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Radiobiological Modeling Based On Track Structure

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ABSTRACT

Since the interaction of beams of charged particles with targets in physics is customarily based on beam fluence and interaction cross section we have chosen the same logical structure for our radiobiological model.

Proceeding from simple to complex systems we have first constructed and verified a track structure model of observable tracks in nuclear emulsions, then of dry enzymes and viruses, of scintillation counters, of TLD's, of the Fricke dosimeter as prerequisite to the construction of a valid radiobiological model.

For this model we require 1) knowledge of the average radial distribution of local dose about the path of an ion, 2) the size of the target volume, and 3) the response of the detector to gamma rays, measured as a function of dose. Requirements 2 and 3 determine detector parameters: the radius of the target volume a_0 , the characteristic dose E_0 at which there is an average of 1 hit per target and C , the hittedness in the sense of the cumulative Poisson distribution, used to approximate the dose-response function after gamma irradiation.

Physical detectors are usually 1 hit, though many hit response has been observed for TLD's, for photoresists and etchable track detectors, and for desensitized nuclear emulsions.

Our requirements are in principle experimentally determinable. Thus, for the Fricke dosimeter E_0 is determinable from the yield as a function of dose while a_0 is from yield as a function of Fe^{++} concentration. Here size is replaced by an effective diffusion length. Hittedness is determinable by comparison of the shape of the dose response curve after gamma irradiation with that of the cumulative Poisson distribution, where the shape can be measured.

Note that this track model is not mechanistic but is rather statistical and parametric. Given the required information we can

translate the gamma ray response to the radial distribution of the probability of target activation about the path of an ion. With use of pseudo-random numbers we can simulate a particle track. Or by radially integrating the probability we can calculate an action cross section. When dealing with a beam of charged particles, or the secondary particles from neutrons, we assume that the Poisson distribution adequately takes care of overlap.

Following the appearance of particle tracks in emulsion we separate tracks into the grain count regime, where tracks appear like beads on a string and the track width regime, where tracks appear like a hairy rope. We must also separate detectors into those which cannot accumulate sub lethal damage and those which can. The former are typically 1-hit, the latter many-hit detectors.

Special consideration must be given to many hit detectors to account for the change in the form of the response of the detector with an increase in the LET of a beam of incident radiation, encompassed in the model as a change from "gamma-kill", where the intersecting secondary electrons from gamma ray photons, or the intersecting delta rays from several ions collaborate to activate a target, typically at low LET, to "ion-kill", where a single passing ion itself generates a sufficiency of delta rays to accomplish the activation, typically at high LET. At intermediate values of the LET the fluctuation in energy deposition allows some of the intersected targets to be activated in the ion kill mode while others are only sublethally damaged by a single ion, so as to be ultimately inactivated by other ions in a beam in the gamma kill mode. For many hit detectors we take the functional form of the response to be a product of one hit to describe the ion kill contribution and many hit target to describe the gamma kill contribution.

Additional complications are imposed by the architecture of biological cells. We do not yet know the identity of the sensitive targets or their properties and so must construct a model which does not require this detailed knowledge. This we have done by assuming that there is a collection of 1-hit targets within the nucleus of the cell, some number m of which must be hit in order to achieve the observed end point. There are thus two relevant sizes, that of the target and that of the volume in which the targets are contained. We therefore require a fourth parameter representing the latter size. We attribute the response to gamma rays to a pair of these parameters, E_0 and m , and use the form of multi-target statistics to describe the response

to gamma rays. The additional parameters, σ_0 , which describes the size of the container and κ which represents target size, are needed to describe the details of the transition of the statistics of response from the multi-target statistics of gamma-kill at low LET to the 1-hit statistics of ion-kill at high LET. These four parameters appear to represent all the (non temporal) information that can be deduced from radiobiological experiments with gamma rays and beams of heavy ions or neutrons, for together with an accompanying set of equations, they appear to be able to reproduce (and even predict) experimental data for cellular survival (and possibly chromosome aberration and transformation) in complex radiation fields once the radiosensitivity parameters for the specific end points are measured.

Although the present model incorporates no mechanism its ability to represent detector and radiobiological data suggests that mechanistic models should have as their goal the derivation of the numerical values of our radiosensitivity parameters, for once these are known the response to most radiations, whatever their quality, can be calculated. This model does not presently accomodate repair, but repair models do not yet accomodate RBE.

INTRODUCTION

The key to track theory is the interplay between the study of heavy ion tracks in emulsion and the inactivation of dry enzymes and viruses by energetic heavy ions and the extension of ideas developed here to the inactivation of biological cells.

I became interested in the study of tracks in emulsion in 1956, through pedagogy, as a possible means of detecting the free magnetic pole in the cosmic rays, for the free magnetic pole seemed to me to be a most suitable device for the teaching of electricity and magnetism (1). Tracks of heavy ions in emulsion looked like a hairy rope. One way to characterize them, and perhaps to distinguish between the track of an ion and a pole, was through their width as a function of range. As a criterion for track width we chose to use the concept of a critical dose, above which the track would be opaque. We thus had to calculate the radial distribution of dose about an ion's path. The scheme worked rather well (2). Our calculated average track width was in reasonable agreement with our measured average track width. Though the pole has still not been found searches continue, some of which are based on criteria which are an extension of our track model, for the pole remains a concept of theoretical interest.

