January 1999

TRACKS TO THERAPY

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PERGAMON

Radiation Measurements

Radiation Measurements 31 (1999) 379–388

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ABSTRACT

Studies of the structure of particle tracks have led to models of track effects based on radial dose and radiobiological target theory that have been very successful in describing and predicting track effects in physical, chemical, and biological systems. For describing mammalian cellular inactivation two inactivation modes are required, called gamma-kill and ion-kill, the first due to synergistic effects of delta rays from adjacent ion paths thus resembling the effects from gamma rays, and the second to the effects of single ion transits through a cell nucleus. The ion-kill effect is more severe, where the fraction of cells experiencing ion kill is responsible for a decrease in the oxygen enhancement ratio, and an increase in relative biological effectiveness, but these are accompanied by loss of repair, hence to a reduction in the efficiency of fractionation in high LET therapy, as shown by our calculations for radiobiological effects in the "spread out Bragg Peak".

KEYWORDS

Tracks; radiobiology; dosimetry; fractionation; radiation therapy.

INTRODUCTION

In 1965 the radial dose model of track structure was created by Katz and Butts to describe the width of heavy ion tracks in emulsion, basing the "track width" on the radial distance at which a characteristic dose from delta rays was experienced. This was the first generally applicable model of track structure. It was preceded by models, by Lonchamp (1953) and by Bizzeti and DellaCorte (1959), which used electron flux and energy flux to describe the track ends, but which did not properly describe the long tracks of energetic cosmic ray particles. Our use of dose as the track width criterion remedied this defect.

A subsequent model of etchable track formation in dielectrics was based on an estimate of the dose for molecular damage and a hypothesis about a channel diameter for penetration of the etching solution and the drainage of its chemical products (Katz and Kobetich, 1968). This proved to be a useful criterion, again based on radial dose, with a revised calculation of electron energy deposition which was also used to recalculate track width (Kobetich and Katz, 1968).

A FIRST APPLICATION TO RADIOBIOLOGY

Shortly after our identification of radial dose as a suitable model for track width, alterations in concept were made to interpret cross sections for the inactivation of dry enzymes and viruses measured by use of beams of heavy ions from HILAC accelerators at Berkeley and Yale (Butts and Katz, 1967). When survival was plotted semilogarithmically against particle fluence, the slope was interpreted as the geometric cross section of these molecules, as if inactivation were caused by the transit of the "core" of a heavy ion track through the molecule, as if a hypothetical "track core" was responsible for the damage. This was taken to be a triumph for radiobiology, for the size of these molecules was not known at that time. Later, when such measurements became available it was

shown that the action cross section was orders of magnitude greater than the geometric cross section (Dertinger and Jung, 1970). In the meantime we had created a new model based on radial dose.

We assumed that the damage was entirely due to delta rays, and that the measured response to secondary electrons from gamma rays must be comparable to the damage from the dose of delta rays about the ion's path. By mapping a fitted gamma ray response into the region about the ion's path we were able to describe the radial distribution of inactivation probability. The radial integral of this probability is the cross-section, in good agreement with measured values. Here, for the first time, a connection was established between the response of a detector to gamma rays and its response to heavy ions. Many times measurements made with heavy ions were not accompanied by measurements made with gamma rays, for the connection between the two modalities was not realized.

