401038

(9)

BNL-41187
CONF-8803[illegible]--1

A Different Approach to Evaluating Health Effects from Radiation Exposure*

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

BEST COPY AVAILABLE

BNL--41187
DE88 009837

*For presentation at the ICBER, Hangzhou, China, March-April, 1988

[1] Brookhaven National Laboratory
This research was supported in part by the U.S. Department of Energy under Contract DE-AC02-76CH00016. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes.
[2] Army Chemical School, Radiation Laboratory, Fort McClellan, Alabama
[3] Laboratory for Nuclear Research (KFA), Juelich, FRG

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

5007448

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, REL (), dose equivalent and rem.

5007449

A Different Approach to Evaluating Health Effects from Radiation Exposure*

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

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".

5007450

The two views were eventually resolved, but only after the second meeting of the ICRU in 1928 ( ). 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 subject. 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

5007451

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 new 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.

5007452

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.

5007453

Next, the phantom must record separately for every discrete hit in 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

5007454

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:

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

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),

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

5007455

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 <u>risk</u> 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.

5007456

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

---

[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).

5007457

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 10^4, 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 micro 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 keV/μ 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 "hit". 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.

5007458

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.

5007459

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 or 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

5007460

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 multiplied 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.

5007461

Derivation of the HSEF

The derivation of the HSEF is described in detail elsewhere (). 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" curves, 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

5007462

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 P_R. 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.

5007463

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.

5007464

The transition from low- to high-level radiation exposure is depicted in Figure 3. 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.

5007465

The present system could in principle obviate the need f 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 HSEP, 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

5007466

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

5007467

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 momentum transfer, rate of deceleration, particularly of one part of an organ relative to another part, and impulse.

REFERENCES

1. Parker, H. and Roesch, W.C. In Clark, G.L. (Ed.) The Encyclopedia of X Rays and Gamma Rays. Chapman and Hall, London; Reinhold, NY, 1963.
2. Rossi, H.H. Specification of radiation quality. Radiat. Res. 10, 522-531, 1959.
3. Rossi, H.H. Energy distribution in the adsorption of radiation. Advances in Biological and Medical Physics, Vol. II, edited by (), pp. 27-85, 1967.
4. Rossi, H.H. Microdosimetry and radiobiology. Radiation and Proton Dosimetry 13-14, 259-265, 1985.
5. Lea, D.E. Actions of Radiation on Living Cells, Cambridge University Press, London and NY, 1956.
6. Bond, V.P. The conceptual basis for evaluating risk from low-level radiation exposure. Critical Issues in Setting Radiation Protection Dose Limits. National Council on Radiation Protection and Measurements, 1982.
7. Bond, V.P. and Varma, M.N. Low-level radiation reponse explained in terms of fluence and cell critical volume dose. Eignth Symposium on Microdosimetry, Julich, pp. 423-439, 1983.
8. Varma, M.N. and Bond, V.P. Empirical evaluation of a cell critical volume dose vs. cell response function for pink mutations in Tradescantia. Eighth Symposium on Microdosimetry, pp. 430-450, 1983.
9. Bond, V.P., Varma, M.N., Sondhaus, C.A., and Feinendegen, L.E. An alternative to absorbed dose, quality, and RBE at low exposures. Radiat. Res. 104, S-52-S-57, 1985.

5007468

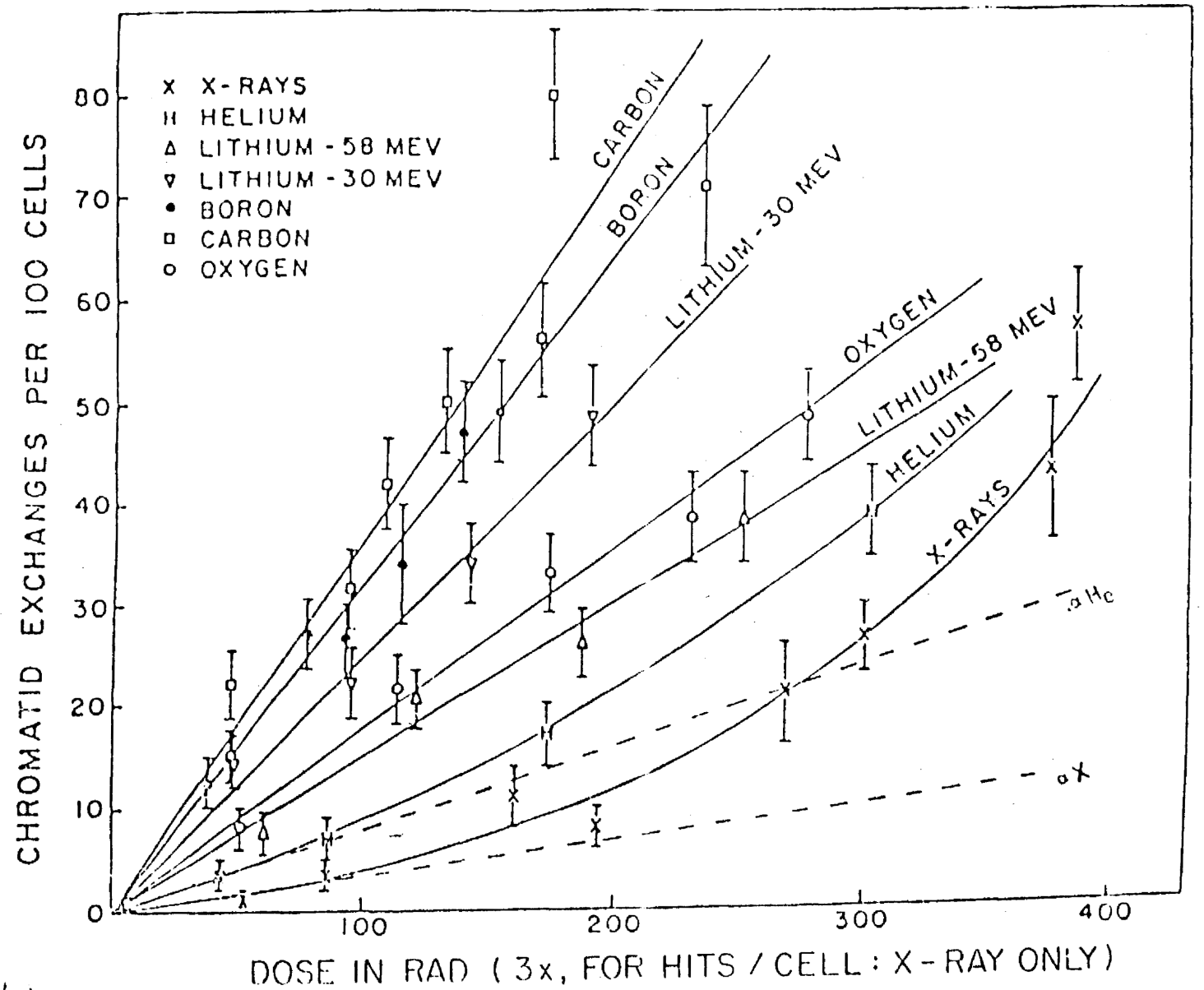
10. Bond, V.P. and Feinendegen, L.E. Intranuclear $^{3}_{H}$ thymidine: Dosimetric, radiobiological and radiation protection aspects. Health Physics 12, 1007-1023, 1966.

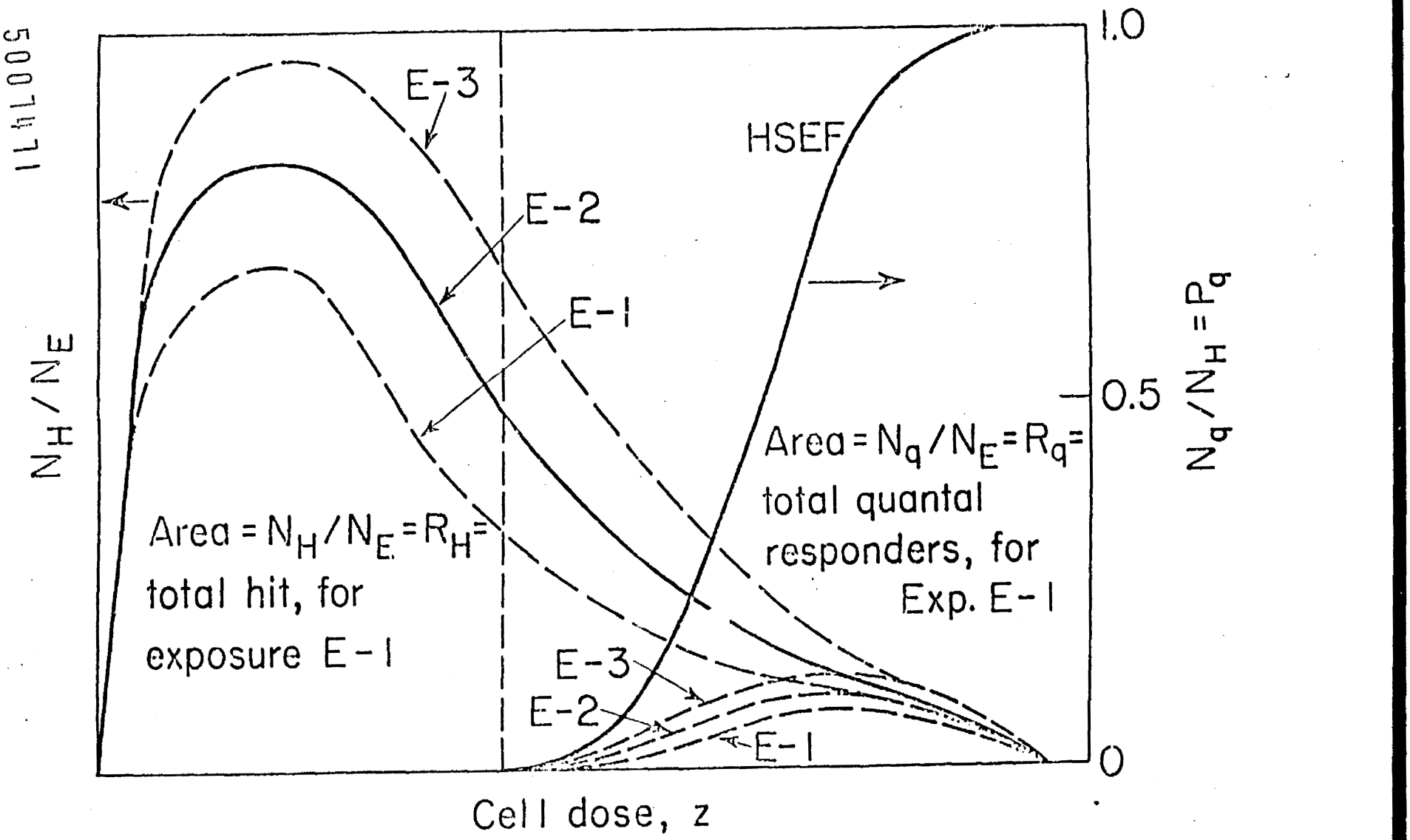
CRP Report No. 63, Tritium and other radionuclides labeled organic compounds incorporated in genetic material, NCRP. Bethesda, MD, 1979.

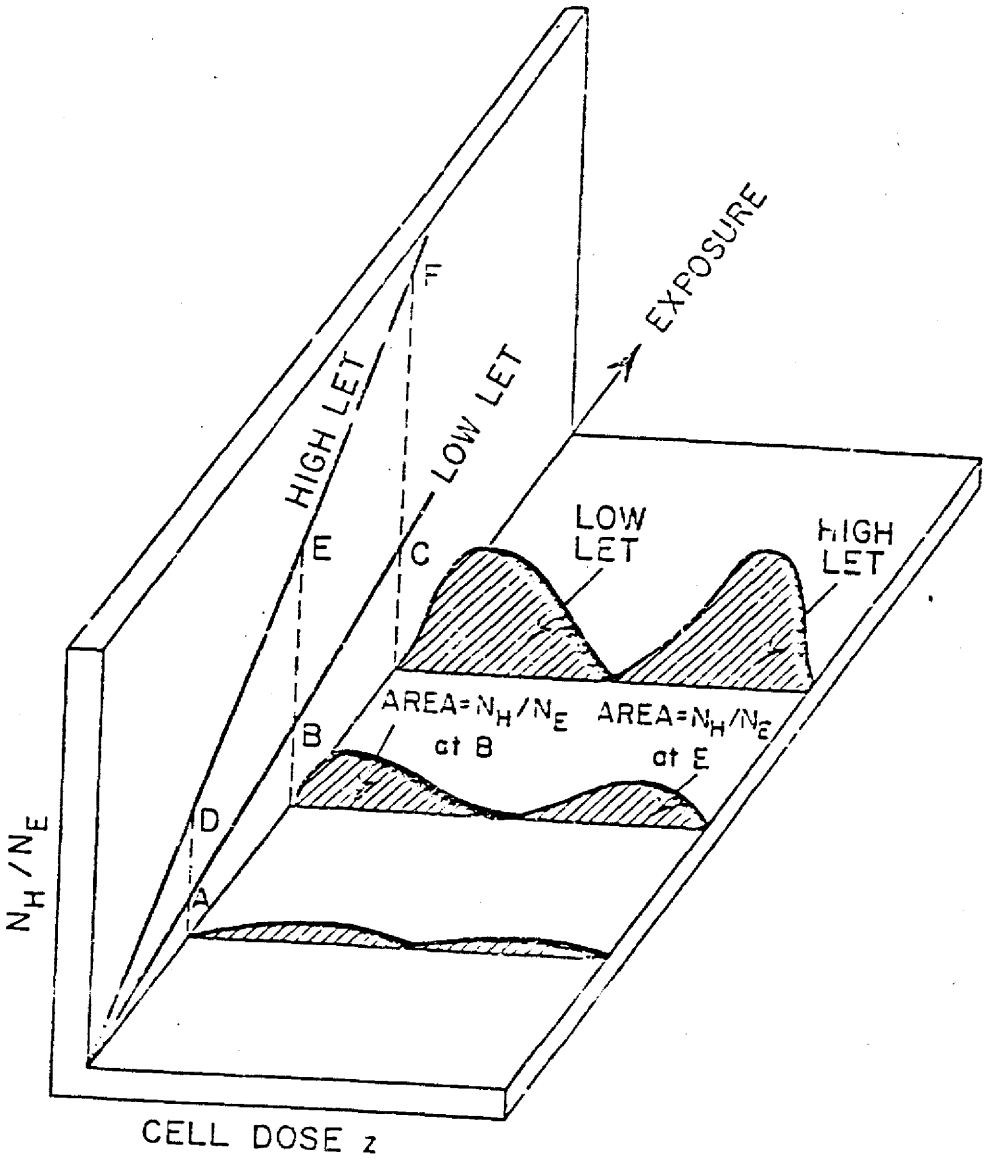
12. Feinendegen, L.E., Booz, J.K., Bond, V.P., and Sondhaus, C.A. Microdosimetric approach to the analysis of cell responses at low dose and low-dose rates. Radiation and Proton Dosimetry 13, 299-306.