This success of our first model of track width in emulsion stimulated the further notion that the same ideas might lead to a better understanding of the rather puzzling concept of "Quality Factor".

We found biological data to which our track concept might be applied in the study of the inactivation of dry enzymes and viruses (3). Here we learned about biological target theory, the notion of hittedness, and the use of the multi target and multi hit models to describe survival curves after gamma irradiation. We could see no basic difference between irradiation with the secondary electrons from gamma rays and irradiation with delta rays, except possibly for their energy spectra and the irradiation time. We assumed that these differences could be neglected. Based on the emulsion work we made a very simple model for the radial distribution of dose based on the simplest model for the delta ray spectrum from the interaction of a passing ion with a cloud of free electrons, and a range energy relationship for electrons. We assumed that the enzymes and viruses could be taken to be point particles having the exponential response to dose of 1-hit detectors. One parameter was needed to describe that response, the D-37 dose. Using this the radial distribution of dose could be transformed to a radial distribution in the probability for inactivating a molecule, that is, the track structure. Radial integration of the radial distribution in probability yielded the action cross section (4).

This innovative work had many consequences. It revealed the basic importance of delta rays in radiobiology. The measured cross sections were a consequence of the response to gamma rays and the delta ray distribution rather than the cross sectional area of the molecule. Here is the underlying conceptual difference between the present model and the associated volume model which preceded it (5). The associated volume model focussed attention on the physical size of the molecule as the source of the action cross section, though somewhat enhanced by the effect of delta rays. We could treat the molecule as a point, in first approximation, and describe the variation of cross section with LET entirely through the effect of delta rays. For most of the available data almost all of the molecules in the immediate neighborhood of the ion's path were inactivated, and so size was obscured. Molecular size could not be directly observed by examining the inactivation cross section for heavy ions. Our perspective proved to be inverted from that of Lea and of Hutchinson, for we saw the cross section as principally due to delta rays with a small

correction for molecular size. We found that size was more easily interpreted from irradiations with light ions like protons and helions than with heavy ions like carbon or oxygen for with light ions we were free from the obscuring effects of overkill.

Our model showed why LET was not a particularly good plotting parameter, and that it might be replaced by an imperfect but better one, z^2/β^2 . It unified our view of low and high LET response. It was the first quantitative theory of RBE. Knowledge of the response to gamma rays alone was sufficient to predict the RBE. The RBE was not a function of the radiation alone but a combined response of radiation and detector. For pedagogic purposes this work is well presented by H. Dertinger and H. Jung in their book, "Molecular Radiation Biology" (Springer-Verlag 1970).

One immediate consequence of the enzyme and virus work was the revision of our model of particle tracks in emulsion, based on the premise that the emulsion could be now thought of as a 1-hit detector. Here the grain size was directly measurable, and it was necessary only to find a fitted value of E_0 , to modify the radial distribution of dose as appropriate to emulsion, and to average the local dose over the volume of an emulsion grain. We could now calculate the probability for making a grain developable, and could account for tracks of low LET particles in the grain count regime, as well as of high LET particles in the track width regime (6). Our assumption of 1-hit response was later directly verified by calculation of the blackness of emulsions exposed to electron beams (7). Subsequently our model was used at Lund university to help identify the tracks of heavy primary cosmic rays by microphotometric measurements of track width (8). These measurements being complicated by optical problems found in the measurement of thick tracks, an empirical adjustment to the theory was required. The width of thin tracks, with fewer optical problems in their measurement, were predicted with pleasing accuracy (9).

The concepts developed in our model of the inactivation of dry enzymes and viruses have served us well in all our track models (10). In all cases we require knowledge of the radial distribution of dose. We make use of the concepts of target theory, and utilize the multi target or the multi hit models to approximate the response of the targets of a detector to gamma rays. We now average the dose in the volume of a detector target to find the radial distribution of the average energy deposition per unit volume (the local dose) in detector targets as a function of their radial distance from the ion's path. We

transform the radial distribution of local dose to a radial distribution of probability for target activation. This can be used directly, in conjunction with a set of random numbers, to produce a simulated picture of a track (11) (in which we neglect the connection between activated targets as lying along the paths of delta rays). It can be integrated to yield an action cross section. We require here 3 detector parameters: the hittedness C (or the target number m), the target radius a_0 , and the dose of gamma rays at which there is an average of 1 hit per target E_0 . Our track model is statistical and parametric rather than mechanistic. This is the basis of its generality.

Some of these features which carry over to radiobiology are best illustrated through particle tracks in emulsion. Photographic emulsions are made up of silver halide crystals dispersed in a gelatin matrix (12). A typical emulsion grain requires a number of optical photons for its activation, but a single x-ray photon, or a single energetic electron suffices to make a latent image. Such an emulsion has exponential response to x-rays or electron beams but many hit response to visible light. Less sensitive emulsions display no electron tracks, sometimes not even the tracks of fission fragments, while blackening after long exposure to x-rays; that is, they have many hit response to electrons or to x-ray photons. An emulsion which does not respond to single electrons, but which does reveal the track of a heavy ion responds analogously to biological cells. If one plotted the surviving fraction of photographic grains, that is, those which were not developed, against absorbed dose, such a survival curve would have zero initial slope after irradiation with electron beams.

