ICRU REPORT 30

Quantitative Concepts and Dosimetry in Radiobiology

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INTERNATIONAL COMMISSION
ON RADIATION UNITS
AND MEASUREMENTS

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(For detailed information on the availability of this and other ICRU Reports see page 66)

Preface

Scope of ICRU Activities

The International Commission on Radiation Units and Measurements (ICRU), since its inception in 1925, has had as its principal objective the development of internationally acceptable recommendations regarding:

(1) Quantities and units of radiation and radioactivity,

(2) Procedures suitable for the measurement and application of these quantities in clinical radiology and radiobiology,

(3) Physical data needed in the application of these procedures, the use of which tends to assure uniformity in reporting.

The Commission also considers and makes similar types of recommendations for the radiation protection field. In this connection, its work is carried out in close cooperation with the International Commission on Radiological Protection (ICRP).

Policy

The ICRU endeavors to collect and evaluate the latest data and information pertinent to the problems of radiation measurement and dosimetry and to recommend the most acceptable values and techniques for current use.

The Commission's recommendations are kept under continual review in order to keep abreast of the rapidly expanding uses of radiation.

The ICRU feels it is the responsibility of national organizations to introduce their own detailed technical procedures for the development and maintenance of standards. However, it urges that all countries adhere as closely as possible to the internationally recommended basic concepts of radiation quantities and units.

The Commission feels that its responsibility lies in developing a system of quantities and units having the widest possible range of applicability. Situations may arise from time to time when an expedient solution of a current problem may seem advisable. Generally speaking, however, the Commission feels that action based on expediency is inadvisable from a long-term viewpoint; it endeavors to base its decisions on the long-range advantages to be expected.

The ICRU invites and welcomes constructive comments and suggestions regarding its recommendations and reports. These may be transmitted to the Chairman.

Current Program

The Commission has divided its field of interest into twelve technical areas and has assigned one or more members of the Commission the responsibility for identification of potential topics for new ICRU activities in each area. A body of consultants has been constituted for each technical area to advise the Commission on the need for ICRU recommendations relating to the technical area and on the means for meeting an identified need. Each area is reviewed periodically by its sponsors and consultants. Recommendations of such groups for new reports are then reviewed by the Commission and a priority assigned. The Technical areas are:

Radiation Therapy
Radiation Diagnosis
Nuclear Medicine
Radiobiology
Radioactivity
Radiation Physics – X Rays, Gamma Rays and Electrons
Radiation Physics – Neutrons and Heavy Particles
Radiation Protection
Radiation Chemistry
Values of Factors – W, S, etc.
Theoretical Aspects
Quantities and Units

The actual preparation of ICRU reports is carried out by ICRU report committees. One or more Commission members serve as sponsors to each committee and provide close liaison with the Commission. The currently active report committees are:

Average Energy Required to Produce an Ion Pair
C_λ and C_E

Computer Uses in Radiotherapy
Definitions and Terminology for Computed Tomography
Dose Specification for Reporting Intracavitary and Interstitial Therapy
Dosimetry of Pulsed Radiation
Fundamental Quantities and Units
High Energy Electron Beam Dosimetry
Measurement of Low-Level Radioactivity in Humans
Methods of Assessment of Dose in Tracer Investigations
Microdosimetry
Photographic Dosimetry in External Beam Therapy
Scanning
Stopping Power

ICRU Reports

In 1962 the ICRU, in recognition of the fact that its triennial reports were becoming too extensive and in some cases too specialized to justify single-volume publication, initiated the publication of a series of reports, each dealing with a limited range of topics. This series was initiated with the publication of six reports.

ICRU Report 10a, *Radiation Quantities and Units*
ICRU Report 10b, *Physical Aspects of Irradiation*
ICRU Report 10c, *Radioactivity*
ICRU Report 10d, *Clinical Dosimetry*
ICRU Report 10e, *Radiobiological Dosimetry*
ICRU Report 10f, *Methods of Evaluating Radiological Equipment and Materials*

These reports were published, as had been many of the previous reports of the Commission, by the United States Government Printing Office as Handbooks of the National Bureau of Standards.

In 1967 the Commission determined that in the future the recommendations formulated by the ICRU would be published by the Commission itself. This report is published by the ICRU pursuant to this policy. With the exception of ICRU Reports 10a and 10e, the other reports of the "10" series have continuing validity and, since none of the reports now in preparation is designed specifically to supersede them, they will remain available until the material is essentially obsolete. All future reports of the Commission, however, will be published under the ICRU's own auspices. Information about the availability of ICRU Reports is given on page 66.

ICRU's Relationships With Other Organizations

In addition to its close relationship with the International Commission on Radiological Protection, the ICRU has developed relationships with other organizations interested in the problems of radiation quantities, units and measurements. Since 1955, the ICRU has had an official relationship with the World Health Organization (WHO) whereby the ICRU is looked to for primary guidance in matters of radiation units and measurements and, in turn, the WHO assists in the world-wide dissemination of the Commission's recommendations. In 1960 the ICRU entered into consultative status with the International Atomic Energy Agency. The Commission has a formal relationship with the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), whereby ICRU observers are invited to attend UNSCEAR meetings. The Commission and the International Organization for Standardization (ISO) informally exchange notifications of meetings and the ICRU is formally designated for liaison with two of the ISO Technical Committees. The ICRU also corresponds and exchanges final reports with the following organizations:

Bureau International des Poids et Mesures
Commission of the European Communities
Council for International Organizations of Medical Sciences
Food and Agriculture Organization
International Council of Scientific Unions
International Electrotechnical Commission
International Labor Office
International Union of Pure and Applied Physics
United Nations Educational Scientific and Cultural Organization

The Commission has found its relationship with all of these organizations fruitful and of substantial benefit to the ICRU program. Relations with these other international bodies do not affect the basic affiliation of the ICRU with the International Society of Radiology.

