THEORY OF RBE

FINAL REPORT

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Robert Katz
Principal Investigator
31 October 1998

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I. Historical Survey of Research Activity

A central theme, that the probability of inactivation of the sensitive targets of a detector by gamma-rays as a function of dose can be mapped into the region surrounding the path of an energetic heavy ion, through the "local dose" deposited by its delta rays in cylindrical shells surrounding an ion's path, has been the continuing basis of the present research. This yields a detailed picture of the structure of the track of a single particle. The product of this probability by the number density of targets in the shell yields the number density of affected targets within the shell. We find the action cross-section for heavy ion bombardment by radially integrating this probability. This model is known as **KATZ THEORY**. Katz has been called the "*father of track structure*", for this concept was created and extended in these investigations, and is now widely applied wherever the effects of heavy ion bombardment are studied.

The track structure model was developed by Butts and Katz in 1964, in an investigation of the width of the tracks of heavy primary cosmic rays in nuclear emulsion, as part of an attempt to identify a hypothetical particle predicted by Dirac and known as the Dirac magnetic monopole. That model, based on a calculation of the radial distribution of dose deposited by delta rays, subsequently proved to be the definitive model for describing particle tracks in nuclear emulsions. And in turn, our model of tracks in emulsion stimulated the creation of the **THEORY OF RBE**, the title of this research program, and the direction of these investigations.

I had been puzzled for some time about the basis of the concept of Relative Biological Effectiveness which was spoken of at the University of Illinois when I was a graduate student in relation to the development of cataracts in those who had participated in the construction of a cyclotron. It was said that they did not know the RBE of neutrons, and so did not properly evaluate the radiation hazard. The term RBE was also mentioned in introductory texts in nuclear physics which I had taught. I knew only that I did not understand the basis of RBE for energetic heavy ions or neutrons.

It appeared to me that the track structure model of particle tracks in emulsion could be connected to the concept of RBE. As part of his thesis research for the Ph. D. at Kansas State University, I asked my student, Jim Butts, to find some biological data to which our model of particle tracks in emulsion could be applied. He turned up a series of measurements of the inactivation cross sections for dry enzymes and viruses by heavy ion bombardment which had been made at Yale and Berkeley, and applied our central concept, that the response of these molecules to the dose of delta rays in cylindrical shells coaxial with the ion's path must be identical to their response to gamma rays. This now classic, revolutionary, work was published in 1967 in *Radiation Research* as the **THEORY OF RBE FOR HEAVY ION BOMBARDMENT OF DRY ENZYMES AND VIRUSES**, thanks to a favorable review by Donald Fluke.

This work completely overturned the way in which these data had been interpreted by a prior, well accepted model, the "*Associated Volume*" model of D. C. Lea. That model attributed the measured cross section to the geometric cross sectional area of the molecule, with a small correction for the effect of delta rays called the associated volume. Indeed that concept was the basis of the experimental investigations which were intended to measure the geometric size of these targets. Our calculation assumed the molecule to be a point particle and attributed the measured cross section entirely to the effect of delta rays.

The experimentally measured cross section was then imagined to be more nearly equal to the cross sectional area of the region in which the dose of delta rays exceeded D-37 for gamma rays (D-37 being the dose at which 37% of the irradiated molecules survived). When later direct size measurements of viruses were made it was found that the cross sections for heavy ion bombardment were orders of magnitude larger than the geometric cross section, in verification of our concepts, and in contradiction of the Lea model. At that time delta rays were thought to have nearly negligible effects in radiobiology.

Further, contrary to the conventional wisdom, our model showed that LET was not a good plotting parameter for the description of the variation of cross section with particle energy but that it should be replaced by z^2/β^2 where z^* is the "effective charge" of the ion and βc is its speed. As shown in the next paragraph, even this is not a good plotting parameter in the region of "thindown". Simply stated there is no universally valid plotting parameter for track data. In spite of our frequently voiced objection to LET it remains the favored reference parameter for heavy ion effects, especially in therapy and protection.

This early model of Butts and Katz in 1967 used a rather primitive calculation of the radial distribution of dose. It used an expression for the delta ray distribution based on the Rutherford scattering of free electrons, assumed that these delta rays were ejected perpendicular to the ion's path, and applied a linear range-energy relation for electrons in aluminum, valid only at the lowest energies, to these molecules. Nevertheless, the model contained the essential features of track structure which created and later came to dominate "TRACK THEORY". Even then it was clear for the first time that there was an unjustified overemphasis on LET in the explanation of RBE. This early publication displayed theoretical plots of inactivation cross section vs. LET which exhibited "hooks" at high LET (the stopping power of the bombarding ions). The cross section increased with LET to a maximum principally determined by the value of D-37 for gamma rays, and then decreased with further increase in LET. These "hooks" had nothing to do with the Bragg peak in energy loss but were due to a phenomenon called "thindown" in the tracks of heavy primary cosmic rays in nuclear emulsion. They were caused by the kinematic limit in the energy of delta rays, such that the secondary electrons (delta rays) ejected in a collision between an electron at rest and an energetic fast heavy ion were limited in speed to twice the speed of the incident ion. Thus the cross section of the track end resembled a sharpened pencil. Since the interaction cross section is the radial integral of the probability for the interaction of delta rays with targets, it cannot exceed the geometric cross section of the "sharpened pencil" and so it is also diminished as the ion approaches the end of its path. At the same time the number of delta rays and the stopping power (LET) increases.

The subsequent observation of thindown, many years later, by Manfred Schäfer, in his bombardment of bacterial spores with heavy ions which seemed very confusing (but which I interpreted from track theory) was convincing evidence to radiobiologists of the significance of delta rays in radiobiology, a concept they had long resisted. Several (notably: Dietrich Harder, David Watt) still do resist, preferring to focus attention on the "restricted energy loss".

This calculation made use of biological target theory, and the response of the dry enzymes and viruses was identified as that of a 1-or-more hit detector, in the sense of the cumulative Poisson distribution.

Our next step, made with E. J. Kobetich, then my graduate student at the University of Nebraska where I had moved in 1966, was to improve our calculation of the radial dose distribution by introducing new electron range-energy relations, some algorithms regarding angular distribution, a more comprehensive delta ray distribution formula, and data on the electron penetration through slabs of material, and to extend these concepts to other detectors. We noted that scintillation counters displayed a response to heavy ions which could be described by our model of a 1-hit detector and that published plots of scintillation efficiency Vs LET displayed thindown effects; that a criterion of minimal dose at a minimal radius for the formation of etchable tracks in plastics could be generated from our track structure calculations. Thermoluminescent dosimeters were shown to display 1-hit characteristics, while supralinearity in LiF was attributed to the existence of 2-hit traps. Subsequent work showed that this 1-hit identification explained the abrupt decline in response of TLD's at the highest values of LET, as

attributable to thindown. The application of the track structure model to TLD's is now fully accepted and is used to explain their response to heavy ions and neutrons. This model also was able to provide a phenomenological explanation of the response of the Fricke dosimeter to heavy ions. It was applied to other problems in radiation chemistry, and fitted the production of HO_2 radicals in water and the production of H_2 in benzene by heavy ion bombardment to a 2-hit process. Thus water could act as a 1-hit detector, in the Fricke Dosimeter, and as a 2-hit detector in the production of HO_2 radicals. The model provided the stimulus for the development of alanine, a near tissue equivalent substance, as a dosimeter (based on free radical production) useful above doses of 1 Gy of low LET radiations. Our efforts resulted in an IAEA contract with CEA, Fontenay aux Roses, France, in which Francis Bermann was the principal investigator and I was the designated collaborator. For this material which we identified as a 1-hit detector, we were able to predict the response to neutrons and heavy ions. As a result of our work and those who followed us (Regulla in Germany, Hansen and Olsen in Denmark, and others), this material is now widely used as a postal intercomparison dosimeter. Its properties have now been the subject of international conferences. Among other places the National Institute of Science and Technology presently makes use of alanine dosimetry for high dose measurements.

By identifying "electron sensitive" nuclear emulsions as 1-hit detectors with a fitted value of D-37 we were able to create the definitive model of the tracks of heavy primary cosmic rays in emulsion. Our model now explained many empirical relations developed in cosmic ray studies. Thus we showed that the variation of the linear density of developed grains with the speed of singly charged particles was fully consistent with the identification of the emulsion as a 1-hit detector. Microdensitometric measurements at Bristol of the optical density profiles of the tracks of heavy ions which served to demonstrate the existence of very heavy ions in the cosmic rays were also consistent with our calculations. These calculations were then used by investigators in Lund to measure the spectrum of heavy primary cosmic rays. We subsequently extended this model of particle tracks in emulsion to desensitized emulsions, interpreted as many hit detectors. To verify this model a computer simulation of particle tracks in many hit emulsions was programmed, and the results were compared to microphotographs of the tracks of argon ions in these emulsions, with remarkable success. The computer simulations were virtually indistinguishable from the real tracks. One could then readily see that 1-hit detectors discriminated against heavy ions, while many hit detectors discriminated against electrons (or gamma rays). Stated another way, as a function of dose 1-hit detectors were more sensitive to gamma rays and less sensitive to heavy ions, while many hit detectors were more sensitive to heavy ions and less sensitive to gamma rays, again as a function of dose. THIS WAS THE BASIS OF THE VARIATION OF RBE WITH LET WHICH HAD BEEN OBSERVED WITH EUKARYOTIC CELLS, FOR CELLS ARE MANY HIT DETECTORS.