One hit emulsions can have a range of sensitivities, that is, a range of different values of E_0 , depending on grain size, and on the degree of sensitization. For the most sensitive of these emulsions the track of a slow proton may verge on the track width regime, while a fast proton exhibits a track in the grain count regime. The tracks of heavier particles may be entirely in the track width regime, at all speeds. At high speeds the track is relatively narrow, becoming wider as the ion slows down, until toward the end of the range the track appears like a sharpened pencil, displaying a feature known as thin-down which has also made its appearance in radiobiology (13). We show a picture of the track of a fast iron nucleus in electron sensitive Ilford G.5 emulsion in Fig. 1.

All of these features arise jointly from the intensity and energy spectrum of delta rays and can be altered by sensitization or

Fig. 1. Track of an iron nucleus in Ilford G.5 emulsion. The ion enters at bottom right and stops at top left. The Bragg peak is at about 30 microns from the stopping end, and is unrelated to thindown. Courtesy P. H. Fowler.

desensitization of the emulsion so that emulsions having identical grain size and development but different sensitivities can produce tracks of the same particle which exhibit widely different appearances, as shown in Fig. 2 (14), showing that knowledge of the energy deposition in small volumes is hopelessly inadequate as a means of characterizing detector response in emulsion. These tracks also illustrate the fact that the properties of a detector and those of the radiation are not separable variables. The track at bottom cannot be obtained from the track at top by a multiplicative sensitivity ratio, as implied by the concept of a Quality Factor.

If a model which treats energy deposition and detector response as separable variables is to be used in biology it must be shown that the range of responses of biological systems is sufficiently narrow as to justify this neglect.

The physical construction of an emulsion as a collection of crystals separated by gelatin leads to interesting properties. Thus, for example, x-ray photons between about 100 and 10,000eV will inactivate a photographic grain, but their secondary electrons lack energy to penetrate a second grain (15). This leads to a curious variation of

Fig. 2. Tracks of Ar ions in differently sensitized Ilford K series emulsions, most sensitive at top and least sensitive at bottom. Note that silver production increases regularly as the stopping end of the track is approached, at left, for the least sensitive emulsion at bottom while it decreases from a maximum for the most sensitive emulsion, at top. At the same distance from the stopping end the stopping power, particle energy, speed, and average energy deposition in a grain are the same for all tracks. The grain size is the same in all emulsions. All were exposed at the same time and developed in the same bath. Yet there are enormous differences in track structure which cannot be simply scaled.

relative response with dose. If 10 keV x-rays were taken as the reference radiation the relative photographic effectiveness of 100 eV photons would be 100. One wonders whether there is here an analogy for the action of soft x-rays on biological cells.

The description of single particle tracks in detectors that consist of collections of simple targets is simplicity itself, though there are a number of neglects that must be discussed further. Complications arise when we speak of the irradiation of many hit detectors with beams of particles, and when the architecture of the detector is complex and poorly known, as in the case of biological cells. For radiobiology a single additional parameter representing the size of the region containing the targets has made it possible to parameterize cellular inactivation, and some cases of chromosome aberration and cell transformation after heavy ion bombardment. Again, the success of our model is based on the fact that its construction is

statistical and parametric rather than mechanistic. But this implies that the changes in the shape of survival curves with changes in LET arise from statistical rather than mechanistic considerations. The conceptual complications associated with LET, with RBE and Quality Factor, arise from the focus on dose as the datum to which biological effect is referred. This has given rise to an extraordinary amount of attention to the fluctuation of energy deposition in micrometer or nanometer sized volumes of different shapes and separation, to special low and high LET targets having different cross sections, responding linearly or quadratically or otherwise to incident particles of different LET, or having different energy deposition thresholds. If instead of measuring dose we could measure the electron fluence at the nucleus of a cell I think we would find that the RBE is 1 for reasonably comparable electron energy spectra.

Just as our model ignores mechanism, so also it evades any need for explicit knowledge of the fluctuation in energy deposition. In the target theory model it is the fluctuation in energy deposition which is responsible for the exponential response of a 1 hit detector to gamma irradiation. We take it that the response to gamma rays incorporates both fluctuation and the properties of the detector, the latter being reflected in the hittness and the characteristic dose E_0 . We have no further need for the specification of fluctuation of gamma ray dose, or of the fluctuation of the radial dose about the path of a heavy ion (16) for we compare the effects produced by an average local dose of delta rays to those produced by an equal (average) dose of gamma rays. By local dose we mean the average energy deposition per unit volume (or per unit mass) in cylindrical shells coaxial with the ion's path, averaged over many ions. Even where the delta rays are sparse, as at large distances from the ions path, this average is a valid quantity, for its effect is compared to that produced by low doses of gamma rays where secondary electrons are also sparse. We compare our average calculation to average measurements. Just as in the case of Monte Carlo calculations, we can convert our average radial distribution in effect to a graphic picture representing an individual track replete with fluctuations. Similarly we have no need for the fluctuation in energy depositions from heavy ion beams or neutrons, for we assume that the Poisson distribution adequately describes these fluctuations. Our assumption seems adequate for our calculations of cellular survival after neutron and pion irradiations agree with experimental observations (17). So also does our model for radiobiology in heavy ion beams (18). We must keep it in mind that