Operating Funds

In the early days of its existence, the ICRU operated essentially on a voluntary basis, with the travel and operating costs being borne by the parent organizations of the participants. (Only token assistance was originally available from the International Society of Radiology.) Recognizing the impracticability of continuing this mode of operation on an indefinite basis, operating funds were sought from various sources.

Financial support has been received from the following organizations:

B.A.T. Cigaretten-Fabriken GMBH
Commission of the European Communities
Council for International Organizations of Medical Sciences
Eastman Kodak Company
E. I. duPont de Nemours and Company
Ford Foundation
General Electric Company
International Atomic Energy Agency
International Radiation Protection Association

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International Society of Radiology
Japan Industries Association of Radiation Apparatus
John och Augusta Perssons stifielse
National Cancer Institute of the U. S. Department of Health, Education and Welfare
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Picker Corporation
Radiological Society of North America
Rockefeller Foundation
Siemens Corporation
Society of Nuclear Medicine
Statens laegevidenskabelige Forskningsrad
U. S. Bureau of Radiological Health of the Food and Drug Administration
World Health Organization

In recognition of the fact that its work is made possible by the generous support provided by these organizations, the Commission expresses its deep appreciation.

Harold O. Wyckoff,
Chairman, ICRU

Washington, D.C.
1 February 1979

Contents

Quantitative Concepts and Dosimetry in Radiobiology

1. Introduction

1.1 Purposes of the Report

This report is in effect a handbook, primarily for the experimental radiobiologist and the radiological physicist; it may also be of value to the hospital physicist and radiotherapist. It deals with dosimetry pertinent to radiobiological experiments, and considers methods of improving the accuracy and intercomparability of dosimetry in radiobiology. It emphasizes the importance of planning the experimental work in a way that makes the dosimetry easier and more accurate and illustrates how this can be done. The report provides discussions of ICRU-defined dosimetric quantities and units that are of importance in radiobiology. In addition, concepts and definitions of importance in quantitative radiobiology are introduced and described. Thus, the material should provide both the physicist and the biologist who wishes to engage in radiobiological experimentation with a fuller appreciation of the range of concepts involved in performing the work in a quantitative manner, the degree of accuracy desired and appropriate, and the difficulties and possible pitfalls associated with achieving that degree of accuracy.

The dosimetry part of the present document is a revision of the ICRU report on radiobiological dosimetry (ICRU, 1963), with additional information on accelerator-produced particle beams. Discussion of radiobiological and allied parameters has been added, not only to provide definitive information and terminology, but to encourage the general use of standardized terminology as well. A large number of radiobiological dose-effect relationships have now been established, and several parameters have been introduced to characterize these relationships (D_0, D_q, n and others). These concepts are discussed and nomenclature is recommended. Other approaches that might be used for such characterization, and the related parameters, are defined and described. No attempt, however, has been made to discuss the validity of existing theoretical models for the interpretation of dose-effect or other relationships.

The effects produced by ionizing radiations in biological systems depend on a large number of factors which may be physical, chemical or physiological. The dose and factors related to it, such as dose rate, dose distribution, and radiation quality, are usually the most important physical quantities. Temperature, moisture content, oxygen concentration, and other physiological and environmental factors can be of considerable consequence, and they should be specified numerically, if possible.

Methods are recommended in the report whereby ionizing radiation may be applied to biological systems with a maximum of accuracy and minimum of ambiguity in dose specification. Radiobiological experimentation is carried out on a great variety of systems, and radiobiological data on human beings, frequently gathered retrospectively, assume considerable importance under a variety of circumstances. Comparisons, interrelationships and an integrated understanding of the effects of radiation will only be possible if adequate dosimetry has been achieved. The objectives of dosimetry and dose specification range from incidental estimates of the radiation dose delivered, to the precise specifications of absorbed dose and other quantities required in the testing of radiobiological theories. It is evident that experimental techniques and the required dosimetric accuracy must vary greatly, and that decisions on these matters must be left to the experimenter. However, the planning of the experiment and the choice of a method of measuring and reporting dose should follow certain general principles to insure that an optimum amount of information is made available. Complete specification of dosimetric parameters may be quite important to an individual wishing to use the data in an attempt to establish correlations or to test a hypothesis, and neither insufficient dose specifications nor uncertainties with respect to accuracy should limit such efforts.

A systematic and detailed treatment of the problems of experimental design and dosimetric techniques was considered to be beyond the scope of this

presentation. Instead, summary reviews of important physical and biological concepts, technical considerations and possible sources of error are given, followed by some examples of acceptable exposure arrangements in which several types of radiation beams are utilized. If different conditions are required, these arrangements can be modified in the light of the general information provided. While principles are frequently developed in the context of x and gamma radiations, many of the considerations presented are shown to apply to particle radiations as well, e.g., fast neutrons, alpha particles, electrons, or other accelerator-produced particle beams, including negative pi mesons and heavier particles. Only a few examples of exposure arrangements are given since the great variability of sources and procedures make it impractical to select standard conditions for exposure to various radiations. Appropriate literature references are given that deal with specific applications of these radiations.

