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TRACK THEORY AND RADIATION QUALITY*

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Abstract

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Radiation detection and damage data from several physical, chemical, and biological systems have been analysed by a unified track theory, in which observed effects are attributed to the interaction of secondary electrons with the medium. Gamma-ray dose-response curves are combined with calculations of the spatial dose distribution about an ion's path to yield dose-response curves (survival curves) for heavy ion bombardment, through appropriately defined parameters. Perplexing phenomena associated with high LET radiation are sorted out according to track regime (grain-count or track-width), inactivation mode (gamma-kill or ion-kill), structural complexity (elementary, cellular, multicellular), and end-point. The central problem in assigning a quality factor to radiation lies in the fact that the variables describing the bombarding particle and those describing the medium are not separable. What seems to be required is a theory of survival curves in which cells are represented by measured parameters, from which their response to a particular radiation environment may be calculated. A start has been made in this direction.

In the past decade a new theory of track structure has been built, based on the concept that track effects arise principally from the interaction of secondary electrons with the surrounding medium, and that the relevent variable is the local dose deposited in sensitive elements by secondary electrons (1-3). Since the response of a system to gamma-rays also arises from the interaction of the medium with secondary electrons, it is possible to use the gamma-ray dose-response (survival) curve as the basis for the understanding of particle tracks. We assert that the probability P for the production of a sensitized (inactivated) element may be written as

$$P = (1 - e^{-\overline{E}/E_o})^m \quad , \qquad (1)$$

where $\overline{E}$ is the dose experienced by a sensitive element, and E_o and m are the extrapolated D-37 dose (for gamma-rays) and the extrapolation number (for gamma-rays).

Where m = 1, the system is said to have a 1-or-more hit response to dose. E_o is then the dose at which 0.63 of the elements are sensitized, or at which there is an average of 1 interacting event per sensitive element. Such a system shows exponential survival to gamma-rays.

Many detecting systems have 1-hit response, including nuclear emulsion, dry enzymes and viruses, and scintillation counters. Current work implies that such a description may also be applicable to the bubble chamber, the observation of free radicals in solids by esr, and to the Fricke dosimeter.

The survival of some cellular systems is given by Eq. (1), with m>1. Their survival curves are sigmoidal rather than exponential, and are usually described as multi-target single-hit

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survival curves. The agreement of Eq. (1) with cellular survival data does not imply that the equation should be interpreted literally, giving the number of sensitive sites in a cell, but rather the equation is to be taken as a useful mathematical form.

Regardless of the value of m, we take Eq. (1) to describe dose-effect relationships of present interest, and interpret it to relate to the impact of the statistical fluctuation in energy deposition on a homogeneous set of detecting elements. While the mathematical form of Eq. (1) arises from consideration of the Poisson distribution, we do not imply that the distribution of energy in sensitive elements is precisely poissonian. The 1-or-more hit criterion is a weak test of randomness, or of the precision with which a particular distribution function resembles the Poisson distribution, for it essentially examines the fraction of a distribution which lies above some critical value. Fortunately, this weak property of a distribution is the property employed by the detectors in which we are interested. Thus we take the Poisson estimate of the number of 1-or-more hit events given by Eq. (1) to apply to the energy distribution arising from gamma-rays. To apply these considerations to particle tracks, we assert that track structure is due to the dose deposited by secondary electrons (delta-rays) ejected from a medium by a passing ion. We must therefore find the spatial distribution of dose deposited by delta rays in the sensitive elements surrounding an ion's path.

In 1-target 1-hit systems events are non-interacting; that is, a sensitive element left unaffected by one radiation event does not remember that it has been irradiated. Multi-target systems may be activated by several successive radiation events when one alone does not produce the tested response. This leads to a distinct difference in the response of these systems to heavy ions. In both cases we expect that the passage of a single heavy ion may activate a sensitive element. We call this behavior ion-kill. In addition, some of the deposited energy from several heavy ions may interact to sensitize an element of a multi-target system collectively, in elements where ion-kill alone would not cause activation. We call this mode of behavior gamma-kill, for it resembles the way in which multi-target systems are activated by gamma-rays.

