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PRINCIPAL INVESTIGATOR: Norman A. Baily
Professor of Radiology

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Introduction

The research program being carried out under this grant has several phases or aspects, each of which complements each other. These can be classified in general as:

(a) Determination of the statistical distribution of the magnitudes of the energy losses by fast charged particles (protons) in tissue-like materials having biologically significant volumes.

(b) Radiobiological modeling.

(c) Experimental testing of the radiobiological models as to their capability for predicting radiation damage in human lymphocytes.

(d) Development of an electronic system for recording, digitizing, and computer processing of biological indicators of radiation damage or other physiological changes incurred during space flight.

All four phases have been given some effort during the past year with the bulk of the effort going into Phase (a). Here we have succeeded in obtaining experimental data having sufficient accuracy to assess the accuracy of available theoretical treatments for all energy losses having an occurrence probability of greater than 10^{-4}.

Microdosimetry

The aims of this aspect of our work are:

1. To examine the accuracy of theories dealing with the statistical frequency distributions of energy losses by fast protons in tissue-like materials having biologically significant volumes. Examples of such

volumes being those of cells, cell nuclei, chromosomes, or large macromolecules such as DNA, etc.

2. To experimentally determine these distributions as a function of particle penetration through soft tissue, bone, or combinations of these.

As a first step in this portion of the program, we have utilized the 47-MeV Alternating Gradient Isochronous Cyclotron at UCLA. The actual proton energy available at the window of our proportional counter is 46.4 ± 0.165 MeV. This energy proton was used for two reasons. First, the solar flare spectrum anticipated within a manned space vehicle peaks at about this energy. Second, the UCLA machine is readily available to us as members of the University family.

Earlier work[1] had concentrated on an examination of the FWHM (Full Width at Half Maximum) of the distribution.

(1) Hilbert, J.W., Baily, N.A., and Lane, R.G.: Phys. Rev. 168, 290 (1968).

While these showed good agreement with the Blunck-Leisegang[2] corrected Vavilov[3] distribution,

(2) Blunck, O. and Leisegang, S.: Z. Physik 128, 500 (1950).

(3) Vavilov, P.V.: Zh. Eksperium, i. Teov. Fig. 32, 320 (1957) [English Transl., Soviet Phys. - JETP 5, 749 (1957)].

obvious discrepancies between theory and experiment at both very low and at large energy losses were evident.

During the past year, 360 hours of Cyclotron time were utilized in obtaining distributions with good counting statistics for the entire distribution. At least 10^3 counts in each of the channels representing 80% of the spectrum were recorded, thus providing a statistical reliability of approximately 3%. These spectra were recorded at very low count rates ($< 10^3$ counts/min.) in order to minimize pile up distortion. This was confirmed experimentally. Data were recorded in 1024 channels using an on-line SDS-925 computer. A program was written which sums over groups of ten channels since these sums represent sufficient resolution for radiobiological purposes.

Due to the difficulty with inverting large matrices, a broadening function assumed to be gaussian was applied to the theoretical distributions. The broadening due to the statistics of ion pair formation and electron multiplication at the counter wire can be shown to be given by[4] where E is the energy available to the counter volume to produce ionization.

$$\sigma_{STAT.} = 0.169 \, E^{1/2}$$

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(4) Campbell, J.L. and Ledingham, D.K.: Brit. J. Appl. Phys. 17, 769 (1966).

The gas utilized was an equimolar mixture of He-CO_2. This gas has an electron density within 10% of that of soft tissue. The stopping power for this mixture is:

$$23.6 \pm 0.1 \text{ MeV/g/cm}^2$$

Table I gives the pertinent parameters.

The average energy losses were: 1.56-, 7.85-, and 15.6 KeV, respectively. These were computed from the value of the stopping power as given by Barkas and Berger[5]. The values of

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(5) Barkas, W.H. and Berger, M.J.: Nat'l Acad. Sci. - Nat'l Res. Council Publ. 1133, 103 (1964).

$\varkappa$, the Vavilov parameter, were: 0.00114, 0.0053, and 0.0099, respectively.

The experimental data are shown in Figures 1, 2, and 3 by the circles. The error bars represent the uncertainty due to statistics only. In order to convert the experimental data which consists of counts per channel -vs- channel number to probability per KeV -vs- KeV, the experimental data were used to determine an average channel number. This was done by numerical integration as follows:

TABLE I

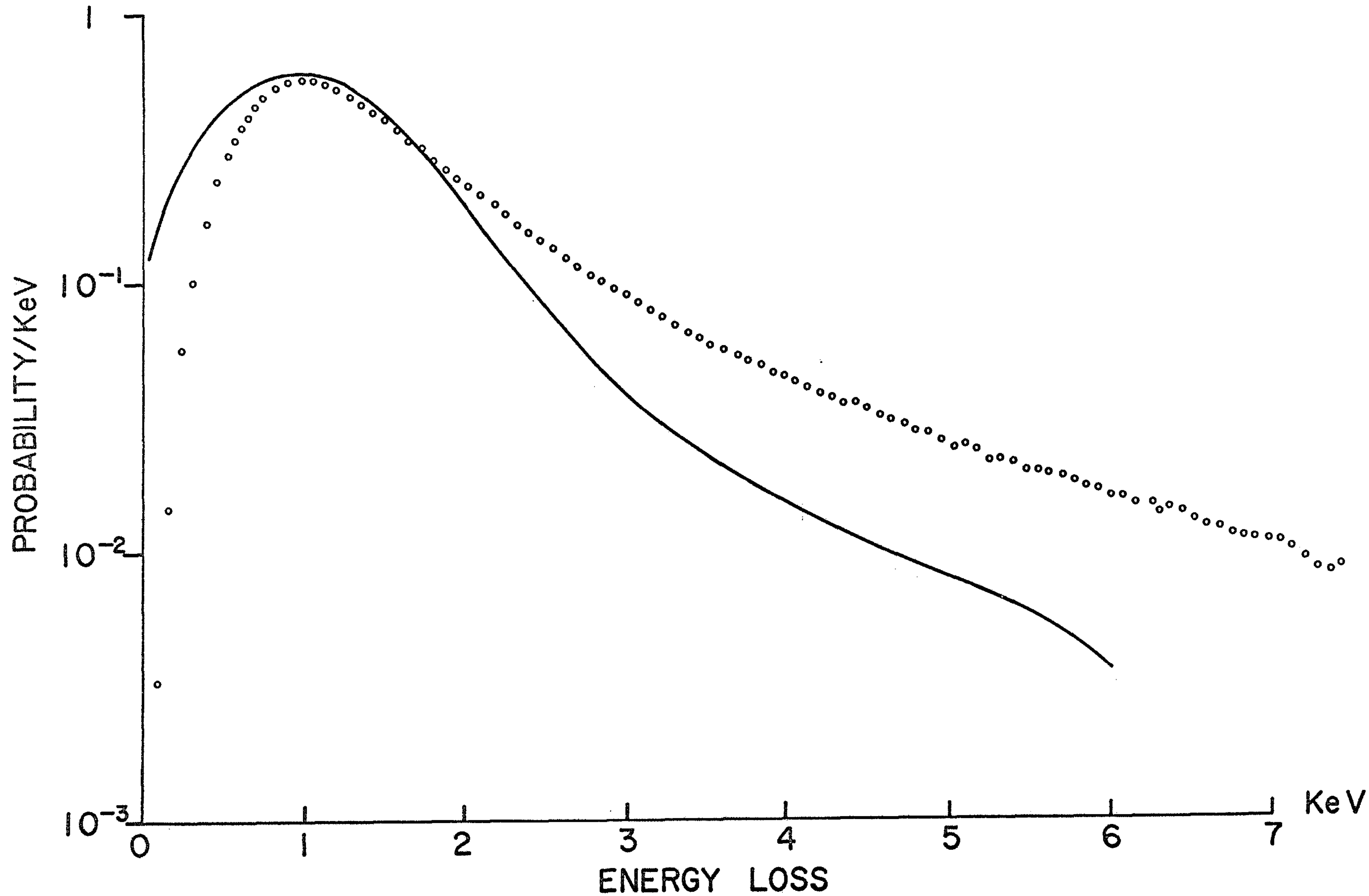
PARAMETERS FOR FREQUENCY DISTRIBUTIONS OF ENERGY

DEPOSITION BY 46.4 MeV PROTONS

PATHLENGTH (g/cm^2)	COUNTER PRESSURE (Torr)	σ_{NOISE} (channels/100 channels FWHM)	$\sigma_{RES.}$ (% FWHM)
1.33×10^{-4}	20	2.2	7.5
6.66×10^{-4}	100	0.9	3.6
1.33×10^{-3}	200	0.6	3.9