THE RADIAL DOSE

Our radial dose calculations were based on "effective charge", on an expression for the delta ray spectrum based on the Rutherford scattering formula, and limited experimental data for electron range-energy relations appropriate to the energy of delta rays from ions having an energy less than 10 MeV/amu as for the HILAC accelerator. Range was taken to be proportional to energy. Electrons were assumed to be ejected normally. Angular distribution and scattering were neglected. The radial dose was then found to be proportional to $z^2/\beta^2 t^2$, where z is the effective charge, βc is the ion's speed, and t is the radial distance, subject to an important kinematic restriction arising from the collision between the bombarding ion and the target electron (assumed to be free and at rest), in that the greatest electron speed is twice that of the bombarding ion. Thus z^2/β^2 became a new characteristic parameter for plotting effects, more valid than LET, though even this parameter failed for ions of low speed where the kinematic constraint on delta ray energies was dominant. Indeed this constraint was responsible for "thindown" in the tracks of heavy ions in nuclear emulsions as the ion approached the end of its range, and for "hooks" at high LET when cross section was plotted as a function of LET (Linear Energy Transfer or stopping power). No such hooks were observed with HILAC or BEVALAC bombardment of enzymes, viruses, or cells, though they made an appearance in plots of scintillation efficiency (Newman and Steigert, 1960) (proportional to cross section) versus LET. Later when the UNILAC accelerator was operational at Darmstadt, these predicted hooks (there identified as Darmstadt Hooks) were found in plots of cross section vs LET in experiments with spores, bacteria, and mammalian cells (Katz *et al.*, 1996). Our program included a continual update of radial dose calculations (Waligorski *et al.*,1986) with corresponding improvement in the calculation of the cross sections for enzymes and viruses (Waligorski *et al.*,1987). Further calculations of the radial dose were based on improved data for electron interactions with matter (Cucinotta *et al.*, 1996). This was further extended to yield the radial distribution of electron spectra from high energy ions (Cucinotta *et al.*, 1997).

At the time of these experiments the prevailing concept for the effects of heavy ions on these molecules was due to Lea (1955), who took the cross section to be geometric, enhanced by a small effect from delta rays, in his "associated volume" model. This was clearly wrong. On the contrary our calculation was based on these molecules as "point targets" and attributed the entire cross section to delta rays. At that time delta rays were held to be of little significance for radiobiology, and any suggestion that they might be of some importance was greeted with vigorous criticism (J.F.Fowler, pvt.comm.). The success of our model also pointed out that a favored criterion for track damage, LET, was wholly inappropriate. Regrettably, though wrong, the LET criterion for damage, though continuously disparaged, has remained favored to this day.

TRACK FORMATION CRITERIA

Our criterion for etchable track formation initially also met with considerable resistance, in the face of a variety of other criteria then proposed (Fleischer *et al.*, 1975), criteria based on LET, on an "ion explosion spike", a "thermal spike", primary ionization, and others. In time, however, it became clear that damage from delta rays was the most consistent criterion for etchable track formation and that

z^2/β^2 was a more appropriate plotting parameter than LET. The radial dose model proved to be preferable for these and many other physical, chemical, and biological systems which have been studied with heavy ion beams although the various "spike" models are regularly resurrected as new phenomena emerge.

Our revised model of track structure, incorporating biological target theory, quickly found application. It yielded the definitive model of the structure of particle tracks in emulsion (Katz and Kobetich, 1969), in which the probability for the creation of a latent image in an emulsion grain was again based on dose, in relation to the number of hits in a grain to create a scored event. We took the dose at which there was an average of 1 hit per target to be a "characteristic dose".

Then the average number of hits per target was measured by the ratio of the average dose in an emulsion grain to the characteristic dose. What had been called "electron sensitive emulsions" were then recast as 1-hit detectors, with a high sensitivity to gamma rays. Such properties as track width, and grain count used in the identification of cosmic rays (Powell *et al.*, 1959) were then readily calculated, and their variations attributed to differences in the characteristic dose arising from emulsion manufacture and development. The emulsion model was used at Lund, Bristol and elsewhere in cosmic ray researches. It provided the foundation for the studies of other track effects in other materials, for the ability to see a track proved to be a distinct conceptual advantage which made it possible to avoid pitfalls which beset radiobiology and other track studies.

For this model we required three parameters of the detector: the characteristic dose, the grain size, and the number of hits needed to activate a grain, though size could be ignored for sufficiently small targets.
We found that variations in manufacture and processing created a range of values of the characteristic dose, and of the "hittedness". With the theoretical model it was possible to simulate tracks in a range of emulsions with a computer, by calculating the probability for latent image creation by the passage of a heavy ion as a function of ion charge and speed, and radial distance from an ion's path.

