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On the Linear Extrapolation to Low Doses

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Abstract

While radiobiological data are conveniently fitted by a linear quadratic formula to data of limited dynamic range at doses typically exceeding 1 Gy, they are extrapolated linearly to doses below a milligray for the evaluation of low dose RBEs. However a single relativistic electron passing through a cell nucleus deposits a "dose" there in the neighborhood of a milligray. The validity of the linear extrapolation then rests on the demonstration that a single electron transit through a cell nucleus can cause inactivation or mutation or can lead to cancer induction. The extrapolation made is a huge one, of some three orders of magnitude, from thousands of electrons traversing a cell to a single cell traversal, and with only qualitative and rhetorical foundation (one track-two tracks), and ignoring the statistical fluctuations of track intersections with targets. Existing data obtained with beams of electrons, protons, X ray photons, incorporated tritium, and ^{125}I demonstrate that hundreds of electrons may traverse a cell for inactivation and millions may be required for cancer induction. If linear extrapolation were valid these numbers would be reduced to one. These contradictions suggest serious reconsideration of accepted radiation protection standards.

Introduction

The linear quadratic model is widely used in radiobiology to fit data of limited dynamic range, nominally not greater than two decades in dose, and at doses in the neighborhood of grays as summarized in NCRP report No. 104 [1]. This model has only qualitative and rhetorical support, in the form of statements about one track and two track effects, as justifying the linear and the quadratic components, respectively, and ignores the statistical fluctuation of track intersections with targets, especially important in the limit of low doses. There is no quantitative theoretical base for such a model other than the assertion that electron track ends *might* act like high LET radiations, a qualified appraisal at best, unsupported by direct experimental evidence, though frequently inferred from energy deposited in small volumes which approximate small sections of DNA at track ends by stopping electrons, or from the number of ionizations therein, both from Monte Carlo calculations. The relation between the linear quadratic formula and the theory of dual radiation action [2] is noted, but it must be pointed out that it is the experimental fit of the linear quadratic formula to data which supports the theory of dual radiation action, rather than the converse. 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 the primary cellular changes*" [3]. It is widely recognized that the linear quadratic formula fails outside its fitted range.

Linear Extrapolation to Low Doses of Low LET Radiations

In NCRP Report 104 [1], observations of biological effects with low LET radiations are extrapolated linearly to doses of 1 mGy and below in order to evaluate the RBE of high LET radiations at low doses. However, a flux of relativistic electrons at which single electrons pass through cells deposits a dose in the neighborhood of 1 mGy. It may be asked, do single electron transits through cells kill, mutate, transform mammalian cells? Do single electron transits induce cancers? It must be kept in mind that the extrapolation involved is substantial, as much as three or four orders of magnitude, frequently from grays to milligrays. But the extrapolation is not only quantitative. It is qualitative as well, pressing on the very validity of the concept of dose. Is there any basic reason why dose, an amorphous concept used to characterise a chaotic distribution of secondary electrons which experience has proven adequate as a plotting parameter when thousands of electrons from orthovoltage X rays or gamma rays traverse cells, should also be valid when single electrons traverse cells, and when the statistical consideration invoked in target theory is ignored?

Experimental Data

Several of the following citations have already been noted [4].

Cole et al. [5] have found that some 500 electrons pass into the nucleus of a CHO cell, on average, for inactivation.

Warters et al. [6] found that some 500 tritium β decays in the nucleus of a CHO cell are required for observable killing.

Geard and Brenner [7] found about 0.002 aberrations per 4.1 MeV proton (LET 10 keV μm^{-1}) per nucleus in Chinese hamster V-79 cells. Thus, about 500 traversing protons are required to produce a chromosome aberration in these cells. These authors concur that changes assessed on a per particle per cell basis transcends reliance on the concept of absorbed dose.

Wilkinson et al. noted that about 0.3 Gy of 280 eV C_k X rays are required to produce about 0.3 chromosome aberrations of any type in asynchronous BHK Syrian hamster cells [8]. This implies that some 28,000 photoelectrons having a range of 7 nm, comparable to the size of a nucleosome, must be liberated in a cell nucleus of approximate volume 500 μm^3 to generate a chromosome aberration.