The "RBE" for 1 hit detectors could never be greater than 1, while the "RBE" for many hit detectors (including cells) could do so at an appropriate bombardment. We raised questions about the meaning of radiosensitivity. As a function of dose cells were far more sensitive to low LET radiations than viruses. Yet as a function of the fluence of incident electrons viruses were far more sensitive than cells. A single electron through a virus could inactivate it, while hundreds of electrons were required through the nucleus of cells for inactivation. Thus the question of radiosensitivity, or of RBE, depends upon whether response is based on dose or fluence. In later sections we return to this question. In this research conceptual questions arise continually, stimulated by our efforts at building a model. When one has a model different questions arise than occur to experimentalists who function without guidance of a model. At the Second Symposium on Microdosimetry, in 1969, where I presented the results of our work on particle tracks in emulsion, I remarked that I had been thinking about extending our work to the survival of biological cells after heavy ion irradiation, possibly by thinking of them as many hit detectors. In the subsequent discussion Harald Rossi made the point, emphatically, that any cellular survival model had to account for the changes in shape of survival curves with changes in the LET of the bombarding ions. At that time this was the most significant problem in heavy ion radiobiology. As discussed in subsequent paragraphs, we solved it. And as yet, no other model has.

Following the meeting I searched for survival data, and focused my attention on a paper by Powers, Lyman and Tobias on the effects of accelerated heavy ions on bacterial spores. There survival curves were plotted as a function of dose, and also so called cross sections were plotted as a function of LET. In a chance meeting with John Lyman, I learned that these were not true cross sections, but were calculated from the final slopes of survival curves, and were inappropriately named. That paper, and the comment of Lyman were the stimulation for my model of cellular survival after heavy ion bombardment.

The concept of cross section is incorrectly used by other authors in several areas of radiobiology. One finds plots of cross section Vs LET in which cross sections for gamma rays and neutrons are plotted from an inappropriate formula, $\sigma = L/D-37$, when L for both neutrons and gamma rays is averaged over secondary particles. Meaningless "initial and final slope cross sections" are found. Because of this I published a paper entitled "Cross Section", hoping (vainly) to diminish the misuse of this concept.

This is only one of many ill advised concepts current in radiobiology which I have tried to correct, but bad habits are likely to prevail for a long time. Other conceptual problems continually recur in radiobiology. Stimulated by our efforts to construct a viable model we ask: why dose? why LET?, why RBE?, why an initial linear slope?, why a linear quadratic model?, why α effects? why β effects?, why quality factor?, why the Sievert? More to these points later. I have asked these questions repeatedly for I hold the linear quadratic model to be false, I hold the initial slope for all survival curves to be in error and to result in extravagant and needless costs for radioprotection. I have written a paper entitled Dose, to emphasize that dose is frequently a meaningless concept, and if dose is meaningless so also is RBE.

In order to account for the shapes of plots of "cross section" Vs LET, and to account for the changing shapes of survival curves I was forced to introduce the concepts of **gamma-kill** and **ion-kill**, later called inter- and intra-track effects. The concept was that low LET particles, of low charge and high speed, had low probability of inactivating cells through which they passed, so that cell killing at high fluence was partly based on contributions from delta rays from adjacent ions, hence inter-track killing. With particles of high charge (and low speed) the probability of cell killing by single charged particles increased. Thus intra-track killing (ion-kill) increased with the LET of the bombarding ions. Ion-kill might then be represented in the same manner as the grain counts in nuclear emulsion thinking of the cells as multi-hit or multi-target detectors, while inter-track killing (gamma kill) might be represented in the same manner as the survival from gamma irradiation. For this component it was necessary to estimate the fraction of the dose in the gamma-kill mode. We estimated this as equal to the fraction of cells not killed in the ion-kill mode. Finally we proposed that the fraction of cells surviving the ion kill mode was the initial population for gamma-kill irradiation. I then wrote some equations to describe this process in which it was necessary to evaluate 4 empirically fitted parameters for each cell line, but that the single set of 4 parameters was required to describe all survival curves obtained with irradiations with gamma rays and a variety of heavy ion beams of different charge and speed. The system succeeded. The 4 parameters were 1) the "characteristic" dose of gamma rays at which there was an average of 1 hit per target, 2) the number of hits per target required to kill cells, 3) the approximate cross sectional area of the cell nucleus, and 4) a parameter called kappa which combined the characteristic dose and the size of an internal target, and which determined the transition from gamma-kill to ion kill with the LET (or more appropriately z^2/β^2) of the bombarding ions. In this system a set of 4 parameters extracted from a limited number of bombardments then described the response of the cells to an arbitrary array of bombardments including mixed radiation fields, provided that the particle-energy spectrum of the field was known.

We set about to test the validity of this scheme, by fitting parameters to all sets of cellular survival data we could find. Our fitting was based on visual examination of calculated and experimental survival curves, but later we applied a computer minimization program to extract parameters. With that program we subsequently showed that we could extract parameters for the cell line from the dose at 10% survival for each of several bombardments, thus reducing the number of data points needed to evaluate parameters from 50 or 100 to a half dozen. From data for secondary particle production for neutrons on tissue, from Caswell and Coyne, we were able to predict survival from neutron irradiations. We were able to predict

survival for experimental mixtures of neutrons and gamma rays. By improvising a crude model of secondary particle production from nuclear projectiles on tissue we were able to calculate cell survival as a function of distance along a particle beam, in agreement with experiments at the Berkeley Bevalac. Using this model we then produced calculations of cell killing in spread Bragg peaks, for use in treatment planning for heavy ion therapy. We showed that isodose profiles did not produce isoeffect profiles, and that one could not produce isoeffect profiles simultaneously for oxic and hypoxic cells in a single port irradiation. We showed that the use of "RBE" in treatment planning was likely to lead to disaster.

Unfortunately many radiation therapists still are persuaded that all they need to treat patients are the dose and RBE. But the problem is far more complex than that, for the spread Bragg peak contains primary particles of a complete range of energies, as well as beam and target fragments. While tissue is different from cell cultures, unless therapists are schooled in a correct model based on cell cultures they will make repeated treatment planning blunders and will impede the progress of hadron therapy.

There is no model presently competitive with the "Katz Model" though an inadequate "copy" authored by Scholz and Kraft has recently emerged, based on a misunderstanding of the meaning of "gamma-kill", an assumption that the entire nucleus of the cell is the target for radiation and is uniformly sensitive, and other errors. A number of other investigators still misinterpret the concept of "gamma-kill" though it has been repeatedly identified with "inter-track" effects. They prefer to think that ion-kill is a "track core" phenomenon while "gamma-kill" arises from the long range delta rays about an ion's path. We have repeatedly stressed that ion-kill refers to effects produced in single particle transits (including the effects of both core and penumbra) while gamma-kill refers to the collaborative effect of delta rays from adjacent ions where a single ion's transit does not by itself result in cell death, but rather causes "sub-lethal" damage. This misinterpretation leads to other misconstructions and conceptual error, as in the work of Scholz and Kraft which is strongly imitative of the work of Butts and Katz, and incorporates only ion kill in its calculation of RBE, though it regards itself as a "refined and more sophisticated version of the track structure approach" which they call the Theory of Scholz and Kraft". A work without originality or merit.

In response to accusations that our "predictions" were made after the fact, we proposed to make a blindfolded prediction of any forthcoming experiment with such beams and asked only that all model builders, including those at Berkeley and Columbia and elsewhere, be requested to join with us in making predictions of the outcome of such an experiment. Our offer was declined. In subsequent years we fitted parameters to upwards of 40 sets of data and have examined the systematics of radiobiological effects through the relations among our parameters. Though there have been many criticisms of our model through the years, there is a general opinion that this is the best model now available.

