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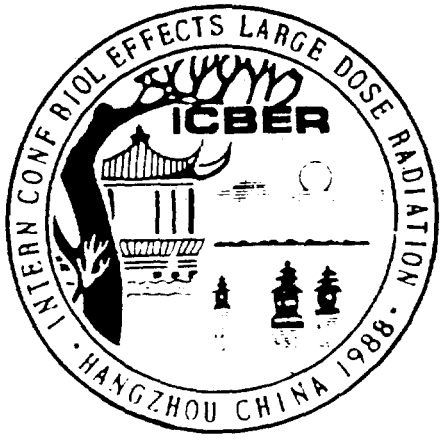

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A Different Approach to Evaluating Health Effects from Radiation Exposure

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ABSTRACT

Absorbed dose D is shown to be a composite variable, the product of the fraction of cells hit (F) and the mean "dose" (hit size) $\bar{z}$ to the hit cells. D is suitable for use with high level exposure (HLE) to radiation and its resulting acute organ effects because F = 1.0, so that D approximates closely enough the mean energy density in both the cell and the organ. However, with low-level exposure (LLE) to radiation and its consequent probability of cancer induction from a single cell, F is $<<1.0$ and stochastic delivery of energy to cells results in a wide distribution of single hit sizes. As a result the expectation value of $\bar{z}$ is constant with exposure, so that only F can vary with D. However, because D is the mean organ- and not cell dose, the apparent proportionality between this quantity and the fraction of cells transformed, obtained with LLE, is misleading. It does not mean that any (cell) dose, no matter how small, can be lethal. Rather, it means that an exposure of a population of the constituent relevant cells of an organ results in a linear increase in the number of cells dosed, but not in cell dose. The probability of such a dosed 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 to that cell is effective. The above precepts are utilized to develop a drastically different approach to evaluation of the risk from LLE, that holds promise of obviating any requirement for use in this region of the principal components of the present system: absorbed organ dose, LET, a standard radiation, RBE, 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 accident statistics and epidemiology (Ph); the latter in the discipline of pharmacology, toxicology, and medicine (Md). The same sets of characteristics that separate low-level exposure (LLE) to radiation from high-level exposure (HLE) require that the primary independent variable be the amount of exposure to agent-carrying objects (charged particles) in the environment of cells for the first; but mean dose to the organ or other cell system for the second.

The basic radiation quantities and units in current use and defined by the ICRU (1) were developed during that era in which a central theme was therapeutic uses and thus 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. The principal variable was, and continues to be organ or tumor absorbed dose, on which depends the fraction of organs or tumors responding quantally (i.e., an all-or-nothing change of state, from one of functional, to essentially permanent dysfunction or death).

However, this 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 either the number of energy-carrying particles per unit area per unit time flowing from the source, or alternatively the total energy flow from a source, per unit area, i.e., either the particle or total energy fluence, or a parameter of these variables. However, from the physician's standpoint, these quantities expressing the strength of either the radiation source or field were considered to be irrelevant: what mattered was that energy 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 duration of time spent in a radiation field calibrated against 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 meant to be interpreted in the physical sense, i.e., as a measure of the field or source strength. 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 approximately 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, with dimensions of energy per unit mass, as the unit of absorbed dose. However, the quantity exposure, with the Roentgen as the unit, was retained. 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 described controversy can be stated as follows: For a physician (or anyone) to estimate the probability of a serious or lethal 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 of the offending agent is the next fall-back position. Exposure is of little or no help in this regard. That is to say, needed for prognosis evaluation is an object-oriented quantity that relates to what is happening in the individual of concern, be that individual an organ or a cell.

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. This decision predated the finding that most human tumors are monoclonal and thus presumably single cell in origin. The use of absorbed dose also became standard practice with studies using "simple cell" preparations. Here a defined cell population can be regarded as the "system" to which an "organ dose" can 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 its application are then presented, following which the method of application is described. This is followed by a more detailed and technical description of the underlying concepts and methodologies. A more detailed critique of the presently used "dosimetric" system is then given.

