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Cellular Inactivation by Heavy Ions, Neutrons, and Pions.

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The delta-ray theory of the inactivation of cells by energetic heavy ions describes cellular survival after heavy ion bombardment through a two-component survival model, in which 4 operational parameters (E_o, m, σ_o, and κ) describe the response of a particular cellular variety in a particular ambient condition, for an arbitrary radiation environment. The quantities m and E_o are the extrapolation number and extrapolated D-37 dose of the survival curve after gamma-ray irradiation. The quantities σ_o and κ are found from the initial slope of survival curves after irradiation with ions of different LET, and are the value of the "saturation cross-section" and the value of $z^2/4\beta^2$ at which "saturation" is achieved, or rather, where the "grain-count regime" terminates. In this regime, the inactivated cells are like beads on the string represented by the ion's path. Cells may be inactivated by the passage of a single ion, with probability $P = (1 - \exp[-z^2/\kappa\beta^2])^m = \sigma/\sigma_o$, where σ is the cross-section for this inactivation mode, called ion-kill, so that the survival probability after irradiation with a beam of particles with fluence F from this mode is $e^{-\sigma F}$ A second inactivation mode results from the capacity of cells to be "bruised" by the delta-rays from a single ion in the beam, to be killed by the delta-rays from subsequent ions, much as cells are inactivated by secondary electrons from gamma-rays. In this gamma-kill mode, with gamma-kill dose (1-P)D, where D is the dose deposited by the heavy ion beam, the survival probability is $1-[1-e^{-(1-P)D/E_o}]^m$. The survival probability after irradiation with a beam of ions is the product of these two independent survival probabilities. These expressions are extended to a mixed radiation environment in which the spectrum of secondary charged particles is known, to yield survival, OER, RBE, the Anoxic-Aerobic Ratio, and the equivalent monoenergetic beam for neutron and stopped negative pion and heavy ion beam irradiation, where appropriate.

I. Introduction

In the delta-ray theory of track structure, secondary electrons are taken to be responsible for the observed effects, with the gamma-ray dose-response curve acting as a transfer function which relates the spatial distribution of dose about an ion's path to the spatial distribution of action.

One-hit detectors are on-off detectors. If they have not been activated by the passage of a first ion, they have no memory of its passage. The probability of activating a "virgin" detector element is the same for the second ion as it was for the first. The interaction of a beam of charged particles with the sensitive elements of a 1-hit detector is appropriately described by the concept of cross-section.

Cells display a more complex response to ionizing radiation, as indicated by their sigmoid response to gamma-rays.

Like the sensitive elements of a 1-hit detector, a cell may be inactivated by a burst of delta-rays accompanying the passage of a single energetic ion, in a mode called ion-kill, described by an inactivation cross-section, σ . But in addition cells may be "bruised" by the passage of a first ion, to be inactivated by the passage of later ions. We take this inactivation to arise from the tangle of delta-rays arising from exposure to the ion beam, describing it through the term gamma-kill, for this inactivation mode resembles the inactivation of cells by the tangle of secondary electrons from different gamma-ray photons. While a single ion may be responsible for ion-kill, only a beam of ions can be responsible for gamma-kill. The distinction between the two modes of inactivation is between ordinary and conditional probability. It is inappropriate to use the concept of cross-section to describe the gamma-kill mode.

Since information relating to the identity, size, and cellular coordinates of the radiosensitive sites is unavailable, we cannot proceed directly from the gamma-ray dose-response relation to the calculation of the cellular ion-kill cross-sections. Instead, we infer the relations we expect cells to obey by first studying a single sensitive element of radius a_o which

responds to gamma-rays according to the multi-target single-hit relationship obeyed by many cells.

II. A Model for Cellular Survival

As for the 1-hit detector, we calculate the ion-kill inactivation cross-section S of the cell-like detector by integrating the probability P for inactivation over all space about the ion's path, as given by the expression

$$P(z,\beta,a_o,E_o,m,t)=(1 - e^{-\bar{E}(z,\beta,t,a_o)/E_o})^m \qquad (1)$$

where E_o and m are the extrapolated D-37 dose and the extrapolation number, respectively, for survival after gamma-ray irradiation, and $\bar{E}$ is the mean dose in a sensitive element of radius a_o whose center is at distance t from the ion's path. We calculate the point distribution of dose according to Butts and Katz[1] and take the sensitive elements to be cylindrical, with axes parallel to the ion's path.

We find the ion-kill inactivation cross-section S by integration of Eq. (1), as represented by the expression

$$S(z,\beta,a_o,E_o,m) = \int_0^{\tau} 2\pi t\ P(z,\beta,a_o,E_o,m,t)\ dt \qquad (2)$$

In Fig. 1, we show the result of numerical integration of Eq. (2) for different values of E_o, a_o, z, β, and m, and plot S/a_o^2 vs. $z^2/\kappa\beta^2$, where

$$\kappa = E_o a_o^2/(2\times10^{-7}\ \text{erg/cm}) \qquad (3)$$

For 1-hit detectors, a_o plays only a minor role in the determination of S, as shown in other studies[2].

