

FLUCTUATIONS IN ENERGY LOSS AND THEIR IMPLICATIONS FOR DOSIMETRY AND RADIOBIOLOGY*

Norman A. Baily and John E. Steigerwalt
Department of Radiology
University of California, San Diego
La Jolla, California 92037

INTRODUCTION

Traditionally all of dosimetry has been based on the measurement or calculation of the average energy deposited in a small volume expressed originally by the Roentgen, a unit of exposure for x and γ -rays, and more recently and of wider applicability by the absorbed dose expressed in Rads. Both are macroscopic concepts since they presume a sufficient number of ionizing events so that statistical fluctuations of energy loss by charged particles (primary or secondary) may be ignored. In the case of very small volumes such as those of importance in radiobiology and where most effects are considered to be due to a very small number of events taking place in this volume the probability of transferring an amount of energy equal to or nearly equal to the average energy loss computed from the charged particle stopping power in most instances is very small. The energy transferred to any particular biological entity is given by a frequency distribution function which in many cases is skewed toward high energy events and therefore the most probable energy loss is considerably less than the average. This is of fundamental importance in predicting radiation damage to the individual cells, chromosomes, molecules, etc. whose cumulative effect we observe. Generally, then, the absorbed dose would only be applicable as a measure of energy delivered when large numbers of individual events are pertinent such as might be found in large masses of material or where the effect observed is due to many events.

In most instances where biological material is being studied, the individual transfers of energy from incident particles to atomic electrons are subject to wide statistical fluctuations¹⁻³. In these cases, the usual concept upon which dosimetry is based (average energy loss or stopping power of charged particles) breaks down, except for the most densely ionizing particles. This is always the case when one considers volumes as small as those associated with the various biological structures of interest in fundamental radiobiology, radiation therapy, and health physics.

As a consequence in almost all cases, energy deposition in the biological volumes involved have a wide separation of the most probable and average energy losses. This state usually exists for most of the radiations currently of interest. Only in the case of very densely ionizing particles such as heavy ions can these considerations be neglected.

There are multiple reasons why this approach has persisted. First, physical determinations of statistical distributions of energy loss have been restricted to pathlengths large compared to those of biological interest and second, many have been examined using instruments which accumulated data over many pathlengths simultaneously thereby masking fundamental physical phenomena. Over

the past few years, the work of Baily and his collaborators⁴⁻⁶ has shown the importance of such considerations for high energy protons (~ 45 MeV).

FUNDAMENTAL CONCEPTS

Despite certain discrepancies between experiment and theory which have been found for energy loss distributions due to single charged particle traversals through small volumes, a rather good representation of the experimental data is given by the theory for those energy losses occurring at and about the most probable value. The discrepancies appear as an excess of high energy events with a subsequent dearth of events lying below that of the most probable energy loss. The average energy loss obtained from theory and experiment show agreement within experimental error. Since the discrepancies mentioned are not large ($\sim 20\%$ excess of high energy events), calculations made using the Blunck-Leisegang corrected Vavilov or Landau theories are sufficiently accurate to examine current dosimetry and radiobiological concepts in the light of these distributions. Major among these are: a) Linear Energy Transfer (LET) and its role in predicting Relative Biological Effectiveness (RBE) or b) the reliability of the use of the average energy deposited to describe the local microscopic dose for a small number of events. As we shall show, the energy range over which these broad distribution functions is important is fairly extensive for most charged particles. Even Compton electrons generated at conventional x-ray energies and protons generated in tissue by fast neutrons fall within the group of particles to which these statistical concepts and associated physical phenomena apply.

Perhaps, in a qualitative way, the extent of the statistical fluctuations are best illustrated by an examination of the distribution functions of the frequency with which energy losses of a given magnitude take place in a given pathlength. Fig. 1 shows such frequency distributions for various charged particles corresponding to a pathlength of approximately 1μ of tissue. The degree of the statistical fluctuations are well illustrated by the four particles chosen. Curve A is that expected from a 50 keV electron; B from a 50 MeV proton; C from an 8 MeV alpha particle; and D from a 24 MeV stripped ^{12}C ion. The spread about the most probable energy loss is also given. This is expressed by the full width at half maximum (FWHM) as a percentage of the most probable energy loss. The ratio of the average to the most probable energy losses for the two lighter classes of particles is given in Tables I and II. These two values will coincide for very densely ionizing particles.