FIGURE 1

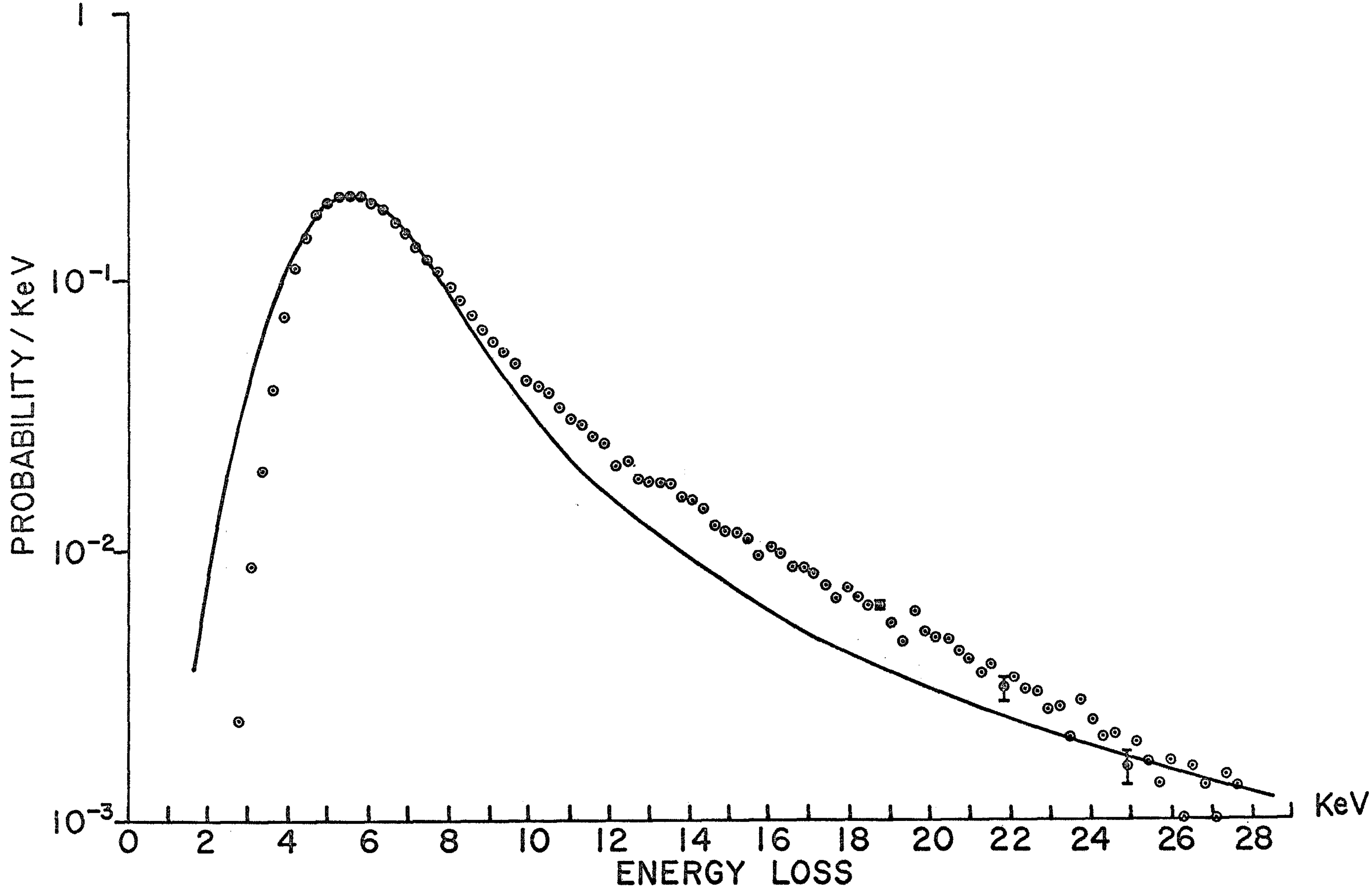
Frequency distribution of energy losses by protons of 46.4 MeV energy in a pathlength of 1.33×10^{-4} g/cm^2.



