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## Theory of RBE for Heavy Ion Bombardment of Dry Enzymes and Viruses

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BUTTS, J. J., AND KATZ, ROBERT, Theory of RBE for Heavy Ion Bombardment of Dry Enzymes and Viruses. *Radiation Res.* **30**, 855-871 (1967).

The response of dry enzymes and viruses to heavy ion bombardment may be predicted from their response to  $\gamma$ -irradiation (and no further knowledge of their size and structure). The molecules are approximated as point particles whose response to ionization is the same for heavy ion bombardment as for  $\gamma$ -rays. From the  $\delta$ -ray distribution formula and an extrapolated range-energy relation for electrons, the radial distribution of secondary ionization energy may be found. Under this dosage distribution the inactivation probability may be found as a function of radial distance from the ion's path, and then may be integrated over all space to find the inactivation cross section. These essentially geometric theoretical relations between the  $\gamma$ -ray  $D_{37}$  values and the inactivation cross section constitute a complete theory of RBE for the heavy ion bombardment of these substances. Theoretical relationships agree with published experimental values to an average deviation of 15% for the enzymes  $\beta$ -galactosidase and trypsin, and for T-1 and  $\phi$ X-174 bacteriophages, when bombarded with ions ranging from  $Z = 1$  to 18, at ion speeds of  $0.07 c$  (2.3 MeV/nucleon) and  $0.145 c$  (10 MeV/nucleon).

### INTRODUCTION

Earlier studies (1) of the width of the track of a heavy ion in nuclear emulsion have been extended to conditions appropriate to the bombardment of dry enzymes

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and viruses, to develop a theory of relative biological effectiveness (RBE) for one-hit processes in these substances.

The theory takes the response of these materials to  $\gamma$ -rays to represent their sensitivity to a (nearly) randomly distributed dose of ionization energy. The dose delivered by a heavy ion is not random, but we may consider the response in cylindrical shells coaxial with the ion's path as if these shells were subjected to appropriate doses of  $\gamma$ -rays. Thus the theory of RBE hinges on knowledge of the transverse distribution of ionization energy. For this knowledge we rely on procedures developed earlier for the study of track width.

The inactivation of biological materials by heavy ions has been measured and interpreted by many investigators (2-8). Since experimental plots of survival versus the dose,  $D$ , of ionizing particles (expressed as the number of bombarding particles per square centimeter) follow an exponential curve of the form  $e^{-SD}$ , the quantity  $S$  (having the dimensions of square centimeters) is called the inactivation cross section. Its reciprocal is the particle dose required to reduce function to 37% of its initial value. Many of these papers present a model for heavy ion interaction which attempts to explain or correlate the measured cross section to the target size or structure, to the linear energy transfer (LET), and so on. The theories offered are usually patterned after the target theory of Lea (2), but they differ in their handling of the "sensitive structure" of the molecule, and the separation of secondary electrons into a "core," in which the dose is perfectly lethal, and a "cloud" of lesser intensity.

From the vantage of the present work it appears that there has been a theoretically unjustifiable preoccupation with the details of the molecular size and structure, and with LET. Inactivation cross sections cannot be derived from LET, since this parameter contains no knowledge of the transverse distribution of energy along the ion's path, and therefore masks the effect of saturation, or "overkill," near the trajectory. For these materials we shall consider that the molecular size affects the cross section,  $S$ , for heavy ion bombardment only very indirectly, through its influence on the  $D_{37}$  for  $\gamma$ -ray inactivation. Speaking very superficially, the cross section is related to the cross-sectional area of a cylinder coaxial with the ion's path within which the dosage of absorbed ionization energy is equal to or greater than the  $\gamma$ -ray  $D_{37}$ . In the present theory there is no arbitrary separation into core and cloud interactions. The quantitatively significant parameter is taken to be the dosage of absorbed ionization energy, delivered to the medium by all electrons ejected from the ion's path. We refer to all these electrons as  $\delta$ -rays.

### THEORY

The simplest biological materials are thought to consist of "targets," or sensitive units, embedded in a passive matrix. We consider here only "one-hit" processes in dry materials, in which a single ionization within the sensitive unit (say, a single

molecule which loses its function if one of its many bonds is broken) is responsible for inactivation.

The probability for inactivation may be described by the Poisson formula (3), which for a perfectly random one-hit process is given by

$$P = 1 - \exp(-D_r/D_r^{37}) \quad (1)$$

where  $P$  is the probability for inactivation when irradiated by a random dose,  $D_r$ , and  $D_r^{37}$  is the random dose for 37% survival. By dose we mean here the energy deposited in the absorbing medium by ionizing radiation.

Since the radiation damage considered here is due to electron interactions with the medium, we would expect the most nearly random interactions to arise when a beam of high-energy electrons strikes a thin section of the material.

While the site of the initial photoelectron or the Compton electron is random in the case of  $\gamma$ -irradiation, the subsequent emission of Auger electrons and the subsequent interactions along the electron tracks are highly correlated to the initial site and to the immediately preceding ionizations. Empirically, for small targets, this departure from randomness does not affect the applicability of equation 1 to  $\gamma$ -irradiations in a detectable way.

In the present work we take the departure from randomness in a small-volume element to be the same for  $\gamma$ -rays and  $\delta$ -rays when the deposited ionization energy is the same. Thus the Poisson formula for one-hit processes is assumed to be equally quantitative for describing the effects due to  $\delta$ -rays as it is for describing the effects due to  $\gamma$ -irradiation. Observed differences in response to heavy ion bombardment and to  $\gamma$ -rays are here ascribed to the grosser differences in the spatial distribution of ionization energy due to the common origin of the  $\delta$ -rays. Instead of an arbitrary separation into core and cloud, we examine the dosage of ionization energy in coaxial cylindrical shells about the ion's path, and for each shell we determine the fraction of lethal events from the  $\gamma$ -ray experience.

