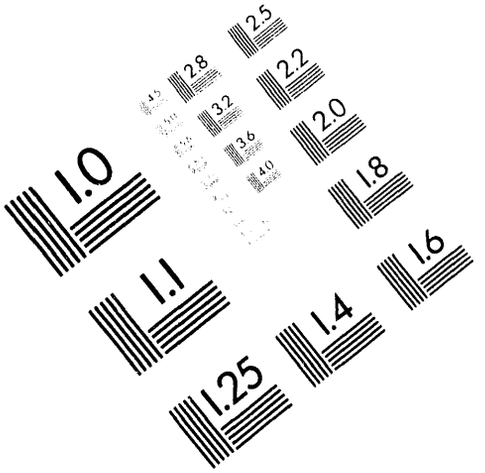

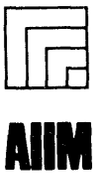

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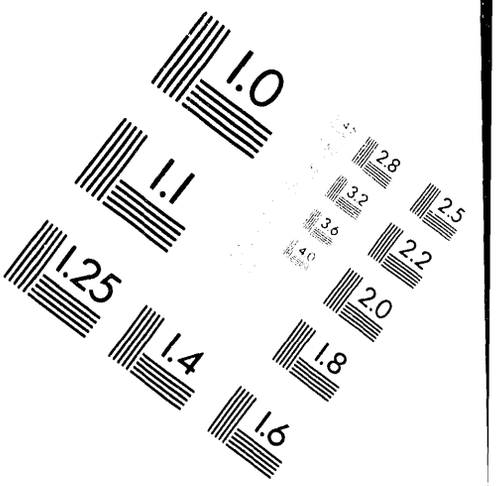

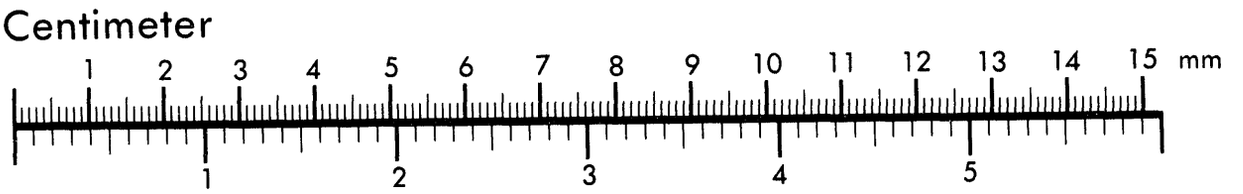

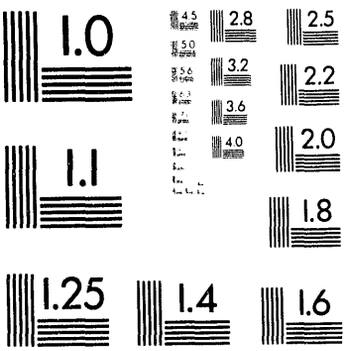

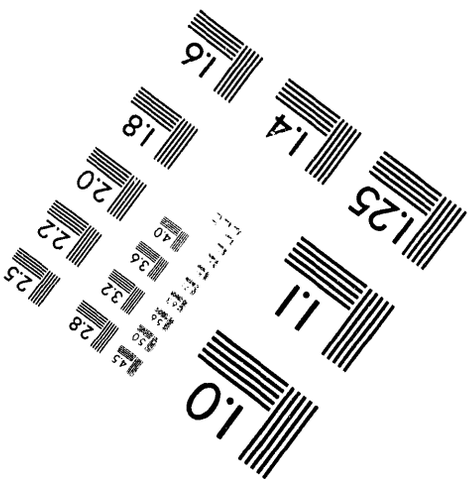

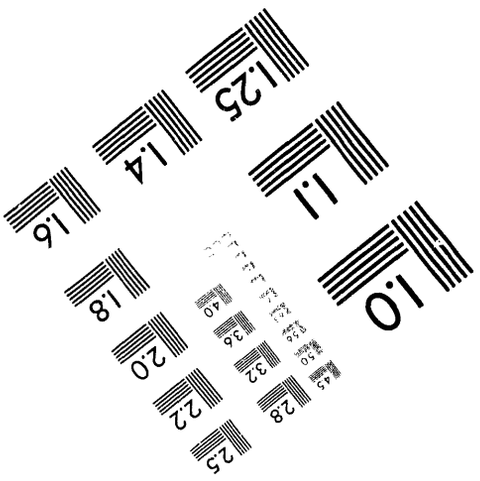

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FROM "MICRO" TO "MACRO" INTERNAL DOSIMETRY

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FROM "MICRO" TO "MACRO" INTERNAL DOSIMETRY

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Abstract--Radiation dose is the amount of radiation energy deposited per unit mass of absorbing tissue. Internal dosimetry applies to assessments of dose to internal organs from penetrating radiation sources outside the body and from radionuclides taken into the body. Dosimetry is essential for correlating energy deposition with biological effects that are observed when living tissues are irradiated. Dose-response information provides the basis for radiation protection standards and risk assessment.

Radiation interactions with living matter take place on a microscopic scale, and the manifestation of damage may be evident at the cellular, multi-cellular, and even organ levels of biological organization. The relative biological effectiveness of ionizing radiation is largely determined by the spatial distribution of energy deposition events within microscopic as well as macroscopic biological targets of interest. The spatial distribution of energy imparted is determined by the spatial distribution of radionuclides and properties of the emitted charged-particle radiation involved. The nonuniformity of energy deposition events in microscopic volumes, particularly from high linear energy transfer (LET) radiation, results in large variations in the amount of energy imparted to very small volumes or targets. Microdosimetry is the study of energy deposition events at the cellular level. Macrodosimetry is a term for conventional dose averaging at the tissue or organ level. In between is a level of dosimetry sometimes referred to as multi-cellular dosimetry. The distinction between these terms and their applications in assessment of dose from internally deposited radionuclides is described.

INTRODUCTION

"In the Beginning there was ... Energy!"

Radiation dosimetry is the study of energy deposited in matter by ionizing radiation. The amount of energy deposited per gram of absorber is determined either by direct measurement, or by calculation when direct measurements are not possible. Internal dosimetry is the science dealing with analysis and measurement of radionuclides taken into the body and the assessment of radiation doses to internal organs and tissues. Occupational exposures to radiation may involve both external and internal exposures. In such cases, doses to internal tissues are evaluated separately, but the total health detriment is considered to be an additive function of the two types of exposures. Systems for dose limitation are based on the sum of the dose to internal organs from external and internal radiation sources (ICRP 1977).

Dosimetry studies are conducted to determine fundamental relationships between energy deposition in biological tissues and resulting endpoints (radiation-induced damage, or biochemical changes). The information provided by dosimetry provides insight into the effects of radiation on living systems. Concepts of dosimetry are useful for correlating microscopic patterns of energy deposition with short-and long-term biological effects that result. An understanding of energy deposition at the molecular level can help us understand the basic mechanisms of radiation interaction that lead to specific types of damage. This understanding can help us better predict the risks associated with radiation exposure.

Purpose

The ultimate objective of dosimetry and microdosimetry, as applied to radiation protection and radiobiology, is to establish dose-effect relationships that will be helpful for setting appropriate radiation protection standards. The purpose of this chapter is to provide a brief review of concepts of dosimetry and to show that the basic principles of dosimetry are the same at the cellular level as they are at the organ level. The differences are primarily in the size of target and

the way results are expressed. This review will show how dosimetry provides understanding about the relationship between the microscopic distribution of dose at the cellular level and resulting biological effects.