Our work is also significant for the evaluation of radiation hazards. We have been led to the conclusion that the widely held belief that all survival curves display an initial linear slope is without experimental or theoretical foundation. It results from a huge linear extrapolation of cellular survival data from observations with low LET radiations made at the level of Grays to milliGrays. When the data are plotted on a linear dose scale, it is easy to overlook uncertainties in the survival at low dose and that the extrapolation is over several orders of magnitude. When data are referred to dose it is easy to overlook that the fluence is such that many, if not most, cells do not experience a particle transit. Thus at 1 milliGray of relativistic electrons there is an average of about 1 electron transit per cell nucleus, meaning that 37% of the nuclei experience no transit, and of course there are many fewer transits for electrons of lower energy at this dose level. But this is the limit set by NCRP for radiation exposure of the general public in 1 year. We have asked for evidence that single electron transits produce cell killing or mutation but have found none. Such evidence should be available from the decay of tritium incorporated in cell nuclei. Yet the survival curves derived from tritium incorporated in cellular DNA have large shoulders, totally invalidating the NCRP wisdom that all radiobiological effects display an initial linear slope. A far worse situation arises from low dose exposure to high LET radiations. Dose is a meaningless quantity when there are fewer than an average of about 3 particle transits per cellular target. If this is taken to be the limit of a meaningful concept of dose consideration of the range of particle LET's (of 5 orders of magnitude) and of the range in the cross sectional area of cellular targets (of 4 orders of magnitude)

suggest that we talk nonsense when we take low dose effects to be effects at the level of centigrays or below, without regard of the radiation or the end point. Thus the concept of low dose RBE's, or the validity of the Sievert as the basis for a measure of radiation hazard are without foundation. These considerations arise from our attempts to produce a theory of RBE which produces verifiable predictions. We conclude that radiation protection standards are excessively severe. Current standards for radiation protection arise from epidemiology (sometimes with questionable inferences drawn from statistics), from committee judgments, from the neglect of highly relevant data, and are untestable. There is much nonsense in the conventional wisdom as practiced by NCRP, resulting in great cost but with little benefit.

A new paper voicing similar objections to radiation protection regulations has recently appeared: "Stimulation Effects Of Ionizing Radiations: New Issue for Regulatory Policy" by Zbigniew Jaworowski, *Regulatory Toxicology and Pharmacology* 22, 172-179 (1995). He makes the additional point that hormesis must also be considered when evaluating low dose effects.

It is interesting that radiobiologists at Berkeley, where I requested beam time, and at NIH where I requested additional support, rejected my proposals for the study of particle tracks in emulsion in support of my attempts to further the development of the Theory of RBE because they saw no connection between radiobiology and nuclear emulsions.

It took many years for my track theory concepts to gain acceptance. Today when I use the words "track theory" to describe my model, reviewers chastise me with the comment that there are now many track theories, evidently unconscious of the fact that these many theories are derivative, that they have been stimulated by my work just as radiobiologists were unconscious of the central role played by particle tracks in nuclear emulsion in the understanding of RBE. Many ill conceived concepts in radiobiology could have been avoided if tracks in emulsion had been studied alongside biological investigations.

Our interpretation of biological effects branches depending on whether the action cross-section is smaller or greater than the physical size of the target, which in the case of cell killing or the induction of chromosome aberrations approximates the geometric cross-sectional area of the nucleus. We refer to the smaller cross-sections as in the grain-count regime and the larger cross-sections as in the track-width regime because of the characteristic appearance of these tracks, like an irregularly spaced string of beads or a hairy rope, respectively, where in nuclear emulsion one counts grains or measures the track width. Our concepts also branch according to whether the detector is able to accumulate sub-lethal damage, for in that case we must separately consider intra-track and inter-track damage (ion-kill and gamma-kill). The transition from the gamma-kill to the ion-kill interaction modes reflects a subtle change in the statistics of the inactivation process which appears as a transition from a shouldered to an exponential survival curve with an increase in LET. We make no distinction between low and high LET targets in radiobiology. We refer to targets in terms of their "hittedness". A 1-hit target responds to single electrons, hence to low LET radiations. A many-hit target requires the transit of more than 1 electron, hence cannot respond to single electrons, and will therefore be relatively insensitive to low LET radiations while responding to high LET radiations. The same targets are responsible for damage with radiations of whatever LET. It is the statistics of the process which is changing.

This model, developed in this DOE supported research, is widely regarded as the best available model for the description of particle tracks, for the interaction of heavy ions with matter, for the explanation of RBE and for similar problems with other detectors. I am told that this work is the most widely referred to construct in radiobiology. I have been called the "father of track structure" for track structure concepts initiated in these investigations are now widely copied in radiobiology and in all branches of science in which the effects produced by energetic heavy ions are studied, in solid state dosimetry, in the formation of "latent tracks" in solids, in radiation chemistry, in the evaluation of radiation hazards from energetic heavy ions as from radon, from cosmic rays in high altitude flight and to astronauts, in treatment planning for hadron therapy, in the possible detection of hypothetical particles such as the Dirac magnetic monopole and so on. As a conceptual clarification in the study of "latent tracks" where many competing constructs are presently used, I have pointed out that track structure from delta rays is indicated whenever

different results are found from bombardment with different ions at the same LET. I have made the only prediction from physics onto radiobiology, in the prediction of "hooks" in plots of cross section vs. LET found many years later in Darmstadt, where it pleases them to refer to these as the "Darmstadt Hooks", but these "hooks" are nothing more than a plot of cross section Vs LET, a variant representation of "thin down" in the tracks of nuclear emulsions.

But further, these investigations have had significant implications for the effects of low levels of low LET radiations, and have illuminated many basic conceptual errors in accepted standards for radiation protection, which should lead to the revision of these standards. Our publication, in 1983, on **QUALITY FACTOR FOR LOW DOSES OF HIGH LET RADIATIONS** recommending a reduction in these factors was followed by a reduction in ICRP recommended values.

In our view a theory of RBE must first describe the tracks of single ions by means of a theoretical action cross section, then account for the effects produced by a beam of monoenergetic ions, and finally the effects produced by a mixed radiation field made up of particles of different charge and speed, electrons, and photons, ultimately translating its findings from a basis of fluence, action cross-section and particle energy spectra to dose. Our model does not include temporal effects, like biological repair. But there is no competitive model which yields cross sections, which explains the variation of RBE with LET, though efforts of our colleagues at NASA (who have collaborated with us in the past decade because of their perception that this theory is the best basis for evaluation of cosmic ray hazards to astronauts) have extended our theory to include repair.

Our ideas have resulted in a substantial clarification of radiation effects in a variety of detectors, including biological cells. Detectors have been parameterized, and through an accompanying set of equations a large amount of data resulting from high LET irradiations have been fitted, and even predicted. For practical purposes the significance of the model is that parameters extracted from a relatively few bombardments with heavy ions make it possible to predict response for neutrons, other heavy ions and mixed fields. We have published a survey of biological radiosensitivity parameters determined over the period of these investigations. There are upwards of 40 sets of radiobiological data which are well described by our parameters. In this survey we examine relations among the parameters, and have found a systematic behavior that may be useful to those seeking an interpretation based on biological mechanisms.

Biologically speaking our model is statistical and parametric rather than mechanistic, and thus is comprehensive, encompassing many different detectors whose mechanism varies widely. In addition to radiobiology the concepts of ion kill and gamma kill have been applied to photoresists, where results analogous to an increase in RBE with LET have been observed. The model is mechanistic only in regard to the physics of track structure. Insights obtained in the study of one detector are transferred to all detectors. In this investigation there has been a cross-fertilization of ideas between nuclear emulsions and viruses, from these to biological cells, and from biological cells to many-hit physical and chemical detectors, and conversely.

Of particular importance is the connection between the response of a detector to gamma rays and its response to heavy ions. These are two aspects of the same phenomenon, much like the response of an electronic circuit to square pulses and its frequency response. In electronics these are connected by a mathematical representation called the Fourier Transform. In radiobiology they are connected by Katz Theory, by the theory developed in these investigations. For 1-hit detectors we can predict the high LET response from their response to gamma rays, and conversely we can predict the response to gamma rays if we know the high LET response over an adequate range of bombardments. Biological cells have a more complex structure. We cannot predict their detailed high LET response from their response to gamma rays alone, as we can for molecular 1-hit detectors. Nevertheless it seems clear that the variation in the shapes of survival curves with changes in LET are due to physics rather than to biology. The biological content of our model rests in the choice of parameters on which to base the theory and in their numerical value, determined from experiment.

While we cannot calculate action cross sections for biological cells from the x-ray response alone, we can go the other way. Knowing the response of biological cells to heavy ions at high dose levels we can extract radiosensitivity parameters which enable us to predict their response to many radiation environments, including X and gamma rays at low dose levels where assay procedures and statistical analyses are weakest. Here is an aspect of our model of importance to radiation protection. The model tells us how to extrapolate to low doses of gamma rays from high LET data measured at high doses. Clearly the basis of the model in action cross sections means that we can calculate biological response at the lowest possible dose level for heavy ion irradiation, that of a single particle. Our model argues against the use of an α - β representation, or a linear extrapolation to low doses, as used by NCRP or ICRP as the basis of RBE calculations. Doses lower than a milligray per year are delivered by a fluence of electrons at which there are fewer than 1 electron traversing a cell per year. Experimental data obtained with tritium incorporated into cell nuclei displays shouldered response curves up to about 500 disintegrations per cell, arguing strongly against the linear extrapolation to low doses. We must conclude that present radiation protection standards for the general public are much too restrictive, based as they are on the linear extrapolation to low doses which has no experimental basis in its extension to cellular radiobiology. Investigations which have searched for a linear component at low doses in investigations for cancer induction by gamma rays have failed to find it.