The formula  $(1 - e^{-SD})$  represents the probability for the inactivation of a target by a beam containing  $D$  particles per square centimeter, where  $S$  represents the probability for inactivation by a single particle per square centimeter. Thus  $S$  is the inactivation probability per (particle per square centimeter), in exact analogy with radioactive decay where the decay constant,  $\lambda$ , is the probability of decay per second, and the probability for decay in  $t$  seconds is  $1 - e^{-\lambda t}$ . If a single particle passes through a thin slab of biological material, the average number of targets hit is equal to the product of  $S$  by the number of targets per square centimeter. Thus we can calculate  $S$  by dividing the average number of targets hit by a particle by the number of targets per square centimeter.

Consider first a thin cylindrical shell of length  $T$ , radius  $x$ , and thickness  $dx$ , concentric with the ion's path. Let  $T$  be sufficiently small that the speed of the ion is nearly constant over the length of the cylinder. The energy per unit volume de-

livered by  $\delta$ -rays (and of electrons arising from the interaction of  $\delta$ -rays with the medium),  $D_\delta$ , is uniform over the shell, and the number of hits inside the shell is given by the product of the volume of the shell, the number of targets per unit volume, and the probability for inactivation under this dose. If  $N_0$  is the number of targets per unit volume, and  $D^{37}$  is the  $\gamma$ -ray dose for 37% survival, the number of hits inside the shell,  $d\mathfrak{N}$ , is given by the equation

$$d\mathfrak{N} = (T2\pi x dx)(N_0)[1 - \exp(-D_\delta/D_\gamma^{37})] \quad (2)$$

We find the total number of inactivations,  $\mathfrak{N}$ , arising from the passage of a single ion by integrating equation 2 over all  $x$ . The cross section is found by dividing the total number of targets hit by the passing ion by the number of targets per unit area, or

$$S = \frac{\mathfrak{N}}{N_0 T} = 2\pi \int_0^\infty x dx [1 - \exp(-D_\delta/D_\gamma^{37})] \quad (3)$$

In the above development an assumption of small targets is implicit. The whole target is assumed to be subjected to the same dose and hence the same inactivation probability. The calculation is then rigorously valid only for point targets but is expected to be a good approximation for the targets in enzymes and bacteriophages. (See the Appendix.)

To evaluate the above expression, we must derive an expression for the  $\delta$ -ray dose,  $D_\delta(x, \beta, Z^*)$ , as a function of the radial distance,  $x$ , from the ion's path. This is done by making use of the well-known  $\delta$ -ray distribution formula:

$$\begin{aligned} dn &= \frac{CZ^{*2}}{\beta^2} \frac{dw}{w^2} & w &\leq w_{\max} \\ dn &= 0 & w &> w_{\max} \end{aligned} \quad (4)$$

where

$$C = \frac{2\pi N e^4}{m c^2} = 1.36 \times 10^{-7} \frac{\text{ergs}}{\text{cm}} = 0.85 \frac{\text{keV}}{100 \mu}$$

which gives the number of secondary electrons ( $\delta$ -rays) per unit length of path having energies in the interval  $w$  to  $w + dw$ , produced by an ion of effective charge  $Z^*e$  moving with speed  $\beta c$ , where  $m$  and  $e$  are the electron mass and charge, and  $N$  is the number density of electrons in the material. The upper limit,  $w_{\max} = 2mc^2\beta^2\gamma^2$ , where  $\gamma^2 = 1 - \beta^2$ , is derived from kinematic considerations in a head-on collision. We approximate biological material by water, for which  $N = 3.35 \times 10^{23}$  electrons/cm<sup>3</sup>. To take into account charge pickup, equation 4 must be supplemented by an expression for the effective charge,  $Z^*e$ , of an ion of atomic number  $Z$  at speed  $\beta c$ . We use an expression given by Barkas (9),

$$Z^*e = Ze[1 - \exp(-125\beta Z^{-2/3})] \quad (5)$$

For convenience we have plotted  $Z^{*2}$  against  $\beta$  in Fig. 1.