Dose Distribution and Track Structure

To find the spatial distribution of the energy deposited by secondary electrons we must know the number of secondary electrons per unit energy interval, per unit solid angle, at a particular energy and angle, per unit path length, knowing the ion, its speed, and the composition of the medium. Then we must know how to take into account the scattering of electrons, and the way in which they deposit their energy in the medium, including their own production of secondary electrons and their back scattering. Most of this information is not known with any precision. A variety of assumptions regarding the electron ejection, the angular distribution, the subsequent energy dissipation and scattering has been employed in these calculations. Fortunately, unless we are interested in events very close to the ion's path, or at distances of the order of the range of the delta-ray of greatest energy, the dose distribution is insensitive to the details of the calculation. Within the limitations in the distance t from the ion's path given above, the

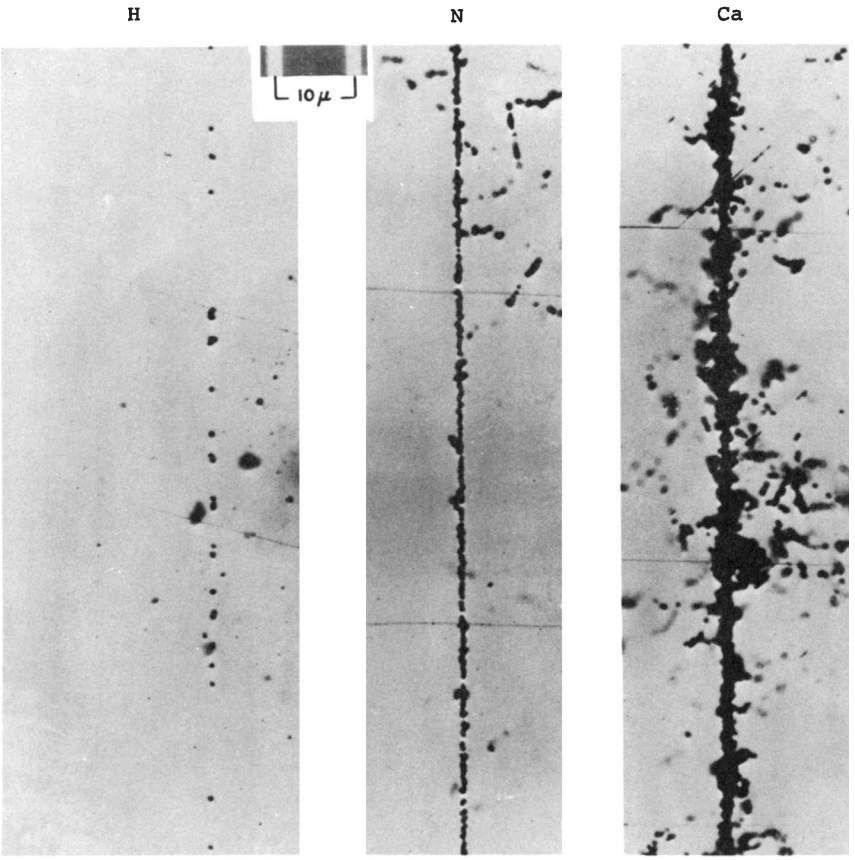

FIG. 2. Tracks of relativistic protons, nitrogen and calcium nuclei in Ilford G.5 emulsion illustrate the grain count and track width regimes, and the transition between them. Courtesy M.M. Shapiro, Naval Research Laboratory.

point distribution in dose varies with the effective charge ze, the relative speed β, and t, as $z\beta^{-2}t^{-2}$. When the energy deposited is averaged over sensitive sites of radius a_0 whose center is t distant from the ion's path, it is found that the sites through which an ion passes experience a dose which varies as $z^2\beta^{-2}a_0^{-2}$, , while sites a diameter or more away from the ion's path experience the point dose distribution above, independent of a_0. These results are shown in Fig. 1. The smaller the sensitive site, the larger the dose it experiences when an ion passes through it.

