(NASA-CR-138250) CONTRAST CHANGES IN FLUOROSCOPIC IMAGING SYSTEMS AND STATISTICAL VARIATIONS OF THESE CHANGES Final Report, 1 Oct. 1972 - (California Univ.) 95 p CSCL 20H G3/24 Unclas 16029

INTRODUCTION

A chapter was prepared for publication in the next edition of Advances In Radiation Biology entitled, "The Radiological Implications of Statistical Variations in Energy Deposition by Ionizing Radiations."

The completed multiwire proportional counter has undergone preliminary testing in the laboratory using a ^{212}Po alpha source. All aspects of its performance seem to be satisfactory.

Studies of the minimum detectability which can be achieved by the digitized x-ray fluoroscopy system have been completed. The studies were conducted using thick water phantoms (10 cm, 15 cm, and 20 cm). These limits were determined for aluminum, air, and three concentrations of Renografin-60 (10%, 25%, and 50%).

Pattern recognition programs have been developed for measurement of gall-stone volumes, bronchi diameters, and vessel diameters. These can be used either with film or by direct processing of the video signal derived from a fluoroscopic screen.

A large flat-screen (14" x 17") fluoroscopic image intensification (x-ray) system has been built and undergone preliminary testing. Performance and sensitivity is better than conventional systems.

One experimental run was made utilizing the UCLA medical cyclotron for determining DNA damage from proton irradiations. The beam was calibrated using an extrapolation chamber so that direct comparison of these results with those obtained using x-rays can be made on the basis of macroscopic exposures. These experiments are designed to test a radiobiological model incorporating stochastic fluctuations of energy deposition for passage of heavy charged particles through biologically significant sites.

I. INTRODUCTION

It would appear to be fairly well established that most if not all radiobiological effects can be attributed to alterations of the normal functioning of individual cells (Elkind, et al, 1967). In many or all instances these alterations appear to be related to damage in the genetic structures (Gray, 1951), such as single and/or double strand breaks (Pollard, 1953), DNA-DNA and/or DNA-protein crosslinks, base damage, etc., which, if unrepaired, can lead to chromosomal aberrations or transcriptional and translational modifications detrimental to normal cell function. In many instances a single or rather few interactions of charged particles with these biological structures are responsible for the observed effects (Fabrikant, 1972). If these observations are indeed correct, then our approach to the dosimetry of ionizing particles requires changes in traditional concepts. The traditional approach makes use of the standard methods of dosimetry which are based upon macroscopic concepts and depends on the validity of calculations based on average values. Validity may be realized in either of two ways. Observations or calculations can be made utilizing either a sufficiently large volume or a sufficiently large number of events per unit volume (Roesch and Attix, 1968) so that in both instances statistical fluctuations of energy deposition do not have to be considered. Such a macroscopic approach has been able to account for many observed radiobiological phenomena but has not been able to provide a fundamental approach leading to a basic theory of radiobiological action.

This was recognized by Rossi, who with his colleagues (1961), introduced and developed the methodology of microdosimetry. This group dealt mainly with energy transfers from low energy heavy particles to biological sites where the statistical variations of energy deposition of individual events are rather minor. In this instance, the character of the frequency

distributions of energy deposition in fundamental biological sites considered is mainly due to pathlength variations of the particles within these sites.

Kellerer (1968) extended these concepts and attempted to develop a method for calculating distributions for those cases where statistical variations of individual energy transfers play an important role. His method is based on the convolution of a single event spectrum. This spectrum is that of particle energy loss due to single collisions. The method has two deficiencies. First, the theoretical spectrum is known to be a poor approximation over a large portion of the energy transfer range (Kellerer, 1968) of interest. Some experimental data is available for the low energy portion of this spectrum but one is forced to utilize the theoretical spectrum which is known to be inaccurate for intermediate energy losses and is only an approximation for the highest energy losses of interest. Second, this spectrum pertains to particle energy loss rather than to energy deposition in the site of interest. Therefore, corrections to the energy loss function produced by outflow and inflow of secondary electrons must be taken into account. Since our knowledge (both experimental and theoretical) of secondary electron production is severely limited, such corrections are very tenuous. To utilize this approach one would need (a) the complete frequency distribution of particle energy loss for single collisions as a function of particle energy, (b) a complete knowledge of secondary electron production, i.e., number produced, energy spectrum, and directional characteristics.

The entire concept of a relationship between energy deposited (absorbed dose) and biological effects observed after irradiation of living tissues by ionizing radiations must be broken down beyond this gross macroscopic approach. This is so because of two facts. First,

the size of the site involved is very small, i.e., of micrometer dimensions or less (nanometers). Second, indications are that individual sites suffer inactivation leading to cell death due to a single or very few events. Consequently, the statistics of energy deposition by charged particles in such sites must play an important role in determining the end or observable effect. It is for this reason that this review will present a comprehensive picture of the physical processes governing the deposition of energy by charged particles in their passage through matter.

As a consequence we have examined on a random basis some radiobiological data involving measurements of relative biological effectiveness (RBE) using these concepts and leading to the use of the most probable energy loss in place of the average energy loss for a determination of absorbed dose. We shall also illustrate how these concepts can be incorporated into current models of radiobiology.

The fundamental physics has been treated by a number of authors. The statistical nature of the energy transfers by fast charged particles to atomic electrons was first treated theoretically by Landau (1944). This work was followed by that of Vavilov (1957). Corrections for resonance-type collisions are discussed by Blunck and Leisegang (1950). Most of the early experiments confirmed these theoretical calculations (Gooding and Eisberg, 1957). However, the pathlengths utilized were rather large compared to those of interest to the radiobiologist. More recently Baily and his colleagues (1970) have shown that for very short pathlengths, discrepancies exist between calculations made using the Blunck-Leisegang corrected Vavilov theories and experiments using fast charged particles. These discrepancies appear as a deficiency in low energy transfers and an excess of high energy transfers, which are probably more important in producing damage to biological systems.

The methods used by Baily, et al (1970), are amenable to the direct measurement of energy deposition by monoenergetic particles (Hilbert and Baily, 1969). The distributions obtained for appropriate pathlengths can then be integrated over the proper pathlength distribution to obtain a frequency distribution of energy deposition for any shape or size biological site. Similarly, integration over particle energy for a non-monoenergetic beam is possible. If the experimental data are measured under the proper geometric conditions which are seldom attainable experimentally no corrections are required. Baily and his group (1972a, 1972b) have obtained spectra for both medium and high energy protons under various conditions such as after passage through various amounts of muscle, bone, and at interfaces between bone and muscle. These data have confirmed the importance of the statistical fluctuations associated with energy transfer when the energy deposition spectra are measured for very short pathlengths. The distributions produced by a primary particle beam which has undergone considerable energy straggling also is subject to statistical fluctuations of the same type.

While this is a possible approach it would require an individual set of measurements to span the pathlength distribution for each specific geometrical situation. Consequently Steigerwalt and Baily (1973) have investigated the feasibility of using Kellerer's program of convolution-deconvolution to shift spectra to both shorter and longer pathlengths. For pathlengths not too different than the initial pathlength, the results have been excellent with only minor discrepancies appearing between calculated (shifted) and experimental spectra. It is felt that corrections for energy inflow and outflow due to gain and loss of secondaries are all that is needed to provide rigorous agreement between calculation and experiment in all situations including pathlengths greatly different than the initial experimentally determined distribution functions.

The loss and gain of secondaries to a specified volume has been investigated by several groups (Gross, et al, 1970; Glass and Roesch, 1972; Wilson and Emery, 1972) under very simplified geometries using wall-less proportional counters. It would appear that the newly developed multiwire proportional counter developed by Charpak (1970) will allow more flexibility and more rapid analysis of the ionization due to the secondary particle flux in and out of a specific site. Further, this instrument lends itself to rapid computer analysis of the experimental data. This topic will be developed further in a subsequent section.

It is also of interest to note that in addition to the discrepancies between experimental and theoretical spectra of energy deposition previously discussed, these statistical processes result in large relative differences between the average and most probable energy losses for both heavy charged particles and electrons when short pathlengths such as are of interest in radiobiology are involved. Since macroscopic dosimetry has as its base the average value of the energy deposited it is pertinent to examine radiobiological data in light of the differences demanded by the microscopic approach to energy deposition.

It is incumbent upon us in either the measurement or calculation of energy deposition in sites as small as those of interest in radiobiology and where either single or few events are involved, to look for methods of measurement and/or calculation other than those which have traditionally been used. This will be required in all cases where the mean energy loss of the charged particle is small compared with the maximum energy which can be transferred in a single collision to an orbital electron.

Through the years it has become increasingly evident that there are many and great deficiencies in the concept of LET when applied to theories purporting to explain radiobiological phenomena. In addition, if one believes implicitly that radiobiological phenomena

are directly related to energy absorbed by biological structures, cells, tissues, etc., then in many instances the physics of energy loss does not allow one to utilize averages in a meaningful way. The average value of energy absorbed in a macroscopic mass is dependent on the stopping power of the charged particles passing through the site under consideration. The LET may or may not be identical with this quantity depending on the particle energies and the geometric configuration under consideration. The size of most biological targets is so small that unless one is willing to postulate a requirement for a large number of events within this site, the statistical fluctuations in amount of energy deposited can be very large. Therefore in many cases of importance in radiation biology, concepts based on averaging may be invalid. In addition, averages over pathlength distributions for the purpose of obtaining an average LET applicable to a specific biological structure may also lead to erroneous conclusions.

II. TRADITIONAL APPROACHES TO MICRODOSIMETRY

Probably the first and certainly one of the early workers in the field was Rossi (and Rosenzweig, 1955). In fact he has suggested that the energy deposited by charged particles and their secondaries in volumes of specified size replace the use of linear energy transfer (LET) as a measure of radiation quality (Rossi, 1959). He has also introduced a new terminology to define certain quantities used in his formulation of the problem.

These are:

1. y - lineal energy - total energy deposited in the volume of interest, divided by the average chord length.
2. $f(y)$ - the probability density of lineal energy.
3. $D(y)$ - the distribution of absorbed dose in y.
4. ϵ - energy imparted.
5. $Z = \frac{\epsilon}{m}$ - specific energy.
6. $f(Z)$ - probability of deposition of a local energy density Z in the irradiated medium.

The main course of microdosimetric arguments is directed at matching experimental effects, which are assumed to be linked in some manner to event frequency on a microscopic scale, with the microdosimetric functions presented above. The latter distribution is a function of site size and shape. In this way one hopes to find trends appearing from various investigations and thereby obtain valuable clues to the fundamental mechanisms of radiobiological damage.

The microdosimetric variables in the above list present the concepts and quantities most often used. Other distributions and variables exist which complement those listed above.

A more complete treatment can be found in the review article by Kellerer and Rossi (1970b). Also, Rossi (1967, 1968) has written several review articles in which practical applications of these variables and the corresponding distributions are discussed in detail. For illustration, the concept of local energy density Z will be discussed. Emphasis will be placed on the physical relationship of this variable with energy absorption patterns. Let us examine in detail what is meant by energy absorption patterns, and what quantities need to be specified and calculated. Consider a microscopic structure of volume V and mass m, which is part of a more complex body, B. Assume that B has been exposed to a dose, D, of ionizing radiation. During the exposure V will accumulate increments of energy, ϵ. These are due to the passage of individual ionizing particles through or near it. At the end of the exposure, V has absorbed a total energy equal to E, comprised of increments of energy depositions, ϵ. For this situation $Z = E/m$. The number of increments, n which contribute to the total E depends, for a fixed D, on the size of V. For sizes of V and D, of interest in microdosimetry, n will in general be small. For repetitions of the application of dose D, the values of n, and consequently that of E, will fluctuate; therefore, n and E are called stochastic variables. Thus, when specifying patterns of energy deposition, one must speak of probability density distributions; i.e., the probability that volume V will absorb energy between E and E + dE when a dose D is delivered to B. It is implicit, that if these probability functions describe and govern the magnitude of the biological effects produced by D, that there must be a large number of target volumes V, which contribute to the observable effect. In the general case there would be a number of such structures, each having its own probability distribution for absorption of energy E. Kellerer assumes that these probability distributions are the significant constructs with which to correlate biological endpoints.

9<

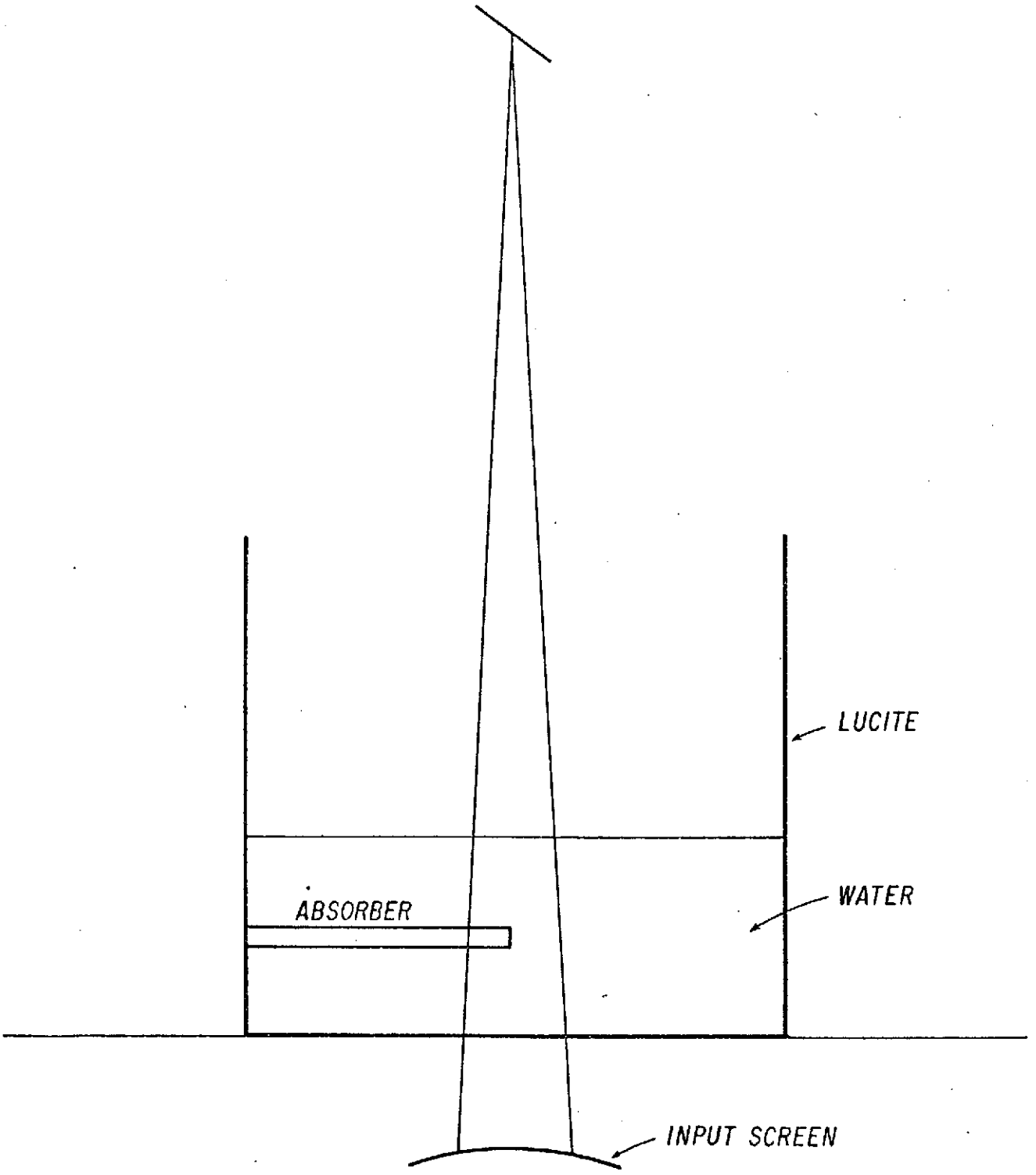

Fig. 1 Water phantom used to determine system response to variations in contrast levels.