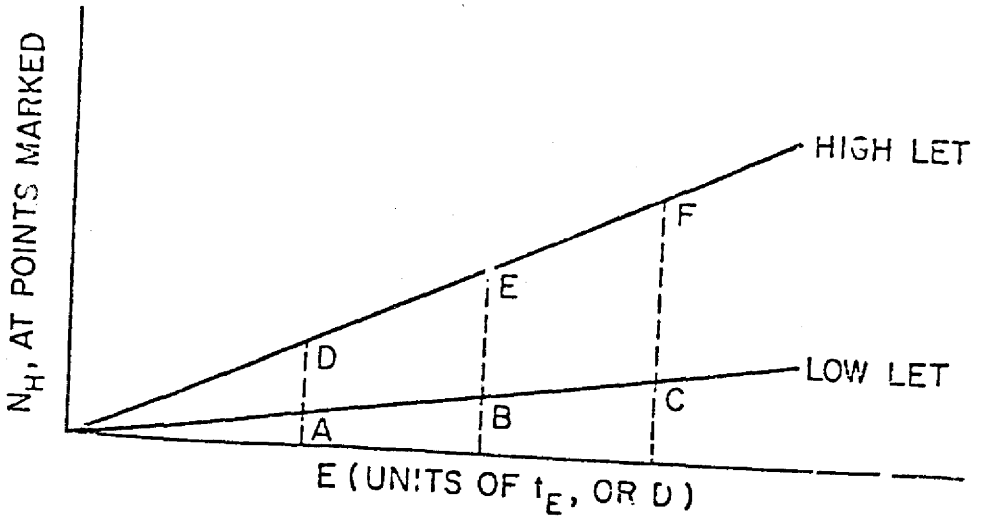
5007469

OLh1005


X X-RAYS
H HELIUM
Δ LITHIUM - 58 MEV
▽ LITHIUM - 30 MEV
• BORON
□ CARBON
○ OXYGEN
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)
CARBON
BORON
LITHIUM-30 MEV
OXYGEN
LITHIUM-58 MEV
HELIUM
X-RAYS
αHe
αX


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


HIGH LET
LOW LET
EXPOSURE
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


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

5007472

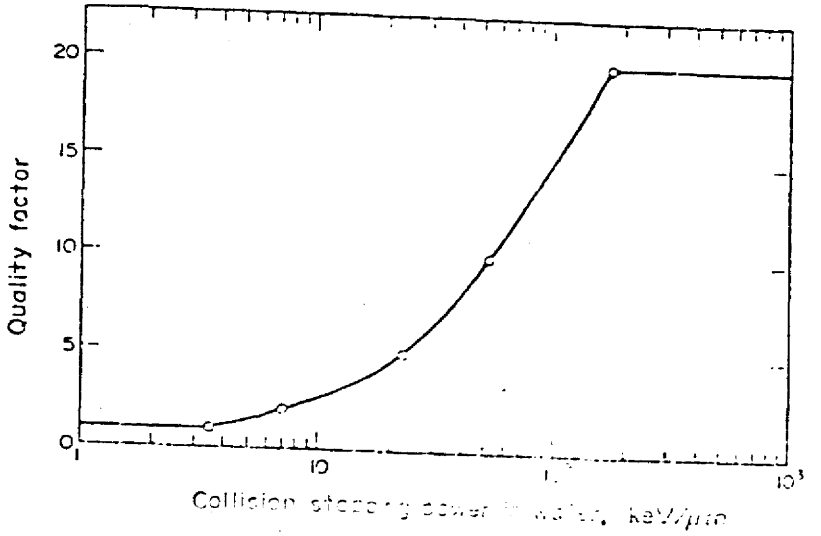
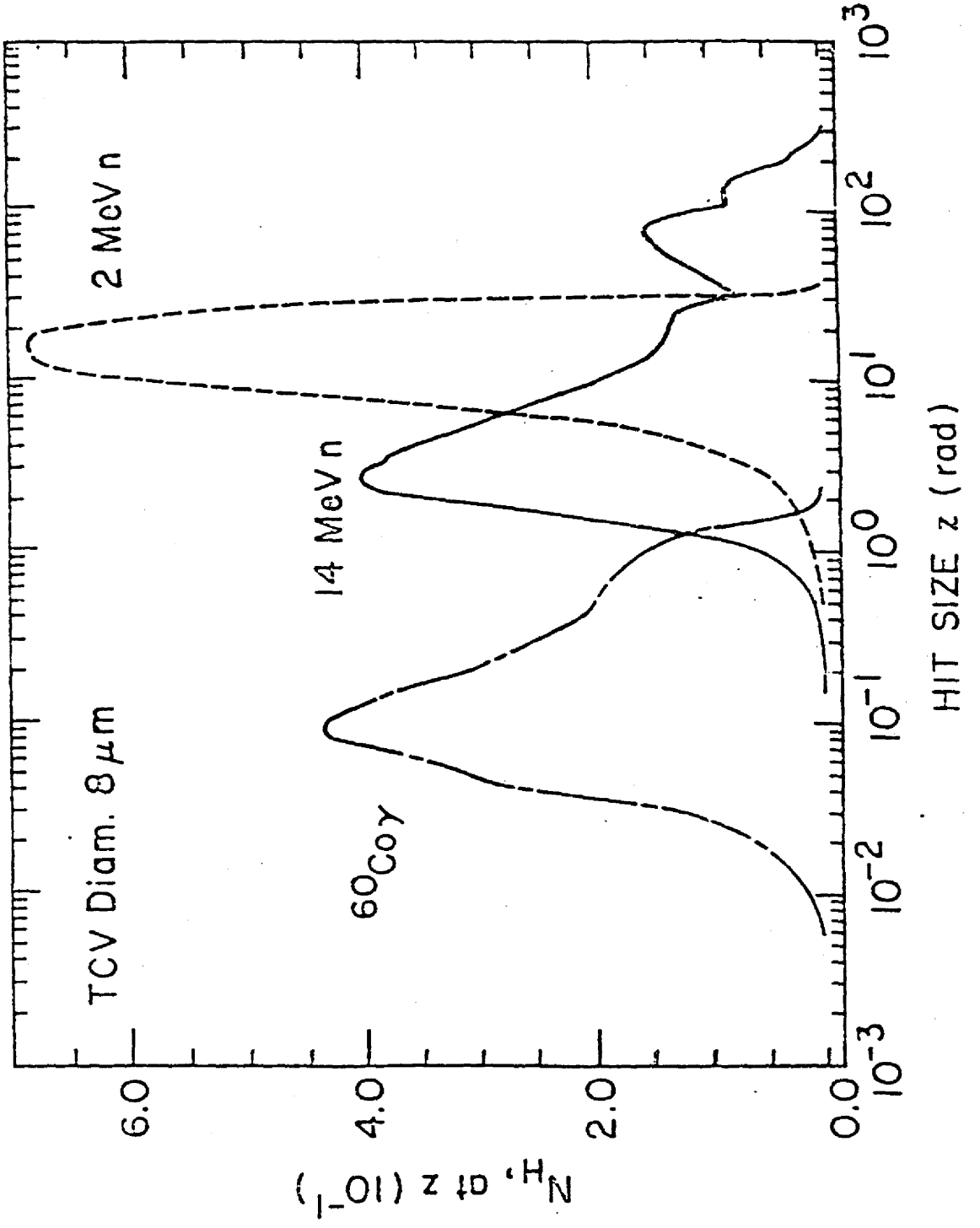


FIG. 1. Quality factor as a function of collision stopping power in water.

5007473


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

5007474

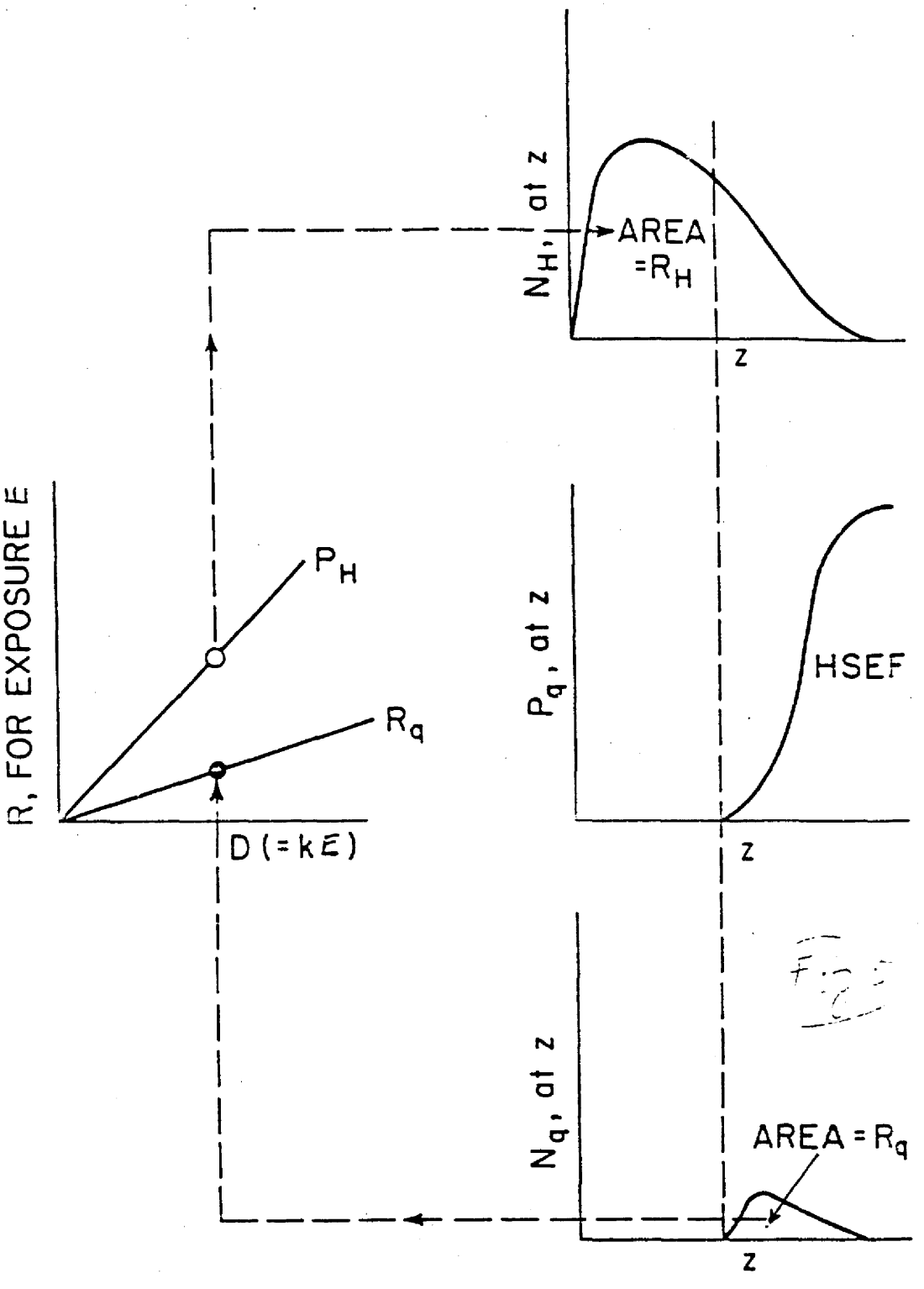
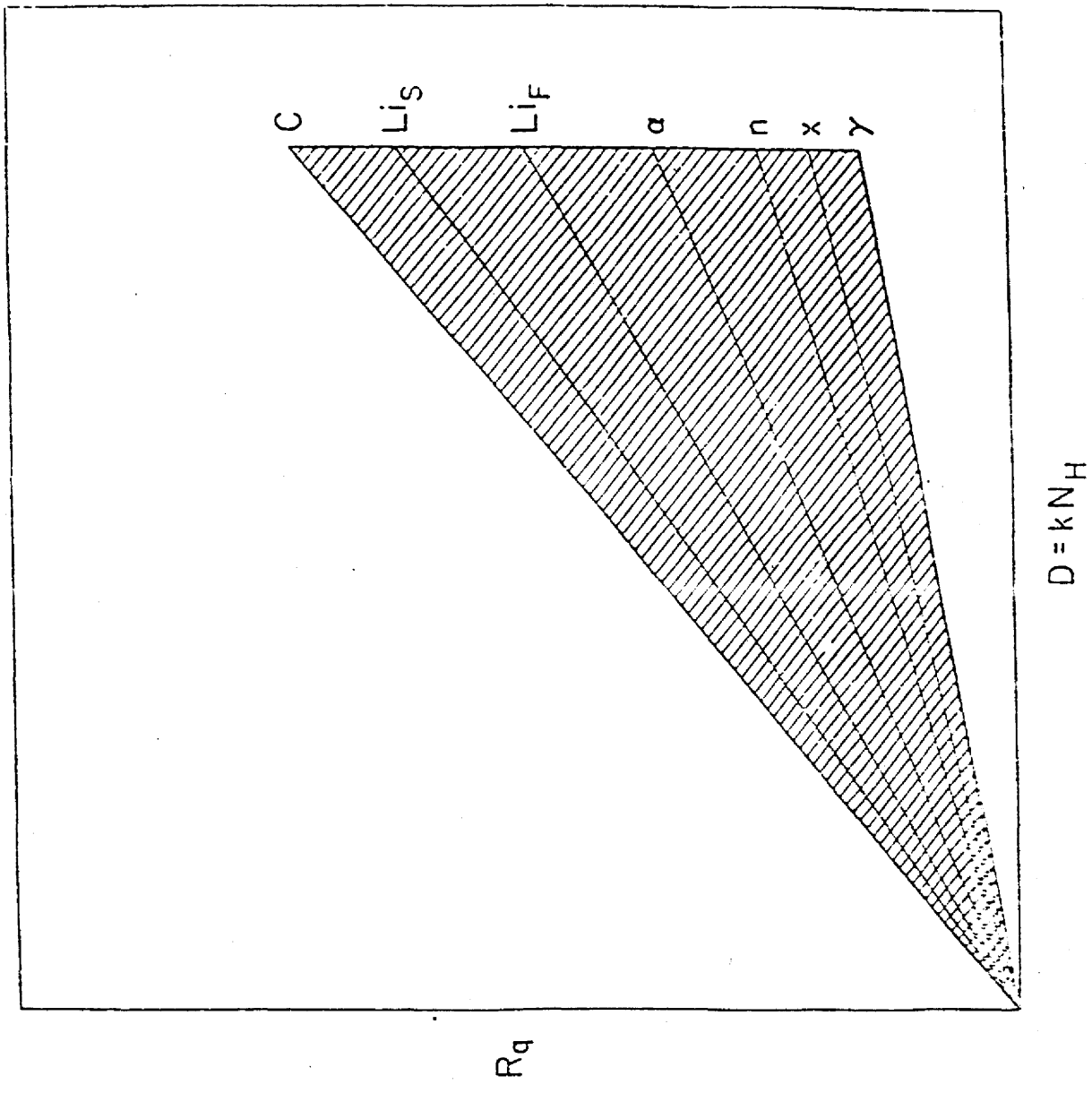