Although the present report is intended to supplant and expand the older ICRU report on radiobiological dosimetry (ICRU, 1963), the reader may find some of the older material to be of value. This report is concerned mainly with techniques, dosimetry, concepts and terminology applicable to external radiation exposures. Although many of the same basic concepts and terminology apply also to circumstances in which animals and human beings are exposed to radionuclides, no attempt has been made to deal extensively with the special problems associated with internal emitters.

2. Quantitative Concepts in Radiobiology

2.1 Dosimetric Quantities

A detailed consideration of the radiation dosimetry required in radiobiology is given in Sections 3, 4 and 5. A brief introduction of the more important concepts is given here to facilitate the discussion of relationships between dosimetric quantities and those describing the degree of biological effect.

Soon after their discovery ionizing radiations were used for clinical treatment and biological experiments. In order to quantify the amount of exposure, and to intercompare irradiation methods and results, a unit for the measurement of radiation dose was needed. Such a unit, the roentgen (r), was introduced in 1928 (Taylor, 1958) by the International Commission of Radiological Units (ICRU). Most of the radiological work during the decades from 1930 to 1960 was based on this unit, which, however, was a unit of exposure and not of absorbed dose. Nevertheless, the unit worked in practice since reproducible application of x rays and gamma rays in the field of radiation therapy needed only an arbitrary but well-defined unit. Intercomparisons of exposure measurement among different nations have yielded values that differ by no more than approximately one percent.

Some limitations in the use of the roentgen and of the corresponding quantity, exposure, arose with the introduction of charged particles and high-energy photon radiation into radiation therapy, since the exposure was defined only for x rays and gamma rays and was useful only for photon energies up to a few MeV.

In 1962 the ICRU proposed a more complete set of physical quantities needed to describe the interaction of a radiation field with matter, including the fluence for characterizing a radiation field, and redefined the absorbed dose for characterizing the energy imparted to irradiated matter (ICRU, 1964, 1971). These well-defined physical quantities are useful in a number of circumstances, but some are of limited applicability for dosimetry in radiobiology. For example, the number of photons impinging per unit area on the irradiated sample (fluence) is rarely useful since many of the photons pass through the sample without interaction, i.e., the fluence alone does not provide the necessary information on those interactions that actually cause the radiation effect. The most appropriate quantity for characterizing the amount of radiation to which the sample has been exposed is the absorbed dose, the detailed definition of which is given in ICRU Report 19 (ICRU, 1971) and discussed in Section 4 of the present report. Absorbed dose is expressed in terms of energy imparted per unit mass of the irradiated material. The SI unit of absorbed dose, J kg^{-1}, has been given the special name of gray (Gy), related to the older unit rad (100 erg g^{-1}) by the relationship

$$1 \text{ Gy} = 1 \text{ J kg}^{-1} = 100 \text{ rad.}$$

The concept of radiation quality as applied to radiobiology has been described in ICRU Report 16, page 1 (ICRU, 1970a).

Specification of radiation quality in radiobiology involves a description of the microscopic distribution of energy deposition (see Section 3.1). The form of the specification required will depend upon the use to be made of the information. If all that is required is an assurance that radiations used by a number of different investigators would not generally be considered to differ appreciably in radiation quality, a simple specification (such as tube voltage and filtration of x rays, the relevant radionuclide for gamma rays, or the beam energy for electrons and heavy particles) should be sufficient, especially for high energy x rays, gamma rays, and electrons. On the other hand, for the interpretation of data relating to the relative biological effectiveness (RBE) of radiations, a description of the microscopic distribution will generally be advisable, which may take into account the radiobiological hypothesis to be tested.

2.2 Quantitative Relationships in Radiobiology

Quantitative relationships are developed in this section to present an adequate background for the development of concepts and definitions, and to provide a more complete understanding of radiobiological effects and of the importance of dosimetry.

Among the various quantitative relationships of interest in radiobiology, the dose response curve is the most prominent and it will, therefore, be discussed in detail. It should be noted, however, that there are other relationships that are of significance. Examples are: the dependence of effect on absorbed dose rate, the dependence of RBE on absorbed dose, and the dependence of the cellular inactivation cross-

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section on linear energy transfer, LET (see Section 3.1). A given dose-effect relationship may change with a physiological variable, such as the oxygen tension in the specimen. The study of such relationships can yield important perspectives on basic biophysical processes that are different from those afforded by dose-response curves.

Functional relationships between biophysical variables can be shown on graphs using either linear or non-linear scales. It is frequently possible to approximate these relations by comparatively simple analytical expressions which, in turn, depend on one or more parameters. Because of the limited accuracy of many radiobiological determinations, it is often possible to fit the data points to more than one function within limits that are statistically acceptable. It is then desirable to derive confidence regions of the parameters of these functions (Kellerer and Brenot, 1973) to evaluate the relative goodness of such fits.

The functions chosen for the fitting process are often selected on the basis of postulated mechanisms (models). It must be stressed, however, that agreement showing the data to be not inconsistent with the model, while a necessary condition for proof, does not in itself constitute proof of the correctness of the model. However, whether the model is correct or not, the analytical expressions and their parameters can be convenient means of characterizing the relationships, and it is to this end that various expressions and parameters are considered in Section 2.2.1.

2.2.1 Dose-Effect Relationships

Radiation in sufficient amount can cause the death of cells, tissues, or whole animals. It can also cause many kinds of functional or phenotypic changes in these specimens. These include, for example, mutagenic, oncogenic or teratogenic changes, as well as cytological changes such as nonlethal chromosome aberrations, small colony formation and other forms of heritable damage.

