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THEORY OF RBE

Progress Report

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Technical Progress Report

DOE Contract No. EY-76-S-02-1671.A002

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Robert Katz, Principal Investigator

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Theory of RBE

ABSTRACT

for

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The shapes of the blackness-exposure curves of special nuclear emulsions after exposure to x-rays of 15-150 kvp have been found to remain constant, at all applied voltages. Since the shapes of these curves mimic those of biological cells (for cell killing vs. exposure), we would expect no change in the RBE of low LET radiations at low dose levels. This finding disagrees with radiobiological findings in which the RBE of gamma-rays relative to x-rays increased at low dose, and was expected (from microdosimetric considerations which could apply equally to emulsions) to approach 4. These contradictory findings need further investigation and interpretation.

A minimal model of a heavy ion beam incorporating secondary and tertiary particle production has been constructed, in support of our investigations of relative effectiveness. The model gives good agreement with depth-dose curves from He to Ar for 8-30 cm of penetration in water. When applied to the survival of T-1 kidney cells using the parameters of the theory of RBE assigned from earlier work and slightly modified to accommodate recently attained levels of hypoxia, we find good agreement with measured values of the RBE and OER in Ar beams, for these cells. Secondary particle distribution alters the depth dose distribution dramatically, but has a much smaller effect on these biological parameters. To illustrate the potential application of the model to heavy particle therapy, we have designed a ridge filter, and find once again that it will be impossible to achieve isoeffect volumes for both oxic and hypoxic cells in a single port irradiation. Where possible, the preferred mode for heavy ion therapy must be symmetric cross-firing, where it is relatively simple to achieve isoeffect volumes for both oxic and hypoxic cells.

The shape of survival curves at low dose is an important aspect of the theory of RBE. In earlier work we have related this shape to the ion-kill cross-section, and thus to find the RBE for high LET radiations. Here we have relaxed the mathematical complexity of the constraint, and simply argue that the function

relating the probability for cell killing to the absorbed dose of gamma-rays must be supralinear if an RBE greater than 1 is to be achieved with any high LET radiation. Thus if one plots the logarithm of the fraction of cells killed vs. the logarithm of absorbed dose of gamma-rays, and if a 45° line is drawn through the lowest dose point, we must see data points above the line, for a cell system which then exhibits an RBE greater than 1 with neutrons or other high LET radiation. This is because the high LET radiation produces its effects principally by concentrating the ionizations produced in the neighborhood of the ion's path, so that at the same level of macroscopic dose, there are microscopic regions in which the dose is high. If this clustering of ionization is to be more effective than a random deposition of ionizations, the advantage must be foreseen in the dose-response curve for gamma-rays at high dose levels. Contrary experimental findings suggest heterogeneous cellular samples, or that temporal differences may be playing a role in cell killing. Both possibilities need further investigation. Theories which do not explicitly include temporal differences between high and low LET radiations cannot violate the constraint. This imposes limits on model parameters. For example, in the α - β model, the ratio α^2/β must be less than 1.5 after gamma irradiation if the system it describes has an RBE exceeding 1 for any high LET radiation. There are many experimental violations of this constraint. Both the experimental findings and their interpretation must be carefully reexamined. We must inquire as to whether the constraint itself has limits, and what they are. But some such constraint is needed to bring a bit more organization into the radiobiological findings and their interpretation.

Monte-Carlo calculations of the electron slowing-down spectra in liquid water from electrons and photons of different initial energies (with Turner, Hamm, Wright, Ritchie, ORNL) demonstrate that the low energy ends of these spectra, below several hundred eV, are congruent, when normalized to equal dose, for electrons and photons from 10 keV to 1 MeV. Similarly the yields for a number of end points - different excitations and ionizations - are equal at the same dose. Neither the number of excitations, the number of ionizations, the number of low energy electrons can be responsible for the differences in RBE for different low LET radiations which are observed experimentally. These differences found biologically, and said to increase at low dose levels, are found in no physical detectors, and are well known only in the radiation chemistry of water (though no enhancement at low dose is reported in aqueous chemistry). The question remains - what are the physical bases of these effects, and why are they not seen in physical detectors.