PROBABILITY/KeV
1
10^{-1}
10^{-2}
10^{-3}
0
1
2
3
4
5
6
7
KeV
ENERGY LOSS

FIGURE 2

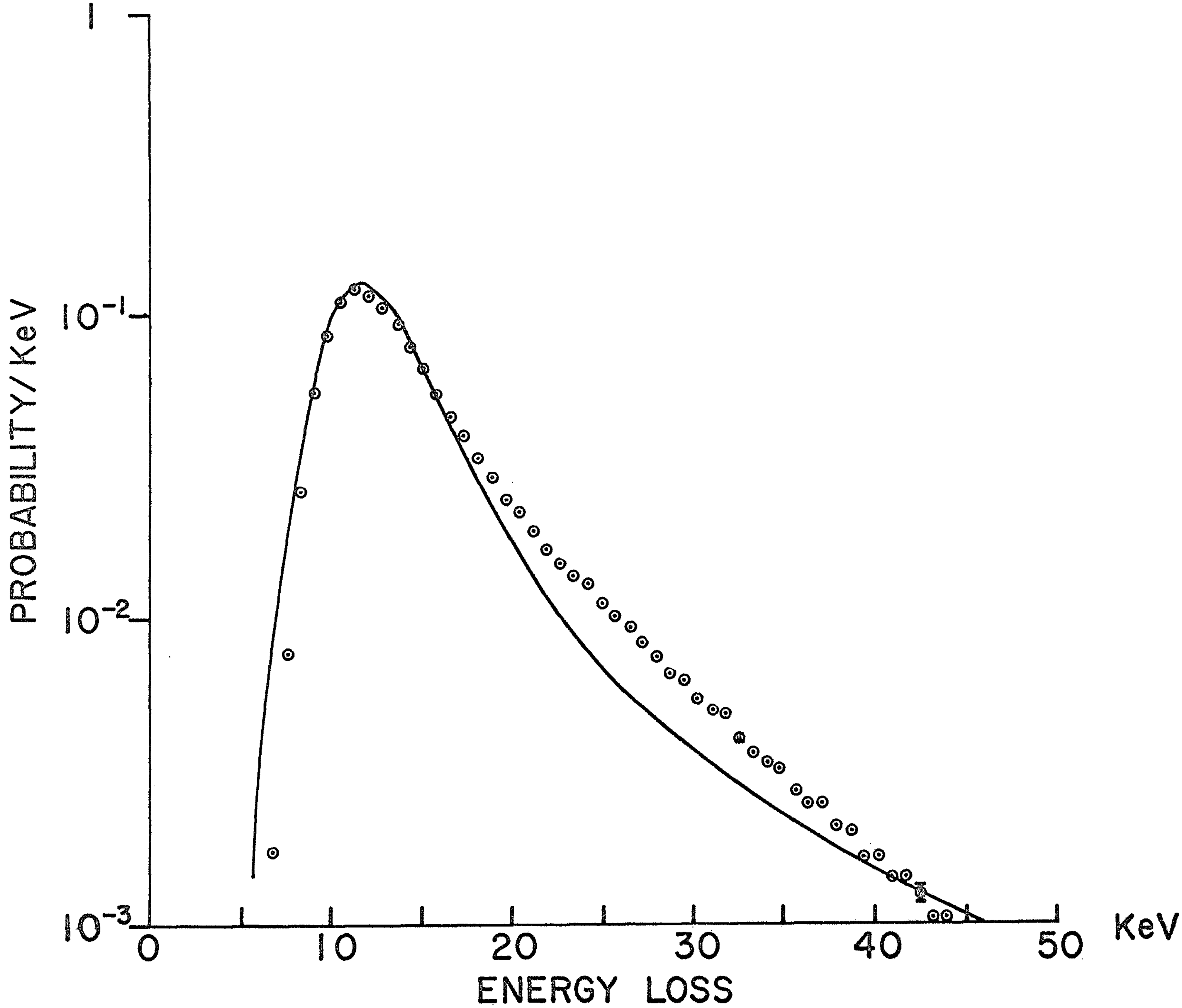
Frequency distribution of energy losses by protons of 46.4 MeV energy in a pathlength of 6.66×10^{-4} g/cm^2.



PROBABILITY / KeV
1
10⁻¹
10⁻²
10⁻³
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
KeV
ENERGY LOSS

FIGURE 3

Frequency distribution of energy losses by protons of 46.4 MeV energy in a pathlength of 1.33×10^{-3} g/cm^2.



1
10^{-1}
10^{-2}
10^{-3}
PROBABILITY/ KeV
0
10
20
30
40
50
KeV
ENERGY LOSS

$$\overline{CH} = \frac{\int_{\emptyset}^{E} n(c)c\,dc}{\int_{\emptyset}^{E} n(c)\,dc}$$

where: $n(c)$ = counts/channel; c = channel number.

The choice of E and the extrapolation of the experimental data to E presents a considerable problem, since theoretically E could be as large as 103.5 KeV. As can be seen from Figures 1, 2, and 3, the experimental data indicate that above a certain energy loss, the frequency appears to decrease exponentially with the magnitude of the individual energy loss. For the two longer paths, the choice is not critical and we have chosen to extrapolate our experimental curves to a value where the count rate should have fallen to 1 count/channel. However, for the shortest pathlength (1.33×10^{-4} g/cm^2), a small uncertainty in the slope of this portion of the experimental data (3%) can shift the average energy (computed as above) by about 10%. We have, therefore, chosen to place the value of the most probable energy loss at that predicted by theory. As will be seen, this is most likely a good assumption since agreement at this energy between theory and experiment for the longer pathlengths is quite good.

In order to compare the experimental results with the Blunck-Leisegang corrected Vavilov distribution, the tables given in NAS-NRC #1133 were extended using those of Börsch-Supan[6].

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(6) Börsch-Supan, W.: J. of Res. Nat'l Bu. Stand. 65B, 245 (1961).

The parameter b^2 was computed for the experimental situation from first principles. The values for these experiments were:

$$b^2 = 40.5,\ 8.15,\ \text{and}\ 4.40$$

The expression, to be numerically integrated, for the Blunck-Leisegang corrected energy loss probability distribution is given by:

$$f(X,\Delta) = \frac{1}{\sqrt{\pi} b\xi} \int_{-\infty}^{+\infty} f_{\nu}(X,\Delta')\, e^{-(\Delta - \Delta')^2/\xi^2 b^2}\, d\Delta'$$

The implications of this equation were discussed in last year's annual report. The notations and definitions used in the equation are:

$f_{\nu}(X,\Delta')$ = energy loss probability.