In general, these changes, including lethality in cell or animal populations, show a greater frequency as the dose increases but the form of the dose-effect relationship may be simple or complex. Also it may change, over a broad dose range, from one simple functional relation to another.

Representative forms of dose effect curves are shown in Figure 2.1, and are discussed later in Section 2.2.4. The effect may start out as a function of dose in linear form (curve *B*), with negative curvature (curve *A*), or with positive curvature (curve *C*). Also the curve may not separate from the abscissa until some finite value of D is reached (curve *D*). At high doses the effect may continue to increase

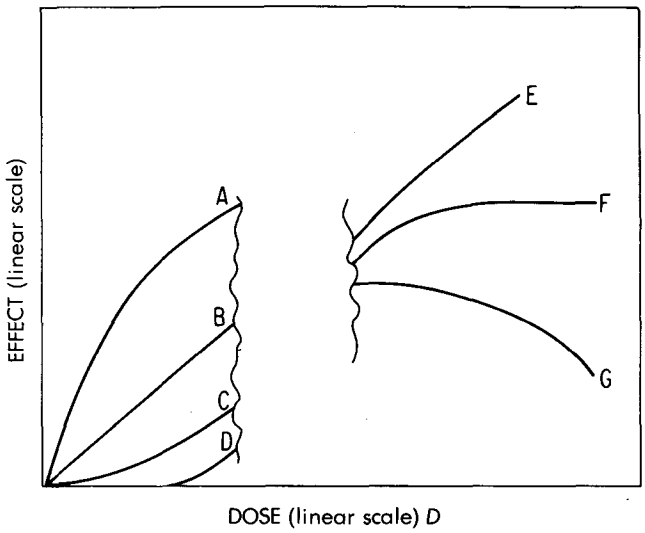

Fig. 2.1. Possible dose-effect relationships in radiobiology. Any one of the curves to the left of the break can, in principle, assume, at higher dose, the shape of any one of the curves to the right of the break.

(curve *E*), saturate (curve *F*, perhaps dictated by a limit on the amount of effect possible), or decline (curve *G*, perhaps as a result of competing processes).

Cell killing and morbidity and/or mortality of tissues, organs and animals are effects of radiation that have been rather thoroughly studied and the form of the dose-effect relationship takes on certain characteristics for given types of cells or tissues and conditions.

To examine these relationships further, it is frequently more convenient to express the response in terms of the "unaffected" members of the population, i.e., the survivors. Furthermore, in practice it is often the fraction of surviving members of the population that is measured, rather than the fraction killed.

In the following discussion a distinction will be made between cell survival curves (the response of a population of single cells, as a function of dose) and tissue and organ survival (the response of populations or subpopulations of cells, organized into tissue, as a function of dose).

2.2.2 Cell Survival Curves

As noted in Section 2.2 above, curves are often fitted to data for convenience, and such fitted curves are not necessarily intended to imply a judgment as to the mechanism of radiobiological action or the validity of a given model. The survival curve of a homogeneous population of single cells (or microorganisms) is generally found to have one of three

shapes (Figure 2.2). The simplest of these is the single exponential, curve A, fitted by the equation:

$$S(D) = e^{-kD} \tag{2.1}$$

where $S(D)$ is the surviving fraction after a single absorbed dose D, and k is the slope of the curve on a semilogarithmic plot. The reciprocal of k, D_0, (the *mean inactivation dose*), is the dose D required to reduce $S(D)$ by a factor of e. The dose to reduce survival to 37 percent [i.e., ~ 100 (1/e) percent] is designated D_{37} and for exponential survival, curve A, $D_{37} = D_0$. As a model of inactivation, in Equation (2.1) the inactivation constant k represents the net sensitivity of each cell and may be associated with a net target volume (Lea, 1946; Hall, 1953). It may also represent the sum of sensitivities contributed by a number of subtargets, each cell having the same number and type. The modification or inactivation of a single subtarget results in the inactivation of the cell. In such an instance, D_0 is less than the mean inactivation dose of any one subtarget, $D_{0,i}$, being given by:

$$\frac{1}{D_0} = \sum_i \frac{1}{D_{0,i}} \tag{2.2}$$

where $D_{0,i}$ is the mean inactivation dose for subtargets of type i.

A population of cells may contain a mixture of two (or more) subpopulations which separately would follow an exponential dose-effect curve. In the simplest case of a mixture consisting of population fractions a and b, $(a + b = 1)$, the survival curve would be:

$$S(D) = ae^{-k_a D} + be^{-k_b D} \tag{2.3}$$

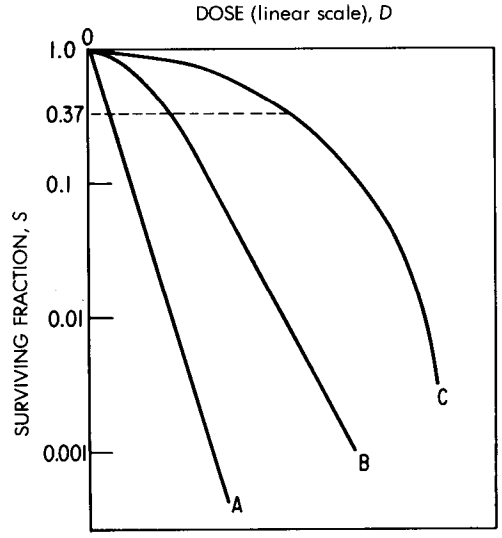

Fig. 2.2. Typical shapes of cell survival curves.