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1. There has been no deviation in program from that proposed in the renewal application, either in technical content or in the level of expenditure. The principal investigator has spent 0.3 time on the project during the academic year and 1.0 time on the project for 2 months in Summer 1978.

2. Following is an index of papers and reports:

L. Larsson, F. E. Pinkerton and R. Katz, Supralinearity in Nuclear Research Emulsions, Radiation Effects 34, 15-24 (1977).

R. Katz, L. Larsson, F. E. Pinkerton and E. V. Benton, Supralinearity and Particle Discrimination in Nuclear Emulsion, Nuclear Track Detection 1, 49-6 (1977).

R. Katz, Track Structure in Radiobiology and in Radiation Detection, Nuclear Track Detection 2, 1-28 (1978).

R. Katz and E. C. Pennington, Radiobiological Aspects of Supralinear Photographic Emulsions, Sixth Symposium on Microdosimetry, Brussels 1978. C00-1671-74.

R. Katz, High LET Constraints on Low LET Survival, Sixth Symposium on Microdosimetry, Brussels 1978. C00-1671-75

R. A. Roth and R. Katz, Heavy Ion Beam Model for Radiobiology, Sixth Symposium on Microdosimetry, Brussels 1978. C00-1671-76

J. E. Turner, R. N. Hamm, H. A. Wright, R. H. Ritchie, and R. Katz, Calculated Electron Slowing Down Spectra for Liquid Water Irradiated by X- and Gamma-Rays, Implications for Photon RBE, Sixth Symposium on Microdosimetry, Brussels 1978. C00-1671-77

This Report C00-1671-78

Fourth Triennial Progress Report C00-1671-79

R. Katz, High LET Constraints on Low LET Survival, Phys. Med. Biol., in press.

R. Katz and E. C. Pennington, Radiobiological Aspects of Supralinear Photographic Emulsion, Phys. Med. Biol., in press.

R. N. Hamm, H. A. Wright, R. Katz, J. E. Turner, and R. H. Ritchie, Calculated Yields and Slowing Down Spectra for Electrons in Liquid Water-- Implications for Electron and Photon RBE. Phys. Med. Biol., in press.

R. A. Roth and R. Katz, Heavy Ion Beam Model for Radiobiology, submitted to Radiation Research.

3. Once again, as in past years, the interplay between models and experiments, between physical and biological detectors, has led to new investigations and sharpened perspectives of radiation action and of RBE.

Our exploration of supralinearity in photographic emulsions has resulted in emulsion-processing schemes in which the resulting blackness-exposure curves (after x-irradiation) match the shape of curves giving the fraction of cells killed vs. the absorbed dose of gamma-rays to which they have been exposed. We have achieved a physical detector whose response characteristic mimics the response of biological systems. The response of emulsion varies from 1 to 4-or-more hit (in the sense of the cumulative Poisson Distribution). We have an emulsion whose response to x-rays is described by the α - β model used widely to describe the survival of biological cells, with parameters that are a close match to V79 Late S hamster cells exposed to gamma-rays. See C00-1671-74.

Using this match as an analogue scheme to investigate low dose effects with low LET radiations, we have exposed these emulsions to x-rays from 15 to 150 kVp. We find no change in the shape of the sensitometric curves at low exposure levels with this range of x-rays. Since our emulsions have very low backgrounds, we can carry our investigations out to two decades and more below saturation blackness, corresponding to 99% (and more) survival of the exposed emulsion grains. Our findings are consistent with earlier work of Dudley (1951) whose sensitometric curves were of the same shape for 33 keV and 1.19 MeV electrons. Thus for the photographic emulsion neither we nor Dudley find a change in the relative effectiveness of low LET radiations at low dose levels.

Since some biological investigations have found otherwise, that the RBE of low LET radiations differs at low dose from the value obtained at high dose, and this finding is supported by the theory of dual radiation action, which we think should also apply to the emulsion as to biology, these results taken together suggest that we need to look again at all experimental data and all interpretations.