Many other detectors yielded to the same calculations. Among these were such physical and chemical detectors as scintillators, TLD's, dye films, color centers, lyoluminescent dosimeters, the Fricke dosimeter (Katz *et al.*, 1986) in which a solution of ferrous ions were converted to ferric ions, yielding a color change in the solution. In all cases the calculation of cross section was central, for this could be converted to yield, to scintillation efficiency, and so on. Thus if σ is the cross section, N is the number density of targets and L the stopping power, σN is the number of activated targets per unit path length, and $\sigma N/L$ is the number per unit energy deposition, related to the G value and the scintillation efficiency. These considerations suggested a new hypothesis (Katz, 1984) for the production of tracks in solid state detectors, and for etching rate, based on the linear density of activated "targets", as yet not susceptible to calculation, though it appears that CR-39 is a 1-hit detector. Our analysis of the response of resists (Katz, 1983) to electron, hydrogen, helium and oxygen irradiation have shown that novolac is a 2 hit detector, and polystyrene is a 6 hit detector with cross sections of 3 and 8×10^{-13} cm^2, and with correspondingly large values of the critical dose.

Where target size was not obvious, it could be inferred from the variation of response with concentration of ferrous ions in the Fricke dosimeter and of thallous ions in NaI(Tl) (Katz and Kobetich, 1960) scintillators. Most behaved as 1-hit detectors. We have found desensitized emulsions (Katz and Pinkerton, 1975) having 2-hit characteristics. Other emulsions had up to 6-hit (Katz *et al.*, 1980) response produced by combining of desensitization in manufacture and discriminating development. Some TLD's exhibit quadratic response to dose, called supralinearity. Two chemical systems were found to be 2-hit detectors (Katz *et al.*, 1989), simply from their response to different heavy ions. These were HO_2 radical production in water and H_2 production in benzene, originally labeled as "track core" effects, and, as seen above, we have noted 2 and 6 hit response in resists.

HEAVY ION RADIOBIOLOGY

The availability of heavy ion LINACs yielding particles up to argon at energies up to about 10 MeV/amu, and the subsequent development of the BEVALAC which yielded particles up to uranium at relativistic speeds, as well as the development of the means of culturing mammalian cells in petri dishes stimulated radiobiological investigation into the biological effects of these particles. This process had begun before our interests in particle tracks. It provided the data against which our model of enzyme and virus inactivation could be compared. Though proton and neutron beams had already begun to be studied as potential modalities for cancer therapy, the availability of beams of energetic heavy ions of sufficient energy to penetrate the human body stimulated the investigation of their physical and biological properties. It had been discovered that cells within a cancer were hypoxic, and as a result were resistant to inactivation by gamma rays. A strong stimulus arose from neutron therapy, where it was found that neutrons could more readily inactivate these hypoxic cancer cells through the heavy ions liberated in nuclear collisions. This suggested a role for heavy ion beams in cancer therapy.

Many investigators joined in the measurement of cellular inactivation by heavy ion beams using bacteria, bacterial spores, yeast cells, a variety of mammalian cells from animal and human tissues, under oxic and hypoxic conditions. Measurements were made of chromosome aberrations, of DNA single and double strand breaks, of mutation induction. Measurements were made of effects on animal tissues in vivo as well as on cells in vitro. Measurements were made with monoenergetic beams and later with range modulated beams intended for therapy.

These measurements stimulated the production of a number of theoretical models, as well as a variety of empirical relationships. Since DNA had been identified as the central target for mutation and possibly for cell killing, Monte Carlo calculations of track structure were produced to attempt to identify the detailed impact of track structure on biological response. Similar efforts were made in experimental and theoretical micro- and nano-dosimetry, with limited success. These efforts were not able to calculate action cross sections, nor did they predict cell killing, though they were able to calculate DNA strand breaks and deletions (Cucinotta *et al.*, 1997).