A number of things important to the production of radiobiological effects take place as particle charge and mass increase and similarly with decrease of particle energy. First, as shown for a heavy charged particle of energy ~ 2 MeV/amu, the distribution function has a gaussian shape and is narrowly distributed about the average energy loss $\left[\Delta X \left(-\frac{dE}{dX} \right) \right]$. Second, as charge and mass decrease, the FWHM increases, but its shape is still primarily gaussian. The peak or most probable energy loss coincides with the average energy loss. Third, as the magnitude of the energy loss decreases relative to the particle's kinetic energy, the curve becomes quite skewed on the high energy end. As a consequence as this trend continues skewness increases and

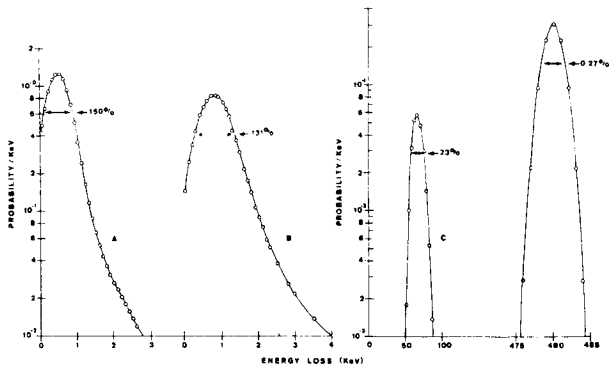


Fig. 1: Frequency distributions of energy loss by various charged particles in a tissue-equivalent medium. The pathlength used in these computations was 10^{-4} g/cm². Curve A is for a 50 KeV electron, B for a 50 MeV proton, C for an 8 MeV alpha particle, and D for a 24 MeV ¹²C stripped ion. Also shown are the spreads about the most probable energy loss expressed in terms of the full width at half maximum as a percentage of the most probable energy loss.

TABLE I

A comparison of average energy loss versus most probable energy loss for protons traversing 1 micron of soft tissue (muscle).

Ep (MeV)	$\bar{\Delta}$, Average Energy Loss (KeV)	Δ_{mp} , Most Probable Energy Loss (KeV)	$\bar{\Delta}/\Delta_{mp}$
1.0	27.1	27.0	1.00
2.0	16.9	15.7	1.08
5.0	8.26	6.31	1.31
10.0	4.64	3.11	1.49
50	1.26	0.669	1.88
100	0.736	0.360	2.04
150	0.549	0.258	2.13
600	0.257	0.109	2.35

TABLE II

A comparison of average energy loss versus most probable energy loss for electrons traversing 1 micron of soft tissue (muscle).

Electron Energy (MeV)	$\bar{\Delta}$, Average Energy Loss (KeV)	Δ_{mp} , Most Probable Energy Loss (KeV)	$\bar{\Delta}/\Delta_{mp}$
0.05	0.667	0.367	1.82
0.1	0.415	0.210	1.98
0.2	0.281	0.133	2.11
0.4	0.216	0.0981	2.20
0.6	0.196	0.0886	2.22
0.8	0.189	0.0848	2.22
1.0	0.185	0.0832	2.23
2.0	0.184	0.0824	2.23
4.0	0.189	0.0843	2.24
6.0	0.193	0.0855	2.25
8.0	0.196	0.0863	2.27
10.0	0.198	0.0868	2.28

the most probable energy loss becomes increasingly less than the average. Since the ratio of these can become quite large, this is of great significance in dealing with fundamental radiobiological (and therefore the ultimate overall) effects involving single or only a small number of interactions.

A measure of this physical phenomena and its possible consequences for dosimetry can best be appreciated by noting the ratio of the average energy loss to the most probable. Tables I and II give this ratio for protons and electrons respectively over a wide range of energies for particles traversing distances approximately equal to 1 μ of tissue. It should be pointed out that this ratio, in most cases, would be even larger if shorter path-lengths were involved.