LEVELS OF DOSE ASSESSMENT

"And there was Mass, both large and small, in the Universe..."

The prefixes "micro" and "macro" stem from the Greek *mikros*, meaning "small," and *makros*, meaning "large." They are used in the context of microdosimetry and macrodosimetry, or small-scale (cellular-level) and large-scale (organ-level) dosimetry. Microdosimetry utilizes random (or stochastic) variables to describe energy deposition in microscopic targets, such as cells and cell nuclei. Macrodosimetry ignores the detail of energy deposition and involves only an assessment of the average dose to an organ, tissue, or the whole body. Microdosimetric variables include the concepts of *specific energy* and *lineal energy*, which correspond to the nonstochastic quantities in macroscopic dosimetry of *absorbed dose* and *linear energy transfer*. These quantities are defined later in the text.

The concepts of micro- and macrodosimetry may be expanded to four distinct levels of dose assessment in the radiological sciences: Organ, tissue/sub-organ, cellular/nuclear, and sub-nuclear (Table 1).

Organ Level

Radiation absorbed doses are commonly determined for the major organs and the whole body using conventional dose-averaging or macrodosimetry. The total energy deposited in the organ over time through complete decay is divided by the mass of the organ. Contributions to organ dose from penetrating radiations from other organs or outside the body are included in the total organ dose. The schema developed by the Medical Internal Radiation Dose (MIRD) Committee of The Society of Nuclear Medicine provide organ-level estimates of dose for medically

administered radionuclides. Epidemiological studies rely almost exclusively on organ or whole-body dose estimates.

Although conventional dose averaging accounts for many complex physical and biological factors that influence the radiation energy imparted to organs of the body, it does not, however, fully account for nonuniformly distributed radionuclides in individual organs or for inhomogeneous dose distributions within organs. Neither does it provide absorbed fractions for beta-particle emitters in small organs or deal at the subcellular level with specific energy distributions for alpha- or beta-emitters.

Tissue/Sub-organ Level

The nonuniform distribution of radionuclides in biolcgical systems produces nonuniform energy deposition at the cellular, multi-cellular, and tissue or sub-organ levels. The "localized" absorbed dose from nonuniform source distributions varies significantly from the whole-organ average dose. Therefore, radiation absorbed doses are often evaluated separately for specific tissues within larger organs. This level of dosimetry involves dose-averaging on a smaller scale than whole-organ dosimetry, and is sometimes referred to as "small-scale" or "multi-cellular" dosimetry.

Multi-cellular dosimetry describes regional variations in absorbed dose in small volumes of tissue consisting of many cells. It is usually applied to the dosimetry of internally deposited beta-emitters, and may involve the calculation of isodose curves describing variations in the local absorbed dose with position or distance from a reference point.

Two examples of dosimetry at the sub-organ level are the assessment of absorbed dose to the bronchial epithelium of the respiratory tract from inhaled radionuclides and the assessment of dose to bone surfaces from bone-surface-seeking radionuclides.

The first example involves inhaled radon progeny, which deposit on mucosal tissues in the nasal-pharyngeal region, in the trachea, on bronchial airway

surfaces, and to some degree in the pulmonary (deep lung) regions of the respiratory tract, but deposition probabilities are quite different for each of these regions. Probabilities of radiation-induced cancer also vary by region, and are related to dose distribution. Thus, it is important to assess dose to specific regions (and even specific cell populations) of the respiratory system.

The second example involves bone-seeking radioelements, which deposit selectively on bone surfaces (e.g., plutonium, americium) or uniformly throughout bone mineral volume (e.g., calcium, radium, strontium, uranium). The average dose to radiation-sensitive osteoprogenitor cells on bone surfaces from plutonium is much greater (and more relevant to biological effects) than is the average dose to total bone volume.

Other examples of small-scale or multi-cellular dosimetry may be cited. One is the assessment of skin tissue doses from highly localized beta-particle sources and the expression of dose variations within small tumors. In these examples, the average dose is highly variable within specific tissues over short distances. Other examples of small-scale or multi-cellular dosimetry include assessment of dose to bladder walls from radionuclides in fluid contents, and dose to lining cells of microvilli in the intestinal tract.

Cellular/Nuclear Level

The biological significance of microscopic distributions of radiation energy in the single cell has long been an important and fascinating research topic in radiation biology. Dosimetry at the cellular level accounts for the statistical aspects of alpha particle track structure, energy distribution patterns and interactions with cells and cell nuclei, and radionuclide distributions within tissues.

"Microdosimetry" is the term used to describe the process involved in determining the statistical distribution of energy deposition in very small targets such as cells and cell nuclei. It provides a method for determining the number and frequency of cells irradiated, the probability densities in specific energy, and the average dose delivered to cells or cell nuclei in the target tissue.

Microdosimetry should not be confused with "microdistribution" analyses used for describing the relative concentration of point sources (i.e., their activity) per unit volume as determined from autoradiography. Microdistribution studies provide important input to microdosimetry calculations.

Sub-Nuclear Dosimetry

The ionization (and excitation) of biomolecules lead to chemical reactions and recombinations of molecules that ultimately produce alterations in the composition and organization of sub-cellular microscopic structures (DNA and chromosomes). All radiation effects, therefore, begin at the molecular or sub-nuclear level of biological organization. When target diameters are less than 1 micrometer, dosimetry is sometimes referred to as "nanodosimetry."

As early as 1922, Dessauer tried to explain the biological effects of ionizing radiation by theorizing that the inactivation of "biological molecules" increased exponentially as a function of dose (Dessauer, 1922). This concept was expanded by Lea (1956) as "target theory," which assumed that the inactivation of molecules was caused by a direct hit from ionizing radiation. It was later learned that multiple targets within the single cell were inactivated by the incident radiation. Some radiation effects were found to be the result of the chemical formation of highly reactive free radicals, which oxidized important biomolelcules in the cell and caused "indirect" radiation damage.

The exact mechanisms of radiation damage leading to different kinds of sub-nuclear effects are still largely unknown. However, much progress has been made in our ability to describe the energy imparted by ionizing radiation at the sub-nuclear level of biological organization.

DOSIMETRIC QUANTITIES AND UNITS

"... and the Energy was deposited in Mass, and the mean ratio of Energy to Mass was called 'Absorbed Dose' ..."

Definitions of dosimetric quantities and units are given in ICRU Report 51 (ICRU, 1993). Physical quantities are properties that can be quantified by measurement or calculation. Units are the standard measures associated with each quantity. For example, *absorbed dose* is a physical quantity defined in units of joule per kilogram (J kg^{-1}). Some of the more important quantities and units in macro- and microdosimetry are given below.

Absorbed Dose

In simple terms, the absorbed radiation dose, D, is a nonstochastic measure of the amount of mean energy, $\bar{\epsilon}$, deposited per unit mass, m, of the absorbing material, or

$$D = \bar{\epsilon}/m \tag{1}$$

The absorbed dose D is actually a statistical mean value. It is a generally applicable quantity for describing the average dose to organs or to the total body. By formal definition, the absorbed dose, D, is the quotient of $d\bar{\epsilon}$ by dm, where $d\bar{\epsilon}$ is the mean energy imparted by ionizing radiation to matter of mass dm.

$$D = d\bar{\epsilon}/dm \tag{2}$$

The absorbed dose is expressed in units of J kg^{-1}, and the special name for the unit of absorbed dose is gray (Gy), where 1 Gy = 1 J kg^{-1} (ICRU, 1993).