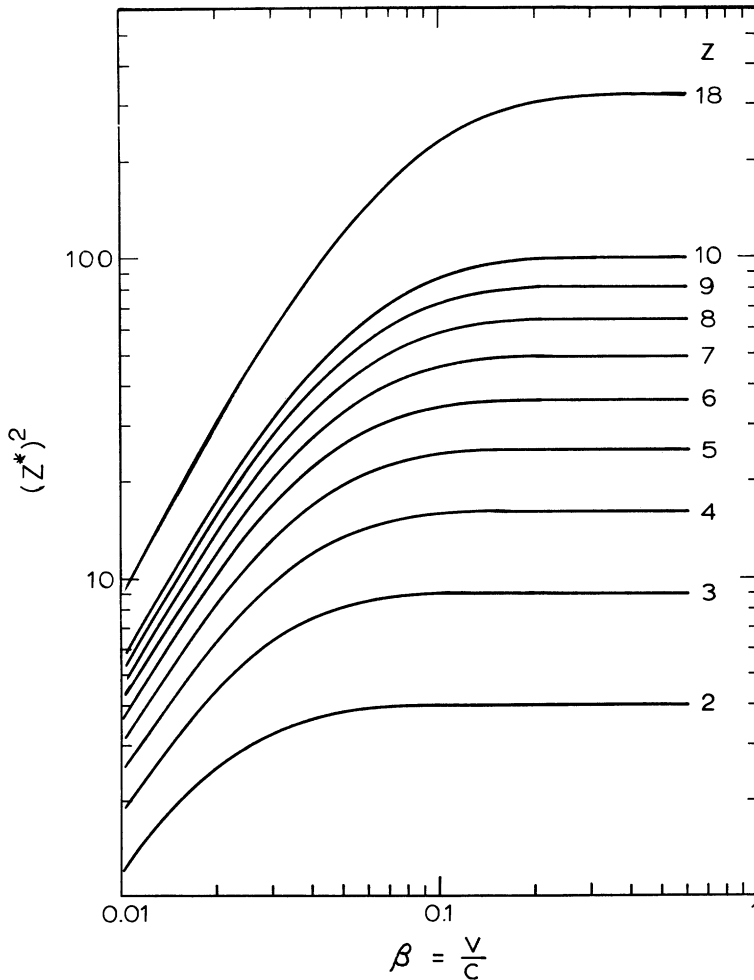


FIG. 1. Effective charge squared ( $Z^{*2}$ ) as a function of  $\beta$  ( $= v/c$ ) for ions whose atomic number ranges from 2 to 18, from equation 5.

It can be shown that electrons of energy  $w$  are ejected at an angle  $\theta$  to the path of the moving ion, given by

$$\cos^2 \theta = w/w_{\max} \quad (6)$$

From equation 4 we can see that the majority of  $\delta$ -rays have energies much less than  $w_{\max}$  and therefore have ejection angles approximately equal to  $90^\circ$ . Thus, to simplify the calculation we shall assume that all electrons are ejected normally to the ions path.

To proceed with the calculation we need a range-energy formula for electrons of

energies 1 keV and lower. Only limited data are available in this energy range, so we assume a relation of the form  $x = kw^\alpha$ , and choose  $k$  and  $\alpha$  to make this power law formula join smoothly with the data obtained by Kanter and Sternglass (10) for electrons of 0.6 keV and above. The adjusted values are:  $k = 10 \mu\text{g}/\text{cm}^2 \text{ keV}$  ( $6230 \text{ gm}/\text{cm}^2 \text{ erg}$ ) in water, and  $\alpha = 1$ . Thus we have

$$x = kw = 6230w \quad (7)$$

which fits the available data to 10% in the region of interest, below 2 keV. Differences between "practical range" and "average range" which can be accommodated by adjusting the value of  $k$  in equation 7 are of little significance in the final result, as discussed in the paragraph below equation 9.

Using the range-energy relation of equation 7, we find that a single normally ejected electron which passes through a cylindrical shell of thickness  $dx$  and radius  $x$  will deposit energy  $dw = k^{-1} dx$  within that shell. To find the total energy deposited within the shell we must find the number of penetrating  $\delta$ -rays arising from the passing ion. If electrons of energy  $w(x)$  just penetrate a shell of radius  $x$ , then the total number of electrons passing through the shell are those having energy between  $w(x)$  and  $w_{\text{max}}$ , found by integrating equation 4 between these limits. We obtain

$$\begin{aligned} n[w(x), w_{\text{max}}] &= \frac{CZ^{*2}}{\beta^2} \int_{w(x)}^{w_{\text{max}}} \frac{dw}{w^2} \\ &= \frac{CZ^{*2}}{\beta^2} \left[ \frac{1}{w(x)} - \frac{1}{w_{\text{max}}} \right] \end{aligned} \quad (8)$$

To find the energy deposited per unit volume in the cylindrical shell, we multiply the energy deposited by each electron by the total number of penetrating electrons, and divide by the volume of the shell ( $2\pi x dx$ ) to obtain

$$\begin{aligned} D_\delta(x, \beta, Z^*) &= \frac{k^{-1} dx}{2\pi x dx} \frac{CZ^{*2}}{\beta^2} \left[ \frac{1}{w(x)} - \frac{1}{w_{\text{max}}} \right] \\ D_\delta &= \frac{CZ^{*2}}{2\pi x \beta^2} \left( \frac{1}{x} - \frac{1}{X} \right) \end{aligned} \quad (9)$$

where  $X = kw_{\text{max}}$ .

In Fig. 2 we have plotted the dose divided by  $Z^{*2}$  against  $x$  for water. The dose drops off very rapidly with distance, and is negligible for the biological materials we are considering at a micron from the ion's path. A slowly moving ion of effective charge  $10e$  liberates enough energy to vaporize water in a cylinder 100 A in diameter. Note that in equation 9, for  $x$  much smaller than  $X$ , the maximum range of a



$\delta$ -ray, we can neglect  $1/X$  in relation to  $1/x$ ; the dose does not depend on  $k$ . In this circumstance the precise form of the range-energy relation for electrons is unimportant.