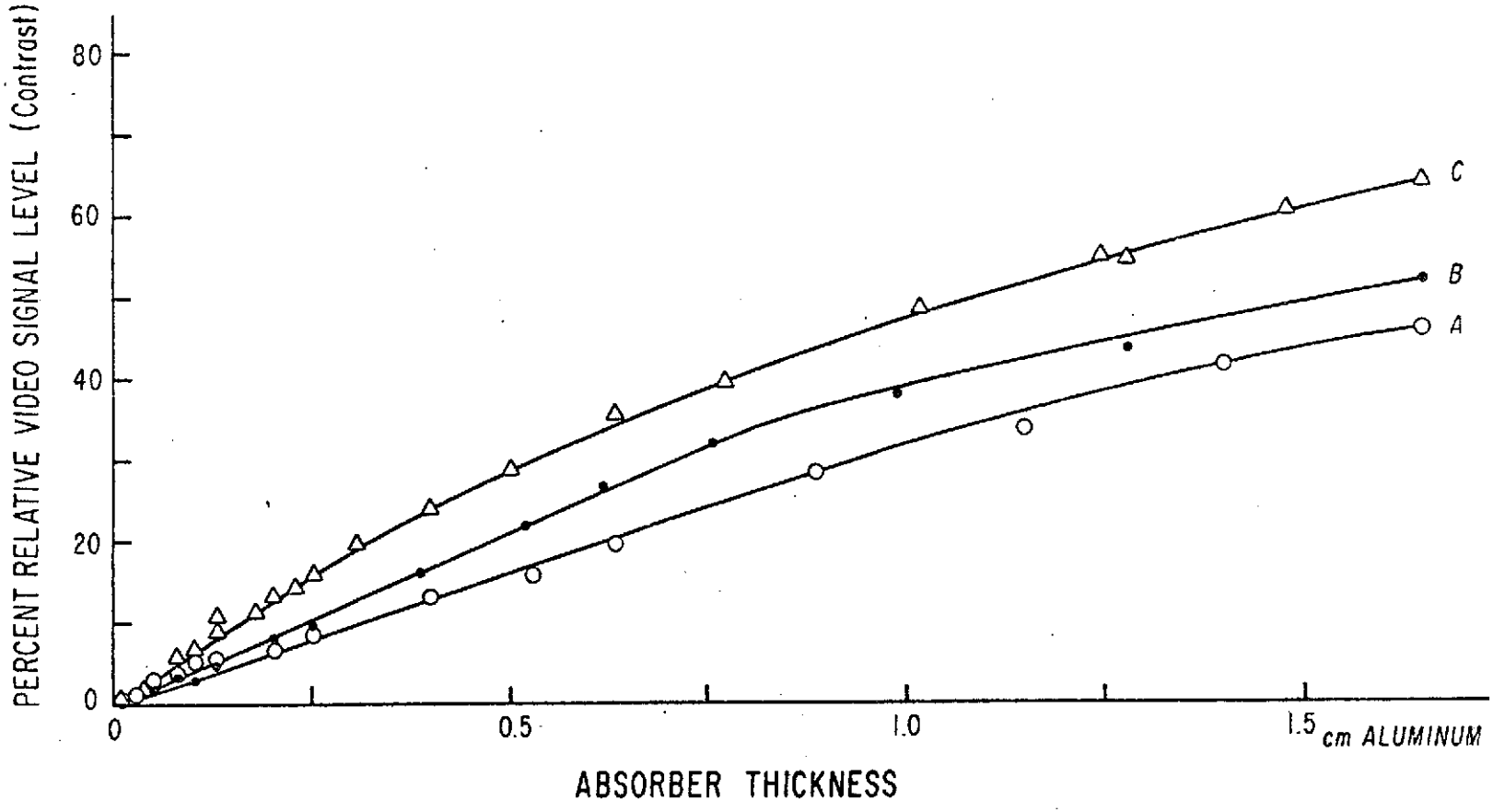

Fig. 2 System response to varying contrast levels produced by aluminum absorbers.
A: 120 kVp, 20 cm water scatterer. B: 100 kVp, 15 cm water scatterer. C: 90 kVp, 10 cm water scatterer.

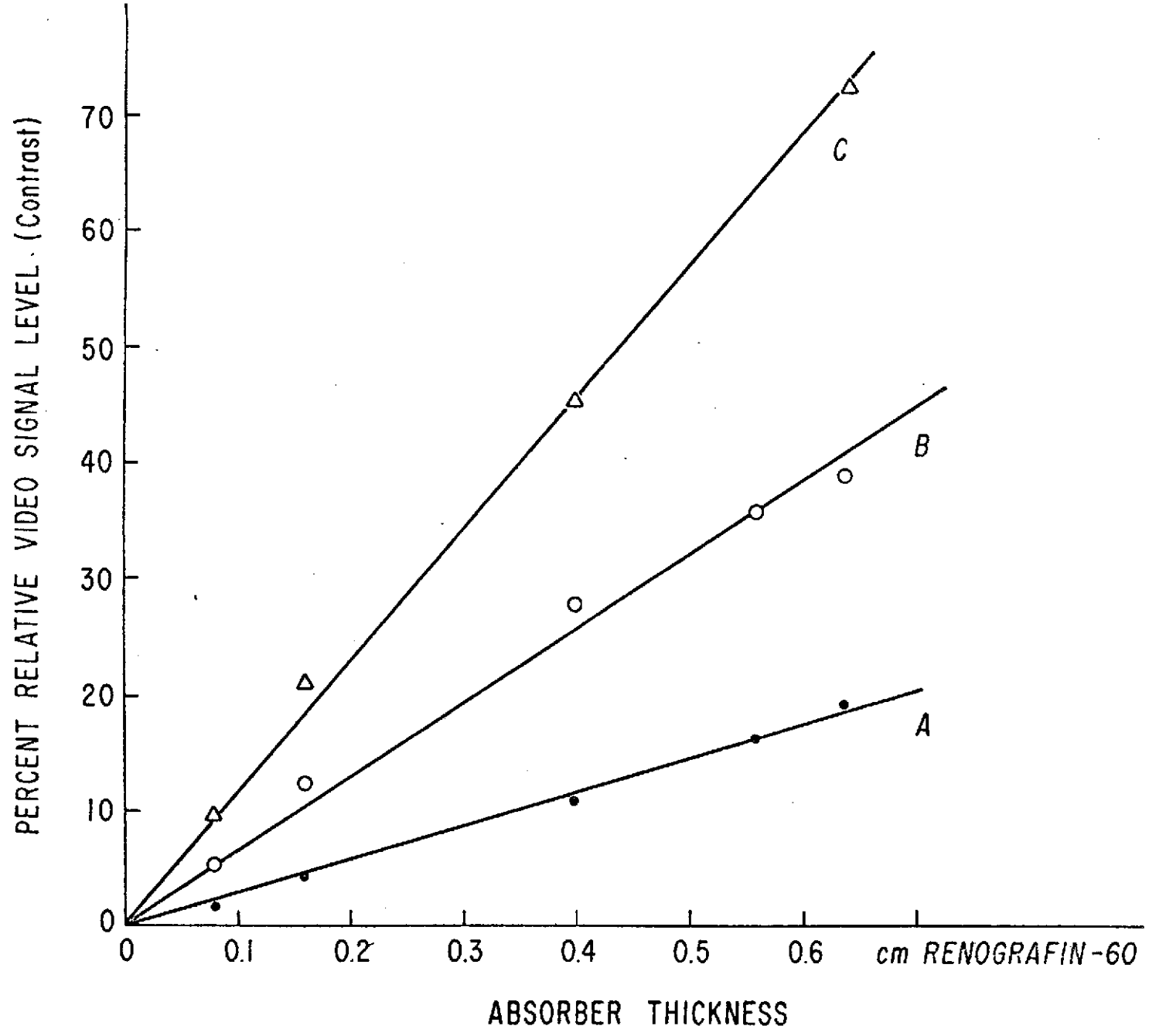

Fig. 3 System response to varying contrast levels produced by several concentrations of Renografin-60. The water depth was 20 cm and the tube potential 120 kVp. A: 10 percent concentration; B: 25 percent, and C: 50 percent.

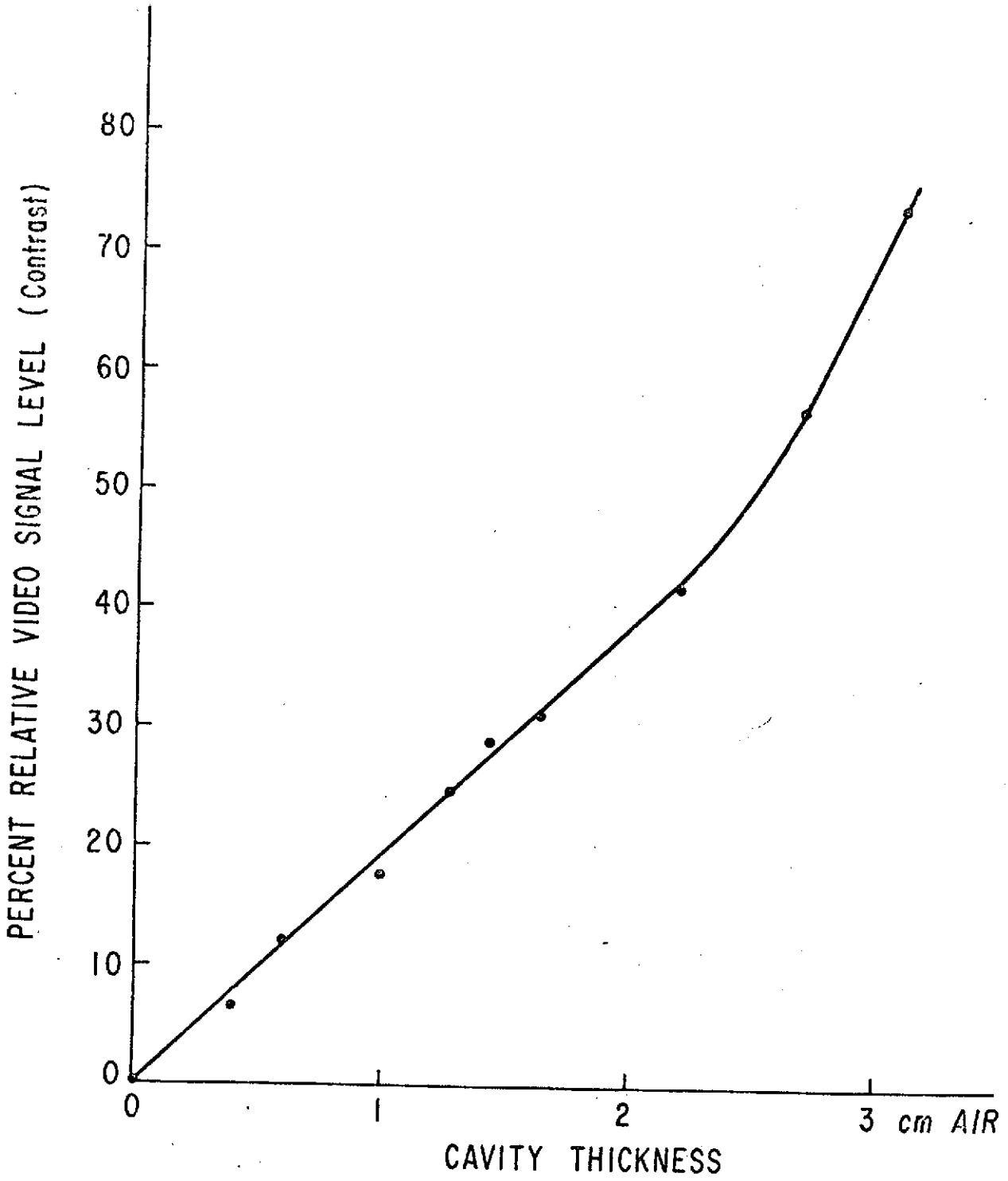

Fig. 4 System response to varying contrast levels produced by air cavities when introduced into 20 cm of water using 120 kVp.

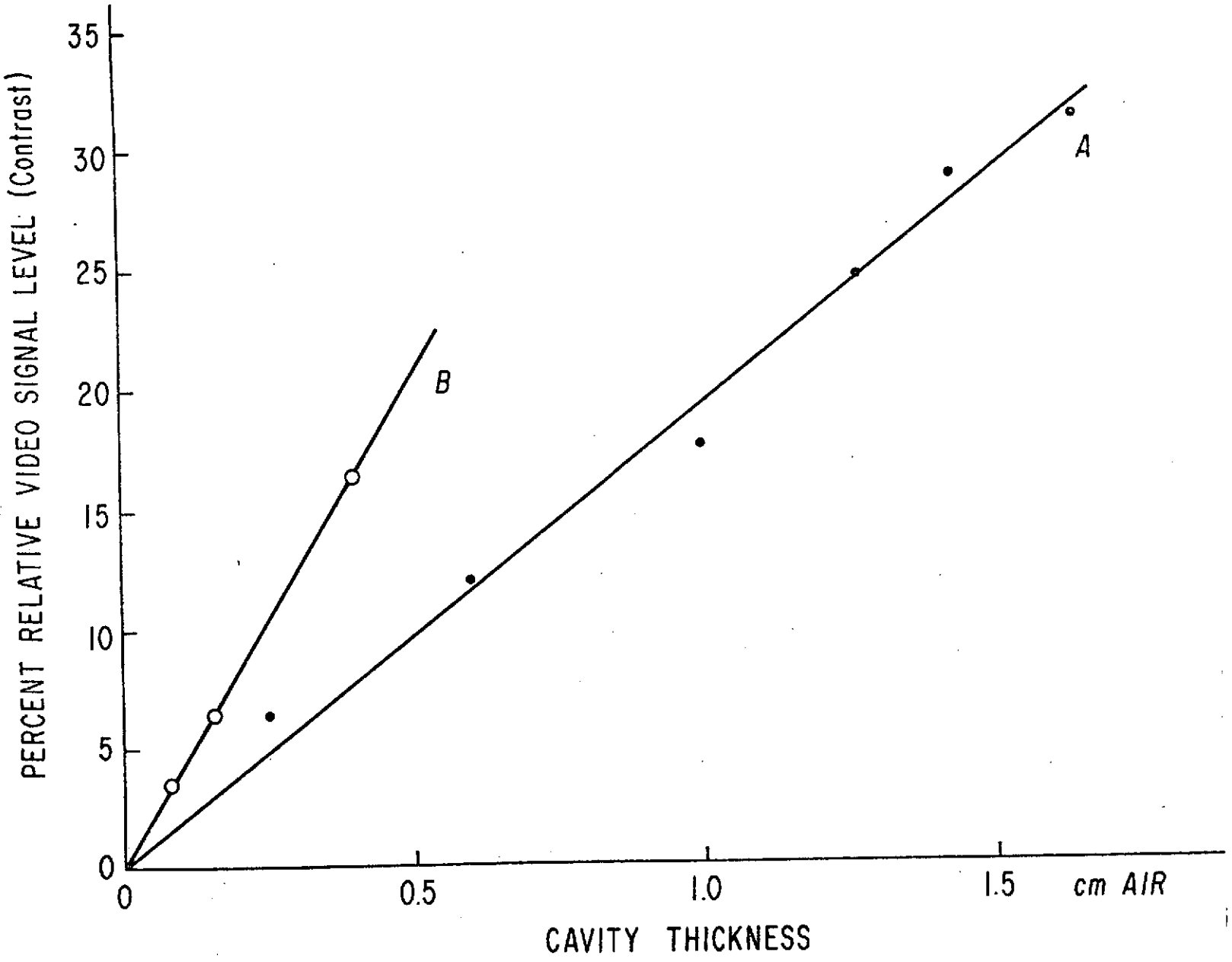

Fig. 5 System response to varying contrast levels produced by air cavities when introduced into 20 cm of water. Curve A, is for 120 kVp (same data as used in Fig. 4), and Curve B, is for 100 kVp.

TABLE I

MINIMUM DETECTABLE CONTRAST LEVELS (C_{min})

Material	Water Depth (cm)	Tube Potential (kVp)	Standard Deviation (percent)	Thickness of Material (mm) Corresponding to C_{min} at 2 σ
Al	10	90	0.849	0.6
Al	15	100	0.465	0.5
Al	20	120	0.723	0.6
10%, Renografin-60	20	120	1.10	0.8
25%, Renografin-60	20	120	0.578	0.2
50%, Renografin-60	20	120	0.828	0.1
Air	20	100	0.797	0.4
Air	20	120	0.802	0.9

FIGURE CAPTIONS

Fig. 1 Water phantom used to determine system response to variations in contrast levels.

Fig. 2 System response to varying contrast levels produced by aluminum absorbers.

A: 120 kVp, 20 cm water scatterer.

B: 100 kVp, 15 cm water scatterer.

C: 90 kVp, 10 cm water scatterer.

Fig. 3 System response to varying contrast levels produced by several concentrations of Renografin-60. The water depth was 20 cm and the tube potential 120 kVp.

A: 10 percent concentration;

B: 25 percent, and

C: 50 percent.

Fig. 4 System response to varying contrast levels produced by air cavities when introduced into 20 cm of water using 120 kVp.

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Curve A, is for 120 kVp (same data as used in Fig. 4), and

Curve B, is for 100 kVp.

THE RADIOBIOLOGICAL IMPLICATIONS OF STATISTICAL VARIATIONS IN ENERGY DEPOSITION BY IONIZING RADIATIONS[1]

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Preliminary results indicate considerable differences exist and these are what would be predicted from the energy deposition distribution functions.

3. Radiobiological Models

The work done on such models is presented in parts 5 and 6 of Appendix I.

4. Electronic Radiography

The use of the electronic radiography system for direct fluoroscopic tomography and for the synthesis of multiple planes has been described in Appendix B of the semi-annual report. The use of this system for cutting body sections through organs in motion should be of particular value to the NASA for cardiovascular studies.

A complete study of the digitized system for detection and quantitation of small changes in tissue masses has been undertaken. The early work was described in Appendix C of the semi-annual report.

Another set of experiments was designed to determine the characteristics of the system's response to split fields having different contrast levels and to determine the minimum detectable contrast levels between the halves under realistic clinical situations. The experimental set-up is shown in Fig. 1. The target-to-tabletop distance was 40 inches. The dimensions of the water phantom were 50 cm x 50 cm x 50 cm. In all experiments the field size was 10 cm x 10 cm at the tabletop. The absorbers or air cavities were placed so as to cover half of the x-ray field and centered at the midpoint of the water scatterer. The water depth ranged between 10 cm and 20 cm, thereby introducing scattering comparable to that which would be present in a clinical situation. The contrasts calculated are all referred to the unperturbed half of the field. Experiments were conducted using aluminum (as an approximation for bone), Renografin-60, and air.

RESEARCH SUMMARY

1. Microdosimetry

The chapter, "The Radiological Implications of Statistical Variations in Energy Deposition by Ionizing Radiations", to be published in the new edition of ADVANCES IN RADIATION BIOLOGY is attached as Appendix I. The work should appear in June 1974. This chapter was written to emphasize the concepts and results developed under the sponsorship of this grant in contrast to the more traditional dosimetric concepts.

One rather large area requires detailed experimental study to complete the physical picture. This is a detailed study of the production of and contributions due to secondary particle production generated by the passage of the primary radiation through the site of interest. To carry out these experiments a multiwire proportional counter capable of simulating volumes corresponding to biological sites has been constructed and tested in the laboratory. Initially, studies using radioactive sources will be continued in the laboratory. Following these, we intend to carry out studies using the UCLA cyclotron which will provide; 27 MeV ^{3}He, 22 MeV protons, 22 MeV α particles, and 11 MeV deuterons. If sufficient funding is available higher energy particle beams at SREL and at Berkeley will be used.