These emulsions have been exposed to individual argon ions of high energy at the BEVALAC. Tracks have been photographed and montages have been made. If we compare tracks in K.5 emulsion with tracks in Ilford K.0 emulsion and in K-3 emulsion. The addition of a few hundred parts per million (presumed) of sensitizer or desensitizer alters the appearance of these tracks from a "hairy rope" which extends for centimeters, to a few isolated grains which seem to terminate after a few tens of microns, though the particle itself has passed through centimeters of emulsion. In this example, all emulsions were processed in what is nominally the same way. The characteristic response of the emulsion changes from 1 to 8 hit, with an accompanying decrease in radiosensitivity. The most sensitive of these emulsions exhibit an RPE less than 1 for all high LET radiations, while the less sensitive exhibit an RPE (relative photographic effectiveness) greater than 1 for some high LET radiation. Yet in every case the size of the sensitive element is the same. We expect these photomontages, and subsequent work with these emulsions, to play an important role as example and counterexample in discussions of the relationship between LET, RBE, and sensitive element size.

In order to analyze experimental results obtained at the BEVALAC, and to design further experiments with emulsion and other detectors, we have built a minimal model of a heavy ion beam. The model is intended to yield good approximations to depth dose curves, and to predict radiobiological data, and this it does. An oversimplified statement of the nuclear collision cross-sections and interactions nevertheless gives fast computation of dose, RBE, and OER in agreement with observation. The beam model will be used to predict the outcome of emulsion and other experiments with detectors. It has been used to design a ridge filter for therapy, and to demonstrate the impossibility of achieving isoeffect volumes with a single ridge filter for both oxic and hypoxic cells, in single port irradiation with heavy ions. For heavy ion therapy symmetric dual port cross-beam irradiation must be the preferred

modality, where possible, for isoeffect volumes are readily achieved in this modality. This conclusion, which we reached some years ago, is simply confirmed here with the new beam model. While the inclusion of secondary particles in the beam model results in dramatic changes in the depth-dose curves, the changes in RBE and OER as a function of depth in the beam are relatively small. C00-1671-76.

The development of new emulsions having the potential to mimic biology has brought to the fore an old question: What is the response of biological systems to gamma-rays, especially at low dose? One cannot mimic biology until there is general acceptance of the characteristic response of biological systems to low LET radiations, so that we know what to mimic. In earlier work we have calculated ion-kill cross-sections which would arise from survival curves which had an initial slope. In that work we found that cross-section was required to increase with the LET in a more than linear way, if the RBE was to exceed 1 with some high LET radiation. We have once again examined this question, of the relation between the shape of the survival curve at low doses and the RBE exhibited with high LET radiations, relaxing the mathematical complexity of the argument. We now find that the probability for cell killing must be a supralinear function of absorbed dose if there is to be an RBE greater than 1 for any high LET radiation (and reciprocally). A departure from this constraint is possible in a theory only if it explicitly incorporates temporal differences between low and high LET radiations. If a departure is found experimentally we should look for its cause in sample heterogeneity, in dosimetry, or we should investigate experimentally whether temporal differences between low and high LET radiations can be demonstrated. Hopefully this constraint will bring some order into the presently contradictory set of experimental data and models which deal with the initial slope of the survival curve. See C00-1671-75.

Our continuing examination of the response of different detectors to ionizing radiations, and our attempts to predict the response to high LET radiations from the response to low LET radiations, have brought some contradictory findings to light. It is generally accepted in biology that orthovoltage x-rays are more effective than Co 60 gamma-rays, and this is thought to be related to track-end effects in some way. Studies of the Fricke dosimeter with electrons and photons have noted that there is a decline in yield as the initial energy of the electron or photon decreases, and that orthovoltage x-rays are less effective than gamma-rays. This difference in more or less effective is related to the difference between a many hit and a one hit detector. But it is striking that these differences in effectiveness of low LET radiations of different quality are not observed in other physical detectors, when the response is given as a function of absorbed dose.

In order to explore the physical basis of these contradictory observations, we have initiated a set of Monte-Carlo calculations (with Turner, Hamm, Wright, Ritchie, ORNL) of the electron slowing down spectrum in liquid water from electrons and photons of initial energy from 10 keV to 1 MeV.