We do not know how to predict the response of cells to ultrasoft x-rays. Many investigators have represented that track end effects for stopping electrons resemble high LET radiations. We have been skeptical of this claim on fundamental physical grounds, for the stopping power of slow electrons is based on an extrapolation from range-energy measurements, and does not truly represent the spatial fluctuations in energy deposition from stopping electrons which scatter widely. Our position has recently been confirmed by Monte-Carlo calculations reported at the 1993 Radiation Research Society meeting by Wilson and others from Battelle Northwest Laboratories who find no justification for the concept of high LET electron track ends.

There are presently conflicting experimental results on the response of cells to ultrasoft x-rays. Earlier claims of a high RBE for ultrasoft x-rays are now challenged, and the claimed biological response has been assigned to dosimetry. The problem of assigning an average dose of highly attenuated x-rays to thick, rounded cells is a challenging one and may well be responsible for earlier claims of biological effectiveness. In any event measurements of the RBE for thin, flattened cells have yielded a value of 1, which is what we would have expected. Our view is based simply on the fact that there is an great abundance of soft electrons in the slowing down spectrum of secondary electrons from X- or γ - rays. There is a further conceptual question regarding ultrasoft x-rays. Dose itself is not a fundamental quantity. It is rather a convenient plotting parameter for gamma rays at high doses, where many electrons pass through a cell. The extension of this concept to very short range electrons which do not pass through a cell is itself questionable, and limits the validity of a comparison on the basis of dose between the response of cells to ultrasoft x-rays and gamma-rays. Thus the interpretation of such RBE's is questionable.

We have long claimed that our analysis of radiobiological data obtained at high doses with high LET radiations could yield predictions of effects at the lowest possible dose levels with both low and high LET radiations, that is with single electrons and single heavy ions. We believe that this prediction is now confirmed, for electrons through survival data obtained with tritium incorporated in DNA, and for alpha particles through experiments with single particle transits through cells.

We have also argued from theoretical grounds that neither single electrons nor single alpha particles could induce cancers. This claim is confirmed by Tubiana through analysis of extensive epidemiological data.

From atomic physics we need the radial distribution of dose from heavy particles. In 1986 Hamm made a Monte Carlo calculation of the radial dose distribution about the path of a proton in liquid water. This has

been the basis of one of our calculations. This work agrees with earlier measurements by Varma et al. and has recently been verified experimentally in gases in experiments in Japan, by Kanai and Kawachi, and through microdosimetric measurements in gases by Metting and again more recently with 21.5 MeV ^{16}O ions using 150 nm sites, in Julich, which when averaged are in excellent agreement with our formulation for water. There are remaining problems in the calculation of the radial dose distribution, especially at large distances from the ion's path, important in connection with the theory of thindown. Our colleague, C. X. Zhang, P. R. China, who first visited us 10 years ago, and again more recently, has made a new calculation of the radial distribution of dose based on a logarithmic approximation to the electron range-energy relation in aluminum and use of a classical angular distribution of delta rays, which is currently being applied to the thindown problem. We have continued to recalculate the radial dose distribution as fundamental to our work, most recently by Cucinotta, more of which later.

From nuclear physics we need the particle-energy spectrum in a radiation field. This component has long been weak. We constructed a primitive beam fragmentation model some years ago with which we were able to demonstrate the ability of the model to calculate biological response curves in heavy ion beams up to the Bragg peak region. NASA-Langley personnel have developed an improved beam model which includes both projectile and target fragmentation. In the past years we have been working with F. A. Cucinotta, NASA, incorporating our theory of RBE with his calculation of the radiation environment in a space vehicle from solar and galactic cosmic rays, including secondary fragments. There we compare estimates of biological damage based on the theory of RBE with that based on quality factor. We have calculated the biological response to beams of protons and heavier charged particles for comparison with published data as a means of verifying and extending our work.

We have extended our calculations to radiation oncology, and have shown that cells experiencing ion-kill are not repairable. Thus beams of carbon and neon ions will not respond to fractionation in the same way as photon therapy. Clinical experience (Castro) has confirmed these calculations for neon. There may be similar problems for neutron therapy. The presumed benefits of heavy ion therapy from lack of sensitivity to oxygenation, or cell cycle position are accompanied by inability to repair. The reduction in OER and the increase in RBE for high LET radiation arises from the fraction of cells inactivated in the ion-kill mode.

We need to know the response of a detector to gamma-rays at all dose levels. For complex structures like biological cells we should like to know the average sizes of its internal targets (for these determine the transition from gamma-kill to ion-kill) and the size of the volume into which these targets are clustered, which for cell killing approaches the size of the cell nucleus. Lacking this information we rely on parameters extracted from experimental data (which reflect this information) to construct the response to heavy particles at the ultimate limit of low dose, the single particle track, and to other radiation environments. Our size estimates are not precise, for they depend on the assumed shape of the target, and are uncertain to within a factor 3, depending on whether the calculation is made for cylindrical or spherical targets. To some extent this affects our calculations of cross section for very heavy ions.

The model has been extended beyond cell killing to mutations in human fibroblasts and to lethal mutations in *C. Elegans*, a "wire worm" in in-vivo experiments. We have analyzed experiments on cancer induction in the Harderian gland from heavy ion bombardment. We have examined older data on the response of several strains of *E. Coli* to x-ray and heavy ion bombardment and have found that 3 *E. Coli* mutants are 1-hit detectors. We have examined other questions in track physics. Thus we have studied the response of the alanine dosimeter to heavy ion and neutron irradiations. We have shown that so-called "track core" effects in radiation chemistry arise from the 2-hit character of the measured response, as in HO_2 radical generation in water and in H_2 production in benzene. We have generated an approximation to the radial dose distribution in several solids from which detectors are made and have then calculated the response of NaI(Tl) scintillators and LiF TLD's to heavy ions, to explain some previously problematic experimental data. Our view that the track core/penumbra model is invalid is now supported by the work of Kraft and his colleagues at GSI, Darmstadt.

Some important aspects of radiobiology remain unresolved. The theory addresses cell killing, transformation, and chromosome aberration. We lack radiobiological guidance which might enable us to predict cancer production from our calculations of transformed cells. Our knowledge of the radial dose distribution is weak within 10 μm of the ion's path, and toward the maximum radial penetration of δ rays. Our model does not yet address cellular repair. These questions are under study. Nevertheless our model has made a significant contribution to the understanding of the effects of high LET radiations which impact on radiation measurement and on the evaluation of radiation hazard. These contributions must be taken into consideration in any discussion of the Quality Factor and of the extrapolation of radiobiological effects to low doses of both low and high LET radiations. We await the response of regulatory agencies.

II. Principal Research Accomplishments

II-A) Radial Dose Distribution

A predictive theory of RBE has been created as an extension of target theory, in which primary ion and the δ -rays generated by its passage through a detector activate its radiosensitive targets. We need to know the number density of these targets, their size, possibly their internal construction, and the probability that they will be activated by secondary electrons from gamma-rays (or another appropriate low LET source) as a function of dose. From atomic physics we need to know the radial distribution of dose from delta-rays about an ion's path. The central theme of our theory is that we can find the radial distribution of activation probability by folding the gamma-ray response function into the radial dose distribution. This introduces neglects, whose importance varies from detector to detector, to which we must remain alert. We enumerate two such neglects. 1) The electron slowing down spectrum from gamma-rays differs from the slowing down spectrum from delta rays in different cylindrical shells about the ion's path. Some detectors are sensitive to details of the electron energy spectrum. 2) The irradiation with gamma-rays may require minutes or hours to reach the level of dose attained close to the ion's path in perhaps 10^{-15} sec by the burst of delta rays. Before our original work track structure was rarely, if ever, mentioned. Now there are many papers on track structure effects at every meeting where radiation effects are discussed.

In collaboration with R. N. Hamm, Oak Ridge National Laboratory, who has made a Monte Carlo calculation of the radial distribution of dose about the path of a proton of energy from 1 to 100 MeV in liquid water, we have found an analytic expression for the radial dose distribution which integrates to within 10% of the stopping power. This expression includes, for the first time, the radial distribution of both primary and secondary energy depositions. We currently inquire as to whether the primary excitations have the same relevance in dealing with dry enzymes and viruses, for radical creation as for cellular end points. The question is presently unclear. Although the calculation is made for liquid water it is in good agreement with experimental data obtained with tissue equivalent gas. We continue to be interested in knowledge of the dose at large distances from the ion's path, for this is important for calculations of thindown. Our colleague, C. X. Zhang has made a new calculation of the radial dose distribution based on the classical angular distribution and a new logarithmic polynomial approximation of electron range-energy relationships which has resulted in an improved approximation to experimental biological thindown measurements. Yet another such computation has been made by F. A. Cucinotta, in extension of earlier work by E. J. Kobetich, making use of newly developed experimental data by M. E. Rudd. This is presently the best available model of the radial dose distribution. We emphasize that precise knowledge of radial dose is central to track structure modeling. In extension of the radial dose calculation Cucinotta has shown that this model implicitly contains knowledge of the radial distribution of electron energy spectra. From these spectra he has been able to calculate the average radial distribution of microdosimetric energy depositions, in agreement with experimental work of Metting.

