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THEORY OF RBE

MASTER

Progress Report

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Technical Progress Report

USERDA Contract No. E(11-1)-1671

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Robert Katz, Principal Investigator

September 1977

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Abstract

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Emulsion-processing combinations have been found which match the response of mammalian cells to x-rays. The grain size of these emulsions is in the implied range of sensitive element sizes in biological cells. The fading of the latent image may parallel biological repair. In consequence studies are under way of the variation in emulsion response to low LET radiations of different quality, of "Elkind repair", and of dose fractionation.

Predictions of OER and RBE of mammalian cells to high LET radiations, from track structure theory, have been verified, once again, in Bevalac experiments.

Experiment has now shown that high temperature traps in LiF respond favorably to neutrons, while low temperature traps respond favorably to gamma-rays. This result is consistent with our identification of supralinear high temperature traps as from an unidentified 2-hit trap structure.

In collaboration with Oak Ridge colleagues, Monte-Carlo studies of the electron slowing down spectra of source electrons from 1 keV to 1 MeV in liquid water are being integrated into the theory of RBE. The yield of several different ions is nearly independent of the initial energy of source electrons. The results raise questions as to the physical basis for biological observations of RBE differences for x- and gamma-rays.

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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 1 month in Summer 1977.

2. Following is an index of papers and reports:

L. Larsson and R. Katz, Supralinearity of Thermoluminescent Dosimeters, Nuclear Instruments and Methods 138, 631-636 (1976).

R. Katz, On remarks by K. Gunther on the application of track theory to neutron irradiations, Int. J. Radiat. Biol. 30, 499-50 (1976).

R. Katz, L. Larsson, F. E. Pinkerton, and E. V. Benton, Supralinearity and Particle Discrimination in Nuclear Emulsions, Nuclear Track Detection 1, 49-61 (1977).

Leif Larsson, F. E. Pinkerton, and Robert Katz, Supralinearity in Nuclear Research Emulsions, Radiation Effects (in press).

COO-1671-72 R. Katz and L. Larsson, Supralinear Detectors in Neutron Dosimetry, Third Symposium in Neutron Dosimetry, Neuherberg/Munchen 1977.

COO-1671-73 This report.

3. These continuing investigations into the Theory of RBE play upon a single set of themes and variations to achieve a unified theory of track structure, and a quantitative formulation of the response of different detectors to radiations of different quality. Sometimes it is biology which takes the lead, sometimes physics,

but in all cases it is the continued intercomparison of the concepts and experiences in different disciplines which has led to the clarification of concepts in radiation research. In the past year we have continued our studies of the multi-hit response of nuclear emulsions, extending the track theory, and examining questions raised originally in connection with radiobiology. The central accomplishment in these investigations has been the development of an emulsion-processing combination that matches mammalian cell survival curves. This implies that we have here the potential for a new kind of dosimetric film, whose response directly matches human tissue, and a new kind of radiotherapeutic film that could be used to test treatment plans by exposure in a phantom.

To compare emulsion response to cellular response we plot the logarithm of the blackness against the logarithm of the exposure, in this case to x-rays, for our emulsions, and plot the logarithm of the fraction of cells killed by the radiation against the absorbed dose (after x-ray or gamma-ray exposure). In particular we have found a nearly perfect match in curve shapes of V79-late S phase Chinese Hamster cells irradiated with ^{60}Co gamma-rays (E. J. Hall, Biological Problems in the Measurement of Survival Curves at Low Doses, in Cell Survival After Low Doses of Radiation, T. Alper, Ed., Wiley 1975) and Ilford K.5 nuclear emulsion specially developed. Another match to the same biological system is found in specially developed K-1 emulsion. In the first case the K.5 emulsion requires twice as much exposure at the same survival level as the hamster cells. In the second case, the doses are nearly identical for the K-1 emulsion and the cells. We have not yet had the possibility to compare the neutron and heavy ion response of these emulsions to the known responses of mammalian cells. In the same way we match the survival curves for anoxically irradiated bacterial spores with K-2.5 emulsion, specially developed, except that the emulsion requires only one fourth the dose to achieve the same fraction of grains "killed".

These emulsions are now being used to examine questions raised in microdosimetry, and in radiation therapy, in regard to the RBE of low LET radiations. Since emulsion response can be made supralinear, it should be expected to be specially sensitive to changes in the distribution of energy deposition events in emulsion grains from x-rays of different quality, so as to alter the apparent hittedness of the dose-response function, and exhibit an RBE which varies with dose level. We have found no evidence for such a change. The question must be examined in greater detail. One simply cannot predict such response from the size of the sensitive element alone. The dose-response characteristic for the sensitive elements of a detector must also be incorporated into any theory of RBE. Biological and photographic sensitive elements are of similar size.