At the low energy end of these spectra, in the track-end region, we find no differences from incident particles of different initial energies. Of course the differences appear and increase as we examine the higher energy portion of the slowing down spectrum. Indeed, we can readily understand how any model of radiation effects which attributes the response preferentially to selected portions of the high energy end of the slowing down spectrum can fit observed differences in RBE. But if it is the low energy end of the slowing down spectrum which is thought to be of the greatest importance, it is difficult to see how RBE differences arise. We also find no differences in the yield of different excitation states, or ionizations, which depend on the initial energies of the electrons or photons.

Since these explanations of the observed values of RBE have been with us for a long time, the calculations must look very carefully into the problems. Future work will examine the distribution in spacings between ionizations, to respond to questions which have been raised in discussions of these findings. But one must also examine the justifications for the choice of sensitive element size (which emphasizes electrons in the slowing down spectrum whose range approximates the diameter of the sensitive element), or the ratio of the number of short tracks (500-5000 eV) to the number of spurs (6-100 eV electrons), for a change in the sensitive element size (an arbitrary fitted parameter for biological cells) or in the definition of the energy interval which defines a short track, will alter the conclusions of the theory. Thus far we have not found an explanation for the contradictory observations of relative effectiveness for different low LET radiations with physical and biological detectors. But we have exposed the question. See C00-1671-77.

The proposed collaboration with Dr. Y. Horowitz, Ben Gurion University of the Negev, Beersheva, Israel, on the study of supralinearity in TLD's, has been funded by the U.S-Israel Binational Science Foundation. This investigation will seek to enhance the supralinearity of TLD powders by altering the dopant and its concentration. We will then examine the response of the "supralinear 2-hit trap structures" to high LET radiations. If, as anticipated, supralinearity is associated with enhanced sensitivity to high LET radiations, and a relative effectiveness greater than 1, we expect to be able to simultaneously measure neutron dose and gamma-ray dose in the same crystal, using different trap structures. The research plan was prepared in close collaboration with R. Katz, who is named as co-principal investigator. The Israeli funding is in support of the work in Israel. The research plan is based on the theory of RBE. At Nebraska the University has purchased a TLD reader, through which to further the collaboration.

At CEA, Fontenay aux Roses, Dr. F. Bermann has completed his investigations of the application of a free radical dosimeter (alanine) to the intercomparison of fast neutron beams. This work was suggested by the theory of the 1-hit detector. In it, measurements were made of radical concentration in alanine after exposure to neutron beams of different energies, and to alpha particles of 4 and 650 MeV. These measurements were compared to calculations of the radical response made in Nebraska, from the theory of RBE: Experimentally the required parameter E_0 is measured with x-rays, while the second parameter, a_0 , required by the theory was assigned arbitrarily to approximate molecular size. For energetic alpha particles the calculated values of the relative effectiveness were smaller than measured values by less than 20%, this difference being reduced to 5% in the Bragg peak. Where the spectrum of neutrons was known, calculated values of the relative effectiveness were in agreement with measured values within experimental uncertainties, for 14 and 7.5 (Hammersmith Hospital) MeV neutrons, and disagreed with average measurements but were within the limits of experimental uncertainty (20%) for fission neutrons. When coupled with the stability of its response at room temperature, its size, tissue equivalence, and non-destructive reading, its linearity, and the ability of the theory to predict response even to an estimated spectrum, the instrument offers many advantages for centralized intercomparisons of dose measurements. The work is described in a final report to IAEA by F. Bermann for Contract No. 1542/R2/RB. It is anticipated that the work will be prepared for publication next year.

In July-August 1978 Dr. A. Chamboudet, Orsay, France visited this laboratory in relation to his studies of radical formation in heavy ion tracks in plastics, especially in relation to the theory of etchable track formation in plastics.

Through that visit he has been stimulated to extend his interests in track formation to a number of other detectors in which chemical physics plays a role, either in the formation of the latent track or its evolution to an observable end point. In future we hope that this work will help to explain the underlying meaning of the radiosensitivity parameters of the theory of RBE in these systems.