We have approximated the radial dose distribution in several solids (Si, Si_2 , LiF, NaI) by correcting for differences in electron density and stopping power from liquid water. We have used these approximations

to calculate the response of NaI(Tl) to fast heavy ions and have shown that track theory yields predictions in agreement with experimental data, contradicting the statement of the investigators that track theory did not account for their data. We have explained that the apparently anomalous response of LiF to stopping heavy ions arises from thindown.

For many years we have argued against the concept of a track core, based on the agreement of our models of the structure of particle tracks with experiment. We note that this judgment has recently been verified by experiment at Darmstadt. Japanese measurements with 18.3 MeV/nucleon helions in tissue equivalent gas are consistent with our formulas for the radial dose distribution in water, except that the measured maximal delta ray penetration is less than that used in our calculations. Other measurements by Metting, and by Kiefer's group at Julich, of the radial variation in microdosimetric energy depositions about an ion's path are in very good agreement with our formulation when these measurements are averaged. Metting's work with several different heavy ions, up to uranium, also confirms the validity of our use of "effective charge" to extend proton calculations to partially clothed heavy ions. An additional result of that work is that the microdosimetric distribution of energy deposits approximates that from 150 keV x-rays, partially supporting our use of X- or γ rays as the basis of calibrating detector response.

It has been frequently stated that one reason the LET is not a good parameter is that it is an average quantity, that one must take into account the microdosimetric fluctuation in energy depositions in order to properly parameterize high LET radiation effects. We do not agree. We seriously question the logical basis of microdosimetry, and hold that its failure to account for high LET and neutron effects is due to conceptual rather than practical difficulties. The problem with LET does not lie with the fluctuations ion energy deposition but rather with the neglect of the radial distribution of energy deposition from delta rays. When delta rays are incorporated into a track structure model, the use of averages (as in the radial distribution of dose) does not negate the model. We make no use of the fluctuation in energy deposition in small volumes either about an ion's path or in a larger medium. We take these fluctuations to be adequately described by a) the response function obtained with gamma rays and b) the Poisson distribution. In this regard the success of our model speaks for us.

II-B) The 1-Hit Detector: Action Cross-Sections

From knowledge of the dose-response relation after gamma irradiation we transform the radial distribution of dose to a radial distribution of activation probability. For generality we take this dose-response function to have one of the forms developed in biological target theory: the Poisson C-or-more hit response, or the many-target, single hit per target response. For the 1-hit detector $C=1$ and the response is exponential. To describe it we need as parameters the D-37 dose and λ , where the target size is a non-negligible fraction of the diameter of the radial dose, we need the target size. By a radial integration of the probability for activation we obtain an action cross-section that frequently can be compared directly to experimental values.

We have long urged investigation of alanine, a 1-hit detector in which stable free radicals are produced after irradiation, both for research and as a dosimeter for x-rays, neutrons, and heavy ions. We are encouraged that others have picked up on these recommendations. The National Institute of Science and Technology now has obtained an esr spectrometer for this purpose, as have other laboratories internationally, as at Neuherberg; Riso; Fontenay-aux-Roses; Zhongshan Univ. P.R.China. Our pioneering work in exploring the properties of alanine with Francis Bermann, Fontenay aux -Roses under IAEA sponsorship and in advocating its use for high dose measurements and as a postal intercomparison dosimeter has born fruit.

We have recalculated cross-sections for the heavy ion inactivation of dry enzymes and viruses, making use of our new semi-empirical interpolation formula for the radial dose distribution. For comparison with experiment we enter an adjusted D-37 dose for gamma-irradiation and an estimated target size into our computer program and find the value which yields the best agreement with observed cross-sections. We find that the average value of the ratio of experimental to fitted D-37 doses to be 1.07 ± 0.18 , while the

average ratio of the experimental to calculated cross-sections is 0.96 ± 0.11 . In spite of neglects our calculations fit these data, for 70 measured cross-sections, of 7 different substances measured by 6 investigators at 4 accelerators, to about 15%, approximately to within the precision of the data itself. For these substances our neglects do not appear to be significant. We consider the enzyme and virus data to be extremely important as a test of any radiobiological model and find it difficult to take seriously proposed models which do not attempt to explain these data. Unfortunately the early investigators did not measure the response to gamma rays at the same time that they measured response to heavy ions. At that time this was not thought to be relevant for the intended purpose, which incorrectly sought to measure the size of a virus by heavy ion bombardments. This goal was shown to be futile in the theory of Butts and Katz. Experimental studies of enzyme and virus inactivation have been suspended for over a decade. We hope that we can encourage experimentalists to resume such studies with the wide range of heavy ion bombardments now available. Dry enzymes and viruses seem to us to be the best available objects for testing track theory.

The expression for the radial dose distribution in liquid water has been applied to the Fricke dosimeter to calculate its high LET response. Our results are in excellent agreement with experiment and leave no doubt that our identification of this system as a 1-hit detector is correct. We require no physical track core, no chemical track core, no array of diffusion constants, chemical equations, reaction rates, differential equations, no blobs, spurs or short tracks as in mechanistic chemical models. It appears to us that the proper role of a mechanistic chemical model is to calculate the numerical values of our radiosensitivity parameters, and to explain quantitatively why this detector has 1-hit character. We cannot understand why this is not done.

The concept of the 1-hit detector is rather pervasive. It must present a puzzle to theorists concerned with mechanistic explanations of detector response that a single model, that of track physics, can account for so many different detectors of different materials and different end-points. But the explanation is simple. Their response is all based on the fact that a single electron passing through the sensitive target of a 1-hit detector can initiate the sequence of events which result in the observed end-point.

When sensitive emulsions are exposed to light many photons must be absorbed to create a latent image. The response to visible light takes the form of a many hit Poisson distribution. When exposed to x-ray photons or electron beams the response is exponential. The emulsion then behaves as a 1-hit detector. Our model yields the radial distribution of developed grains about an ion's path on the basis of the measured grain size and a single parameter, the D-37 dose for gamma-rays, at which 63% of the grains are made developable. From this we can get the linear grain count for tracks in the grain count regime, or the photometric track width in the track width regime. In both cases our calculations compare well with experimental data. We have constructed computer models of particle tracks whose appearance is virtually indistinguishable from microphotographs of actual tracks, in the grain count regime. Recent work has emphasized the importance of the narrowing of a particle track as the particle approaches the end of its range. This image, called "thin down" has been used by us to predict and explain a decline in inactivation cross section with an increase in LET after uranium bombardment of mammalian cells. This view now is universally accepted for cells and for many other detectors. There is no room for doubt as to the identification of the basis of thin-down as due to the kinematic limitation on delta ray energies as the ion approaches the end of its path. In this region the speed of the ion rather than LET or z^2/b^2 determines the cross-section and hence the radiation response. Our theory of particle tracks in emulsion is accepted as the definitive model of this phenomenon.

Our original motivation for the study of particle tracks was to attempt to identify the track of a Dirac magnetic monopole in cosmic rays. We created a model which described the signature of the monopole in both emulsion and in etchable plastic track detectors. Those criteria were used by P. B. Price in an abortive attempt to display a track which he identified, prematurely, as a discovered monopole. Interest in the monopole continues in particle physics, for it appears to be demanded by the unified field theory. The

structure of its track remains one of the possible means of monopole identification. It is interesting how this motivation has led to track structure models in many disciplines, and especially in radiobiology.

Emulsions may also serve to clarify concepts connected with the RBE of soft x-rays. At photon energies between 100 and 10,000 eV some emulsions have grains that can be activated by a single absorbed photon, while secondary electrons are not energetic enough to penetrate a second grain. In this energy interval the relative effectiveness as defined biologically is inversely proportional to photon energy. To find the effectiveness relative to hard x-rays or gamma-rays we need to estimate the average number of developable grains per photon. But, if we compare 100 eV photons to 10,000 eV photons the Relative Photographic Effectiveness is 100. We see that relative effectiveness based on dose does not shed much light on this phenomenon. The high RPE is of little significance. Here is a phenomenon where photon fluence yields an appropriate description, and where photon dose leads to confusion.