We now incorporate equation 9 into equation 3 to find an explicit equation for

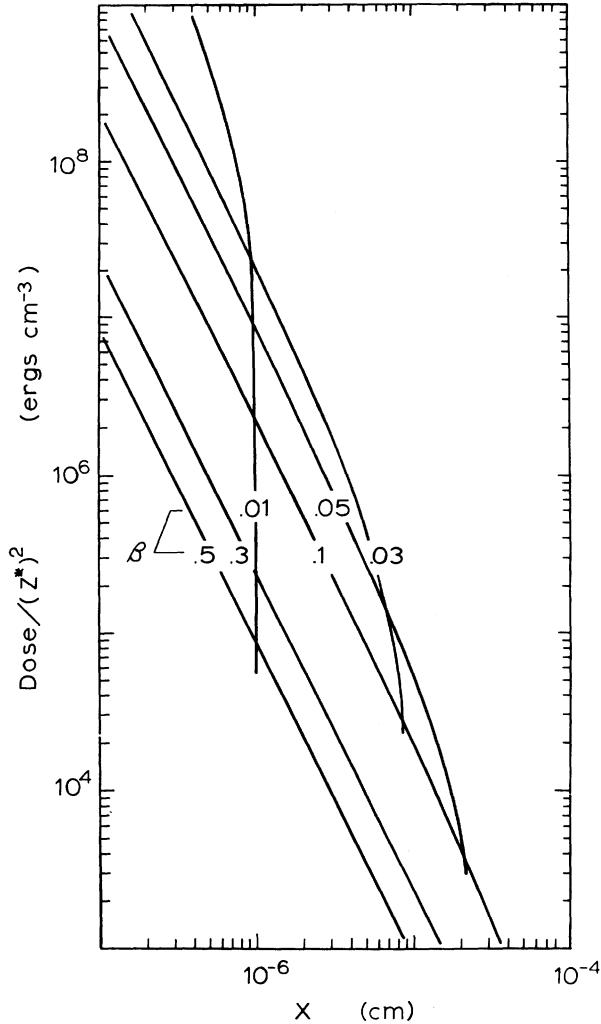


FIG. 2. Dose of ionization energy arising from  $\delta$ -rays ejected by an ion of effective charge  $Z^*$ , in water, as a function of radial distance from the ion's path, with  $\beta$  as parameter. The curve for  $\beta = 0.01$  is to be taken as representing the greatest possible outward extension in the distribution of ionization energy, for in this case the approximation that electrons of energy below 1 keV are ejected normally is clearly incorrect.

the cross section,  $S$ , as

$$S = 2\pi \int_0^x x d\bar{x} \left\{ 1 - \exp \left[ -\frac{CZ^{*2}}{2\pi x \beta^2 D_{\gamma}^{37}} \left( \frac{1}{x} - \frac{1}{\bar{X}} \right) \right] \right\} \quad (10)$$

The results of numerical integration of equation 10 are plotted in Fig. 3, with  $\beta$  as a parameter. The family of curves provides for the easy determination of the theoretical cross section,  $S$ , for a wide range of the parameter  $D_{\gamma}^{37}/Z^{*2}$ .

For completeness the theoretical results shown in equation 10 and in Fig. 3 have been recalculated to produce a theoretical graph of  $S$  versus LET in Fig. 4, where  $D_{\gamma}^{37}$  and  $Z$  are used as parameters to describe the family of curves.

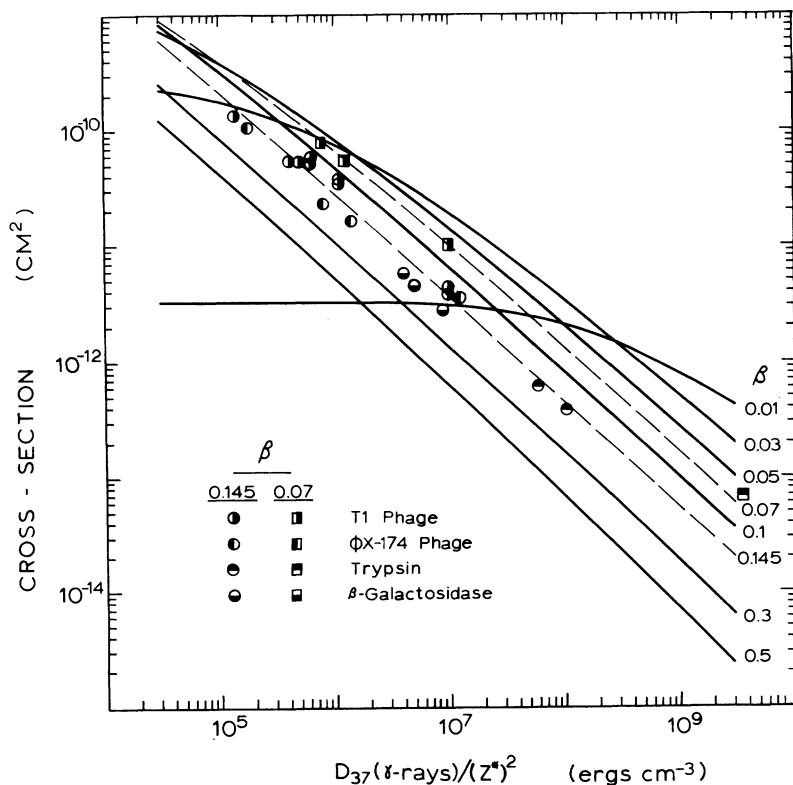


FIG. 3. Theoretical relationship between cross section and  $D_{\gamma}^{37}$  for a variety of bombardments. The theoretical curve for  $\beta = 0.01$  is to be taken as an upper limit on the cross section, as explained in the legend to Fig. 2. Unadjusted experimental data for two viruses and two enzymes are shown superimposed on the theoretical curves. Circles should be compared to the dashed line for  $\beta = 0.145$ , while squares should be compared to the solid line for  $\beta = 0.07$ . Experimental points have been drawn so that the radius of the circle, and the half side of the square, represents a 10% uncertainty.

Another parameter of interest, the RBE, has been calculated from the relation

$$\text{RBE} = \frac{SD_{\gamma}^{37}}{\text{LET}} \quad (11)$$

and plotted against LET in Fig. 5, again with  $D_{\gamma}^{37}$  and  $Z$  as parameters.

For both Fig. 4 and Fig. 5, LET has been calculated from energy loss tables for protons in the usual way.

