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Theory of RBE

Robert Katz, Principal Investigator
Department of Physics
The University of Nebraska
Lincoln, Nebraska 68588-0111

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There has been no deviation in the program from that proposed in the grant application, either in technical content or in the level of expenditure. The principal investigator has spent 0.25 time on the project during the academic year and will spend 1.0 time for two months in Summer 1992.

Following is a list of papers, reports, lectures:

W. Hofmann, R. Katz, and C. X. Zhang. RISK ASSESSMENT OF LUNG CANCER AT LOW DOSES OF ALPHA PARTICLES, Proceedings of Workshop on Occupational and Environmental Radiation Protection. Hong Kong 7-9 December 1987. (this is an older paper that I have received from China in May 1992).

Luo Daling and R. Katz, THINDOWN IN LiF (TLD-100), Nuclear Science and Techniques (China), in English. 2, 147-152 (1991).

F. A. Cucinotta, J. W. Wilson, L. W. Townsend, J. L. Shinn and R. Katz, LET ANALYSES OF BIOLOGICAL DAMAGE DURING SOLAR PARTICLE EVENTS, 21st International Conference on Environmental Systems, July 15-18, 1991 San Francisco.

F. A. Cucinotta, R. Katz, J. W. Wilson, L. H. Townsend, J. Shinn and F. Hajnal, BIOLOGICAL EFFECTIVENESS OF HIGH ENERGY PROTONS; TARGET FRAGMENTATIONS. Radiat. Res.127,130-137 (1991).

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- F. A. Cucinotta, R. Katz, J. W. Wilson, L. W. Townsend, J. E. Nealy and J. L. Shinn, CELLULAR TRACK MODEL OF BIOLOGICAL DAMAGE TO MAMMALIAN CELL CULTURES FROM GALACTIC COSMIC RAYS. NASA Technical Paper 3055, (1991)
- R. Katz and M. N. Varma, RADIAL DISTRIBUTION OF DOSE. IN "Physical and Chemical Mechanisms in Molecular Radiation Biology", edited by W. A. Glass and M. N. Varma, Plenum Press New York (1991).
- R. Katz and R. Zachariah, E. COLI B MODELED AS A 1-HIT DETECTOR. 9th Int. Congress of Radiation Research, Toronto 1991.
- R. Katz, BOOK REVIEW. "ION TRACKS AND MICROTECHNOLOGY: PRINCIPLES AND APPLICATIONS", by R. Spohr. Radiat. Res. 125 (1991)
- R. Katz, COMMENT ON "MICRODOSIMETRY AND KATZ'S TRACK STRUCTURE THEORY" BY MARCO ZAIDER [Radiat. Res. 124, S16-S22, 1990]. Letter to the Editor, Radiat. Res. 126,629(1991).
- R. Katz, F. A. Cucinotta, J. W. Wilson, Duc M. Ngo, A MODEL OF CELL DAMAGE IN SPACE FLIGHT. NATO Conference, Armacao de Pera, Portugal (1991)
- R. Katz, TRACK THEORY, A BASIS FOR EXTRAPOLATIONS TO LOW DOSES AND MIXED RADIATIONS FROM HIGH DOSE MEASUREMENTS WITH GAMMA RAYS AND HZE PARTICLES. Workshop on Biophysical Modeling of Radiation Effects. DOE-CEC. Padua 1991. Institute of Physics Publishing Ltd pp 1137-143 (1992)
- R. Katz, TRACK PHYSICS MODEL OF RADIATION EFFECTS, RADECS 91. First European Conference on Radiation and its effects on devices and systems. Montpellier, France, Sept. 1991.
- F. A. Cucinotta, J. W. Wilson, L. W. Townsend, J. L. 'Shinn and R. Katz, TRACK STRUCTURE MODEL FOR DAMAGE TO MAMMALIAN CELL CULTURES DURING SOLAR PROTON EVENT'S, Nucl. Tracks and Radiat. Meas. 20, 177-184 (1992).
- R. Katz, D. Ngo, F. A Cucinotta and J. W. Wilson, CELLULAR TRACK MODEL FOR HEAVY ION BEAM STUDIES, Radiation Research Society, Salt Lake City (1992)
- F. A. Cucinotta, J. W. Wilson, R. Katz and G. D. Badhwar, KATZ MODEL PREDICTION OF C. ELEGANS MUTAGENESIS ON STS-42 Proposed NASA TM (1992)

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- R. Katz and M. P. R. Waligorski, COMMENT ON NCRP REPORT NO. 104, "THE RELATIVE BIOLOGICAL EFFECTIVENESS OF RADIATIONS OF DIFFERENT QUALITY, submitted to Health Physics (1992)
- F. A. Cucinotta and R. Katz, RADIOSENSITIVITY PARAMETERS FOR LETHAL MUTAGENESIS IN C ELEGANS to be published
- J. L. Shinn, R. Katz, F A. Cucinotta, J. W. Wilson and Duc M. Ngo, CELLULAR TRACK MODEL FOR HEAVY ION BEAM STUDIES to be published
- R. Katz and R. Zachariah EXPERIMENTAL AND THEORETICAL CROSS SECTIONS FOR E. COLI MUTANTS B, B/r,  $B_{s-1}$  AFTER HEAVY ION IRRADIATION. to be published.