X = pathlength (g/cm^2).

Δ = energy loss in pathlength X.

$$\xi = X(0.301)\,\frac{Z^2 MC^2}{\beta^2}\;\frac{\sum Z}{\sum A}$$

$\beta = v/c$ where v = speed of incident particle.

MC^2 = rest energy of electron.

Z^2 = charge of incident particle.

Z_{eff} = effective atomic number of medium.

$\sum Z / \sum A$ pertains to one molecule of medium.

$\overline{\Delta}$ = average energy lost in pathlength X.

The expression for the energy loss given in terms of Landau's parameter λ is:

$$\Delta = \xi\lambda + \overline{\Delta} + \xi\ (1 + \beta^2 - \gamma + \ln \varkappa)$$

where:

γ = Euler's constant = 0.577

$\varkappa = \xi/\epsilon_{max}$

ϵ_{max} = Maximum energy which can be imparted to an electron in a single collision by a particle of atomic mass A and charge Z = 103.5 KeV for 46.4 MeV protons.

To evaluate this integral, we make the transformation:

$$\alpha = 2\lambda + 23$$

$$\delta = 2\lambda' + 23$$

Then:

$$f(X,\alpha) = \frac{1}{\sqrt{\pi} b\xi} \int_{-\infty}^{+\infty} f_{\nu}(X,\delta)\, e^{\frac{-\xi^2 \left[1/2(\alpha-\delta)\right]^2}{\xi^2 b^2}} \frac{d\delta}{2}$$

Let α and δ go from 1 - 86 to λ and λ' go from -11 to 48.0. This is sufficient range to cover the region of interest. α, δ are stepped by units.

The input data required by the program are ξ, b, $\varkappa$, β^2, $\bar{\Lambda}$, γ, and the Vavilov distribution corresponding to the particular value of $\varkappa$.

The computer program described in the semi-annual report has been modified to incorporate a broadening function assumed to have a gaussian shape and whose sigma is:

$$\sigma_{\text{Total}} = \sqrt{\sigma^2_{\text{Stat.}} + \sigma^2_{\text{Noise}} + \sigma^2_{\text{Res.}}}$$

The computed curves are then directly comparable to that drawn from the experimental data. These are shown as the solid lines in Figures 1, 2, and 3. The error bars shown for the experimental data represent the counting statistics only.

Good agreement is found for the larger pathlengths for energy losses around the most probable. However, there is a considerable discrepancy for the shortest pathlength even for this part of the distribution. A comparison is given in Table II. We had previously reported good agreement for all these pathlengths based on an approximation of b^2. More exact calculation of this parameter reveals this discrepancy in the Blunck-Leisegang treatment. In all three instances, the theoretical curve predicts considerably more events at low energy transfers and considerably less at high energy transfers. In fact, the actual differences are greater than we have found since our experimental data does not include losses due to high energy delta rays. The differences demonstrated are extremely important for radiobiology since damage probably only occurs with the deposition of

TABLE II

COMPARISON OF THEORETICAL AND EXPERIMENTAL DISTRIBUTION FUNCTIONS

FOR POINTS ABOUT THE MOST PROBABLE ENERGY LOSS

	FWHM (KeV)		PER CENT FWHM/E_{MP}	
Pathlength (g/cm^2)	Experiment	Theory	Experiment	Theory
1.33×10^{-4}	1.285	1.46	132	150
6.66×10^{-4}	3.96	3.94	72.0	71.6
1.33×10^{-3}	11.5	11.6	55.7	54.3

of some minimum energy loss[13]. Such differences serve to emphasize the need for good experimental data taken under realistic geometrical conditions and for biologically meaningful volumes (shape and size).

While the Vavilov theory correctly describes the general shape of the frequency distributions quantitative agreement at small values of $\varkappa$ is not satisfactory. The correction introduced by Blunck and Leisegang while giving good agreement in some cases for the FWHM does not correctly predict the large number of high energy events nor the deficit of low energy events. Such discrepancies increase with decreasing $\varkappa$'s. In the case of high energy proton effects in tissue, this is the case of interest. A new method for the calculation of energy loss distribution has been introduced by Kellerer[7]. Such discrepancies as exist in the experimental data cannot

(7) Kellerer, A.M.: Proc. of the Symposium on Microdosimetry, EVR 3747 d-f-e, 57 (1967).

be attributed to secondaries escaping from the counter volume. Indeed if these exist, the differences between theory and experiment are even larger than shown in the preceding sections. We have obtained the listing and card deck from Kellerer and will shortly have a comparison between our data and the distributions predicted by his theory.