The principal point of the proposed approach is not necessarily to alter the estimates of the risk of exposure as derived using present methodologies, although such a result is probable. Rather, it is to show that the present Md framework in which LLE risk assessment is presently cast is conceptually inappropriate and misleading, and should be replaced by one appropriate for Ph.

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 can be shown to be proportional to, and a dependent parameter for the quantity exposure of the cell population comprising the elements of the organ system, expressible in terms of the parameter particle fluence. That is to say, D is proportional to the number of primary particles per unit area, which is a descriptor of the radiation source, and of the radiation field 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 expressed in terms of particle fluence, to

which the cell population of an organ or other cell population of interest is exposed.

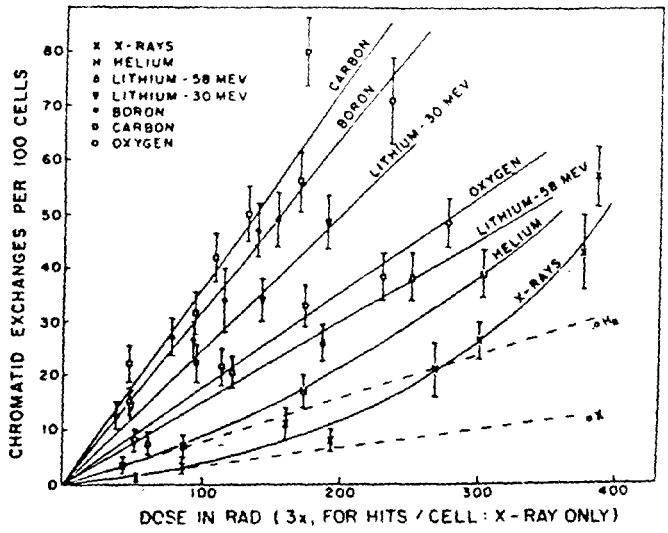

Fig. 1 Conventional absorbed dose-cell quantal response functions for radiations of a wide range of qualities (from Ref. 2). It is indicated on the abscissa that the absorbed dose, in cellular terms, translates with LLE, into number of hits/cell (the numerical value given for hits per cell, which changes with radiation quality, is for x-rays only).

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 number of cells dosed at all and in amount of energy deposited in the individual cells--not with physical quantities that relate only to what may be in the environment of the cells.

The solution to this problem must lie in the same approach used by the physicians, who had no direct way of determining the dose that the living tumor or normal tissues were receiving from a given exposure. That is to say, since the requirement is to estimate the doses to living cells, the characteristics of a "cell phantom" must be outlined. However, in doing so one must keep in mind that, unlike the early (and present) physicians who

operated in an Md mode, the problem must be approached from the Ph, i.e., epidemiological and accident statistics standpoints. This is, of course, because any transfer of radiation energy to the individual cells 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. In other words, the dose, to be relevant, must be registered in individuals at the level of biological organization at which the initiation 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 separate quantities are needed.

The first requirement, to be able to register the number of cells hit and dosed during any given exposure period, can be accomplished if the phantom response is determined electronically. This provides for the short recovery time needed in order that many hits per cell can be recorded (i.e., if an array of phantom cells registers a total of x hits during an exposure time t, then a single "rapidly recovering" phantom 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 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.

Next, the phantom must record separately every discrete hit on the phantom cell, as well as the amount 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 arranges the stochastically delivered cell doses neatly in order of increasing magnitude. Thus we have the exact analogue of what is commonly used in pharmacology and toxicology to

construct an organ dose-organ response curve--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 function provides the conditional probabilities that, if hit, and if a dose of a given magnitude is received, a given cell will respond quantally. Thus this function is the cell analogue of the "organ dose-organ response" curve. Such curves have been derived for several cellular end points (3). We thus have three probabilities to be evaluated, 1) that, with a given amount of exposure, a cell will be hit, 2) that the dose to the cell will be of a given size, and 3) that the cell will respond quantally. It is these probabilities that permit the estimation, for a given exposure, of the fraction of those exposed cells 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

