THEORY OF RBE

FOURTH TRIENNIAL REPORT

for period 1 January 1967 - 31 December 1978

PREPARED FOR THE DEPARTMENT OF ENERGY

UNDER CONTRACT NO. EY-76-S-02-1671.A002

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DISCLAIMER

ABSTRACT

for

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THEORY OF RBE

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From a single set of themes, the Theory of RBE has developed a picture of the response of many detectors to radiations of different quality. Formulas of the theory and a set of experimental parameters for each detector, lead to predictions of detector response to different radiation fields, which serve also as a test of the theory. Many tightly held concepts in radiation physics have been shaken. We have predicted that detector response is not a single valued function of LET, or REL. We have invented a characteristic parameter κ, combining both radiosensitivity and sensitive element size, in a way suitable for describing detector response as a function of z^{*2}/β^2 of monoenergetic incident particles, and encompassing the transition from grain-count to track-width regimes, the variation of OER and RBE with "LET" as well. We have emphasized the importance of delta-rays in track structure, and have shown that it is this which responsible for the multiple valuedness of response with LET and even with z^{*2}/β^2. We have predicted that quality factors are misleading, that one cannot combine high and low LET response linearly to find the response to a mixed environment, and have shown how we can predict biological response in complex radiation environments, such as neutrons, pions, or heavy ions, contaminated with electrons and gamma-rays, and spread by a ridge filter. We have sought to identify the basic aspects of detector response which lead biological substances to exhibit an RBE greater than 1 with high LET radiations, and have used that result to discover physical detectors having that property. Currently, studies of these detectors (supralinear emulsions and TLD's) are being made to find the extent to which their properties can be adjusted to mimic the response of biological cells and tissues to radiation fields of different quality, and to use them as testing grounds for models of radiation action.

I. Principal Research Accomplishments

a) Outline of the Theory. The THEORY of RBE is an extension of target theory. It seeks to account for the response of radiation detectors to radiation environments of different quality, including electrons, photons, heavy ions, neutrons, and pions, of different energy spectra and degrees of contamination.

The theory starts with a dose-response curve obtained with each detector, after gamma-irradiation. This is applied to the radial distribution of dose about the path of single heavy ions, to find the radial distribution of response. By integrating the radial response we find the effect of the passage of a single ion through a detector, in a track-segment irradiation. By integrating along the path we find the effect of a stopping fragment. A simple extension of the calculation makes it possible to calculate the effect of a beam of particles, or an irradiation with neutrons, or a mixed radiation environment.

The calculation must branch, depending on whether the detector has the capacity to accumulate sub-lethal damage.

The preceding description is adequate for 1-hit detectors, which do not have the capacity for accumulating sub-lethal damage, but must be extended for detectors that can, like biological cells, or special research emulsions. Here it has been necessary to subdivide the response into the part "ion-kill", to represent inactivation by a single heavy ion, and "gamma-kill" to represent the accumulation of damage from the delta-rays of many heavy ions, and from low LET contamination. The theory then gives the fraction of the dose in these two modes, and indicates how they are to be combined to predict the observed effects.

Following target theory, we have taken detector response to be of the form "many hits in a single target", or "one hit in each of many targets", and have been able to identify detectors in which these functional forms provide reasonable descriptions of response, after gamma-irradiation, and after heavy ion bombardment.

The simplest case is that of the 1-hit detector, in which we see exponential response. Such a detector cannot accumulate sub-lethal damage. For such detectors the response to high LET radiations is always less than for low LET radiations at the same dose - the RBE for high LET radiations is always less than 1.

Next we have the many-hit in a single target detector. We have been able to develop special nuclear research emulsions so as to display hittedness from 1 to 8. These emulsions have the capacity to accumulate sub-lethal damage. They mimic the response of biological systems, to low and to high LET radiations.

We are currently making a detailed investigation of the properties of these emulsions, and are especially interested in their ability to display a Relative Photographic Effectiveness greater than 1 at an appropriate heavy particle bombardment.