In photographic emulsion we can see the entire structure of a track. By application of Eq. (1) to Fig. 1 (or its equivalent for emulsion), we can simulate the distribution of developed grains about an ion's path, knowing the value of E_0 appropriate to the emulsion and its processing, for comparison with observation. If we represent the dose deposited in an emulsion grain through wich an ion passes as

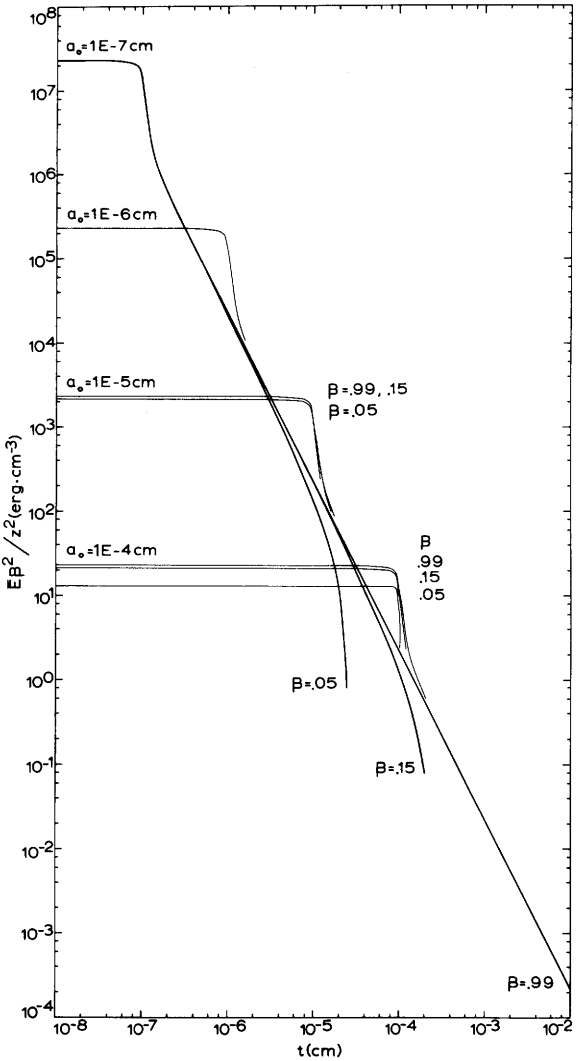

FIG. 1. The mean dose $\bar{E}$ deposited by secondary electrons in a short cylinder of radius a_0, whose axis is parallel to and t distant from the path of an ion of effective charge ze, moving at relative speed β, for a range of values of a_0. In water.

$$\bar{E} = \varepsilon z^2/\beta^2 \qquad (2)$$

where ε takes account of the size of the grain and other emulsion properties, we find that the probability P of making a grain developable, or the fraction g/g_o of intersected grains made developable by a passing ion, is given by

$$P = g/g_o = 1 - e^{-\varepsilon z^2/\beta^2 E_o} \quad . \qquad (3)$$

Note that the properties of the charged particle and those of the medium are not separable. Equation (3) cannot be written as the product of two factors, one of which describes the ion and the other of which describes the emulsion. Experiment shows that Eq. (3) describes the "grain-count" regime well. For example, relativistic protons give a track which is open and grainy, like beads on a string, in Ilford G.5 emulsion. If this emulsion is bombarded with other ions, the grain density increases with increasing z, until, at about z = 8, the track becomes fully closed. At higher z we move into the "track-width" regime, where the track diameter is greater than the grain diameter, as shown in Fig. 2. So long as we remain in the grain-count regime, the grain count appears to approach a saturation value as z increases. We pass beyond this saturation in the track width regime, and now the mass of developed silver, or the cross-section of the track, can increase to a limit imposed by the range of the most energetic delta-ray rather than by the size of the grain. Questions of track regime play an important role in the understanding of biological inactivation by heavy ions. Experimental findings show that the inactivation cross-sections of dry enzymes and viruses do not saturate with increasing LET, because most of these bombardments are in the track-width regime. The approach to saturation in the extrapolated cross-section obtained with cellular bombardments by heavy ions with increasing LET is because most of these bombardments are in the grain count regime. The increase in cross-section of human kidney cells beyond a saturation value, when they are bombarded by argon ions, shows that the track-width regime has been reached.

If experimental conditions do not permit observation of the details of track structure, we compare theory to experiment by integrating P, Eq. (1), about the path of an ion to find the (track-segment) probability for inactivation of a sensitive element by the passage of a single ion (ion-kill), according to

$$S = \int_0^\infty 2\pi t \; P \; dt \quad . \qquad (4)$$

Equation (4) was first applied to the theory of RBE of dry enzymes and viruses, where m = 1, with good results (1) as shown in Fig. 3.