N_H, at z
AREA
$=R_H$
z
R, FOR EXPOSURE E
P_H
R_q
D (= kE)
P_q, at z
HSEF
z
N_q, at z
AREA = R_q
z

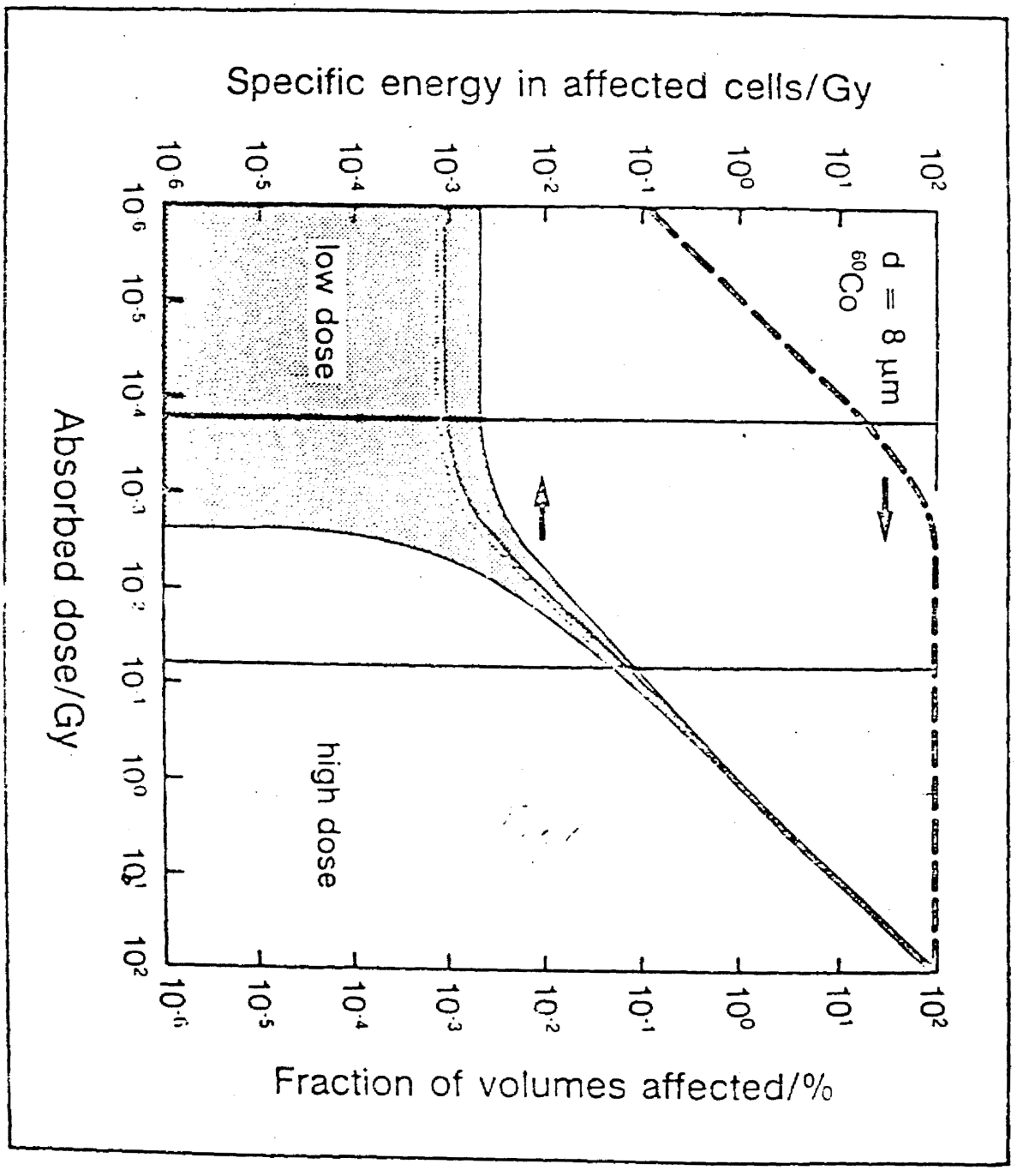
Fig 2



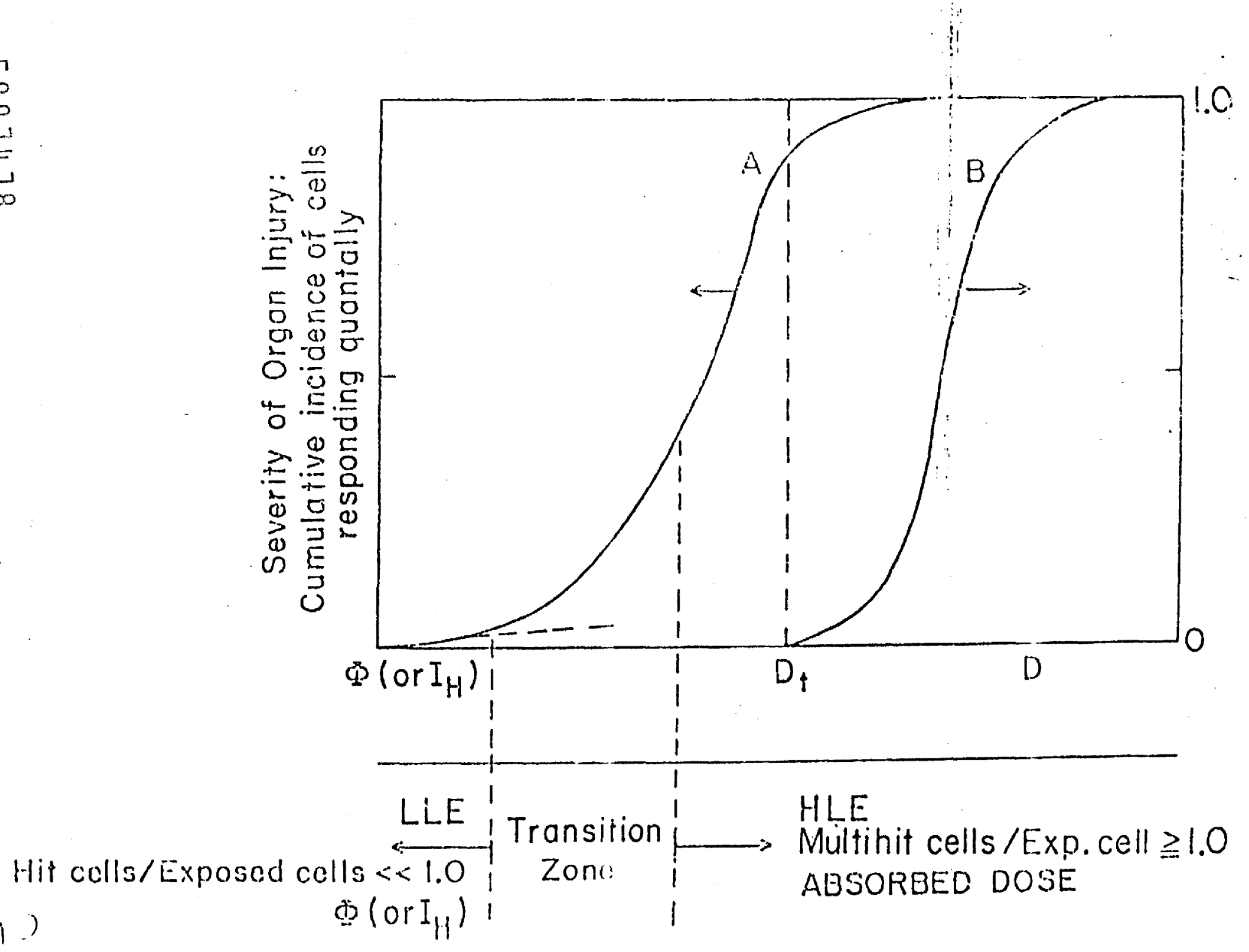
17

5007476

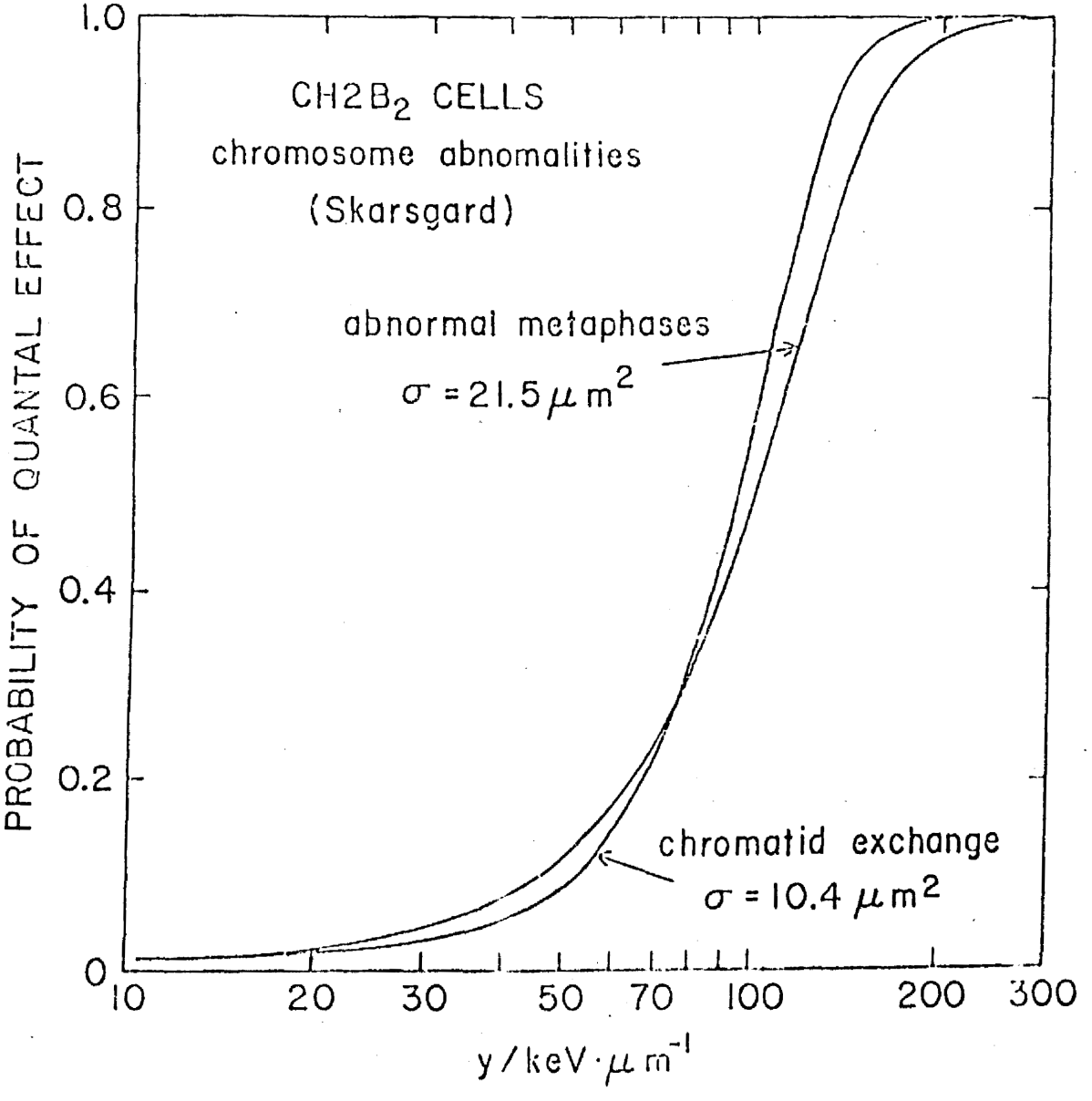
LLNL005


Specific energy in affected cells/Gy
Absorbed dose/Gy
Fraction of volumes affected/%
low dose
high dose
d = 8 µm
60Co

8L4L005


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

bLhLOOS


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

BNL-41186

ACUTE RADIATION SYNDROMES AND THEIR MANAGEMENT

BNL--41186

DE88 009839

E.P. Cronkite

Medical Department

Brookhaven National Laboratory

Upton, New York 11973

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

This research was supported by the U.S. Department of Energy under Contract DE-AC02-76CH00016. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes.

DISTRIBUTION

5007480

ABSTRACT

Radiation syndromes produced by large doses of ionizing radiation are divided into three general groups depending on dose of radiation and time after exposure. The CNS syndrome requires many thousands of rad, appears in minutes to hours, and kills within hours to days. The GI appears after doses of a few hundred to 2000 rad. It is characterized by nausea, vomiting, diarrhea, and disturbances of water and electrolyte metabolism. It has a high mortality in the first week after exposure. Survivors will then experience the HD as a result of marrow aplasia. Depending on dose, survival is possible with antibiotic and transfusion therapy. The relationship of granulocyte depression to mortality in pigs and human beings is illustrated. The role of depth dose pattern in mortality of radiation exposure is described and used as an indication of why air exposure doses may be misleading. The therapy of radiation injury is described based on antibiotics, transfusion therapy, and use of molecular regulators. The limited role of matched allogenic bone marrow transplants is discussed.

5007481

INTRODUCTION

From perusal of the older literature and review of the Japanese experience at Hiroshima and Nagasaki (1), it appeared necessary to consider some broader aspects of radiation injury in general, such as the syndromes produced by radiation injury, the influence of depth dose of radiations, the unresolved question of lethality of radiation in man, the role of dose rate, and repair of injury during chronic exposure to radiation as in fallout fields decaying with the -1.2 law. Studies on pure radiation injury generally involve a single dose of x-ray or gamma rays at different dose rates, and it is rare to find sufficient data to evaluate the influence of depth dose patterns within the experimental subject. When one considers the numbers of animals used, the steepness of the sigmoidal radiation lethality curve between 10% and 90% mortality, the practice of studying animals exposed to single dose of radiation, one must consider the possibility that lethality differences observed may represent chance variation, not related to any therapy used. In a retrospective literature evaluation, these are questions that cannot be evaluated definitively. In respect to therapy, vast human clinical experience on use of antibiotics in management of trauma and thermal burns in man and for management of marrow aplasia produced by agents other than radiation, it can be categorically stated that antibiotics increase the survival rate of patients with extensive burns, trauma and individuals with temporary marrow hypoplasia. A crucial problem in radiation injury is whether the bone marrow will regenerate before the commensal or invading pathogenic bacteria develop resistance to the antibiotics available.

Radiation Lethality - The Classical Syndromes Produced by Uniform Whole-Body Irradiation:

The radiation syndromes produced by exposure to ionizing radiations are highly dependent on the energy of the radiation and hence to the depth dose patterns which will be considered later. Three, somewhat arbitrary and overlapping syndromes are illustrated in Figure 12.