These radiobiological measurements generated a challenge, for their results were difficult to interpret. In particular the survival curves, plotted semilogarithmically as the fraction of surviving cells Vs dose, were curvilinear at low LET and gradually changing their shape to exponential at high LET. The curves found at lower LET could be approximated by straight lines having different slopes at low dose and at high dose. This stimulated another inappropriate construct (because a cross section is only related to exponential survival curves, by definition), interpreted incorrectly as an initial slope cross section and a final slope cross section, and with the so-called (final slope) cross section plotted against LET. This plot also had a curious shape. The challenge was to produce a model which fitted these data and from which predictions could be made. This mission was accomplished by a revision of our model used for the structurally simpler detectors whose response to heavy ions we had studied earlier.

A MODEL FOR CELLULAR INACTIVATION

To explain these results we introduced two new concepts, called ion-kill and gamma-kill. We proposed that single heavy ions at low fluence could inactivate the cells whose nuclei they intersected, probabilistically, with exponential response to fluence, in the process called ion-kill, as with particle tracks in emulsion in the grain count regime. But since cells could store sub-lethal damage, cells not inactivated in single particle transits might be partially damaged though not killed. At high fluence delta rays from adjacent ions could intersect in cell nuclei and collaborate in killing of cells not first inactivated in the ion-kill mode. This process was called gamma-kill, since it resembled inactivation by gamma rays. We might also, as in emulsions, spores and bacteria, have a grain count regime and a track width regime. In the latter case we would expect to observe "thin down" exhibited as hooks in plots of cross section vs LET. Since cells could be expected to have two separate characteristic sizes, that of the nucleus and of an unidentified intra nuclear target, we expected that at least 4 parameters would be required instead of the 3 parameters required for simpler systems.

Collected Formulas of the Track Theory of Cellular Survival

Track Segment Bombardment ----------

Probability for ion-kill $P = [1 - \exp(-z^2/\kappa\beta^2)]^m$ 1

Effective charge $z = Z[1 - \exp(-125\beta Z^{-2/3})]$ 2

Gamma-kill dose $D_\gamma = (1 - P)D$ 3

Heavy ion dose $D = FL$ 4

Surviving fraction $N/N_o = \Pi_i \times \Pi_\gamma$ 5

Survival probability in the gamma-kill mode

$$\Pi_\gamma = 1 - [1 - \exp(-D_\gamma/E_o)]^m \quad 6$$

Survival probability in the ion-kill mode

$$\Pi_i = \exp(-\sigma F) \quad 7$$

Ion-kill cross section $\sigma = \sigma_o P$ 8

particle fluence F, relative speed β, LET L, atomic number Z

Cell parameters: E_o, m, κ, σ_o

Mixed Radiation Field ----------

Total dose $D = D + d$ 9

Heavy ion dose $D = \sum_j \sum_k F_{jk} L_{jk}$ 10

Dose of gamma-rays, muons, energetic electrons d

Gamma-kill dose $D_\gamma = \sum_j \sum_k F_{jk} L_{jk} (1 - P_{jk}) + d$ 11

Survival probability in the gamma-kill mode. Equations 11 and 6.

Survival probability in the ion-kill mode

$$\Pi_i = \exp[-\sum_j \sum_k \sigma_{jk} F_{jk})] \quad 12$$

j,k designations for particles of type j moving at speed β_k.

We require knowledge of the particle-energy spectrum at each point in the radiation field. Single parameter reductions of a radiation field cannot predict cell survival curves.

Fig. 1. Collected formulas of the track theory of cellular survival.