Limitations of the Absorbed Dose Concept

For most purposes in radiation protection, radiation biology, and medical radiation therapy, the average dose to tissue is an adequate parameter for evaluating biological effectiveness of radiation exposure. However, the use of dose averaging over large masses may not be appropriate if the objective is to better understand the specific effects of different kinds and distributions of radiation energy imparted to cells and cell nuclei.

Internally deposited radionuclides distribute nonuniformly in tissue. Radiations (alpha and beta particles) emitted by radionuclides in the body produce nonuniform energy depositions in the form of ionizations and excitations along particle tracks. Charged-particle ranges are short, and the host organ or tissue is seldom irradiated uniformly. The important target is usually not the organ as a whole, but rather individual cells or nuclei within cells. Since radiation effects begin at the cellular level, the variation in dose to individual cells will lead to a wide variation in effects at the cellular level. Conventional dose-averaging neglects track structure details, target cell characteristics, and fluctuations in dose to microscopic units (cells and cell nuclei). These distributions are best described using microdosimetric quantities.

Specific Energy

The specific energy, z, is a stochastic quantity used in microdosimetry. It has units similar to absorbed dose (1 Gy = 1 J kg^{-1}). Specific energy describes the dose to a very small target in terms of the ratio of energy and the mass of the site. Specific energy imparted is defined in ICRU Report 33 (ICRU, 1980) as the quotient of ϵ by m, where ϵ is the energy imparted by ionizing radiation to matter of mass m in a very small target.

$$z = \epsilon/m \tag{3}$$

The mean specific energy, $\bar{z}$, is the absorbed dose, D,

$$\bar{z} = D \tag{4}$$

and the absorbed dose, D, is equal to the limit of $\bar{z}$ as the mass, m, approaches zero.

$$D = \lim_{m \to 0} \bar{z} \tag{5}$$

Thus, the absorbed dose is defined as a point function to allow absorbed dose to be expressed in terms of spatial variation in D at the multi-cellular level. This is purely a theoretical concept; the absorbed dose may be calculated but not measured at a point having zero mass.

The specific energy imparted to a small target may be due to one or more energy deposition events. An exact value for the specific energy cannot be predicted for a microscopic volume of tissue or a cell nucleus, even under fully defined

irradiation conditions. Instead, the possible values of the specific energy are described by a probability density, $f(z)$.

The probability density in specific energy, $f(z)$, also includes the probability that no energy is deposited in a site, or $z = 0$. This component, called the delta function, δ, is the fraction of unirradiated sites.

$$\delta = e^{-M}, \quad \text{or} \quad M = -\ln \delta \tag{6}$$

where M is the mean number of hits per site. The delta function is a useful parameter for interpreting microdosimetric distributions and the results of radiobiology experiments.

Linear Energy Transfer

The point function defined for absorbed dose may also be used to describe the distribution of absorbed dose in linear energy transfer at a point of interest. Linear energy transfer (LET) or linear collision stopping power, L, of an absorbing material, for a charged particle, is the quotient of dE by dl, where dE is the mean energy lost by the particle, due to collisions with electrons, while traversing a distance dl in the absorber (ICRU, 1993).

$$L = dE/dl \tag{7}$$

The unit of LET is J m^{-1}, which may be expressed in keV μm^{-1}. The concept of LET was introduced by Zirkle (1940) to distinguish between radiations that exhibit different track ionization densities. As a general rule, the LET increases with particle charge and decreases with particle velocity.

Limitations of the LET Concept

The LET is the average value of the energy deposited along complete tracks of charged particles. Two different types of charged particles may have similar LET but different velocities; since their patterns of local energy deposition may be quite different, they will not produce equivalent biological effects at the cellular level.

For a given particle and energy, the LET is a mean value for the distance dl, and LET does not refer to discrete energy-loss events along microscopic segments of

the particle path. Thus, LET is a nonstochastic quantity, and certain aspects of importance to microdosimetry are neglected by the linear energy transfer concept: the progressive change in the rate of energy transfer along the track of an ionizing particle as its velocity decreases, the fact that a particle path has a finite range that may end part-way into a site, the radial energy profile around a particle track, and the random generation of excitations, ionizations, and secondary electrons (delta rays) produced along the track by the primary particle. These distributions are best described using microdosimetric quantities.

Lineal Energy

Lineal energy, or event size, y, is the quotient of ϵ by $\overline{l}$, where ϵ is the energy imparted to matter in a microscopic volume of interest by an energy deposition event, and $\overline{l}$ is the mean chord length in that volume (ICRU, 1993).

$$y = \epsilon/\overline{l} \tag{8}$$

The unit of lineal energy, as with LET, is J m^{-1}, which may be expressed in keV μm^{-1}. If lineal energy is measured in a sphere with diameter d, then the mean chord length is two-thirds the diameter.

$$\overline{l} = 2d/3 \tag{9}$$

and $$y = 3e/2d \tag{10}$$

Lineal energy is therefore a stochastic quantity subject to a geometric cutoff rather than an energy cutoff. For spherical sites, lineal energy, l, and specific energy, z, due to a single energy deposition event are related by

$$z = (4/\rho A)y \tag{11}$$

where ρ is the density of matter in the volume, and A is the surface area. The mean lineal energy, $\overline{l}$, is similar in concept to the LET, and has the same dimensions and units. However, LET is a nonstochastic quantity, whereas lineal energy is a stochastic quantity.

THE 'DOSE EQUIVALENT'

"... and the concept was applied to all the face of the Earth ..."

The dose equivalent is a weighted absorbed dose designed for radiation protection purposes. It serves as a basis for defining exposure limits on a common scale for all types and qualities of ionizing radiation. By definition (ICRU, 1993), the dose equivalent, H, is the product of D and Q at a point in tissue, where Q is the quality factor at that point.

$$H = DQ \tag{12}$$

The unit of dose equivalent (J kg^{-1}) is the same as for absorbed dose, and the special name for the unit is sievert (Sv), where 1 Sv = 1 J kg^{-1} (ICRU, 1993).

The quality factor, Q, at a point in tissues, has been defined by the ICRU (1993), as

$$Q = 1/D \int_L Q(L)\, D_L\, dL \tag{13}$$

where D is the absorbed dose at that point, D_L is the distribution of D in linear energy transfer L, and $Q(L)$ is the corresponding quality factor at the point of interest. The purpose for this definition of quality factor is to allow one to measure radiation interactions with a detector (such as a tissue-equivalent proportional counter) to infer quality factor and dose equivalent. This makes it possible to have a direct-reading measure of dose equivalent in rem or sievert.

Limitations of the Dose Equivalent

The sievert is not a physical quantity, as is the absorbed dose, but rather a unit of "assumed equal biological effectiveness," i.e., the multiple of an arbitrary value of Q, for use in radiation protection standards.

Limitations of the Concept of Quality Factor

The quality factor, Q, weights the absorbed dose for the biological effectiveness of the radiation producing the absorbed dose. The quality factor was chosen to encompass appropriate values of the relative biological effectiveness of the

radiation, independent of the organ or tissue, or the biological endpoint under consideration (ICRU, 1993). It applies primarily to low-dose radiation exposures and does not hold linearly with increasing levels of absorbed dose.