The experimental results using 45 MeV protons comparing frequency distributions of energy deposition for bone and muscle were included as Appendix A in our semi-annual report.

2. Radiation Biology

Our cooperative experimental program involving Dr. K. Wheeler of UCSF has been initiated. Proton irradiations at the UCLA cyclotron have been carried out. These are designed to study the ratio of non-reparable to reparable damage in DNA as a function of different energy deposition patterns generated by x rays vs. heavy fast charged particles.

The results are shown in Figs. 2 through 5. The values of the ordinate were computed by selecting two adjacent areas occupying a tabletop area of 1.5 cm^2 (320 picture elements) each having its horizontal center line at the center of the x-ray field and interior edges 1 cm from the absorber or cavity edge.

Fig. 2 shows the response curves obtained for aluminum absorbers. A was obtained using 120 kVp and a water depth of 20 cm. B represents the data for 100 kVp and 15 cm of water. C was obtained using 90 kVp and 10 cm of water.

Fig. 3 shows the results for various concentrations of Renografin-60. A is for a 10 percent solution, B for 25 percent, and C for 50 percent. The thickness of the water phantom was 20 cm and the tube potential 120 kVp. The Renografin-60 solutions were contained in plexiglass containers having a thickness of 0.25". These were supported on a platform of 0.25" polystyrene. Equal thicknesses of these materials were placed in the other half of the field and the water level reduced accordingly.

Figs. 4 and 5 show the results obtained with air cavities. The geometry was identical to that used to obtain the Renografin-60 data. Fig. 4 shows the complete response while Fig. 5 shows the data obtained for thin cavities on an expanded scale. The data in Fig. 4 was obtained using 120 kVp and 20 cm water. Curve A, in Fig. 5 is the same data plotted on an expanded scale, while B is that obtained using a potential of 100 kVp and 20 cm water.

Using the slope of the initial straight portions of these curves (or straight lines), one can obtain a value for the minimum degree of contrast that can be reliably differentiated in each case. We choose to use a value of two standard deviations to determine these. The results are shown in Table I. In all cases less than 1 mm of material can be detected even in the presence of a large scattering volume. In previous work we have found that the addition of a 12:1 moving grid was found to improve the contrast of the image substantially.

However, in clinical use this would, of course, increase the patient dose. We have not measured this effect quantitatively.

In all cases the response, when treated as contrast, shows a linear response with absorber thickness up to considerable thicknesses. This is not a case of small absorber thickness giving a truly exponential response and being approximated by a linear function. The data does not plot linearly when treated semi-logarithmically. If we ignore scattering and other perturbing factors such as curvature of the input screen and inverse square effects, the conatrast or relative video signal levels are given by:

$$C = 1 - e^{\mu_2 t} \; e^{-\mu_1 t} \qquad (1)$$

where; μ_2 = attenuation coefficient of water

μ_1 = attenuation coefficient of absorber

t = absorber thickness.

For small t, this reduces to:

$$C = \mu_1 t(1 + \mu_2 t) - \mu_2 t \qquad (2)$$

At larger thicknesses the response does not remain linear but decreases in the case of absorbers which are more dense or have a greater linear absorption coefficient than water and increases more rapidly with cavity size in the case of air. In the manner in which our data was computed Equation (1) becomes for air cavities,

$$C = 1 - e^{-\mu_2 t} \; e^{\mu_1 t} \qquad (1^1)$$

and for small cavities,

$$C = \mu_2 t (1 - \mu_1 t) - \mu_1 t \qquad (2^1)$$

where; μ_1 = attenuation coefficient of air

t = cavity thickness

The minimum detectable contrast seems to be mainly limited by scatter and electronic noise. Both of these are amenable to improvements in the experimental set-up. However, decreasing scatter by the addition of a grid with a higher ratio would involve an increase in patient dose. Signal-to-noise ratios can be increased by any number of electronic improvements in circuitry, system configuration, and digitization equipment.

The linearity of the system's response to changes in contrast over a rather large range of clinically interesting values will tend to make quantitative determinations simple, accurate, and allow extrapolation of experimental data for other calculations. The values given in this paper would certainly be different using another system or with a change in components. However, we feel the values given, the form of the system's response, and minimum detectable contrasts are typical of what can be expected from this type of system.

CONCLUSIONS

1. The response of digitized fluoroscopic imaging systems is linear with contrast over a rather wide range of absorber and cavity thicknesses.

2. Contrast changes associated with the addition of aluminum, iodine containing contrast agents and air of thicknesses 1 mm or less can be detected with a 95% confidence level.

3. The standard deviation associated with such determinations using clinically available x-ray generators and video disc recording is less than 1 percent.

A large flat screen x-ray image intensifier has been constructed and some preliminary results obtained. Sensitivity achieved makes dose reduction a factor often greater than previously reported for our system using a conventional x-ray image intensifier. A paper describing these results and a comparison of the images obtained with that of the conventional device will appear shortly in the bulletin of the SPIE.

PAPERS PRESENTED AT MEETINGS

1. Detection Capability of Differential Radiographic Absorption Through the Use of Fluoroscopic Images, Crepeau, R.L., Baily, N.A., 12th Ann. San Diego Biomed. Symp.
2. Frequency Distributions of Energy Deposition by 44 MeV Protons at Bone-Soft Tissue Interfaces, Baily, N.A., Steigerwalt, J.E., and Hilbert, J.W., 1973 Annual Meeting of the AAPM.
3. Electro-Fluoroplanigraphy, Baily, N.A., Lasser, E.C., and Crepeau, R.L., 1973 Annual Meeting of the AAPM.
4. The Calculation of Proportional Counter Energy Deposition Spectra from Experimental Data, Steigerwalt, J.E., and Baily, N.A., 1973 Annual Meeting of the AAPM.
5. Differential Radiographic Absorption Measured From Digitalized Fluoroscopic Images, Crepeau, R.L., and Baily, N.A., 1973 Annual Meeting of the AAPM.
6. Electronic Tomography, Baily, N.A., Crepeau, R.L., and Lasser, E.C., Symp. on Electronic Imaging Techniques in Diagnostic Radiology, Univ. of Pittsburgh, 1973.

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1. Applications of A Digitalized Radiographic-Fluorographic Processing System to Physiologic Data Extraction, Crepeau, R.L., Baily, N.A., and Silverman, N.R., Proc. of the San Diego Biomed. Symp., 11: 317-322 (1972).
2. The Calculation of Proportional Counter Energy Deposition Spectra From Experimental Data, Steigerwalt, J.E., Baily, N.A., Rad. Res. 51: 480 (1972).

3. A Video-Roentgenography System For Special Procedures and The Acquisition of Quantitative Data, Baily, N.A., Lasser, E.C., and Crepeau, R.L., Proc. of the 3rd Int. Conf. on Medical Physics, Gothenburg, Sweden, 1972, 2.7 (1972).

4. Electro-Fluoroplanigraphy, Baily, N.A., Lasser, E.C., and Crepeau, R.L., Radiology 107: 669-671 (1973).

5. The Calculation of Proportional Counter Energy Deposition Spectra From Experimental Data, Steigerwalt, J.E., Baily, N.A., Rad. Res. 53: 1-14 (1973).

6. Detection Capability of Differential Radiographic Absorption Through the Use of Fluoroscopic Images, Crepeau, R.L., Baily, N.A., Proc. of the 12th San Diego Biomed. Symp., 277-283 (1973).

7. Frequency Distributions of Energy Deposition by 44 MeV Protons at Bone-Soft Tissue Interfaces, Baily, N.A., Steigerwalt, J.E., and Hilbert, J.W., AAPM Quarterly Bull. 7: 101 (1973).

8. Electro-Fluoroplanigraphy, Baily, N.A., Lasser, E.C., and Crepeau, R.L., AAPM Quarterly Bull. 7: 91 (1973).

9. The Calculation of Proportional Counter Energy Deposition Spectra from Experimental Data, Steigerwalt, J.E., Baily, N.A., AAPM Quarterly Bull. 7: 101 (1973).

10. Differential Radiographic Absorption Measured From Digitalized Fluoroscopic Images, Crepeau, R.L., Baily, N.A., AAPM Quarterly Bull. 7: 91 (1973).

11. The Calculation of Proportional Counter Energy Deposition Spectra From Experimental Data. II. Very Small Energy Losses and High Energy Delta Rays, Baily, N.A., Steigerwalt, J.E., Rad. Res. 56: 213-221 (1973).

12. Frequency Distributions of Energy Deposition by 44 MeV Protons at Bone-Soft Tissue Interfaces, Baily, N.A., Steigerwalt, J.E., and Hilbert, J.W., Rad. Res. 56: 205-212 (1973).

13. An Electro-Fluoroplanigraphy System For Clinical Use, Baily, N.A., Lasser, E.C., and Crepeau, R.L., Invest. Radiol. 8: 276-277 (1973).

PAPERS IN PRESS

1. Electronic Tomography, Baily, N.A., Crepeau, R.L., and Lasser, E.C., Proc. of the Symp. on Electronic Imaging Techniques In Diagnostic Radiology.
2. The Radiobiological Implications of Statistical Variations In Energy Deposition By Ionizing Radiations, Baily, N.A., Steigerwalt, J.E., Advances in Radiation Biology Vol. V.
3. Performance of a Large Screen Fluoroscopic Imaging System, Baily, N.A., Crepeau, R.L., Proc. of the SPIE.
4. Capabilities of Fluoroscopic Systems to Determine Differential Roentgen Ray Absorption, Baily, N.A., Crepeau, R.L. Radiology.

PERSONNEL PARTICIPATING IN PROGRAM

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2. John E. Steigerwalt, Assistant Research Radiation Physicist
3. Ronald L. Crepeau, Assistant Developmental Engineer
4. Earl M. Raeburn, Lab Technician
5. Elliott C. Lasser, Professor of Radiology

APPENDIX I

His work also provides a method with which to calculate these probability distributions of energy deposition through the use of a primary characteristic spectrum of energy losses by the primary charged particle suffered in individual collisions with electrons of the absorbing medium. The relation between this characteristic spectrum and the resultant energy loss distribution of the primary charged particle after undergoing many collisions can then be described by a compound Poisson process. For the case of many collisions these distributions of energy loss can often also be described by conventional straggling theories such as those of Bohr, Landau, and Vavilov. Kellerer has written a computer program to find solutions to the compound Poisson process starting with the primary characteristic single collision spectrum, $\omega(\epsilon)$. These solutions are characterized by the mean energy loss, $\bar{\Delta}$, of the primary charged particle. The problem remains how to relate these energy loss distributions to the energy deposition distributions which one would find in the microvolume V. Kellerer has shown that the transport of energy out of V by energetic secondary particles can be accommodated by the theory through a suitable modification of $\omega(\epsilon)$. Roesch and Glass (1971) have indicated that energy depositions in V, caused by interactions of the primary particle exterior to V, can be included in the calculations for the resultant energy deposition distributions. This is done through a further modification of $\omega(\epsilon)$. They have also shown that distributions generated using the compound Poisson process and the modified $\omega(\epsilon)$, are correct solutions to the energy deposition distribution function. The difficulty with this technique lies in the lack of an adequate knowledge of $\omega(\epsilon)$ and with the formidable task of performing the modifications of $\omega(\epsilon)$ due to the lack of knowledge about delta ray production. Further difficulties lie in the fact that contributions to energy deposition in V by other primary particles which do not enter V must be estimated since this again depends upon a comprehensive knowledge of delta ray contributions.

The previous discussion was limited to the distribution of energy deposited in V by a single event. The situation when V is subjected to a flux of particles must also be considered. In this case information about the primary particle flux is necessary as well as a knowledge of the shape of the microvolume. The incident flux distribution and the shape of V combine to give a resultant pathlength probability distribution. This distribution gives the probability that a primary particle chosen at random will have a pathlength in V between x and $x + dx$. The preceding information is then sufficient to predict the resultant energy deposition distribution in V. A complication to this type of calculation is that the modifications to $\omega(\epsilon)$ discussed above will depend on the locations of the particle track in or with respect to V. $\omega(\epsilon)$ will of course be different for each energy included in the incident primary particle spectrum.

Since each energy deposition spectra can be derived from the modified form of $\omega(\epsilon)$, it follows that there exists a relationship between any two energy deposition spectra which differ in their mean energies. Kellerer has also written a computer program which enables this type of transformation to be made. That is, given one distribution function corresponding to a particular pathlength, if geometry and size do not vary too greatly, a new distribution function corresponding to another pathlength can be generated by either a convolution or deconvolution (shift) of the original distribution function.

For direct measurement of the event size Rossi and Rosenzweig (1955) developed a spherical tissue equivalent proportional counter which subsequently has been utilized by a large number of other investigators. The method is restricted to certain types and energies of radiation. The resultant measurements are characteristic only of the particular geometry in which they were made. Furthermore, track or pathlength distributions are folded together with the distributions of the statistical fluctuations of energy deposition in the resultant measured distribution functions.

Since spheres may or may not be a good approximation to the volume of interest in any particular instance, several investigators have considered pathlength distributions in cylinders (Birkhoff, et al, 1969; Kellerer, 1971b), and others have built such shaped counters (Srdoč and Kellerer, 1972). Other variations such as twin active volumes (Burlin, et al, 1972), and wall-less counters (Glass and Roesch, 1972; Wilson and Emery, 1972) have been investigated. It is clear from these efforts that an alternate and straightforward approach is that of determining the frequency distributions of energy deposition in specific pathlengths (Baily, et al, 1970), calculating the effects of perturbing parameters such as delta ray loss and gain, and computing from these the desired frequency distributions of energy deposition (Hilbert and Baily, 1969) for any desired volume. This approach is further facilitated by use of the method recently published by Steigerwalt and Baily (1973). This situation is entirely analogous to that which existed in macrodosimetry where, until the rather recent advent of computer calculation of, for example, isodose curves, each new irradiation geometry, or different radiation energy, demanded a completely new experimental investigation. It is therefore important that we make use of basic physical data, i.e., the empirically or experimentally derived frequency distribution functions of energy deposition, and utilize computational techniques which allow generation of these distributions for any pathlength needed in the calculation. The desired distribution functions can then be derived from a limited amount of experimental data. Computers can be used for combining the individual distributions into distributions for the shape and size of the desired volume. These distributions will then be subject to future considerations involving radiation effects and for purposes of formulating radiobiological models.

A general theoretical approach to the problem of determining the statistical patterns of energy absorption produced by charged particles traversing low atomic number materials has been formulated by Kellerer (1968). This method can be applied to the experimental distributions discussed here. In addition to the stochastic aspects, there are several other aspects to this problem which must be considered. The first is that a distinction must be made between the energy lost by the primary charged particle when it passes through the structure under investigation and the energy which is deposited in its volume. The energy actually deposited is very strongly geometry dependent. Second, an account must be made for energy deposited in the structure by primary particles which do not pass directly through it. This requires a comprehensive knowledge of geometry and delta ray contributions.

III. FUNDAMENTAL PHYSICS OF ENERGY DEPOSITION

A. STRAGGLING THEORIES

When monoenergetic charged particles are incident on an absorber of thickness x, the emerging particles will not all have the same energy due to the randomness of the interactions between the primary particles and the electrons of the absorbing medium. This randomness of energy transfer is said to introduce statistical fluctuations into the energy losses of fast charged particles in absorbers. The spectrum of energies of the emerging particles can be described by straggling functions which are denoted by $f(x, \Delta)$. $f(x, \Delta)$ is called the probability density distribution function of particles of incident energy E_o in penetrating an absorber of thickness x, and describes the relative number of particles which have lost an energy Δ. The residual energy of these particles then is $E = E_o - \Delta$. $f(x, \Delta)$ is interpreted in the following way: Experimentally, when N_o particles penetrate a depth x of an absorbing media, the number of emerging particles which have lost energies between Δ and $\Delta + d\Delta$ is given by $N_o f(x, \Delta) d\Delta$.

In some instances of interest to microdosimetry there is a finite probability for a particle to traverse a small pathlength without undergoing an interaction and therefore it will not suffer any energy loss. It is important to note that the energy lost by a particle, Δ, is given by $E_o - E$ where E is the measured energy of the particle when it emerges from the absorbing material. No information is given by the function $f(x, \Delta)$ about the details of the collisions or the manner in which the energy loss Δ is distributed in the absorber. However, the nature of $f(x, \Delta)$ does yield limited information about this distribution.

The straggling distribution $f(x, \Delta)$ can be one of the starting points for microdosimetric calculations. The actual energy deposition patterns however are modified by additional factors which transform $f(x, \Delta)$ to a different distribution function from that representative of only energy loss by the particle in traversing a fixed pathlength of a given material.

The shape of $f(x, \Delta)$ depends on many factors. The factors associated with the incident particle are its incident energy, its charge, and mass.

The shape of the distribution function can be described in terms of its moments. These are expressed by,

$$M_n = \int_o^\infty \Delta^n \, f(x, \Delta) \, d\Delta \qquad (1)$$

The first moment, M_1, is then just the mean value of the energy loss usually written as $\overline{\Delta}$.

The second moment is a measure of the width or spread of the distribution function.

The skewness is;

$$\frac{M_3 - M_1 M_2 + 2M_1^2}{M_2^3} \qquad (2)$$

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and the variance is given by;

$$\frac{M_2 - M_1^2}{M_1^2} \tag{3}$$

The primary single collision spectrum of a charged particle, $\omega(\epsilon)$, specifies the probability of an energy transfer of magnitude ϵ in a single collision between a primary charged particle and an electron of the absorbing medium. Generally, $\omega(\epsilon)$ is derived assuming that the electrons in the absorbing medium are free, that is, not influenced by the atomic binding. This is a good approximation for values of ϵ which are large with respect to the binding energies. If relativistic effects and other factors relating to the atomic binding are not considered then $\omega(\epsilon) \propto 1/\epsilon^2$.