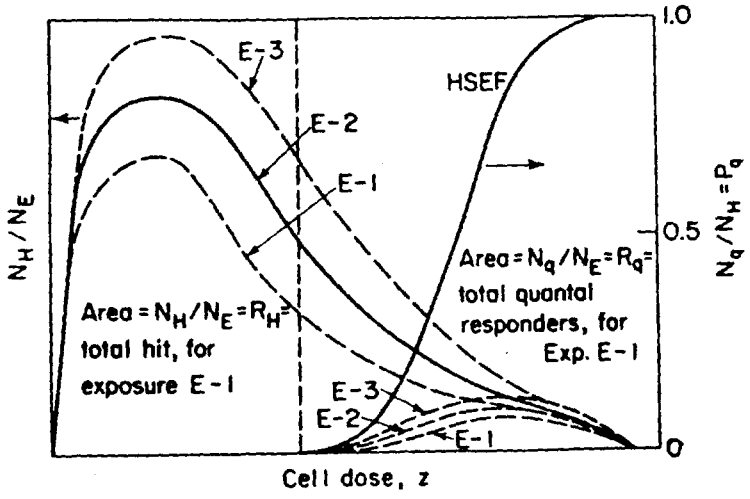

Fig. 2 Schematic distributions of cell doses for three levels of exposure to a radiation of a given quality or mixture. Note that only the areas under the distribution and not the shape increase with exposure. The smaller distributions in the lower right region result from multiplying the larger distributions by the HSEF shown.

particle collisions, for a radiation of a defined 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 hit, that increases. Note also that each distribution represents a graded series of cell doses. Also shown is the S-shaped curve, an HSEF (hit-size effectiveness function), the relationship discussed above 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 related to single cell-initiated endpoints, i.e., the fraction of those cells exposed during a given exposure that will respond quantally.

What has been referred to above as a "cell phantom" actually is much more than the cell analogue of an organ phantom. Rather than simply determine a dose to a single cell, it 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 might more appropriately be called a "cell risk meter", rather than a "microdosimeter".

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

Dose Confused with Exposure

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

$$D = \left(\frac{z_{1a} + z_{1b} \cdots}{N_E}\right) = \left(\frac{z_{1a} + z_{1b} \cdots}{N_H}\right) \cdot \frac{N_H}{N_E} = \bar{z}F^{*}, \quad (1$$

*$\bar{z}$ is designated $\bar{z}^{\dagger}$ in ICRU publications to specify that the mean is to hit cells only.

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 F is the 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,

$$F = \Phi t_E = \bar{\Phi} \sigma , \qquad (2)$$

in which Φ is the field strength measured as fluence rate (units of particles cm^{-2} t^{-1}), which expresses the rate of exposure (of cells) to the energy-conveying charged particles; t_E is the exposure time; $\bar{\Phi}$ 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),

$$D = \bar{z}\bar{\Phi}\sigma , \qquad (3)$$

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

Eq. (1) confirms that stated above, namely that D to the organ system is not a dose to the cell, and that its equivalent is required for the level of biological organization, the cell, that is appropriate to the "late single-cell initiated effects" of LLE, mutagenesis and carcinogenesis. D conceptually becomes the exposure of the cell population, to which N_H/N_E is proportional, that is to say, the "object-oriented quantity" N_H/N_E, as seen in Eq. (3), is proportional to the primary independent "field-oriented" variable the exposure E, for which $\bar{\Phi}$ can be used as a parameter.

With D becoming $\bar{\Phi}$ conceptually, a rational basis for the "linear-non-threshold" relationship is provided. Although from toxicological principles 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 reasonable.

The fact that D is effectively exposure and not dose also provides insight into what the basic problem is when one attempts, as is done in Fig. 1, to express the biological response of cells 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 two of the curves given in Fig. 1. In the upper panel is a three-dimensional schematic, on the exposure-N_q/N_E plane of which is depicted the same curve and labeled points shown in the lower panel. On the N_q/N_E-cell dose plane are the cell dose distributions, i.e., the relative numbers of cells dosed, as a function of the cell dose, z.

