THEORY OF RBE

Progress Report

Robert Katz

University of Nebraska
Lincoln, Nebraska

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Abstract

for

Technical Progress Report

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Predictions from the Theory of RBE have been verified for dosimeters and biological systems in a range of radiation environments. Included are the response of alanine to fast neutrons, of the dye-cyanide dosimeter to 3 MeV protons, of the Fricke dosimeter to 4 GeV nitrogen ions, the survival of mammalian cells after irradiation with mixtures of neutrons and gamma-rays, beams of GeV nitrogen and oxygen ions, and spread out He beams, the RBE of spread out He beams as experienced by mouse skin. In-vitro cellular radiosensitivity parameters yield RBE-Dose relations for neutrons of different energies that are consistent with in-vivo measurements, for human and animal systems. New radiosensitivity parameters have been evaluated. A statistical procedure is being employed to find optimal values of the parameters, and to assign confidence limits from the data. Ridge filters for 3, 5, and 10 cm wide isosurvival regions for Bevalac ions have been designed. Collaborations to refine parameter assignments and identify radiation response from molecular structure have been initiated for alanine and for dye-cyanide. Cellular radiosensitivity parameters have been incorporated into Oak Ridge energy diffusion codes, for predicting biological response in neutron and pion irradiations.

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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 during the period 1-31 July, 1974.

2. Following is an index of papers and reports:

- COO-1671-54 R. Katz, Bevalac Experiments Suggested by Track Theory, Round Table Conference on Heavy Ion Research in Radiological Physics and Radiation Chemistry with Bevalac ions, Berkeley, 1973.
- COO-1671-55 R. Katz and S. C. Sharma, Heavy Particles in Therapy, an application of track theory. Phys. Med. Biol. 19, 413 (1974).
- COO-1671-56 R. Katz and S. C. Sharma, Cellular Survival in a Mixed Radiation Environment, Int. J. Radiat. Biol., in press.
- COO-1671-57 R. Katz and S. C. Sharma, OER for Mixed Neutrons and Gamma-Rays, Brit. J. Radiology, in press.
- COO-1671-58 R. Katz and S. C. Sharma, The Initial Slope of the Gamma-Ray Survival Curve in the Theory of RBE. Sixth L.H. Gray Conference, London, Sept. 1974.
- COO-1671-59 R. Katz and S. C. Sharma, RBE-Dose Relations for Neutrons and Pions, Second Symposium on Neutron Dosimetry in Biology and Medicine, Neuherberg-Munich, Oct. 1974.
- COO-1671-60 This Report.

3. The THEORY of RBE has grown in its scope and applicability since its conception just prior to the initiation of the present contract. Growing out of the study of particle tracks in emulsion, the first application of the theory was to the inactivation of dry enzymes and viruses. Since then the basic principles of the theory have been applied to an ever increasing number of different dosimeters and biological systems. In the past year predictive calculations from the theory have been made and verified, for a number of different detectors, physical as well as biological, in a variety of radiation environments. Its utility for a variety of applications receives a growing audience. It has served to stimulate investigations in atomic physics, in radiation chemistry, and in the study of dosimetry and radiobiology.

The synergistic effects of neutrons and gamma-rays have been widely studied by many investigators. Over the past two years theoretical calculations of cellular survival, OER, and RBE of human kidney cells in environments of 14 MeV neutrons and gamma-rays, in different proportions, have been made in Nebraska, in parallel with experimental studies of CHO cells at Glasgow. The systematic changes in RBE and OER observed with CHO cells are in remarkable agreement with the changes calculated for kidney cells with changes in the fraction of the dose delivered as gamma-rays. Our results are a direct consequence of the principles of the theory of RBE, and the breakdown of the inactivation into an ion-kill and a gamma-kill mode. See COO-1671-56. These results are a direct experimental test of the theory.

A semi-empirical formula, by Hall, for the OER for mixed neutrons and gamma rays has been compared to calculations from the theory of RBE for different cells, and different neutron fields, at different survival levels. We find the Hall formula consistent with calculations from the theory of RBE to about 5%. For this formula to be applied the RBE of the neutron field, and the OER of both the neutron and gamma-ray field must be measured. The formula then gives the OER of the mixed neutron-gamma environment. The theory of RBE goes about the problem in a different way. We must first measure cellular radiosensitivity parameters, and then must know the particle-energy spectrum of the field. From these quantities we calculate cellular response to an arbitrary field at an arbitrary dose level. See COO-1671-57.

The applicability of in-vitro radiobiology to in-vivo systems (including the response of tissue to radiation) has been a matter of some discussion. Many investigators have questioned the value of radiobiological investigations of bacterial spores, for example, to radiation protection or to cancer therapy. Some have taken the view that the value of the RBE for mammalian tissue is the central datum of interest if one is interested either in radiation protection or therapy. The present investigation has taken a broader view. In its application to biological cells, the principal stimulus for the development of the theory was experimental data obtained with bacterial spores, and indeed, these data retain their importance as a test of the theory. The same formal structure which applied to bacterial spores was found to apply to mammalian cells in culture. Using

that theoretical structure, and the radiosensitivity parameters fitted to mammalian cells, we have calculated RBE-Dose relations for neutrons of different energies, as experienced by these cells. Our calculations are in the nature of a prediction, for they extend to very low doses, far below those which are used experimentally in the measurement of survival curves. The importance of these results is that our calculated relationships are entirely consistent with in-vivo cellular and tissue data. We find that the RBE-Dose relationships observed for skin (mouse, rat, pig, human) are quantitatively consistent with our calculations for HeLa and human kidney cells. As a result, it is possible for us to venture a prediction of the RBE of any radiation field as it will be measured with skin reactions, by making the calculation for HeLa and kidney cells. We have done this for a spread-out helium ion beam, for mouse skin, in agreement with experiments of Leith et al. . Similar agreement is found for lens opacification, and other in-vivo tests. It is interesting and significant that calculations for aerobically irradiated cells agree with observations for normal tissue, while calculations for anoxically irradiated cells agree with calculations for tumors. See C00-1671-59. These results emphasize a unity between in-vitro and in-vivo radiobiology, between bacterial spores and tumors, through the connection developed in the theory of RBE. They offer the hope that a quantitatively meaningful system of dosimetry can be developed in which accurate predictions of tissue response can be made from physical measurements of the radiation field. They suggest that it will be possible to provide a therapist with a means of translating clinical experience from one high LET modality to another.