The Central Nervous System Syndrome

After large doses of several thousand rad, the Central Nervous System (CNS) syndrome is produced. Death may occur during exposure in some

5007482

laboratory animals that is preceded by hyper-excitability, ataxia, respiratory distress, and intermittent stupor. Doses capable of producing this syndrome are uniformly fatal. This syndrome has been observed in a few casualties described by Hubner et al. (2). If an occasional person were to survive the CNS syndrome, the individual has yet to experience the Gastrointestinal syndrome (GIS).

laboratory animals that is preceded by hyper-excitability, ataxia, respiratory distress, and intermittent stupor. Doses capable of producing this syndrome are uniformly fatal. This syndrome has been observed in a few casualties described by Hubner et al. (2). If an occasional person were to survive the CNS syndrome, the individual has yet to experience the Gastrointestinal syndrome (GIS).

The Gastrointestinal Syndrome

The GIS, when produced by doses in excess of 1100 rad, will be fatal within 3-9 days in laboratory animals and probably this also applies to human beings. The range in survival results from species and strain variations. It is named the GIS syndrome because of the marked nausea, vomiting, diarrhea, and denudation of the small bowel mucosa. The severe and persistent GIS is a uniformly fatal syndrome in most laboratory animals. It was observed in Japan and described by Oughterson and Warren (1), and in some accidents by Hubner et al. (2). In dogs, Brecher et al. (3), have prolonged life by intensive administration of intravenous fluids and plasma. It is of interest that animals surviving doses up to 1200 rad will regenerate the mucosa of the small intestine as described by Brecher et al. (4). The survivors of this syndrome have then to experience the sequelae of bone marrow depression, which has been termed the hemopoietic syndrome (HS) and was commonly observed in the Japanese exposed to nuclear radiation in Hiroshima and Nagasaki.

The Hemopoietic Syndrome

The HS is not necessarily fatal. It is a clinical picture that is seen in the lethal range for all mammals including man. The lethality levels reported represent the LD_{50} for the sequelae of bone marrow depression, namely, granulocytopenia with susceptibility to bacterial infection, thrombocytopenia with susceptibility to diffuse purpura and

5007483

anemia from suppression of red cell production and hemorrhage. Detailed descriptions of this syndrome in man and animals are described (1,2,5-13).

This picture of the three radiation syndromes, which overlap to a certain extent, is based primarily upon animal experimentation. Human experience (1,2,14-20) indicates that man corresponds reasonably closely to the general mammalian response. There are some differences in respect to the time of occurrence of signs and symptoms. The experience of the Japanese at Hiroshima and Nagasaki exposed to gamma radiation from a high-altitude nuclear device in which the fireball did not touch the ground are described in detail by Oughterson and Warren (1). Rubner and Fry (2) have gathered together the total human experience in radiation injury and its management, with the exception of the Japanese atomic bomb casualties and the Marshallese fallout casualties.

Radiation Injury in the Japanese at Hiroshima and Nagasaki:

The CNS was not observed by the Japanese at Hiroshima or Nagasaki (1,15,24), nor would one have expected it to be observed since doses to produce the syndrome were well within the area of total destruction and no survival. The GIS, with deaths in the first week, are well documented clinically and pathologically as are deaths from the HS (1,15,18). In the case of man, the sequential sequence of deaths and depression of blood counts is different from that in animals. It takes longer for the HS to develop in man. For example, deaths from infection were most prevalent in the second to fourth weeks (maximum incidence during third week) and from hemorrhagic phenomena during the third to sixth weeks (maximum incidence in the fourth week). Deaths from radiation injury were occurring in the Japanese as late as the seventh week. This is in contrast to other animals, where deaths from the acute phase are uncommon later than the thirtieth day after exposure. The correlation of neutrophil counts with mortality, is shown in Figure 2. The data in Figure 2 are based on dogs that were exposed to a nuclear bomb in the Pacific proving ground. Comparable observations were made in the Japanese at Hiroshima and Nagasaki and are illustrated in Figures 3 and 4. In addition, it was shown that lowest leukocyte counts in the Japanese were observed in the fifth to the sixth week after exposures to the nuclear radiation (2%). A comparable sequence in the depression of granulocytes was also seen in the Marshallese exposed to fallout radiation (5).

5007484

Probability of Survival following Exposure to Whole-Body Radiation:

The probability of survival can be related to symptomatology in man. The following analysis is based on the observations made on the Japanese in Hiroshima and Nagasaki (1). Individuals exposed in the lethal range (where some, but not all, die in the first several weeks after exposure) can be divided according to signs and symptoms, into groups having different prognosis. Thus, they may be divided into three groups in which survival is, respectively, improbable, possible and probable. This grouping was originally made by Cronkite (7). It is apparent that there is no sharp line of demarcation among the groups.

Survival Improbable: If vomiting occurs promptly or within a few hours and continues and is followed in rapid succession by prostration, diarrhea, anorexia, and fever, the prognosis is grave. Death will probably occur in 100% of these individuals within the first week. It is assumed that extensive administration of fluids and plasma may extend the life of these individuals so they may survive to develop the hemopoietic syndrome.

Survival Possible: Vomiting may occur, but will be of relatively short duration followed by a period of well-being. In this period of well-being, marked changes are taking place in the hemopoietic tissues. Lymphocytes are profoundly depressed within hours and remain so for months. The neutrophil count falls to low levels, the degree and time of time of maximum depression depending upon the dose as illustrated by Jacobs et al. (20). Signs of bacterial infection may develop when the total neutrophil count falls below 500/μl. Platelet count may reach very low levels after two weeks. Evidence of bleeding may occur within 2-4 weeks. This group represents a lethal dose range in the classical pharmacological sense. In the higher exposure groups of this category, the latent period lasts from 1-3 weeks with little clinical evidence of injuries other than slight fatigue. At the termination of the latent period, the patient may develop purpura, epilation, or cutaneous ulcerations, infections of wounds or burns, diarrhea and/or melena. The mortality will be significant. With therapy, antibiotics and/or sulfonamides the survival time can be expected to be prolonged and if sufficient time is provided for bone marrow regeneration the survival rate will be increased substantially. In Japan,

5007405

many soldiers had nausea and vomiting, recovered, felt well, returned to duty to later develop purpura, epilation, oral cutaneous lesions, and then died of infection. This is well-documented by Oughterson and Warren (1). Despite the chaotic conditions that existed in Hiroshima, the data of Nikuchi and Nakisaka (19) indicates that there was more rapid decrease of granulocytes in individuals that could be assigned to the Survival Improbable and Survival Possible as compared to the Survival Probable group.

Survival Probable: This group consists of individuals who may or may not have had transient nausea and vomiting on the day of exposure. In this group, characterized by the Marshallese (6), there is no further evidence of effects of exposure except the hematologic changes that can be detected by serial studies of the blood with particular reference to granulocytes, lymphocytes and platelets. The lymphocytes may reach low levels early, within 48 hours, and show little evidence of recovery for many months after exposure. The granulocytes may show some depression during the second and third week. However, considerable variation is encountered. A late fall in the granulocytes during the 6th or 7th week after exposure may occur. Platelet counts reach the lowest levels at approximately the 30th day at the time when maximum bleeding was observed in the Japanese who were exposed at Hiroshima and Nagasaki. The lowest platelet counts were also seen in the Marshallese exposed to fallout radiation [illegible] days after exposure. In this group individuals with neutrophil counts below 1000/µl may be completely asymptomatic. Likewise, individuals with platelet counts of 75,000/µl or less may show no external signs of bleeding. Even though the defenses against infection are lowered by this sublethal dose of radiation, individuals with these severe degrees of hematologic depression may not develop infection. It is generally believed that premature administration of antibiotics prophylactically may jeopardize the probability of recovery in Survival Possible group by allowing bacteria to develop resistance to antibiotics.

Effects of a Single Dose of Gamma Radiation

Analysis of a Possible Human LD_{50}

In the first place, in all reality, the mortality response of man to radiation is not known with any degree of precision. One should think of the LD_{50} in the classic pharmacologic sense; that is, the mortality

5007486

response to radiation in the absence of treatment and other complicating factors. The LD_{50} will be increased by the use of antibiotics to control infections, by platelet transfusions to control bleeding, and the hemopoietic molecular regulators now available to stimulate an earlier recovery of hematopoiesis. In 1947 Lewell (21) surveyed the opinion of radiologists of the 50% lethal dose of radiation in man. Their estimates varied considerably and the average was close to 450 rad, the commonly stated LD_{50}.

Many sources of data bear on the LD_{50} value for man and each has several shortcomings. These sources include radiation mortality data on large animals, the data from the Japanese exposed at Hiroshima and Nagasaki, the Marshallese data and data from patients given therapeutic total body radiation. The effects of geometry of exposure and energy of radiation on the mortality response is crucial (22-24). Bond and Robertson (23) observed that the small animals appear to have a high LD_{50}, whereas large animals have a low LD_{50}. It would be logical from this to argue that man may have a low LD_{50}. In fact, one does not really know how to extrapolate from animals to man. In principle, at least, one might think that in Hiroshima and Nagasaki where many individuals were exposed, one would have a rather good idea of the radiation LD_{50} for man. This is not the case, however, because of the complicating factors of trauma, thermal injuries, poor nutrition, and, most importantly, the inability to really assign radiation doses to individuals that survived or died.

Cronkite and Bond (25) have approached the problem of LD_{50} in man by looking at the Marshallese response to 175 rad total body irradiation and the response of animals in general. Figure 5 illustrates an approach to estimating human LD_{50}. It is believed that the Marshallese were exposed to a near maximal sublethal dose of radiation. It would appear that 200 rad uniform total body irradiation would anchor the lower part of the mortality curve. Certainly, in dogs and swine, if the dose of radiation were increased by 100 rad over that received by the Marshallese, one would be well into the lethal dose range. If one adds 50 rad to the estimated 175 rad that the Marshallese received, one has a probable low lethality of about 5-10%, of approximately 225 rad. If one uses the same slope for man as for dogs, the 90% mortality is about 500 rad. The midpoint between LD

5007487

10% and 90% is approximately 300 rad. Thus, one can make a first guess that the LD_{50} for manis in the vicinity of 360 rad midline in the absence of complicated thermal burns, trauma, or any effective therapy. This estimate is bolstered by the fact that patients given therapeutic total body irradiation have severe hematopoietic depression occurring at dose levels of about 200 rad.

Probable Effects of Therapy

On clinical grounds, one would think that the combined use of antibiotics, fresh whole blood and platelet transfusions when needed, would increase the survival rate. It has been clearly shown by Miller et al. (26) that antibiotics increase the survival rate of irradiated mice. Furth et al. (27) obtained no marked benefit from antibiotic and transfusion therapy in their studies. Subsequent studies by Sorenson et al. (28) and Perman et al. (29) have clearly shown that one can consistently reduce mortality from a near 100% fatal dose to about 10% mortality in dogs by the combined use of high dosage of successive antibiotics and whole blood transfusions supplemented by platelet-rich plasma when red cells are not needed. This enables one to shift the sigmoidal dose mortality curve of uncomplicated whole body radiation injury to a much steeper one shifting the LD_{50} from approximately 300 rad in the dog to a little over 400 rad. The 5% mortality is shifted from roughly 200 rad to about 400 rad resulting in a nearly vertical sigmoid mortality curve. After doses in excess of 500 rad little benefit is observed and with greater doses no animals survive, although the survival time is moderately increased. Thus, one can anticipate that antibiotics, blood transfusions and platelet transfusions would benefit human beings.

The relationship of mortality to depression in the granulocyte count in dogs and man further points up the important role of infection and value of antibiotics. In Figure 2 is shown the granulocyte count in dogs that were exposed to gamma radiation from a nuclear bomb and the correlation with percent mortality. The granulocyte curve at the far left is in dogs that were exposed to about 600 rad midline dose. Note that the blood counts declined and all animals were dead by the seventh day of exposure. At autopsy infection was clearly the major cause of death. In the next curve the mortality was also 100% with a slower decline in granulocyte count along with a longer survival time. At autopsy the major cause of

5007488

death was ascribed to infection and complicated by hemorrhage. The next curve shows a slower decline in the granulocyte count with a mortality of 80%. The animals at autopsy showed infection and hemorrhage as causes of death. The curve showing the least decline in the granulocyte count had a mortality of 10% with hemorrhage and infection the causes of death.

In Figures 3 and 4, the critical role of the granulocyte count in the Japanese as a determinant of mortality is illustrated. Figure 3 plots the mortality against the blood counts observed in the third, fourth, and fifth weeks. The lower the white count the higher the mortality. Figure 4 correlates the mortality at the end of nine weeks with the lowest white count observed. The most clearcut correlation of the importance of infection is in the work of Miller et al. (29), shown in Figure 5. In this figure, there is a clearcut correlation of mortality with the fraction of animals having positive blood and splenic bacterial cultures. Subsequent studies in Russia and the U.S. extend and confirm the role of infection. Silman an and Izvekova (30) have studied a whole series of antibiotics and their use in the treatment of radiation injury in mice, rats, and rabbits. They administered kanamycin, erythromycin, tetracycline, ampicillin, oxacillin, and oletetrine. The antibiotics were administered twice a day by mouth for a total of 20-25 days starting 24 hours after irradiation with a lethal dose of gamma rays. A combination of antibiotics was more effective than single antibiotics. The combination of kanamycin with tetracycline or erythromycin, or tetracycline with ampicillin was most effective. The antibiotic combinations changed a near 100% mortality, to more than 50% survival. Chernov et al. (31) and Trushina et al. (32) administered hexamine prior to exposure of dogs and monkeys followed by the administration of antibiotics. In the case of dogs, penicillin and streptomycin were used. The survivals increased from 11% to 9%. In their studies on monkeys, a combination of kanamycin, oletetrine, streptomycin, and penicillin was used. There was an increase in survival from 20% to 50%.

The Effects of Geometry of Exposure and Radiation Injury on Depth-Dose Curves and Biological Effectiveness

The inadequacies of using an air dose of radiation for prognosis will be illustrated by showing the influence of exposure geometry and energy on

5007489

depth-dose and biological effect. Figure 7 shows the influence of exposing a Masonite phantom to 2000 kVp x ray from a single direction than when the exposure is bilateral with half of the dose given to each side (33). The dose in the phantom was measured by Sievert ionization chambers and is expressed as percent of the surface dose. In the case of the unilateral exposure, the dose falls off as it is attenuated by inverse square and absorption so that the exit dose is about 40% of the entrance dose. Thus the bone marrow of large animals being exposed would have a progressively decreased dose as the beam is attenuated. However, with bilateral exposure there is very uniform deposition of energy throughout the tissue equivalent phantom. The biological consequences of the different dose pattern are great. It is of considerable importance to bear these differences in mind when evaluating therapy of radiation injury and trying to make an animal experimentation as comparable as possible to an assumed real-life human exposure.