there are some effects for which we need averages and others for which we need to focus on fluctuations. The exposure of a photographic film is based on the average light intensity. Its graininess depends on the fluctuation in photon fluence across the face of the film (19). Graininess is a second order effect. Radiobiological data are rarely if ever sufficiently precise to reveal second order effects. In consequence we rarely need to make explicit use of the fluctuations in energy deposition.

RADIAL DISTRIBUTION OF DOSE

The principal contributions of atomic physics to track structure are related to the radial distribution of dose. For Monte Carlo calculations one needs collision cross sections (or mean free paths) for electron and ion collisions with atoms and molecules, differential in energy and angle. At most the information is available for a few gases, and over a very limited range of bombarding ions, and ion energies. There are few direct measurements of the radial dose distribution, all of which are in gases. We have made calculations in a number of different ways. We require a source function giving the energy spectrum of delta rays. Typically this is an approximation differential in energy, based on the Rutherford formula for the collision of an ion with a free (or bound) electron. Various approximations are made for the angular distribution. Most commonly this is approximated as normal ejection (Butts and Katz, 1967), though other angular distributions have been assumed (20). The energy deposition by delta rays have been based on range energy measurements in aluminum and other substances, and on electron energy dissipation measurements (21). One finds that these calculations yield similar results over the central portion of the radial distance interval, namely that the dose varies inversely with the square of the radial distance from the ion's path. Large differences exist close to and far from the ion's path. None of our earlier calculations represented the contribution of primary excitations and ionizations. Others, expanding on this work, frequently represented the primary contribution as contained within a fictitious track core, taken to have a diameter given by the Bohr adiabatic radius or by the radius of the target.

Our most recent effort (22) has been based on a Monte Carlo calculation of the radial distribution of excitations and ionizations from the primary ion and delta rays in liquid water, from protons of energy between 1 and 100 MeV. The histograms resulting from averaged repeated calculations have been approximated analytically by a semi

empirical algorithm developed as in our earlier calculations from range energy relations for electrons in aluminum, the Rutherford formula for electrons bound with an arbitrary energy of 10 eV, and an assumption of normal ejection. The formula was corrected by a β dependent multiplicative factor adjusted to fit the Monte Carlo calculation. We show our rather complex algorithm in Appendix A. With this algorithm we have made new calculations of the response of the Fricke dosimeter to heavy ions (23) and of the inactivation of dry enzymes and viruses (24) with improved results. Indeed we believe the agreement between theory and experiment for dry enzymes and viruses to be the best agreement between theory and experiment for any radiation detector.

We show a comparison of measured and calculated cross sections for enzymes in Fig. 3,

Fig.3. Measured and Calculated cross sections for enzyme inactivation.

and of the radial distribution of inactivated virus molecules about the path of a heavy ion in Fig. 4.

RADIOBIOLOGY

Our radiobiological model rests on a foundation of biological target theory.

Fig.4. Computer simulation of the radial distribution of inactivated virus molecules about the paths of several ions. The simulated section is 1 molecule in thickness.

We take it that there are biological systems which respond to single hits, and that these display exponential response to gamma rays, and to all other ionizing radiations. These are typified by dry enzymes and viruses which are well described by our track model. For such detectors the RBE for heavy ions is always less than 1 because of overkill in the high dose, central region of the track. Much of this data is in the track width regime, so that the size of the target plays only a minor role in response, as does the primary ionization and excitation from the passing ion. One hit detectors cannot display dose rate effects. One hit detectors always have an RBE less than 1. One hit detectors have an exponential response to gamma rays.

Radiobiological terminology with its reference to dose is sometimes misleading. If we ask whether a mammalian cell is more radiosensitive than a virus molecule the answer is universally yes. Yet a single passing electron can inactivate a virus while it takes hundreds of electrons through the nucleus of a cell to inactivate it. A cell is a many hit (or preferably many target) detector to x-rays or energetic electrons. It is this which determines the character of its response to x-rays and the difference in the character of its response to energetic heavy ions. The character of the damage by low and high

LET radiations is sufficiently different that we should look into the character of particle tracks in radiobiology (25) as we consider the concept of dose and dose equivalent (26). The distribution of sublethal damage from x rays and from heavy ion beams at "equivalent doses" based on a single end point such as cell killing is not at all equivalent.