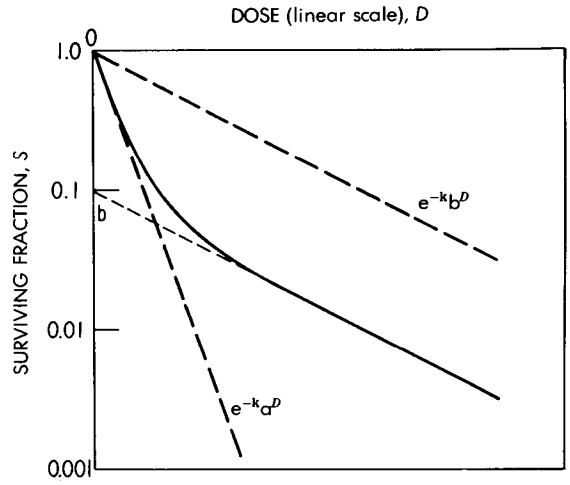

Fig. 2.3. A mixed population response of two subpopulations of cells, each of which survives exponentially (see Equation 2.3).

As shown in the example in Figure 2.3, where $k_b = 0.2k_a$ and b comprises 10 percent of the population, the survival curve of the resistant b cell extrapolates to b since, for large doses, only the second term in Equation (2.3) contributes significantly to survival. In the instance where more than two exponentially surviving subpopulations are involved, the initial slope will tend to reflect the most sensitive and the final slope the most resistant moiety.

A second survival curve frequently observed is B in Figure 2.2. Such a curve may be described by the "multitarget, single-hit" survival expression:

$$S(D) = 1 - (1 - e^{-k_n D})^n \tag{2.4}$$

where the inactivation constant k_n is the sensitivity of each of n targets, each of which must be hit to kill a cell. Shoulder-type survival curves that appear to have a negative initial slope and that become exponential at survivals below about 10 percent may be more closely fitted by a "modified multitarget, single-hit" curve:

$$S(D) = e^{-k_1 D}[1 - (1 - e^{-k_n D})^n] \tag{2.5}$$

Here, cells in a homogeneous population are inactivated by the radiation according to two different modes; these may reflect characteristics of the cells, the radiation, or both. In the first mode, the survival of cells is reduced exponentially within an effective inactivation constant k_1. In the second mode, survival is reduced according to Equation (2.4) with k_n representing the effective inactivation constant of each of n targets, each of which must be inactivated for a cell to be killed by this mode. Clearly, if k_n approaches zero or if n approaches infinity or unity, simple exponential survival results, Equation (2.1). Similarly, if k_1 approaches zero, the initial slope of

the survival curve will approach,

$$\frac{dS(D)}{dD} = -nk_n e^{-k_n D}(1 - e^{-k_n D})^{(n-1)} \qquad (2.6)$$

and this expression is zero at $D = 0$.

This relationship between the survival parameters in Equation (2.5) and the quantities identifiable on a survival curve is shown in Figure 2.4. The initial slope of the curve gives ${}_1D_0$ since ${}_1D_0 = 1/k_1$. If the effective mean inactivation dose for each of the n targets is ${}_nD_0 = 1/k_n$, then with $1/D_0$ being the slope at large D,

$$\frac{1}{D_0} = \frac{1}{{}_1D_0} + \frac{1}{{}_nD_0} \qquad (2.7)$$

For $n > 1$ one has;

$${}_1D_0 > D_{37} > {}_nD_0 \qquad (2.8)$$

The shoulder width (sometimes termed quasi-threshold dose) of the curve, D_q, is equal to the dose at which a back extrapolation of the exponential part of the curve crosses the level at which the surviving fraction is equal to 1.0; the back extrapolation intersects the ordinate at the extrapolation number, n. The parameters n, D_q, and D_0 are related,

$$\frac{D_q}{D_0} = \ln n \qquad (2.9)$$

where $\ln n$ is the *normalized shoulder, width* i.e., the shoulder width, normalized by D_0.

In the instance of a heterogeneous population in which each fraction survives according to Equation (2.5), the following relationships hold: ${}_1D_0$ will be related to the reciprocals of the initial slopes of each curve by,

$$\frac{1}{{}_1D_0} = \sum_i \frac{u_i}{{}_1D_{0,i}} \qquad (2.10)$$

where u_i is the fraction of cells of initial slope $1/{}_1D_{0,i}$, ($\Sigma u_i = 1$). The extrapolation number observed will not reflect the distribution of n values in the population if the D_0 values differ. In that case, the observed value for n will be approximated by,

$$n \simeq u_r n_r \qquad (2.11)$$

where u_r is the fraction of the population having the largest D_0. On the other hand, if all moieties of the population have the same D_0, n will be an average value, i.e.,

$$n = \sum_i u_i n_i \qquad (2.12)$$

In addition to the foregoing effects on the extrapolation number that are observed with a mixed population, when the population mixture also involves D_0 differences, the survival curve will frequently contain inflexions (e.g., see Elkind and Sinclair, 1965; Elkind and Whitmore, 1967; Sinclair, 1966, 1969). Further, in addition to controlling the magnitude of the extrapolation number observed, Equation (2.11), the cells having the largest D_0 will constitute the principal survivors after large doses as sketched for exponential survival in Figure 2.3.