The lowest set of curves of Fig. 1 are plotted for m=1, $E_o=10^6$ erg/cm^3, and $a_o=10^{-4}$, 10^{-5}, and 10^{-6} cm. Because of the particular choice of plotted parameters the functional relationship between S and z^2/β^2 is displaced horizontally at different choices of $E_o a_o^2$ and is displaced vertically at different choices of a_o. The hook shaped branching of the curve sets with decreasing β of the incident ion is caused by the decreasing radial distance τ to which the delta-rays penetrate[1]. There is no "plateau" near $S = \pi a_o^2$.

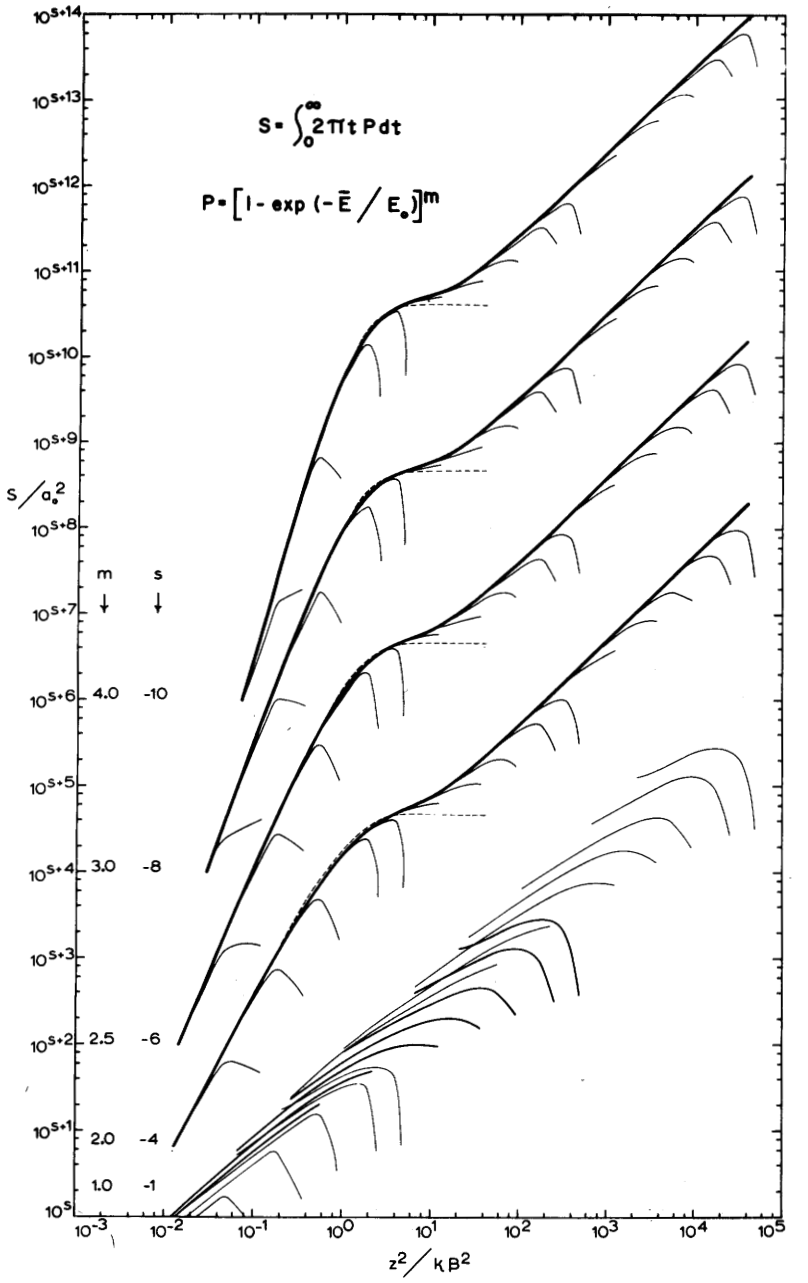

Fig. 1. S/a_o^2 vs. $z^2/\kappa\beta^2$, for constant Z (1,2,5,10,20,50,100) at varying values of β, for m = 1, 2, 2.5, 3, and 4. See the discussion of Section II.

Other calculated curves are grouped according to the value of m.

There is a distinct difference between the multi-target and single target calculations, in that the envelopes of the multi-target curves pass through a distinct change in slope, or plateau, in the neighborhood of $S/a_o^2 \simeq 1.4\pi$, at $z^2/\kappa\beta^2 \simeq 4$, as we pass from the grain count regime to the track width regime. In the grain-count regime the slope of the envelope is m. In the track-width regime the slope is 1.

Calculations are made for a range of values of E_o and a_o. For the more sensitive detectors ($E_o = 10^6$, 10^4 erg/cm^3), the larger sensitive volume radii ($a_o = 10^{-4}$, 10^{-5}, 10^{-6} cm), and slow ions ($\beta \lesssim 0.1$), there is branching of the curves below the main envelope, as associated with τ. We show branching for $E_o = 10^6$ erg/cm^3, for comparison with the 1-hit case.

In the grain-count regime, at low values of $z^2/\kappa\beta^2$, the envelopes of the plotted multi-target curves of Fig. 1 are well approximated by the expression

$$S/S_o = (1 - e^{-z^2/\kappa\beta^2})^m \qquad (4)$$

as shown by the dashed lines on the figure, with the point of intersection of the curve envelopes and the dashed curves lying nearly at S_o when $z^2/\beta^2 = 4\kappa$.