We are also interested in supralinearity in TLD's, for this phenomenon also appears to be due to 2-hit traps. To pursue this matter further we have engaged in a collaborative investigation with Dr. Y. Horowitz, Israel, which is funded by the Binational Science Foundation there. Dr. Horowitz will investigate the influence of dopants on supralinearity, with the (presumed) consequent enhancement of high LET response.

The theory has raised many questions, for which we continually seek additional illumination.

Biological and chemical systems, but not physical detectors, reveal differences in response to low LET radiations of different qualities, as with orthovoltage x-rays and gamma-rays. Yet the theory of RBE ignores the difference in the energy spectra of secondary electrons from gamma-ray photons and from heavy ions (delta-rays). The question is then, how is one to interpret the effect of low LET quality. Explanations which have been offered assert that the difference may be due to the number of "track-ends", or alternately attribute the effect to differences in the relative number of electrons in the slowing down spectrum above 1 keV or so. To begin to track this problem down, we have collaborated with a group at ORNL (Hamm, Wright, Turner, Ritchie) in pursuing Monte Carlo calculations of electron energy deposition. We are certain that the number of low energy track-ends per rad is independent of initial electron or photon energy, and so can rule out this explanation. If high energy electrons are responsible for the differences in observed effects, we must sort out why this is true for chemistry and biology, but not for physical detectors. Here our new emulsions should play a valuable experimental role, for they presently approximate some of the characteristics of biological systems (dose-response curves, sensitive element size). Indeed we have already used them in that way, and find that there is no difference in dose-response curve shape after irradiation with x-rays from 15 to 150 kVp. Thus with emulsions there is no change in "RBE" with dose , even when the dose response curves and sensitive element sizes match biology, for radiations of different quality. If not track ends, or sensitive element sizes, or the shape of the biological dose response curve, then what do we attribute these RBE changes to?

As a special tool for the study of the contribution of track structure to RBE we have constructed a computer model of particle tracks. Here we enter into the program the size of the sensitive element (the emulsion grain), the dose E_0 at which there is an average of 1 hit per sensitive element, and the "hittedness" of the emulsion. The program then displays a representation of the track left by a heavy ion of atomic number Z moving with speed βc through the detector. It was through this simulation that we originally discovered many-hit emulsions. We have continued to develop it to overcome computer problems in displaying "thick tracks", in the track-width regime, and have now done so. The program is useful in extracting a maximum of information from a single track in emulsion. With it we are attempting to simulate the appearance that a track in biological tissue would have if "killed cells" were visible. We think this to be an important aspect of all radiobiological theories. We now have made photomontages of actual tracks of argon ions in the Ilford K-series of nuclear emulsions, to display the dramatic changes which can take place with the addition of a few hundred parts per million of dopants. The emulsions vary both in E_0 (and thus in radiosensitivity) and in hittedness. They represent a new set of track models for radiobiology. We are presently attempting to simulate these tracks. We expect to expose other emulsions to these and other ions, to develop the plates by different processing schedules, and to compare the parameters we extract by computer simulation with those we measure directly by x-ray sensitometry. This procedure will represent a test of our theory of track structure. These emulsions will also be exposed sensitometrically to heavy ion beams, for a comparison of the measured with predicted values of the "RBE".

We have a theory of cell killing by different radiation environments. To use it we must first measure the four cellular radiosensitivity parameters, by fitting the mathematical form of the model to cellular survival experiments obtained at a variety of bombardments, from gamma-rays to heavy ions. We are then in a position to predict cellular survival, RBE, and OER in any radiation environment. To apply these results to the latest experiments in radiobiology at the BEVALAC we have had to construct a beam model, which gives dose, and secondary and tertiary particle production as a function of depth in a phantom. This has been done, with good agreement with measured depth dose and depth RBE-OER curves. The model will now be applied to further radiobiological studies, as for heavy ion therapy, and for the analysis of our emulsion irradiations at the BEVALAC.

