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Dose

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COMMENTARY

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The universal use of dose as a normalizing parameter in radiobiology is based entirely on the availability of measuring instruments. It is a poor basis for predicting or understanding the relationship between an irradiation and the resulting end point. Energy deposited is not the cause of an interaction. It is a secondary effect. The interaction is best described by fluence and cross section. Energy deposited depends principally upon inelastic collision cross sections for the interaction of electrons with molecules. Especially for heavy-ion bombardments, for high-LET radiations, inelastic electron collision cross sections relate only remotely to the observed end points of interest. When dose is used to describe effects observed with radiations of different "quality," response predictions can be very wide of the mark. One way to describe such a relationship is through the relative biological effectiveness (RBE). If we consider the RBE to be a correction factor to be applied to a prediction of response based on dose, we find that its values range from 0.01 to infinity. It is apparent that in general dose is a useless predictor of response, except in narrowly defined circumstances.

INTRODUCTION

An irradiation of matter with γ rays results in a chaotic tangle of secondary electrons of different energies and ranges of such complexity that it is impossible to trace the contributions of individual electrons to the observable end point. As a practical convenience such an irradiation is considered to be amorphous, neglecting the chaotic tangle of secondary electron paths of which it is composed. It is then described by dose, the energy per unit mass, whose principal virtue is that it is measurable. But what is actually measured is the ionization in a gas, converted to energy deposited by use of a w value, the energy per ion pair. For this tangle of secondary electrons dose is best understood as a surrogate for electron fluence. It is a macroscopic quantity which experience has shown to be a useful plotting parameter for γ rays, orthovoltage X rays and megavoltage electron beams, in that differences in dose to produce the same effect with these radiations approximate only 10 or 15%. The effect of beams of megavoltage protons may be equally described by dose provided that the effects of secondary nuclear fragments from the irradiated target may be neglected. But energy deposited is not a fundamental quantity for the description of radiation effects. Energy can be deposited in many ways: by heat transfer, by visible light or by microwaves, none of which is suitable for the production of effects that are generated by ionizing radiations. Indeed, dose is often misleading, even with ionizing radiations. If we ask whether mammalian cells are more sensitive to radiation than enzymes, we can get two contradictory answers. The answer based on the inactivation dose is yes; the inactivation dose lies in the neighborhood of several grays for mammalian cells, and in the neighborhood of 100 kGy for enzymes. Yet an answer based on fluence, on the number of electrons which must transit the target to induce inactivation, is no. While a single electron passing through an enzyme molecule can inactivate it (for enzymes are one-hit detectors), hundreds of electron transits are required to inactivate a mammalian cell (*1*).

TARGET MOLECULAR WEIGHT

For targets of molecular size, like dry enzymes and viruses, a concept called target molecular weight has been introduced (*2*). It is assumed that some number like 75 eV of "energy deposited in a molecule" is required for its inactivation. When the product of the dose of γ rays and molecular mass equals or exceeds 75 eV, inactivation is assumed to take place. Then measurement of the dose at which there is an average of one interaction per molecule, the D_{37}, is taken to be a measure of molecular mass. But energy deposited in a target by γ rays is a strange concept. Molecular physicists who bombard molecules with beams of electrons never speak of energy deposited in a molecule as a result of dose and molecular weight. They measure the electron energy loss

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to produce a particular excitation or ionization, but this is not the same thing as the product of dose and molecular mass. No, in this construct dose is surrogate for electron fluence and molecular mass is surrogate for the inelastic electron-molecule ionization cross section, while energy deposited is surrogate for the product of fluence and cross section. Energy deposited in a molecule is simply an inappropriate concept made plausible through use of an implausible numerical criterion.

MICRODOSIMETRY

While the energy deposited by γ rays at large doses can be imagined to be deposited "homogeneously" relative to the size of biological targets, the energy deposited by the nuclear fragments arising from a neutron irradiation is much more heterogeneous. This has led to measurement of energy deposited in small gaseous proportional counters, scaled by density to cellular volumes of micrometer or nanometer diameter. One then speaks of microdosimetry as opposed to macrodosimetry, or inappropriately of nanodosimetry as reflecting the effective size of the target volume. The difference in response of biological systems to neutrons is then attributed to the increased granularity of energy deposition. But in the many years since the introduction of microdosimetry, and in spite of the enormous efforts on its behalf, microdosimetry has not led to any fundamental understanding of radiobiology. Quoting Kellerer, "Concepts of microdosimetry are of course essential in any analysis of the action of ionizing radiation on the cell. Their employment has led to important insights but not, as yet, to a quantitative treatment of primary cellular changes" (*3*). And in spite of several modifications of the original concept, it has not succeeded in deriving a single cross section, even for the inactivation of dry enzymes and viruses. It has not been able to account for the variation of RBE with LET, or for thindown, or for the quantitative response of cells to neutrons, for which it was originally devised (*4*). Indeed it is *a priori* impossible for microdosimetry to yield a calculation of cross sections (*5*). This is because the microscopic distribution of energy depositions is detached from the ion paths which created these distributions. And additionally because energy depositions in small volumes cannot be correlated with the probability for generation of a specific observable end point. We are faced with a conceptual failure rather than one of the detailed lack of knowledge of target size, shape, density or identity. In contrast, a competing construct based on fluence, that of track theory, has succeeded in describing all of these (*6*).