We interpret S_o as the "saturation cross-section",marking the transition from the grain-count to the track-width regime, and occurring at such a value of z^2/β^2 that every sensitive element through which the ion passes is sensitized.

This interpretation implies that S/S_o is the fraction of track segments in which there is a sufficient production of delta-rays to cause ion-kill. We therefore write that when

$$\begin{aligned} &S/S_o < 1, \text{ in the grain count regime, } P = S/S_o, \\ &S/S_o > 1, \text{ in the track-width regime, } P = 1 \quad , \end{aligned} \qquad (5)$$

where P is the fraction of the dose deposited in the ion-kill mode.

We assume that the inactivation of sensitive elements by a single ion can only take place in the ion-kill mode, so that the process is fully described by the cross-section S. A beam

of particles of fluence F and LET L, deposits a total dose D = FL in a thin specimen of the medium, of which an amount PD is deposited in the ion-kill mode, and an amount (1-P)D is deposited in the gamma-kill mode.

We assume that the inactivation of sensitive elements by a beam of ions proceeds independently in these two modes, with exponential survival characteristic of the ion-kill mode, and sigmoidal survival characteristic of the gamma-kill mode. We therefore write that the surviving fraction N/N_o of a population of "cell-like" sensitive elements after irradiation is

$$N/N_o = e^{-SD/L} \left(1 - \left[1 - e^{-(1-P)D/E_o}\right]^m\right) \qquad (6)$$

From Eq. (6) we may find the logarithmic derivative of the surviving fraction with respect to the dose, which we identify as the radiosensitivity k, and find its initial and extrapolated values to be

$$k_{in} = S/L \quad ; \quad k_{ext} = S/L + (1-P)/E_o = k_{in} + (1-P)/E_o \qquad (7)$$

Note then that the initial slope of the survival curves after heavy ion irradiation serves to determine the ion-kill cross-section (in the grain-count regime), while the final slope may be used to define a quantity sometimes called the extrapolated cross-section, S_{ext}, according to the expression

$$S_{ext} = k_{ext}L = S + (1-P)L/E_o \qquad (8)$$

The difference between the initial and final slope of the survival curves relates entirely to the quantities describing gamma-kill.

Providing that we do not take the details of the model too literally, we expect that most of these results apply to biological cells whose gamma-ray dose-response curve is representable by the mathematical form of the multi-target single-hit model. Since this form can be derived from other assumptions which imply different interpretations of its parameters, we must treat the parameters of the model as a compact and efficient set of radiation properties (for it has been shown that Eq. (6) gives a good fit of survival data[3]), but we must divorce both κ and S_o from a_o. Thus we consider Eq. (3) as not relevant to cellular behavior, and consider the ordinate of Fig. 1 as giving the

relative cross-section for biological inactivation rather than the explicit value of S/a_o^2. Without formal justification, we make the inductive leap to assert that Eqs. (4)-(8) describe cellular survival when the parameters of the model S, and S_o, are replaced by the cellular cross-sections σ , and σ_o.

This implies that the parameters E_o and m, κ and σ_o are operational parameters (whose microscopic interpretation awaits further investigation of the radiation response of cells), to be determined from the shape of experimental survival curves after gamma-ray irradiation, and from a plot of the ion-kill cross-sections (from the initial slopes of survival curves after heavy ion irradiation) vs. z^2/β^2. Note that the theory demands that the slope of a log-log plot of σ vs. z^2/β^2 be m, at low values of z^2/β^2, and that we may find κ as the value of $z^2/4\beta^2$ at which $\sigma = \sigma_o$. Such operational parameters have been determined earlier for bacterial spores, haploid yeast, HeLa, Chinese hamster, and T-1 human kidney cells from the data of both Barendsen and Todd, as shown in reference (3).

By use of Fig. 1, we extend our earlier studies of the survival of T-1 human kidney cells to the track width regime. In Figs. 2 and 3 we show recalculated survival curves for Ne and Ar irradiation as heavy lines, based on the radiosensitivity parameters determined earlier[3]. It is quantitatively clear that at the highest LET, the bombardments have entered the kidney cell track-width regime.

In the extrapolation of cellular radiation data to cosmic rays, and other energetic ions, the radiation parameters found from survival data obtained with ions moving faster than 0.1c should be used, to avoid complications arising from the branching in Fig. 1.

Note especially that these results imply that there is no saturation of σ with increasing LET for cells as for 1-hit detectors. This expectation, that the cellular inactivation cross-sections increase beyond a plateau marking the end of the grain-count regime, is verified for human kidney cells, in the data of Todd.

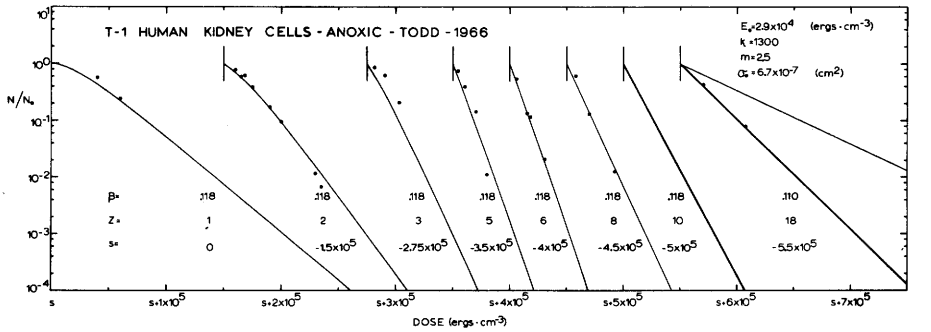

Fig. 2. Survival data (Todd) for anoxically exposed T-1 human kidney cells are superimposed on a family of theoretical curves (light lines) calculated from parameters fitted in earlier work[3] on the cellular grain-count regime. From Fig. 1, and the originally fitted parameters, the inactivation cross-section in the track-width regime is reevaluated, and the new survival curves are shown as heavy lines, here compared to data obtained with argon (Z=18) bombardments.