In collaboration with Dr. F. Bermann, CEA, Fontenay aux Roses, France, we have compared the theory of a 1-hit detector to experiment, with alanine as the test object. In this amino acid, ionizing radiation produces free radicals, which are measured by esr spectroscopy. Radicals produced are stable in time, and to normal fluctuations in ambient temperature. Its response is nearly exponential with the absorbed dose of gamma-rays, and is well approximated as having exponential response, with $E_o = 1.1 \times 10^7$ rads, and a sensitive element of molecular size, with radius, $a_o = 5$ Å. Its response is linear over a wide range, from a background level of about 10 rads to megarads. Theoretical predictions of response to neutrons of different energy spectra have been in good agreement with measurement, for energies above about 7 MeV. With energetic He ions theory and experiment are in good agreement at energies below 30 MeV, and disagree by up to 20 % at higher energies where $z^{*2}/\kappa\beta^2 < 1$. This experimental result has stimulated a more detailed reexamination of our calculation of the radial dose distribution, to be undertaken in the future. The alanine work in France was supported by the IAEA in its efforts to provide postal intercomparison dosimetry, for which this system appears to offer great advantages. A single center could readily provide worldwide calibration of x-ray, gamma-ray and electron therapy units at minimal expense. Since the theory of RBE also provides prediction of the response to energetic high LET radiations, such an intercomparison dosimeter could be useful for neutron and other high LET intercomparisons as well.

In sum then, these continuing investigations have produced a predictive theory of RBE which sorts out the characteristics of those detecting systems for which the RBE can exceed 1, and tells us also the value of z^{*2}/β^2 at which the RBE is at maximum value, in terms of experimental radiosensitivity parameters. It provides a logical structure and a computational procedure through which to understand and predict the effects of mixed radiation fields. It provides a logical structure through which to stimulate the reexamination of biological data which display internal contradictions, as where a linear or sublinear response to gamma-rays is accompanied by an RBE greater than 1. It has provided the guidance through which we have discovered physical detectors having the capability to mimic and even to match the response of biological systems to radiations of different quality.

II. Plans for Future Work

Our ongoing investigations into the Theory of RBE continually generate new research problems and new research directions, all interconnected with the main body of the theory.

We are concerned with the question of RBE for different low LET radiations, at low dose levels as well as high, and with the physical justifications for the differences which are observed with biological and chemical as opposed to physical dosimeters. We wish to consider the explanantions that have been offered for these observations, consisting principally of an emphasis on the portion of the electrons slowing down spectrum in the region 1 to 10 keV - though somewhat differently clothed in different models. We will pursue this question by Monte Carlo calculation, in collaboration with others, and through analogue experiments with photographic emulsions, wherever this procedure is consistent with the explanations which have been offered.

In our calculations we have neglected the contribution of direct excitations and direct ionizations to the effect observed with high LET radiations. We have done this because the effects are close to the ion's path, where they are often in the saturation region of detector response. That is, when $z^{*2}/\kappa\beta^2 > 1$, for a particular detector (identified by the value of the parameter κ), we expect the effect of delta rays alone to saturate response close to the ion's path. Thus there may be a problem for energetic ions of low Z, as with fast He ions in alanine, but not for the same detector irradiated with Ne ions. We must reexamine this neglect, and the overall calculation of the radial distribution of dose. This we will do by methods we initially used a decade or so earlier, but comparing them to methods used by later investigators who have imitated our calculations and have perhaps improved upon them. We will seek collaboration with others skilled in Monte Carlo calculations to make such calculations about an ion's path, for whatever results can be gained from it, for it will be difficult to get a full Monte Carlo treatment valid for GeV protons, simply because of the large radial distance to which electrons penetrate. It may be possible to devise a provisional hybrid procedure which uses Monte Carlo methods for the first micron of radial distance, and other procedures for the remainder of the "penumbra". But this calculation should be carefully refined, as the precision of experiment is also refined.

