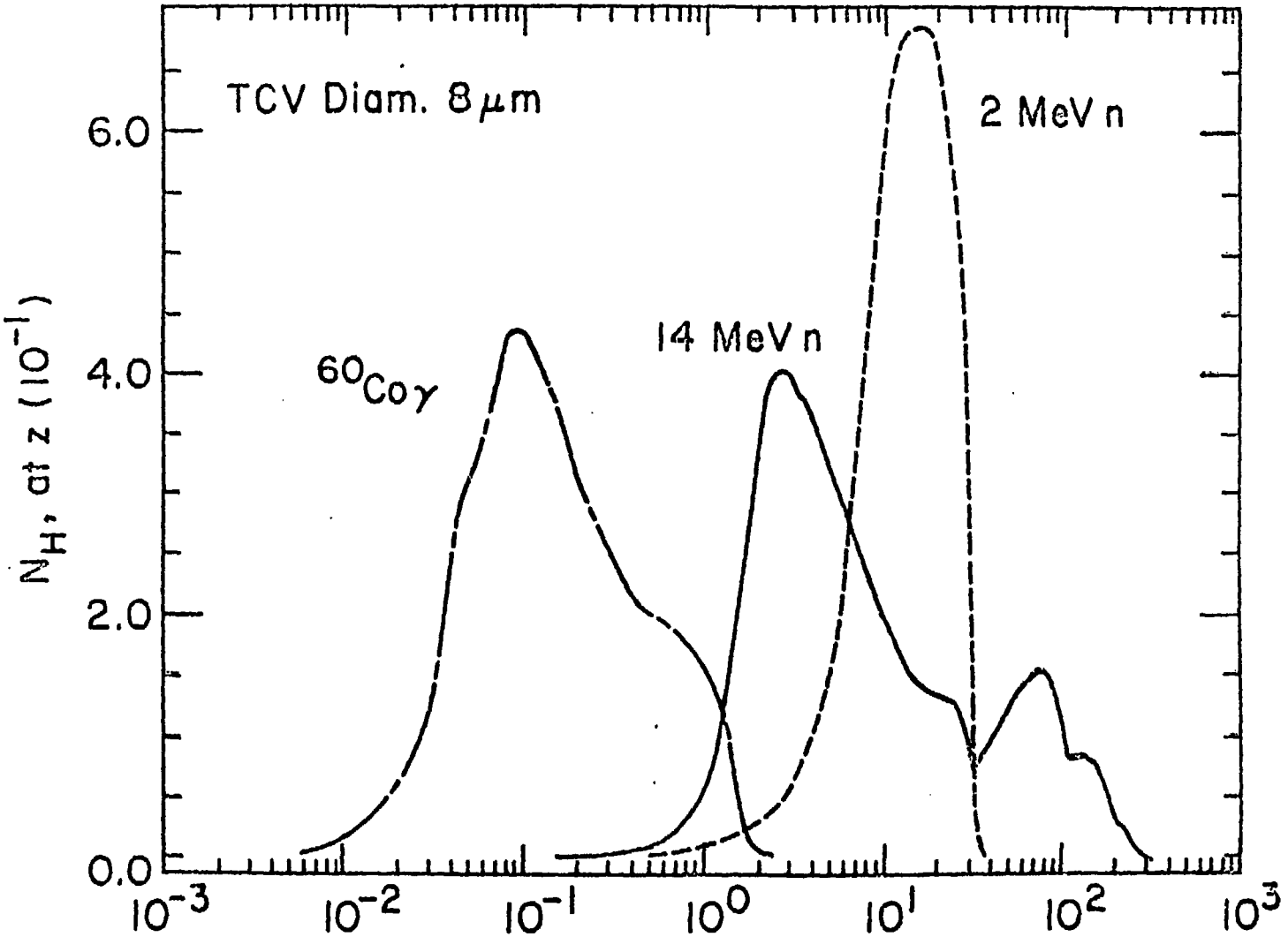