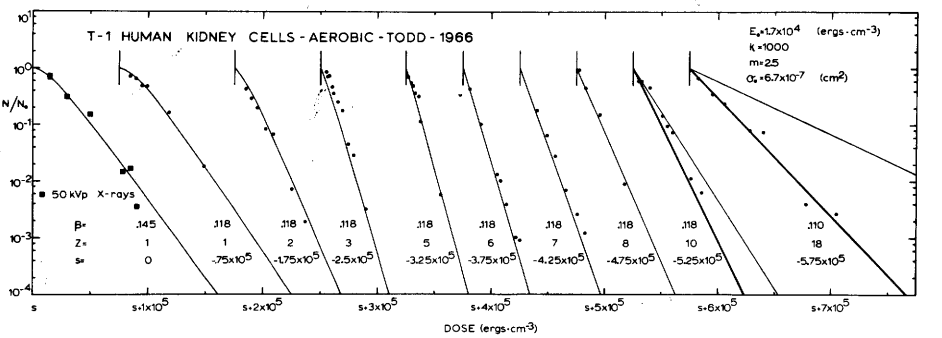

Fig. 3. See caption to Fig. 2. Aerobic irradiation.

III. Response of Cells to a Mixed Radiation Environment

The extension of the model of cellular survival after exposure to monoenergetic heavy ion beams, developed in the preceding section, to a mixed radiation environment is straightforward in concept, though cumbersome in notation, because of the necessity to accomodate a description of the radiation environment, including secondary particles.

The total ion-kill survival probability, Π_i, is taken to be the product of the separate ion-kill survival probabilities of each of the constituents of the radiation environment.

The total gamma-kill survival probability, Π_γ, is found from the total gamma-kill dose.

The product of these two independent survival probabilities is taken to be the surviving fraction of cells after a dose D is deposited, or

$$N/N_o = \Pi_i \times \Pi_\gamma \qquad (9)$$

When a mixed beam of heavy ions is incident on a thin specimen, we may characterize the j'th component of the beam by its fluence F_j, its deposited dose D_j, and the ion-kill probability of its interaction with the specific cellular variety irradiated at the relative speed β_j with which the beam passes through the specimen. We then write

$$N/N_o = e^{-\sigma_o [\sum_j (P_j F_j)]} \left(1 - (1-e^{-[\sum_j (1-P_j) D_j/E_o)^m}\right) \qquad (10)$$

Such a description is suitable to a beam of heavy ions dispersed by straggling, or by a ridge filter, and is capable of giving the surviving fraction, OER, RBE, AAR (Anoxic-Aerobic survival Ratio) , as a function of depth, where cellular radiation parameters are known.

In a particular exposure, the radiation environment may consist entirely of a beam, as described by Eq. (10), or entirely of secondary particles , as for neutron irradiations, or of a mixture of the two, as for irradiation with a beam of stopping pions. In the following paragraphs we treat only of survival after a secondary particle irradiation. The extension to a mixed beam and secondary particle environment is evident.

We represent the number of primary particles per unit volu me by Y, the total absorbed dose by D, the gamma-kill dose by D_γ, the range of an ion of atomic number Z and initial kinetic energy T_j by R_{Zj}, and the number of secondary charged particles of atomic number Z and initial kinetic energy T_j, per unit kinetic energy interval per absorbed primary particle per unit volume, by dN_{Zj}/dT_j. We find it convenient to introduce the notation

$$\bar{P}_{Zj}T_j = \int_{T_j}^{0} P(Z,T)\ dT = \int_{R_{Zj}}^{0} P(Z,T)\ L(Z,T)\ dr, \qquad (11)$$

$$\bar{\sigma}_{Zj}R_{Zj} = \int_{R_{Zj}}^{0} \sigma(Z,T)\ dr = \int_{R_{Zj}}^{0} \sigma_\circ\ P(Z,T)\ dr = \sigma_\circ \int_{T_j}^{0} P(Z,T)/L(Z,T)\,dT \qquad (12)$$

Here, $\bar{P}_{Zj}$ is the fraction of the initial energy of a secondary particle of atomic number Z and initial energy T_j which is delivered to the ion-kill mode. Similarly $\bar{\sigma}_{Zj}$ is the average ion-kill cross-section for a stopping particle of range R_{Zj}.