Various attempts have been made to derive the more general functions $f(x, \Delta)$. Usually the derivations hold only for a limited range of absorber thickness x. Thus one can speak of thin absorbers where $\omega(\epsilon)$ does not change appreciably as the primary particle traverses the absorber, and thick absorbers where the variation in $\omega(\epsilon)$ with the energy of the primary particle must be considered. These regions can be specified roughly by the value of the mean energy loss to the incident energy, $\overline{\Delta}/E_o$. Microdosimetry mainly is concerned with straggling functions where $\overline{\Delta}/E_o$ is small. Thus, this discussion will not be concerned with the straggling distributions for absorbers which produce large energy losses, as discussed by Tschalar and Maccabee (1970) and by Payne (1969), or even with the conventional straggling as derived by Bohr. It will be sufficient to state that in the case of many collisions $f(x, \Delta)$ is simply a gaussian distribution with a variance,

$$\sigma^2 = 4\pi e^4 z^2 NZx \tag{4}$$

where: N = number of atoms/cm^3

Z = atomic number of the absorbing media

x = pathlength

$\not{z}$ = charge of particle

It is important to note that for particles like electrons or protons the variance is independent of particle energy and that for heavy particles it is dependent on the charge state of the particle.

The derivation of $f(x, \Delta)$ for cases of importance to microdosimetry was first attempted analytically by Landau (1944). His method calculates an approximate solution to the transport equation which describes collisions which change the population of primary particles within any arbitrary energy interval. The solution is a function of a universal dimensionless parameter, λ. All that is necessary to obtain a Landau solution is to relate this universal parameter, λ, to the parameters of the primary particle and of the absorbing material. The Landau function has been tabulated by Börsch-Supan (1961). Landau has given the conditions $\xi << \epsilon_{max}$ and $\xi >> \epsilon_o$ for the region of validity of the solutions. Here ϵ_o is an energy on the order of magnitude of atomic energies and

$$\xi = \frac{2\pi N e^4 \rho}{m v^2} \frac{Z}{A} x. \qquad (5)$$

These conditions imply that the absorbing material must be thin but that there must be a large number of collisions which contribute to Δ. The Landau solution is characterized by a skewed shape with the most probable energy loss less than the average energy loss.

Blunck and Leisegang (1950) have calculated a correction term to this solution taking into consideration the effect of atomic binding on $\omega(\epsilon)$. Fano (1963) has described a

numerical method for applying this correction term to any $f(x, \Delta)$.

Vavilov (1957) has derived a more general solution for the straggling distribution for thin targets. His method was similar to that of Landau, but his solutions are valid over a wider range of energy losses. His solution converges to Landau's for small energy losses and for large energy losses his functions are of the gaussian shape given by Bohr. His solution provides a smooth transition for intermediate values between the two regions. Similar to the Landau solution, the Vavilov formulation also requires a large number of collisions for validity and must be evaluated numerically. Seltzer and Berger (1964) give tabulations of Vavilov's solutions for a wide selection of the appropriate parameters.

Kellerer (1968) has demonstrated that the shapes of $f(x, \Delta)$ of interest for microdosimetry are influenced strongly by $\omega(\epsilon)$. Thus there is considerable interest in the ability to solve for the straggling functions $f(x, \Delta)$ directly from manipulations of $\omega(\epsilon)$. Kellerer showed how to accomplish this and has written a computer program which enables one to solve for $f(x, \Delta)$ for an arbitrary mean number of collisions contributing to $\overline{\Delta}$. This technique is limited only by an imprecise knowledge of $\omega(\epsilon)$. Basically, he takes the probability of n collisions as being given by Poisson statistics and calculates the probability that n collisions will result in an energy loss, Δ. These probabilities are then combined for all possible values of n.

B. EXPERIMENTAL

In this section we are concerned with single event distributions of energy deposition. These distributions give the probability that a given energy will be deposited in a site by one traversal of a charged particle through the site. For a detailed knowledge of energy deposition

in a biological site it is important to know how well stopping power calculations will predict the energy deposited in a single event. This information can be obtained by examining distributions which apply to a single pathlength. A narrow, gaussian shaped distribution peaked around the calculated average energy deposition indicates good results can be obtained by use of stopping power calculations. On the other hand, a broad distribution signifies that energy deposition straggling is important and that stopping power calculations are of little use in predicting the actual shape of the energy deposition distributions. If one is dealing with a curve of the latter type, i.e., a broad single event distribution, it is still possible that the biological site can be described to a good approximation by average value calculations. This circumstance occurs when there are many events occurring in the site. In this case, the detailed distribution of energy deposition in the site can be derived from the single event distribution. If there are N traversals of the site, the mean of the resultant distribution will be N times the mean of the single event distribution, $\overline{\Delta}$. As N becomes large, the shape of the energy deposition distribution becomes gaussian in shape and is centered around $N\overline{\Delta}$. Such distributions can only result when, (a) the site is large, or (b) the particle is very heavily ionizing.

Early and most current experimental investigations of microdosimetric energy deposition patterns utilize detectors, usually proportional counters, which are characterized by a pathlength distribution governed by the shape and size of the tissue volume synthesized. The resultant experimental frequency distribution of energy deposition events is therefore a function of a particular pathlength distribution and of the stochastic nature of the energy transfer encounters. The major disadvantages of this type of investigation are that first, the resultant distribution functions are dependent upon source and sensitive volume geometries. Second, the results do

not provide direct information with which one can readily compare experimental vs. theoretical results. For fast charged particles there are other more serious difficulties such as buildup of secondary particles in the counter walls or absorption differences due to differing pathlengths in the walls.

The early experiments using both electrons and protons did not shed any light on applications in radiobiology since the pathlengths used were much larger than those pertinent for radiation effects produced in biological structures. Since electrons are difficult to work with experimentally and since theoretical considerations show that results obtained with other charged particles should provide the desired information, protons can be used to provide the basic information required. This basic information can be used to calculate frequency distributions of energy deposition events over a wide variety of conditions from a limited amount of experimental data thereby obviating the necessity for generating such data from difficult and time consuming experiments applicable to only one specific set of conditions.

Initial experiments by Hilbert, et al (1968), showed the Vavilov (1957) distribution as tabulated by Seltzer and Berger (1964) cannot be used to predict frequency distributions of energy loss by fast charged particles over pathlengths small enough to be of interest in radiobiology or to shed light on energy transfers to the small sites of interest. However, when corrected in the manner outlined by Blunck and Leisegang (1950), good agreement was found between experimental and theoretical values of the full width at half maximum (FWHM) for these distribution functions of energy loss.

Experimental distribution functions corresponding to energy deposition for fixed pathlengths at various depths in tissue were investigated by Hilbert and Baily (1969). These investigators also examined the problems associated with folding such functions into composite

functions for the purpose of obtaining distribution functions of energy deposition for various sizes and shapes of biological sites. The major problem in arriving at such distributions of energy deposition from basic data is the lack of sufficient information about delta ray production. They were also able to show that application of conventional microdosimetric techniques (Rossi-like chambers) to measurements in charged particle beams will generally lead to distorted results. The situations considered showed that relatively few pathlengths need be simulated to approximate the distribution in any given spherical volume. In many cases of cylindrical sites the situation is even less complicated.

The statistical distribution of energy deposition events over short pathlengths is not adequately described by any single parameter. Therefore Baily, et al (1970), undertook a systematic investigation comparing experimental distribution functions obtained with a high degree of statistical significance to those generated from the Blunck-Leisegang corrected Vavilov theory. They found a consistent deviation from theory which increased as the pathlength decreased further and further into the region of greatest interest for radiobiology. Although the mean energy loss in all experimental distributions was the same as that predicted by stopping power theory, there were more large energy events and less low energy events in the experimental distributions functions than that predicted from theory. This indicates that the loss of energy from the sensitive volume of the counter by delta rays is not a major factor for these cases. As the pathlength decreases, or the primary particle energy increases, this condition would not be expected to be valid. The implications of this finding could be of great importance for a proper understanding of the mechanisms producing biological changes in irradiated tissues. An empirical discovery was that when the logarithm of probability/unit of energy loss was plotted vs. energy loss, the high energy tail of the distribution function could

be approximated by a straight line of constant slope over a large region of energy losses. A result for 46.4 MeV protons traversing a tissue path of approximately 1 micron is shown in Fig. 1. The stopping power of this energy proton is approximately equal to that of a 20 keV electron.

In most situations (radiobiological) it is necessary for the beam to penetrate a finite amount of tissue before reaching the critical site. In such a case the beam will be degraded in energy by both electronic and nuclear scattering as well as inelastic interactions, and, in addition some loss of primary particles may have occurred. The changes this produces in the frequency distribution of energy deposited in short pathlengths has been studied comprehensively by Baily, et al (1972a, 1972b), over a wide range of absorber thickness and particle energy. They were able to clearly demonstrate a transition from the region where statistical fluctuations of energy deposition dominate to that where a significant spread in beam energy has taken place and provides the major influence on the resultant distribution function. In no instance was it found that the macroscopic value of the absorbed dose which is based on the average value (stopping power) adequately defined the energy delivered by single particle traversals to a structure having dimensions associated with biologically sensitive sites. Therefore, only if many events in the same site should be involved would such measurements or calculations have validity. The results show that for large thicknesses of absorbing material broader distribution functions are obtained than from a monoenergetic primary proton beam whose energy was equal to that calculated from the residual range of the 44.3 MeV protons. The distribution functions which illustrate this fact are shown in Figs. 2 and 3. Curve A in Fig. 2 represents the frequency distribution obtained after passage through 1.54 g/cm^2 of Shonka muscle (Shonka, et al, 1958). Curves B and C of Fig. 2 are the distributions of energy loss after passage through 1.60 g/cm^2 and 1.63 g/cm^2, respectively. In Fig. 3 the frequency distributions obtained after passage of the beam through 1.63 g/cm^2, 1.74 g/cm^2, 1.79 g/cm^2,

and 1.85 g/cm^2 of Shonka muscle are shown as Curves A, B, C, and D.

The percent FWHM decreases steadily from a maximum for the undegraded beam through that value obtained after passage through 1.63 g/cm^2 (Curve C of Fig. 2, and Curve A of Fig. 3) then starts to increase again. This is a logical consequence of having introduced a significant spread of energies in the proton beam with the energy spectrum having a low energy tail.

The pertinent quantitative data obtained are given in Table I. ← Table I

It is clear that for absorber thicknesses of less than approximately 1.6 g/cm^2, the statistical fluctuations in energy loss are the dominating factors in determining the character of the frequency distributions of energy loss by 45 MeV protons traversing short pathlengths. As expected, the fractional width of the distribution becomes narrower with decreasing beam energy and the average energy loss increases. This continues until energy straggling of the incident beam becomes dominant. It appears from the data that a loss of proton energy of about 75% is required to reach the point where the straggling of the primary beam has introduced a sufficient spread in energy, in particular a low energy tail, so that this becomes the dominant factor in determining the character of the energy deposition pattern. These factors are evidenced by the steady decrease in the width of the energy loss functions through the first 1.63 g/cm^2 of absorber thickness and the subsequent broadening of these with further degradation of the beam. Of prime importance is the fact that in no instance do these functions approach relatively narrow gaussian functions which are commonly used to calculate LET distributions from the stopping power of the charged particles. For all distributions the most probable energy loss is significantly lower than the average energy loss. Therefore in biologically significant volumes and for an effect dependent on a single or small number of traversals, the actual energy delivered to the majority of targets will be

incorrectly inferred if absorbed dose is used. The data is illustrative of the behavior of all charged particle radiations.

Similar experiments have been carried out using much higher energy particles (Baily, et al, 1972b). In this case in addition to ionization by the primary protons, there will be ionization by secondary (cascade) protons, by nuclear reaction products and by pions which have been produced in the irradiated tissues by the primary particles. Discrepancies between experiment and theory for the primary distribution functions were similar for 600 MeV protons to those shown for 45 MeV protons. However, the contribution to the total ionization by processes other than direct action by the primary beam were found to be that predicted by the calculations of Turner, et al (1964), and Wright, et al (1969). The degree to which these contribute is a function of the amount of tissue penetrated before the beam reaches the sensitive site. This is illustrated in Table II.

The values given in Table II were obtained from frequency distribution curves measured under appropriate geometric conditions. The contribution from excitation products is seen as an increase in the fraction of large energy events. Similarly pion and cascade proton contributions which increase in number with increasing absorber thickness are seen also as an increase in this part of the distribution function.

There are several possibilities open to us for determining microscopic patterns of energy deposition. First, we can simulate as closely as possible the conditions applying to the actual biological exposure. While this method can be made to yield very accurate data by careful selection of the proper instrumentation, it is expensive and difficult, and our lack of knowledge of certain physical parameters makes the choice of instrument design an unknown factor for many practical situations which we might wish to simulate. Second, we might calculate the

distribution functions for discrete pathlengths and by using the pathlength probability distribution, calculate the distribution functions for any desired shape or volume. This method also poses a number of problems: (1) Pure theoretical considerations do not yield correct distributions of energy loss. (2) Even using empirically fitted tails to these does not solve the entire problem since our knowledge of delta ray production is incomplete. (3) The theory does not apply to many cases of interest. (4) The effects of degradation of the beam by passage through absorbers is not susceptible to easy or reliable calculational techniques.

A third method has recently been demonstrated by Steigerwalt and Baily (1973) and successfully applied to both low and medium energy (45 MeV, 600 MeV) protons. This method is able to take a limited amount of experimental data and subject it to convolution and deconvolution techniques thus generating the data (other pathlengths) required for folding into distribution functions of energy deposition corresponding to any shape or size of sensitive volume. This method also preserves the irradiation conditions under which the original experimental data were taken. The transformation uses a compound Poisson process suggested by Kellerer (1970a). Moderate shifting of the mean energy of the experimental distribution functions (repeated if necessary) has produced excellent agreement between theory and experiment. Factors affecting the resultant distributions required for application in predicting actual energy deposition in a particular biological site such as pathlength distributions can easily be determined and applied by calculational procedures or as corrections. Some of the more important corrections which still need investigation are those required for the delta rays so that probabilities for contributions and losses due to secondaries can be properly applied.

Using moderate shifts of the mean energy (0.75 - 1.5) it has been shown that the greater portions of all distribution functions so far investigated can be fitted with good

agreement. This method could become a powerful tool for calculating many distributions using relatively little experimental data. This technique is especially attractive in the case where deposition of energy is due to a few primary interactions. In such cases the basic theoretical approaches to energy loss functions subject to stochastic principles are not applicable due to the limitations of the applicability of transport theory when too few collisions are involved. An investigation using 600 MeV protons (Baily, et al, 1973) having pathlengths producing mean energy losses as low as 117 eV has shown that good agreement is obtained between experiment and calculation if one uses shift factors based on experimentally determined mean values rather than tabular values based on stopping power theory.

In using this method (Baily, et al, 1973), the calculations may be terminated at any arbitrary spectrum whose mean energy is $\overline{\Delta}_f$, and which may be either less than or greater than $\overline{\Delta}_i$ the mean energy of the initial spectrum. Given an initial distribution function $f(\Delta, \overline{\Delta}_i)$, the final distribution function $f(\Delta, \overline{\Delta}_f)$, can be obtained by taking the Fourier transform of the initial distribution function

$$F(t, \overline{\Delta}_i) = \int_0^\infty e^{it\Delta} f(\Delta, \overline{\Delta}_i)\, d\Delta \tag{6}$$

To calculate a final distribution, use is made of the relation (Steigerwalt and Baily, 1973):

$$\ell n\,[F(t, \overline{\Delta}_f)] = s\,\ell n[F(t, \overline{\Delta}_i)] \tag{7}$$

in order to find the new function $F(t, \overline{\Delta}_f)$.

s is a shift factor numerically equal to $\overline{\Delta}_f/\overline{\Delta}_i$. The function $f(\Delta, \overline{\Delta}_f)$ is then reconstructed from $F(t, \overline{\Delta}_f)$ by making use of its Fourier transform,

$$F(t, \overline{\Delta}_f) = \int_0^\infty e^{it\Delta} f(\Delta, \overline{\Delta}_f)\, d\Delta \qquad (8)$$

Combining the distribution functions expected from the stochastic processes occurring over discrete pathlengths into those applicable for a biologic site is a relatively simple matter, with the exception of corrections for delta ray contributions and losses. Pathlength distribution functions for spheres and cylinders of various height to diameter ratios have been calculated by Birkhoff, et al (1969). In many cases of interest only a few discrete pathlength distribution functions are required for the generation of the desired distribution. For most geometries the shape and characteristics of the resultant distribution function are governed by those of the functions obtained over discrete pathlengths.

C. THE ROLE OF ENERGETIC SECONDARY PARTICLES

Microdosimetric distributions of energy deposition are sought because a correlation is expected to exist between these patterns of energy deposition and the biological damage which is produced. In addition, it is felt that these patterns illuminate the fundamental processes involved in radiation biology. The factors needed to describe these patterns of energy deposition can be divided into two main categories. First, the nature of the primary beam and a specification of the secondary radiation produced or a spatial pattern of ionization densities produced by these must be known. Second, the characteristics of the sites, with regard to their general shape, size, number and location is of prime importance. The sites, by definition, can be affected when energy is deposited within them, and thus contribute to the biological endpoint under consideration. At this time the exact nature of such sites is not known with certainty.