The third shape of survival curve observed with cells is C in Figure 2.2. In contrast to A and B – where the relative effect per unit dose is constant (A) or approaches a constant value (B) – in this case the relative effect per unit dose increases throughout the range of observation (Sinclair, 1966). In general, the rate of increase may be such that a polynomial in the dose is required to describe the data adequately; i.e.,

$$S(D) = e^{-(\alpha D + \beta D^2 + \gamma D^3 \ldots)} \qquad (2.13)$$

where $\alpha, \beta, \gamma, \cdots$ are constants.

In practice, however, a constant rate of increase of the slope of the curve on a semilogarithmic plot, is often found to be adequate, i.e.,

$$\frac{-d[\ln S(D)]}{dD} = \alpha + 2\beta D \qquad (2.14)$$

i.e., the first derivative of the curve is a straight line, as has been pointed out using practical examples (Sinclair, 1966):

$$S(D) = e^{-(\alpha D + \beta D^2)} \qquad (2.15)$$

where α has the same relationship to curve C in Figure 2.2 that k_1, i.e., $(1/{}_1D_0)$ has in Figure 2.4. In a mixed population one deals with a superposition of

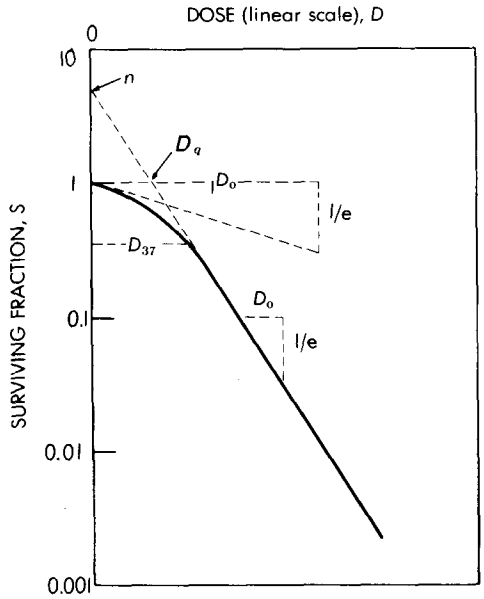

Fig. 2.4. Modified multitarget, single-hit inactivation (Equation 2.5).

functions of the form of Equation (2.15) with different parameters α and β, which may result in an overall survival curve resembling that obtained with Equation (2.5). The initial slope of the resulting curve is given by,

$$\alpha = \sum_i u_i \alpha_i \qquad (2.16)$$

but in general the moiety with the smallest β will largely control the observed survival at high doses. The expression containing a linear plus a quadratic term seems to fit many experimental circumstances and has been the basis of several recent theoretical approaches.

A method of describing a survival curve independent of particular models is also useful (Kellerer and Hug, 1972), which will now be summarized: A survival probability $S(D)$ represents an integral probability distribution. As such, its negative derivative, $s(D)$, is a differential probability distribution, Figure 2.5. A survival curve may be characterized in part by its moments and its average dose $\overline{D}$;

$$\overline{D} = \int_0^\infty Ds(D)\mathrm{d}D \qquad (2.17)$$

i.e., the first moment of the differential distribution; or equivalently

$$\overline{D} = \int_0^\infty -S(D)\mathrm{d}D \qquad (2.17a)$$

the area under a linear plot of the survival curve. The second moment of the distribution is,

$$\overline{D^2} = \int_0^\infty D^2 s(D)\mathrm{d}D = 2\int_0^\infty DS(D)\mathrm{d}D \qquad (2.18)$$

and from the first and second moments the variance may be determined,

$$\sigma^2 = \overline{D^2} - \overline{D}^2 \qquad (2.19)$$

Of particular interest is the "relative steepness" of the curve, ψ,

$$\psi = \overline{D}^2/\sigma^2 \qquad (2.20)$$

where σ is the standard deviation of D about $\overline{D}$. For an exponential survival curve, $S(D) = \mathrm{e}^{-kD}$, the mean dose is $\overline{D} = 1/k$, and $\sigma = \overline{D}$ and $\psi = 1$. For curves having shapes B and C in Figure 2.2, $\psi > 1$; in general, the smaller the initial slope, and the broader the shoulder width D_q relative to the mean dose, the smaller σ will be and the larger ψ. This is illustrated in Figure 2.5. The upper panel shows $S(D)$ plotted on log-linear coordinates. The negative derivative of the linear curves, $s(D) = -\mathrm{d}S(D)/\mathrm{d}D$, is sketched in the lower panel. Taking A to be exponential, the relative

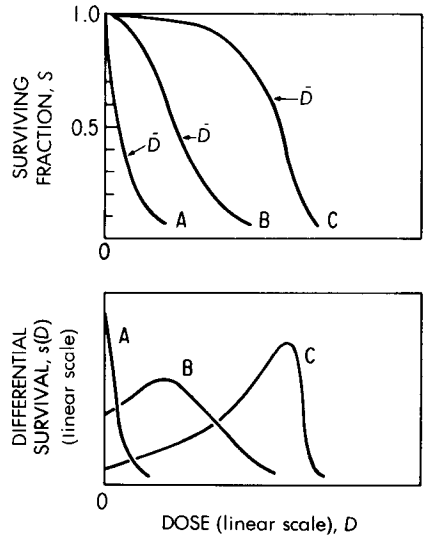

Fig. 2.5. Examples of the relationship between $s(D) = \left(\frac{\mathrm{d}(S)D}{\mathrm{d}D}\right)$ and $S(D)$ for three survival curves having characteristically different slopes. The steepness of these curves have the relationships given by Equation (2.21).

steepness of the three curves is:

$$\psi_A < \psi_B < \psi_C \qquad (2.21)$$

the subscripts referring to the curves in Figure 2.5.