Similarly Raju et al. [9] have reported on the killing of 25% of a culture of V-79 hamster cells by 1 Gy of C_k X rays, citing an energy loss rate crudely estimated to be about 40 keV mm^{-1}. The extrapolation from the experimental dose of 1 Gy to that of a single such photon per cell nucleus is more than four orders of magnitude.

Bettega et al. [10] found the survival of C3H 10 T1/2 cells after 31 MeV proton irradiation (LET 1.83 keV μm^{-1}) to be well described by a multitarget model with m = 3.3, approximately equal to those found from a track theory fit of high LET data [11], as cited by Katz and Cucinotta. A similar analysis of transformation data obtained with low LET protons yielded a value of m = 5.1, (Note that the symbol m is used to represent the extrapolation number of consistency with track theory notation while Bettega uses the symbol n.) These data imply a very strong plateau with virtually no effect at low dose, and very high RBE for alpha particles, contradicting a linear extrapolation to low doses of low LET radiations. These measurements were carried to doses of 0.01 Gy, below the range of much radiobiological data obtained with mammalian cells.

Single electrons through cells are even more unlikely to cause cancers. A plot of electron- induced carcinogenesis in rat skin, by Burns and Albert [12] displays nearly quadratic response with dose, with tumors per rat at 99 weeks as end point. The lowest dose point is at about 0.7 Gy with a yield of 0.01 tumors per rat. For electrons of LET 0.34 keV μm^{-1}, one finds the fluence to be about 1280 electrons μm^{-1}. Taking the cell area to be about 100 μm^2, about 12,800,000 electrons pass through a cell to induce a cancer in rat skin at this dose level.

Quoting Broerse [13] "Our studies on a rat mammary carcinogenesis after fractionated irradiations with relatively low doses of gamma radiation revealed quadratic dose-response curves without a significant linear component for the induction of carcinomas."

One cannot ignore these results. One must question the extrapolation of the "linear quadratic model" fitted typically at doses exceeding 1 Gy and extrapolated to doses below 1 mGy to lay the basis for the calculation of RBEs for high LET particles at low doses. A question must also be raised regarding the use of such extrapolations to set low dose limits for the purpose of radiation protection.

Relation to Track Theory

Track theory assumes that radiation effects in many detectors are due to secondary electrons. Detectors are classified according to their structures, simple or complex like biological cells, and according to their "hittedness," the number of electrons that pass through targets in order to activate them. Many physical detectors and some biological detectors (some *E. coli* mutants) are one hit detectors. For these, a linear extrapolation to low dose is precisely correct. One hit detectors display an exponential response to gamma rays, have no dose rate dependence, and display an RBE never greater than 1 to high LET radiations. Several many hit physical and chemical systems have been found.

In track theory biological cells are treated as many target detectors, with extrapolation number typically 2, 2.5, 3, or 4, as fitted to data arising from HZE bombardments. This is an integral part of the theory rather than an empirical low dose extrapolation. It is assumed that a detector cannot display an RBE greater than 1 if a single electron suffices to activate its targets. The discrimination in favor of high LET arises from the random chaotic distribution of secondary electrons from gamma rays, which make it unlikely that more than one electron will traverse a target, while the concentration of delta rays about an ion's path implies that several electrons from a single ion (thus at low dose of heavy ions) can readily penetrate a target. Calculation has placed limits on the values of α and β in the alpha beta model that can yield an RBE greater than 1 [14]. In essence these imply that the dose-response curve is not readily distinguishable from a multitarget model, as consistent with the work of Bettega. The success of the track model in fitting high LET data from track segment irradiations and mixed radiation fields supports the use of the multitarget model for the description of low doses of low LET radiations.

Some further comments on track theory in relation to low doses are offered by Katz and Hoffman [15].

An interesting discussion of the different perspectives of the linear quadratic model and the track physics model has recently been provided by Goodhead [16] with particular emphasis on the implications for dose limits in radiation protection. Quoting Goodhead, "The (Katz) model leads to very dramatic differences in predicted risk at low doses compared to most other models and conventional risk estimation. Because of the very major implications that this would have, if true, there may be strong grounds for critical evaluation of the model if it is indeed to be applied to low dose, risk problems rather than confined to high-dose therapy related applications."