To create a mathematical model of cell survival (later to be applied to cell transformation, and chromosome aberrations) we imagine that the sensitive targets in a cell are distributed through the nucleus, like beans in a bean bag, and that some number m of these must be activated for reproductive death to occur. The beans are taken to have radius a_0 , and are contained in an enclosure within the cell nucleus, of cross sectional area is σ_0 , the latter being the plateau value of the inactivation cross section of a cell often achieved with bombardment with Ne ions at about 10 MeV/amu. In mammalian cells the beans may possibly be chromosomes, as suggested the near equality of our parameters for survival and freedom from chromosome aberrations in Chinese Hamster cells. See Fig. 7.

Since we do not know the architecture of the cell nucleus we attempt to eliminate its details from consideration. We calculate action cross sections after irradiation with a range of ions and ion speeds for a large number of targets, varying their radii a_0 , their characteristic dose E_0 , and their target number m , taking their survival after gamma irradiation to follow the multi target model, and utilizing a calculation of the mean radial dose deposited in a short cylinder of radius a_0 whose axis parallels the ion's path, shown in Fig. 5. These cross sections are then plotted in a normalized way as shown in Fig. 6. There we see hooks arising from thin down, found experimentally with very heavy ions. In the region where hooks are not easily observed experimentally we find that the envelope of these plots varies as an exponential function to the m 'th power rising to a plateau visible for $m > 1$, signalling the end of the grain count regime and then increasing linearly with z^2/β^2 in the track width regime, until thin down dominates and the rising cross section terminates in a hook as the kinematic limit on delta ray energies limits the cross section to the area of delta ray penetration. We assume that the target cross-sections determine the cellular cross sections, but that the cellular cross sections are larger in the nominal ratio of target area to nuclear area. Our formulas for survival curves after irradiation with monochromatic beams of heavy ions, in the grain count regime, are

Fig. 5. Mean energy density (local dose) in a cylindrical target whose axis is parallel to the ion's path, normalized as to ion charge and speed. This calculation is made from the radial dose distribution of Appendix A.

reviewed in Appendix B. The manner in which we treat mixed radiation fields is a simple extension of these formulas and is described elsewhere (17).

This 4 parameter model of cellular survival has been applied to a wide variety of data on the survival of biological cells in vitro. We have applied a non-linear parameter fitting program to evaluate uncertainties in these parameters (27). In some cases a single set of data points at about 10% survival from each of several high LET bombardments has sufficed to yield a set of parameters from which the entire set of survival curves could be calculated. The model predicted "thindown", seen as the decline in cross section with an increase in LET found 15 years after the prediction, in experiments with very heavy ions in Darmstadt. For mixed radiation fields the model demands knowledge of the energy spectra of all primary and secondary heavy ions in a radiation field, as well as the dose of its low LET (gamma rays and electrons) contamination in order to predict radiobiological effects. Given that knowledge and the radiosensitivity parameters which describe the cellular end point of interest, we can calculate the dose of gamma rays yielding that end point. The equations of our model can be programmed onto a hand held calculator (28). This seems

Fig. 6. Calculated cross section S for targets of radius a , having characteristic dose E_0 from an m target model. Calculations made from several different sets of ion and target parameters are seen to have a common envelope, determined by the extrapolation number m , when the plots are appropriately normalized. This leads to the parameter κ , Eq. B.7, which determines the variation of ion kill cross section with the charge and speed of the bombarding ion, Eq. B.5, and the transition of the shape of the survival curves from the statistics of gamma kill to that of ion kill.

a much more suitable way of evaluating the "dose equivalent" than the present use of untestable "quality factors" which ignore variations of RBE with end point, with dose, and with the energy spectrum of neutron irradiations.

Most recently we have found radiosensitivity parameters for survival and transformation for C3H10T1/2 cells (29) and for chromosome aberrations in chinese hamster cells (30), from data obtained from accelerated heavy ions. For the first time we have also tentatively fitted cellular radiosensitivity parameters based on x-ray and neutron data to cell killing in tradescantia.

Since, for cell survival, we have been able to predict response to neutrons, to heavy ion beams in the spread Bragg peak, and to very heavy ions from cellular radiosensitivity parameters we can have a reasonable expectation of similar success for these mutations.

For the chinese hamster cells the parameters obtained for cell killing and for the absence of chromosome aberrations are very similar. Indeed if the data for absence of chromosome aberrations are plotted on the same graph as cell survival we find that the data for absence of aberrations lie astride our calculated survival curves, fitted to the cell survival data years ago. This suggests strongly that cell killing arises from chromosome aberrations. We display these results in Fig. 7.

Fig. 7. Survival and freedom from chromosomal aberrations in chinese hamster cells. The data points for normal metaphases (freedom from chromosome aberrations) lie astride the survival curves calculated from parameters fitted to the survival data.