Our identification of supralinearity in TLD's as due to the presence of 2-hit traps has resulted in a collaborative investigation with Dr. Y. Horowitz, Beersheva, Israel. In support of that investigation the U.S. Israel Binational Science Foundation has awarded him a grant, for our work. This effort has already begun, in Israel, with initial steps taken for the production of TLD powders with a range of dopants and dopant concentrations. We seek to enhance the supralinear response, and to investigate the response of the 2-hit traps to high LET radiations. Supportive experimental work will be carried out in Nebraska, where the theory of RBE will be used to guide the high LET investigations.

Work with supralinear emulsions, begun three years ago, will be continued. At that time we had identified 8-hit response in some Ilford K-2 emulsions, from the appearance of particle tracks. Since then we have equipped a sensitometry laboratory to carry out parallel investigations with x-rays, as demanded by the theory, and have verified our prediction of supralinear response to x-rays from the appearance of particle tracks. Our efforts have been to survey the response which could be achieved with emulsions of different type, developed with graded developers of different activity. We have sought to achieve 2-hit response, of sensitivity sufficiently high to make the track of an alpha particle visible, as an approximation to the response of mammalian cells. We have now achieved such response. We will continue our study of these emulsions, to find the limit of sensitivity that can be achieved with 2-hit response, and at the same time will look into the response of these emulsions to other high LET radiations - to heavy ions, to neutrons, and to pions, and subsequently to find the response to mixed high and low LET fields, say electrons and pions. As these materials approach more closely to biological response characteristics, we will use them to test different models of radiation action, as these seem to be applicable. We hope, through the growing ability of these materials to mimic biology, to stimulate biologists and therapists to attempt to assign radiosensitivity parameters to the cells and tissues they irradiate. From the point of view of the Theory of RBE, radiosensitivity parameters must be assigned to tissues in order that treatment planning achieved in one installation, with one high LET modality, can be transferred to another high LET modality. With emulsions we also expect to examine the relationship between fading of the latent image and biological repair, as in Elkind recovery. The emulsion should be a useful modeling system through which to examine dose-rate effects, and the influence of fractionation in therapy. We will keep these questions in mind as we pursue our emulsion investigations.

III Students Trained (Number preceding name is number of publications from this work)

3 J. J. Butts PhD 1966 Kansas State ... Aerospace Corp.

8 E. J. Kobetich PhD 1968 Nebraska ... Arco Co. Munroville PA

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4 M. Homayoonfar PhD 1971 Nebraska ... Pahlevi Univ., Teheran

2 B. Ackerson BS 1969 Nebraska, PhD 1976 Colorado... Bu Stds, Boulder

1 C. Sorenson BS 1969 Nebraska, PhD 1977 Colorado... Kansas State Univ, Manhattan

1 T. Furtak BS 1969 Nebraska, PhD 1976 Iowa State

2 F. Pinkerton BS 1976 Nebraska, graduate study at Cornell

3 R. A. Roth Krauter, BS 1977 Nebraska, graduate study at Nebraska

B. L. Krauter, BS 1976 Nebraska, graduate study at Nebraska

1 Bruce Fullerton, BS Nebraska 1978

D. L. Wilson, ... ISCO Corp, Lincoln Nebraska 1978

J. J. Darland, BS Nebraska 1978 ... Texas Instruments Dallas, TX

1 E. C. Pennington, BS Nebraska 1978, graduate study at U of Texas, Arlington

Yuen-ling Chang, undergraduate

Albert Sau Fai Li, undergraduate

Ronald L. Rosman, undergraduate

Joann M Motycka, undergraduate

Louise M Beyea, undergraduate

3 Dr. L. Larsson (postdoc) 1975-77 ... CEAVERKEN AB, Strangnas, Sweden

Dr. Y. V. Rao (postdoc) 1977-78

Dr. M. P. R. Waligorski (postdoc) 1978-79

IV Bibliography

Refereed Journals

J. J. Butts and R. Katz, THEORY OF RBE FOR HEAVY ION BOMBARDMENT OF DRY ENZYMES AND VIRUSES, Radiation Research 30, 855-871 (1967)