The combination of the size of the biological material and the pattern of energy deposition which is due purely to the physics involved, prompts one to re-examine the use of macroscopic dosimetry units such as the rad asking if it is really suitable for use as a biological measure of radiation effects. Indeed if an

adjustment of this unit were to be made representative of the actual probability for delivering a specified amount of energy to a small volume, we might even appear to question some of the attributes usually associated with parameters such as LET, rate effects, etc.

While we do not mean to suggest that a more proper parameter would be based on one simple number such as the most probable energy loss, we do feel that a more careful consideration of fundamental physical phenomena should be given to the associated probabilities for energy deposition before ascribing certain biological factors to various types and energies of ionizing radiation since most biological effects seem to be caused by a relatively small number of events. The requirement for having only a small number of significant events as indicated by the magnitude of the extrapolation numbers combined with the small volumes involved when considered in light of the energy deposition frequency distributions gives a high probability for many types of radiation to deliver a total effective dose considerably less than that to be expected from the macroscopic (rad) dose. The magnitude of the discrepancy will, of course, depend on the type radiation and its energy.

CONSIDERATIONS INVOLVING R.B.E.

TABLE III

Comparison of normalized values of the ratio $\bar{\Delta}/\Delta_{mp}$ to some R.B.E. values reported for LD_{50/30} survival experiments in mice and survival and proliferation of Chinese hamster cells.

Proton Energy (MeV)	Irradiation Particle and Energy	$\bar{\Delta}/\Delta_{mp}$ (normalized)	R.B.E.
	592 MeV Protons ⁷		0.98, 1.06, Mice (relative to 250 kVp x-rays)
600		1.19	
	138 MeV Protons ⁸		1.07, Mice (relative to ⁶⁰ Co)
150		1.05	
	55 MeV Protons ⁹		1.3 - 2.3, Mice (relative to ⁶⁰ Co)
50		1.19	
	Fast Neutrons ¹⁰		2.18, Chinese Hamster Cells (relative to 280 kVp x-rays)
1.0		1.97	

A consideration of the actual energy likely to be absorbed in a biological structure as compared to that ordinarily specified by the absorbed dose leads one to question the validity of many values of R.B.E. reported or even to ask the question is the effect real. It is therefore of interest to examine this problem by assuming some other value of energy absorbed other than that measured or calculated by macroscopic concepts. Although an exact treatment would require a rigorous statistical treatment we have found that a simple adjustment of the dose gives values in agreement with those found experimentally by assuming that the most probable energy loss is more representative than the average energy loss. Looking at this problem then from the viewpoint of the initial experiment if the dose to the small biological volume had been specified by the actual amount of energy absorbed then many

differences in R.B.E. values attributed to a true biological effect would not have been found.

To explore this hypothesis, we have assumed that the ratio of

$$\Delta_{mp}/\bar{\Delta}$$

where: Δ_{mp} = the most probable energy loss, and

$\bar{\Delta}$ = the average energy loss

is a measure of the effective dose delivered to the individual elements of which the test material is composed and that the observed effect is the accumulation of damage to these elements.

The values of the inverse quantity given in the Tables I and II show a striking parallelism to many reported R.B.E. values for these radiations. We have therefore utilized these in the manner postulated above to calculate values of the R.B.E. we would have expected to have been found. This was done by adjusting the dose ratio from which the R.B.E. was obtained by the ratio of the $\Delta_{mp}/\bar{\Delta}$ ratios of the test radiation to that of the standard radiation.