It is interesting to examine the range of parameters for survival, chromosome aberration, transformation, and mutation induction that we have found. These range over many orders of magnitude, as shown in Appendix B, Table B.1. For these end points we have calculated RBE's as a function of dose for neutron and alpha particle irradiations. The RBE's for neutrons of energy between 1 and 14 MeV lie in a narrow range, within about factor 2 above and below the RBE's for

stopping alpha particles. For different end points the determining factor seems to be the extrapolation number m . End points having the same extrapolation number display very similar response. In all cases our extrapolation number after gamma irradiation is greater than 1, and may be as high as 3. While extrapolation number is notoriously imprecise when determined by simply making a statistical fit to survival curves obtained after gamma irradiation, we believe that our procedure yields a much tighter constraint, for it is determined by simultaneously fitting a set of 4 parameters to a set of survival curves obtained after irradiation with particles of a wide range of LET. Our results imply that the linear extrapolation of radiobiological data to low doses of gamma rays is not correct. We suggest that a conservative extrapolation to low doses of gamma rays is quadratic, and for those cases where we find the extrapolation number m to be 3, the extrapolation to low doses of gamma rays is cubic, and to low doses of alpha particles is quadratic. To this end we are very interested in some results for the induction of skin cancers in rats by electrons, where the results are represented by the authors to be quadratic, and which on our analysis seem to be better represented by a cubic function (31).

Finally, we have calculated the dose of gamma rays giving the same response (for the single end point represented by a set of parameters) for several of these end points. When we compare this to the gamma ray dose implied by the ICRU recommended average quality factor for neutrons and for alpha particles of 25, we find our calculation to yield a higher effective gamma ray dose below about 1 rad and a lower effective dose above 1 rad of high LET radiations, as shown in Fig. 8.

Using track physics as a guide we have attempted to understand some chinese epidemiological data for lung cancer induction at low doses of alpha particles (32). From these data we prefer a quadratic extrapolation to low doses of alpha particles, and find this to be not inconsistent with the judgement of other investigators, or with our evaluation of cellular radiosensitivity parameters, or with the work of Burns and Albert. We find a linear extrapolation to low doses of electrons or x-rays inconsistent with available data. From these data we find it impossible to determine excess lung cancers from alpha particles over normal fluctuations below a cumulative exposure of 15 working level months.

Incidentally, the historical development of our notions of track theory as applied to radiobiology is given in our papers in the

Fig. 8. Calculated values of the x-ray dose which yields the same surviving fraction of chinese hamster cells as the indicated doses of stopping alpha particles or of neutrons of different energies. Also shown is the x-ray dose calculated on the basis of a quality factor of 25. We suggest that such calculations should be considered as a basis for the conversion of Grays into Sieverts for they seem less arbitrary and more closely related to observation than the use of a quality factor.

Proceedings of the several Symposia on Microdosimetry, from the Second onwards. In some of the earlier symposia these papers are accompanied by useful and interesting discussion.

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APPENDIX A: RADIAL DOSE ALGORITHM

Our most recent algorithm for the radial distribution of dose around the path of a heavy ion in liquid water, $D_2(t)$, elaborated elsewhere (Waligorski, 1986), is summarized below. We show in Fig. A.1 the Monte Carlo histogram and a plot of our analytic fit to that histogram, from Eq. A.1.

$$D_2(t) = D_1(t)(1 + K(t)) \quad (\text{A.1})$$

Fig. A.1. Radial distribution of dose in liquid water, from the Monte Carlo Calculation, Eq. A.4 of Zhang, Dunn, and Katz, and the corrected formula, Eq. A.1, empirically fitted to the Monte Carlo calculation.

where:

a) for $t > B = 0.1\text{nm}$:

$$K(t) = A \left[\frac{t-B}{C} \right] \exp - \left[\frac{t-B}{C} \right] \quad (\text{A.2})$$

$$B = 0.1\text{nm}$$

$$C = 1.5\text{nm} + 5\text{nm} \times \beta$$

and $A = 8\beta^{1/3}$ for $\beta < 0.03$

or $A = 19\beta^{1/3}$ for $\beta > 0.03$

b) for $t < B = 0.1\text{nm}$:

$$K(t) = 0 \quad (\text{A.3})$$

and

$$D_1(t) = \frac{Ne^4 Z^{*2}}{\alpha mc^2 \beta^2 t} \left[\frac{\left[1 - \frac{t+\theta}{T+\theta} \right]^{1/\alpha}}{t+\theta} \right] \quad (\text{A.4})$$

where $D_2(t)$ is the dose deposited in a coaxial cylindrical shell of thickness dt at a distance t from the path of an ion of effective charge Z^* moving with a relative velocity $\beta = v/c$ (c is the speed of light) through the detector medium containing N electrons per cm^3 . m is the mass of the electron. The Rutherford cross-section for delta-ray production from atoms having ionization potential $I = 10$ eV, normal ejection and a power law range (r) - energy (w) relationship for electrons, are assumed. The range-energy relationship is based on a two-component fit to the available experimental data concerning ranges of electrons in aluminium:

$$r = k w^\alpha \quad (\text{A.5})$$

where

$$k = 6 \times 10^{-6} \text{ g cm}^{-2} \text{ keV}^{-\alpha} \quad (\text{A.6})$$

$$\text{For } w < 1 \text{ keV } \alpha = 1.079 ; \quad \text{for } w > 1 \text{ keV } \alpha = 1.667 \quad (\text{A.7})$$

θ is the "range" of an electron of energy $w = I$; that is,

$$\theta = k (0.010 \text{ keV})^{1.079} = 4.17 \times 10^{-8} \text{ g cm}^{-2} \quad (\text{A.8})$$

The kinematically limited maximum delta-ray energy is:

$$W = 2mc^2 \beta^2 / (1 - \beta^2) \quad (\text{A.9})$$

This translates to the maximum range of delta-rays:

$$T = k W^\alpha \quad (\text{A.10})$$

where the choice of α depends on the relative velocity β of the ion.