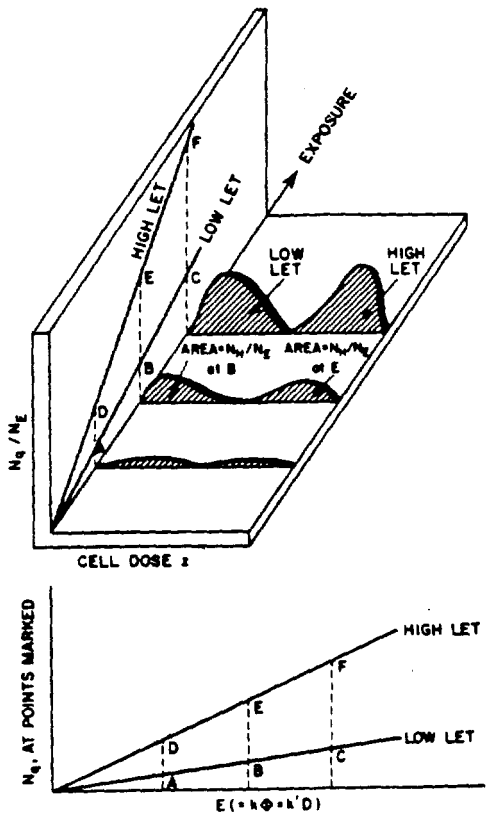

Fig. 3 A three-dimensional schematic plot, designed to show that any single point on a given conventional absorbed dose-response curve does not represent a single value of cell dose. Rather, each point, for any quality radiation, represents an entire distribution of cell doses, as shown on the plane representing N_q/N_E vs z.

It then becomes additionally clear that each point on 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 $D = \bar{z}F$, in that obviously, to have a $\bar{z}$, there must exist a corresponding distribution. The number of dosed cells at each value of 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. (4-6) 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 more illuminating to describe the instrument approach.

A microdosimeter can be regarded as simply a proportional counter containing tissue equivalent gas. Even though 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

[1]The idea of discrete, stochastic high-density energy depositions resulting from radiation exposure probably originated early with Dessauer's "point heat" theory (7) and was certainly well appreciated by Lea (8). However, these ideas were not formally developed until the "microdosimeter" was invented by Rossi (4-6). Its use has been more in the context of a substitute for the quantity LET, to describe energy depositions within a non-anatomically defined "gross sensitive volume" within the cell. The idea of a "cell dose" was probably first applied practically by Bond and Feinendegen (9), and developed in NCRP Report No. 63 (10). The practical application of the microdosimeter as a cell phantom with which stochastically delivered cell doses could be determined is relatively recent (Bond et al., Feinendegen et al., Refs. 11-14).

terms of the size of the ion cascade, is taken as the magnitude of the hit, i.e. the "hit size" or cell dose. Thus, one obtains not only the distribution of the stochastically delivered hit sizes, but also the total number of discrete hits for the given amount of exposure. Since the instrument represents a single cell, the readout can be in terms of hits/exposed cell. The microdosimeter registers essentially all impinging charged particles. However, with scaling factors as large as 10^8, and with extremely small exposures, it provides the ratio hit/(hit plus unhit) cells, i.e., the fraction of exposed cells hit at least once. It can quantify "interspersed" 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. The mean time between dose deliveries 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.

Examples of microdosimetric distributions, for radiations of three LET's are shown in Figure 4. The amount of energy deposited has been designated the "specific energy" (4-6), 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 verb, and for brevity, it

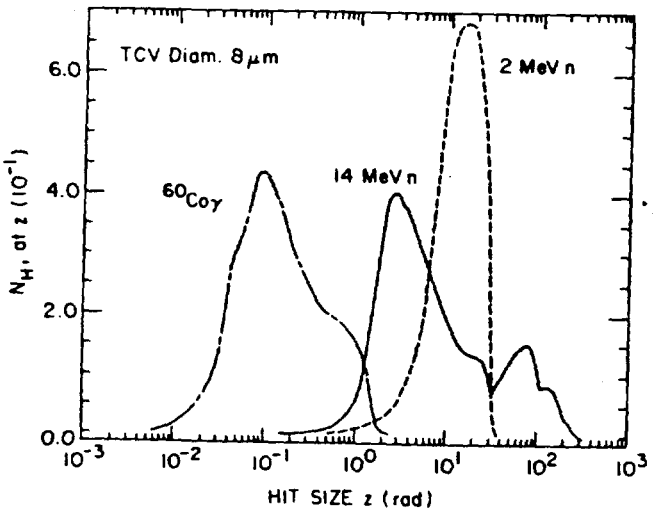

Fig. 4 Microdosimetric z distributions for three radiations of different qualities. Note that the variance of the mean value can be quite large, and that the distributions overlap.