Kellerer has endeavored to improve the theoretical results by first, including the third moment of the distribution in the calculation. He is able to do this since instead of using the transport equation to obtain a mathematical solution, he has derived it from a generalized treatment of the compound Poisson statistics. Second, he attempts to correct the well known failures of the $1/E^2$ collision spectra for small energy losses. To do this, he makes use of the experimental data of Rauth and Simpson[8] at low energies, the $1/E^2$ relation at high energies and interpolates between the two by requiring agreement with the stopping power. He imposes

(8) Rauth, A.M. and Simpson, J.A.: Rad. Res. 22, 643 (1964).

the conditions that in the region of interpolation that both cross-sections and stopping power must have the correct values.

In order to facilitate our investigations of these distributions at depth in tissue or at bone-soft tissue interfaces, we have designed and built a cylindrical, tissue-equivalent proportional counter. A cross-sectional drawing is shown in Figure 4. The design parameters and dimensions were chosen to ensure uniform field, minimum absorption and scattering by the chamber, minimal flow turbulence, and allow the use of the coincidence technique developed in this laboratory. Figure 5 is a section through the center of the counter showing the method of introducing calibration sources. When not in use, the sources can be removed and a button restoring the original geometry put in its place.

Radiobiological Modeling

An important objective in the program is to utilize the physical data obtained from the various cyclotron runs and apply it as a test of a radiobiological-radiochemical damage model. An attractive model can be formulated based on the occurrence of a certain amount of energy deposited within a given critical volume within a given time period. Several such models have been given a rough formulation. As an initial attempt to correlate the physical data with biological and/or chemical data, we have chosen the experimental data obtained by the following[9-13] authors. The formulation of such a model if successful should then serve as the

(9) Benton, E.V. and Nix, W.D.: Nuclear Insts. and Methods, 67, 343 (1967).

(10) Bateman, J.L., Johnson, H.A., Bond, V.P., and Rossi, H.H.: Rad. Res. 35, 86 (1968).

(11) Mortimer, R., Brustad, T., and Cormack, D.V.: Rad. Res. 26, 465 (1965).

(12) Kochanny, G.L., Jr., Timnick, A., Hochnadel, C.J., and Goodman, C.D.: Rad. Res. 19 462 (1963).

(13) Smith, H.H. and Rossi, H.H.: Rad. Res. 28, 302 (1966).

FIGURE 4

Cross-section of cylindrical, tissue-equivalent proportional counter.