Values of Q are chosen by committee, somewhat arbitrarily, to be related to the LET, L, of the radiation in water, because the effectiveness of radiation with respect to endpoints of concern to radiation protection (i.e., chromosome aberration, mutation, transformation) increases with increasing LET values. The quantity Q is not to be confused with the 'relative biological effectiveness' (RBE), which applies to specific radiation endpoints, radiation qualities, dose rates, and cell types relative to a standard radiation parameter such as ^{60}Co gamma rays. Since the energy spectrum of radiation from charged particles inside the body cannot be determined, values of Q have been approximated for electrons, neutrons, protons, and alpha particles (ICRU, 1986).

The ICRP currently recommends the values of Q for both internal and external radiation sources, expressed as "radiation weighting factors" (ICRP, 1991):

TRACK STRUCTURE AND IONIZATION PATTERNS

Microdosimetric analysis of energy deposition patterns requires consideration of the physics, biology, and geometry of charged-particle track interactions with living cells. This includes a physical description of the radiation energy imparted, identification of sensitive targets in tissues, and geometrical analysis of target size of and distance from radiation sources inside the body.

Molecular Ionizations

Charged-particle radiation interacts with atomic electrons of the matter through which it passes, and energy is imparted with each interaction. The charge and mass of the particle, its initial energy, and the matter through which it travels determine the pattern of energy loss, the distance traveled, and the direction taken by the particle. Ionizations and excitations are produced when the energy

is transferred from the particle to the medium. On the average, about 34 electron volts (eV) are expended for each ion pair produced; thus, many atoms or molecules are ionized during the interaction of charged particles with matter. This amount of energy also includes energy loss by excitation events. The resultant ionization pattern leads to free-radical production and other chemical changes, and is directly associated with the eventual subcellular biological damage.

Charged particles have different velocities and mean rates of energy deposition in absorbing media. For example, a 1-MeV proton is a slow, heavy particle that produces several thousand ionizations along its path through the nucleus of a cell, whereas a faster 1-MeV beta particle (electron) may produce less than 100 ionizations in the same nucleus. The path of the proton is a short, straight line, but the electron will take a circuitous, almost arbitrary and crooked path as it interacts with atomic nuclei in its path. A single, heavy proton has a high probability of damaging or killing the cell, whereas many thousand electron interactions from sparsely ionizing radiation may be required to produce the same degree of intracellular damage. Fewer cells, however, will be traversed by the heavy, charged particles. These considerations have important implications for radiobiological interpretation.

Track Characteristics

Charged-particle tracks from protons and alpha particles consist of a densely ionized central core and radial secondary ionizations or electron 'delta rays'. Figure 1 shows a small (0.1-μm) segment of a hypothetical proton track in water, where primary ionizations are designated by x's, and secondary, delta-ray interactions are shown with solid dots. Relative specific ionization increases with distance traveled by the particle, to a maximum near the end of the track (discussed further in the next section).

DOSIMETRY FOR MICROSCOPIC TARGETS

"...from the Greatest to the Least of all of the Masses..."

Even on a microscopic scale, dose is the energy imparted divided by the mass of the target. For a given charged particle track, the microscopic dose is dependent on two factors: target size, and target location in relationship to the track. Four hypothetical targets are shown relative to the track segment illustrated in Figure 1; they represent unit-density, spherical targets with diameters varying from 5 to 50 nm in the positions indicated. If the ionizations are counted, a dose to each sphere may be calculated by dividing the ionization energy (represented by the number of x's and solid dots) by the mass of the spheres drawn. The differences in dose among the four sites along the same track is due to the differences in target size and number of ionizations within each. In this example the dose in specific energy is found to be 1.5×10^5 Gy for diameter = 5 nm; 5.2×10^4 Gy for diameter = 10 nm; 1.7×10^4 Gy for diameter = 20 nm; and 8.6×10^3 Gy for diameter = 50 nm.

In practice, an *approximate* dose to cells and cell nuclei may be determined by the same method. Consider, for example, a 5.5 MeV alpha particle from ^{241}Am that traverses the center of an 8-μm-diameter sphere. The range of this alpha particle is about 40 μm in unit-density material, such as water or tissue. Therefore,

$$D \approx \epsilon/m, \tag{14}$$

where ϵ = (8/40) 5.5 MeV,

= 1.1 MeV, or 1.76×10^{-6} erg, and

where m = (volume) (density)

= $d^3/6\pi$ g cm^3

= 2.68×10^{-10} g. Therefore,

D = 1.76×10^{-6} erg/2.68×10^{-10} g

= 6.57×10^3 erg/g, or 65.7 rad, or 0.657 Gy

For random traversals through the 8-μm sphere the energy imparted per track will range from something slightly greater than zero (grazing hits) to the maximum imparted by a track passing through the center of the sphere. The average energy imparted per traversal will be (2/3) (0.657) = 0.438 Gy.

Relative Specific Ionization

In the above example, an average linear energy is used to estimate the dose to an 8-μm diameter sphere from a 5.5 MeV alpha particle. However, the relative specific ionization (or ionization density) varies along the alpha particle track, as described by the familiar Bragg curve (Figure 2), such that the rate of energy transfer increases with distance traveled until the end of the track is reached. This variable rate of energy deposition per unit track length must be taken into account in microdosimetry calculations.

EXPERIMENTAL DETERMINATIONS OF z AND y

"And an accounting was made of all that was done on the Earth...."

Values of the specific energy, z, or of the lineal energy, y, may be calculated or determined by experimental measurement. A tissue-equivalent proportional counter containing tissue-equivalent gas at low pressure and density may be constructed to simulate the sensitive volume of a unit-density target of 1 μm or less.

Energy Density as a Function of Mass

For each target, a specific energy ($z = \epsilon/m$) is calculated; alternatively, a lineal energy ($y = \epsilon/l$) is recorded for each interaction in the detector. Figure 3 shows the dose, or specific energy density, as a function of the mass for which energy density is determined (Rossi, 1968). The horizontal line emerging from the scatter of points shows the relative range of target sizes for which absorbed dose, D, may be established from a single measurement. A significant tissue volume for determining absorbed dose should consist of at least 1 cm^3, or about 1 g solid tissue (NCRP, 1971). The dotted region in Figure 3 shows the range for which statistical dose fluctuations are important. Since each dot represents a measurement in ϵ/m for an individual target or measurement, the variations in local dose increase with smaller target size. Figure 3 shows that the average dose becomes less and less indicative of the complete dose distribution with smaller and smaller target sizes. Thus, for very small sites, the concept of

absorbed dose becomes meaningless, and the dose is best represented by a statistical distribution (or probability density) in specific energy.

Probability Densities in Specific Energy

Statistical distributions are used to describe alpha-particle doses to microscopic targets in biological systems; they include the probability that targets are missed and no energy is imparted. Probability densities are calculated by determining the spatial distribution of alpha sources relative to the target cells or cell nuclei and determining the frequency distribution of particle track lengths between alpha sources and target cell nuclei. This calculation provides the mean specific energy (absorbed dose), and the probabilities that cells or nuclei are missed, hit once, hit twice,..., or *n* times. This dosimetric information allows for interpretation of experimental data in fundamental radiobiological terms. Contributions from delta-ray secondaries, the relative specific ionization as a function of track length, and energy of recoil are taken into account.

A simple model of a body organ containing a uniformly distributed radionuclide is given in Figure 4. The model organ is a flask containing a solution of living cells and radionuclide sources. If the radionuclide sources emit heavy, charged particles, individual cells will be irradiated. Doses to individual cells will vary, depending on the length of each particle track through the cells and the number of times each cell is hit. One may determine the frequency distribution of specific energies received by the cells. Taken into consideration are all possible angles of alpha particle traversal through the site, and all possible distances between the radionuclide sources and the cells.