With systems displaying 1-hit response, all charged particle bombardments must give exponential survival, with the surviving fraction at a fluence F = 1/S of incident ions being 1/e. The radiosensitivity k for these processes may be written as

$$k = S/L \quad , \qquad (5)$$

where L is the specific energy loss (LET_∞) of the ion. Again ion parameters and detector parameters are not separable. In a single medium, S depends on z^2/β^2, but k depends additionally upon L.

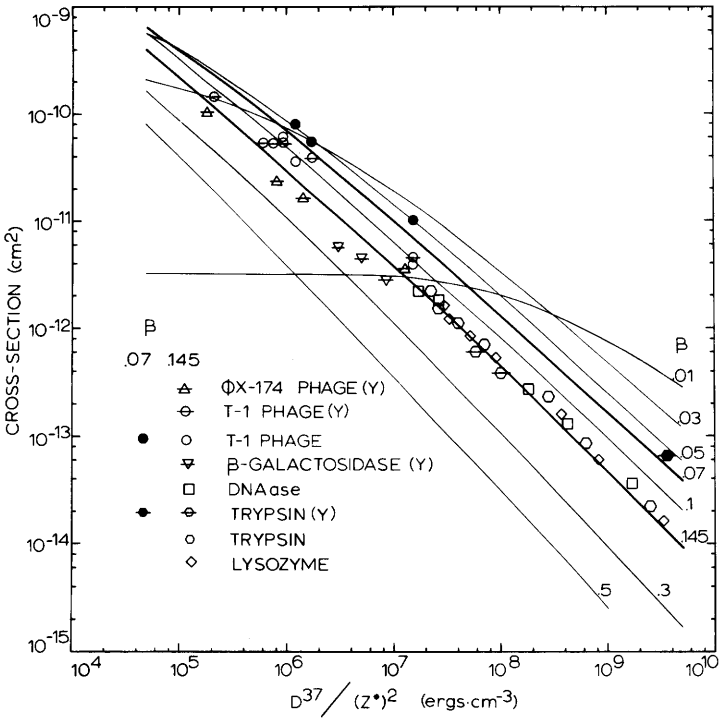

FIG. 3. Cross-section for the inactivation of dry enzymes and viruses divided by the square of the effective charge number of the bombarding ion. Plotted points crossed with a horizontal bar were obtained at the Yale HILAC (Y), while other points were obtained at the Berkeley HILAC. Lines arise from the theory [1].

Integration of Eq. (4) when m>1 is shown in Fig. 4 , for several illustrative cases. Here we plot the cross-section S against z^2 of the bombarding particle, under circumstances where "saturation" is observed at $z^2 = 90$. In the grain-count regime, we may approximate the cross-section for ion-kill by raising the right hand side of Eq. (3) to the m'th power.

Cellular Survival

The model for cellular survival is based on the preceding discussion of particle tracks in emulsion and in dry enzymes and viruses. Cells may be inactivated by an ion-kill mode, as photographic grains are sensitized. Again we divide the track structure into a cellular grain-count regime and a cellular track-width regime. In the grain-count regime, we infer that a cell has an ion-kill inactivation cross-section σ , which rises to a "saturation"value σ_o with increasing z^2/β^2 of the bombarding ion, and exceeds this value as the bombardment passes into the track-width regime. In the grain-count regime, we say that the probability P for the inactivation of a cell by the passage of a single ion is equal to σ/σ_o , and is given by