has commonly been called a "hit". Also, with the diameter of the TCV specified as a nucleus of 8 microns in diameter, the term "elementary dose" 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 substantial advantages of using the cell 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 "object-oriented" quantities, on which the extent and severity of effect resulting from radiation exposure depends. 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 often essentially impossible to define adequately these variables. Even if defined, they are too remote from the biological effect to be satisfactory for quantitative prediction purposes. Microdosimetry in principle obviates any requirement for their measurement.

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 cell doses, into concrete values. Even though it is usually not possible to designate which living cell is hit, or to assign any particular cell dose to any given cell, it is possible to state accurately the relative numbers that were hit at any given value of cell dose, 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 incomplete and misleading to present the data in terms of a "linear-no-threshold" relationship. Rather, as shown also in Fig. 2 the data should be presented as distributions of hit cells, the area of the distribution representing the total amount of exposure. 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 (11-14). 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. 5.(3). The use of these curves is now discussed, following which their derivation is summarized.

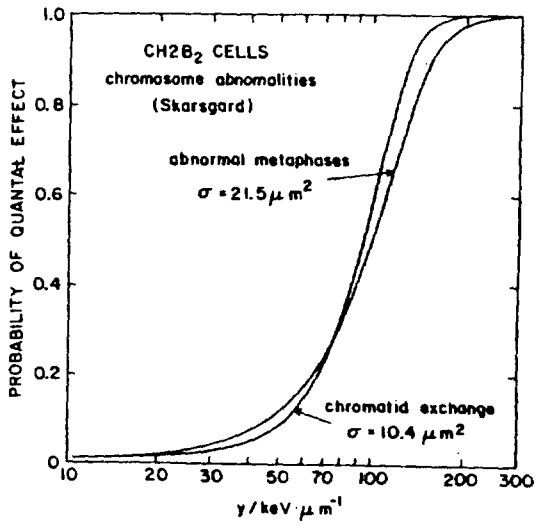

Fig. 5 An HSEF derived from the data shown in Fig. 1 (from Ref. 3). The two curves are for different chromosome aberrations.

Use of the HSEF

The use of the HSEF is shown schematically in Fig. 2. For any one or combination of 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 dose point on the distribution obtained with LLE only, 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 actual result in the given cellular system, i.e., the excess incidence, in that system, of transformed cells resulting from the given exposure. Such a value can be obtained in this manner 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. 6. 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

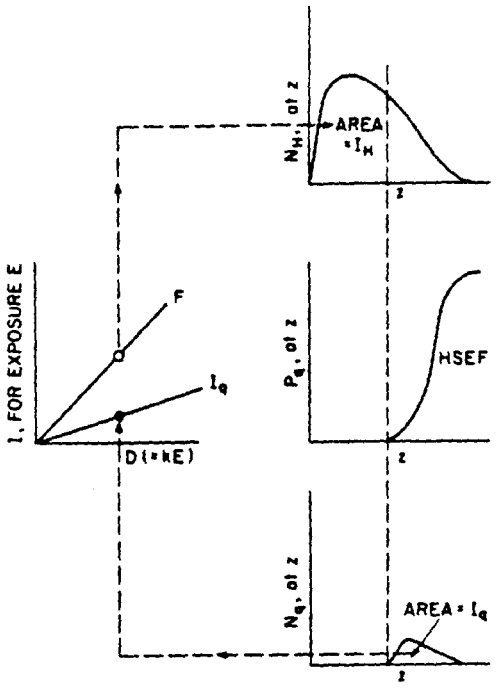

Fig. 6 Schematic plot showing the use of a normalized z distribution. Multiplication of this distribution by the HSEF permits one to estimate the fraction of cells responding quantally (solid circle on the curve marked I_q in the left panel), from the fraction of cells hit and dosed (open circle on the curve marked F).

exposure E (the open circle on the curve marked F). This single curve is for any LET radiation, or mixture, obtained with LLE only. The hit size distributions for the given radiation are provided in the upper right hand corner. This distribution, as opposed to those in Fig. 2, 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 respond quantally. Multiplying this value by the number of hit cells given by the open circle in linear curve F in the left panel yields the total incidence I_q of quantally responding cells, for exposure E, shown as the solid circle on curve I_q.