Figure 8 shows a comparison of bilateral exposure to 4 Pi exposure 33). This situation is important when trying to evaluate the hazards of fallout irradiation with its wide range in energy and the radiation exposure approaching 4 Pi source. Since fallout radiation is delivered from a planar source, the usual narrow beam geometry is not applicable. In such a diffuse 360 degree field, the decrease of dose with depth in tissue is less pronounced than that resulting from a bilateral exposure to an x-ray beam because fallout from inverse square is in effect neutralized. For the same energy, the dose at the center of the body is approximately 50% higher than would result from a given air dose with narrow beam geometry. Figure 8 further illustrates the depth-dose curve from an experimental situation using spherically oriented cobalt-60 sources with a phantom placed at their center, compared with a conventional bilateral depth-dose curve obtained with a single Cobalt source (34). In the latter case, the air dose is usually measured at the point subsequently occupied by the center of the proximal surface of the patient or animal with respect to the source. For the field case, all surfaces are "proximal" in the sense that air dose measured anywhere in the space subsequently occupied by the individual is the same. It is this air dose which is measured by field instruments; it does not bear the same relationships as the surface dose and the depth dose as air dose measured in a "point source" beam in the

5007490

clinic or laboratory. It would appear under these circumstances and in most experimental conditions that the midline dose, rather than dose measured in air, would be the better common parameter in terms of which to predict biological effect. On this assumption, air dose value should be multiplied by approximately 1.5 in order to compare their effects to those of a given air dose from a "point source" beam geometry delivered bilaterally. Furthermore, the geometry of radiation from a fallout field is not identical either to the geometry of bilateral point sources or the spherically distributed sources since the plane source delivers a radiation largely at a grazing angle. However, the total field situation is better approximated by solid than by plane geometry.

Figure 9 shows depth-dose curves for different types of radiation to provide an idea of the difference in absorption of energy throughout a large animal body thus injury (in the lethal range) to the important target cell, the hematopoietic stem cell, which determines whether the bone marrow will regenerate. These depth-dose curves are determined in unit density material using small Sievert chambers implanted at 5 cm intervals in the phantoms. The doses are expressed as percent of the entrance air dose. Curve A represents the depth-dose curve from 250 kVp x ray. This is a commonly used energy of radiation in animal studies. Note, the surface dose is about 40% greater than the entrance air dose and this falls off very rapidly with depth in the tissue so that approximately in the midline corresponding to man it would be 60% of the entrance to the important target cell, the hemopoietic stem cell, which determines bone marrow regeneration. Since bone marrow was distributed throughout the body in the bones, the amount of energy deposited in the hemopoietic stem cell varies by a very large factor. The curve B shows a similar depth-dose curve for 2000 kVp x ray. Curve C is the initial bomb gamma radiation and curve D is cobalt-60 gamma radiation. It is evident that for the same air dose, injury to hematopoietic stem cells scattered throughout the bone marrow varies considerably and thus would be expected to result in different lethal dose curves.

5007491

The Effect of Different Radiation Depth-Dose Curves on Mortality in Mammals

Tullis et al. (35, 36) has studied this in the laboratory and in the atomic bomb field tests with swine as the target animals. This is illustrated in Figure 10, showing the sigmoid dose mortality curves for unilateral 2000 kVp x ray, bilateral 2000 kVp x ray, and the mortality from the highly energetic prompt gamma radiation from a fission bomb. The LD_{50} from unilateral 2000 kVp x ray is 500 rad in air. Bilateral 2000 kVp resulted in an LD_{50} of 400 rad in air. The initial bomb gamma radiation with LD_{50} was about 230 rad in air. These air doses can be converted to midline tissue doses based on comparative studies on depth-dose curves to 300, 220, and 184 rad. The differences are explained in part by lack of homogeneity in distribution of dose. In the case of the unilateral 2000 kVp x ray, tissues distal from the midline received much less than 300 rad and tissues proximal to the midline received more. In the case of bilateral 2000 kVp x ray, tissues proximal to and distal from the midline receive a greater absorbed dose. In the case of the prompt gamma radiation, tissues proximal to the midline receive a greater dose and those distal a lesser dose, and hence a higher and lower survival of hemopoietic stem cells on opposite sides of the midline.

As a result of the effect of energy and geometry of exposure, measured radiation doses in air are of relatively little use in predicting survival. For practical clinical management, it is the opinion of this author that one should be guided by the clinical and hematologic course and not by estimates of radiation doses in air or doses estimated by biological dosimetry.

Fallout Radiation Exposure of the Marshallese

The energy of a fallout field determines, in addition to the geometry of exposure, the depth-dose pattern. Figure 11 shows the energy spectrum of 4-day old fallout. The original source is the energy of inherent gamma emissions from the major components of the 4-day fallout. The solid black histogram is calculated distribution of energy taking into account Compton scattering. Thus the energy to which an individual is exposed varies from a few keV with little penetration to a peak at 1600 KEV. The effect of this energy distribution in the geometry of exposure on depth-dose curves is shown in Figure 12. The depth-dose curves of a fallout field and

5007492

gamma radiation are shown. The doses of radiation to the surface and the first few millimeters of the body were substantially higher than the midline dose of gamma radiation. The curves presented are a percent of the 3 cm dose of radiation. In addition, the clinical observations of the skin lesions forcefully demonstrated that the dose to the skin varied considerably between individuals and over the surface of any given individual because of the spotty nature of the radiation burns to the skin.

Another feature of fallout radiation is its decay. The fallout arrived about 4-5 hours after detonation. Figure 13 shows the accumulation of dose as a function of time after detonation. The dose rate decreased continuously as the fallout material decayed. The major portion of the dose was received at a higher dose rate. By the time that 90% of the dose had been received, the dose rate had fallen to less than 40% of initial value and thus is much different from any animal exposure condition in the literature. The influence of a dose rate falling by a 1.2 power function is not known.

Repair of Radiation Injury

This has been considered in some detail in a report of the NCRP (37). In the NCRP dissertation, it was stated that 150 rad over one week, 200 rad over one month, or 300 rad over four months is believed to be sublethal and that no medical care would be required. However, 250 rad over one week, 350 rad over one month, or 500 rad over four months is estimated to be in the 5% mortality range and that some medical care will be required. When 450 rad is received over one week, 600 rad or more over one month or longer, the mortality without therapy is estimated to be 50% or more and extensive medical care will be required. These are doses of rad in air and not midline tissue dose in rad.

Whether studies on mice are applicable to man is not known. In recent unpublished studies, we have investigated the influence of varying the time interval from 1-24 hours between 2.5 Gy, 250 kVp x ray to mice, for a total of 10 Gy. This is shown in Figure 14. At intervals of 1 and 2 hours, no mice survive 30 days. As the interval between the 2.5 Gy increments are increased, there is an apparent cyclic change in the fraction surviving. When the interval is 22 or 24 hours between the 2.5 Gy increment, 100% of the mice survive. Figure 15 shows the hematopoietic stem cell (CFU-S) per

5007493

leg in normal mice and mice receiving a single dose of 100, 200, or 300 rad and the mice receiving 1000 rad in a single dose or 1000 rad in four 250 rad increments 24 hours apart. All 1000 rad animals died by the 11th day after irradiation and the survivors had a very low CFU-S content of about 1 per leg. Animals receiving a 250 rad dose at 24 hour intervals had an equal depression of their CFU-S, followed by an exponential recovery to near normal levels by 30 days after exposure.

Therapy of Whole Body Radiation Injury

Bacterial infection has long been established as the major cause of death in the irradiated animal in the LD_{50} range. The commensal organisms living primarily in the gastrointestinal tract are the usual organisms that kill the animal that is irradiated in the LD_{50} range (11, 26, 38-40). The use of antibiotics as an effective treatment was first shown by Miller et al. (41) with the administration of streptomycin in mice. In addition, germ-free animals have been studied (42, 43) and these animals live longer, dying from hemorrhage and anemia rather than infection in the absence of bacteria. The effectiveness of antibiotics falls off as one nears the 100% lethal dose level since bone marrow regeneration is delayed so long that bacteria develop resistance to the antibiotics being used before bone marrow regeneration ensues. Taketa (44) has intensively studied the roles of water-electrolytes and antibiotic therapy against the acute intestinal radiation death in the rat. In these studies it was clearly shown that microorganisms play a prominent role in the genesis of acute intestinal death in the rat, and this was modified by the use of antibiotics and intensive administration of water and electrolytes. It is a beneficial effect not limited to rodents. Dogs have been treated with success with antibiotics, fluid replacement, and blood transfusion. A dramatic improvement in mortality was obtained by Coulter et al. (45), Hammond (46), and Allen et al. (47). In the latter study, blood transfusions were combined with successive antibiotics. In view of the fact that commensal organisms of the intestine are frequently cultured from the blood of the fatally irradiated mouse, Webster (48) tested the effect of oral neomycin therapy upon the mortality from whole body x-irradiation of rats. Graded doses of radiation were used from 700 rad through 2500 rad. Neomycin treatment resulted in significant prolongation of the mean survival time at

5007494

irradiated animals at exposures between 800 and 1500 rad. After 1500 rad and 2500 rad there was a small, but consistent prolongation of the mean survival time. For exposures between 700 and 1100 rad, the 30-day lethality was consistently lower for the neomycin-treated rats. Jorenson et al. (28) and Perman et al. (29) discussed earlier have clearly established an effective treatment of fatally irradiated dogs utilizing successive antibiotics, fluids, platelet transfusions, and whole blood as needed. Shalnova (49) published an English-language review of all of the work done in Russia before 1975 on antibiotic therapy in radiation injury. The essence of the work is: 1) apply broad-spectrum antibiotics insuring suppression of microproliferationusing a purposeful alternation of antibiotic cycles with different preparations; 2) use antibiotics to create bacterial static concentrations of antibiotics, not only in the blood and tissues but also in places of naturaloccurrence of microbes such as the gastrointestinal tract and respiratory tract; 3) utilize antibiotics as early as possible, and before infectious foci have developed.

The Management of Whole Body Radiation Injury With or Without Combined Burns and Wounds

As discussed earlier, estimates of the air-exposure dose are of little value for two reasons. First, one needs to know the depth-dose distribution and second, the dose estimates are generally inaccurate, bearing on the high side initially and then declining as further studies and analyses are made.

The first step is to determine the severity of the radiation injury on the basis of signs and symptoms. If there are no abnormal symptoms such as nausea, vomiting, or diarrhea, the dose of radiation is in all probabilityin the sublethal range. If there is severe nausea, vomiting, and diarrhea as discussed earlier, the individuals will fall into the severe gastrointestinal syndrome. If the early symptomatology subsides and there is a feeling of well-being with rapidly developing changes in the hematologic picture with developing lymphopenia, neutropenia, and thrombocytopenia, the individuals would fall into the hematopoietic syndrome. The following therapeutic regimen is proposed:

1. If the exposure involves contamination with radioactive materials, the individuals should be monitored for radioactivity and decontaminated as promptly as possible.

5007495

2. If exposed to neutrons, a whole body count should be made to estimate the amount of radionuclides produced.

3. Medical history, physical examination, and laboratory studies including a complete hematologic evaluation should be done as promptly as possible. Cytogenetic preparations of direct bone marrow and phytohemagluinin stimulated peripheral blood lymphocytes should be set up for later analysis of biological dose estimate. As soon as possible, the lymphocytes should be obtained while still available, before lymphopenia sets in, for human lymphocyte (HLA) typing and storage for later mixed leukocyte cultures. The results of the tissue typing will be useful for matching of granulocyte, platelet transfusions and the identification of a possible bone marrow donor.

4. In the early stages, the first five days, fluid and electrolyte balance must be monitored closely and restored by the appropriate intravenous or oral solution.

5. Reverse isolation techniques to prevent ingress of pathogens to the irradiation individuals are generally believed to have been effective in preventing infections in patients undergoing treatment for leukemia and subsequent bone marrow transplantation. This would probably be a useful procedure in the event of a potentially fatal irradiation accident. If possible, the individual should be admitted to a modern laminar air-flow room with a complete regimen of skin sterilization, sterile diet, and non-absorbable antibiotics for sterilization of the gastrointestinal tract. If this is not feasible, measures should be initiated to prevent commensal and pathogenic infections. Reduction in the gastrointestinal flora is desirable, and this can be accomplished with oral, non-absorbable broad-spectrum antibiotics such as neomycin and antifungal agents such as nystatin.

6. Platelet transfusions, preferably fresh, should be given when the platelet count approaches 25,000 and repeated to maintain levels above this.

If the patient should become refractory to random donor platelets, the use of HLA-matched platelets from unrelated donors may become necessary. A family-member transfusion should not be administered until the possibility of bone marrow transplantation has been excluded because such transfusions might sensitize the patient to the antigens of a possible donor.

5007496

7. Granulocyte transfusions would be desirable to prevent infection in patients with a granulocyte count falling below 200/μl. Admittedly, these are not practical on any large scale.

8. Infection is the greatest threat to life. The onset of significant fever greater than 38°C should arouse strong suspicion of infection in the granulopenic patient. Fever with clinical signs of bacterial infection, or fever sustained more than 24 hours is an indication for initiating systemic antibacterial therapy even though cultures are negative. Since the most likely agent is an organism from normal bowel flora, initial therapy should include aminoglycoside and carbenicillin with additional antibiotics being added as indicated by bacterial culture sensitivities that are obtained. If cultures are negative or fever persists, therapy with a combination of trimethoprim and sulfamethoxazole or with amphotericin may be considered. After initiation of broad-spectrum antibiotic therapy, it should be continued until the granulocyte count rises above 500/μl, fever subsides, and evidence of infection disappears.

9. Washed packed red blood cells should be given as indicated to keep the hemoglobin above 8.5 g.

10. All blood products should be irradiated with 2 000 rad before infusion into the patient in order to kill lymphocytes that might proliferate and impair the possibility of a bone marrow transplant.

11. Bone marrow transplantation will only rarely be indicated in an irradiation casualty because uncertainty about the magnitude of the radiation dose, inhomogeneity of the dose, and the requirement that the dose be within the limits of rescue of bone marrow transplantation, approximately 800-2000 rad. Below 800 rad immunity is not sufficiently suppressed and transplants are rejected. Above roughly 2000 rad there is no therapy. From the lymphocytes collected promptly, the casualty will have been HLA-typed and donors will have been identified. A genetically identical twin is the ideal donor. In one irradiation casualty exposed to approximately 600 rad showed a rapid hematopoietic recovery following the transfusion of bone marrow from his twin. Although radiation dose was used above as an indication for bone marrow transplantation, it is to be noted from the earlier discussion that doses and the depth-dose curves are not known with any degree of certainty and the doses used above were based on experimental conditions where radiation was delivered in a manner to give uniform whole body distribution of absorbed energy.