$$P = \sigma/\sigma_o = (1 - e^{-z^2/\kappa\beta^2})^m \quad . \qquad (6)$$

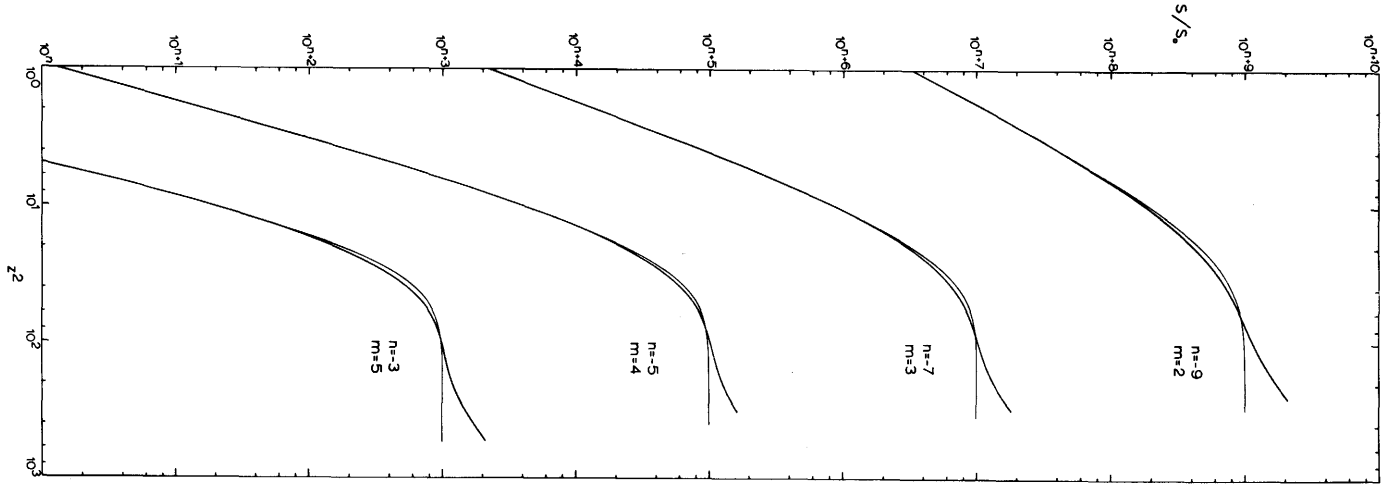

FIG. 4. The inactivation cross-section S of a sensitive cylinder whose gamma-ray survival curve follows the functional form of multi-target single-hit statistics. The cross-section rises to a "saturation" value S_0, as z of the bombarding particle increases, at constant β, and then increases again in the trackwidth regime. On the grain count regime, the function is well approximated by $[1-\exp(-x)]^m$. In the figure, m is the exponent (extrapolation number) while n is a vertical displacement parameter.

An initial population N_o of cells survives to population N' under ion-kill, according to the usual expression

$$N'/N_o = e^{-\sigma F} \quad , \qquad (7)$$

where F is the fluence of bombarding ions. Since cells remember that they have been exposed to radiation not sufficient to activate them, and respond to additional exposure from subsequent bombardment, we divide the dose into two fractions, one of which is responsible for ion-kill, while the remainder is available for gamma-kill. We assert that a fraction P is the ion-kill dose, and a fraction (1-P) is the gamma-kill dose. The distinction between ion-kill and gamma-kill doses arises from fluctuations in the delta-ray production along the path of the particle, as well as from the characteristics of the sensitive elements of the system. We take the survivors N' of the ion-kill dose to be the initial population for the gamma-kill exposure. If E is the total dose deposited by the fluence F of heavy ions (E = FL), the gamma-kill dose is (1-P)E, and we may write an expression for the surviving fraction of cells as

$$N/N_o = e^{-\sigma F} \left(1 - [1 - e^{(1-P)E/E_o}]^m\right) . \qquad (8)$$

From Eq. (8), we find the extrapolated radiosensitivity k to be

$$k = \sigma_o P/L + (1-P)/E_o \qquad (9)$$

by expanding the square bracket, as appropriate to the region of high dose, and finding the dose increment which reduces the surviving population by a factor of e.

Equations (6) and (8) have been fitted to cellular survival data through the four fitted parameters E_o, σ_o, κ, and m. Data obtained under a single set of ambient conditions with particles of different LET are fitted with a single set of parameters, suggesting that there may be no need for assuming that there are different sensitive sites sensitized at low LET from those sensitized at high LET. The parameters E_o and m represent the extrapolated gamma-ray D-37 dose and the gamma-ray extrapolation number, though they are obtained from all the data and not from the gamma-ray survival curve alone. The parameter σ_o is the saturation value of the extrapolated cross-section, while κ is related to the size of the sensitive element.

Equation (8) has been fitted to survival data for bacterial spores (4), haploid yeast (5), T-1 human kidney cells (7,8), Chinese hamster cells (6), and HeLa cells (9), with parameters given in Table I. Survival curves for some of these cases are shown in Figs. 5-7, with experimental data superimposed. It is interesting that the oxygen effect is reflected principally in E_o, implying that the oxygen effect is associated with gamma-kill rather than with ion-kill.