Figure 5 shows the frequency distribution of doses received by 8-μm-diameter spherical cells (solid line) following a two-hour irradiation by $^{241}AmO_2$ particulates in solution at a concentration of 1.15×10^5 Bq mL^{-1} (3.1 μCi mL^{-1}). The average dose delivered is 0.7 Gy (70 rad), although some cells receive up to 3 Gy. The delta function is 0.22, indicating that 22% of the cells are not irradiated, and thus received no radiation dose.

Figure 5 also shows the distribution of doses to just the nuclei within the cells. The probability of a nucleus being irradiated is smaller than the probability of a whole cell being irradiated. However, if the nucleus is hit by an alpha particle, it receives a greater dose in specific energy than does the cell. The average dose to all cell nuclei is still 0.7 Gy, although 58% remain unirradiated (delta = 0.58). The difference between the two distributions is attributable to the effect of target size.

Factors that affect the probability density in specific energy include:

- diameter of the target
- geometrical distribution of distances between sources and targets
- number of nuclear transformations per source
- concentration of sources in the volume (number per unit volume)
- energy of the particles emitted

Factors that *do not* affect the probability density include:

- concentration of targets (number per unit volume) and therefore
- the distance between targets

ABSORBED DOSE DISTRIBUTIONS FOR BETA-PARTICLES IN TISSUE

"...among the Weak as well as among the Strong..."

Beta particles are electrons or positrons ejected from unstable atomic nuclei. Some of the nuclear decay energy is emitted simultaneously by neutrinos, and excess energy is emitted in the form of one or more gamma rays. As light-weight charged particles, beta particles lose energy during interactions with the atomic nuclei of absorbing matter, slow down, and are scattered over highly tortuous, circuitous paths rather than along straight tracks. Beta particles may also produce secondary electron tracks and low-energy photon brehmsstrahlung. The total path length of a beta particle may be greater than its mean range by a factor of from about 1.2 to about 4. Thus, beta particles are characterized by a spectrum of electron energies. The unpredictability of the beta particle's initial energy and path makes conventional microdosimetry impracticable. Beta-emitting radionuclides also distribute nonuniformly in tissues.

Beta emissions produce nonuniform energy distributions in targets that are small relative to the maximum beta-particle range. Even the concept of beta-particle range is imprecise. Beta-particle range is usually defined in term of the X_{90} distance. The X_{90} distance is the radius of a sphere in which 90% o the beta energy is deposited for a point source located at the center of the sphere. The maximum beta range is approximately 1.8 times the X_{90} distance, i.e., the radius of a sphere in which 99% of the beta energy is deposited. For example, the maximum (99%) range of the beta particles from iodine-131 (average energy = 183 keV) is about 1.5 mm, but 90% of the beta energy is absorbed within a radius of 0.8 mm from a point source in unit-density material. Yttrium-90 has a more energetic beta emission spectrum (average energy = 931 keV) and a maximum range of about 9 mm in tissue.

Internal beta dosimetry is frequently based on Loevinger's empirical formula for the beta point-source dose-rate distribution in a homogeneous medium (Loevinger, Holt, and Hine, 1956; Fitzgerald, Brownell, and Mahoney, 1967), or on Berger's compilations of absorbed dose around beta-emitting point sources in water and other media (Berger, 1971). According to Berger, the basic formula for the average dose $D(x)$ at distance x from a beta point-source of average energy $E\beta$ is

$$D(x) = [A\ Y\ k\ E\beta\ F\beta(x/X_{90})] \ / \ [4\ \pi\ \rho\ x^2\ X_{90}] \qquad (15)$$

where A is the source activity, Y is the beta yield per disintegration, k is an energy conversion constant, $F\beta(x/X_{90})$ is the scaled absorbed dose distribution that is a function of the distance from the source as a ratio of the distance to the X_{90} distance, and ρ is the density of the absorbing medium. Doses to volume elements are obtained by integrating the formula over the appropriate regions of interest. This approach forms the basis for determining radiation doses to small organs, to regions within organs, and to regions where source distributions are heterogeneous.

Dose rates from beta-emitting sources can be calculated from a combination of experimental and theoretical data. The tables of Berger (1971) provide distributions of absorbed energy around point sources in water for 75 radionuclides. The dose rates to any point in a homogeneous material of low atomic number, as a function of distance, may be calculated from these data for

many geometries. The fraction of emitted beta energy absorbed in the source medium may also be calculated.

The short range of beta particles means that there will be significant differences in the localized dose for inhomogeneous source distributions compared to uniformly distributed sources. The volumetric integrations outlined above are performed numerically from information about the source distribution as a function of position, and depends on the shape of the target.

CONCLUSIONS

"And it was Good!"

The concepts of average dose and linear energy transfer have severe limitations and may not be appropriate for dosimetry at the cellular level. If the concept of average or absorbed dose is used to describe the effects of radiation on cells, then it is also important for the investigator to show that "average dose" has significance in the context in which it is used. At low doses of alpha or beta radiation, this level of significance is rarely attained, and microdosimetric analysis or localized dosimetry must be used.

It is frequently assumed that biological effects will be a simple function of average dose. However, closer examination using microdosimetry or localized dosimetry shows that this is not necessarily the case. Radiation effects begin at the cellular level of biological organization. Radiation dosimetry at the cellular level is particularly important for internally deposited alpha- and beta-emitting radionuclides.

Microdosimetry and localized dosimetry are tools for studying the dose to small targets in living tissue, and are particularly useful in cases where the variation ϵ/m from D exceeds 20%. Dose calculations are complex, and generally require computer programs. The investigator must define the target and its size, determine the source characteristics and the radionuclide activity per unit mass for each region in which targets are located, describe the activity per radioactive particulate, state the geometrical relationship between the activity

and the targets, and account for the biological retention of the activity in the region over time.

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REFERENCES

Berger, M. J. Distribution of absorbed dose around point sources of electrons and beta particles in water and other media. MIRD pamphlet No. 7. J. Nucl. Med. 12 (suppl No. 5); 1971.

Dessauer, F. Point heat theory. Z. Phys. 30:288; 1922.

Fitzgerald, J. J.; Brownell, G. L.; Mahoney, F. J. Mathematical theory of radiation dosimetry. New York, NY: Gordon and Breach Science Publishers; 1967.

International Commission on Radiation Units and Measurements. Radiation quantities and units. Bethesda, MD: ICRU; ICRU Report No. 33; 1980.

International Commission on Radiation Units and Measurements. The quality factor in radiation protection. Bethesda, MD: ICRU; ICRU Report No. 40; 1986.

International Commission on Radiation Units and Measurements. Quantities and units in radiation protection dosimetry. Bethesda, MD: ICRU; ICRU Report No. 51; 1993.

International Commission on Radiological Protection. Recommendations of the ICRP. Oxford, UK: ICRP; ICRP Publication 26; 1977.

International Commission on Radiological Protection. 1990 recommendations of the International Commission on Radiological Protection. Oxford, UK: ICRP; ICRP Publication 60; 1991.

Lea, D. E. Actions of radiation on living cells, 2nd ed. New York, NY: Macmillan; 1956.