Baarli and Bonet-Maury⁷ using 592 MeV protons found an R.B.E. of 0.98 for this radiation when they compared the dose for obtaining LD_{50/30} survival of mice to the dose required for a similar survival level using 250 kVp x-rays. In other tests, values of 1.06 were found. Adjusting the magnitude of the dose in each case by the ratio of $\Delta_{mp}/\bar{\Delta}$ assuming a mean electron energy of 100 KeV for the 250 kVp x-ray spectra gives a value of 1.19. Since the frequency distribution of the energy depositions for 600 MeV protons is a more highly skewed distribution than would be found for the mixed electron energy spectra associated with a 250 kVp x-ray generator the answer obtained is not unreasonable. If one were to include as highly probable events those close to but greater than Δ_{mp} , we should improve the agreement. We have done similar comparisons for a group of biological experiments using various proton energies and fast neutrons. The results are shown in Table III. While these are selected references and by no means represent the bulk of the literature, no special effort was made to pick biological data to match that obtained from the physical

measurements. The correlation with our oversimplified analysis is striking particularly in view of the fact that Δ_{mp} is almost certainly too low a value to be considered as a single parameter dosimetric value.

A similar approach can be used with the data presented by Barendsen, et al.¹¹ for electrons and x-radiation. Assuming an average energy of 700 keV for the beta spectrum used and an effective energy of 100 KeV for the 200 kVp x-rays used, we can compare the difference in biological effects produced with the ratio of $\bar{\Delta}/\Delta_{mp}$ for electrons having these energies. The biological effects (R.B.E.'s) showed a difference of 12%. The difference in the energy loss ratios is also 12%.

A recent series of experiments by Cerček, et al.¹² using 380 MeV protons and ⁶⁰Co γ-rays obtained R.B.E. values of 1.3 - 1.4 for these protons in several biological materials. Using the data in Table I and that of Wright, et al.¹³ for the fraction of dose delivered by heavy ions and pions, we would obtain a dose ratio (based on Δ_{mp}) of 1.13. If the narrowing of the frequency distribution which occurs with very densely ionizing particles was taken into account agreement would be even closer (Fig. 1). Many other examples where such agreement is found could be cited.

Examination of Table II together with the reasoning suggested would also explain the fact that in many instances, no significant changes in R.B.E. were found for L.E.T.'s as widely different as those associated with ⁶⁰Co and 200 kVp x-rays (0.27 KeV/μ in the case of ⁶⁰Co and a mean L.E.T. of 1.8 KeV/μ for a 200 kVp lightly filtered x-ray beam). In fact, with increases in photon energies up to 22 Mevp, R.B.E.'s have been found to change by only 10 to 15 per cent.

It should be realized, however, that for any meaningful application of the physical factors that we have pointed out requires a theory incorporating the probability for events of a given size in the volume of

interest corresponding to the number of events expected or required for damage or death.

Another aspect of this problem has to do with the possible requirement for deposition of a minimum amount of energy in the critical site. In an unpublished paper, Katz and his collaborators¹⁴ have obtained very good agreement with published R.B.E. values based on cell survival curves when values of 5 to 250 KeV are used as the minimum required value of the energy deposition in the sensitive site. Frequency distribution functions automatically provide: first, the fraction of events depositing energy greater than a certain energy and second, the fraction of the total energy deposited in event sizes greater than a given value. Two typical curves of this type are shown in Figs. 2 and 3. In addition to furnishing a ready source of information which can be used in Katz's¹⁴ or similar formulations, the data when presented in this manner serves to further illustrate the importance of taking into account possible differences in the values of $\bar{\Delta}$ and $\bar{\Delta}_{mp}$ and the associated changes in probability for events close to the average energy loss. For example, the data illustrated in Figs. 2 and 3 represent the frequency distributions for 46.4 MeV protons passing through 1.33×10^{-4} g/cm² of a tissue-equivalent gas (equal electron densities). The fraction of the total energy delivered to the gas by the proton in its passage through it in event sizes greater than $\bar{\Delta}$ (1.56 KeV) is 60%, while the fraction delivered by events having energy losses greater than $\bar{\Delta}_{mp}$ (0.90 KeV) is 88%. Similarly, Fig. 3 shows that the fraction of events occurring with energy losses greater than $\bar{\Delta}$ is only 35%, while those occurring with losses greater than Δ_{mp} is 73%.

This type of data also lends itself to interpretations of the shape of survival curves in lieu of the simple concepts of the hit theory. Both shoulder extension and slope of the exponential portion can be analyzed using data similar to that shown.