5007497

Hematopoietic Molecular Regulators in the Management of the Bone Marrow Hypoplasia

In the last ten years several molecular regulators of hematopoiesis have been identified, purified, sequenced, and by recombinant DNA techniques are being produced in large amounts. These are interleukin-1 and 3, granulocyte- macrophage colony-stimulating factor, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and erythropoietin. Interleukin-1, a product primarily of activated monocyte or macrophages, stimulates T-cells, endothelial cells, and fibroblasts to produce granulocyte-macrophage colony- stimulating factor. The latter accelerates the production of granulocytes and macrophages in vitro and upon in vivo administration produces a granulocytosis with accelerated production of granulocytes. It also increases the effectiveness of the functional granulocytes in phagocytosis and bacterial killing. Granulocyte colony-stimulating factor accelerates in vitro the production of granulocytes in colonies and in vivo accelerates the production of granulocytes and improves the phagocytic and bacterial-killing capacities (50-55). IL-1 has been used as a radioprotector. When administered 20 hours prior to irradiation, IL-1 turns a near 100% lethal dose of radiation in the mouse to near 100% survival. When administered four hours before or 48 hours before, it is ineffective (50). GM-CSF and G-CSF have been administered to primates and shown to produce a sustained granulocytosis of 4-5 times the normal level as long as the materials are administered. It has been given to primates and mice in which the marrow has been suppressed by radiation or chemicals and the granulocyte counts are increased (51-54). Erythropoietin has been shown to be of major benefit in stimulating the production of red cells in individuals with severe anemia as a result of renal failure (55). It is assumed that these agents or combinations will be of potential benefit in the treatment of individuals with bone marrow suppression as a result of whole body irradiation. On the other hand, it is conceivable that forcing cells into mitosis before DNA is adequately repaired may fix genetic injury and result in either an early failure of the mitotic capacity of pluripotent stem cells or an earlier and increased incidence of leukemia. These are possibilities that need to be explored experimentally.

5007498

REFERENCES

1. Oughtersen, A.W. and Warren S. (1956) Medical Effects of the Atomic Bomb in Japan, McGraw Hill Book, Inc., New York.
2. Hubner, K.F. and Fry, S.A. (1980) The Medical Basis for Radiation Preparedness, Elsevier North Holland, Inc., New York, Amsterdam and Oxford.
3. Conard, R.A., Cronkite, E.P., Brecher, G., and Strome, C.P.A. Experimental therapy of gastrointestinal syndrome produced by lethal doses of ionizing radiation. J. Appl. Physiol. 7, 227-233, 1956.
4. Brecher, G., Cronkite, E.P., Conard, R.A., and Smith, W.W. Gastric lesions in experimental animals following single exposures to ionizing radiation. Amer. J. Pathol. 34, 105-119, 1958.
5. Cronkite E.P. and Bond, V.P. (1960) Radiation Injury in Man, Charles C. Thomas, Springfield, IL.
6. Cronkite, E. P. and Bond, V.P. (1956) Some Effects of Ionizing Radiation on Human Beings, A Report on Marshallese Exposed to Fallout Radiation, U.S. Government Printing Office, T.I.D. 5358, Washington, DC.
7. Cronkite, E.P. (1957) The diagnosis, prognosis and treatment of radiation injury produced by atomic bombs. Radiology 56, 661-669.
8. Cronkite, E.P. and Brecher, G. (1955) Protective effect of granulocytes in radiation injury. Ann. N.Y. Acad. Sci. 59, 815-833.
9. Bond, V.P., Silverman, M.S. and Cronkite ,E.P. (1954) Pathogenesis and pathology of radiation infections. Radiat. Res. 1, 339-400.
10. Cronkite, E.P. and Brecher, G. (1952) Defects in hemostasis produced by whole body irradiation in the dog. 5th Annual Conf. on Blood Coagulation, Josiah Macy Foundation, New York.
11. Miller, C.P., Hammond, C.W. and Tompkins, M. (1951) The role of infection in radiation injury. J. Lab. Clin. Med. 38, 562-571.
12. Jacobson, L.O. (1954) Modification of radiation injury in experimental animals. Amer. J. Roentgenology and Rad. Therapy 72, 543-555.
13. Hale, W.J. and Stoner, R.D. (1954) Effect of radiation on immunity I. Radiat. Res. 1, 459-470.
14. Hempelman, L.H., Lisco, H., and Hoffman, J.G. (1952) The Acute Radiation Syndrome: A Study of Nine Cases and a Review of the Problem. Ann. Int. Med. 36, 279.

5007499

15. LeRoy, G.V. (Jan. 1950) Hematology of Atomic Bomb Casualties. Arch. Int. Med. 86, 691.

16. Hasterlik, R.J. (1953) Clinical Report of Four Individuals Accidentally Exposed to Gamma Radiation and Neutrons, Argonne National Laboratory.

17. Guskova, A.K. and Baisogolov, G.D. Two Cases of Acute Radiation Disease in Man. Presented at the International Conf. on The Peaceful Uses of Atomic Energy, Geneva, July, 1955.

18. Kikuchi, T. et al. (Feb. 13, 1960). Studies on the atomic bomb injuries in Hiroshima City. Report to the Special Research Committee on the Atomic Bomb Disasters, Japan.

19. Kikuchi, T. and Wakisaka, G. (1952) Hematological investigations of the atomic bomb sufferers in Hiroshima and Nagasaki City, Acta Scholae Medicinalis, Univ. of Kyoto 30, 1-33.

20. Jacobs, G.J., Lynch, F.S., Cronkite, E.P. and Bond, V.P. (1963) Human radiation injury - a correlation of leukocyte depression with mortality in the Japanese exposed to the atomic bombs. Military Med. 128, 732-739.

21. Newell, R.R. (1950) Human tolerance for large amounts of radiation. Radiology 54, 598-601.

22. Bond, V.P., Cronkite, E.P., Sondhaus, C.A., Lipsie, G., Robertson, J.S. and Borg, D.C. (May 1957) Influence of exposure geometry on pattern of radiation dose delivered to large animal phantoms. Radiat. Res. 6, 554-572.

23. Cronkite, E.P. and Bond, V.P. (1956) Effects of radiation on mammals. Ann. Rev. Physiol. 18, 483-526.

24. Bond, V.P. and Robertson, J.S. (1957) Vertebrate radiobiology (lethal actions and associated effects). Ann. Rev. Nuclear Sci. 7, 135-162.

25. Cronkite, E.P. and Bond, V.P. (1960) Diagnosis of radiation injury and analysis of human lethal dose of rdiation. U.S. Armed Forces Med. J. 11, 249-260.

26. Miller, C.P., Hammond, C.W. and Tompkins, M. (1950) Reduction of mortality from x-radiation by treatment with antibiotics. Science 111, 719.

27. Furth, J., Coulter, M.P., Miller, R.W., Howland, J.W. and Swisher, S.N. (1953) The treatment of the acute radiation syndrome in dogs with aureomycin and whole blood. J. Lab. Clin. Med. 41, 918.

5007500

28. Sorenson, D.K., Bond, V.P., Cronkite, E.P. and Perman, V. (1960) An effective therapeutic regimen for the hemopoietic phase of the acute radiation syndrome in dogs. Radiat. Res. 13, 669.

29. Perman, V., Sorensen, D.K., Usenik, E.A., Bond, V.P. and Cronkite, E.P. (1962) Hemopoietic regeneration in control and recovery of heavily irradiated dogs following severe hemorrhage. Blood 19, 738.

30. Tumanian, M.A., Izverkova, A.V. (1974) The effectiveness of treating infectious complications of radiation sickness with antibiotics. Antibiotiki (Moscow) 19: 913-917.

31. Chernov, G.A., Trushina, M.N. and Suvorov, N.N. (1973) Radioprotective effectiveness of peroral administration of nexamine in dogs. Radiobiologiya 2, 464-466.

32. Trushina, M.N., Znamenski, V.V., Chernov, V.A., and Lember V.A. (1973) Radioprotective action of hexeamine in the case of peroral administration in monkeys. Radiobiologiya 2, 719-722.

33. Bond, V.P., Imirie, G.W., Cronkite, E.P. and Stickley, E.E. (1959) Distribution in tissue of dose from penetrating gamma and neutron radiation in radioactivity in man. George R. Meneely, Ed., Charles C. Thomas, Springfield, IL, pp. 173-184.

34. Tullis, J.L., Chambers, Jr., F.W., Morgan, J.E. and Zeller, J.R. (1952) Mortality in swine and dose distribution studies in phantoms exposed to supervoltage roentgen radiation. Am. J. Roentgenol. Radium Therapy 67, 620-627.

35. Tullis, J.L., Lamson, B.G. and Madden, S.C. (1954) Mortality in swine exposed to gamma radiation from an atomic bomb source. Radiology 62, 400-415.

36. Radiological Factors Affecting Decision-Making in a Nuclear Attack, NCRP No. 42, 1974, National Council on Radiation Protection and Measurements, NCRP Publications, P.O. Box 30175, Washington, DC 20014.

37. Miller, C.P., Hammond, C.W. and Tompkins, M. (1950) Reduction of mortality from X-radiation by treatment with antibiotics. Science 111, 719-720.

38. Silverman, M.S., Greenman, V., Chen, P.H. and Bond, V.P. (1958) Bacteriological studies on mice exposed to supralethal doses of ionizing radiations. Radiat. Res. 8, 123-130.

5007501

39. Consherry, L., Marston, R.Q. and Smith, L.W. (1953) Naturally occurring infections in untreated and streptomycin-treated X-irradiated mice. Am. J. Physiol. 172, 359-364.

40. Miller, C.P., Hammond, C.W., Tompkins, N. and Shorter, G. (1952) The treatment of post-irradiation infection with antibiotics: an experimental study on mice. J. Lab. Clin. Med. 39, 462-479.

41. McLaughlin, M.M., Bacquisto, M.P., Jacobus, D.P. and Horowitz, R.E. (1964) Effects of the germfree state on responses of mice to whole-body irradiation. Radiat. Res. 23, 333-339.

42. Ledney, G.D. and Wilson, R. (1965) Protection induced by bacterial endotoxin against whole body X irradiation in germfree and conventional mice. Proc.Soc.Exp.Biol.Med. 118, 1062-1065.

43. Taketa, S.T. (1962) Water-electrolyte and antibiotic therapy against acute (3- to 5-day) intestinal radiation death in the rat. Radiat. Res. 16, 312-326.

44. Coulter, M.P., Furth, F.W. and Howland, J.W. (1952) Therapy of the X-irradiation syndrome with terramycin. Am.J.Pathol. 28, 857-881.

45. Hammond, C.W. (1954) The treatment of postirradiation infection. Radiat. Res. 1, 448-458.

46. Allen, J.G., Moulder, P.V. and Emerson, D.M. (1951) Pathogenesis and treatment of the postirradiation syndrome. JAMA 145, 704-711.

47. Webster, J.J. (1967) The effect of oral neomycin therapy following whole-body X-irradiation of rats. Radiat. Res. 32, 117-124.

48. Shalnova, G.A. (1975) Some problems of antibiotic therapy in radiation sickness. J. Hyg. Epidemiol. Microbiol. Immunol. 19, 138-147.

49. Neta, R., Douches, S., and Oppenheim, J.J. Interleukin 1 is a radioprotector. J. Immunol. 136, 2483-2488, 1987.

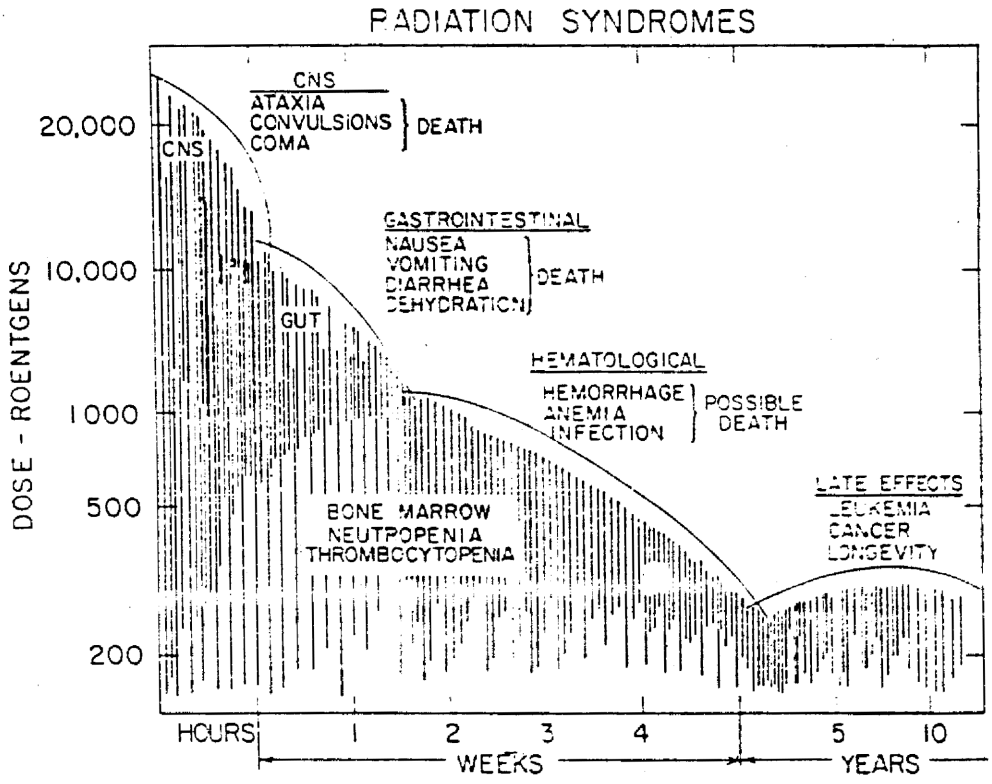
50. Komiyama, A.A., Ishiguro, T., Kabuo, et al. Increases in neutrophil count by purified human CSF in chronic neutropenia of children. Blood 71, 41-45, 1988.

51. Donahue, R.A., Wayne, E.A., Stone, D.K., et al. Stimulation of hematopoiesis in primates by continuous infusion of recombinant human GM-CSF. Nature 321, 872-875, 1986.

52. Welte, K., Bonilla, M., Gabrilove, J.L., et al. Recombinant Human granulocyte-colony stimulating factor in vitro and in vivo effects on myelopoiesis. Blood Cells 13, 17-30, 1987.

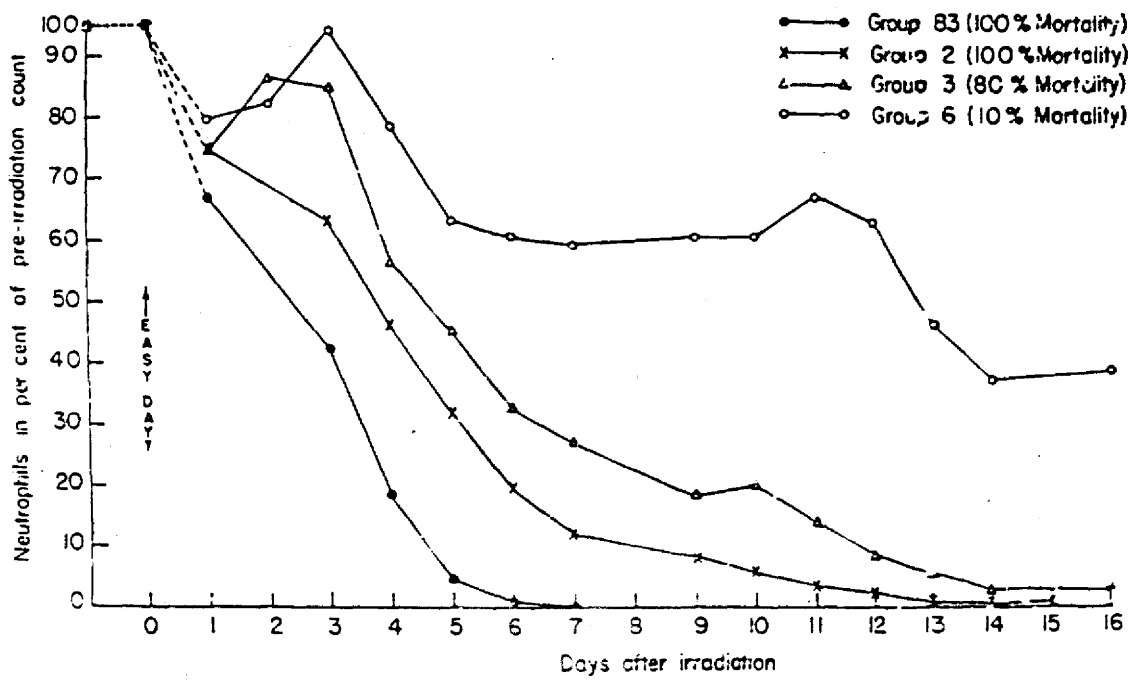
5007502

Figure 1. Schematic presentation of radiation syndromes produced by total body irradiation as a function of dose and time after irradiation



5007503

Figure 2. Sequential neutrophil counts in dogs exposed to nuclear bomb gamma radiation in relation to mortality.