Dose is an amorphous macroscopic quantity. Little is gained by examining the fluctuation of energy deposition in small volumes, in an attempt to replace the macroscopic distribution by a structured microscopic one. For dose to be meaningful many electrons, often of different energies, must pass through target volumes. Dose is a statistical concept. It is based on averages. When only one or two or a few electrons pass through such a volume, the meaning of dose is changed qualitatively. In this regard it is like the concept of temperature, which is meaningless when applied to a collection of only a few molecules. When an irradiation is altered from one in which electron ranges can be substantially greater than the diameter of a target to one in which they are all much smaller, as in the case of ultrasoft X rays, the meaning of dose and its relationship to response are changed both qualitatively and quantitatively. We must raise these questions when interpreting the difference between doses measured for the same end point between ultrasoft X rays and γ rays (*7*).

HEAVY IONS

The response of a detector to doses of energetic heavy ions can be related to its response to γ rays only through a complex calculation whose first step requires the determination of the average dose in a target from δ rays as a function of the radial distance of the target from the ion's path. The radial gradient in the dose deposited by δ rays necessitates the use of the average dose. Prediction of the response of one-hit detectors to heavy ions from the measured dose–response function for γ rays is fairly straightforward. Prediction of the response of eucaryotic cells is more complex because of the greater complexity of their structure.

For one-hit detectors, where the response to γ rays is exponential, the radial distribution of inactivation probability about an ion's path is found by combining the radial distribution of dose with the dose–response relationship for γ rays. This is integrated radially to find the cross section, σ. When a beam of heavy ions is used to irradiate a population of one-hit targets, the survival probability Π_i after fluence F is given as

$$\Pi_i = e^{-\sigma F}. \quad (1)$$

We imagine a "bean bag" model for eucaryotic cells in which the beans are presumed to be targets distributed through the cell nucleus, whose size, uniformity, radiosensitivity and location are unknown. We further simplify the target distribution for purposes of calculation, representing it by a hypothetical internal target of radius a_0, target number m and characteristic dose (at which there is an average of one hit per target) D_0. We calculate the probability of inactivation of such a target located at radial distance t from the ion's path from the average dose experienced by the target and the multitarget, single-hit per target model which approximates the response of the cell to γ rays and once again radially integrate the probability to find the cross section for target inactivation. The cross section for *cellular* inactivation is asserted to be proportional to the cross section for target inactivation. But this cellular inactivation cross section is not

the whole story. It describes the inactivation at low fluence when there is no probability that δ rays from adjacent ions can intersect the target volume. We call the inactivation by δ rays from a single ions by the term "*ion kill*," for it is described by Eq. (1), used to calculate the inactivation of one-hit detectors by a beam of ions.

At high fluence the problem is more complex for we must deal with both *intra*track effects called ion kill and *inter*track effects called *gamma kill*, described by the same equation as used to calculate the effects of a γ irradiation. Taking a cue from the appearance of particle tracks in emulsion (*8*), we speak of a *grain-count regime* where inactivated cells are distributed like beads on a string and a *track-width regime* when the track of inactivated cells resembles a hairy rope. In the grain-count regime we assume that the gaps in the bead string are of cells which are damaged only partially or sublethally. In the track-width regime the fraction of cells which are sublethally damaged is small, and may be neglected in first approximation. Sublethally damaged cells in the gaps may be damaged further by δ rays from adjacent ions at high fluence, to be killed in the gamma-kill mode. If P is the fraction of intersected cells which are killed in the ion-kill mode, we take P also to be the fraction of the energy deposited in the ion-kill mode, and therefore $(1 - P)$ of the energy is deposited in the gamma-kill mode. If the survivors of the ion-kill irradiation are taken to be the initial population in the gamma-kill irradiation, we can apply the dose $(1 - P)FL$ to our equation for cell survival from γ rays to find the probability for survival, $\Pi\gamma$, in the gamma-kill mode. Then the product of the ion-kill and gamma-kill survival probability represents the survival probability, P, after the irradiation,

$$\Pi = \Pi_i \Pi_\gamma . \qquad (2)$$

This results in a set of equations containing four cellular radiosensitivity parameters which are fitted to experimental data from a limited set of bombardments with γ rays and energetic heavy ions. Once these parameters have been determined for a specific end point, the equations enable us to predict response for a wide variety of radiation fields provided that the secondary particle-energy spectrum is known.

Note that the response is described in a mixed manner, with the ion-kill part based on fluence while the gamma-kill part is based on dose. What is fundamentally different about the two modes is the different statistical formulation applicable to the two interaction modes.