It is emphasized that the "normalized distributions" approach depicted in Fig. 6 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. Conceptually, the "T" in LET is not the average mean of the energy depositions in tissue. Rather, it refers to the amounts of energy deposited in the cell TCVs--the cell doses.

The approach described above applies strictly only to LLE and to "simple cell" systems. Since at least the bulk of human cancers are monoclonal, and thus presumably of single cell origin, an HSEF could also be determined for carcinogenesis in mammals. However, the HSEF would apply only to those malignantly transformed cells, for a given exposure, that were expressed as a cancer. Required additionally would be a relationship for the incidence of expressed cancers as a function of the total number of transformed cells. It is possible, with present advances in the identification of cell types, that this relationship could be determined directly.

Derivation of the HSEF

The derivation of the HSEF is described in detail elsewhere (3,11-13). The basic input information consists of quite accurately determined organ absorbed dose-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 number of hits per cell and the hit-size distributions. These distributions overlap, as can be seen in Figure 4. It is reasonable to assume that hits of a given size in a small enough target 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 independent of assumptions or theories about molecular or other subcellular mechanisms of action of the radiations. In other words, most if not all of available models or theories of radiobiological action begin with assumptions about mechanisms, e.g., that 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" curves shown in Fig. 1 can be pointed out immediately. For instance, although the response is of individual cells, the "dose" is the average for 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, Fig. 1 shows a number of "dose response" curves 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, by suitable choice of particle and energy, more and more curves can readily be added to the set until the roughly triangular area represented by the curves is filled in completely and constitutes an area (Fig. 7). 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.

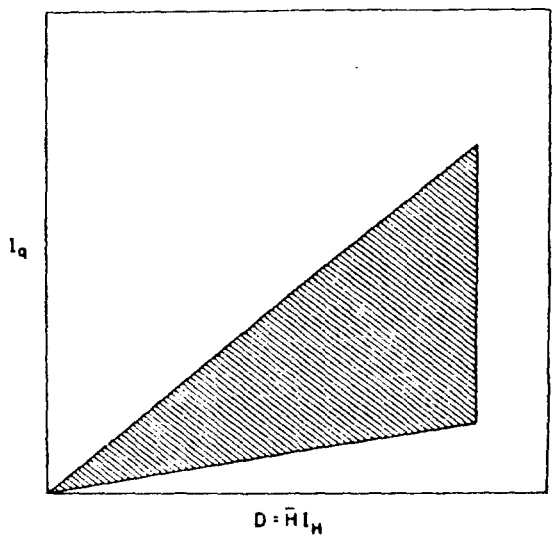

Fig. 7 Schematic based on Fig. 1, indicating that, with LLE, one can in principle fill in completely the "triangular area" represented by the family of curves shown in Fig. 1. This can be done simply by appropriate choices of particle type and energy. The plot indicates that any discrete values of RBE that may be derived from the curves in Fig. 1 are arbitrary and unique to a particular set of circumstances. This indicates the need for a different approach, such as that involving the HSEF.

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. 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 might better be characterized as large- and small cell dose-producing radiations.

High-Level Exposure

The above discussion has referred principally to "low-level" exposure. The differences between low- and high- level exposure are shown in Figure 8, for a low-LET radiation only. The heavy solid line, first horizontal and then diagonal, is for the specific energy (cell dose), vs. the absorbed dose to the organ. The upper dotted line is for the fraction of cells hit, i.e., the number of hits per cell, as a function of organ absorbed dose.