We have analyzed old data for the survival of several strains of E. coli to x-rays and heavy ions, from Japan (Takahashi), Russia (Kovalev), and Canada (Haynes), and have shown that these are 1-hit detectors with reasonably close values of the D-37 dose. Yet their response to UV is widely different, with clear inference (in one case) of repair. We hope to revive interest in the measurement of the response of bacteria to X-rays and to heavy ions. We have found 3 E. coli mutants to be 1-hit detectors while a fourth is not. The response of *Shigella sonnei* to heavy ions, measured long ago by Brustad yields the interesting inference that these are 1 hit detectors when irradiated aerobically but are many hit detectors when irradiated hypoxically (our interpretation). As yet we know of no suitable biologically mechanistic explanation of these results.

We have analyzed published data on chromosome aberrations in Chinese hamster cells, and have shown that parameters for this end point closely match those for cell killing. We have found parameters for the survival of *Tradescantia*. We have explained that the normalized yield (events/rad/Dalton) is simply proportional to the RBE, for 1-hit detectors. Our analysis of experimental cross sections for single and double strand breaks for SV-40 virus in EO buffer shows them to exhibit 1-hit response. We have developed a new formula for the RBE at very low doses of high LET radiations, taking into account that there can be no gamma kill when the separation of ions exceeds the range of delta rays. We have shown that a dose weighted average of the RBE's of the components of a mixed field yields the RBE of the mixture only for 1-hit detectors, although this recipe is widely used for cells, and a similar incorrect recipe is used by ICRP for neutrons and other high LET radiations. With NASA colleagues we have made calculations relevant for the evaluation of radiation hazards in space flight.

We have found that the use of dose as the basis for comparison of the effects of radiations of different quality frequently leads to confusion. In our own work calculations of the response to high LET radiations are based on particle fluence and action cross sections, with the final results translated from fluence to dose for comparison with experimental data. We consider dose to be a good variable only in the comparison of low LET radiations, like electrons and photons in the energy interval from about 100 keV to several MeV, where the slowing down spectra of secondary electrons are not appreciably different for the secondary electrons of energy below 1 keV, where the atomic and molecular collision cross sections are highest. As in the soft x-ray work, when the photon energy descends below 100 keV, even to below 1 keV the electron slowing down spectrum differs greatly from that obtained with 100 keV or 1 MeV photons in the electron energy region below 1 keV, and dose becomes a misleading reference parameter. RBE then loses its significance. We have recently prepared a paper entitled "Dose" which further explores these questions.

We consider our work with emulsions a significant aspect of the theory of RBE, for it is the only observable test of the extrapolation of radiation effects to the lowest possible dose, the track of a single particle. Perhaps our prediction and identification of thindown in radiobiology based on our emulsion work and the observations of the preceding paragraphs will serve to persuade skeptical radiobiological colleagues that silver bromide crystals can serve as a useful model for radiobiology. Their skepticism has been an impediment to our work and theirs.

This model of the response to heavy ions of the 1-hit detector is one substantial accomplishment of these researches. It has established the role of delta-rays in the production of radiation effects. Thirty years ago delta rays were thought to yield a small correction to target size in the measurement of cross sections. Our work showed them to be the dominant effect. Indeed the theory of Butts and Katz took a virus to be a point particle and calculated the cross sections solely from the influence of delta rays, counter to the associated volume hypothesis of Lea which had dominated earlier thinking.

Even for these conceptually simple detectors our theory shows that the parameters of the detector and those of the radiation are not separable variables, that one simply cannot speak of a multiplicative quality factor for a high LET radiation field, neglecting the role of the detector.

Even for these simple detectors our theory shows that there is no meaningful single parameter reduction of a complex radiation field which can predict the relative response of all 1-hit systems. One hit detectors exhibit a grain-count regime, where the activated targets are like beads on the string of the particle's path and the cross-section is less than the geometric cross-sectional area of the target, and a track-width regime, where the activated targets cluster about the ion's path like a hairy rope and the action cross-section can be many times greater than the geometric cross-sectional area of the target. In the grain-count regime the cross-section increases with an increase in LET, but in the track width regime the action cross-section first increases with an increase in the LET of an ion, as the ion slows down, and then decreases with a further increase in LET as the kinematic limit on delta-ray energies constrains the damaged region to the region penetrated by delta rays. For 1-hit detectors the size of the cross section is more related to the diameter of the δ ray brush than to the size of the target. This can be seen most clearly in photographs of heavy ion tracks in electron sensitive emulsions. Many of these generalities are applicable to more complicated detectors, like biological cells. Characteristically the "RBE" of a 1-hit detector never exceeds 1, and declines with an increase in LET. For these detectors a linear extrapolation to low doses is precisely correct. These are potent generalizations, useful in radiobiology and in dosimetry.

II-C) Many Hit Detectors

We have long known that desensitized nuclear emulsions behave like many hit detectors. So also are some photoresists, and some etchable solid state nuclear track detectors. We continually search for others, and have found hints that quartz and NaCl thermoluminescence may be 2-hit phenomena. We think that supralinearity in LiF (TLD-100) arises from 2-hit processes. Specialists use other terminology, for they speak of a "track interaction model" and of the supralinearity arising in the heating stage, but these are simply other ways to describe a 2-hit process. The clearest case of 2 hit phenomena of chemical interest is in heavy ion radiolysis where data on HO_2 radical production in water and H_2 production in benzene by heavy ions fit the 2-hit model very well. It is interesting here that two different end points in liquid water behave differently. The Fricke dosimeter has 1 hit response while HO_2 radical production has 2 hit response. These many hit detectors are of interest because they simulate the response of biological systems. When we say of cells that the RBE exceeds 1 for high LET radiations we are simply saying that cells are discriminating detectors, that they discriminate against low LET radiations in favor of high LET radiations. But this is precisely what a 2 hit detector does.

II-D) Biological Cells

More complicated problems arise when the detector is capable of accumulating sub-lethal damage, or when its internal architecture is complex and unknown, as in the case of biological cells. These are so complex that it seems foolhardy to undertake to construct a mechanistic model of radiation effects, except perhaps for well specified, uniquely caused end-points.

When a detector is capable of accumulating sub-lethal damage we must first account for the effects produced by the passage of isolated single particles (ion-kill), and then supplement this by the effect of overlapping delta-rays (gamma-kill) from different particles in sensitive targets not activated by ion-kill. Several authors have misunderstood our model, and have wrongly identified the effects of the track core as ion kill, and the effects of the penumbra as gamma kill.

We consider the survival probability of biological cells after the irradiation to be approximated as the product of the survival probability in the ion-kill mode and the survival probability in the gamma-kill mode. The survivors of the ion-kill mode are taken to be the initial population for the gamma kill mode. We neglect repair, or fading, or the possibility of enhanced effects at very high dose rates. We ignore the internal architecture of the nucleus of a biological cell, representing its effect as if there were a single target of sub-nuclear size whose dose-response is described by the multi-target formula, and assume that the calculated cross-section for this target is proportional to the ion-kill action cross-section of the cell. We think this to be consistent with our "bean bag" model of a cell, in which the targets are beans (perhaps chromosomes) and the bag is the nucleus. From these ideas we develop a set of equations which describe the effects to be observed at high dose, based on a set of four experimental parameters based on normalized plots from calculations of ion kill from our model. These are then evaluated by fitting our formulas to experimental data that arise from irradiation of specific cells in a specific ambience. Thus there are four parameters describing an aerobic irradiation, and four describing a hypoxic irradiation. Because two of the parameters have the same value in these two cases we require a total of six parameters in all to find the OER. This parametric model fits much (though not all) experimental data obtained with heavy ions on mammalian cells. It yields the RBE - LET curves. It has predicted the thin-down hooks. It has been extrapolated to mixed radiation environments. Though it is imperfect, this model is widely regarded as the best quantitative model in radiobiology.

By a clever calculational device due to Cucinotta, radiosensitivity parameters separately fitted to mutation induction and to cell killing have been joined in the calculation of mutations per survivor, by considering that the target for mutation, in a single chromosome, is spatially separated from the targets for cell killing. The result is in good agreement with measurements of mutants per survivor for high LET irradiations. This is yet another example of the advantage to this DOE sponsored program from our collaboration with NASA.

From these parameters, our formulas, and knowledge of the particle-energy spectrum of an arbitrary radiation field we can calculate cellular survival, RBE, and OER for that field. And although there are no presently confirming data, we believe that we can make predictions of chromosome aberration and cellular transformation in these fields, based on the success of our cell survival calculations. We have made successful calculations of cell killing for neutron, ion, and heavy ion irradiation, including range modulated ion beams intended for therapy frequently making predictions in real time. Our work with particle beams and neutrons is now being extended by a collaboration with Cucinotta, NASA, who has joined a NASA model of beam penetration and fragmentation to our theory of RBE.