The correlation between the patterns of energy deposition and a specified biological endpoint must be treated using theoretical models of radiation damage. The selection of relative locations of such sites plays a role in the construction of these models especially with regard to those aspects influenced by a multiplicity of sites which must be inactivated to produce the desired endpoint. For example, can the effect being observed result from the passage of one primary particle whose secondaries deposit energy in multiple sites simultaneously? Can damage be a consequence of energy deposition in multiple sites by independent events? If the answers to these questions are positive then undoubtedly energetic secondary electrons play an important role.

Models in general incorporate experimental data in their formulation, since the derivation of the totality of the complex interactions between a charged particle and a target from first principles cannot be completely described at the present time. Single event spectra are needed to determine the energy deposition distributions of independent events. These distributions have been measured with a simple proportional counter. Measurements of the simultaneous deposition of energy in multiple sites require other ins truments and techniques. In addition, measurements must include descriptions of the ionization density surrounding the path of a single charged particle.

The measurement of single event spectra by a proportional counter has been treated earlier and in most cases is a routine procedure. However, to make measurements of simultaneous energy deposition events in various regions requires more complex and flexible apparatus. Ideally, we should like to be able to simulate the shapes of various regions, for which energy deposition distributions are desired, as well as their geometric relationships, with a single, versatile instrument. For a single region of arbitrary shape, in principle, measurements of

this type could be done with a properly designed proportional counter. Usually this means a very difficult electrostatic design problem and correspondingly difficult construction techniques. Such an apparatus, once built, generally cannot be easily modified to accommodate other geometrical structures. As is the case with all proportional counters which provide microdosimetric measurements, wall effects will be present and must be estimated and corrections to the experimental data made. Such corrections can be minimized with 'wall-less' designs. To investigate multiple regions, the design and construction of appropriate measuring instruments become more complicated. For example, Burlin, et al (1972), describe an instrument designed to measure energy deposition in dual cylindrical sites, and are able to measure single event spectra in each volume, either separately or one in coincidence with the other. They are able to adjust the distance between the volumes up to a separation of about 9 diameters. Thus one is able to look at secondary radiations in each of the volumes produced by a primary particle passing directly through one volume. The models which can utilize such information must then be restrictive in their assumptions about site geometry.

Perhaps a more general approach could be given by the use of a multiwire proportional counter (Charpak, 1970). Such counters have been used mainly in high energy physics as position sensitive detectors. Basically, these counters are constructed with many coplanar parallel wires each acting ideally as an independent proportional counter. Typical spacings between wires are approximately 2 mm with perhaps a total of 50 to 100 wires incorporated into a single instrument. A particle passing through the counter will develop a pulse on various wires depending on the counter operating pressure, the resultant distribution of the ionization in the counter, and on the counter gain. Two counters of this type, with wires mutually perpendicular, operated in coincidence, thus are able to give two dimensional

position information of the path of a charged particle with resolutions on the order of a millimeter. For microdosimetric studies, the counter must be used in a different operational mode. This mode would require the pressure of the counting gas to provide distances between wires which would approximate typical biological sites and also provide energy deposition information.

During the past few years the use of multiwire proportional counters has grown at a very fast rate. Many improvements leading to larger sizes, better spatial resolution, and to experiments utilizing stacks of such counters have been made. Much work, followed by significant achievements, has been published dealing with preamplifiers, amplifiers, and read-out systems.

Applications to microdosimetry are presently being explored. These applications are to use such instruments for the determination of energy deposition distributions using the wire spacing to define pathlength and for the determination of the spatial distribution of energy deposition by secondary particles surrounding the path of a charged particle. Both of these applications are in the exploratory stages.

The value of such an instrument is that in addition to examining the probability for events occurring simultaneously at sites separated by chosen arbitrary distances, the ionization density surrounding a charged particle track could then be measured. To accomplish this with a plane array of parallel wires the sensitive volumes associated with each wire must be exposed only to those secondaries which are ejected in a direction nearly parallel to the plane of the wires and approximately perpendicular to the primary track. The wires at various distances from the particle track would produce pulses proportional to the ionization density produced by energetic secondary radiations reaching these areas. The wires very close to the primary track would produce pulses which correspond to the ionization density produced

by both low energy secondaries, and by the more energetic secondaries which deposit energy near these wires as they move out to larger distances. By changing the angle of the counter plane with respect to the direction of the incident particles, approximate three dimensional ionization densities can be measured (symmetry in the azimuthal plane is assumed). This type of information can be collected for various types of primary beams. The technique gives distributions of ionization densities but gives no direct detailed information about the individual spectra of emitted delta rays. This type of information would be very difficult to derive from such measurements. This is so because a pulse developed on a given wire is due to the sum of the ionization produced by the many secondary particles entering its sensitive region. These secondary particles which are produced by the primary, are emitted with a distribution of initial energies. Each particle in a given energy interval is subject to a unique straggling distribution corresponding to a given pathlength interval, which is determined by the wire spacing. This consequently results in variations in the energy loss in the sensitive region of each wire. Thus the amplitude of the composite pulse is a complex function of the gas pressure in the counter, the initial energy distribution of the secondaries, and the straggling. To obtain probability distributions, one would have to measure the distributions of ionization produced in the region of each wire. An initial distribution of secondary energies would then have to be found which is consistent with the measured ionization density distributions mentioned above.

The most important practical details connected with the operation of the multiwire proportional counter in this mode and the interpretation of the output are:

1) keeping the gain uniform for all the wires;
2) accounting for the signal amplitudes induced on one wire by pulses developed in adjacent wires;

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3) estimating the solid angle subtended by each wire with respect to the primary particle track, and physically limiting the sensitive region on each wire to the approximate region of interest.

Essentially, measurements made with a multiwire proportional counter yield the ionization produced as a function of radial distance from a primary charged particle track, with a limited lateral extent. Such information can be used to determine ionization densities in sites at a given distance from a primary charged particle track. Descriptions of ionization densities in multiple sites resulting from the passage of a single primary charged particle can then be inferred. For primary particles which pass directly through a site, estimates could then be made of energy transport into and out of the site. These would be a function of the position of the chord traversed by the primary particle. Such distributions are of course needed in many instances for folding individual spectra into a composite distribution. The composite distribution obtained would then correspond to that expected from a uniform beam irradiating an arbitrarily shaped site. We feel that measurements of this type are essential to continued progress in the studies of the relation between basic energy deposition patterns and biological damage.

The multiwire proportional counter can be thought of as a series of cylindrical sites. Glass and Roesch (1972) have described an experimental apparatus which approximates a cylindrical site. They have made measurements of single event spectra produced by protons passing directly through the site and also by secondary radiations generated by protons passing externally to the site. By examination of one wire of the multiwire proportional counter at a time, similar experimental distributions should be attainable.

Pathlengths on the order of 10^1 to 10^3 $\mu g/cm^2$ are currently obtainable through the use of a proportional counter. The description of energy deposition in the sites of dimensions on the order of 10^{-1} $\mu g/cm^2$ at the present time cannot be obtained experimentally. They can either be calculated or derived from experimental spectra taken at larger pathlengths. There is evidence (Kellerer and Rossi, 1971a), however, that much can be explained with energy deposition in sites of dimensions of about 10^2 $\mu g/cm^2$. Thus, while the distributions relevant to sites where the fundamental damage mechanisms are occurring cannot always be measured, it seems worthwhile to pursue the measurements which can be made with proportional counters. Assume that we consider a pathlength of 10^2 $\mu g/cm^2$. The lateral extent of the ionization density produced will depend on the maximum energy of the secondary electrons produced by the incident particle. No rigorous theoretical treatment exists nor is experimental data available pertaining to secondary electron production. Toburen and Glass (1972) have measured the distributions of energy transferred to electrons in single events from protons having energies in the range of 0.3 to 2 MeV. The difficulty still remains of incorporating such data into measured or calculated energy deposition distributions for a given site size. The secondary electron production plays an important role in the transfer of energy from the primary particle to the site under consideration. A knowledge of the properties of these secondaries is essential to solutions of the energy deposition problem in biological structures. Baily, et al (1970), have shown that theoretical calculations for the energy straggling of protons become progressively poorer as the pathlength decreases. The same phenomena would also be expected for the energetic secondary electrons. These two factors indicate that an experimental approach should be investigated. Measurements made with a multiwire proportional counter possibly could become the next step which will provide useful microdosimetric information for smaller sites, ionization patterns associated with the delta rays, and probabilities for multiple site interactions.

The determination of frequency distributions of energy deposition in small volumes corresponding to biologically sensitive sites and their application to radiobiological theory and modeling are still in a very early stage of development. The extent and the scope of the implications posed by the use of a statistical treatment of stochastic parameters have largely been ignored. Physical research leading to a better understanding of these distributions particularly with respect to the contributions and deletions caused by secondary charged particles entering and leaving a selected volume are certainly necessary. But of even greater importance are biological experiments designed to test, elucidate, and provide data on theories and models based on this concept. These can either confirm or deny the basic concepts of microdosimetry which lie primarily in stochastical aspects of energy deposition. Hopefully such experiments will also lead to further elucidation of the fundamental mechanisms involved in the production of radiobiological effects in living tissues.

IV. IMPORTANCE OF STATISTICAL PROCESSES

The role of statistical processes in energy transfer by charged particles to atomic electrons which results in energy deposition in a specific site may be of extreme importance in radiobiological processes. The macroscopic concepts upon which traditional radiation dosimetry is based (average energy absorbed) can only have microscopic validity under certain specific conditions. These conditions are, first, that a large number of individual events or particles which traverse the site, each depositing energy, are required to produce the observed effect. Second, the magnitude of the volume or mass of the specific biological structure is such that the energy transfer per particle traversal is large compared to the maximum energy which it can transfer in a single collision. Third, the observed effect is due not to the change in function of fundamental tissue components but as the result of a summation of damage and interaction of energy deposition in many individual sites. However, if we take the view that radiation effects observed are due to disruption of molecular bonds, genetic structures, or very specific cellular functions then we are forced in many cases of interest to consider variations in energy deposition eitherdue to pathlength differences in the site under consideration or to statistical fluctuations of energy loss by the ionizing particle. Pathlength distributions in various geometrically shaped sites have been well treated by Birkhoff, et al (1969). The applicability to radiobiology of the statistical concepts previously discussed does not seem to be generally recognized by the radiobiologist.

The energy range and the type of primary or secondary particle for which these statistical concepts must be considered are very extensive. Even Compton electrons generated

at conventional x-ray energies, and protons generated in tissue by fast neutrons are in many cases of sufficient energy to make the use of statistical treatments necessary in order to properly and accurately describe the energy deposition in individual biological structures. Figure 4 illustrates the degree to which these effects are manifest for a pathlength of 1 μ in muscle.

Fig. 4 →

Curve A represents the energy loss distribution function of a 50 keV electron traversing this amount of muscle tissue, and Curve B is that for a 50 MeV proton. For shorter pathlengths than 1 micron the distribution functions would be even broader and more highly skewed. Curve C is that for an 8 MeV alpha particle, and D for a 24 MeV (stripped) ^{12}C ion.

In addition to the change in the most probable and average energy losses, the change in percentage energy spread about the most probable value is readily apparent with changing energy deposition. Also, a distinct change in skewness takes place. With increasing energy deposition, the distribution becomes more nearly gaussian. The spread in event size is sometimes expressed in terms of the percent full width at half maximum (FWHM) of the distribution function although this is only a partial description. The values for the examples shown in Fig. 4 are 150%, 131%, 23%, and 0.27%, respectively. The ratio of the average to the most probable energy losses for the two lighter classes of particles is given in Tables III and IV. This ratio approaches unity for densely ionizing particles. In addition, we must also consider the particles' pathlength. The smaller the pathlength the greater will be the statistical straggling.

Tables III + IV

The series of changes which occur in both the overall shape and width of the frequency distribution functions representing the energy deposition in short pathlengths or in small volumes are undoubtedly of importance in the production of biological effects if energy deposition plays any part except that of providing an initiating event. Comparisons of the biological effects caused by different radiations, when viewed in reference to measurements of the absorbed dose, could be dramatically affected if the actual dose in individual sites were used. The characteristics associated with each distribution function are defined to a high degree of accuracy by the particle's mass, charge, kinetic energy, the pathlength distribution which describes the sensitive site, and the electron density of the biological matter.

From Fig. 4, the following points should be noted. 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 $\Delta X(\frac{dE}{dX})$. Second, as charge and mass decrease (8 MeV - α particle), the FWHM increases, but its shape is still primarily gaussian. The peak or most probable energy loss usually coincides with the average energy loss. Third, as the magnitude of the energy loss decreases, relative to the particle's kinetic energy, such as is the case for protons and other fast charged particles, the curve becomes quite skewed with a tail on the high energy end. As a consequence of this increase in skewness, the most probable energy loss becomes increasingly less than the average.

The ratio of average to most probable energy losses can become quite large (Tables III and IV) so that in the instance postulated, i.e., short pathlengths through sensitive

biological sites and radiobiological effects in such sites being due to single or a small number of events, there will be only a small population of biological sites which absorb energy close to the average value and therefore the macroscopic concept of absorbed dose is likely to lead to erroneous conclusions about the properties of various types of radiation and their ability to produce radiobiological damage.

The combination of these patterns of energy deposition whose shapes are due purely to the statistical fluctuations involved in the loss of energy in short pathlengths together with the assumption that a single or a small number of events in an individual site produces the biological damage observed, prompts one to re-examine the use of the macroscopic dosimetry unit, the rad, and ask if it is really suitable for use as a measure of radiobiological effects. Simple consideration of the probabilities as illustrated by the character of the frequency distribution functions leads one to immediately question whether or not attributes of various types of radiation which have been associated with LET, dose rate, etc. are not more properly accounted for by the total distribution of energy deposition events which reflects the relatively high probability that in many instances a dose significantly less (or significantly greater) than was measured or calculated macroscopically will be deposited in or is responsible for the damage in individual sites such as cells, chromosomes, DNA, etc.

The above illustration for one specifically chosen pathlength is meant only to illustrate the general principle. For shorter pathlengths which are most certainly of more importance in the case of biological structures, these effects are exaggerated. Conversely, in the case of larger specific sites these statistical variations will not be as severe. In this latter case the situation is very much simplified. As the site gets larger the average energy deposited increases because of the increased number of collisions. With this increase in the number of

collisions the distribution becomes gaussian in nature and its relative half-width becomes narrower and narrower. In addition the values of the most probable and average energy depositions become one and the same. In this instance absorbed dose as expressed by the macroscopic unit, the rad, becomes a better measure of the situation.

V. AN ILLUSTRATION OF POSSIBLE RADIOBIOLOGICAL INTERPRETATION

We recognize that biological data taken under different conditions and by various investigators often represents conditions not directly comparable. One quantity which minimizes such variables is that of RBE since it is incumbent on the investigators to compare the results of irradiations using two different types of radiation beams. Presumably all biological and physical aspects have been held constant for both irradiations except for the change in beam characteristics. Consequently in using this data we have not made any adjustments or interpretations of our own but simply quote the values arrived at by the author as published in the literature.

The treatment which follows is based on microdosimetric considerations which indicate that for low dose rates the cell is very unlikely to be traversed by more than one charged particle. In a 1μ site these probabilities range from 10^{-1} to 10^{-3} events/rad. The probabilities for dual traversals are the above squared. It is, therefore, obvious that in all cases of practical importance a dosimetry system based on average values of highly skewed distributions cannot give insight to the actual mechanisms of RBE. The assumptions we have made to obtain the comparisons in this section are: first, that the probability for a cell to suffer more than one or two energy deposition events is small, and second, that in the case of skewed

distribution functions of energy deposition the value of a dose computed using the most probable energy deposition will be closer to the energy actually received by individual sites than one based on the average value.

This treatment in no way attempts to explain differences in RBE due to true differences in biological response, but only those which might be due to the actual amount of energy deposited in the critical site. The assumption can also be made that several interactions, n, are necessary to produce the observed effects. Here too, a similar statement can still be made since the composite energy deposition distribution will still be skewed; however, the average energy deposited will be n times the average energy of the single event distribution. Only when n becomes large will the average energy deposition of the resultant distribution coincide with the most probable energy deposition.

As it has been shown, the ratios of the average to most probable energy deposition in small volumes by the two types of particles previously considered (protons and electrons) for single events can differ substantially from unity. Some of these ratios aregiven in Tables III and IV. Recall that the macroscopic dose D gives an average value of energy deposition which is considered to be applied uniformly to each microscopic volume, where D actually corresponds to the average energy deposition occurring in many sites. Let us make the assumption that only a single interaction is required to produce the observed effects and that the probability of multiple events in a small volume (site) is close to zero. Under these conditions the majority of sites will have absorbed energy equal to the most probable energy deposition. It is our contention that the most probable energy deposition in the sites corresponds more closely to the conditions required by the concept of dose D, or actual energy deposited than to the average energy deposition. In other words, some

portion of the applied dose, particularly those large events depositing energy in excess of that required for producing the biological effect, is inefficient in producing the observed effect. A correction to D with the idea of producing another macroscopic quantity $\mathcal{D} = \alpha D$ which more nearly describes the energy deposition in small sites is worth exploring. Rossi, et al, (1961) have previously explored concepts of this sort. By examining the macroscopic details of energy deposition it is fairly obvious that a rough correction factor is given by taking $\alpha = \Delta_{mp}/\overline{\Delta}$ for any given radiation. By continuing this line of reasoning one can assume that $\mathcal{D}$ is the macroscopic quantity which describes biological effects and it is desirable to formulate views of RBE factors in terms of it. The simplest manner to do this would be to assume the equality of $\mathcal{D}$ for equal effects by two radiations. This is equivalent to assumptions that the stochastic effect might account for at least some of the reported values of RBE and that the range of values of the observations are due to a misapplication of dosimetric concepts and that perhaps no real difference in biological effect exists for the two radiations under comparison. This type of evaluation should therefore provide some insight into the validity of microscopic vs. macroscopic dosimetry concepts. We wish to make very clear, however, that we are not proposing a dosimetry system based on another single parameter which would substitute for the average energy deposited. In all likelihood, if any single parameter at all would suffice, it would be a complicated function of the entire microscopic energy deposition. We only wish to show that a rigorous treatment which utilizes the frequency distributions of energy deposition for dosimetry systems as well as radiobiological models must be considered.