The parameters $\overline{D}$, σ, and ψ reflect the shape of the survival curve mainly at low doses or in the first decade of survival. In a mixed population, σ^2 will be larger than the mean of the variances for the subpopulations. For this reason, the steepness of a mixed population generally will always be less than the average steepness of the subpopulations. Although increasing steepness qualitatively reflects increasing shoulder width, ψ and $\overline{D}$ do not uniquely specify a survival curve even in the high survival region.

2.2.3 Organ and Animal Survival

An organ can be regarded simplistically as a population of mostly functional cells, the size of which is maintained within rather narrow limits. The cell population may respond to radiation exposure as described above, i.e., the surviving fraction or the fraction of functionally-intact cells will decrease with increasing dose. The functional capacity and even viability of the organ will be jeopardized when the surviving fraction, or surviving functional fraction, has fallen below some critical level, which will differ among organs and from animal to animal. Organ failure may in turn lead to illness or death of the individual, in hours to days or weeks following exposure. Further, the numbers of animals committed to a given experiment is frequently limited to fewer

than 100 for practical reasons. Such animal survival data are frequently plotted on linear coordinates (Figure 2.6).

Tumor sterilization concerns the integrity of one or more populations of cells considered as a whole, in the same way that lethality in an animal may depend on the integrity of individual organs. The number of tumors ordinarily available for test is also limited by practical constraints; as a consequence, a linear plot is most frequently encountered in this case as well (Figure 2.6).

In Figure 2.6, curve A could correspond to the fraction of animals surviving, for a given length of time, t, as a function of dose; the *lethal dose* for 50 percent survival scored at a specified time, t, after irradiation is designated the $LD_{50/t}$. In connection with tumor irradiation, frequently the proportion that does not regrow in a given length of time is plotted as curve B, for example. The 50 percent dose in this case is designated *tumor control dose*, $TCD_{50/t}$, where t is the period of observation after exposure. In the instance where tumor sterilization is plotted, the 50 percent effective dose would be designated TCD_{50}.

The slope $s\,(D)$ of the survival curve represents the rate of inactivation at that particular dose level and usually maximizes at 50 percent survival. In many practical situations, the variation of the slope about this maximum approximates closely to a normal (Gaussian) distribution in which case $\bar{D} = LD_{50}$. Then the survival curve, as the integral of a normal distribution, may be redrawn on probit scales (Finney, 1952), which transform such a curve into a straight line, curve A Figure 2.7. The mean inactivation dose corresponds to the dose for 50 percent

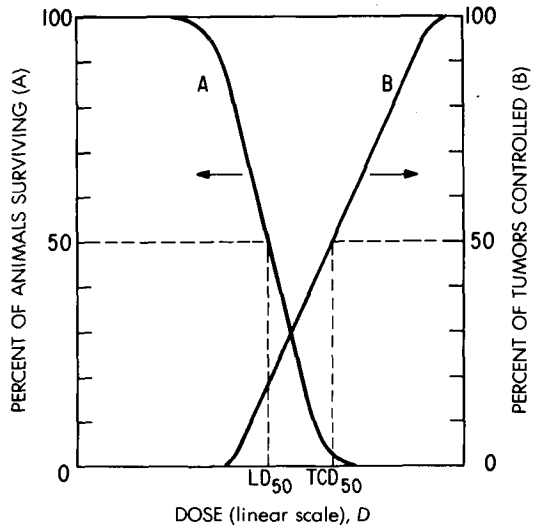

Fig. 2.6. Percent of animals surviving, A, or percent tumors controlled, for a specified minimum length of time, B. (Curve A, left ordinate; e.g., animal survival. Curve B, right ordinate, tumor control).

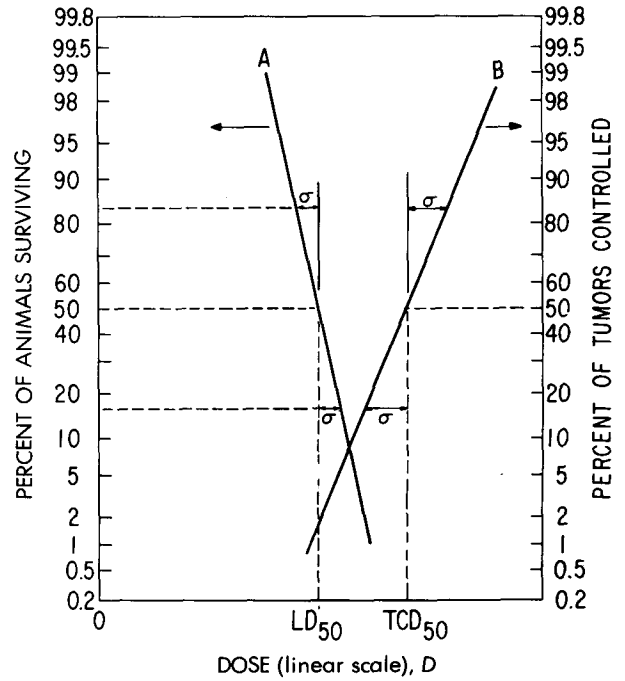

Fig. 2.7. Probit plots of population survival and tumor control.

survival, and the standard deviation of the dose may be read from the probit plot as the dose increment between survivals 16 percent and 50 percent or 50 percent and 84 percent. Or, more conveniently, the spread in response can be specified in terms of the doses corresponding to 90 percent and 10 percent survival read off from the straight line probit plot (extrapolated beyond the experimental data if necessary). An analogous situation exists for curve B in Figure 2.7, for tumor cure.