The model that was constructed represented that cells surviving ion-kill, represented by a cross section and a particle fluence, were the initial population of cells for the gamma kill process, to be calculated as if these cells were irradiated by gamma rays. As an approximation, the fraction of cells surviving the ion kill mode was also taken to represent the fraction of dose available to the gamma kill mode. This led to a set of equations describing track segment irradiation (Katz *et al.*, 1971). And a simple extension (Katz and Sharma, 1973) in which all cells surviving the ion kill mode in a mixed

radiation field was taken to represent the initial population for the gamma-kill mode. And the sum of the gamma-kill doses in each track segment was taken to be the total gamma-kill dose. Thus it was possible to predict survival from neutron iradiations, and cell survival in the spread out Bragg peak, in agreement with experimental findings. The equations of the model are shown in Fig. 1. A typical set of fitted survival curves after a series of heavy ion bombardments is shown in Fig. 2. The data are for the survival of aerobically irradiated hamster cells after irradiation with x-rays and with different ions, from He to Ar at energies up to about 10 MeV/amu, at the HILAC accelerator. The calculated curves are from 2 sets of parameters, visually fitted (m = 2.5) and fitted by a computer minimizing routine (m = 2.97).

This model has proved to be remarkably successful. It required a set of 4 radiosensitivity parameters, to be extracted by fitting equations of the model to a limited series of survival curves obtained with track segment bombardments, simultaneously, with a single set of parameters required to produce survival curves for all data. Parameters which have now been extracted from about 40 sets of survival data (Katz *et al.*, 1994) is paper references to the original published data are quoted. The model has been extended to include mutations per survivor (Cucinotta *et al.*, 1996) by an ingenious calculation which recognizes that mutations are created at a specific gene, but damage leading to cellular inactivation may take place anywhere within the cell nucleus. Once these parameters were known, the equations of the model could predict the response to arbitrary irradiations provided that the dose and the particle-energy spectra were known at all points in the irradiated field. Thus it was possible to predict results from neutron irradiations, and for survival at different points in the field of a range modulated heavy ion beam, called the spread out Bragg peak. We predicted the response to a mixed field of neutrons and gamma rays (Katz and Sharma, 1974), and so on.

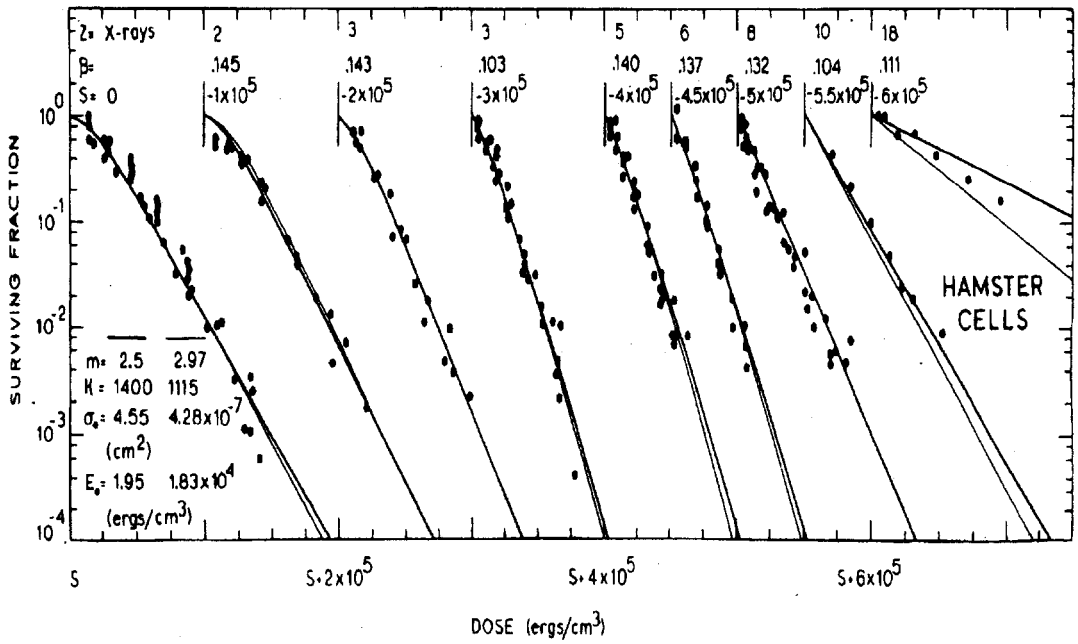

Fig. 2. Survival data for Hamster cells irradiated at the HILAC accelerator with ions from He to Ar at energies up to 10 MeV/amu, and with x-rays. The fitting parameters are from the equations of Fig. 1 and arise from visual fits (m=2.5) and from a computer minimizing program (m=2.97). Reference to the original paper is given in Katz *et al.* (1994).