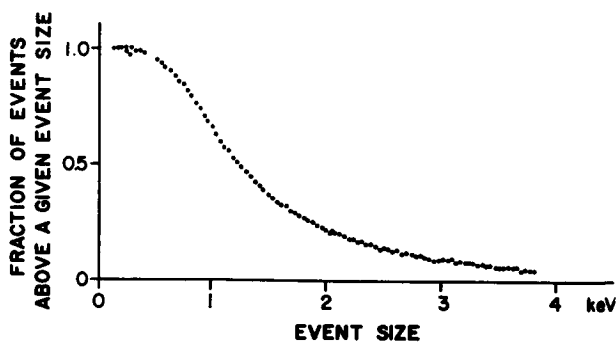


Fig. 2: Fraction of events depositing energy in amounts greater than a given size when a 46.4 MeV proton traverses 1.33×10^{-4} g/cm² of tissue-equivalent material.

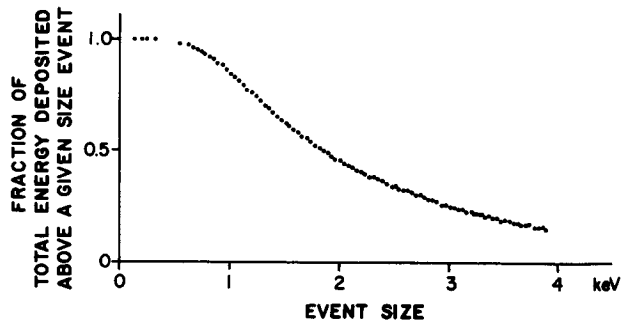


Fig. 3: Fraction of the total energy which is lost in individual events having energy losses greater than some given energy. The data was experimentally determined for 46.4 MeV protons in their passage through 1.33×10^{-4} g/cm² of tissue-equivalent material.

Rate effects can also be considered in the same light. For example, if the critical energy required for recording of damage corresponds to a low probability event, recovery should be more probable since the time available for it would be greater. Low dose effect data should therefore shed much light on this interesting possibility. In fact, an obvious consequence, which is, of course, observed experimentally, is the relatively larger rate effects found for low L.E.T. radiations. In terms of the distribution functions, this might be explained by the

relatively lesser fraction of the dose being delivered by events having large energy depositions in instances where the critical energy required to produce the effect is considerably larger than the most probable energy loss.

DISCUSSION

The treatment presented has ignored the fact that under certain conditions many biological effects studied yield R.B.E. values considerably in excess of the ratios tabulated. This definitely shows the naivety of the approach and the need for considerable refinement or possibly a total change in concept. Further, one should not take this presentation as a basis for the elimination of all real biological differences. It is most likely that to properly account for the experimental data, a combination of real biological differences and a correct and rigorous accounting of energy deposition patterns are required.

Further, if one considers that frequency distributions having a high degree of skewness have higher probabilities for large events than do for example a narrow gaussian, irradiation by a beam having such a distribution will contribute some events although they might be rare to an effect having a threshold requirement far above Δ_{mp} or even $\bar{\Delta}$. When compared to a heavily ionizing particle beam having a narrow gaussian spread at or above this threshold, we might then find very large values of the R.B.E. The smaller the critical site the greater the apparent effectiveness of the more densely ionizing particle would become. Similar considerations were used by Rossi¹⁵ to elucidate the probability of scoring a hit within a sensitive volume by the secondary electrons produced in irradiations using ⁶⁰Co gamma rays and for the secondary protons produced by irradiation with 1 MeV neutrons.

A further test of these concepts requires a theory incorporating the probability for a given size energy deposition in specific biological entities when single or relatively few events are postulated for production of an observed biological effect. This statistical treatment of the individual components would then have to be averaged over the large number of cells, chromosomes, etc. in an attempt to reproduce experimental survival curves, numbers of breaks, deletions or even overall effects on whole organs or organ systems.

CONCLUSION

Serious consideration of the physics of energy deposition seems to indicate that a fundamental change in the interpretation of absorbed dose is required at least for considerations of effects in biological systems. In addition, theoretical approaches to radiobiology and microdosimetry would seem to require statistical considerations incorporating frequency distributions of the magnitude of the event sizes within the volume of interest.

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