The present theory, which yields the inactivation cross section,  $S$ , as a function of  $D_{\gamma}^{37}$ ,  $Z$ , and  $\beta$ , thus constitutes a complete theory of RBE for heavy ions and one-hit processes in dry enzymes and viruses.

### RESULTS

Experimental cross sections obtained for the enzymes  $\beta$ -galactosidase and trypsin and T-1 and  $\phi$ X-174 bacteriophages by investigators using the Yale and

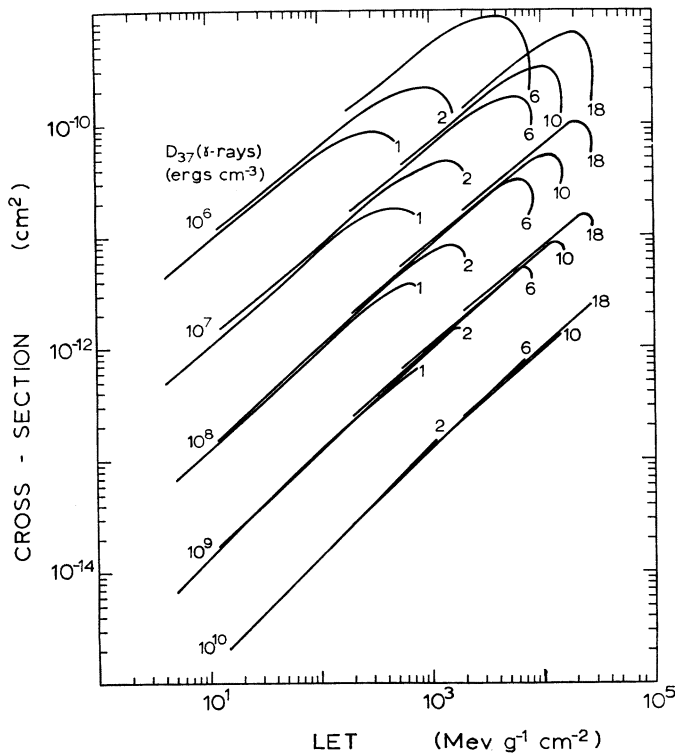


FIG. 4. Theoretical curves of cross section versus LET for one-hit processes in dry enzymes or viruses. Families of curves for different sensitivities ( $D_{\gamma}^{37}$ ) branch according to the atomic number of the bombarding ion.

Berkeley heavy ion accelerators are shown in Table I. These materials were bombarded with ions whose atomic number ranged from 1 to 18, at energies of 2.3 and 10 MeV/nucleon. Experimental values of the cross section,  $S$ , the  $\gamma$ -ray  $D^{37}$ , and the physical target areas derived from conventional target theory (assuming spherical targets) are also quoted.

The theory has been compared with experiment in two ways.

In Fig. 3 we have plotted the unadjusted experimental relationship between the cross section  $S$  and the parameter  $D_{\gamma}^{37}/Z^{*2}$ . The value of the effective charge comes

TABLE I.

## INACTIVATION OF ENZYMES AND BACTERIOPHAGE BY PARTICLE BOMBARDMENT

Superscripts in the left hand column refer to the sources of the data. Experimental D-37 doses for  $\gamma$ -rays are given in the left hand column, together with the adjusted D-37  $\gamma$ -ray dose (theory) used to obtain the theoretical values of the cross section. Powers of ten are shown in parentheses.

SUBSTANCE	BOMBARDMENT		CROSS - SECTION (cm <sup>2</sup> )	
	Z	$\beta$	EXPERIMENT	THEORY
<u><math>\beta</math>-Galactosidase</u> <sup>4</sup> target area=3.1 (-13) cm <sup>2</sup> D-37 for $\gamma$ -rays exp: 3.1(8)erg/cm <sup>3</sup> theory: 5.0(8) "	6	0.145	2.8 (-12)	2.7 (-12)
	8	"	4.5 "	4.6 "
	9	"	5.7 "	5.6 "
<u>Trypsin</u> <sup>4</sup> target area=6.0 (-14) cm <sup>2</sup> D-37 for $\gamma$ -rays exp: 3.6(9)erg/cm <sup>3</sup> theory: 4.5(9) "	1	0.065	6.7 (-14)	4.6 (-14)
	6	0.145	3.8 (-13)	3.7 (-13)
	8	"	6.1 "	6.1 "
<u><math>\phi</math>X-174 Phage</u> <sup>5</sup> target area=1.0 (-12) cm <sup>2</sup> D-37 for $\gamma$ -rays exp: 5.0(7)erg/cm <sup>3</sup> theory: 8.0(7) "	2	0.145	3.5 (-12)	2.0 (-12)
	6	"	1.6 (-11)	1.4 (-11)
	8	"	2.3 "	2.4 "
	18	"	1.0 (-10)	8.9 "
<u>T-1 Phage</u> <sup>5</sup> target area=1.2(-12) cm <sup>2</sup> D-37 for $\gamma$ -rays *exp: 3.9(7)erg/cm <sup>3</sup> theory: 3.5(7) "	2	0.145	4.4 (-12)	4.2 (-12)
	6	"	3.8 (-11)	3.0 (-11)
	8	"	5.3 "	5.0 "
	9	"	5.3 "	6.1 "
	10	"	5.4 "	7.2 "
	18	"	1.4 (-10)	1.8 (-10)
<u>T-1 Phage</u> <sup>6</sup>	2	0.085	1.0 (-11)	0.87 (-11)
	2	0.156	0.38 "	0.38 "
	6	0.073	5.4 "	6.0 "
	6	0.140	3.6 "	3.1 "
	8	0.069	7.9 "	9.2 "
	8	0.133	5.9 "	5.5 "

\* This is an average of 5.5(7) ergs/gm<sup>5</sup> for Co<sup>60</sup>, 4(7) ergs/gm<sup>7</sup> for Co<sup>60</sup>, and 2.3(7) ergs/gm<sup>8</sup> for 65kV Peak x-rays. The most recent study of T-1 phage dosimetry<sup>11</sup> gives 5.7(7) ergs/gm.