Loevinger, R.; Holt, J. G.; Hine, J. G. Internally administered radioisotopes. In: Hine, G. J.; Brownell, G. L., eds. Radiation dosimetry, New York, NY: Academic Press; 1956.

National Council on Radiation Protection and Measurements. Basic radiation protection criteria. Washington, DC: NCRP; NCRP Report No. 39; 1971.

Rossi, H. H. Microscopic energy distribution in irradiated matter. In: Attix, F. H.; Roesch, W. C.; eds. Advances in radiation dosimetry, vol. 1. pp. 43-92. New York, NY: Academic Press; 1968.

Zirkle, R. E. The radiobiological importance of the energy distribution along ionization tracks. J. Cell. Comp. Physiol. 16:221; 1940.

Table 1. Levels of Dose Assessment, Range of Approximate Target Mass (g) and Diameters (m) for Each Level, and Applications

TARGET LEVEL	APPROACH	APPLICATIONS
1. Organ mass = 1-10^{5} g dia. = 1-60 cm	Macrodosimetry (conventional dose-averaging)	General assessments, medical dosimetry, and epidemiology
2. Tissue/sub-organ mass = 10^{-4}-10^{2} g dia. = 0.05-6 cm	Small-scale, multi-cellular dosimetry	Respiratory tract, bone surface, skin, organ wall, and tumor dosimetry
3. Cellular/nuclear mass = 10^{-12}-10^{-7} g dia. = 1-100 μm	Microdosimetry	Alpha-particle dose distributions, and *in vitro* studies in radiation biology
4. Sub-nuclear mass $\leq 10^{-12}$ g dia. $\leq$ 1 μm	Nanodosimetry	Theoretical radiation biology, and DNA damage studies

Table 2. Values Chosen for Q, the Quality Factor (Radiation Weighting Factor).

Type and Energy Range	Q, or Radiation Weighting Factor
Photons of all energies	1
Electrons of all energies	1
Neutrons, energy < 10 keV 10 to 100 keV >100 keV to 2 MeV >2 MeV to 20 MeV >20 MeV	5 10 20 10 5
Protons, energy > 2 MeV (not recoil)	5
Alpha particles, fission fragments, and heavy nuclei	20

Figure Captions

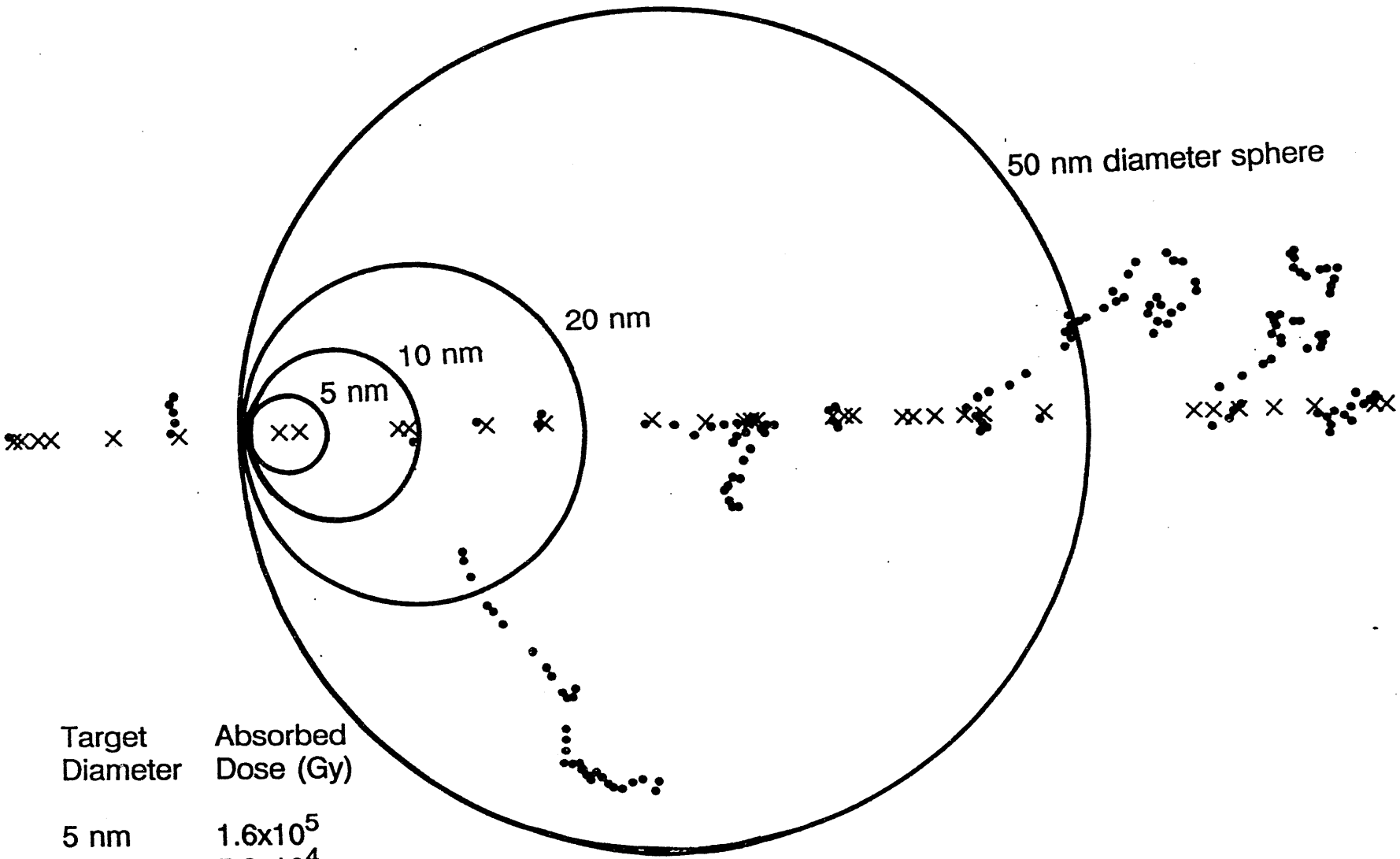
Figure 1. Computer-simulated Proton Track Segment (0.1-μm) in Water. Primary ionizations are indicated by x's, and secondary ionizations are shown with solid dots. Superimposed spheres represent targets for dose calculations.

Figure 2. Bragg Ionization Curve. Relative specific ionization with distance traveled by a charged particle.

Figure 3. Variation in Dose as a Function of Target Mass, and Convergence of Specific Energy to Absorbed Dose. From Rossi (1968); used by permission.