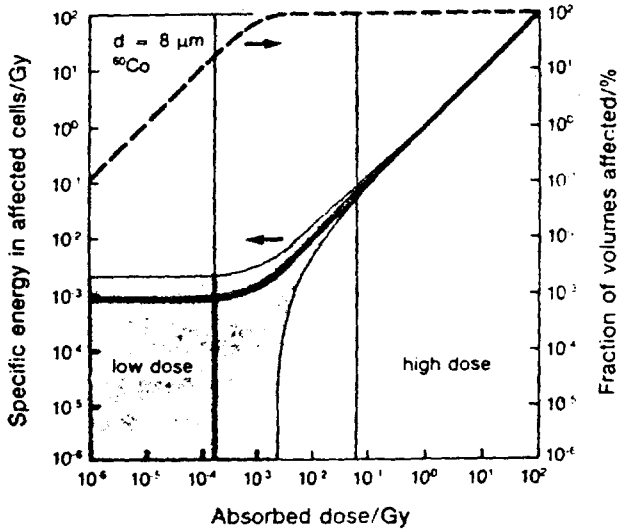

Fig. 8 Relationship between the specific energy, i.e., cell dose, as well as the fraction of affected target-containing volumes within a cell, and the organ absorbed dose in Gy. Note that at large organ doses, cell and organ dose approach being equal, and the variance becomes small. At low organ doses, the expectation value of the cell dose becomes constant, although the variance of that mean is quite large. At these low organ doses, it is only the fraction of cells hit and dosed that can increase with organ absorbed dose.

Where the solid line becomes diagonal, in the upper large-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 mean energy density in the organ as the absorbed dose. In other words, in these high-exposure regions, the cell dose and the organ dose are, for all practical purposes, identical. One can then 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, at the bend in the curve, the exposure splits into independent components, the mean cell dose $\bar{z}$ and the number of hits per cell, F. 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 F, the number of hits per exposed cell. Thus, with LLE, neither the dose to the cells nor the mean dose increases; it is only the number of cells dosed that can increase.

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

The transition from low- to high-level radiation exposure is depicted in Figure 9, for cell lethality only. Note the initial linear increase in the LLE region, in the number of quantal responders as a function of D. 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. In this region, some of the organs and therefore the organisms, at a given value of D, will fail functionally and die, and the fraction will increase to unity as D increases. 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 average 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 the number of cells hit, the distribution of hit sizes, and an HSEF, are required for risk evaluation.

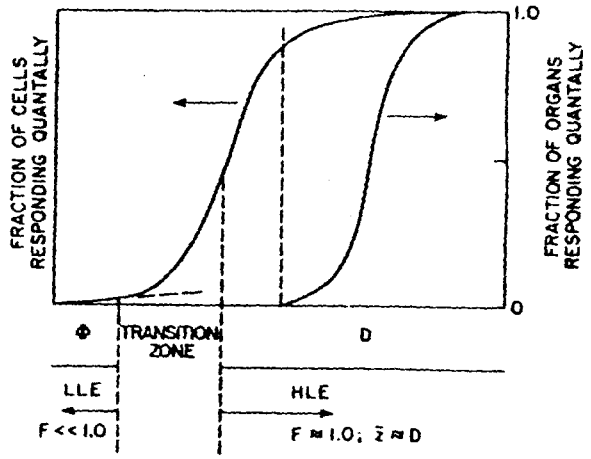

Fig. 9 Schematic showing the transition, for cell lethality, from LLE where absorbed dose is not appropriate, to HLE where it is. Key is curve A, which is both an exposure-quantal (lethal) response function for cells, and a dose-effect curve for the next highest level of biological organization, the organ. At low exposures the focus is on evaluating the number of cell elements responding quantally. At large exposures the focus is on the degree to which function of the cell system, the organ, has been compromised by massive cell killing. This determines the probability of the organ, and therefore the organism responding quantally (lethally).

Relationship between RBE and the HSEF

As seen from Eq (1) above, the organ absorbed dose D is equal to $\bar{z}F$. Thus the RBE, with LLE, is simply the ratio of $\bar{z}F$ for the standard radiation, divided by $\bar{z}F$ for the test high-LET radiation. However, since F varies with radiation quality, the values of F should be made equal if RBE is to be a measure of the influence of quality only, as indicated by

the value of $\bar{z}$ alone. Then the RBE would be simply the ratio of the value of $\bar{z}$ for the standard, to that of the high-LET radiation.