TABLE I—Continued

LET (Mev gm cm <sup>-2</sup> )	RBE	
	EXPERIMENT	THEORY
1630 2860 3580	0.33 0.31 0.31	0.52 0.50 0.49
160 1630 2860	0.53 0.52 0.49	0.81 0.64 0.60
182 1630 2860 12800	0.60 0.31 0.25 0.26	0.55 0.43 0.42 0.35
182 1630 2860 3580 4380 12800	0.59 0.57 0.45 0.36 0.30 0.26	0.51 0.40 0.38 0.37 0.36 0.31
426 162 4290 1720 7350 3260	0.57 0.57 0.31 0.51 0.26 0.44	0.45 0.51 0.31 0.40 0.27 0.37

from measurements of the range of accelerated heavy ions of known initial speed in emulsion. The half-shaded squares represent materials irradiated at  $\beta = 0.07$ , while the half-shaded circles come from irradiations at  $\beta = 0.145$ , and are to be compared with appropriate dashed lines on the figure, representing the theoretical relationship. Notice that there is agreement between theory and experiment to four orders of magnitude in the plotted parameters, to a maximum deviation of 30%, and to an average deviation of 15%. The radius of the plotted circle has been chosen to represent a 10% error.

Since any error in the experimental  $D_{\gamma}^{37}$  for a biological material will be seen as an error in each of the points for that material in Fig. 3, we have sought to compare theory to experiment in another way. By trial we have found "theoretical" values of  $D_{\gamma}^{37}$  whose substitution into equation 10 produced values of the cross section  $S$  in good agreement with experiment, as shown in the column of Table I entitled Cross-section, Theory. The experimental values of  $D_{\gamma}^{37}$  and their "theoretical"

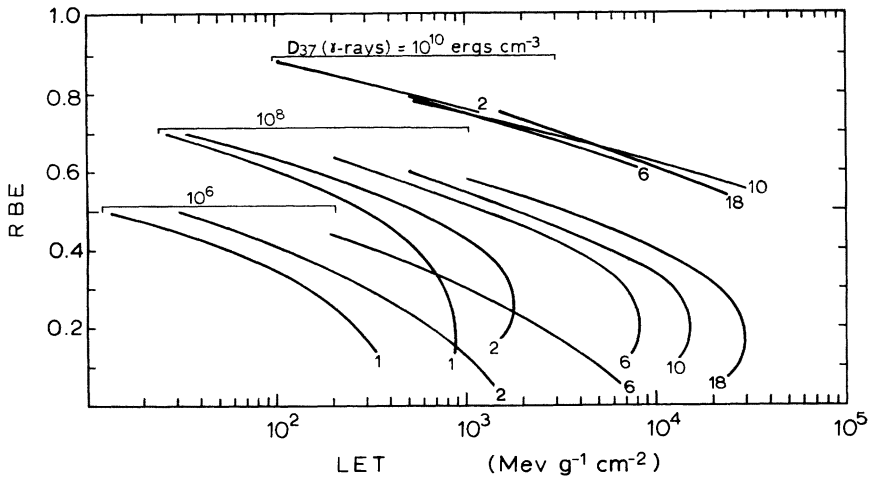


FIG. 5. Theoretical curves of RBE versus LET for one-hit processes in dry enzymes or viruses. Families of curves for different sensitivities ( $D_{\gamma}^{37}$ ) branch according to the atomic number of the bombarding ion.

counterparts are given in the first column of the table. Note that the adjusted "theoretical"  $D_{\gamma}^{37}$  is larger than the experimental values in three cases and smaller in one.

Table I also gives LET, experimental RBE, and theoretical RBE, the latter determined by use of the "theoretical"  $D_{\gamma}^{37}$  value. In Fig. 4, which gives  $S$  as a function of LET, these data fall within a rectangle approximately bounded by  $10^2 < \text{LET} < 10^4$  ( $\text{MeV gm}^{-1} \text{cm}^2$ ) and  $4.5 \times 10^{-14} < S < 1.37 \times 10^{-10} \text{ cm}^2$ . These curves show that in the limit of small LET (fast ions) and large  $D_{\gamma}^{37}$  (insensitive materials) the cross section is simply proportional to LET, while at the opposite limits (high LET and sensitive material) the relationship is complicated by saturation or overkill near the ion's path.

The theoretical curves of RBE versus LET, shown in Fig. 5, are for three values of  $D_{\gamma}^{37}$ . The experimental data referred to above all lie within a range  $0.3 < \text{RBE} < 0.6$ . For a given ion at small values of LET, the RBE is larger for hard-to-kill materials. In the limit of small LET all ions converge to the same RBE, the convergence being more rapid for large values of  $D_{\gamma}^{37}$ . Again, these effects can be understood qualitatively in terms of saturation near the ion's path. At small LET and large  $D_{\gamma}^{37}$  (corresponding to small target size), the ionization is more nearly random, and there is less chance for multiple hits, resulting in RBE values approaching unity.

#### DISCUSSION

Let us consider the simplifying assumptions used in the calculations, and the limits these place on the expected validity of the results.