Initial studies of fading of the latent image have been undertaken with supralinear emulsions. We have simulated "Elkind Repair", found with biological cells. Though these studies are only initiated, it is not unreasonable to consider the emulsions as modeling systems through which to study dose-rate effects, or the effects of fractionationation in therapy. As always we expect to find differences between silver bromide crystals and biological cells. It is the nature and extent of these differences which will tell us what is uniquely biological.

The ability of emulsion to match biological curves reopens a question examined earlier in these continuing studies of RBE. Just what is the shape of the biological dose-response curve, especially at low doses. Our arguments have been refined. If the response of a detector is linear at all dose levels, there can be no change in its dose response curve when irradiated with heavy ions. If its response to x-rays is sublinear the RBE for heavy ions must always be less than 1. If it is supralinear, then there will be some heavy ion irradiations for which the RBE will be greater than 1. Biological experiments tend to differ with these logical constraints. We must infer either that the biological system is changed during the irradiation, or that the characteristics of the irradiated cells are heterogeneous. These options will be examined further with emulsions, where we can easily make measurements at 99% survival, and sometimes even down to 99.5 % survival, depending on the degree of background fog.

These investigations of the properties of emulsion have required the development of equipment, theory, and new computational programs. Thus we have purchased a Torrex 150 x-ray unit, a Macbeth densitometer, a Victoreen condenser R-meter, and a Frigidheat heat pump (for temperature control of emulsion processing), principally with University funds, and are now constructing an electronically controlled shutter with which to make x-ray sensitometric exposures. A collaboration has been initiated with Prof. E. V. Benton, University of San Francisco, for the exposure of emulsions to Bevalac beams, so that we may make direct comparison of emulsion properties at high LET with those of biological systems.

The systematics of cellular radiosensitivity parameters makes it possible to estimate altered parameters for a cell line when new levels of hypoxia are achieved. From such estimates we have been able to predict values of the OER and RBE for mammalian cells irradiated in "submarine experiments" at the Bevalac with carbon and argon ions. To facilitate the use of the theory of cell survival by experimenters at Berkeley and elsewhere, programs have been written for the HP-67/97 calculators to calculate the response of cells to a variety (gamma-ray, neutron, heavy ion, pion) of radiation environments. These calculations and programs have already found application in experiment and in the evaluation of radiation hazard.

Our analysis of the supralinear response of TLD's, as possibly from a mixture of 1- and 2-hit traps suggests that the 1-hit traps would discriminate against high LET radiations, while the 2-hit traps would discriminate against low LET radiations. In LiF the 1-hit traps are dumped at low temperatures, while the 2-hit traps require higher temperatures. This phenomenology has already been used to make measurements of gamma-rays and of neutrons in a mixed radiation environment, with a single crystal.

To further study the 2-hit trap structure we have initiated a collaboration with Dr. Y. Horowitz, Ben Gurion University of the Negev, Israel, and have jointly written a proposal to the US-Israel Binational Science Foundation. It is intended that his group grow crystals intended to exhibit supralinearity, and that we jointly measure their response to x-rays, neutrons, and heavy ions. We here will carry out the theoretical investigations in relation to the theory of RBE.

A question of long standing in radiation research is the RBE of gamma-rays in relation to orthovoltage x-rays. The question has been broadened to include the relative effectiveness of a range of low LET radiations (electrons of different energies, x-rays of different photon spectrum) at a range of dose levels, in physical, chemical, and biological systems. To the present investigator, the physical explanations offered to account for observed differences have not seemed sound. In collaboration with H. A. Wright, R. N. Hamm, J. E. Turner, and R. H. Ritchie, Oak Ridge, Monte Carlo calculations of the slowing down of energetic electrons in liquid water have been analyzed, in relation to the theory of RBE. We find the yield of a variety of physical end-points, and w-values to be nearly independent of the energy of source electrons, from 1 keV to 1 MeV. In two decades of energy degradation, the slowing down spectrum has lost memory of the energy of the source electrons. If it is the low energy end of the slowing down spectrum that is principally responsible for radiation effects in biology, we must search for some other explanation of the variation in RBE with radiation quality than the initial physical stage of the radiation process. Differences in the microdosimetric Y and Z spectra between x-rays and gamma-rays arise principally from electrons between 5 and 50 keV in the slowing down spectra. At these energies the mean free paths for successive ionizations are so much greater than the spacing between strands in DNA that they must correlate with some other effect if they are to be biologically significant.