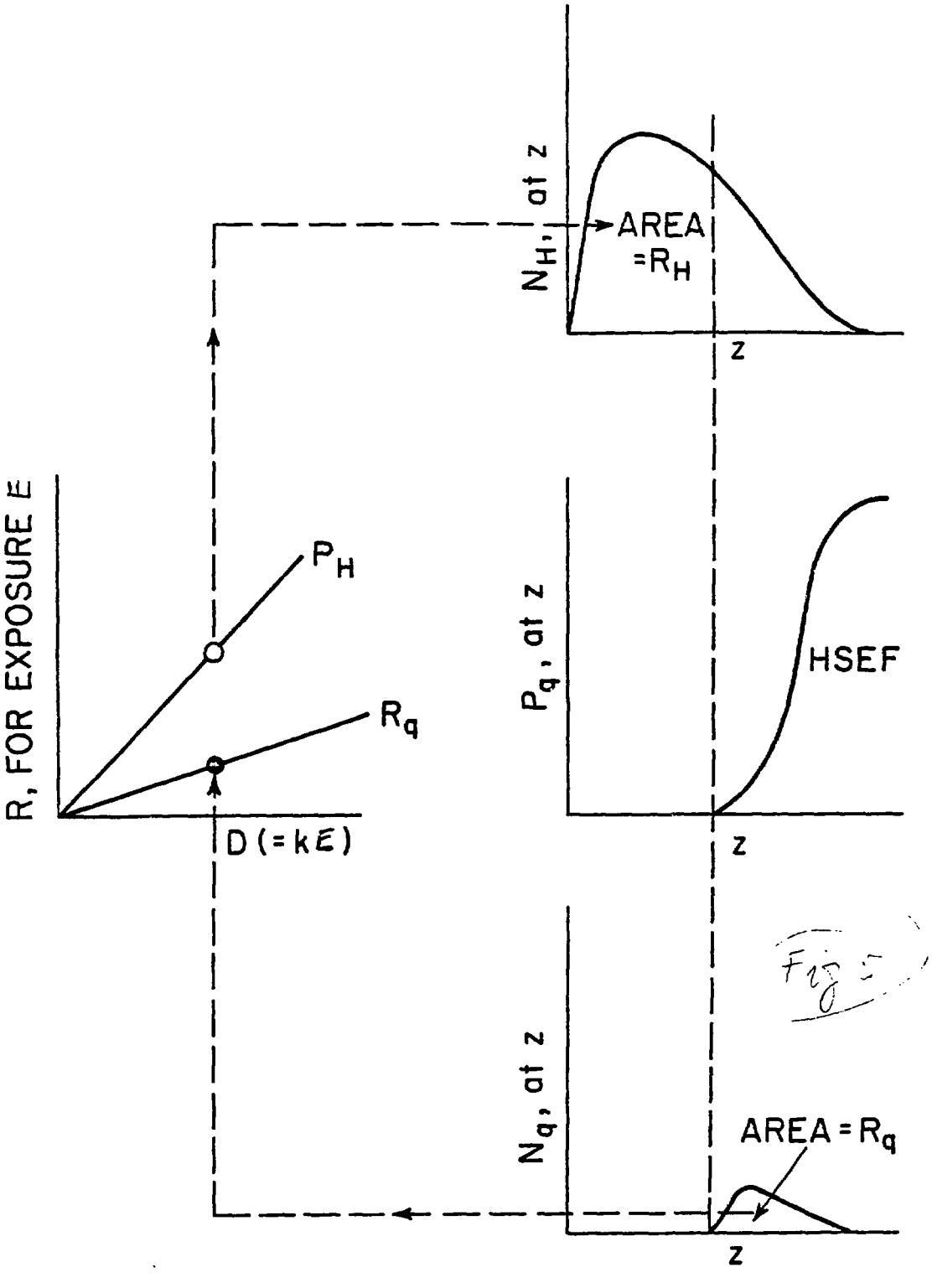
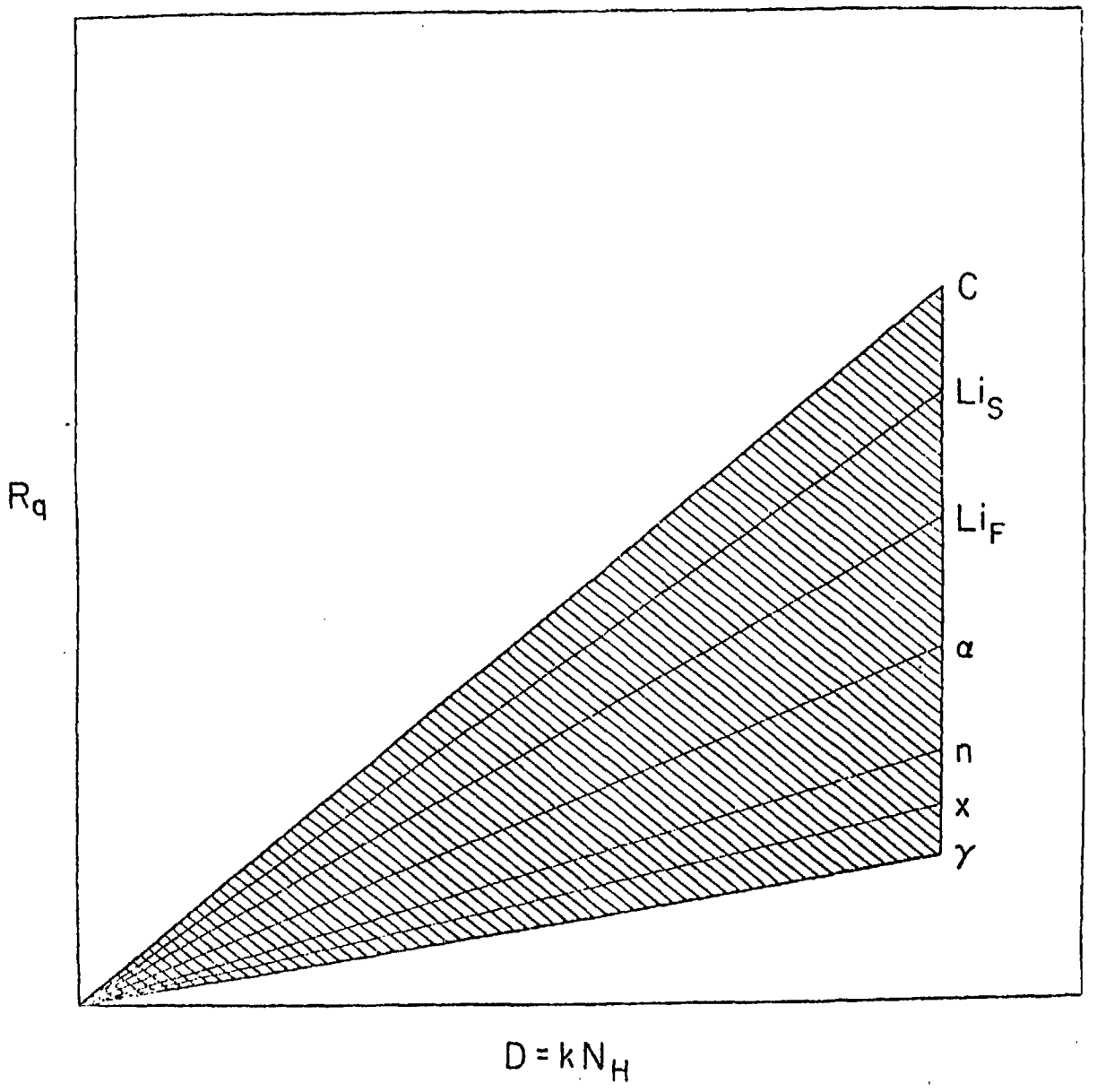