CYLINDRICAL PROPORTIONAL COUNTER

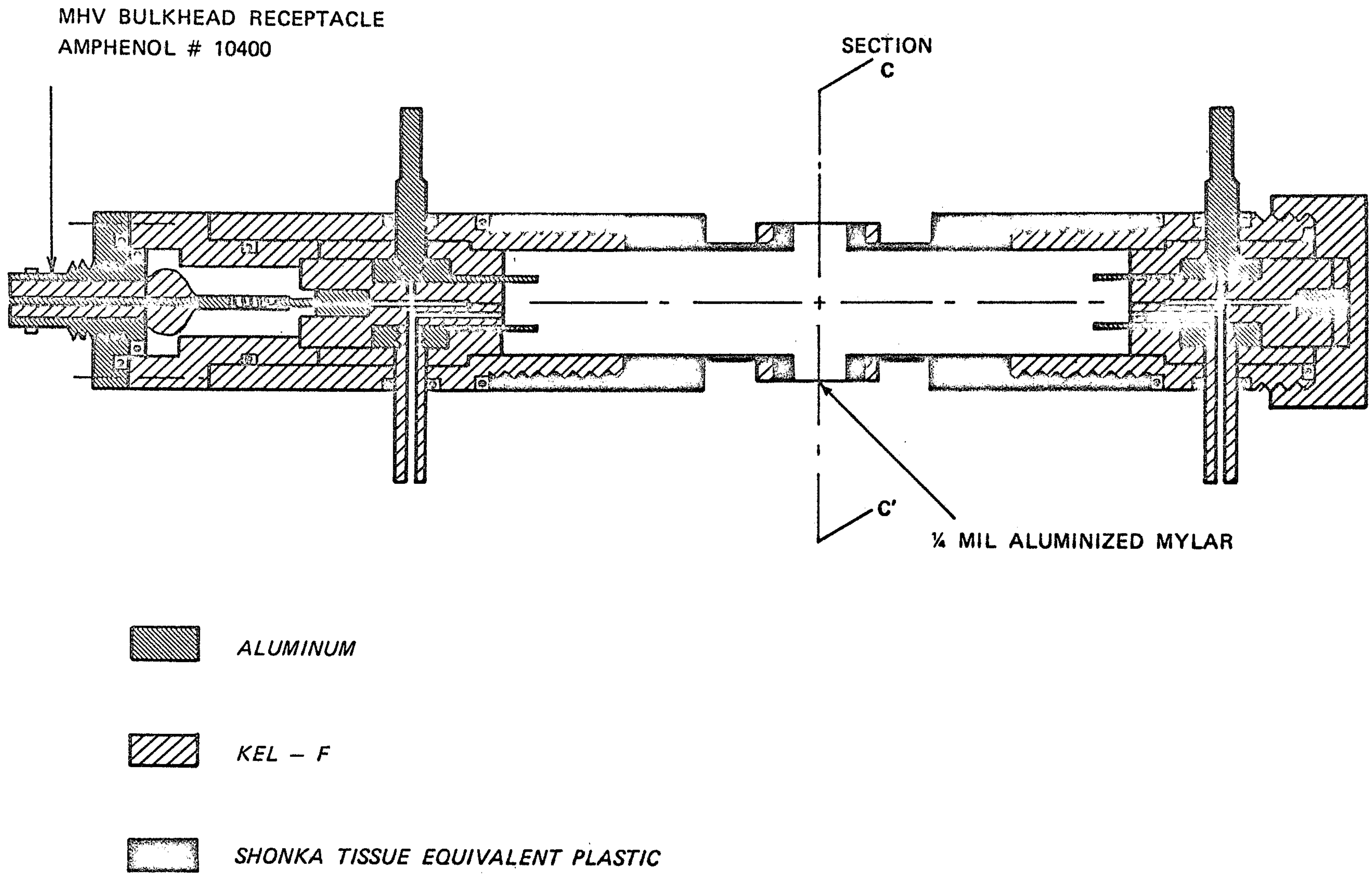
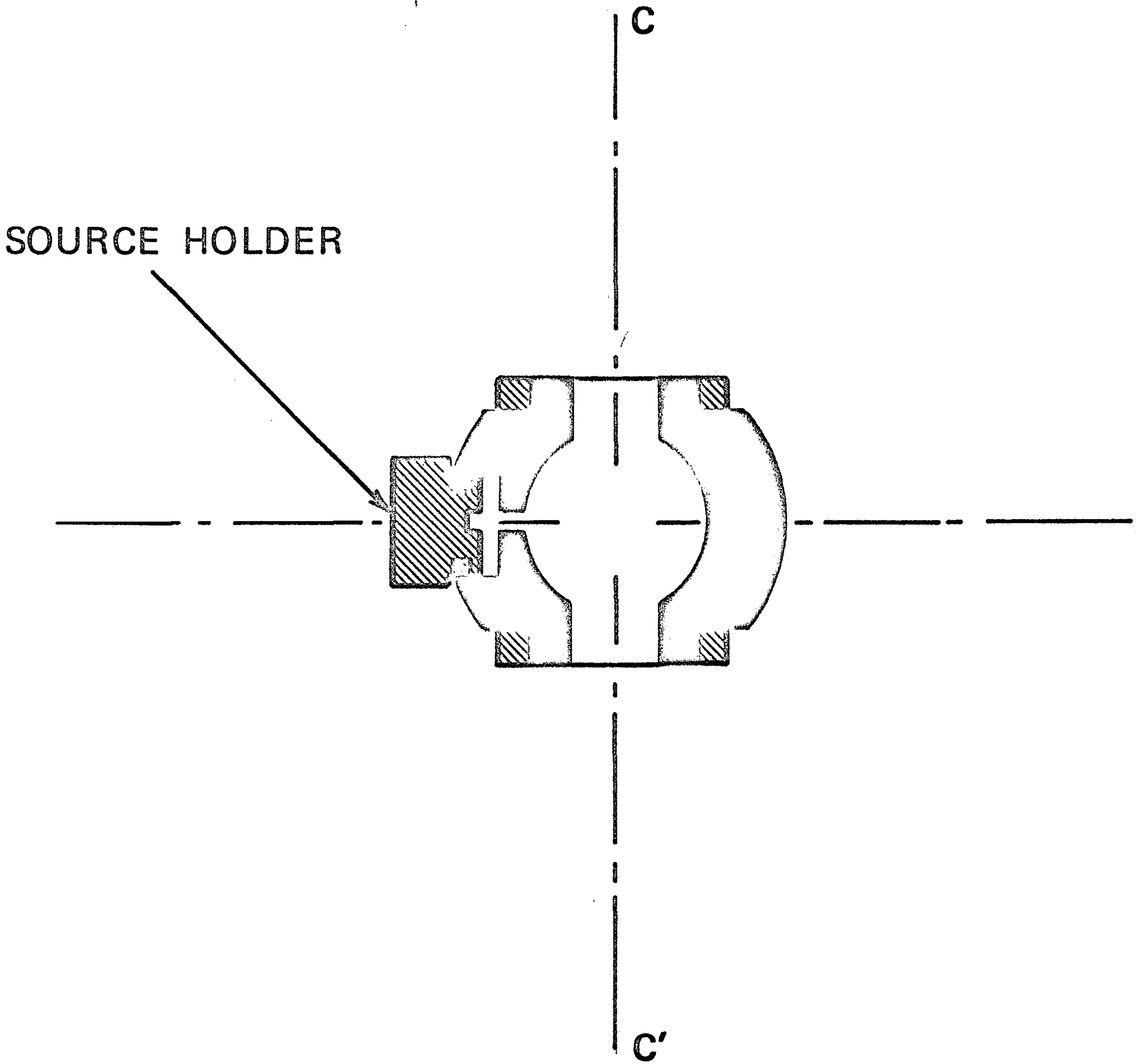