TREATMENT PLANNING FOR HIGH LET THERAPY

This model of cellular inactivation by high LET radiations has been coupled with a NASA model of beam penetration, which includes nuclear fragments from both projectile and target, for purposes of treatment planning. Now we have noted that ion-kill is a much more severe interaction than gamma-kill, and that it is responsible for the high RBE of heavy ion irradiation, as well as the equal response of oxic and hypoxic cells, and the insensitivity to cell cycle stage. These were thought to be advantages of high LET radiations. These supposed advantages are coupled with lack of cellular repair, as observed in split dose and delayed plating experiments. Thus we must expect that fractionated dose, an essential part of photon therapy, will not have the advantages for high LET irradiation as it has had for photon irradiation. These conclusions are confirmed by clinical experience at Berkeley with neon (Castro, 1995).

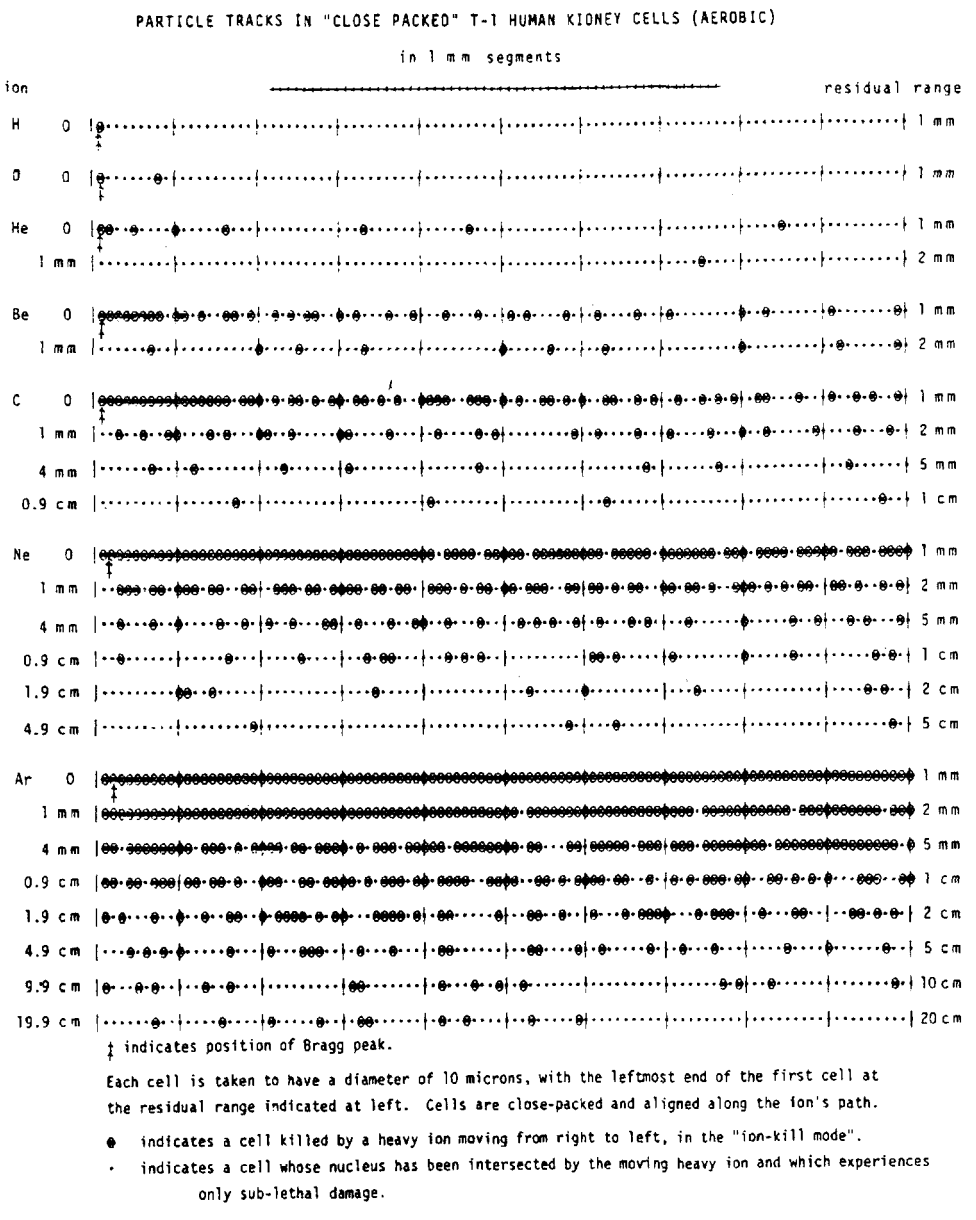

Fig. 3. Calculated particle tracks from a series of ions from H to Ar. The calculations are made by dividing the track length into intervals where the increment in β is 0.01. The probability for ion-kill is then calculated from Fig. 1, eq.1, using parameters for human kidney cells. The distribution of killed cells within the interval is found by application of random numbers.

We first display (Fig. 3) a set of calculated tracks of a variety of heavy ions in an "emulsion" of biological cells, to indicate the distribution of cells inactivated in the ion-kill mode along the ion's path. There we note the few ion-killed cells from protons and helions, but the increasing linear density of such cells near the end of the range for ions of increasing atomic number. The density of such cells is responsible for the increase of RBE (relative biological effectiveness) and the decrease of OER (oxygen enhancement ratio) with LET, but accompanying these desirable effects there is the undesirable effect of lack of repair from radiation damage. These conclusions are derived from calculations of cell survival under oxic and hypoxic conditions dispayed in references quoted in Katz *et al.*, 1994.