Once again, consideration of Eqs. (6), (8), and (9) shows that the parameters describing the bombarding ion and those describing the cellular system are not separable. It is not possible to write a formula for survival curves as a product of two factors, one representing the properties of the bombarding ion, and the other representing the properties of the cellular system.

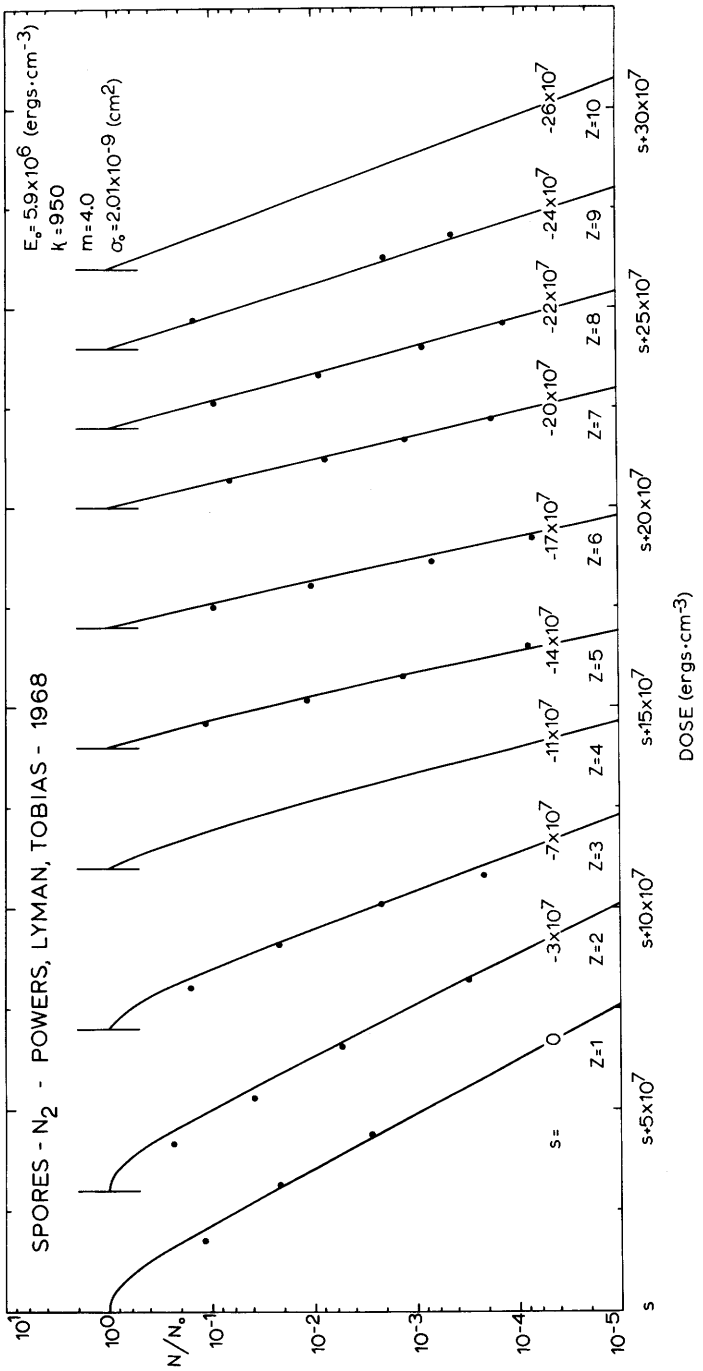

FIG. 5. Bacterial spores, N_2. Survival data from Powers, Lyman, and Tobias [4] for spores irradiated with heavy ions of given z and β are superimposed on fitted survival curves which are nested by use of a horizontal displacement parameter s.