E. J. Kobetich and R. Katz, ENERGY DEPOSITION BY ELECTRON BEAMS AND DELTA RAYS, Physical Review 170, 391-396 (1968)

R. Katz and E. J. Kobetich, RESPONSE OF NAI(Tl) to ENERGETIC HEAVY IONS, Physical Review 170, 397-400 (1968)

R. Katz and E. J. Kobetich, FORMATION OF ETCHABLE TRACKS IN DIELECTRICS, Physical Review 170, 401-405 (1968)

E. J. Kobetich and R. Katz, WITTH OF HEAVY ION TRACKS IN EMULSION, Physical Review 170, 405-411 (1968)

E. J. Kobetich and R. Katz, ELECTRON ENERGY DISSIPATION, Nuclear Instruments and Methods 71, 226-230 (1969)

R. Katz and E. J. Kobetich, FORMATION OF PARTICLE TRACKS, Radiation Effects 3, 169-174 (1970).

R. Katz and E. J. Kobetich, PARTICLE TRACKS IN EMULSION, Physical Review 186, 344-351 (1969)

R. Katz and E. J. Kobetich, RESPONSE OF NUCLEAR EMULSION TO ELECTRON BEAMS, Nuclear Instruments and Methods 79, 320-324 (1970)

B. Ackerson, C. M. Sorensen, and R. Katz, ANALYSIS OF A BREAKUP USING MEAN TRACK WIDTH AND BLOB MEASUREMENTS, Nuclear Instruments and Methods 47, 402-425 (1971)

T. E. Furtak and R. Katz, SIMULATION OF PARTICLE TRACKS IN EMULSION, Radiation Effects 11, 195-199 (1971)

R. Katz, S. C. Sharma, and M. Homayoonfar, IRRADIATION EQUIVALENCE, Health Physics 23, 740-742 (1972)

R. Katz, S. C. Sharma and M. Homayoonfar, DETECTION OF ENERGETIC HEAVY IONS, Nuclear Instruments and Methods 100, 13-22 (1972)

R. Katz, B. Ackerson, M. Homayoonfar and S. C. Sharma, INACTIVATION OF CELLS BY HEAVY ION BOMBARDMENT, Radiation Research 47, 402-425 (1971)

R. Katz and S. C. Sharma, RESPONSE OF CELLS TO FAST NEUTRONS, STOPPED PIONS AND HEAVY ION BEAMS, Nuclear Instruments and Methods 110, 93-116 (1973)

R. Katz and S. C. Sharma, HEAVY PARTICLES IN THERAPY, AN APPLICATION OF TRACK THEORY, Physics in Medicine and Biology 19, 413-435 (1974)

R. Katz and S. C. Sharma, CELLULAR SURVIVAL IN A MIXED RADIATION ENVIRONMENT, International Journal of Radiation Biology 26, 143-146 (1974).

R. Katz and S. C. Sharma, OER FOR MIXED NEUTRONS AND GAMMA-RAYS British Journal of Radiology 47, 823 (1974).

R. Katz and S. C. Sharma, RBE-DOSE RELATIONS FOR NEUTRONS AND PIONS Physics in Medicine and Biology 20, 410-419 (1975).

R. A. Roth, S. C. Sharma, and R. Katz, SYSTEMATIC EVALUATION OF CELLULAR RADIOSENSITIVITY PARAMETERS, Physics in Medicine and Biology 21, 491-503 (1976).