In general, the more heterogeneous the population of cells may be in any one animal or tumor, the more uncertain will be the association of the doses at the 50 percent effect level, with the response of a given subpopulation. But, in addition, if there is variability from animal to animal, or tumor to tumor, this will lead to a shallower dose-effect curve; that is, a curve with larger σ (Kellerer and Hug, 1972). As a consequence, the steepness ψ, will be less.

2.2.4 Curves of Functional or Phenotypic Change

Among the cells, tissues, or animals that may survive radiation exposure, induced changes in cells may become manifest. These may take various forms and may give rise to, for example, mutagenic, oncogenic, or teratogenic alterations. Such changes are usually detected as low frequency events, their frequency initially increasing with dose, sometimes to a plateau before a possible decrease. When the popula-

tion at risk is large enough, it may be useful to plot the induction frequency *vs.* dose on semilogarithmic coordinates as is done in the case of cell survival, or even on full logarithmic coordinates. When tissues or animals are exposed, the limited data that result from experiments of conventional size are more commonly plotted on linear coordinates.

In Figure 2.1, the induction of phenotypic change $E(D)$ is plotted on linear coordinates to show that for small doses, the curve may have one of several shapes, and for large doses it may assume a maximum or a plateau. Frequently, such data may be fitted by a polynomial:

$$E(D) = \alpha D + \beta D^2 + \gamma D^3 \cdots\cdots \qquad (2.22)$$

where it is assumed that $E(D)$ is the induced rate above the controls, although for a limited dose range, a linear, a quadratic, or a linear plus a quadratic dose dependence is usually sufficient. A full-logarithmic plot may be useful in making graphical estimates of the exponents since the slope of a straight line region gives the power of the dose that dominates in that region (e.g., Figure 2.8). A plot of $E(D)/D$ as a function of D is also in wide use, particularly since it yields α as the intersection of the curve on the ordinate, and β as the slope of the straight line obtained, provided that terms with an exponent of 3 or higher are non-contributory.

Phenotypic or functional changes require that the properties of at least one cell be altered. The susceptibility to alteration may depend on many factors and these may vary among cells. Consequently, the dose dependence of induced changes could reflect a mixed population response. In that event, α is given by Equation (2.16) but, in general, the moiety with the largest value of β will control the magnitude of $E(D)$ at doses in the quadratic region of the induction curve.

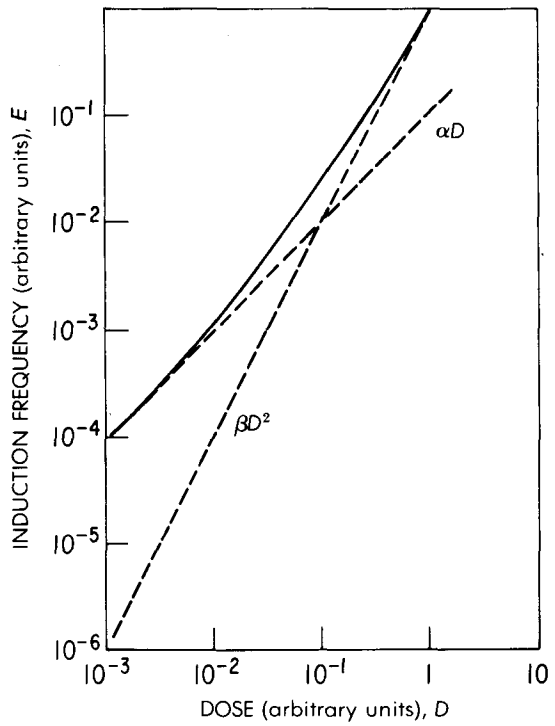

Fig. 2.8. Linear and quadratic dose dependencies of an induced phenotypic or functional change.

2.3 Damage and Repair

2.3.1 Repair, Repopulation, and Recovery

When the degree of a radiation effect depends upon the overall dose delivery time—i.e., the dose rate, or the protraction of a fractionated dose sequence—this frequently reflects the biochemical and biophysical interplay of reparative processes. Even if the end point of interest reflects the response of a population of cells or an organism as a whole, reparative processes may start in the individual cells that comprise the target.

Definition:

Repair: The partial or complete restoration of functional integrity in cells following damage caused by radiation.

Operationally, repair means that after irradiation a cell responds as though it had received a smaller dose than under conditions in which damage is more fully expressed. The ability to observe repair implies, therefore, that a comparison is made with a treatment of reference. *Full repair* indicates that cells respond as though they had not been previously irradiated. (Repair embraces processes sometimes referred to as: bypassing of damage; shedding of damage; compensating for damage; elimination of damage; and/or the specific biochemical reversal of damage.)

Definition:

Repopulation: The replacement of functional cells (usually by proliferation) following or during an irradiation.

Repopulation refers to those cells upon which the biological end point depends and usually reflects increases in the numbers of differentiated cells as well as their progenitors. Repopulation may result from cells that were unaltered by the radiation (e.g., due to migration into the irradiated field) but may also reflect a contribution from surviving cells. In a given case, repopulation could be influenced by systemic responses induced by the radiation (e.g., homeostatic responses).

Definition:

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