By summing over the initial kinetic energy intervals ΔT_j of the initial-kinetic-energy-distribution, and over the atomic numbers Z of the secondary ions, we find the total dose D, the gamma-kill dose D_γ, and the ion-kill and gamma-kill survival probabilities, for use in Eq. (9). Thus

$$D = Y \sum_Z \sum_{T_j} [(\Delta T_j)\ (dN_{Zj}/dT_j)\ T_j] \qquad (13)$$

$$D_\gamma = Y \sum_Z \sum_{T_j} [(\Delta T_j)\ (dN_{Zj}/dT_j)\ (1-\bar{P}_{Zj})\ T_j] \qquad (14)$$

$$\Pi_\gamma = 1 - [1 - e^{-D_\gamma/E_\circ}]^m \qquad (15)$$

$$\Pi_i = \exp -\{Y \sum_Z \sum_{T_j} [(\Delta T_j)\ (dN_{Zj}/dT_j)\ \bar{\sigma}_{Zj}R_{Zj}]\} \qquad (16)$$

For the calculation of the survival of cells after exposure to 14 MeV neutrons and stopped pions, we employ these equations, the secondary charged particle spectrum arising from the irradiation of tissue with 14 MeV neutrons, of Caswell[4], and the secondary particle spectrum from the capture of negative pions in light elements, of Guthrie, Alsmiller, and Bertini[5], taking tissue to be of unit density and having the composition

given by Alsmiller, Armstrong, and Bishop[6]

The results of calculations of the survival of T-1 human kidney cells irradiated aerobically and anoxically with 14 MeV neutrons, stopped negative pions, and 10 MeV protons, are shown in Fig. 4. The curves indicate that the OER for stopped pions is intermediate between that to be found for 10 MeV protons (or gamma-rays) and 14 MeV neutrons.

The problem of calculating survival curves for 14 MeV neutrons on T-1 human kidney cells has been studied by Bewley[7], and later by Curtis[8], who used LET as the basis of their extensions of experimental data obtained with monoenergetic heavy ion beams to the secondary particle spectrum arising from neutron irradiation, though in different ways. Survival curves calculated by Curtis are similar to those of Bewley. In Fig. 5 we compare the present calculation, the calculation of Bewley, and the data of Barendsen and Broerse[9,10]. Sources of error in the present calculations arise from the original assignment of cellular radiation parameters, from the calculations of the secondary particle spectrum, from uncertainties in the LET. We show as dashed lines the calculated neutron survival curves for the initially assigned parameters for kidney cells (Barendsen)[3] and as solid lines the calculated neutron survival curves found by alteration of σ_o from the initially assigned value of 5.4×10^{-7} cm^2 to a value of 6.3×10^{-7} cm^2 and other radiation parameters left unaltered. The spread of the experimental data for cellular survival after monoenergetic heavy ion irradiation allows both sets of parameters.

From his results Bewley suggested that LET is not an adequate measure of radiation quality, and attributed the discrepancy between his calculations and the observed data, in part, to the neglect of delta-rays in a calculation based on LET.

IV. Heavy Ion Radiotherapy

Estimates of the survival of T-1 human kidney cells exposed aerobically and anoxically, as a function of depth in tissue, have been made for ideal beams (without straggling) and for the mixed beams arising from a simple straggling model.

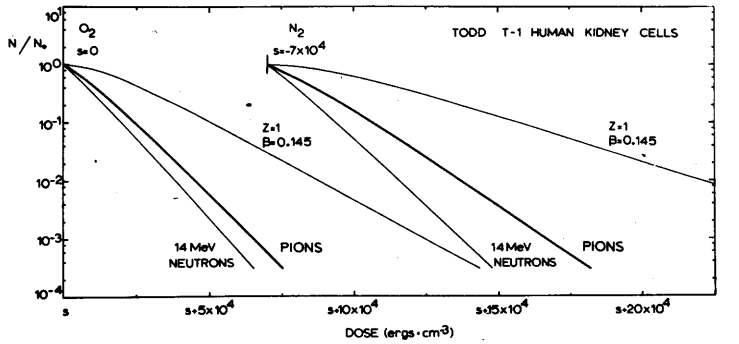

Fig. 4. Calculated survival curves for T-1 human kidney cells, for irradiation with 10 MeV protons, stopped pions, and 14 MeV neutrons. Cellular parameters are based on the survival data of Todd.

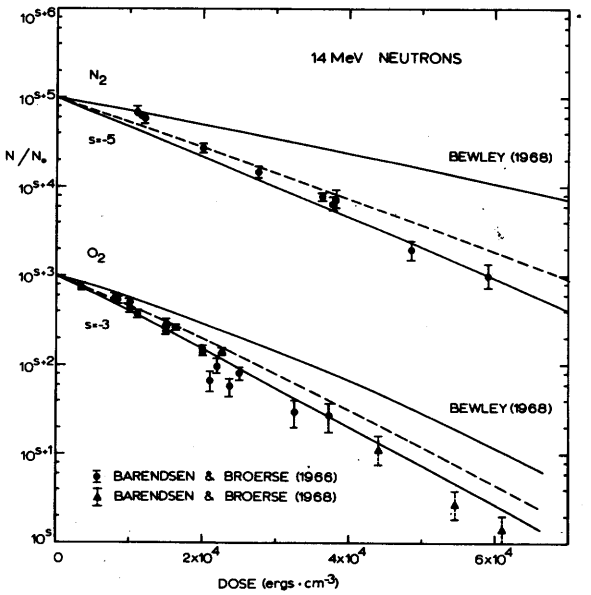

Fig. 5. Calculated survival curves for T-1 human kidney cells irradiated with 14 MeV neutrons, based on the heavy ion data of Barendsen et al., are compared with survival data for these cells obtained after exposure to 14 MeV neutrons by Barendsen and Broerse[9,10]. The upper curve in each of the two curve groups is calculated by Bewley, using LET as the basis of extending the heavy ion data to neutrons. The dashed curve in each group is based on parameters for these cells which we evaluated in our initial fit of the heavy ion data[3]. The solid curve passing through the data points is based upon a reevaluation of the radiosensitivity parameters consistent with both neutron and heavy ion data, and is possible because of the spread in the data points, which makes a unique assignment of parameters impossible.