The initial slopes of survival curves have occupied the attention of radiobiologists for some time. These are difficult to measure, and yet are of substantial importance in interpreting radiobiological results, and in their implications for radiation protection and the evaluation of hazard. The theory of RBE may make an important contribution here, for the RBE of a cellular system to high LET radiation is directly related to its response to small doses of gamma-rays. A system having exponential survival, a 1-hit detector, clearly experiences overkill close to an ion's path, and so must display an RBE less than 1 to all high LET radiations. A system having a shouldered survival curve after gamma-rays (such as the multi-target single hit form) displays an increasing RBE with an increase in LET, through a maximum. A product form, such as the two-component model suggested by some investigations, will yield a result depending on whether the exponential or multi-target factor dominates. Our calculations indicate that if there is an observable initial slope in the two component model, then the 1-hit exponential form dominates and the RBE will be less than 1, for all high LET radiations. Experience seems to contradict these theoretical requirements, but there would be no conflict between experiment and theory if it could be shown that contrary experiments were performed with heterogeneous populations of cells. We suggest that no meaningful experimental statement about the initial slopes of survival curves can be made unless there is an accompanying quantitative evaluation of population heterogeneity. See C00-1671-58.

Radiosensitivity parameters have been extracted from available data for several new systems. We have found parameters for mouse bone marrow cells, for kidney cells treated with IUdR, for artemia eggs, for the eggs of the rice weevil (*T. confusum*), for the inactivation of invertase and ribonuclease, the production of single strand breaks in ϕ X-174, the production of F^1 color centers, and the darkening of silver activated phosphate glass. We are concerned with the application of a parameter seeking computer program to determine the best values of radiosensitivity parameters and their 95% confidence limits. Thus far the best available biological cell data is for bacterial spores for which the confidence limit uncertainties are about 5%. The best mammalian cell data yields an uncertainty of about 15%. We are concerned with the use of this program to design radiobiological experiments intended to obtain more precise evaluations of the parameters.

Using available parameters we have predicted the outcome of a variety of experiments with human kidney cells, including survival, OER, and RBE after exposure to beams of N and O ions of GeV energy, and of spread out He ions. We have used the results of these calculations to predict the RBE of the spread out He beam as experienced by mouse skin. Parameters extracted from HILAC bombardments of *T. Confusum* eggs were used to predict the outcome of BEVALAC experiments with these eggs. With our published parameters for the standard Fricke dosimeter we calculated the ratio of plateau to peak yield in the GeV N beam, in agreement with experimental findings of Appleby in this beam. Our predictions of the "RBE" of the dye-cyanide dosimeter exposed to 3 MeV protons agree with experimental findings of Rosenstein.

In collaboration with F. Bermann and H. Francois, CEA, Dosimetrie Physique, Fontenay-aux-Roses, we are interested in the response of the alanine dosimeter to radiations of different LET. With their new finding for the D-37 of this substance to gamma rays (free radical production, measured by esr), our calculations for fast neutron irradiations are in agreement with the yield measured in London and Prague. We have initiated measurements of the yield in other radiation environments. The sensitive element of this dosimeter is of the size of a pencil eraser, and is made of a mixture of alanine, wax, and polythene. It is tissue equivalent, and relatively stable to time and temperature variations. It seems a good candidate for a postal dosimeter for the intercomparison of dosimetry at different installations and with radiations of different quality. Our choice of this substance for this purpose is based on the systematics of the response of the 1-hit detector. It has already been pointed out in the annual report of this unit that the track structure theory offers criteria of choice in the selection of different dosimeters for different radiation fields and different dose levels. Another possible choice of joint interest is the use of amino acids and body sugars as internal dosimeters, through the phenomenon of optical rotation.

These and other successful predictions from the theory of RBE have led to the possible engineering use of the theory, in the design of dosimeters, and of radiation environments for therapy, in the prediction of the outcome of experiments with biological cells in radiation fields spread out for therapy. As pointed out by J. Booz, in his paper in Vienna in 1974, in the symposium on the Biological Effects of Neutron Irradiation, " ... it is necessary...

to underline the great merits of the delta-ray model of KATZ. So far it is the only calculation that covers the biological response from low LET to high LET with only 4 parameters."

The theory has now been incorporated into Oak Ridge energy diffusion codes for neutrons and pions, principally in relation to cancer therapy. It has been used at Nebraska to calculate (and predict) the outcome of irradiations with spread heavy ion and pion beams, for the use of the therapist contemplating use of these new modalities. At Nebraska, ridge filters to produce iso-biological-effect regions have been designed for use with BEVALAC neon beams, to produce iso survival regions, for kidney cells, 3, 5, and 10 cm wide. The computer program for this purpose, NERIDGE, and its results have been communicated to John Lyman, at the BEVALAC.

These and other matters are discussed in COO-1671-54 and 55.