The result is shown in Fig. 10, in which an HSEF, i.e., the probability of a cell responding quantally, Pq, vs. z is plotted. In using the HSEF, the entire distribution of z is multiplied by the HSEF to obtain values for the cell risk from a radiation of any quality. However, as seen in the Fig, the RBE utilizes only the mean values of z, and as such the RBE ratio provides an indication of the effectiveness of a radiation that delivers predominantly high cell doses, relative to the standard that delivers essentially only small cell doses. Thus it is seen that the RBE is at best simply a crude method of approximating in stepwise fashion what an HSEF presents as a continuous function. It is conceptually questionable because as used it is a confounded ratio, and employs only average values of cell dose. The latter would be valid only if the cell risk were proportional to cell dose, which it clearly is not.

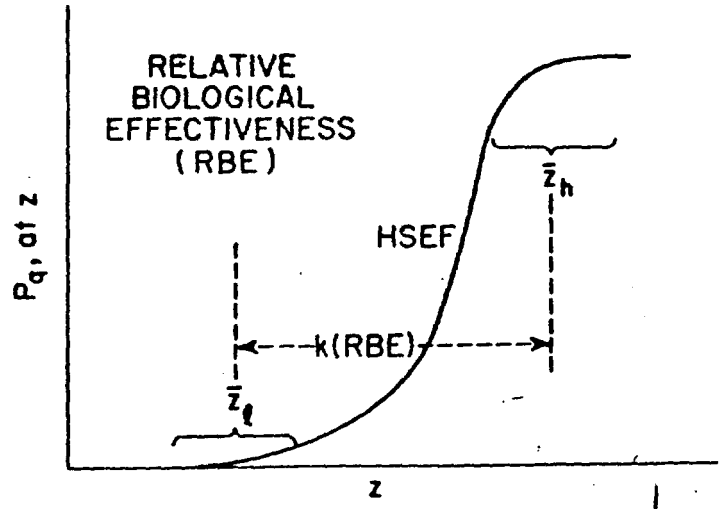

Fig. 10 Relationship between the HSEF and RBE, taken as the ratio of $\bar{z}$ for the standard, to that for a high-LET radiation. The RBE is a crude approximation to the HSEF, in that it is the ratio of the mean of the relatively large cell doses delivered by a high-LET radiation, to the mean of the relatively low cell doses delivered by the low-LET standard radiation. See text for additional explanation.

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 evaluating 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, while LLE, for radiation quality and LET; field quantities; a "standard radiation", linear "dose effect" and "dose response" relationship; risk coefficients; RBE; Q, dose equivalent and rem.

The proposed approach embracing the HSEF permits the estimation, with any exposure, of the (fractional) number of cells in the individual that are transformed. Assuming all exposed normal individuals have approximately the same number of relevant cells, we then can have, in principle, a population of individuals with known and equal numbers of transformed cells. With a graded series of exposures, these numbers could then be correlated with cancer incidence, in animals or in human beings. The result would be a relationship for cancer risk as a function of the number of transformed cells in the individual.

HSEF's for macro accidents, although they can be and are obtained in experiments in which stochastic energy transfer is simulated, are not used or even referred to operationally. The obvious reason is that a quantal response which may result can be readily observed, so that neither a dose concept nor dose-response relationships are required for practical risk evaluation. Similarly, quantal responses of cells can, in most laboratory experiments using "single cell systems", be observed promptly. Thus it is only for appreciably delayed responses, such as cancer or heritable

defects, that a complete approach to risk assessment at the time of exposure must involve the HSEF for cells.

Since the HSEF approach could replace the present approaches using LET, it has significance with respect to differences in "track structure" seen with radiations of different "quality". Some of the severity of cellular effect that has been ascribed to LET and track structure differences, may well be due to a difference in dose to the cells. With most, particularly planned transfers of chromosomal agents, 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 interpretation of a "linear, non-threshold" curve (for exposure and not dose) also changes with the HSEF approach. That is to say, following any amount of population exposure, there of course can be stochastic interactions with health consequences. It is true that "any amount", i.e., as little as a single encounter, could be lethal. However, the conditions for this are 1) one must first have experienced such an encounter, and 2) it must be of a size such that the dose transferred is large enough to have some tangible probability of causing a quantal response.

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