For the latter case we imagine that an initially monoenergetic beam is composed of several groups of ions whose intensities and range-energy relations differ in such a way as to yield the straggling gaussian[11] for a beam of particles of the chosen initial energy. To this mixed beam, made up of groups of ions of different energies at the same depth, we apply Eq. (10).

In Fig. 6 we show the survival, in the Bragg peak, of kidney cells exposed to the indicated fluence of protons, and nitrogen and neon ions, incident on the "tissue" at an initial energy of 300 MeV/amu, with the dose delivered in 20 equal fractions, separated by the repair time. The results of irradiation with the straggling beam are shown by solid lines, while the results anticipated for an ideal beam are shown as dashed lines. Aerobic irradiations are plotted as heavy lines or dashes, while anoxic irradiations (N_2) are plotted as light lines or dashes. The effect of fractionation is calculated by dividing the total fluence by the number of fractions, and raising the resulting surviving fraction to a power equal to the number of fractions. In each irradiation, the fluence is chosen so that the survival at the surface after 20 fractions exceeds 0.5, as shown by dashes alongside the surviving fraction axis. At depths almost up to the Bragg peak, the ideal beam calculations provide a good estimate of the survival calculated with the straggling beam. Note also that there is a substantial difference in the survival of aerobically and anoxically irradiated cellsinto the far side of the Bragg peak, according to the present calculations. This result is displayed more clearly in Fig. 7. In short, the present model does not support the view that the differences between the survival of aerobically and anoxically irradiated cells vanish in the Bragg peak, for ions of an initial energy of 300 MeV/amu.

V. Acknowledgements

We thank Dr. R. S. Caswell for his unpublished results on the secondary particle spectrum in tissue from 14 MeV neutrons. We thank Rose Ann Nelson for her help in the course of these investigations and in the preparation of manuscript for publication. This work is supported by the AEC and the NSF.

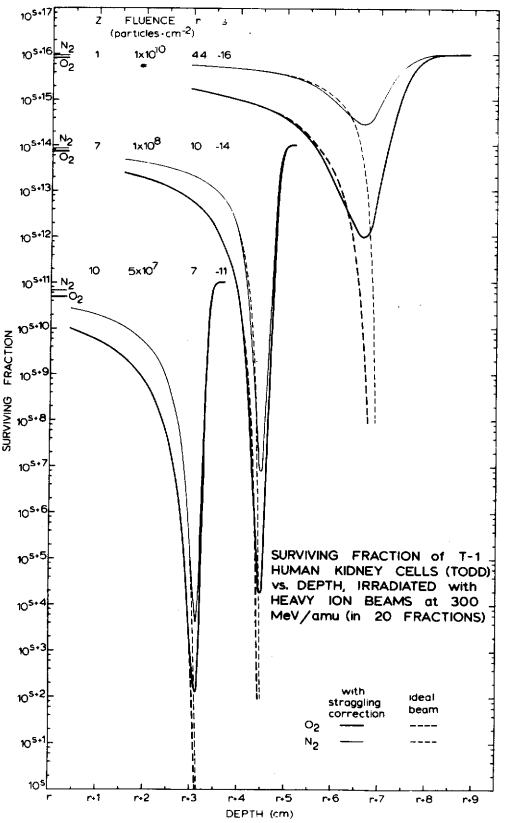

Fig. 6. Cellular survival vs. depth in water, for the aerobic and anoxic irradiation of human kidney cells with proton, nitrogen, and neon ion beams having an initial energy of 300 MeV/amu, at the indicated fluence, delivered in 20 fractions. Heavy dashes alongside the survival axis show the survival at the entering surface. Calculations made with a straggling correction are shown as solid curves, while those made for an ideal beam (with no straggling or scattering) are shown as dashed curves. The fluence chosen is one where the surface survival is not less than 0.5, for the fractionated bombardment. Note that the difference in survival between the anoxic and aerobic exposure persists into the far side of the Bragg peak.