In the following illustration an attempt is made to explain differences in RBE for various types and energies of charged particle beams. In particular, RBE values will be

related to the constants α given for each radiation beam. Perturbations which are introduced by use of a uniform site size in the illustrations are ignored although undoubtedly some of the experimental material reported by investigators involves multi-hit phenomena. Similarly, no correction has been introduced for energy influx and outflow due to secondaries. This correction would not alter materially the basic skewed shape of the distributions, but a change in the average and most probable values of energy deposition would be expected. Biological recovery factors are also not considered.

The illustration will be approached in the following logical sequence:

a) For equal effect $\mathcal{D}_{ref} = \mathcal{D}_{test}$

b) The macroscopic doses are given by

$$D_{ref} = \frac{1}{\alpha_{ref}} \mathcal{D}_{ref} \qquad D_{test} = \frac{1}{\alpha_{test}} \mathcal{D}_{test}$$

c) Reported values of RBE are given by

$$RBE = \frac{D_{ref}}{D_{test}} = \frac{\alpha_{test}}{\alpha_{ref}} \frac{\mathcal{D}_{ref}}{\mathcal{D}_{test}} = \frac{\alpha_{test}}{\alpha_{ref}}$$

d) A comparison will be made between reported values of RBE and the value of the expression $\alpha_{test}/\alpha_{ref}$ for the radiations used.

The consistency with which the comparisons made in part d) agree can be taken as an indication of the validity of the assumptions made for the illustration.

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The values of RBE to be cited are those of the authors referenced. No attempt was made to employ only one specific endpoint nor was a comprehensive survey of RBE literature made. Many of the values of RBE reported were evaluated by the authors on the exponential portion of the survival curves where it can be argued that recovery phenomena must be considered. However, despite these obvious deficiencies of detailed analysis there exists a striking similarity between the quoted radiobiological results and values of $\alpha_{test}/\alpha_{ref}$. The data given in Tables III and IV have been calculated for an arbitrary pathlength of 1 micron in soft tissue. This data is necessary to calculate the appropriate values of α. The values of $\alpha_{test}/\alpha_{ref}$ expressed as 'expected RBE' have been presented in Tables V and VI for two test radiations consisting of various energy protons and electrons and with reference radiations of 50 keV and 1 MeV electrons. These reference radiations are considered to be applicable to experiments conducted with the standard radiations of 200 - 250 kVp x rays and Co^{60} gamma rays.

The comparisons between quoted experimental results and appropriate values of 'expected RBE' will be made and discussed in the following sections. The values are also dependent on site size or particle pathlength. Changes of the order of two in pathlength produce changes of about 20% in the ratio of average to most probable energies.

A. X RAYS, γ RAYS, AND ELECTRONS

Using 20 MeV electrons, Kim, et al (1968), found no significant difference in biological effectiveness using both survival and extent of recovery from sublethal irradiation of HeLa S-3 cells in culture when this quantity was measured at depths corresponding to both the 100% and 25% values of the absorbed dose. These were found at absorber thicknesses of 1.0 g/cm^2 and 8.7 g/cm^2. If we make allowance for the fact that due to the build-up of

secondaries, the beam after penetration of 1.0 g/cm^2 has a lower mean energy than its initial monochromatic value, and that we have a slowly changing value for the ratio of average to the most probable energy loss, it is not unreasonable to assume that this ratio is approximately 2.3 (Table IV). After penetration of 8.7 g/cm^2 of tissue (muscle), the residual range of the electrons is 0.589 g/cm (Berger and Seltzer, 1964). This corresponds to an electron energy of approximately 1.3 MeV. The ratio of average to most probable energy losses at this depth would then be approximately 2.2. In view of the many assumptions made, this difference in ratios is not significant. The value of unity for the RBE which was found by Kim is then to be expected due to the near equality of the values of $\Delta_{mp}/\overline{\Delta}$ for these reference and test radiations. Focht, et al (1968), obtained similar experimental results in their studies of the production of radiation cataracts.

Sinclair (1962) compared the LD_{50} and ^{59}Fe uptake in several biological systems using 200 kVcp x rays, ^{60}Co γ rays, and 22 MeVp x rays. When the 200 kVcp data was used as the reference, the average of his values for RBE were 0.872 for ^{60}Co and 0.826 for 22 MeVp. Assuming 50 keV and 6 MeV for the average values of the electron spectra, Table V yields values of 0.816 for ^{60}Co and 0.809 for 22 MeVp. Using ^{60}Co as his standard, the average values found by Sinclair were 1.15 and 0.998 for 200 kVcp and 22 MeVp, respectively. Table VI yields values of 1.22 and 0.990.

In the paper by Barendsen, et al (1963), values for the RBE of 2.2 MeV beta rays obtained using various survival levels of human kidney cells (T_1) are given using 200 kVp x rays as the standard. The average of the values obtained was 0.865. The mean value of the electrons in this beta ray spectra is approximately 1 MeV. The predicted RBE for this energy electron given by Table V is 0.816.

B. HIGH ENERGY PROTONS

Even though there is a vast literature reporting measurements of RBE using x rays, γ rays, and electrons, there is a fair degree of consistency for the values reported. In the case of primary proton comparisons this does not exist. Even the same investigators using identical beams and dosimetry systems report a considerable spread in values for different biological systems. These may be due to differences in recovery factors, site size, or in certain instances the existence of an energy threshold for observable damage to take place. The following examples indicate the spread in values obtained and compare these with a calculation using the method described above.

Using the data in Tables III, V, and VI for protons and the values given by Turner, et al (1964), and Wright, et al (1969), for the fraction of the total dose delivered by heavy particles produced in nuclear interactions, we would predict RBE's of 1.17, 0.992, and 0.968 for protons having initial energies of 600 MeV, 400 MeV, and 150 MeV, respectively, when referred to the gamma rays of ^{60}Co or values of 1.03, 0.980, and 0.860 when referred to an x-ray spectrum having a mean electron energy of 100 keV. Some experimental values which have been reported are discussed below.

Using 592 MeV protons, Baarli and Bonet-Maury (1965) found values of 0.98, 1.06, 1.03, and 1.01 for four different endpoints in mice when compared to 250 kVp x rays. A value of 1.03 is given above.

Using several test systems, Čerček, et al (1969), obtained values of approximately 1.3 and something greater than one for the RBE of 380 MeV protons when compared with ^{60}Co and a value of 1.4 when compared to 30 kVp x rays. A value of 1.15 has been reported by Lindsay and Dalrymple (1967) for 400 MeV protons referred to 2 MeV x rays. These values are considerably higher than could be accounted for by use of our numbers combined with the

physical data given by Turner, et al. It should also be pointed out that at this energy, a lesser proportion of the total absorbed dose is delivered by heavy ions than there would be delivered at 600 MeV where in general the observed RBE's have been considerably lower. Other high energy proton data taken at 730 MeV (Ashikawa, et al, 1963) showed a spread of values ranging from 0.770 to 1.25. In addition to the use of varying endpoint values and different biological systems, it must always be remembered that in general, high energy proton dosimetry is difficult and therefore subject to significant error. Another factor which cannot be ignored is that in many instances, because of secondary build-up, extreme care in choosing the measurement system must be exercised.

At lower energies (138, 150, and 185 MeV) values for RBE's have been reported ranging from as low as 0.75 to as high as 1.15 (Lindsay and Dalrymple, 1967; Stenson, 1969; Traynor and Siegel, 1968). The low value (0.75) (Lindsay and Dalrymple, 1967) was found relative to 220 kVp x rays, while the higher values were referred to 2 MeV x rays. The values obtained from Tables V and VI and the data of Turner, et al, are 0.968 and 0.860 for 150 MeV protons relative to ^{60}Co and 100 keV electrons (220-250 kVp x rays), respectively.

C. HEAVY CHARGED PARTICLES

Our analysis is not of sufficient detail to make meaningful comparisons between experimental data and values derived from frequency distributions of energy loss. In addition, any requirement for minimum energy deposition will be extremely important in this case, since the characters of the two distribution functions are radically different and therefore have a large difference in the absolute values of the most probable energy losses. However, the values calculated in Tables V and VI would lead one to expect RBE's of the order of two when compared to fast electrons or protons. Todd (1967) has reported values based on the inhibition of colony formation by T_1 cells from a value slightly greater than one, to about three, for heavy ions ranging from deuterium to carbon-12 measured at the 1% survival level and referred to low energy x rays. Perhaps a better comparison is with the data of Deering and Rice (1962) who compared the 1/e values taken on the linear portion of the logarithmic survival curves for 40 MeV α particles, 69 MeV lithium ions, 105 MeV carbon ions, and 130 MeV oxygen ions with 250 kVp x rays. The values obtained were 1.45, 1.86, 2.36, and 1.24, respectively. The low value obtained with oxygen ions is probably due to a saturation effect of usable energy deposition. That is a significant portion of the energy deposited in each critical site was in excess of that required for cell death.

The comparison of these values of RBE reported with the values obtained from the adjustment of the absorbed dose levels used in the experiments is entirely based on the concept that a single or at least a small number of events in a small sensitive site caused the observed effect. In addition, we have assumed that the true dose delivered, in terms of true energy deposition to such sites is more properly specified by the most probable rather than the average energy deposited. This appears to be a reasonable hypothesis since in the case of

highly skewed distributions the probability for an amount of energy to be deposited in a single or few events is significantly less than that for depositing an amount of energy at or close to the most probable value of the distribution function. There is nothing in this formulation which would explain the variations of radiosensitivity with degree of oxygenation, dose rate, or recovery. There is, of course, another reason for examining values of RBE and that is certain biological specimens have shown very high values of the RBE for neutrons vs. x rays for producing genetic effects in plants. On an energy basis such as assumed above, the existence of a threshold, that is a certain minimum amount of energy deposition in a critical site could account for these also. This could take place in the following manner. If one considers the type of curve illustrated by Fig. 6, we see that for fast charged Fig. 6 particles the fraction of total energy delivered (absorbed dose) in large events falls off very rapidly. In the case of low energy protons generated by a neutron beam, the fraction of events depositing large amounts of energy would be considerably greater.

We have compared the fractions of energy delivered in events greater than some minimum for neutrons of 1 MeV delivered to a 1 micron spherical mass of soft tissue (muscle). Very close to 100% of the dose was found to be delivered in single events of 20 keV or more. We compared this with a similar plot for 50 keV electrons. Here it was found that fractions of 0.5, 10^{-1}, 5×10^{-1}, and 10^{-2} of the total energy delivered in single events was greater than; 0.8, 1.6, 2.1, and 2.6 keV. For dual events these threshold energies were 0.9, 1.3, 1.4, and 1.6 keV. Therefore, if such minimum depositions of energy were required to produce the observed effects, RBEs of 5, 10, 50 or 100 would have been observed. One might then postulate that in those cases where no minimum is required RBEs of approximately 2 might be expected but where a specific minimum energy deposition is required considerably higher values of RBE would be observed.

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The behavior of the observed values of RBE with dose rate can be easily explained in terms similar to that used by Kellerer and Rossi (1972) by involing temporal considerations and postulating an interaction between two independent events.

The main point we wish to make is the importance of considering the character of the distribution functions of energy deposition when studying the biological effects of ionizing radiations. These concepts are valid for observed phenomenon in cells or similar structures and also in considering mechanisms for producing overall effects observed in complicated living systems. Concepts based on the average of a large number of events are probably of little value when attempting to make comparisons of effects produced at different beam energies or by different kinds of radiation. A further point of importance is that where a threshold energy deposition is required for production of damage, two radiations having widely different average or most probable energy losses per traversal of the sensitive site can still produce the observed effect. However, if one is a densely ionizing particle and the other a lightly ionizing particle having a highly skewed distribution, the probability per rad for producing the effect will be quite different in each case. This would result in large measured values of RBE when such experiments are based on absorbed dose measurements.

The processes which take place when living tissues absorb energy from ionizing radiations and which produce molecular and other changes clearly depend on the microscopic energy deposition distribution. These are dose dependent only if; the energy deposited in the critical site from a single event was insufficient to produce the change, or if more than one site required simultaneous energy deposition. In the case of single or very few event requirements the absorbed dose which is based on average values of the microscopic distribution will not be useful in providing information on these fundamental processes.

Similarly, average values of the distribution function f(Z, D) will not be appropriate since we must deal with each site as a single entity to predict the overall response of the test material to a given amount of irradiation. If only events are required, that is there is no minimum requirement on the magnitude of energy deposition, then only the probability for an interaction defines the magnitude of the effect observed. If on the other hand some threshold of energy deposition is required to produce an observable effect then the effective probability will be less than when no threshold exists. By using both a knowledge of absorbed dose and the pertinent distribution function for energy deposition we should be able to; predict for any type of ionizing radiation the effect produced by comparison to some other reference radiation whose dose vs. effect responses are well known. Second, we should be able to acquire further insight into fundamental mechanisms associated with radiobiological action, and, third, we should be able to account for real biological differences in RBE, dose rate response, and the interaction between damage and recovery mechanisms.

In this next section we shall attempt to illustrate how such concepts might be applied to current theories and models.

VI. MODELING BASED ON MICRODOSIMETRIC CONCEPTS

As a start on this difficult problem we have formulated two oversimplified models, both ignoring such important biological parameters as repair and recovery, dependence on dual events, dual or multiple site inactivation and diffusion of radicals or other reactive species. The first of these is based on simple hit theory which postulates that if a critical site is traversed or hit, then the biological event is presumed to have occurred. Such a simple formulation yields the familiar exponential relationship expressed by

$$S = e^{-\frac{D}{D_O}} \tag{9}$$

where, S = surviving fraction of exposed population

D = absorbed dose

D_O = mean lethal dose (the dose required to reduce the survival to 1/e of its original value).

Using this simple relationship we can imagine that our original population consists of a large number of sub-populations each having enough members for statistical validity. Since microdosimetric concepts demonstrate that the individual energy deposition events have a wide distribution of values we can then make the assumption that if only single traversals are considered each of our sub-populations will receive an absorbed dose in accordance with this distribution function. This presumes a large number of critical sites with respect to the available ionizing particle flux or the total dose delivered. The fraction of the population designated as $N_{O\,n}$ (subgroup, n), having received a dose Δ_n would then be

$$N_{O\,n} = N_O \, f(\Delta)_{\Delta = \Delta_n} \, d\Delta \tag{10}$$

where, $$N_O = N_{O1} + N_{O2} + N_{O3} + \ldots + N_{On} \quad (11)$$

and, $f(\Delta)_{\Delta = \Delta_n}$ = probability for sub-population n receiving a given dose, $d_n = D \frac{\Delta_n}{\bar{\Delta}}$.

The number of sites having a probability of having zero hits during the irradiation is then,

$$N = N_{O1} e^{-\frac{d_1}{D_O}} + N_{O2} e^{-\frac{d_2}{D_O}} + \ldots + N_{On} e^{-\frac{d_n}{D_O}} \quad (12)$$

$$= N_O [f(\Delta)_{\Delta=\Delta_1} d\Delta \, e^{-\frac{D\Delta_1}{D_O\bar{\Delta}}} + f(\Delta)_{\Delta=\Delta_2} d\Delta \, e^{-\frac{D\Delta_2}{D_O\bar{\Delta}}} + \ldots$$

$$+ f(\Delta)_{\Delta=\Delta_n} d\Delta \, e^{-\frac{D\Delta_n}{D_O\bar{\Delta}}}] \quad (13)$$

$$= N_O \int_O^{\Delta_{max}} f(\Delta) \, e^{-\frac{D\Delta}{D_O\bar{\Delta}}} \, d\Delta \quad (14)$$

or

$$S = \int_{O}^{\Delta_{max}} f(\Delta)\ e^{-\frac{D\Delta}{D_O \overline{\Delta}}}\ d\Delta \qquad (15)$$

Here, $f(\Delta)$ is the frequency distribution function of energy depositions in a specific type of critical site. It is a function of site size, shape, the type and energy of the primary radiation, and the amount of tissue penetrated before the beam reaches the critical site.

This simple approach is easily extended to the single hit multitarget model where,

$$S = 1 - (1 - S_1)^m \qquad (16)$$

where;

m = the number of targets required to be hit for an inactivation to take place and,

$$S_1 = \int_{O}^{\Delta_{max}} f(\Delta)\ e^{-\frac{D\Delta}{D_O \overline{\Delta}}}\ d\Delta \qquad (17)$$

The case of single targets requiring multiple hits can also be handled routinely by using the usual statistical formulation, our sub-population concept, and a suitable transformation of $f(\Delta)$ the frequency distribution of energy deposition for single traversals. This is easily done by convoluting $f(\Delta)$ the required number of times (the number of hits required in the critical site) for inactivation.

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In the case of single hits (single or multiple sites) requiring a minimum of energy deposition, the lower limit of integration would simply be the threshold value. In such cases a knowledge of the fraction of events and/or the fraction of the total energy deposited by the beams exceeding some minimum is of value. This information can easily be obtained from the frequency distribution function $f(\Delta)$ pertinent to the situation of interest. Examples of such data are given in Figs. 5 and 6. ^

Figs. 5 & 6

Another approach to formulating a single target-multihit model requiring a minimum deposition of energy in the whole target site can be made using Poissonian statistics in combination with the frequency distribution of energy loss pertinent for the situation under consideration.