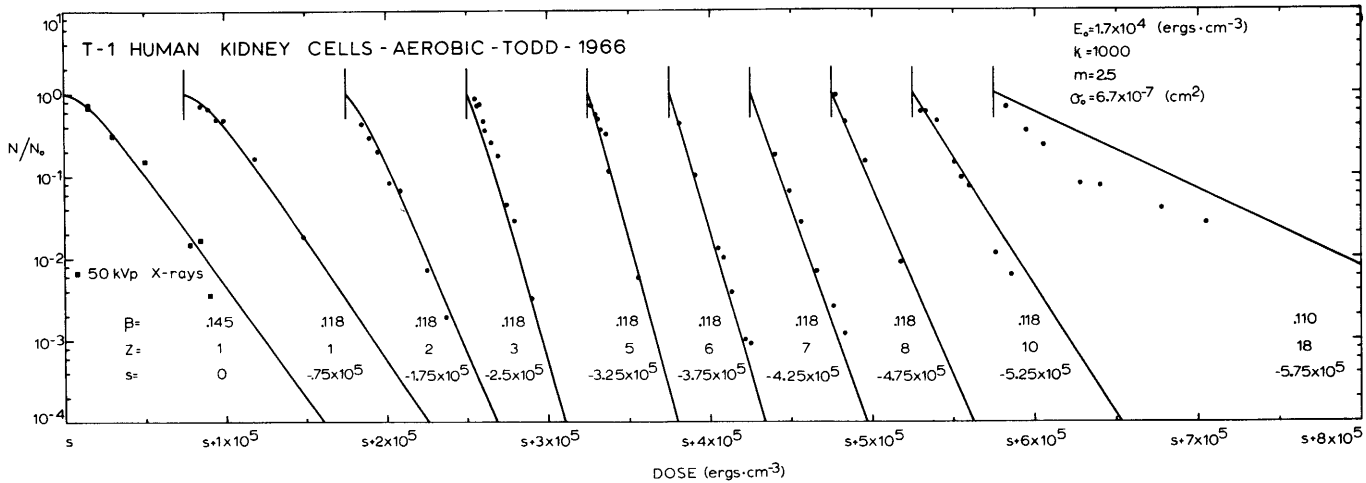

FIG. 6. T-1 human kidney cells - aerobic. Survival data from Todd [8] are superimposed on fitted survival curves for given z and β, nested by use of a horizontal displacement parameter s. Data obtained with 50-kVp X-rays are compared to calculations for 10-MeV protons. The departure of the data from the curve for Z = 18 is evidence that kidney cells are in the trackwidth regime at this bombardment.

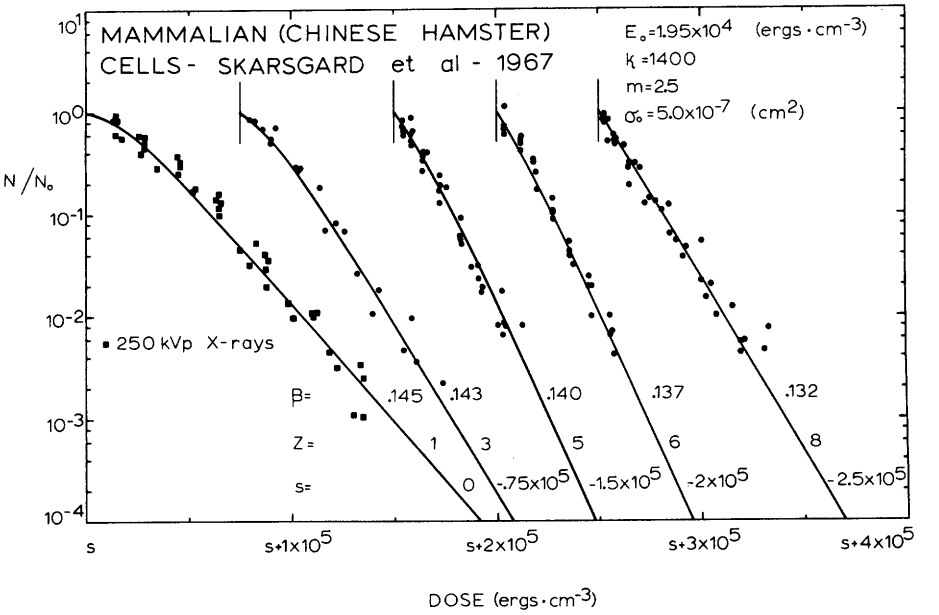

FIG. 7. Chinese hamster cells. Survival data from Skarsgard et al. [6] are superimposed on fitted survival curves. Data obtained with 250-kVp X-rays are compared to a curve calculated for 10-MeV protons.