## DISCUSSION

Our attention has been focused on several topics of importance to the theory of RBE.

- A) Improvement in our knowledge of the radial distribution of dose about the path of an energetic heavy ion in different media. Our analytic expression for the radial dose distribution is presently segmented into two parts, for very low and for high energy ions. This is because the range energy data for electrons in aluminum falls into two parts, with the range proportional to the electron energy at low electron energies, and varying as the 5/3 power of the energy at higher energies. We are presently interested in developing a single continuous expression, valid for all ion energies, based on a formula by Weber which we used some 20 years ago in calculation the penetration of electron beams in matter. Additionally, our colleague, C. X. Zhang, Zhongshan University, Guangshou, China is independently working on a model to accomplish the same result based on a logarithmic expansion of the range-energy relation for electrons in aluminum. Zhang published a calculation of the radial dose distribution during his stay in Lincoln several years ago and continues an active program in track physics with his group in China.
- B) We are interested in the response of different E.Coli mutants to ionizing radiations. We have recently encountered data from Japan (T. Takahashi), from the Soviet Union (E. Krasavin) and Canada (R. H. Haynes) which deals with the response of these bacteria to energetic heavy ions and x-rays. The radiobiological data for three E. Coli mutants are well fitted by our model of a 1-hit detector, with different values of the D-37 dose for gamma rays. A manuscript is in preparation. These mutants all have double stranded DNA, but respond as 1-hit detectors. We ask whether it is possible that inactivation in these cases is by the indirect effect, so that their response would parallel our finding that both single and double strand breaks in SV-40 DNA in EO buffer behaved as 1-hit detectors. We note with great interest that Dietrich Schulte-Frohlinde is scheduled to present a paper entitled "The Radiation Death of an E. Coli Cell" at the Gordon Research Conference on Radiation Chemistry July 6-10, 1992. We hope that his fundamental mechanistic analysis will explain why these mutants are 1-hit detectors

and will yield the numerical value of their D-37 doses. We had extensive discussions with Prof. Krasavin at the Toronto meeting. He is the author of two books on his researches with E. Coli, in Russian. As a result of our discussions he is translating these into English. Also it was at the Toronto meeting that we learned of old data of Robert Haynes on his experiments with HZE bombardments of E. Coli. His only records of these data appear as a plot in a publication with LD-90 plotted against LET. It is these data that we have reworked for comparison with track theory.

C) For many years we have held that a basic contribution of physics to high LET radiobiology awaited the development of a proper model of fragmentation, both of the projectile and the medium, in regard to the penetration of heavy ions in matter. Our theory of RBE requires knowledge of the particle-energy spectrum of the radiation field in order to calculate biological effects. Earlier on we showed that our theory and its fitted biological radiosensitivity parameters were suitable for calculating cell survival after neutron irradiation and from heavy ion beams, when such information was available. An improved fragmentation model has been produced by investigators at NASA-Langley. There we are collaborating with Frank Cucinotta and his colleagues toward the calculation of radiobiological effects within space vehicles from solar and galactic cosmic rays making use of this fragmentation model and of our theory of RBE.

We have applied this model to the calculation of RBE for energetic proton beams, taking target fragmentation into account, to excellent effect, in agreement with published results. We find that an RBE exceeding one found with proton beams is attributable to target fragmentation. These results should be of interest in proton therapy, for it was at the Toronto meeting that heavy emphasis was placed on needed knowledge of proton RBE's by Herman Suit who directs proton therapy at Harvard.