Let $f_n(\Delta)$ be the frequency distribution for deposition of a total energy equal to Δ when a critical target site of volume v has been traversed by n particles. We define a constant, α, which is descriptive of the beam and site geometries:

$$\alpha = \frac{\text{hits/cm}^3}{\text{Rad}} .$$

The total number of hits per unit volume N is then, $\alpha D \frac{\text{hits}}{\text{cm}^3}$ where D is the dose in Rads. The average number of hits is therefore, $\alpha D v$.

If the number of hits, (n), being considered is small, the probability of having n hits is given by a Poisson distribution. In this case it may be written as,

$$P_n = \frac{(\alpha v D)^n \; e^{-\alpha v D}}{n!} \qquad (18)$$

The probability that the volume v is not hit is,

$$P_O = e^{-\alpha v D} \qquad (19)$$

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Therefore the total probability, $P(\Delta)$, that a volume irradiated to a total dose D and absorbing an energy between Δ and $\Delta + d\Delta$ is just the sum of products of the probabilities for undergoing n hits and the probability $f_n(\Delta)$ for absorbing energy between Δ and $\Delta + d\Delta$ for n interactions.

$$P(\Delta)\,d\Delta = \sum_{n=1}^{\infty} P_n f_n(\Delta)\,d\Delta \qquad (20)$$

The survival is just the probability for a critical site having a volume v, irradiated to a dose D absorbing energy Δ where Δ is less than some critical energy threshold Δ_c. The probability, P_c, for this is then,

$$P_c = P_O + \sum_{n=1}^{\infty} P_n \int_O^{\Delta_c} f_n(\Delta)\,d\Delta \qquad (21)$$

The type of survival curves predicted by this model for single hits in multitargets are shown in Fig. 7. A, is that predicted for a single hit model, while B and C are those calculated for the case requiring single hits in two and three sites, respectively. The usual semi-logarithmic response can be arrived at by requiring some combination requiring a given fraction of single site damage and the rest in multi-site events. No modification for recovery or repair has been considered although these phenomena do occur. These of course must enter. Nor has any cut-off or threshold energy requirement been introduced to modify the fraction of events effective in producing damage. ∧

Fig. 7 →

Curves such as those shown in Fig. 7, A, have been observed both in UV and x irradiated DNA (Elkind and Whitmore, 1967). More recently Baarli, et al (1973), have

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reported similar survival curves for type B spermatagonia in mice when exposed to both 400 MeV neutrons and 95 MeV stopped negative pions. Control populations which were x-irradiated showed the normal expected type of survival curves. Since nuclear spallation processes are involved one conclusion which can be drawn is that only one energy deposition event is required in a given site, but that if sufficient energy is deposited, repair, even at low dose (macroscopic) levels, is not possible.

Experiments to test this hypothesis are presently underway. Confirmation would lend more confidence in using and expanding concepts based on statistical consideration of energy deposition in radiobiological modeling.

A similar approach can be used to introduce the energy deposition distribution functions into any biologically acceptable model provided it: first, is based on effect proportional to energy deposited in a critical site, and, second, damage or observable effect is considered to be due either to a single or at most a few energy depositing events.

Kellerer and Rossi (1972) in their recent review article have clearly demonstrated how to introduce the function $f(\Delta)$ into their theory of dual radiation action. Our function $f(\Delta)$ is the equivalent of their function $f(Z_1)$. We shall, therefore, not discuss this theory further but simply refer the reader to the original paper.

In the case of the Katz (1973) model these microdosimetric concepts could be introduced into the formula for the extrapolated cross-section by replacing the LET and single valued dose functions by the energy loss distributions pertinent to the particle type, energy, and site geometry.

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FIGURE LEGENDS

Figure 1: Frequency distribution of energy losses for 46.4 MeV protons in equimolar mixture of He-Co_2 in a pathlength of 1.33×10^{-4} g/cm^2. Circles show experimental data, while the solid line is fully corrected theoretical function. (From Baily, et al, 1970.)

Figure 2: Pathlength, proton energy, and absorbing material are the same as given for Fig. 1. Curves A, B, and C were obtained after passage of the beam through 1.54 g/cm^2, 1.60 g/cm^2, and 1.63 g/cm^2 of Shonka muscle, respectively. (From Baily, et al, 1972a.)

Figure 3: Pathlength, proton energy, and absorbing material are the same as given for Fig. 1. Curves A, B, C, and D were obtained after passage of the protons through 1.63 g/cm^2, 1.74 g/cm^2, 1.79 g/cm^2, and 1.85 g/cm^2, respectively, of Shonka muscle. (From Baily, et al, 1972a.)

Figure 4: Frequency distributions of energy loss by various charged particles in a tissue-equivalent medium. The pathlength used in these computations was 10^{-4} g/cm^2. 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 ^{12}C stripped ion.

Figure 5: Fraction of events depositing energy in amounts greater than a given size when a 46.4 MeV proton traverses 1.33×10^{-4} g/cm^2 of tissue-equivalent material.

Figure 6: 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/cm^2 of tissue-equivalent material.

Figure 7: Survival curves predicted by a model incorporating stochastic energy deposition processes. A. Survival curve predicted for single hit processes. B. Single traversals in two sites. C. Single traversals in three sites.

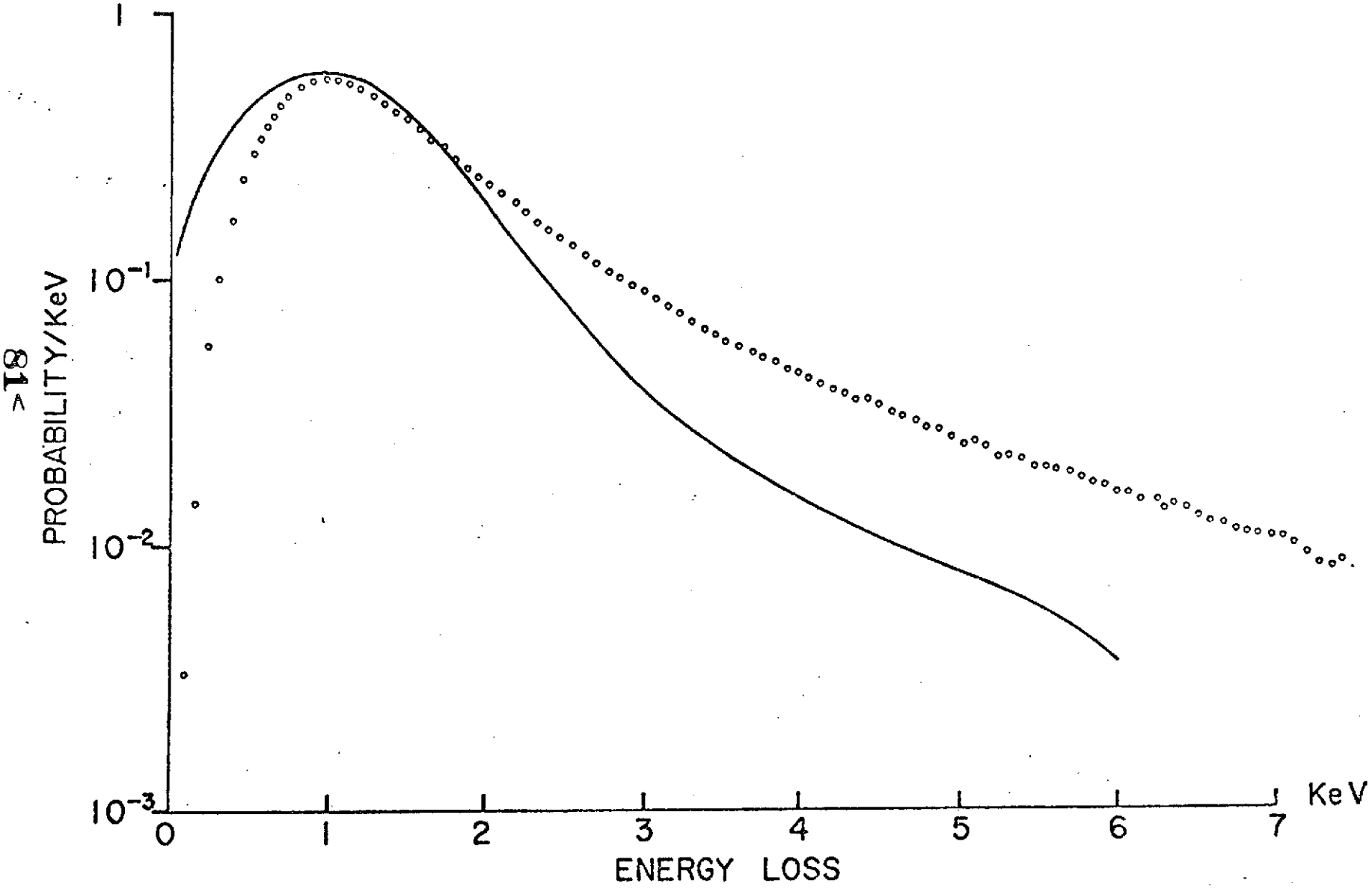
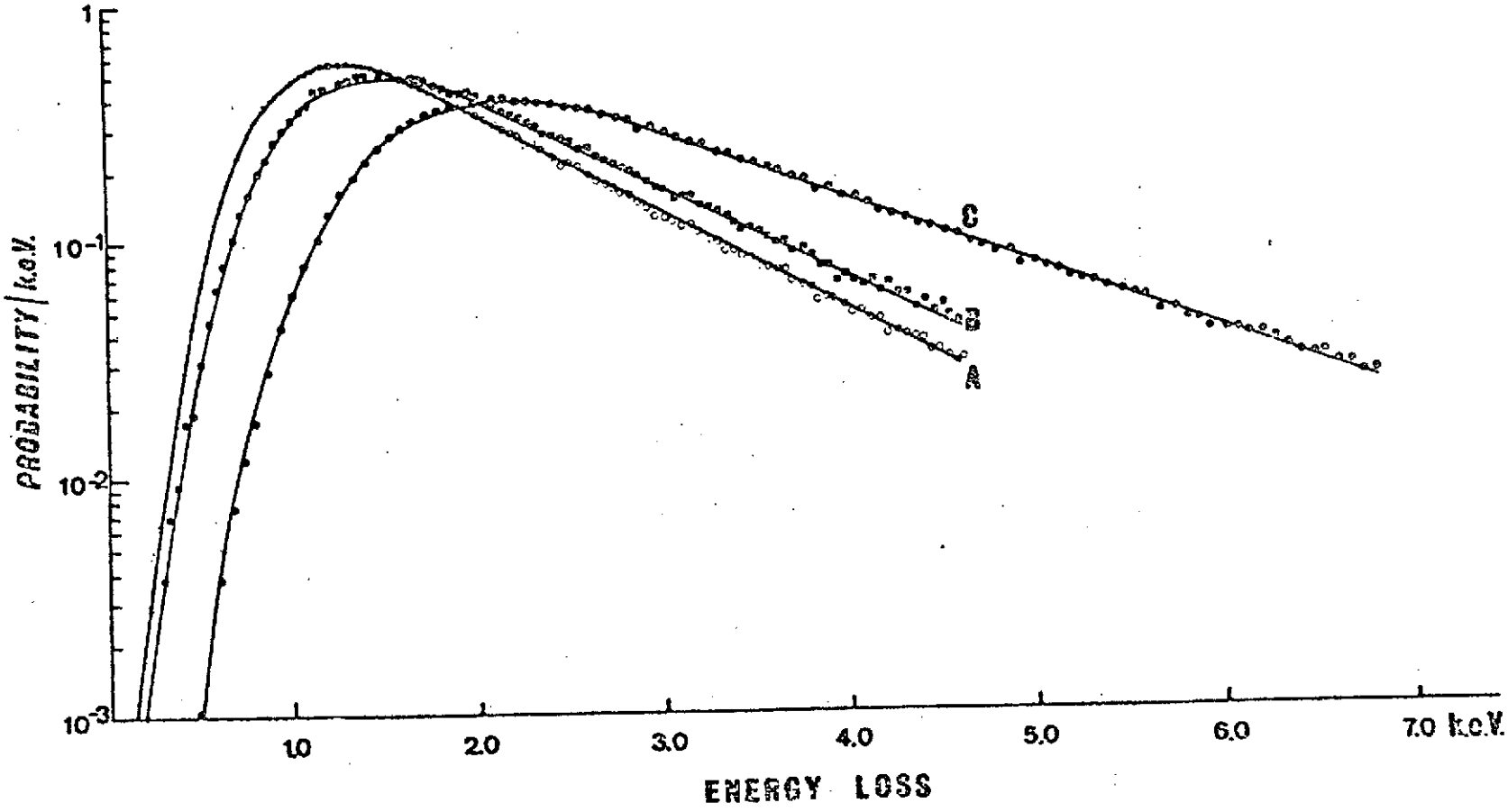


Figure 1


1
10^{-1}
10^{-2}
10^{-3}
PROBABILITY / k.e.V.
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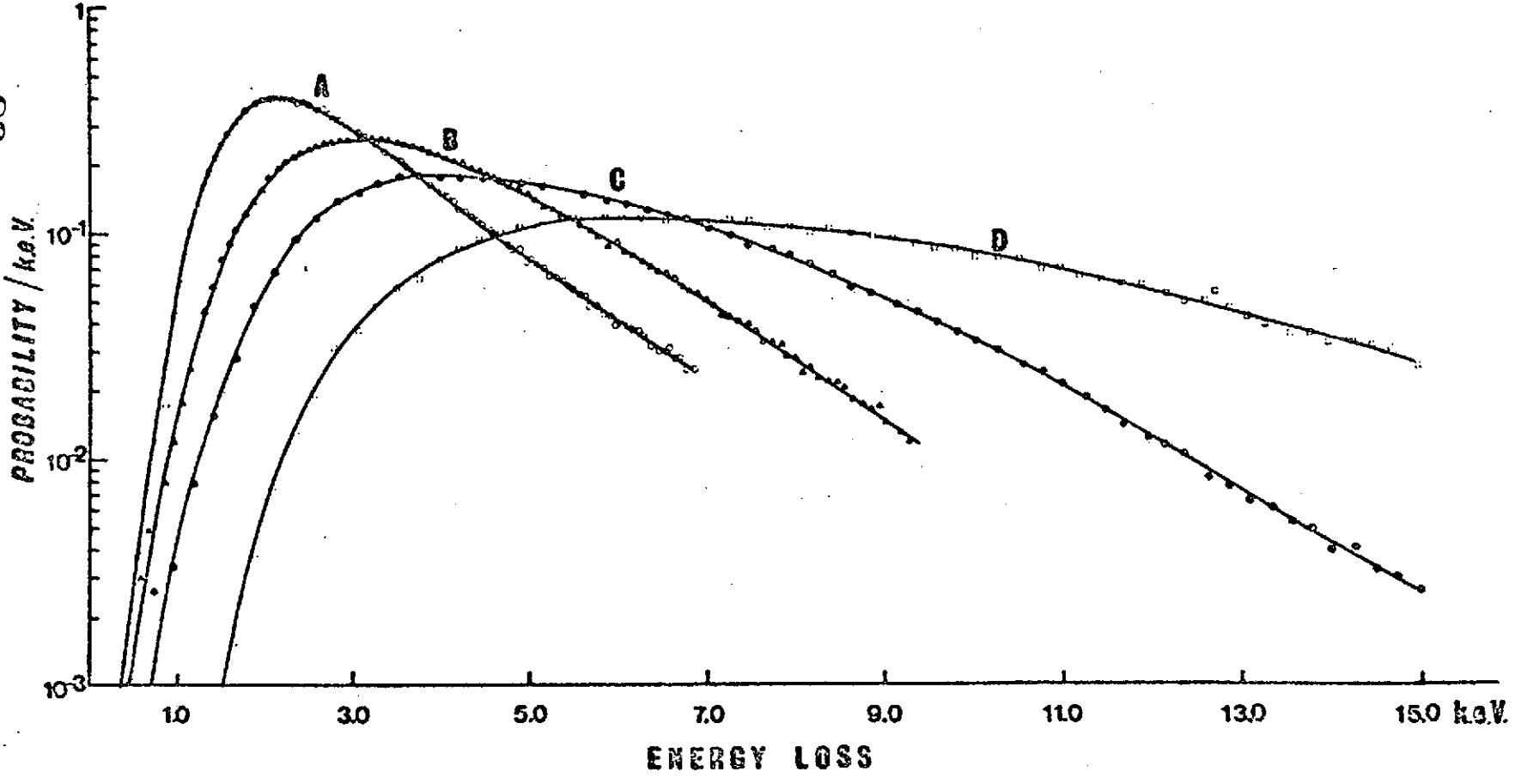
2.0
3.0
4.0
5.0
6.0
7.0 k.e.V.
ENERGY LOSS
C
B
A

Figure 2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10^{-1}
10^{-2}
10^{-3}
A
B
C
D
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11.0
13.0
15.0 k.e.V.
ENERGY LOSS