In all calculations, water, of density 1, was used as an approximation to the biological material. This is permissible, since the cross section is in most cases only weakly dependent on density. A calculation has shown that a change in the assumed density of the materials in Table I results in only a slight change in the adjusted  $\gamma$ -ray  $D_{37}$ . A change in the density of the medium from 1.00 to 1.35 causes the theoretical curves of Fig. 3 to shift by less than a line width in most cases, and by less than experimental uncertainty in all cases. The weak dependence on density may be understood by considering equation 9. At distances  $x$  from the ion's path much less than the range  $X$  of the most energetic  $\delta$ -ray, the dosage of deposited ionization energy,  $D_\delta$ , is proportional to density, since the constant  $C$  in this equation contains the electron density of the material as one of its factors. In the computation of cross section in equation 3 we are concerned with the ratio of  $D_\delta$  to  $D_\gamma^{37}$ . Since the dosage of ionization energy for 37% survival under  $\gamma$ -irradiation is also density-dependent, this ratio is independent of density for small  $x/X$ . At low ion speeds, where the cross section is limited by the range of the most energetic  $\delta$ -ray, density variations become significant. In Fig. 6 we have plotted the cross section in square centimeters versus the parameter  $D_{37}(\gamma\text{-rays})/(Z^*)^2$ , in units of ergs per gram, for material of density 1.35 and 3.00.

Electron range-energy relations determined in aluminum at energies from 0.6 to 10 keV (10) were linearly extrapolated to energies below 1 keV, and applied to water. Secondary electrons are assumed to affect the determination of range-energy relations in the same way that they affect the biological material. Thus the energy loss determined from these range-energy relations is assumed to include primary and secondary processes, and to take account of scattering as well.

For simplicity in the calculation, electrons are assumed to be ejected normally to the ion's path. This assumption should introduce most serious error at low  $\beta$ . In the  $\beta = 0.01$  curve of Fig. 3, the cross section approaches a constant value at low  $D_\gamma^{37}/Z^{*2}$ , because in the limit of very sensitive materials  $S$  is determined by the maximum range of a  $\delta$ -ray, and is given by  $S = \pi X^2$ . If angular ejection is taken into account, the more energetic  $\delta$ -rays are thrown forward, and  $S$  is considerably smaller than shown in the figure. The curves for  $\beta = 0.01$  in Figs. 2 and 3 are to be taken as arising from upper limits on  $S$ .

Our extrapolated range-energy relation yields ranges below experimental practical ranges for electrons of energy above 5 keV. For such electrons our range-energy relationship yields an energy loss rate which is too high. To some extent this error compensates for the error made in assuming normal ejection, for higher energy electrons.

Yet another oversimplification arises from electron binding. The  $\delta$ -ray distribution formula which we use is for free electrons. Errors arising from electron binding in the K-shell of oxygen may be expected to appear for cross sections smaller than  $10^{-12}$  cm<sup>2</sup>.

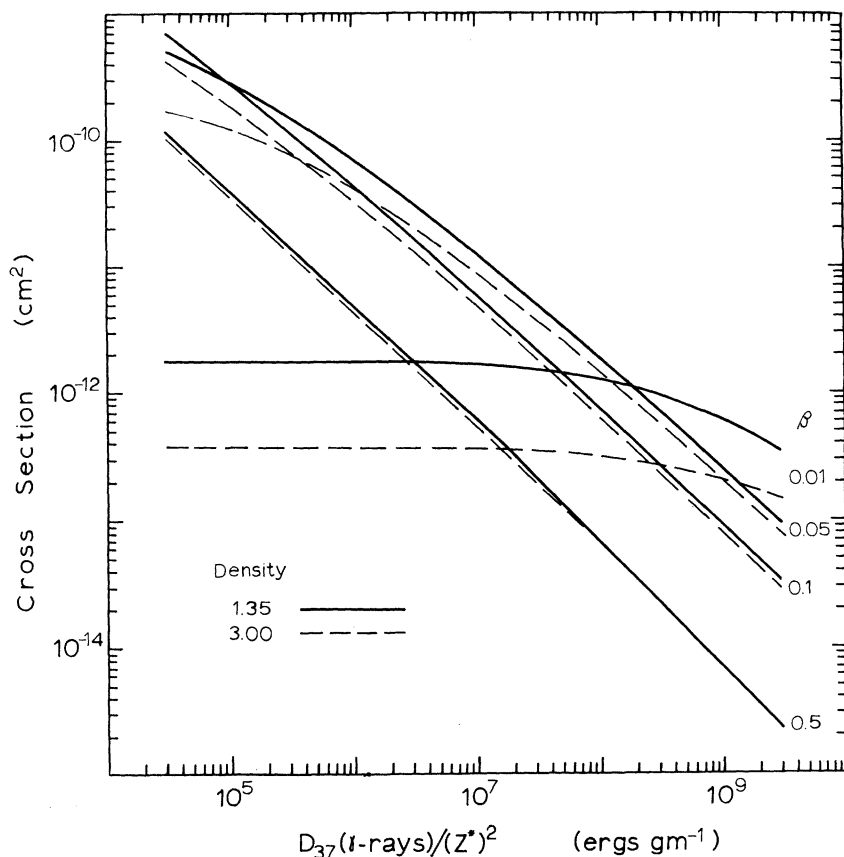


FIG. 6. The effect of density on the relation between cross section and the  $D_{37}$  dose for  $\gamma$ -rays is shown here, repeating the calculations of Fig. 3 for materials of density 1.35 and 3.00. Where the bombarding ion moves sufficiently fast that the cross section is not determined principally by the range of the most energetic  $\delta$ -ray, density effects are not of great significance.