This is agreed. There are strong grounds for critical evaluation of both the track physics model and conventional risk models. A recent paper by Hofer et al. [17] suggests that cell death is associated with higher order structures in the cell nucleus than DNA segments. This may alter perspectives in some conventional risk models. Track physics rests upon agreement with experiment for a wide variety of detectors and endpoints. The agreement with radiobiological data is extensive though not universal. There is no equivalent experimental basis for the linear quadratic model.

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References

1. NCRP. *The Relative Biological Effectiveness of Radiations of Different Quality.* Report No. 104 (Bethesda, MD: NCRP) (1990).
2. Kellerer, A. M., and Rossi, H. H. A Generalized Formulation of Dual Radiation Action. *Radiat. Res.* **75**, 471-488 (1978).
3. Kellerer, A. M. A Generalized Formulation of Microdosimetric Quantities. *Radiat. Prot. Dosim.* **31**, 9-16 (1990).
4. Katz, R., and Waligórski, M. P. R. Comment on N.C.R.P. Report No. 104, "The Relative Biological Effectiveness of Radiations of Different Quality." *Health Phys.* **63**, 465 (1992).
5. Cole, A., Meyn, R. E., Chen, P. M., and Hittelman, W. Mechanisms of Cell Injury. In: *Radiation Biology in Cancer Research,* Eds. R. E. Meyn and H. R. Withers (New York: Raven Press) pp. 33-58 (1980).
6. Warters, R. L., Hofer, K. G., and Harris, C. R. Radionuclide Toxicity in Cultured Mammalian Cells: Elucidation of the Primary Site of Radiation Damage. *Curr. Topics Radiat. Res. Q.* **12**, 389-407 (1977).
7. Geard, C. R., and Brenner, D. J. Chromosomal Changes per Cell Nucleus per Charged Particle. *Radiat. Prot. Dosim.* **31**, 285-289 (1990).
8. Wilkinson, R. E., Goodhead, D. T., and Thacker, J. Induction of Chromosome Aberrations by Very Short Tracks at Different Stages of the Cell Cycle. *Radiat. Prot. Dosim.* **13**, 161-165 (1985).
9. Raju, M. R., Carpenter, S. G., Chmielewski, J. J., Shillaci, M. E., Wilder, M. E., Freyer, J. P., Johnson, N. F., Sebring, R. J., and Goodhead, D. T. Radiobiology of Ultrasoft X-rays. *Radiat. Res.* **110**, 396-412 (1987).
10. Bettega,. D., Calzolari, P., Ottolenghi, A., Talloni-Lombardi, L. Oncogenic Transformation Induced by High and Low LET Radiations. *Radiat. Prot. Dosim.* **31**, 279-283 (1990).
11. Katz, R., and Cucinotta, F. A. RBE vs. Dose for Low Doses of High LET Radiations. *Health Phys.* **60**, 717-718 (1991).
12. Burns, F. J., and Albert, R. E. Radiation Carcinogenesis in Rat Skin. In: *Radiation Carcinogenesis*, A. C. Upton, R-E. Albert, F. I. Burns, and R. E. Shore (Amsterdam: Elsevier) pp. 199-214 (1986).
13. Broerse, J. J. Tumor Induction in Animals and the Radiation Risk for Man. In: *Biological Effects and Physics of Solar and Galactic Cosmic Radiation* (Portugal: NATO Advanced Study Institute) (1991).
14. Katz, R. High LET Constraints on Low LET Survival. *Phys. Med. Biol.* **23**, 909-916 (1978).
15. Katz, R., and Hoffman, W. Biological Effects of Low Doses of Ionizing Radiations: Particle Tracks in Radiobiology. *Nucl. Instrum. Methods* **203**, 433-442 (1982).
16. Goodhead, D. T. Biophysical Modeling in Radiation Protection. In: *Biophysical Modeling of Radiation Effects,* K. H. Chadwick, G. Moschini, and M. Varma (Bristol: Adam Hilger) pp. 113-124 (1992).
17. Hofer, K. G., Van Loon, N., Schneideman, M. H., and Charlton, D.E. The Paradoxical Nature of DNA Damage and Cell Death Induced by ^{125}I Decay. *Radiat. Res.* **130**, 121-124 (1992).