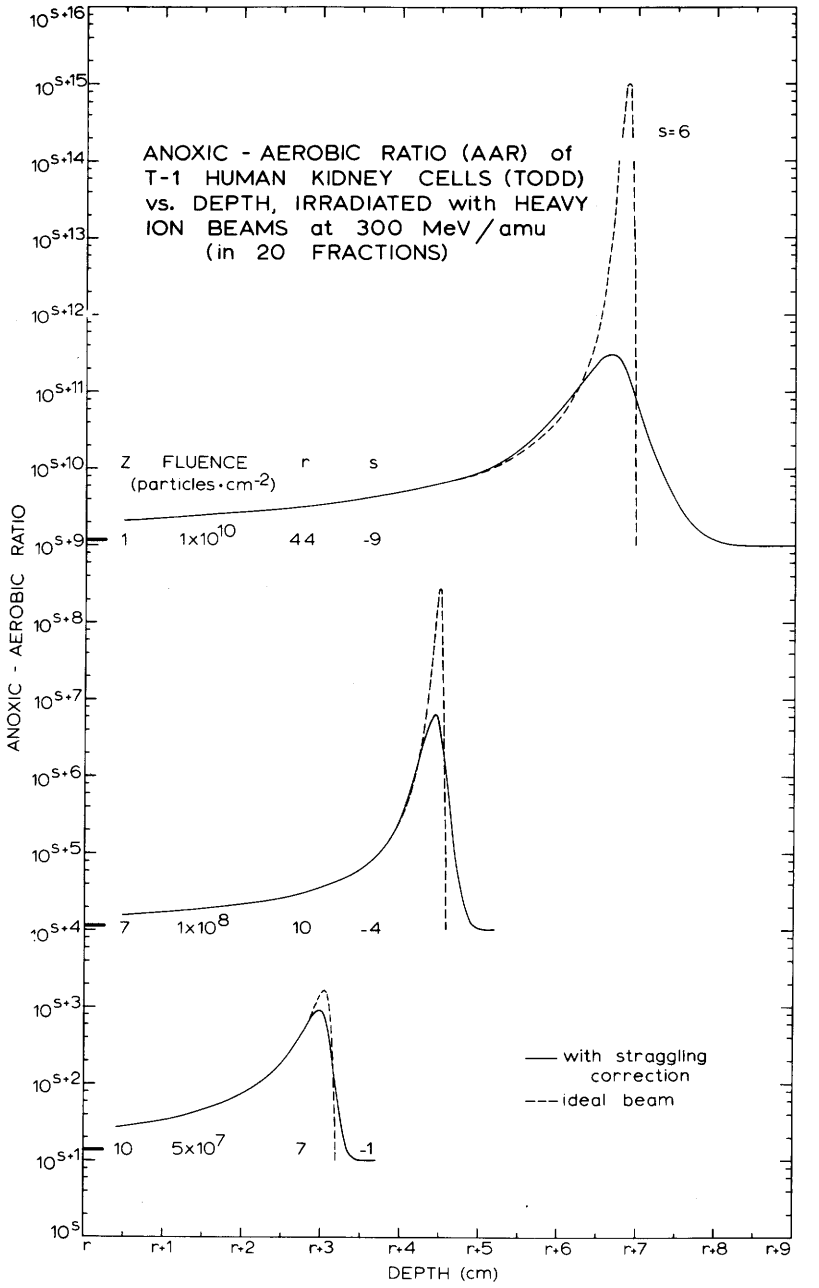

Fig. 7. Anoxic-Aerobic Survival Ratio (AAR) vs. depth, for the bombardments of Fig. 6. Solid curves arise from calculations made with a simple straggling correction. Dashed curves are for an ideal beam. Again the value of the AAR at the entering surface is shown as a heavy dash alongside the AAR axis.

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D I S C U S S I O N

Mr BARENDSEN

I am convinced that you have made a very useful analysis of the relative contributions of energy deposited close to the ion track and away from it through delta-rays respectively, although I have a few points to question about what you denote as "ion kill". However, with respect to the application to calculations of the survival of cells after irradiation with neutrons or with pi-mesons, I think I have one particular objection. You derive the efficiency per unit dose for fast neutrons from experiments with heavy ions in which the particles have traversed the cells completely. In the case of heavy ion experiments, however, a particular traversal of a particle may have caused damage in various places of the total sensitive structure. Consequently, if it were possible to split up the track of that particular particle into five or six short pieces and distribute them randomly among a number of cells, then that same amount of primary damage might kill more cells than in the case in which a single track passes through only one cell. Therefore, in the case of fast neutrons, where we have short recoil tracks, these short recoil tracks might be more effective in comparison with the same energy deposition for the same type of track due to a single particle being able to pass through one particular cell. This difference between energy deposition by several short tracks and one long track may well be the reason why you had to adjust the cross-section derived from heavy ion data by 20%. I think it is necessary to try to understand the basic aspects of energy deposition patterns and I would be hesitant to apply an arbitrary correction in order to obtain a better fit. Maybe my suggestion can help to calculate the correction quantitatively.

Mr KATZ

It is not possible to disagree with your point, but your heavy ion survival data have so much uncertainty that either of the two choices of δ we have made is possible. In all the mammalian cell data there is a substantial spread and a certain amount of fortuitous selection of parameters is possible.

Mr BARENDSEN

I would like to make one more remark about the correlation of parameters derived from cell survival curves with sites or structures in a cell which we suppose are involved in the induction of cell reproductive death. BRAM and RIS recently published two papers in the "Journal of Molecular Biology", 55 (1971) 325-336 and 58 (1971) 277-288, in which they showed that the overall shape of nucleo-histone is a very long cylinder with a diameter of 80-120 Å. This structure would consist of a DNA double helix, supercoiled or folded to make a thicker fibre of about 100 Å diameter. This structure itself can be envisaged to have a significant rigidity. As a consequence, a heavy ion passing through it perpendicular to its axis will not cause damage in another part of this complex, or at least the probability is very small. In the case of low LET radiation, however, two electrons might cause damage in the same complex, but with a spacing of, say, 1000 Å. Two such damaged places in the same structure might lead to cell lethality through a cumulative action. Thus it is also possible that the dimension of the critical structure dimension for alpha-particles is of the order of 100 Å, while with regard to X-rays an interaction distance may be found to be considerably larger. Thus knowledge of the structure of DNA-histone complex in the cell may be important with regard to the interpretation of deductions made by Mr ROSSI and Mr KELLERER in a recent paper in "Radiation Research" and by myself some years ago.