We calculate:

$$\text{for } \beta < 0.03 \quad \alpha = 1.079, \text{ and for } \beta > 0.03 \quad \alpha = 1.667 \quad (\text{A.11})$$

For water:

$$\frac{2\pi N e^4}{mc^2} = 1.369 \times 10^{-7} \frac{\text{erg}}{\text{cm}} = 8.5 \text{ keV mm}^{-1} \quad (\text{A.12})$$

The effective charge number of an ion of atomic number Z moving with relative speed β is

$$Z^* = Z[1 - \exp(-125\beta Z^{-2/3})] \quad (\text{A.13})$$

In the preceding formulas the expression $D_1(t)$ was calculated from the Rutherford formula, and includes only half the energy deposited by the ion. Provisionally we think of it as the energy deposited by the delta rays. The contribution $K(t)D_1(t)$ is generated from a Monte Carlo calculation of the radial dose distribution in liquid water, and provisionally is thought to represent the excitation energy contributed by the primary ion. Together, as in Eq. (A.1), these integrate radially to give the stopping power of a proton in liquid water to within 10% over a wide range in proton speeds. The contribution from $K(t)$ principally appears as a "hump" in a plot of the radial dose distribution at radial distances 1-10nm.

We find that the contribution of the primary energy to the action cross section of a 1-hit detector varies with its radiosensitivity and target size, and with the charge and speed of the bombarding ion. Essentially it can be expected to be more important in the grain count regime, where the track can be thought of as a "string of randomly separated beads", and diminishes in importance in the track width regime, where the track is like a "hairy rope", and there is much overkill in the innermost 10 nm from the ion's path.

Our present calculation for water is remarkably close to an earlier calculation which assumed classical ejection of delta rays except for the hump at low t due to primary interactions (33) as shown in Fig. A.2. The "extended target" calculation now proceeds as follows: We calculate the average dose distribution, $E(z, \beta, t, a_0)$ in a sensitive element of radius a_0 , represented by a chunky cylinder of this radius, the axis of which lies at the distance t from the ion's path, by integrating the radial distribution of dose over its volume. We then

Fig. A.2. A comparison of the present formula with an earlier calculation (Katz, 1968) made from experimental data on energy dissipation by beams of electrons, and assuming different angular distributions for the ejected electrons. We display the results of a calculation in which it was assumed that the angular distribution was according to a classical elastic collision between an electron and an ion. Very similar results were obtained from an assumption of normal ejection. In the region beyond the "hump" the two calculations yield results which are remarkably similar.

calculate the radial distribution of probability and thence the action cross section.

APPENDIX B: THE CELL SURVIVAL MODEL

Detailed descriptions of the cellular track model have been given elsewhere (11). Here we present only the main concepts of the model and list the equations used in our calculations. Following our earlier studies of the appearance of particle tracks in nuclear emulsion (6), the model distinguishes between the "grain-count" regime where inactivations occur randomly along the particle's path, and the "track width" regime where the inactivations are distributed like a "hairy rope". The transition from the grain-count to track width regime takes place in the neighbourhood of $Z^2/\kappa\beta^2$ of about 4; at lower values we are in the grain-count regime, at higher values in the track width regime.

To accommodate for the capacity of cells to accumulate sub-lethal

damage, two modes of inactivation are identified, namely "ion-kill" (or "intra-track") and "gamma-kill" (or "inter-track"). In these two inactivation modes it is the statistical character of the inactivation which is changing rather than the fundamental physical interaction. Effects are referred to dose rather than to the number of electrons passing through the nucleus.

Cells inactivated by the passage of a single heavy ion are said to be inactivated in the ion-kill mode with inactivation cross-section σ whose value is less than σ_0 in the grain-count regime and greater than σ_0 in the track width regime. The fraction of "track segments" inactivating cells in the ion-kill mode in the grain-count regime is taken to be σ/σ_0 , which is equal to P , the probability for inactivation in the ion-kill mode. P also approximates the fraction of the dose deposited in the ion-kill mode. The RBE goes through a maximum when $P \sim 0.5$. Cells not inactivated in the ion-kill mode can be sublethally damaged by the δ -rays from the passing particle and then inactivated, in the gamma-kill mode, by cumulative addition of sublethal damage due to δ -rays from other passing ions. Survival in the gamma-kill mode is taken to follow the m -target statistics of inactivation by secondary electrons from X-ray or gamma-ray photons.