Our calculations of the variation in the cellular inactivation cross-section with LET have been extended from the grain count regime to the track width regime, appropriate to experiments with Ar, Kr, Xe, Pb, and U. Thus we have been able to calculate the "hooks" in plots of cross section Vs LET for spores, bacteria, and mammalian cells, making use of our latest radial dose distribution calculations, by Zhang and by Cucinotta, in good agreement with measurements made at Darmstadt by Manfred Schafer and others.

In a qualitative way our model predicted the biological track width regime some 20 years ago, in 1973, as an obvious extension of the characteristics of particle tracks in electron sensitive nuclear emulsions. It predicted the characteristic hook like shapes of the plots of cross-section vs. LET, again from our observations of the thin-down of heavy ion tracks in nuclear emulsions and from our cross-section calculations for 1-hit detectors. This was done before the Darmstadt accelerator was commissioned, in 1975. It was there that the first experimental confirmation of thin down in radio biology was observed,

with bacterial spores in 1981. But many years earlier thindown, or hooks in plots of the response of scintillators Vs LET was observed at Yale.

Biological cells are the most complex of the many hit detectors. There are different end points of interest: cell killing, chromosome aberrations, transformation, strand breaks, mutation induction, and others. Repair must be taken into account. For a single end point in a single ambience our present model requires four parameters, without repair. To include repair will certainly require more parameters. Unfortunately there are few experiments which have adequately described repair phenomena after a wide range of irradiations of different quality. This poses an impossible challenge to a phenomenological model. There is no suitable mechanistic model presently available. If we are to devise a parametric model of repair we must do it intuitively and use it to stimulate experimentation. Such a model is presently being constructed by Wilson and Cucinotta, NASA, who seek to join a model based on chemical kinetics to "Katz Theory", in the manner of physical boundary value problems.

To some of our colleagues our four parameters are excessive. We are astonished that so few parameters are able to accomplish so much. After all three parameters are required for the simplest physical systems. It is astonishing that the enormously more complex biological system can be accommodated with four, and that the same four parameters (in concept if not in magnitude) suffice for the different end points of cell killing, transformation, and chromosome aberration. Indeed we now have confidence that we can incorporate our 4 parameter model into the NASA beam calculations, for with only numerical changes in our 4 parameters we can explore a wide range of biological response.

We have recently surveyed the radiosensitivity parameters collected over 25 years of study of radiobiological data measured by many different investigators, on different test objects and end points at different installations. There are more than 40 sets of data involved, for mammalian cell killing, mutation, and transformation, for yeast, for bacterial spores, *Tradescantia*, *E. Coli*, *C. Elegans*, *Artemia* eggs, and other substances. We have made a tentative assignment for cancer induction in rat skin from limited data. We find systematic relations among these parameters which hold across the different substances and end points. We hope that these relationships will stimulate a new attempt at mechanistic biological interpretation of these data.

II-E) Implications for Radiation Protection

Our models have lent themselves to some generalizations, important to guide radiobiological experiments, and to suggest a more suitable structure for the evaluation of the equivalent dose of high LET radiations than the quality factor conversion of Grays into Sieverts that is currently in use. One possible avenue which we wish to explore lies in the determination of effective values of our parameters P and L from microdosimetric spectra. Long since, we have shown that the effect of a mixed radiation field in its action on a particular cell line can be represented through an effective hypothetical track segment bombardment, or through the ion kill probability P and an effective LET of that bombardment. We might effectively join microdosimetric measurements to track physics, to their mutual advantage by use of such a procedure. The data we presently need for making a calculation for a mixed radiation field is its particle-energy spectrum. Unfortunately this cannot be measured. It is only calculable from a model. For practical purposes the evaluation of P and L from microdosimetric data would greatly facilitate application of our model to radiation protection.

In fitting parameters to experimental data for cell killing, chromosome aberrations, and transformations, we found that the extrapolation number for gamma irradiation, m , is equal to 3 (though 2 is an equally likely possibility for transformations) This implies a cubic extrapolation to low dose for gamma rays and a quadratic extrapolation for alpha particles. This is not inconsistent with experimental studies of cancer induction in rat skin by electrons or with our analysis of epidemiological data for cancer induction by radon daughters. If $m = 3$ we expect plots of RBE Vs neutron dose to have slope $-2/3$. If $m = 2$ we expect that slope to be $-1/2$.

We must examine presently known discrepancies between the demands of our model and observation. One important discrepancy, observed with biological cells, is that our demand for a zero initial slope to a survival curve after low LET radiations as prerequisite to an RBE greater than 1 for high LET radiations which seems inconsistent with experiment. Some of this discrepancy is surely due to the experimental extrapolation of cellular response from readily measured effects at doses of Grays to immeasurable response at doses of milligrays. Other possible explanations lie in the heterogeneity of the cellular populations, and in the difference in the time scale of heavy ion and gamma ray bombardments.

In heavy ion radiobiology much data lacks dynamic range, making it unsuitable for analysis. This is the case where investigators have not made use of facilities at heavy ion accelerators at Berkeley. Thus data obtained at the Columbia University facility at RARAF typically lacks dynamic range and cannot be parameterized uniquely by our model. Even at Darmstadt bombardment with ions of low or intermediate atomic number is not possible for administrative reasons. When investigators use local cyclotrons or van de Graaf accelerators, or where they habitually use neutrons as a source of "high LET radiations" the experimental findings are not suitable for evaluation of radiosensitivity parameters. Additionally all high LET data should be accompanied by data obtained with gamma rays. Some investigators remain unaware of the direct connection between the response of cells to gamma rays and their response to heavy ions. This was certainly true for the early studies of the response of dry enzymes and viruses to high LET radiation, but occasionally persists to this day.

Our model has predicted that single electron transits through cells do not lead to cell killing, and that neither single electrons nor single alpha particles induce cancer. These predictions are confirmed by recent studies by Tubiana based on extensive epidemiological data. We suggest that these results demand revision of radiation protection standards.

II-F) Implications for Radiation Oncology with Heavy Ion Beams

We have noted that ion-kill is a much more severe interaction than gamma-kill. Cells inactivated in the ion-kill mode do not display repair, as noted in split dose and delayed plating experiments. Our analysis has shown that the fraction of cells experiencing this mode of inactivation is responsible for both the increase in RBE and the decrease in OER in the response of cell cultures to high LET radiations. Thus the inability to repair is coupled to both high RBE and low OER. We have calculated the response of cells to range modulated beams of H, He, C, and Ne, at fluences yielding 30% survival in the spread Bragg peak. There we display dose, survival, RBE, and fraction of the cells surviving the ion-kill mode, and predict that both carbon and neon beams will not respond to fractionation in the same way as in photon irradiation. For He and H beams there is some ion-kill at the end of the spread peak, and it remains a problem for oncologists to overcome, though the lighter ions are clearly more satisfactory than heavy ones. The question at issue is the choice between radiation therapy and radiation surgery. But it is clear that treatment planning based on RBE and dose and the skills of an oncologist honed on photon therapy will not yield acceptable treatment plans for carbon and neon beams. Indeed RBE is a totally inappropriate concept for it is based only on cell killing, ignoring the distinction between ion-kill and gamma-kill, and repair. For clinical practice we will require a collaboration among oncologists, radiobiologists and radiation physicists to extract radiosensitivity parameters for tissues being irradiated, to incorporate into our models for, our own parameters are extracted from cell cultures in vitro. These beam models developed at NASA yield knowledge of the nuclear fragments from both projectiles and targets so as to give the spectrum of ions in the treatment volume, enabling us to incorporate the Katz theory of cellular survival, thus to give a description of killed cells in both the gamma-kill and ion-kill modes. My NASA collaborators and I hope to extend these calculations to neutron therapy to anticipate problems which may arise from ion-kill there.

III. Students Trained and Associated Personnel

Given at left is the number of publications resulting from work here. At right is last known employment.