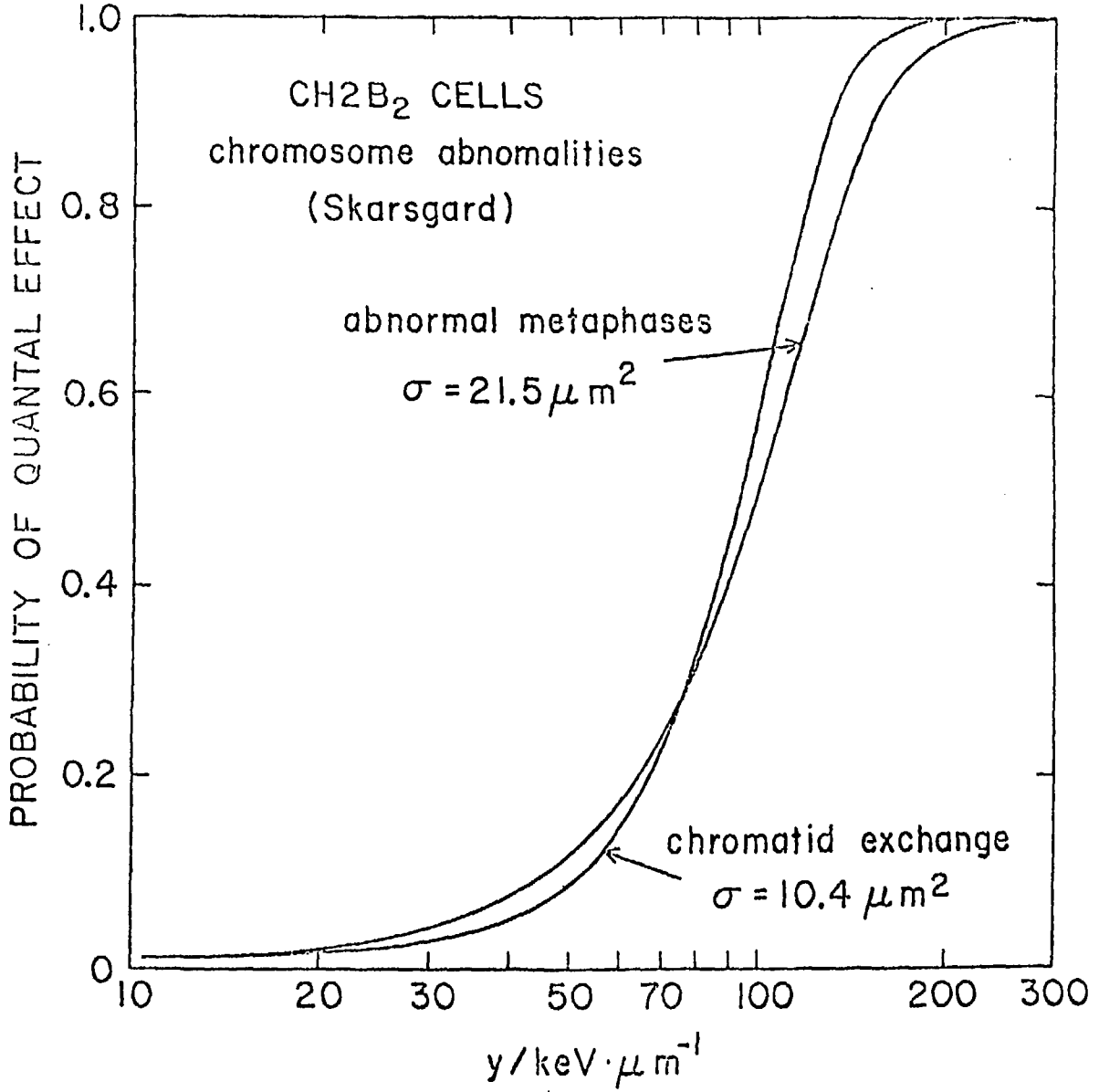