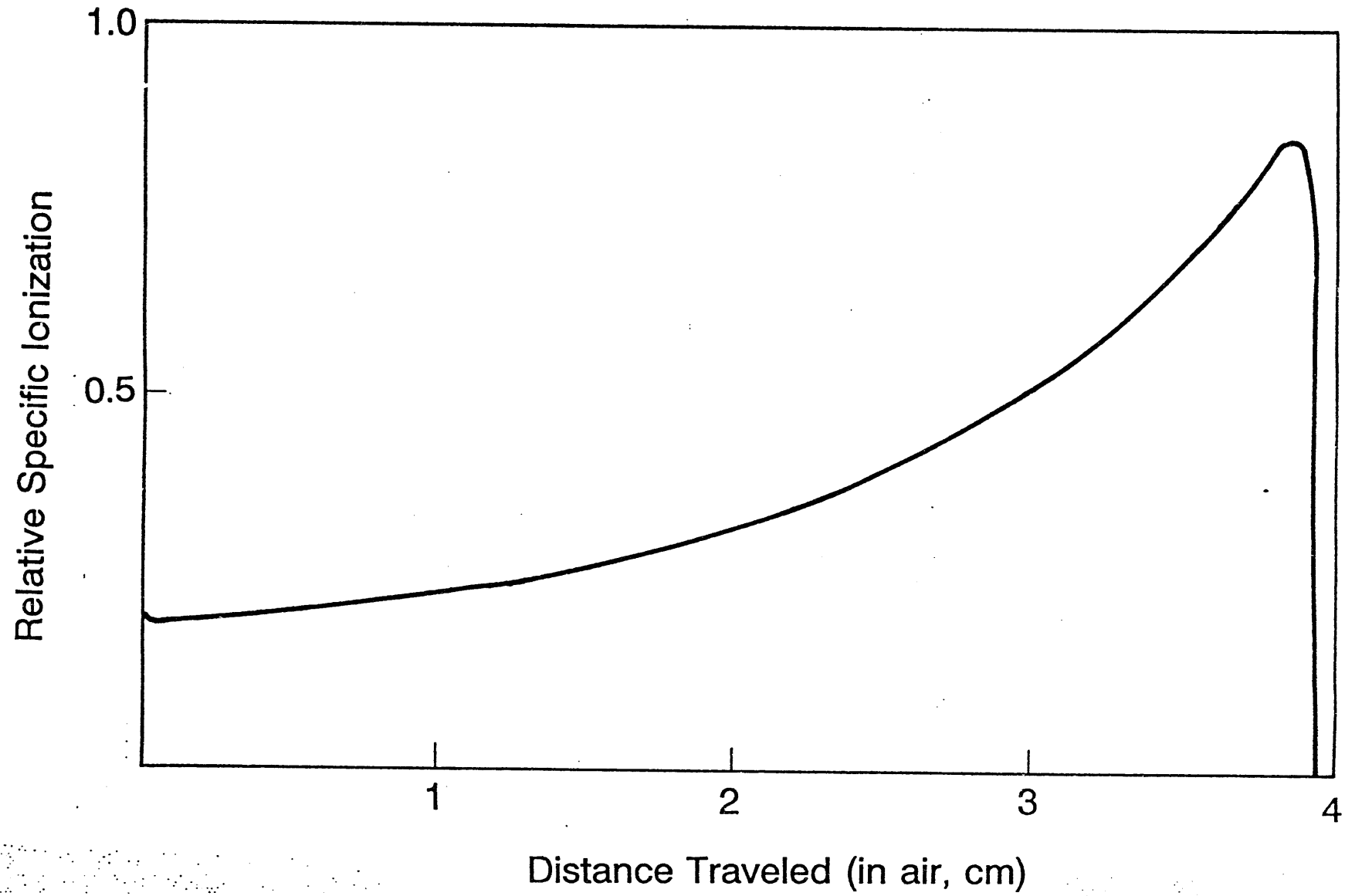
Figure 4. A Simple Model of a Body Organ Containing a Uniformly Distributed Radionuclide in a Solution of Living Cells.

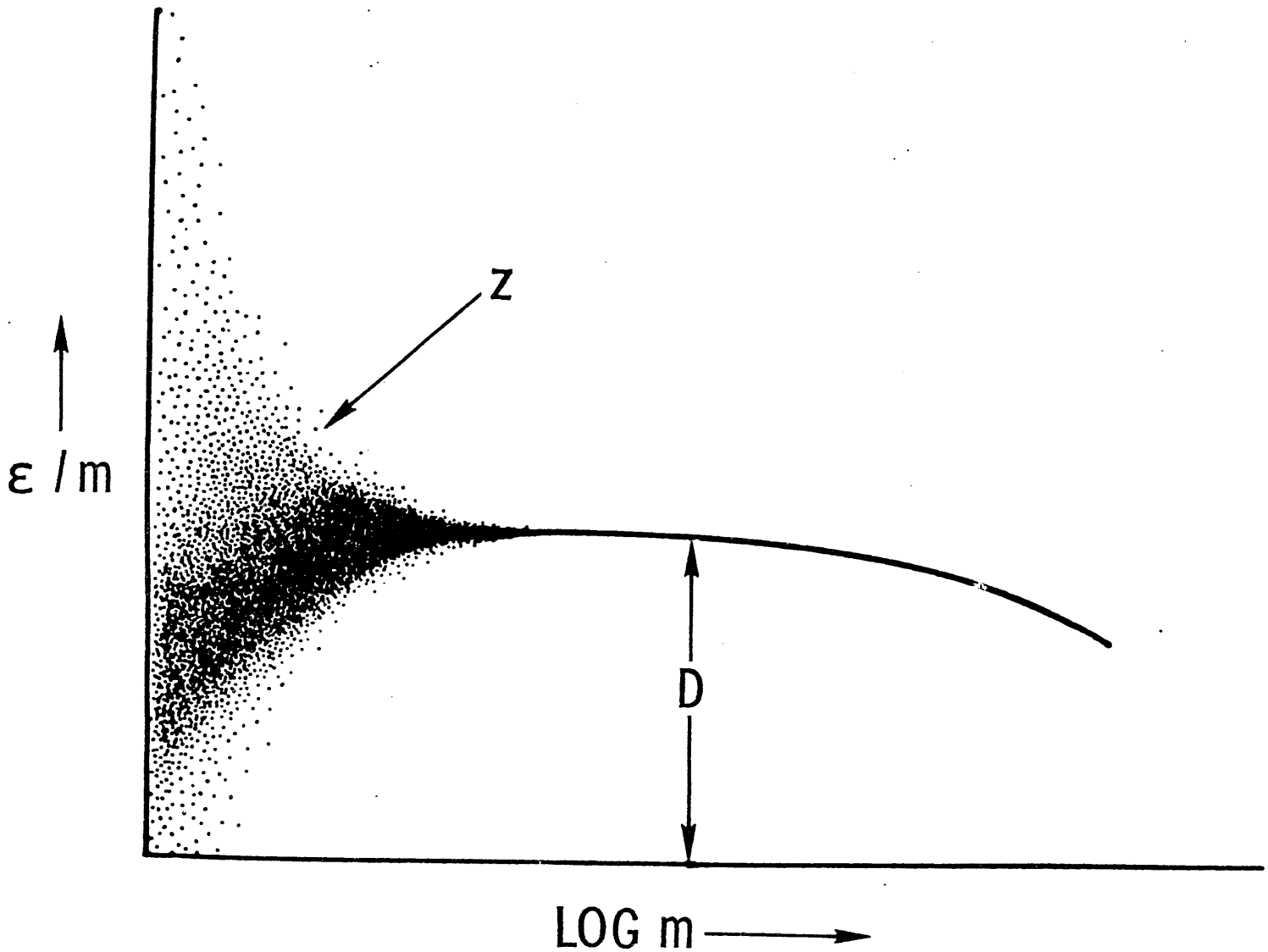
Figure 5. Probability Density in Specific Energy for Cells and Cell Nuclei after Irradiation *In Vitro* by $^{241}AmO_2$ Alpha Particles (1.15×10^5 Bq mL^{-1} for 2 h).