R. Katz and F. E. Pinkerton, RESPONSE OF NUCLEAR EMULSIONS TO IONIZING RADIATIONS, Nuclear Instruments and Methods, 130 p. 105-119 (1975).

R. Katz, B. G. Fullerton, Jr., R. A. Roth and S. C. Sharma, SIMPLIFIED RBE-DOSE CALCULATIONS FOR MIXED RADIATION FIELDS, Health Physics 30, p. 148-150 (1976).

L. Larsson and R. Katz, SUPRALINEARITY OF THERMOLUMINESCENT DOSIMETERS. Nuclear Instruments and Methods. 138, 631-636 (1976).

R. Katz, On the Remarks of 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 EMULSION, Nuclear Track Detection. 1, 49-61 (1977).

L. Larsson, F. E. Pinkerton, and R. Katz, SUPRALINEARITY IN NUCLEAR RESEARCH EMULSIONS, Radiation Effects 34, 15-24 (1977).

R. Katz, TRACK STRUCTURE IN RADIOBIOLOGY AND IN RADIATION DETECTION, Nuclear Track Detection 2, 1-28 (1977).

R. Katz, HIGH LET CONSTRAINTS ON LOW LET SURVIVAL, Phys. Med. Biol.

R. Katz and E. C. Pennington, RADIOBIOLOGICAL ASPECTS OF SUPRALINEAR PHOTOGRAPHIC EMULSION, Phys. Med. Biol.

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.

R. A. Roth and R. Katz, HEAVY ION BEAM MODEL FOR RADIOBIOLOGY. Submitted to Radiation Research

Plus - a chapter in Topics in Radiation Dosimetry (1972), and 75 papers presented at meetings and topical conferences.

V .The Present State of Knowledge

Within broad outlines and to the present state of much existing data, the variation in radiation sensitivity with radiation quality is now described by the theory of RBE, for a large number of detectors.

We continue to require improved knowledge of electron and photon energy dissipation in matter, and of the radial distribution in excitations, in ionizations, and dose about the path of a heavy particle. We continue to require systematic investigations of detector response as a function of charge and velocity of incident ions. We continue to require the study of track structure in emulsions.

Stimulation provided by the success of this theory has engaged the attention and interest of many investigators, who themselves are looking into calculations of the radial distribution of effect and of dose about the path of a heavy particle, who are applying our model of heavy particle response, either directly or in a modified form, to detecting systems in which they are interested. It is only through the attention of many investigators, in many disciplines, that we will be able to fill out the details that are required to verify, to correct, and to sharpen the theory of RBE.

One area in which clear knowledge is very much lacking is in the knowledge contributed by atomic physics. We do not really know relevent cross sections with which to make Monte Carlo calculations. We do not know the "effective charge" of a heavy particle passing through matter. Indeed we suspect that the concept of "effective charge" is a misleading one, in regard to delta-ray production, and that one cannot scale up the production of delta rays from a proton to a heavy ion by multiplication with an effective charge (squared) factor. We do not properly know delta ray production at all proton energies, in all material, from theory or from experiment, and the problem is compounded for very heavy ions. We do not know the range and stopping power for slow electrons, or slow protons, or slow heavy ions. In the contributions of nuclear physics we do not know the secondary particle spectra from fast neutrons in matter, nor do we know of nuclear fragmentation for constructing beam models. We do not know well the secondary particle production from absorbed pions. The contributions to track physics from these areas of limited knowledge leads to neglects and approximations which contribute to the uncertainty in the theory of RBE. In many cases, we have found the best way to get a reasonable grip on the fundamental information we need is to "guess", and then to predict the response of a detector using that guess, to be checked by experimental observation on the detector.