The Estimate of Hazard

The fits of Eq. (8) to cellular survival data shown in Figs. 5-7 are typical of the fits which have been obtained with the substances listed in Table I, with the listed parameters. We therefore infer that Eq. (8) describes the survival of other cellular systems, and that the four parameters of the model are a compact description of cellular radiation properties. While their meaning awaits a better understanding of cellular structure and function, it should be possible to apply them to the problem of the evaluation of hazard in an arbitrary radiation environment, as well as to radiotherapy. The significance to be attached to the differences in the numerical values of the parameters for different cellular specias is somewhat uncertain. In the case of mammalian cells, it may be unwise to attribute significance to differences less than those arising from the measurements of Todd (8) and of Barendsen et al (7) on T-1 human kidney cells.

There is a suggestion in these results that the parameters of normal mammalian cells (hamster and kidney) lie in a restricted region of parameter space. This would make it possible to simplify the calculation of radiation hazard.

There is also the suggestion that the parameters of diseased cells (HeLa) may lie outside the region of parameter space appropriate to normal cells. Such a difference would make it possible to design more effective therapy.

Only further investigation can determine the validity of these suggestions.

TABLE I. PARAMETERS OF THE THEORY OF CELLULAR SURVIVAL, OBTAINED BY FITTING EXPERIMENTAL SURVIVAL DATA

Species		σ_o cm^2	E_o erg/cm^3	κ	m
Bacterial Spores	N_2	2.01×10^{-9}	5.90×10^{6}	950	4
	O_2	"	4.70×10^{6}	800	"
	H_2S	"	1.10×10^{7}	1100	"
Haploid Yeast		1.33×10^{-8}	4.00×10^{5}	1800	2
T-1 Kidney	N_2	6.70×10^{-7}	2.90×10^{4}	1300	2.5
(Todd)	O_2	"	1.70×10^{4}	1000	"
T-1 Kidney	N_2	5.40×10^{-7}	4.60×10^{4}	1900	2.5
(Barendsen)	O_2	"	1.80×10^{4}	1400	"
Chinese Hamster		5.00×10^{-7}	1.95×10^{4}	1400	2.5
HeLa		5.60×10^{-7}	1.40×10^{4}	750	3

To the extent that existing estimates of radiation quality, of RBE, of OER, are based on the data used in the present investigation, the theory of track effects in cells may make it possible to generate a more realistic estimate of radiation hazard than has heretofore been available.

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DISCUSSION

H. H. EISENLOHR: You mentioned that your track theory can explain the LET response of the Fricke dosimeter. If I remember correctly, the Fricke dosimeter and the Fricke copper dosimeter have opposite behaviours in this respect. Can your theory explain this difference?

R. KATZ: We have given no thought to the Fricke copper dosimeter, having studied only the Fricke dosimeter. It seems clear that the postulate of a response which is one hit to dose, and a "sensitive volume" (or diffusion length) radius of 5 - 20 Å will yield the observed variation of response with LET.

Tikvah ALPER: You stated that your analysis of Todd's data demonstrated no requirement for invoking two different critical sites in which absorption of energy might lead to cell death. Have you applied your analytical method to data of the type which led to such a model being invoked, e. g. those for which my model was invoked?

Secondly, would your four parameters be sufficient to account for data such as I have published? Data showing, for example, survival curves of different shapes (with and without "shoulders", i. e. demonstrating "ion-kill" and "gamma-kill") and widely different values of D_0, depending entirely on the post-irradiation conditions of culturing bacteria irradiated together?

R. KATZ: I have not attempted to analyse your data, since I am concerned with variations in survival curves arising from variations in LET or z/β of the bombarding particle; your work has not been concerned with these variations.

Secondly, others have also proposed that cells might be inactivated in different modes. For example, in their analysis of plots of the extrapolated cross-section as a function of LET, some workers have divided these graphs into a cross-section σ_1 (important at low LET), and a second cross-section σ_2 (important at high LET). The first of these might vary directly with LET, while the second varies quadratically. The interpretation has been advanced that σ_1 represents a site inactivated by one ionization, while σ_2 represents another site which requires two inactivations. According to the present model the low LET part of the extrapolated cross-section arises from "gamma-kill" and should not be discussed in the language of cross-section, since overlapping delta-rays from several ions are principally responsible for gamma-kill. The fact that one set of parameters is applicable at all LET in the present model argues against two different kinds of sites.

Finally, the curves on the slide you have shown arise from X-ray irradiation and are therefore all gamma-kill; I have not considered the data you show.