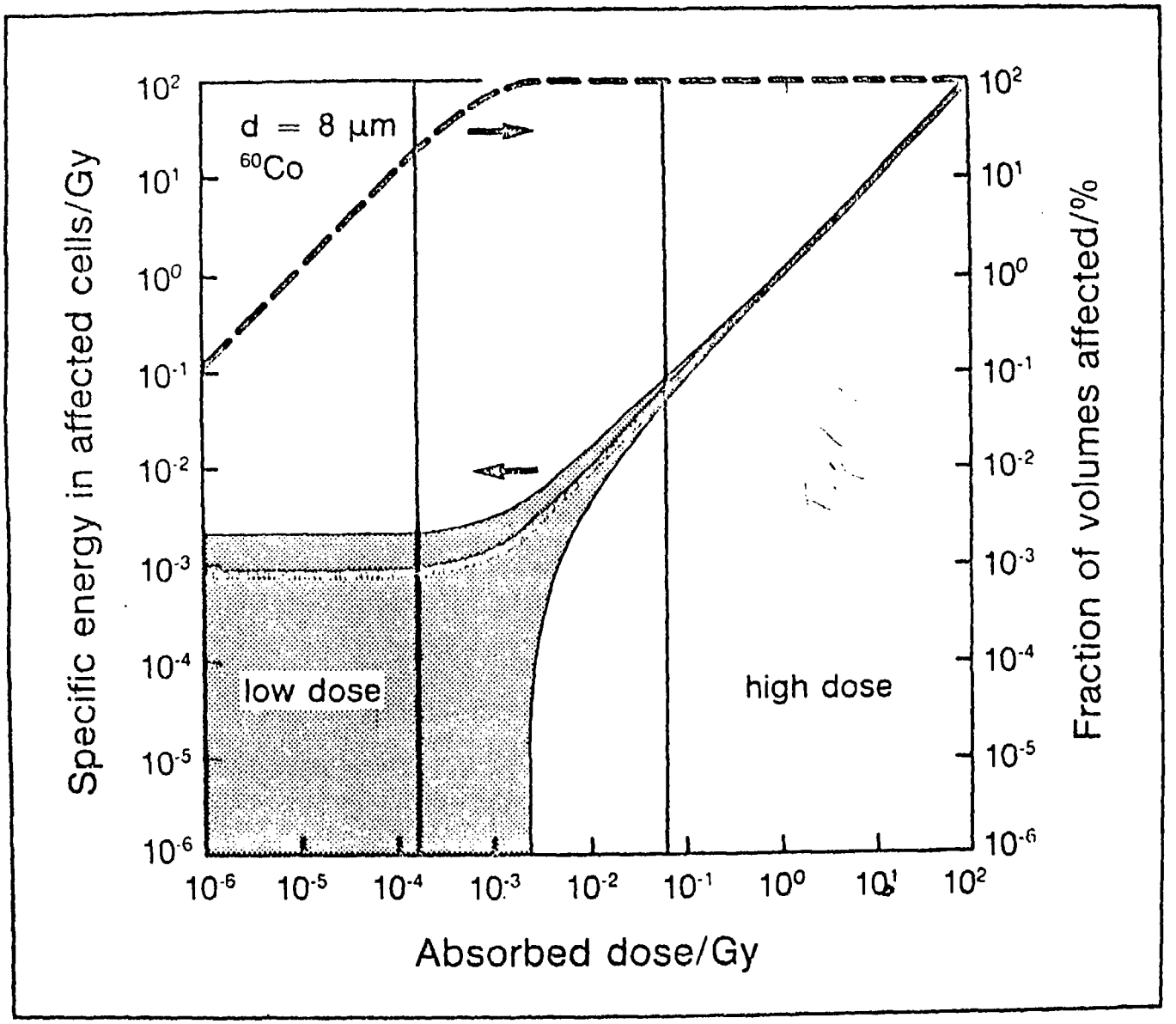
FIG. 1. Quality factor as a function of collision stopping power in water.