FIGURE 5

Section of tissue-equivalent proportional counter showing insert for calibration sources.


C
SOURCE HOLDER
C′

foundation for further detailing of the processes by which radiation damage occurs. In more practical applications, a knowledge of the physical processes involved, the proper distribution functions, and a radiobiological model would then allow prediction of type and extent of radiation effects for any kind or energy of incident radiation.

Single-Scan TV

The use of a single-scan TV digital system to provide high resolution low dose roentgenograms is under active investigation. The video disc recorder and all components for camera and x-ray unit control circuits are now on hand and construction of the circuits is well under way. The disc recorder acquired is a single head type MVR-100. The x-ray equipment to operate this unit has been ordered. This equipment has a 150 Kvp, 1,000 MA generator, and experimental table with undertable image (9") amplifier and an 875 (20 MHz) TV system.

As the first step toward digitization, we have ordered a Video Converter (Model No. 201A) from Colorado Video, Inc. The unit is an electronic sampling scan converter which accepts standard, composite, TV signals and reduces the video bandwidth to the audio range. This will allow the use of a low speed inexpensive ADC to feed the information to a standard computer for on-line processing and pattern recognition routines. The output signal format consists of a line rate of 60/sec., scanning vertically top to bottom with an adjustable scan rate ranging from 4 to 10 seconds.

At present, we are investigating: analogue to digital converters; buffer storage including pre-processing for the computer; and a laboratory video camera with stable, independent synchronization.

Objectives for the Next Period

1. Microdosimetry.

During the next year, we will attempt to accomplish the following:

(a) Obtain theoretical distributions using the method of Kellerer.

(b) Extend the data obtained using 46.4 MeV protons to higher energies using both the Harvard Cyclotron and the S.R.E.L. Cyclotron.

(c) Using the UCLA Cyclotron (46.4 MeV), study frequency distributions for: ~20 MeV protons; energy degraded beams (depth dose); bone-tissue interfaces; and air tissue interfaces.

(d) Investigate the production and influence of delta rays on these distributions.

(e) Expose human lymphocytes to beam geometries similar to those used to obtain the physical data so that more meaningful and applicable data will be available for modeling.

2. Radiobiological Modeling.

Using the basic concept of the necessity for depositing a minimum energy per event in a given critical volume, we hope to be able to use the physical data already obtained to formulate a model which correctly predicts the results on LET already published. If such a model indicates results along these lines, the concept of point heat or thermal spikes will be introduced. If results from the human lymphocytes are available, these will be utilized in this model.

3. Single-Scan Video Processing.

It is expected that in the earlier portions of the coming year, a complete system will be operating so that various applications can be explored. Some of those contemplated are: acquisition of information directly from the fluoroscopic screen and transfer of data from roentgenogram to computer. The applications which will be explored are: direct processing of bone density measurements in space, chromosome characterization, calculation of heart volume, and pattern recognition routines for comparison or change of blood vessel diameter, calcifications, etc.

Publications During This Period

1. Baily, N.A. and Frey, H.S.: The Measurement and Characteristics of Depth Dose Patterns Due to Proton Beams, Health Phys. 16, 349-358 (1969).

2. Baker, V.D., Miller, W.B., and Baily, N.A.: Single-Scan TV Radiography, Radiology (In Press).

3. Hilbert, J.W. and Baily, N.A.: Proton Microdosimetry, Radiology 92, 168-9 (1969).

4. Hilbert, J.W. and Baily, N.A.: Energy Deposition in Microscopic Volumes by High Energy Protons, Rad. Res. 39, 1-14 (1969).

5. Baily, N.A. and Steigerwalt, J.E.: Frequency Distributions for Very Small Energy Losses by 46-MeV Protons, Bull. of the Amer. Phys. Soc. II, 14, 846 (1969).

Personnel Participating In Program

1. Norman A. Baily, Ph.D. - Professor of Radiology
2. John E. Steigerwalt, Ph.D. - Assistant Research Physicist
3. Jerald W. Hilbert, Ph.D. - Supervising Hospital Radiation Physicist