5007504

Figure 3. Mortality (died within 9 weeks) related to WBC level Hiroshima and Nagasaki

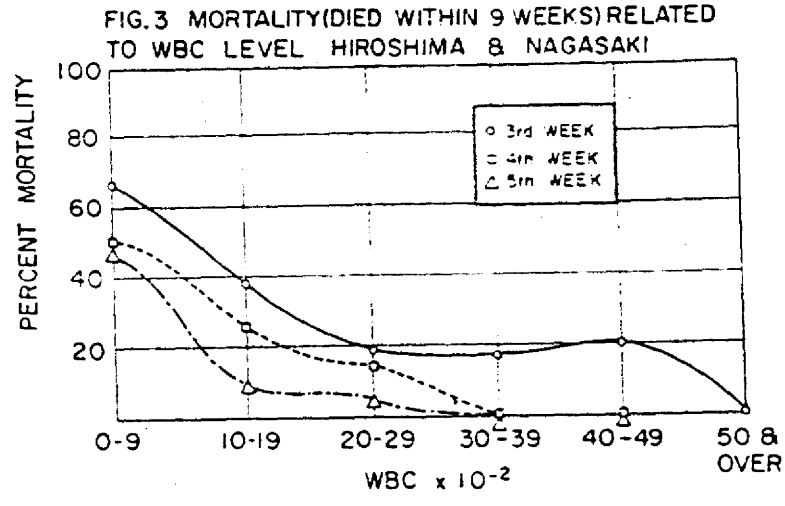
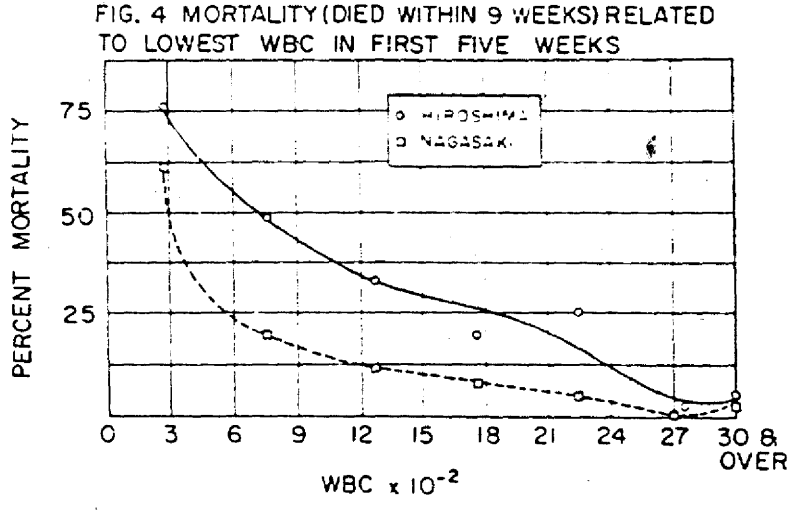


Figure 4. Mortality (died within 9 weeks) relate to lowest WBC in first five weeks.



50071505

Figure 5. Schematic presentation of likely and unlikely radiation lethal dose curves for man from Cronkite and Bond (25).

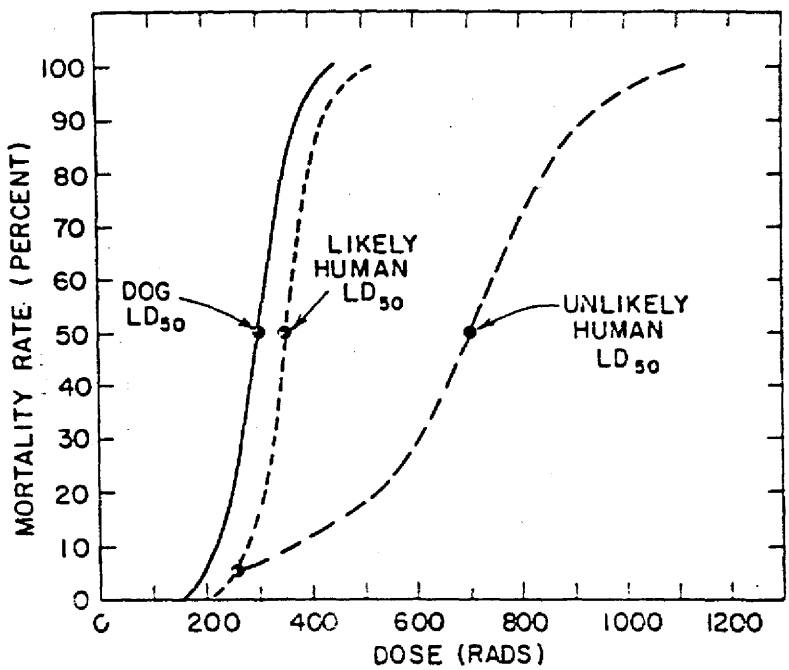


Figure 6. Frequency of deaths, positive blood and splenic cultures by days after irradiation with 450 r (200 KV X-ray). Death frequency based on 262 mice. Frequency of cultures based on 35 cultures performed daily. (Miller, C.P., Univ. Chicago, 1949, unpublished).

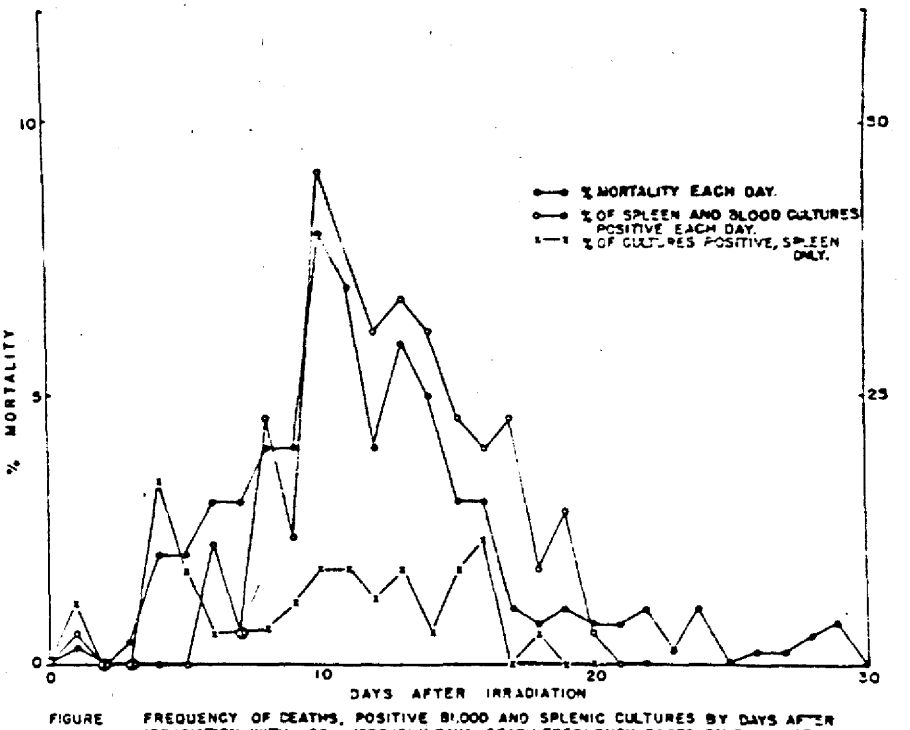
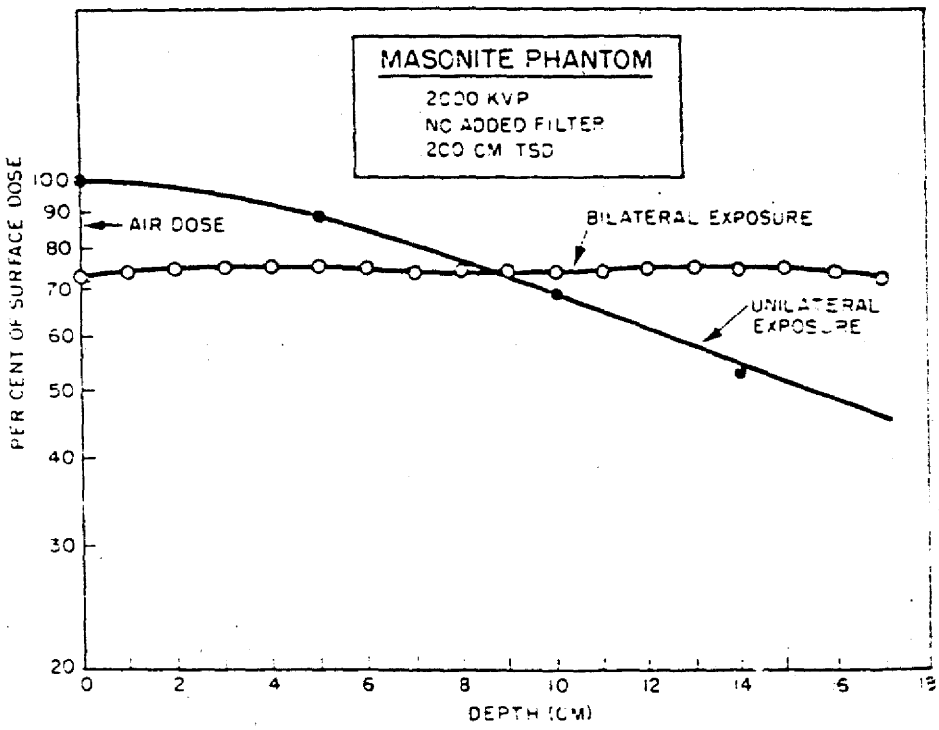


FIGURE FREQUENCY OF DEATHS, POSITIVE BLOOD AND SPLENIC CULTURES BY DAYS AFTER IRRADIATION WITH 450 r (200 KV X-RAY). DEATH FREQUENCY BASED ON 262 MICE. FREQUENCY OF CULTURES BASED ON 35 CULTURES PERFORMED DAILY. (MILLER, C.P. UNIV. CHICAGO, 1949, UNPUBLISHED)

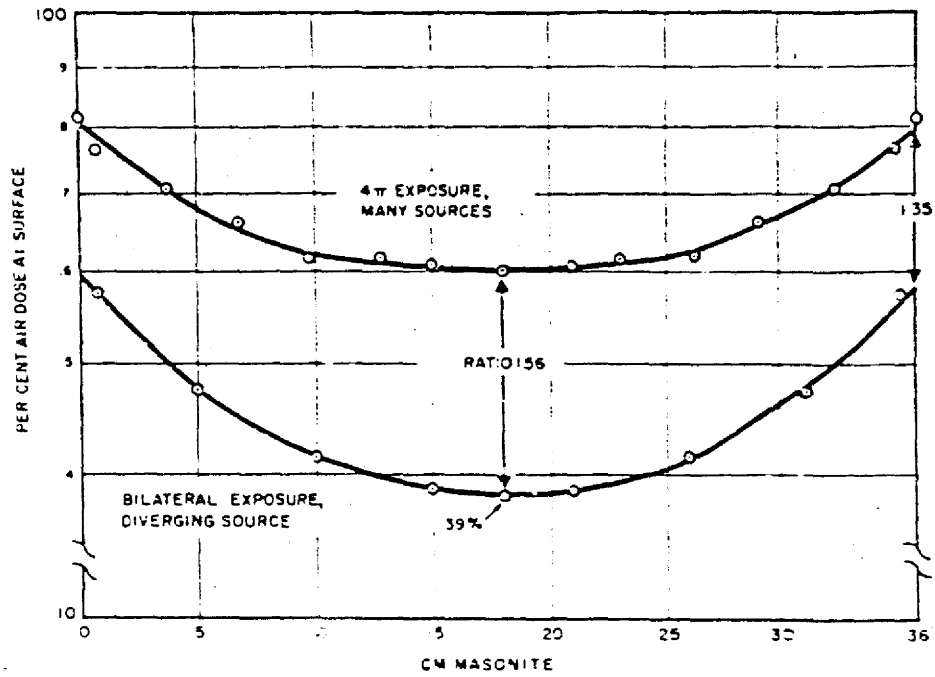
5007507

Figure 7. Depth-dose curves for 200 kVp x ray expressed as percent of surface dose for unilateral and bilateral radiation exposure from Bond et al. (34).



5007508

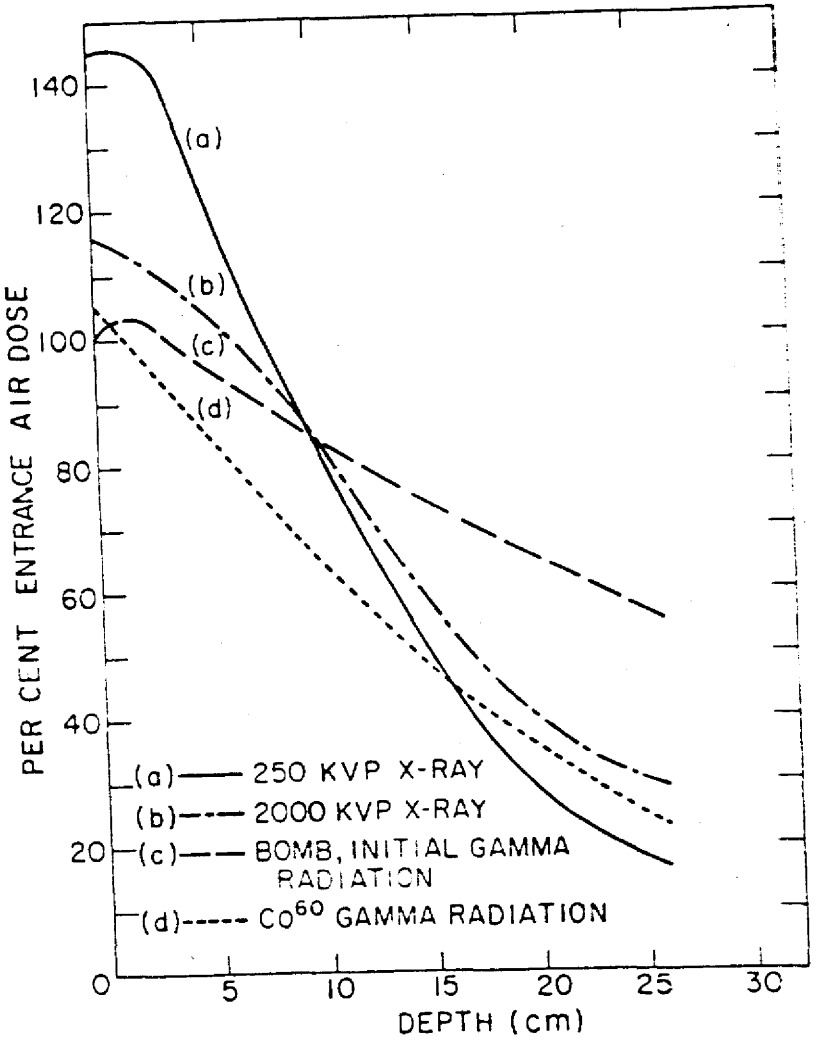
Figure 8. Comparison of depth-dose curves expressed as percent of air dose for bilateral and 4 Pi exposure from Bond et al. (34).