There is still controversy, in radiobiology, as to the shape of the survival curve of cells in culture after irradiation with low LET radiations of different quality. Different investigators find different curve shapes even with what is the same cell system, to the best of their knowledge. And the problem is compounded with neutrons, with pions, and with heavy ions. One needs simple, generally accepted logical constraints upon experimental results that lead an investigator to reject inconsistent information. We have proposed one such constraint, that cell killing must be supralinear in gamma-ray dose if the RBE is to be greater than 1 for any high LET radiation, realizing that this constraint is violated by a number of experimental investigations. Only by proposing and subsequently attempting to defeat such constraints is it likely that a homogeneous and accepted body of information about this fundamental set of data will be achieved. One needs constraints on models as well. The supralinear constraint we have proposed makes an attempt to limit the parameters of different models in the same way that it limits data. There is little point in devising models to fit data which is itself internally inconsistent.

Very little is known about the behavior of different detectors, in a way which leads to a prediction of radiation response, from first principles. The closest we have come is in the calculation of w values in gases, and even this is incomplete. In biology it is thought that the sensitive site is associated with DNA, but we do not know the size of the sensitive sites, nor how many there are nor where they are located in the nucleus of the cell, let alone a detailed recipe for the inactivation that leads to cell killing. There are similar problems in other detectors. In some relatively simple cases, in molecular detectors, the location of the radical leading to the observed effect can be stated. But in such detectors as TLD's the nature of the trap structure and the recipe for the evolution of the luminescence is not well known. There are similar problems for photographic emulsion. In these detectors we need to know much more solid state physics. For many-hit detectors, only recently discovered, attempts to outline the nature of the process from first principles are even more speculative.

The range of information needed about different detectors is quite variable. In some cases, as in biology, we are not even sure about the shape of the dose-response curve. In dealing with tissues where a dose-response curve is difficult to quantify, it would be desirable if therapists could be persuaded to attempt to guess at tissue radiosensitivity parameters, for the design of treatment programs with particle beams, where even more careful systematization is needed than with photons, or electrons, or neutrons, beacuse of the difficulty of achieving isoeffect volumes. With physical detectors we need experimental information at a much wider range of bombardments than has been available. In many cases we need to enquire as to whether a model which fits data at low energies, fits it as well at high energies, or at high Z. In almost all cases we need to be able to understand the radiosensitivity parameters of the detectors from first principles.

In an ideal world there would be ample resources available for such a comprehensive program, under a single coherent direction. As things presently stand these needs and objectives are obtained by persuasion. In relation to the theory of RBE we are fortunate in having been able to engage the interest and attention of other investigators in other laboratories, to look upon problems generated by the theory as their own.

V. Funding

External funding of these researches at the University of Nebraska has been:

NSF GP7256	Tracks of Heavy Ions in Emulsion 5/1/67-6/14/69	$ 32,500
NSF GP13478	Particle Tracks in Emulsion 6/15/69-6/14/70	14,900
NSF GP23129	Particle Tracks and Related Phenomena 6/15/70-6/30/72	15,000
NSF GI35136	Application of the Theory of Track Effects to Radiotherapy 7/1/72-3/31/76	100,100
NSF APR 71-01925	" 4/1/76-9/30/78	75,000

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Calendar 1967	20,000
1968	22,000
1969	22,000
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1971	25,000
1972	25,000
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1978	62,500

International Atomic Energy Agency, Contract # 1629/RB — 12,000
Special Photographic Emulsions for High LET Dosimetry
6/1/75-6/30/78

U.S. Israel Binational Science Foundation
Relative Effectiveness (RBE) vs. LET in TLD's
Principal Investigators: Y. Horowitz, Ben Gurion Univ, Israel
R. Katz, Univ of Nebraska
Duration: 5/2/78 - 5/1/81
First years funding IL 245,000 (approximately $15,000)

Also of interest to these investigations:

International Atomic Energy Agency Contract # 1542/RB
Adaptation d'un dosimetre a radicaux libres a l'intercomparaison des etallonages en neutrons rapides
Principal Investigator: F. Bermann, CEA, Fontenay aux Roses, France
Consultant R. Katz, Univ of Nebraska
Duration: 10/15/74-3/31/78