The NASA beam model is now being applied to the calculation of cell survival and mutation with heavy ion beams using our theory and parameters. Some years ago we developed a rather crude model of beam fragmentation that adequately described cell survival upstream of the Bragg peak but was inadequate downstream of the peak. The present model yields a proper description of heavy ion radiobiology at all positions along the heavy ion beam.beyond the Bragg peak to the very end of the beam. With no change in our radiobiological model or its parameters we achieve good agreement with the data of Blakely. A manuscript is now in preparation. A long time ago we proposed to NIH and to LBL that our radiobiological model was capable of predicting HZE effects in the LBL beams and that we needed only a proper beam model which could yield knowledge of the particle-energy spectrum in the beam, including all fragments. We further proposed that no new radiobiology would arise from experiments with heavy ion beams of initial energy approximating 400 MeV/amu, or of mixed radiation fields, if we could predict the outcome of such experiments from parameters extracted from experimental data at energies less than 10 MeV/amu. Neither of these groups expressed interest in our proposal. With the advent of the NASA beam model, created to treat the effects of cosmic radiation in space, our proposals are now fully validated. It is regrettable that neither NIH nor LBL gave credence to our proposals According to the NASA investigators there is no other radiobiological model suited to making radiobiological predictions in space.

- D) We are currently examining a new set of radiobiological data dealing with an organism rather than with cells. Data for lethal mutations in a nematode (a "wire worm") induced by gamma rays and heavy ion beams, studied by G. A. Nelson and colleagues, yield to our 4-parameter model of biological effects. This is the first time our 4-parameter model has been applied to an organism. The parameters we find for lethal mutation in this organism are in the neighborhood of parameters found earlier for cell transformation, but are remote from those found for cell survival. A manuscript is in preparation. We think this finding to be a significant extension of "Katz Theory".
- E) Cucinotta is currently attemmpting to apply our 4-parameter model to data on the prevalence of cancer induction in the Harderian gland by HZE particles. The data available are relatively crude, giving neither the number of cells at risk nor the number of cancers induced. We utilize parameters earlier obtained for cell transformation, but with an adjustment of the D-37 dose for gamma rays, Since the number of cells at risk is not known the model used asserts proportionality between the probability for transformation and the "prevalence." The work is in progress.
- F) There are subtleties in the analysis of radiobiological data that seem to have escaped the attention of many investigators. These hinge on whether an effect can be produced by the passage of a single electron through a target or whether an accumulation of damage from the passage of several electrons is required. In the first case cross section and particle fluence are the best bases for analysis, for all particles. In the second case we appropriately describe the effects of electron beams and gamma rays by macroscopic dose, and the effects of heavy ions by fluence and cross section. In dealing with cellular response we speak of gamma-kill and ion-kill to represent what was later called inter- and intra-track effects.by Kellerer and Rossi. It is important to note that for low LET bombardments inter-track effects predominate over effects produced by single ions. Here a dose description is valid and the RBE is nearly one, for the effects are produced by overlapping secondary electrons. At high LET effects are primarily produced by single ions, where the fluence description is valid. Since we here deal with systems requiring that several electrons penetrate a target, the RBE exceeds one at low "dose" where it is unlikely that several electrons from y irradiation will penetrate a target, but single heavy ions deliver these several electrons and produce the measured end point. These are subtle points and have still not been widely recognized.

We find also that there is a confusion on the part of some investigators as to what constitutes a 1-hit detector. This is especially the case in relation to microdosimetry. The 1-hit concept is based on particle fluence, as appropriate to the cumulative Poisson distribution. Saturation effects have to do with the number of available cells rather than with the energy deposited in single cells. We find this confusion prevalent in the inclusion of saturation effects in microdosimetry.

Absorbed dose is an appropriate descriptor of biological effects in some detectors with some irradiations, while particle fluence is more appropriate with other detectors and with other irradiations. Track physics has helped to sort these out. The confusion in this field arises from an attempt to use a single set of descriptors for all

effects with all radiation environments in all detectors. This has been the case with the widespread use of LET, Dose.and RBE.

Our track structure model has been abundantly criticized because of its use of an "amorphous" track model. This is puzzling. Dose is an excellent parameterization of the effects induced by the chaotic distribution of secondary electrons from gamma rays and orthovoltage x-rays. Yet dose is an amorphous parameter. What better way is there to use the response of a detector to gamma rays as a transfer function to calculate its response to heavy ions than through an amorphous track structure utilizing the radial distribution of dose. No better way has arisen in the 30 years since I created Katz theory.