This model for heavy ion inactivation is not meant to replace target theory in its application to X-ray or  $\gamma$ -ray inactivation, where the theory relates a hypothetical random dose to the correlated dose produced by these radiations by use of a calculated "overlap" factor. The function of the present model is to relate heavy ion inactivation cross sections to  $\gamma$ -ray inactivation doses through the spatial distribution of ionization energy arising from the ion's passage. It must be emphasized that the present model depends on target size only insofar as the  $\gamma$ -ray  $D_{37}$  depends on target size, and, accordingly, the broad range of agreement between the predictions of the model with experiment implies that measured heavy ion cross sections are only indirectly related to the actual physical cross section of the target, for these materials.



In view of the many neglects and approximations, the final case for the present model rests on its agreement with experiment. As shown in Fig. 3, all experimental data published in *Radiation Research* to the date of preparation of this paper, dealing with the interaction of heavy ions on dry viruses and enzymes, are in agreement with the theory to about the accuracy of the experimental measurement. Indeed, we may infer that biological materials have been too long neglected as practical radiation detectors capable of spatial resolution to molecular dimensions, and below, for the one-hit character of these materials implies resolution at the level of the single bond. As an oversimplified clarification of the present work, we may view the one-hit curve for a given  $D_\gamma^{37}$  as a quantitative relation between response and exposure for the enzyme or virus, much like a photographic sensitivity curve ( $H$  and  $D$  curves) relating blackness to exposure. Experimental verification of the calculation of the cross section is then like experimental verification of the distribution of blackness about the path of an ion, and constitutes an experimental verification of the model of the transverse distribution of ionization energy which is here presented.

Viewed in such a perspective the present work represents the application of biological detectors to the resolution of a hitherto unsolved physical problem—that of determining the transverse distribution of ionization energy about the path of a charged particle.

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#### APPENDIX

##### CONCERNING THE VALIDITY OF THE POINT TARGET APPROXIMATION

The assumption of point targets must be justified. In the integration of inactivation probability over all values of  $x$ , equation 10, we have assumed that each extended molecule is subjected to a uniform dose field, so that each vital bond experiences the same dose and has the same inactivation probability. The expression  $1 - \exp(-D_i/D_\gamma^{37})$  represents the probability for inactivation of the molecule through inactivation of any one of its  $m$  vital bonds. If the dose varies rapidly with position, as for molecules close to the path of a bombarding ion, we first must calculate the probability for survival of each bond separately, and find the probability for the survival of a molecule as a result of these independent processes by taking the product of the bond survival probabilities.

Consider a target located with its "center of gravity" at distance  $x$  from the ion's trajectory. Let the target have  $m$  vital bonds located at distances  $x \pm y_i$  from the ion's path, where  $i = 1, 2 \dots m/2$ . The probability of inactivation of the target is

then given by

$$1 - \text{probability of survival} = 1 - \prod_{i=1}^{m/2} \exp \frac{-D_\delta(x + y_i) - D_\delta(x - y_i)}{mD_\gamma^{37}}$$

$$= 1 - \exp \frac{-\sum_{i=1}^{m/2} [D_\delta(x + y_i) + D_\delta(x - y_i)]}{mD_\gamma^{37}}$$

where  $D_\delta(x \pm y_i)$  is the dose delivered by  $\delta$ -rays at distance  $x \pm y_i$  from the trajectory, and  $D_\gamma^{37}$  is the  $\gamma$ -ray dose producing 37% survival. From equation 9 we have

$$D(x \pm y_i) = Q \left\{ \frac{1}{x^2} \left( 1 \pm \frac{y_i}{x} \right)^{-2} - \frac{1}{xX} \left( 1 \pm \frac{y_i}{x} \right)^{-1} \right\}$$

where  $Q = CZ^{*2}/2\pi\beta^2$ . Expanding in terms of  $y_i/x$  we obtain

$$D_\delta(x + y_i) + D_\delta(x - y_i)$$

$$= Q \left\{ \frac{2}{x^2} \left[ 1 + 3\left(\frac{y_i}{x}\right)^2 + \dots + \right] - \frac{2}{xX} \left[ 1 + \left(\frac{y_i}{x}\right)^2 + \dots + \right] \right\}$$

For small values of  $y_i/x$  this becomes, after second and higher order terms have been dropped,

$$D_\delta(x + y_i) + D_\delta(x - y_i) \simeq 2Q \left[ \frac{1}{x^2} - \frac{1}{xX} \right] = 2D_\delta(x)$$

and the probability of kill may be written as

$$1 - \exp \left[ - \sum_{i=1}^{m/2} \frac{2D_\delta(x)}{mD_\gamma^{37}} \right] = 1 - \exp \left[ - \frac{D_\delta(x)}{D_\gamma^{37}} \right]$$

which is the expression that we have used. Therefore the point target approximation is certainly valid for values of  $x$  greater than approximately three target radii. By doing the numerical integration in two parts we have determined that the contribution from the domain  $x$  less than three target radii averages 20% of the total cross section for the twenty-two theoretical cross sections listed in Table I and ranges from 5% (for  $Z = 8$ ,  $\beta = 0.145$ , T-1 phage) to 40% (for  $Z = 1$ ,  $\beta = 0.065$ , trypsin). This does not mean that the error is 20%, but only that on the average 20% of the calculated cross section is questionable, owing to variation of dose over the target. To clarify these points, a calculation was made, taking into account the spatial distribution of bonds in extended molecules in the region below three target radii, and the variation of dose with distance from the ion's path in this region. The molecules were approximated as chunky cylinders with axes parallel to the ion's path and with volumes determined from the  $D_\gamma^{37}$ . Additional calculations of

this sort are being undertaken to attempt to set limits on the validity of the point particle approximation for a wider range of bombardments and target sizes than have been considered here. For the substances and bombardments herein considered, the chunky cylinder calculation agrees with the point particle approximation to 5%.

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