Target Diameter	Absorbed Dose (Gy)
5 nm	1.6×10^5
10 nm	5.2×10^4
20 nm	1.7×10^4
50 nm	8.6×10^3

Fisher Fig 1


1.0
0.5
Relative Specific Ionization
1
2
3
4
Distance Traveled (in air, cm)


z
ε / m
D
LOG m

CELLS PLUS ACTIVITY IN SOLUTION

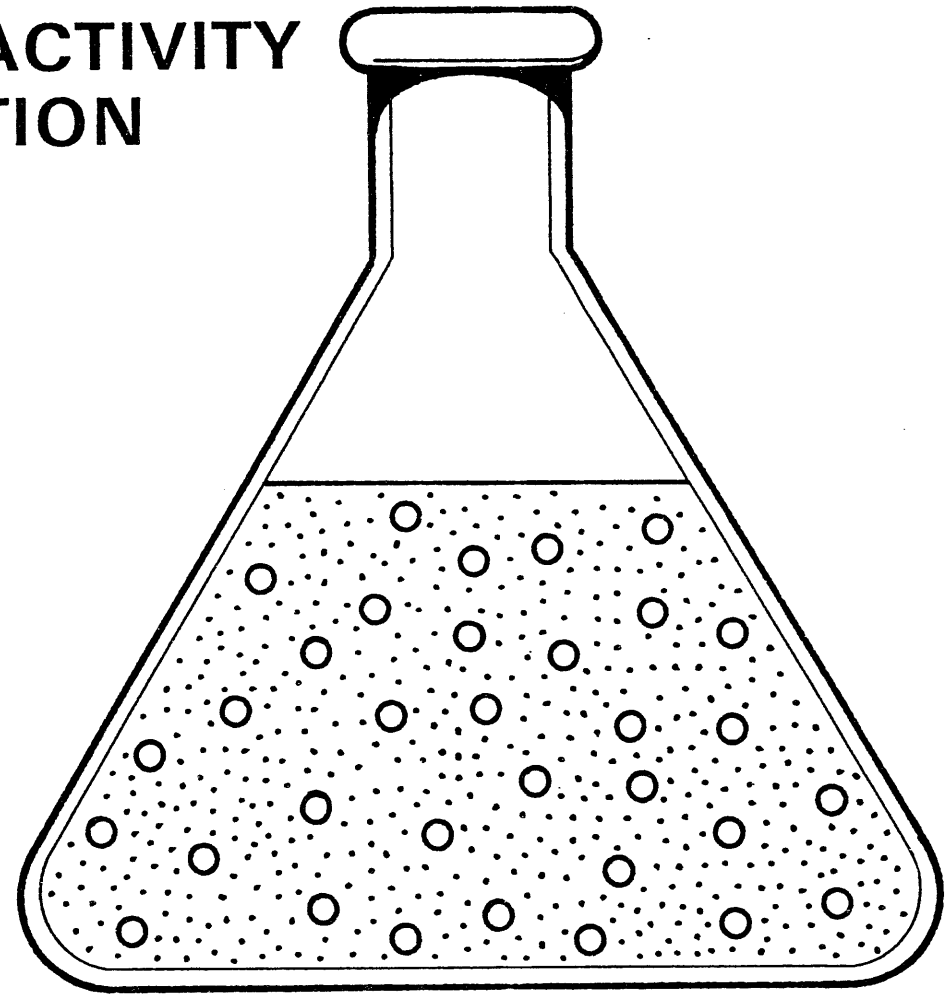
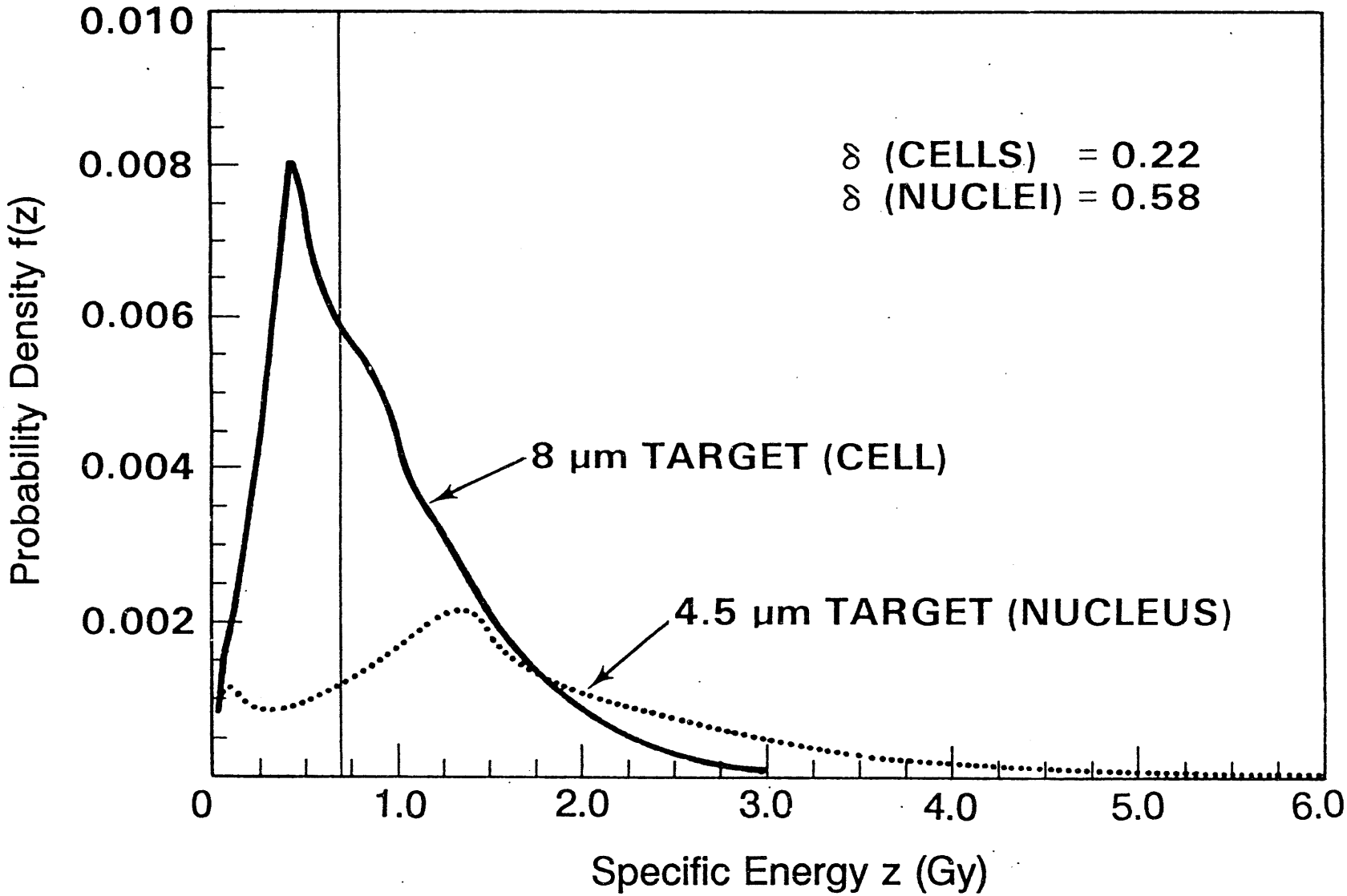


FIGURE 4.


0.010
0.008
0.006
0.004
0.002
Probability Density f(z)
δ (CELLS) = 0.22
δ (NUCLEI) = 0.58
8 μm TARGET (CELL)
4.5 μm TARGET (NUCLEUS)
0
1.0
2.0
3.0
4.0
5.0
6.0
Specific Energy z (Gy)

Fisher Fig. 5

II

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