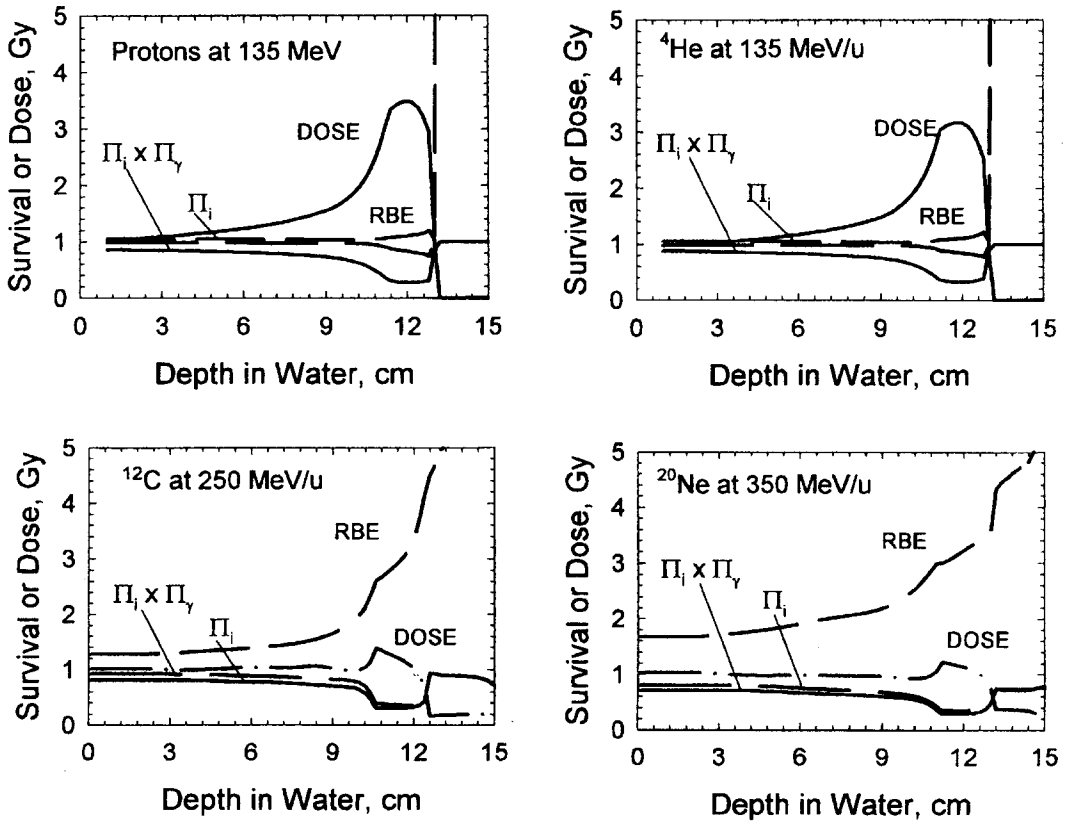

Fig. 4. A hypothetical treatment plan for range modulated ion beams (H, He, C, and Ne) to yield a spread Bragg peak of 2 cm width, with the surviving fraction of cells in the peak being 30%. We show the dose distribution, the RBE, the fraction of cells surviving ion-kill (Π_i) and the fraction of cells surviving the irradiation, as the product $\Pi_i x \Pi_\gamma$. Note the great difference in the effect of ion-kill from proton and neon irradiations and the small difference between carbon and neon, suggesting that problems with fractionated therapy already experienced with neon beams will be repeated with carbon.

We have calculated treatment plans for H, He, C, and Ne for spread out Bragg peaks of 2 cm width, and have displayed cell survival, dose, RBE, and the survival from the ion kill mode, in Fig. 4. These display similar patterns for C and Ne beams. Here Π_i refers to the probability of survival from damage in the ion-kill mode, while $\Pi_i x \Pi_\gamma$ refers to the net survival probability from both ion-kill and γ-kill (see Fig. 1). The high fraction of cells inactivated in the ion-kill mode in the spread Bragg peak there clearly implies that repair will be limited. Instead of repair the killed cells may be replaced by Repopulation, as with scar tissue, leading to fibrosis. We anticipate that fractionation problems will

be encountered with C beams, now contemplated for therapy in Japan and in Germany, similar to problems experienced at Berkeley with neon beams by Castro. We anticipate similar problems with neutron therapy. Note however the small fraction of cells inactivated in the ion-kill mode with H and He beams, implying that fractionated therapy will have fewer problems there.