G). In regard to the important issue of the effects of low doses of radiations there has again been much confusion. There is very little sound data extending down to 0.1 rad. Yet it is in this region, and below, that radiation protection interest centers. With heavy ions we are frequently interested in irradiations where at most one particle passes through a cell. Track theory enables us to sort these effects out. From theory we have shown that the RBE of High LET radiations varies as (1/m - 1) at these low doses (where m is the extrapolation number parameter of track theory, typically between 2 and 4). Recent experimental work by Bettega et al. at doses down to 0.01 Gy are consistent with our theory. These investigators found that the survival of C3H10T1/2 cells at low doses of gamma rays was consistent with the multi-target model we use, with extrapolation number 3, which we have found from our analysis of data obtained with high doses of high LET radiations. Further the RBE from low doses of alpha particles was consistent with our model. Others are also beginning to understand that this important issue hinges on whether all radiobiological effects in cells and tissues can be initiated by the passage of a single electron through a cell nucleus. There are important data available that clearly imply that single electrons passing through a cell nucleus do not always kill a cell or induce a mutation or a cancer. We have pointed this out in a letter submitted to Health Physics in relation to the widely accepted linear extrapolation to low doses which we hold to be incorrect. The linear extrapolation to low dose is based on fitting a linear-quadratic expression to data obtained at doses in the neighborhood of hundreds, or even thousands of rads and extended to the region of interest in radiation protection by 3 or 4 orders of magnitude. Normally such an extrapolation would be considered extravagent. Yet it is freely accepted in radiation protection circles. In his paper for the Padua DOE-CEC meeting Goodhead has made note of this point. We are glad to have stimulated his attention. He points out that there may be significant consequences for radiation protection if Katz theory is right, and that this issue must be resolved. It is a point we have been trying to make for many years.

We note that Gerhard Kraft with a student, Michael Scholz, are attempting to develop an improved model of "Katz Theory". According to them Katz Theory is the best presently available model of HZE radiobiology, but that it has some shortcomings that they wish to correct. We welcome their interest. The shortcomings are said to be largely those of interpretation of the structure and parameters of the theory rather than its use of an amorphous track structure and the mapping of gamma-ray dose response

data into the region about the ion's path., for this is the central contribution of Katz Theory.

Dudley Goodhead also finds the theory to be the best available, but that the interpretation of its parameters is not consistent with his view of the driving mechanism in radiobiology, namely the energy deposited in small volumes of DNA. Again we welcome his interest. Our interpretation of our size parameters is otherwise, for we find that our size parameters and data are not inconsistent with assigning responsibility for cell killing to chromosomes. We note also that there is a fundamental difficulty with assigning responsibility to energy deposition in small volumes, in that no direct experimental calibration is possible None has been achieved in the 30 years since the advent of Microdosimetry. Hopefully these issues will be resolved in further discussions.

H. We note with interest a new paper by R. Mazzei and O. A. Bernaola, "Track experimental data related to post irradiation dynamic processes" in press in Nuclear Instruments and Methods in Physics Research B in which a criterion for track etching in plastics proposed by Katz and Kobetich in 1968 is found to be correct, experimentally, though rejected earlier, by Fleischer, Price, and Walker in their book "Nuclear Tracks in Solids (1975). Our criterion was based on our amorphous track model, and suggested that an appropriate criterion for the formation of etchable tracks was one of minimal dose at minimal distance. Mazzei and Bernaola find the minimal distance to be 25 Angstroms. Our initial guess was 17 Angstroms in Macrofol. Though not related to radiobiology it is yet another indication that size assignments from track theory are sometimes close to the mark.

## **PERSONNEL**

Budget limitations have served to limit our staff. We presently employ Ph. D. candidate Rashidah Zachariah on an hourly basis rather than as a graduate research assistant. We are also working with M. S. candidate Mark Rueden, who is presently self supporting. We have no funds for graduate assistantships, for postdocs or for senior visitors. Robert Katz is presently retired, but is on annual half time reappointment at the University of Nebraska, for which he teaches one course per year, and continues his research and continues to direct and teach students. The time he now spends on research is substantially greater than that which he spent when he was employed full time. Most particularly his present calendar freedom makes it possible to participate in more conferences, to give more lectures, and to work more directly with colleagues in other institutions than heretofore.

In effect our staff is augmented by our colleagues at NASA at no expense to DOE. We are fortunate to have the collaboration of Frank Cucinotta, Larry Townsend, John Wilson, Judy Shinn and others there who have joined with us in pursuit of the Theory of RBE, because of our mutual interest in HZE radiobiology. This extremely fortunate collaboration has been possible only because I continue to work and continue to be supported post retirement, for our collaboration began after my official "retirement".

We continue to collaborate with Mike Waligorski, who is now in charge of a dosimetry laboratory in Krakow. Independently he pursues several topics closely related to the Theory of RBE. Whenever possible we seek to bring him to Lincoln for further consultation and collaboration but again funds for such visits are limited. These occasions arise when he is in the United States to attend a scientific meeting. Our Chinese colleagues now also pursue an active program related to the subject of these investigations. They have investigated the response of a new 2-hit virus, they have studied alanine and other free-radical dosimeters, and are interested in a new formulation of the radial distribution of dose. Professor Zhang intends to participate in the next microdosimetry meeting in Gatlinburg. If possible we should like to bring him to Lincoln for some days to further our mutual interests.

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