DEPTH DOSE DISTRIBUTION IN CYLINDRICAL PHANTOM, Co^{60} FACILITY, NMRI

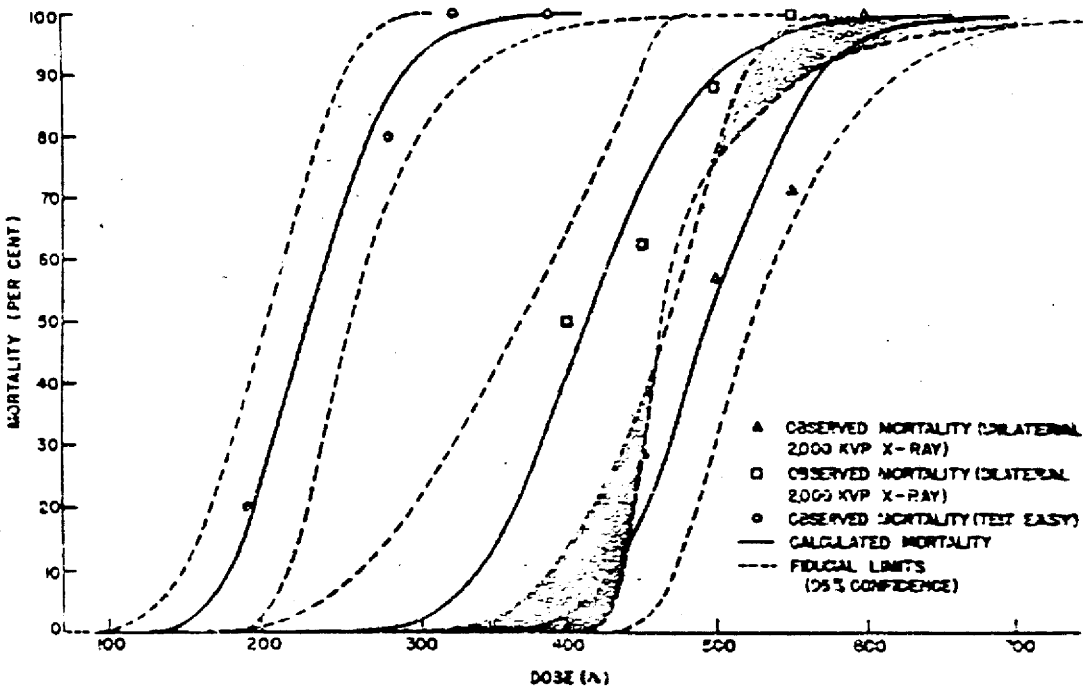
5007509

Figure 9. Comparison of depth-dose curves in Masonite phantom expressed as percent of entrance air dose for diverse sources of radiation from Bond et al. (34).



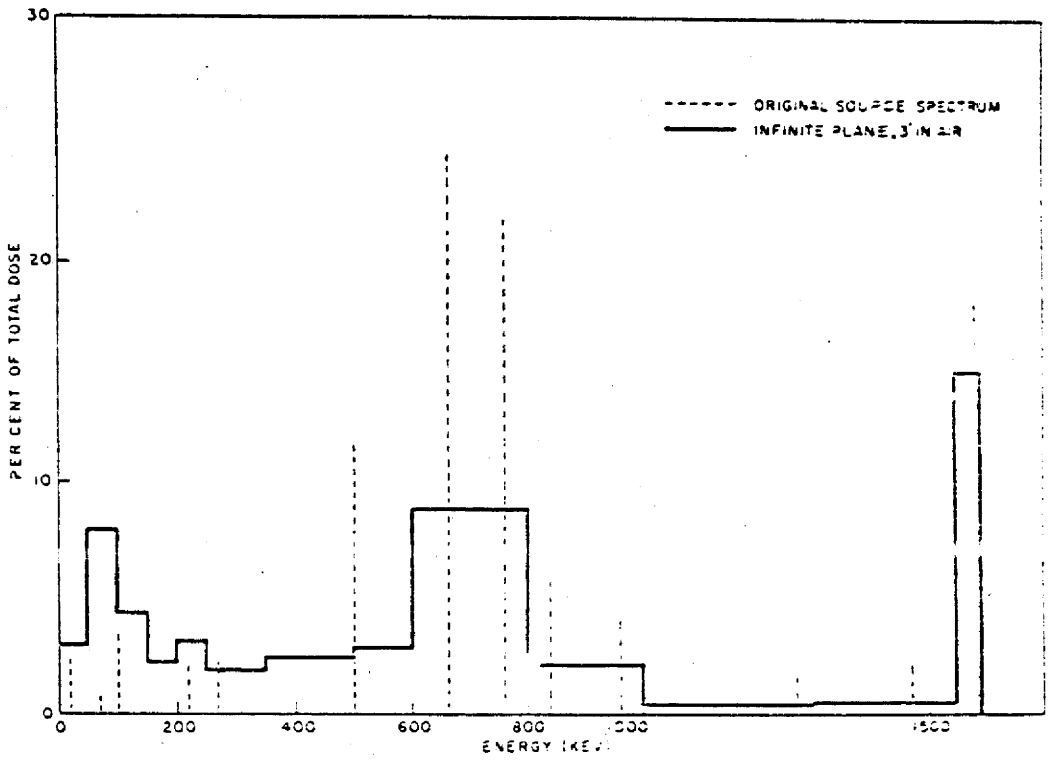
5007510

Figure 10. Radiation lethal dose curves for swine exposed to unilateral or bilateral 2000 kVp x ray and prompt atomic bomb gamma radiation.



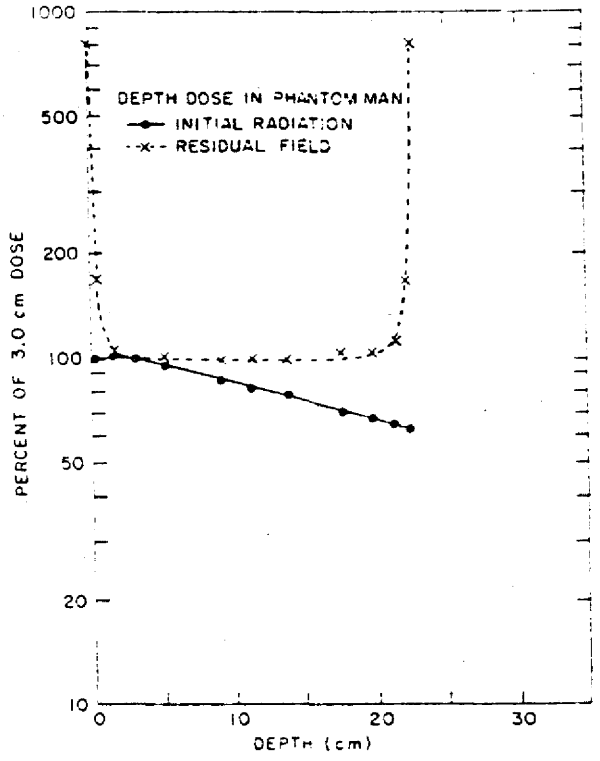
5007511

Figure 11. Inherent gamma emissions from fallout (mixed fission products) and the histogram of degraded energies produced by Compton scattering at level of infinite plane 3 feet in air above uniformly distributed fission products from Cronkite et al. (4).



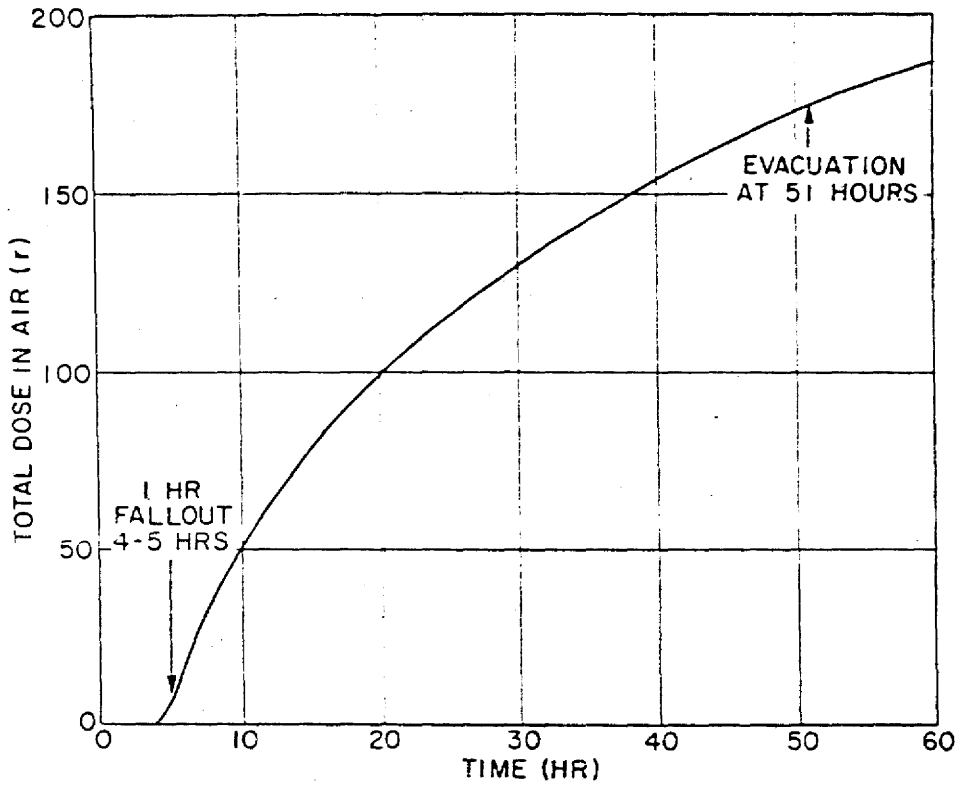
5007512

Figure 12. Depth-dose curves for fallout field and bomb gamma radiation. The dose is expressed as percent of the 3 cm dose because of the high beta component at the surface from Cronkite et al. (4).



5007513

Figure 13. The accumulation of radiation dose in air as a function of time after commencement of fallout on Rongelap from Cronkite et al. (4).



5007514

Figure 14. The percentage of mice surviving 30 days after exposure to 1000 rad given in increments of 250 rad at 1 to 24 hour intervals to illustrate repair of lethal injury.

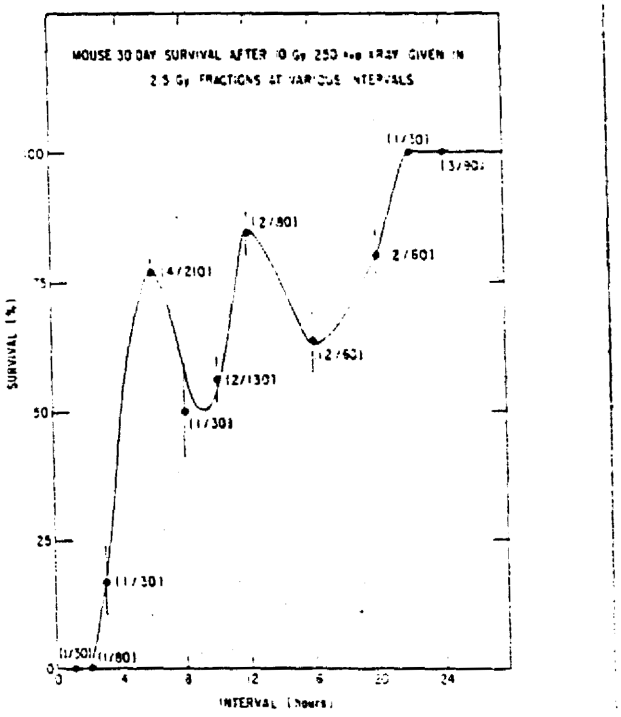
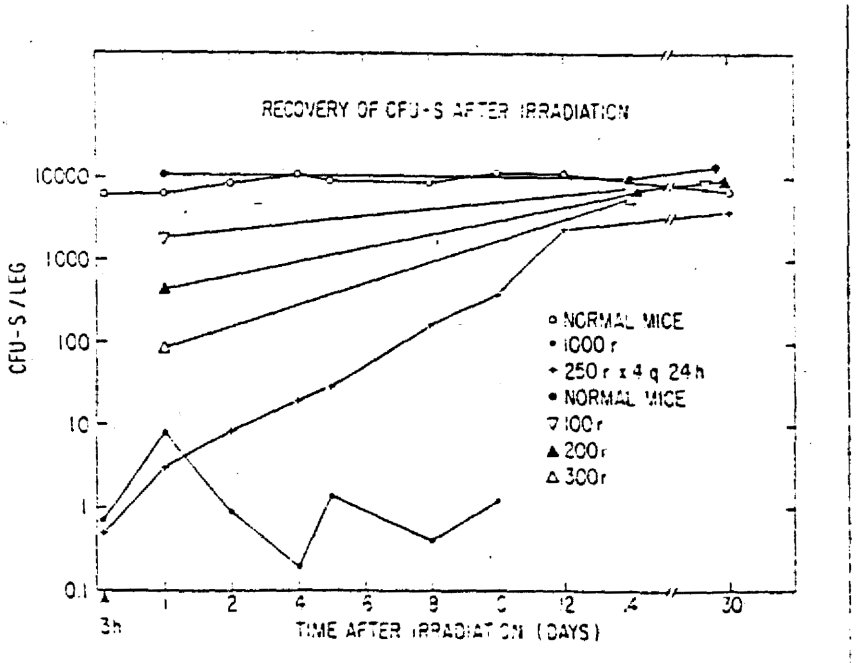


Figure 15. The sequential changes in the 10-day CFU-S in control non-irradiated mice, mice exposed to 100,200,300 or 1000 rad in a single dose and mice exposed to 1000 rad given in increments of 2 5 rad at 24-hour intervals.



5007515