Figure 3

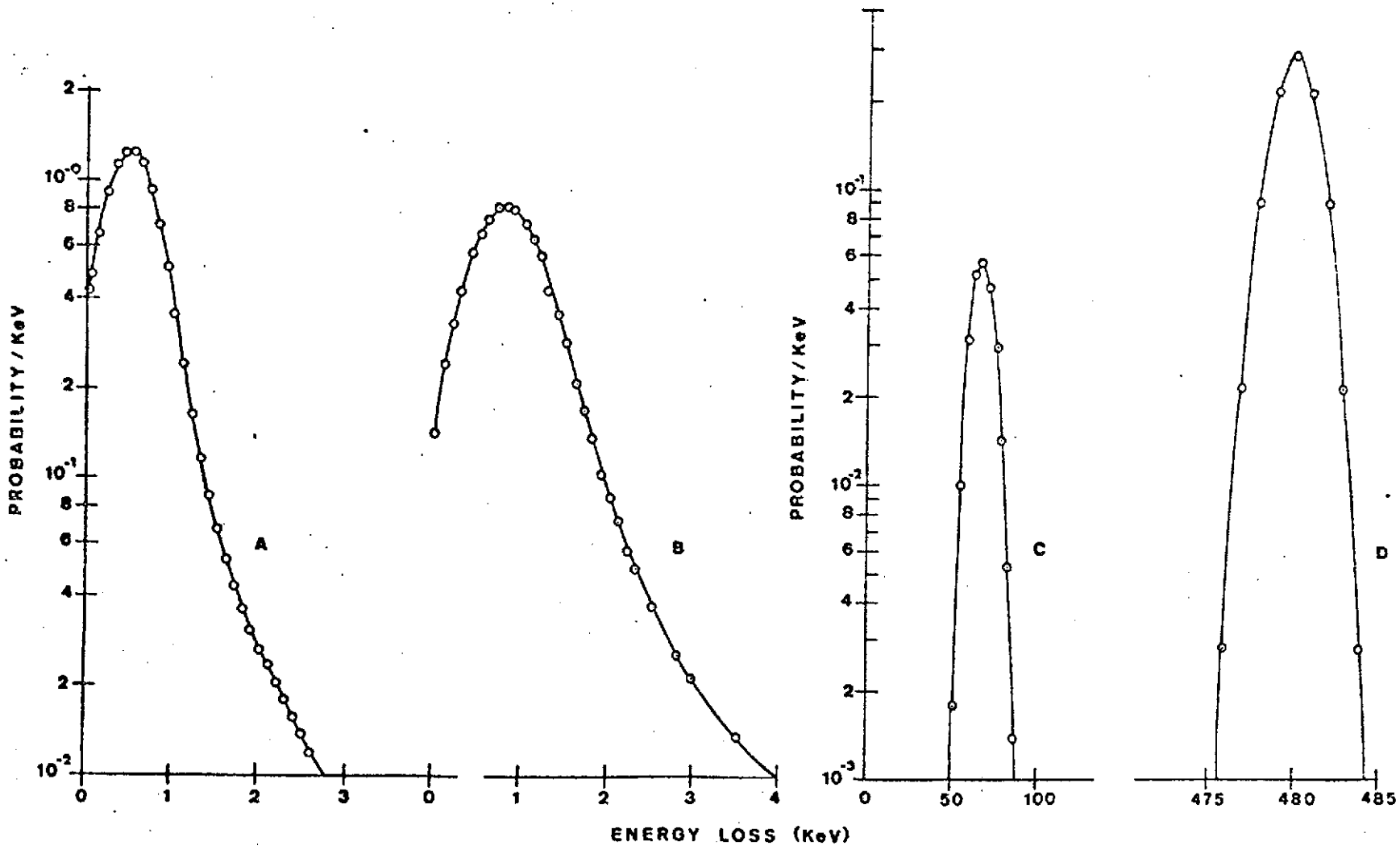
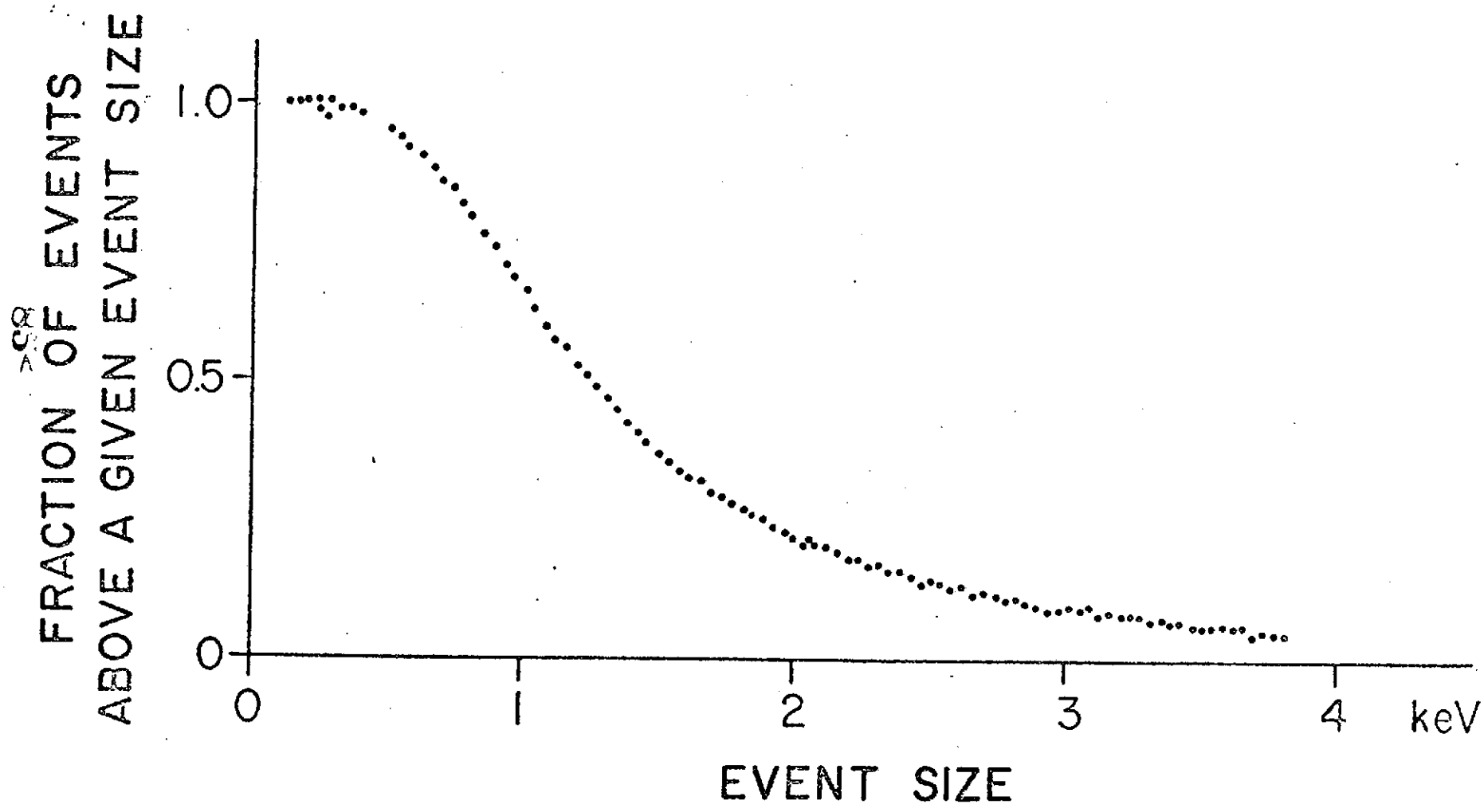


Figure 4


FRACTION OF EVENTS
ABOVE A GIVEN EVENT SIZE
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0.5
0
0
1
2
3
4
keV
EVENT SIZE

Figure 5

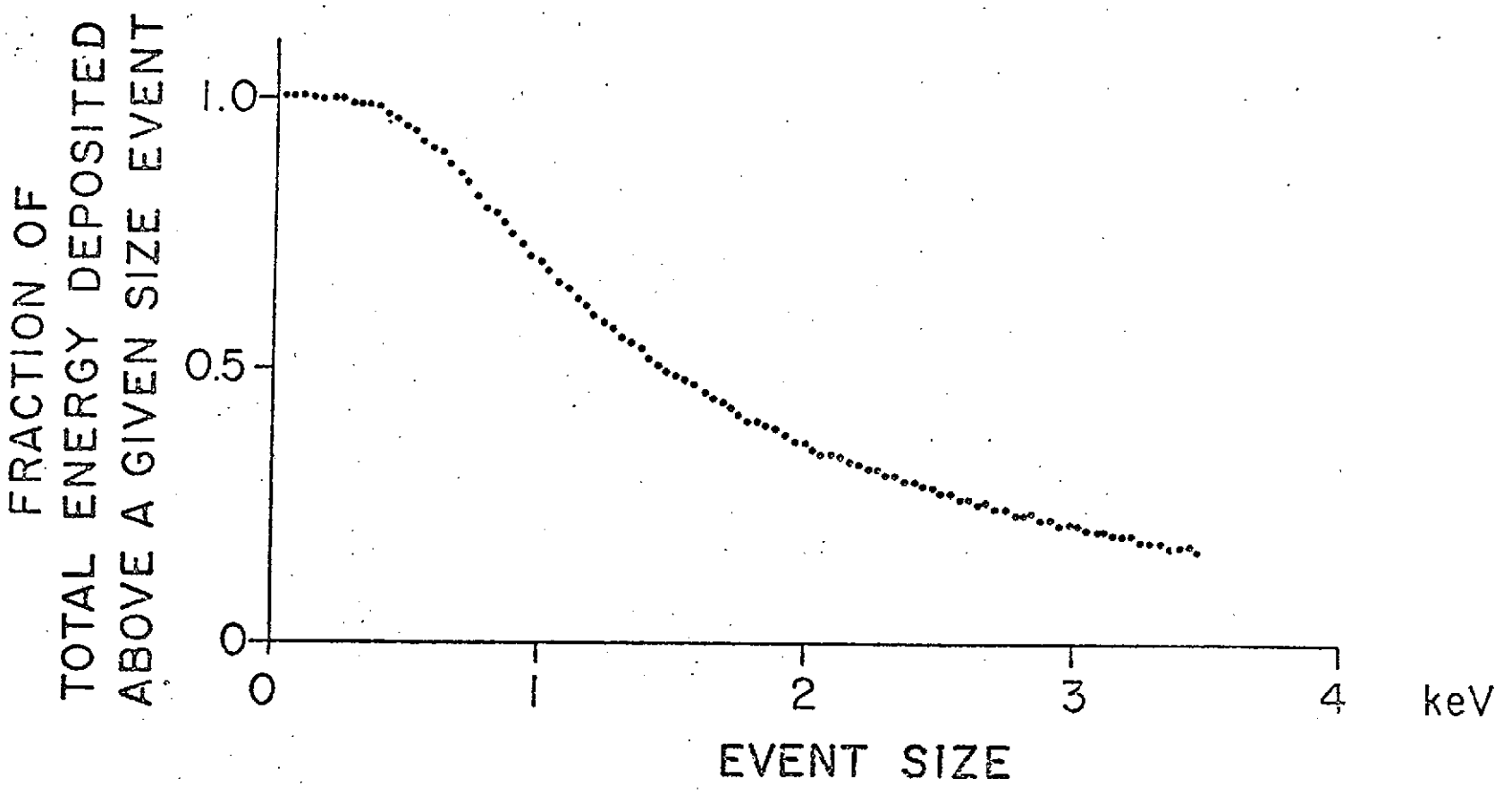
FRACTION OF
TOTAL ENERGY DEPOSITED
ABOVE A GIVEN SIZE EVENT
1.0
0.5
0
0
1
2
3
4
keV
EVENT SIZE

Figure 6

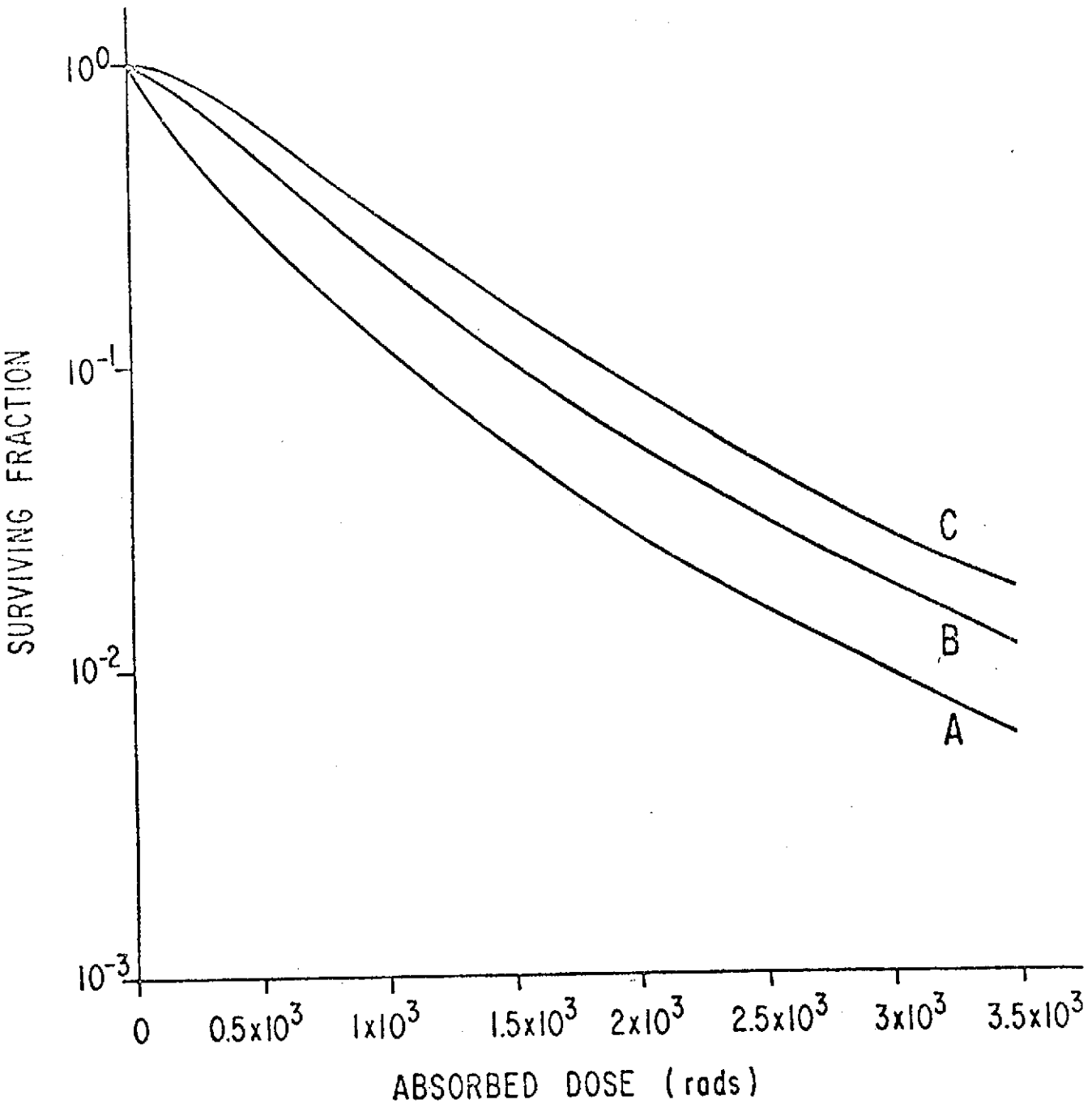
SURVIVING FRACTION
10^0
10^{-1}
10^{-2}
10^{-3}
C
B
A
0
0.5×10^3
1×10^3
1.5×10^3
2×10^3
2.5×10^3
3×10^3
3.5×10^3
ABSORBED DOSE (rads)

Figure 7

TABLE I[a]

Characteristics of frequency distributions for 44.3 MeV protons after passage through various thicknesses of muscle-equivalent plastic.

Absorber thickness--Shonka muscle (g/cm^2)	Average energy loss, $\bar{\Delta}$ (keV)	Most probable energy loss, Δ_{mp} (keV)	$\Delta_{mp}/\bar{\Delta}$	Slope of high-energy tail (probability/keV)/keV	FWHM %
0	0.809	0.43	0.53	0.86	133
0.22	0.856	0.46	0.54	0.85	130
0.44	0.919	0.53	0.58	0.86	126
0.66	0.997	0.61	0.61	0.87	118
0.99	1.17	0.72	0.62	0.84	114
1.54	1.95	1.30	0.67	0.86	111
1.60	2.20	1.50	0.68	0.88	109
1.63	2.94	2.15	0.73	0.55	100
1.74	4.13	3.00	0.73	0.55	113
1.79	5.67	3.90	0.69	0.47	129
1.85	8.49	6.10	0.72	0.41	136

[a]From Baily, et al (1972a).

TABLE II[a]

Fraction of total absorbed dose delivered by 600 MeV protons due to secondary particles other than electrons.

Depth in tissue (cm)	Fraction of total absorbed dose by all secondaries except electrons		Fraction of total absorbed dose delivered by nuclear excitation products	
	Theory	Experiment	Theory	Experiment
0.5	0.16	0.23	0.08	0.10
21	0.48	0.52	0.06	0.07

[a]From Baily, et al (1972b).

TABLE III

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

Proton Energy (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 IV

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

TABLE V

Expected R.B.E. calculated from the values of the ratios of average to most probable energy losses when the value of this ratio for 50 keV electrons is taken as the reference value.

Electron Energy (MeV)	Expected R.B.E.	Proton Energy (MeV)	Expected R.B.E.
0.05	1.00	1.0	1.82
0.1	0.919	2.0	1.69
0.2	0.863	5.0	1.39
0.4	0.827	10.0	1.22
0.6	0.820	50	0.968
0.8	0.820	100	0.892
1.0	0.816	150	0.854
2.0	0.816	600	0.774
4.0	0.813		
6.0	0.809		
8.0	0.802		
10.0	0.798		

TABLE VI

Expected R.B.E. calculated from the values of the ratios of average to most probable energy losses when the value of this ratio for 1 MeV electrons is taken as the reference value.

Electron Energy (MeV)	Expected R.B.E.	Proton Energy (MeV)	Expected R.B.E.
0.05	1.22	1.0	2.23
0.1	1.13	2.0	2.06
0.2	1.06	5.0	1.70
0.4	1.01	10	1.50
0.6	1.00	50	1.19
0.8	1.00	100	1.09
1.0	1.00	150	1.05
2.0	1.00	600	0.950
4.0	0.995		
6.0	0.990		
8.0	0.983		
10.0	0.978		

FINAL REPORT

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