A. Students Trained

3	J.J. Butts	PhD 66	Aerospace Corp.
8	E.J. Kobetich	PhD 68	Arco Co.
	G.J. Hofer	MS 69	National Semiconductor
11	S.C. Sharma	PhD 71	Univ of Kentucky
4	M. Homayoonfar	PhD 71	Pahlevi Univ, Iran
2	B. Ackerson	BS 69	Oklahoma State Univ
1	C. Sorenson	BS 69	Kansas State Univ
1	T. Furtak	BS 69	Iowa State Univ
2	F. Pinkerton	BS 76	General Motors Res. Labs.
3	R.A. Roth-Krauter	BS 76	IBM-Austin
	B. Krauter	BS 76	IBM-Austin
1	B. Fullerton	BS 78	Texas Instruments
	J.S. Darland	BS 78	Texas Instruments
	D.L. Wilson		ISCO Corp.
1	E.C. Pennington	BS 78	Univ of Texas-Arlington
2	Y.L. Chang	BS 79	Texas Instruments
2	A.S. Lee	BS 79	Univ of Western Ontario
2	R.L. Rosman	BS 79	Univ of Chicago
	J.M. Motycka	BS 79	
	S. Amthor		
	C. Wan	BS 83	
	W. Flack	BS 83	Arizona State Univ.
	D. Miller	BS 82	Bell Labs, Naperville
	C. Judge		
	K. Dicke	MS 84	Bell Labs, Naperville
1	D. Dunn	BS 84	
	D. James	BS 84	
	M. Garwood		
	B. Oberg	BS 85	Bell Labs, Naperville
2	G. Sinclair	BS 86	
	K. Jarzynka		
1	G. Danialy		
	A. Hussein		Centel, Kansas City
	K. Williams		
1	Kim Sum Loh		Lincoln Tel. and Tel.
3	Guo-Rong Huang		Lincoln Tel. and Tel.
	Akhwand Mahmood		
	Steven Wu		
1	Scott Wesely	BS 90	
	Mark Rueden		
2	Rashidah Zachariah	M.S. 93	

B. Postdoctoral Research Associates

3	L. Larsson	75-77	Ceaverken AB, Sweden
	Y.V. Rao	77-78	
5	M.P.R. Waligorski	78-80, 85-86	Inst. of Nuclear Physics, Krakow

C. Scientific Visitors

	Dr. A. Naharin	79-80	Yavne Nucl. Res. Center, Israel
7	Dr. W. Hofmann	81-82	Univ of Salzburg, Austria
3	Dr. Zhang Chunxiang	83-84	Zhongshan Univ, P.R. China

D. Foreign Collaborators

Dr. F. Bermann	CEA, Fontenay aux Roses, France
Dr. Y. Horowitz	Ben Gurion Univ, Israel
Dr. M. Waligorski	Inst. of Nuclear Physics, Krakow
Dr. Johnny Hansen	Riso National Lab, Denmark
Dr. Kjeld Olsen	Herlev Hospital, Copenhagen
Dr. Werner Hofmann	Univ of Salzburg, Austria
Prof. Zhang Chunxiang	Zhongshan Univ, P.R. China

E. Principal NASA Collaborators

F. A. Cucinotta	NASA Langley Research Center
J. W. Wilson	NASA Langley Research Center

IV. Bibliography

Addendum Katz vita

Appended to this report.

V. The Present State of Knowledge

Within broad outlines, and to the present state of much existing data the variation in radiation response with radiation quality (for high LET radiations) is now described by the Theory of RBE for many different physical and biological detectors. Nevertheless we do not have a good understanding of the effects of low energy x-rays, nor of dose rate effects with either low or high LET radiations. We lack essential knowledge from both nuclear physics and atomic physics. However, it represents a substantial step forwards that we can enumerate our needs. Track theory has told us that from nuclear physics we need to know the particle-energy spectrum in a radiation field, that neither dose nor microdose measurements nor LET distributions will suffice to predict the response of a detector or a biological system. For this there is only very limited experimental data. We are now helped by work at NASA-Langley, by a model of neutron interactions and of nuclear fragmentation which we currently are using through collaboration with F. A. Cucinotta, in work presently directed toward the biological effects of solar and galactic cosmic rays in space vehicles. We need much more experimental information on the radial distribution of dose from partially clothed (with atomic electrons) energetic heavy ions of high atomic number, up to uranium, at radial distances from the ion's path from about 1 Angstrom to the maximal radial penetration of delta rays.

For critical studies of radiobiology to be used in the development and testing of models we need to have studies of simple systems. Radiobiology is very complex. We need better data for the inactivation of enzymes and viruses with protons and heavy ions, to uranium, which are accompanied by similar measurements with gamma-rays and x-rays of different energies. The precision of these measurements should be to a few percent. Next we should have studies of viruses, bacterial spores, and bacteria, next mammalian cells, well identified as to type and uniformity, with synchronized populations, then tissues and organisms. We need assays of the fraction of cells surviving and the fraction of cells in which there are no chromosome aberrations. Wherever possible we need radiobiological work done with incorporated tritium and reported in terms of the number of decays in the cell as well as in terms of the dose deposited. Such work has been done by Hofer and collaborators, We need much more, in different systems, and for

different end points, with synchronized cells, We need a better assay than colony formation to evaluate cell killing at low doses, where it introduces much uncertainty in the study of the initial slope of survival curves. We need to be certain of dosimetry. We need to know the smallest number of transformed cells that can be injected in an animal to lead to the expression of a tumor. We need more and better data for cell transformation from a range of x-ray and high LET irradiations. We find that studies of transformation of C3H10T_{1/2} cells after x-ray, neutron, and heavy ion irradiations by different investigators are not consistent with each other. Reported RBE's are therefore not very meaningful. We need studies of repair after irradiation with a range of particles from low to high LET. It would be very helpful if an assay could be developed that would separate cells inactivated by gamma kill from those inactivated by ion kill, for it presently appears that only the former are repairable. To be useful to the theory of RBE experiments should be made with a broad spectrum of ions over a range of particle speeds and atomic number, and always accompanied with measurements made with gamma-rays. Early work on the inactivation of dry enzymes and viruses by heavy ions frequently did not include the response to γ rays. Perhaps this was because investigators saw no relation between them. But this relationship is central to track theory. Measurements made with neutrons or with the spread Bragg peak, or where there are many secondary fragments are of practical use but of little value in the development of a theory unless the data are very clean and display little scatter. Cell killing is a rather gross end point. If we are to seek to develop ab initio mechanistic models, as opposed to parametric ones, we must find end-points associated with unique genetic sites. It might be reassuring if ab initio mechanistic models could first be developed for physical systems, like radical formation in alanine, or TLD's, or sensitization of nuclear emulsion.

Studies of the response of physical detectors to x-rays and high LET radiations are particularly helpful to the development of the theory of RBE. In particular we want to know the response of alanine, a substance of dosimetric importance, and of many hit detectors such as desensitized emulsions, some TLD's, plastic track detectors, and photoresists to energetic heavy ions. We have repeatedly demonstrated the importance of such work to elucidate radiobiology and to advance dosimetry. The presently growing use of alanine as a postal intercomparison dosimeter is in part due to our early recognition of its usefulness and our efforts to engage others in this work.

We can anticipate that the neglects of the present theory will become more significant when more accurate measurements of the cross-sections for dry enzymes and viruses are made, when more accurate biological information is available. While presently our need from atomic physics is primarily for knowledge of the radial distribution of dose, we can anticipate that in future a more precise description of the radial pattern of excitations and ionizations will be needed. The accumulation of this information is slow. We do not now know how to scale doubly differential cross-sections for electron ejection from protons to partially clothed heavy ions. For this purpose we now use an expression for effective charge which is surprisingly useful, though conceptually wrong. For the ultimate calculation of action cross-sections we need to have this information compactly represented, preferably in analytical form.

In sum this has been an extremely successful project. It has more than fulfilled its promised program, to develop a theory of RBE. We are told that, in what we have undertaken, we lead the world.

VI. Funding

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

NSF GP7256	Tracks of Heavy Ions in Emulsions	5/67-6/69	\$ 32,500
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NSF GP23129	Particle Tracks and Related Phenomena	6/70-6/72	15,000

NSF GI351356	Application of the Theory of Track Effects to Radiotherapy	7/72-9/76	100,100
NSF APR71-01925	Application of the Theory of Track Effects to Radiotherapy	4/76-9/78	75,000
AEC AT(112-1)-1671	Theory of RBE		
DOE EY-76-S-022-1671	Theory of RBE		
DOE FG-02-88ER60634	Theory of RBE		
		1967	20,000
		1968	22,000
		1969	22,000
		1970	22,000
		1971	25,000
		1972	25,000
		1973	25,000
		1974	25,000
		1975	50,000
		1976	52,500
		1977	52,500
		1978	62,500
		1979	62,500
		1980	62,000
		1981	67,000
		1982	70,000
		1983	60,000
		1984	66,000
		1985	60,000
		1986	60,000
		1987	54,000
		1988	54,000
		1989	47,000
		1990	49,300
		1991	48,000
		1992	48,000
		1993	48,000
		1994	45,000
		1995	42,000
	no cost extensions from	1996	
IAEA 1629/RB	Special Photographic Emulsions for High LET Dosimetry	6/75-6/78	12,000
U.S.-Israel Binational Science Foundation	RBE vs. LET in TLD's Y. Horowitz and R. Katz	5/78-5/81	
IAEA 1542/RB	Adaptation d'un dosimetre a radicaux libres a l'intercomparaison des etallonnages en neutrons rapides. F. Bermann (R.Katz, consultant)		
Max Kade Foundation	Post Doctoral Research Exchange Grant Dr. Werner Hofmann	81/82	26,080
IAEA	Training Grant Dr. M. P. R. Waligorski	85/87	16,000
NASA Grant NAG-1-1447	Theoretical evaluation of the radiation hazards from cosmic rays within space vehicles.	8/92-12/96	70,000

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