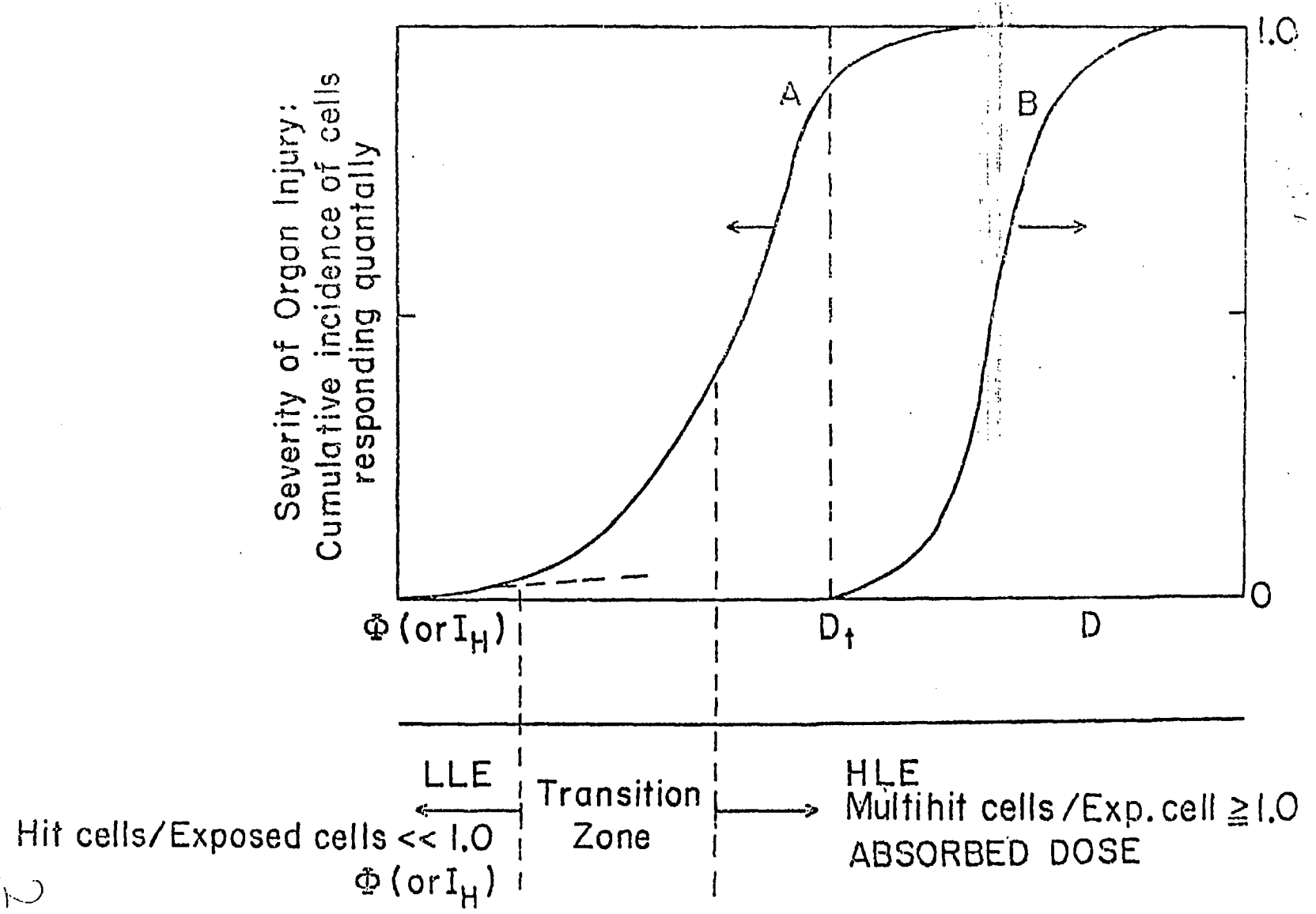

TCV Diam. 8 μm
2 MeV n
14 MeV n
60Co γ
6.0
4.0
2.0
0.0
N_H, at z (10^{-1})
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
HIT SIZE z (rad)


R, FOR EXPOSURE E
P_H
R_q
D (= kE)
N_H, at z
AREA
$= R_H$
z
P_q, at z
HSEF
z
N_q, at z
AREA = R_q
z


C
Li_S
Li_F
α
n
x
γ
R_q
D = k N_H


CH2B2 CELLS
chromosome abnomalities
(Skarsgard)
abnormal metaphases
σ = 21.5 μm²
chromatid exchange
σ = 10.4 μm²
PROBABILITY OF QUANTAL EFFECT
1.0
0.8
0.6
0.4
0.2
0
10
20
30
50
70
100
200
300
y / keV · μm⁻¹


d = 8 µm
60Co
low dose
high dose
Specific energy in affected cells/Gy
Fraction of volumes affected/%
Absorbed dose/Gy
10^2
10^1
10^0
10^-1
10^-2
10^-3
10^-4
10^-5
10^-6


Severity of Organ Injury:
Cumulative incidence of cells
responding quantally
1.0
0
A
B
Φ (or I_H)
D_t
D
LLE
Transition
Zone
HLE
Multihit cells / Exp. cell ≧ 1.0
Hit cells/Exposed cells << 1.0
Φ (or I_H)
ABSORBED DOSE