These results show that treatment planning based on RBE and dose, and the clinical experience of an oncologist honed on photon therapy, will be inadequate for high LET radiations. Even with proton and He beams our calculations show that the search for a proper therapeutic RBE for these modalities will be futile, and that oncologists must incorporate ion kill in their conceptual structure. for even with these relatively low LET ions, effects of nuclear collisions in the production of ion-kill inactivation will generate significant differences that are not reflected in RBE. The RBE for cell killing is not the RBE for all end points.

We anticipate new dosimetric problems. We do not presently have a dosimetric system able to measure the particle-energy spectrum in a beam. LET distribution alone is not enough. Because of the dual nature of the response to these radiations, reducible to an ion-kill probability and a gamma-kill dose, it may be possible to produce a dosimetric system which measures these quantities. For the ion-kill probability one possibility is to make use of 2 hit or many hit detectors. It is possible that a selection of nuclear emulsions or track etch detectors of different sensitivities and hittedness may display regions of increased ion kill probability.

The interests of many others which has led to the construction of heavy ion accelerators, and their application in measurement of the properties of dosimeters and biological cells, has led this activity from tracks to therapy. Our latest insight into problems of repair and fractionation, in treatment planning for fractionated therapy should prove of assistance to the oncologists who are responsible for cancer therapy. We need assistance from oncologists, radiobiologists and radiation physicists, for it will be their insights, not ours, which may extract radiosensitivity parameters from clinical experience with tissues at risk.

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