Mr KATZ

I agree with everything you say, except your final conclusion. Our differences are based on what are obviously two different views of a heavy ion track. You say a high LET track has a core of essentially infinitesimal thickness, perhaps 50 or 100 Å, with a few hairs of delta-ray tracks sticking out of it somewhere. In the classical manner of LEA you must make a delta-ray correction with appropriate overlap factors. And you say that, if this goes through the DNA somewhere, there will not be much happening 100 or 500 Å away. You see a track as a test-tube brush with no bristles; I see it as a test-tube brush with no central wire. I see the core as a psychological problem in perception. You

see the core as having reality. I say that you have come to this core conclusion by looking at the tracks of protons and alpha-particles in cloud chambers. I say that, if you look at the tracks of heavy ions from cosmic rays in emulsion, you will see this fantastic brush of secondary electrons extending tens or hundreds of μ from the path of the particle, and that the only difference between the very heavy track and the track of a proton is that there is the factor Z^2 fewer delta-rays. The relative spatial distribution of the events is the same. I find no basis whatever for the assertion that there is a track core in which something different happens than that which happens in the delta-ray cloud. And it is this which is responsible for the gamma-kill portion of the model. I think it is certainly true that a heavy ion can produce damage in one part of a helix through some of its secondary electrons, and can produce damage in another part of its helix through another of its secondary electrons. And of this we must disagree until you surgically remove the wire from your test-tube brush.

Mr ROSSI

I have tried to keep quiet, but I have to come in here. The distinction made by Mr KATZ concerning his picture and that of Mr BARENDSEN may or may not be correct. But I maintain that Mr KATZ is axially oscillating his test-tube brush; he takes the blurred mean values, and that is what he is plotting. Now means and averages are all right if they are the right averages. If, as we maintain, the biological effect depends on the square of energy concentration, Mr KATZ is taking the wrong kind of average and no reference to "averages" or "fluctuations" is meaningful. This is the core of our disagreement.

Mr KATZ

The point at issue between us as to whether one must look at the detailed fluctuations that you see in microdosimetry is a disagreement I have never understood. The γ-ray dose response curve arises from the fluctuations in energy deposition throughout a sample uniformly irradiated with γ-rays. Hence, when we use an average dose and from it take the survival probability to be that measured in a γ-ray survival curve, we believe we are automatically taking the correct fluctuation distribution in the specimen, weighted in the correct way for the particular detector under examination. But in both cases, whether explicitly, as in microdosimetry, or implicitly, in the way in which I used γ-ray survival curves, it is the fluctuation in energy deposition which is responsible for the effect. Otherwise we could obviously not have a grain count regime. If fluctuations were not involved, then every grain through which an ion passed would either be developable or not developable. The fact that some are developed when others are not arises from the fluctuation in energy deposition or from the fluctuation in delta-ray production. So I do not see that there is really any difference in the point of view we take.

Mr BOOZ

I have two comments. First a comment on your nice picture where you compared the track structure of an ion to a brush without the central wire. Does this picture not contradict with your own theory distinguishing between ion kill and γ-kill? You either have a qualitative difference between these two things, i.e., a difference between the track core and the delta part, or you have not. The other comment is on your recommendation that the biological significance of your four parameters should be disregarded. Did I understand you correctly that you asked us not to care about the significance of the values m and D37?

Mr KATZ

I would be delighted to be able to say in biological terms something about the meaning of the four parameters, or to have anyone of you tell me something that can contribute to the understanding of the meaning of these four parameters. Similarly, for tracks in emulsion, for lithium fluoride or for any of the detectors, I want to know from first principles precisely which cross-sections are involved. I see this only in a very clouded way. I do not pretend that I understand these things. But I do know that, if one parametrizes one's detector in this way, one can understand track structure. One can understand the way in which a particle interacts with the medium through which it passes. I leave it to you that there are two separate problems. One is an understanding of track structure and the other is an understanding of the detailed physics, chemistry, biology of the detecting system. And a misunderstanding of track structure leads to bad biology, leads to bad physics, leads to bad chemistry. And one of those misunderstandings is the assumption that LET is a proper parameter. Another is the notion that a track is a wire without hair. Another is the misunderstanding that the straight part of the cellular survival curve can be represented by a cross-section which is interpreted by track segment analyses.

Now to your first question. There is no contradiction whatever. Clearly this is not some point I have ignored. The ion-kill part does not depend on the wire threading through the cell. It depends on the fact that, in the time of 10^{-15} sec in which the ion passes the cell, a sufficient burst of secondary electrons has passed through the cell to inactivate it. That has nothing to do with the wire part. It has to do with the fluctuations. The fluctuations come as a fluctuating density of "hairs" along the brush. The difference between ion-kill and γ-kill does not arise from a cored structure. It arises from the nature of the fluctuations. When we have a large enough fluctuation along the track to kill a cell by the passage of a single particle, that is ion-kill. When we have too few secondary electrons, all we have done is given the cell a bruise. The cell is damaged but not inactivated. More bruises from other delta-rays, from other ions are needed for inactivation. That is γ-kill.