Dose is properly used to describe the effects of secondary electrons from γ rays, and of δ rays in cylindrical shells surrounding an ion's path, but not of the total effect of the ensemble of shells. Effects in these shells are not simply related to the energy deposited in them from either the intra- or the intertrack contributions.

MIXED RADIATION FIELDS

To treat a mixed field composed of assorted ions and γ rays, we must know the particle-energy spectrum of the ions and the dose of γ rays. We then find the ion-kill survival probability for each of the ion components. Next we add all the gamma-kill doses together with the dose of γ rays to find the gamma-kill survival probability. These are multiplied together as in Eq. (2) to find the surviving fraction of the cell population. The dose of such a field is the sum of the products of F and L for each of the components of the field together with the dose of γ rays. For heavy ions, for neutrons and for mixed radiation fields the macroscopic dose is hopelessly inadequate as a predictor of response.

OTHER MODELS

Algorithms based on microdosimetry have been advanced as suitable for predicting the response of cells to mixed fields of radiation. One of the most recent of these is called *hit-size effectiveness* (*9*), said to provide a direct connection between a microdosimetric pulse-height distribution and the probability for cell killing or mutation. This model is inconsistent with the above discussion and has not been demonstrated to yield a calculation of cross sections or to correlate with cell survival in general. While the track-structure model above has been applied to a number of physical, chemical and biological one-hit detectors, and to upwards of 40 sets of data for cell survival, mutation and transformation, obtained with a sequence of γ-ray and track-segment heavy-ion irradiations[1] and has been used to predict the response of beams of heavy ions, neutrons and mixed radiation fields, to calculate thindown in bacteria and mammalian cells,[2] the application of other models to existing data is as yet extremely limited.

DOSE AND RESPONSE: PRACTICAL PROBLEMS IN RADIATION DOSIMETRY

The connection between dose and response through track theory is complicated, for it requires the determination of a set of radiosensitivity parameters, the calculation of the particle energy spectrum of the radiation field (for this cannot presently be measured), and the measurement of the γ-ray dose. In earlier work we have shown that a complex radiation field may be represented by a virtual track-segment irra-

[1]C. Zhang and R. Katz, Thindown in radiobiology: *E. col.* B/r, B_{s-1}, *B. subtilis* spores and V-79 Chinese hamster cells. Manuscript submitted for publication.

[2]R. Katz, R. Zachariah, F. A. Cucinotta and C. X. Zhang, Survey of cellular radiosensitivity parameters. Manuscript submitted for publication.

diation with a hypothetical particle of such charge and speed that both ion-kill cross section and the fraction of the deposited energy in the gamma-kill mode equal that of the complex field in question. There need not be a real physical ion having the charge of the hypothetical particle, for this is an "as if" irradiation. At present such an "equivalent irradiation" can be found only by theoretical calculation for specific end points and specific radiation fields. However, the calculation can be made for irradiation with a known spectrum of energetic neutrons for which the secondary particle spectrum in tissue is known, for example. Once this is done the calculation of cell survival, mutation or transformation for a known dose of these neutrons with a known γ-ray contamination is readily accomplished, even with hand-held programmable calculators.

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REFERENCES

1. R. Katz and M. P. R. Waligorski, On the linear extrapolation to low dose. *Radiat. Prot. Dosim.*, in press.
2. F. Hutchinson and E. Pollard, Target theory and radiation effects on biological molecules. In *Mechanisms in Radiobiology* (M. Errera and A. Forssberg, Eds.), pp. 71–92. Academic Press, New York and London, 1961.
3. A. M. Kellerer, A generalized formulation of microdosimetric quantities. *Radiat. Prot. Dosim.* **31**, 9–16 (1990).
4. H. H. Rossi, Microdosimetry and radiobiology. *Radiat. Prot. Dosim.* **13**, 259–265 (1985).
5. R. Katz, Cross section. *Appl. Radiat. Isot.* **41**, 563–567 (1990).
6. R. Katz and S. C. Sharma, Response of cells to fast neutrons, stopped pions and heavy ion beams. *Nucl. Instrum. Meth.* **110**, 93–116 (1973).
7. D. T. Goodhead, J. Thacker and R. Cox, Effectiveness of 0.3 keV carbon ultrasoft X-rays for the inactivation and mutation of cultured mammalian cells. *Int. J. Radiat. Biol.* **36**, 101–114 (1979).
8. C. F. Powell, P. H. Fowler and D. H. Perkins, *The Study of Elementary Particles by the Photographic Method.* Pergamon Press, New York, 1959.
9. M. N. Varma, V. P. Bond and G. Matthews, Hit size effectiveness theory applied to high doses of low LET radiation for pink mutation in tradescantia. *Radiat. Prot. Dosim.* **13**, 307–309 (1985).
10. R. Katz, B. G. Fullerton, Jr., R. A. Roth and S. C. Sharma, Simplified RBE-dose calculations for mixed radiation fields. *Health Phys.* **30**, 148–150 (1976).