In the grain-count regime the surviving fraction of a cellular population whose radiosensitivity parameters are m , E_0 , σ_0 and κ , after track-segment irradiation with an ion dose D of a fluence of F particles of atomic number Z , effective charge value Z^* , relative speed β and stopping power L (LET_∞), is found from the expressions:

$$\frac{N}{N_0} = \Pi_1 \times \Pi_\gamma \quad (\text{B.1})$$

where the ion-kill mode survival probability is:

$$\Pi_1 = \exp(-\sigma F) \quad (\text{B.2})$$

the gamma-kill mode survival probability is:

$$\Pi_\gamma = 1 - \left[1 - \exp\left(\frac{-D_\gamma}{E_0}\right) \right]^m \quad (\text{B.3})$$

and the gamma-kill dose fraction is:

$$D_\gamma = (1-P)D \quad (\text{B.4})$$

where

$$\frac{\sigma}{\sigma_0} = P = \left[1 - \exp \left[\frac{-Z^{*2}}{\kappa \beta^2} \right] \right]^m \quad (\text{B.5})$$

In the track-width regime, where $P > 0.98$, we take:

$$\Pi_\gamma = 1 \quad (\text{B.6})$$

and find σ from the "track width" which increases linearly with Z^*/β while the inactivation cross-section increases with Z^{*2}/β^2 up to a limit set by the maximum radial range of δ -rays. This is the "thin-down" region (13).

To find the cross section in the track width regime, including thindown region, a separate calculation must be made. First we must find the "target cross section" S , for targets of radius a_0 found from κ and E_0 according to

$$\kappa = E_0 a_0^2 \times 5 \times 10^6 \text{ erg}^{-1} \text{ cm} \quad (\text{B.7})$$

and having multi target response to gamma rays characterized by E_0 and m found for the cell. This must be multiplied by the ratio of the plateau value of the cellular cross section σ_0 to the plateau value of the target cross section S_0 to yield the cellular action cross section in the track width regime. In this region we make the approximation that there is no gamma kill dose, though in the outer reaches of the track width some small fraction of the energy lost by the ion is deposited in the gamma kill mode.

To calculate RBE at a given "kill" (transformation) or survival level we use the definition:

$$\text{RBE} = \frac{D_X}{D} \quad (\text{B.8})$$

where

$$D_X = - E_0 [\ln(1 - (1 - N/N_0)^{1/m})] \quad (\text{B.9})$$

is the X-ray dose after which this level obtains, and D is the corresponding ion dose.

All our calculations pertain to water so the ion dose is always

$$D = F L \quad (B.10)$$

When "cross-sections" and RBE's are calculated from the final slope of the survival curves, we refer to the cross-section and the RBE as "extrapolated" and in the grain count regime we write

$$\sigma_{\text{ext}} = \sigma_0 P + (1-P)L/E_0 \quad (B.11)$$

and

$$\text{RBE}_{\text{ext}} = (\sigma_0 E_0 / L) P + (1-P) \quad (B.12)$$

To calculate the effective charge value of an ion of atomic number Z moving with a relative velocity β we use the expression:

$$Z^* = Z[1 - \exp(-125\beta Z^{-2/3})] \quad (B.13)$$

We calculate the stopping power and range in water of an ion of atomic number Z with the aid of Janni's proton stopping power and range tables (34) and the expressions:

$$L(Z, \beta) = L(p, \beta) [Z^*/Z_p^*]^2 \quad (B.14)$$

where Z^* and Z_p^* are the effective charges of the ion and proton, respectively (from eq. B.13) and $L(p, \beta)$ is the stopping power, in water, of a proton at the same speed β , and

$$R(Z, \beta) = (A/Z^2) [R_p(\beta) + C(\beta)] \quad (B.15)$$

where A is the ion mass number (in amu), $R_p(\beta)$ is the range, in water, of a proton of the same speed β and $C(\beta)$ is a β -dependent range correction term after Barkas and Berger (35).

Our treatment of transformations (29) are based on data obtained with the BEVALAC accelerator by Yang et al. (36), use the same set of equations as for cell killing, and take cell killing and transformation to be independent processes that take place along the same particle track. Our parameters for chinese hamster cells are based on the data of Skarsgard et al. (37) while the parameters for tradescantia are based on the data of Underbrink et al. Here we have attempted to

extract parameters from data obtained with x rays and neutron irradiations of two different energy spectra, ignoring possible gamma ray contamination (38). The separate sets of parameters for survival, chromosome aberration and for transformation, as shown in Table B.1. Where two sets of parameters are shown, the data do not permit a clear distinction between them.

Table B.1 PARAMETERS FOR SURVIVAL, ABERRATIONS, TRANSFORMATIONS

	m	κ	E_0 cm³ 64	σ_0 cm ²
CH2B ₂ Chinese Hamster Cells				
Skarsgard et al. 1967 (37)				
survival	3	1100	1.82	4.3×10^{-7}
abnormal metaphases	3	900	1.82	3×10^{-7}
chromatid exchanges	2	1400	25	6.5×10^{-9}
C3H10T1/2 Mouse Cells				
Yang et al. 1985 (36)				
survival	3	750	1.7	5×10^{-7}
transformations	2	750	180	1.2×10^{-10}
"	or 3	475	50	7×10^{-11}
Tradescantia				
Underbrink et al. 1978 (38)				
survival	2	1000	2.1	3.5×10^{-7}
"	or 1.5	1900	2.6	4.0×10^{-7}

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