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Introduction

The general aims of the research undertaken under this grant were:

1. To investigate and clarify in a quantitative manner the transfer of energy from high-energy protons to tissue in both macro and micro volumes.

2. To test the Blunck-Leisegang theory of the statistical distributions of small energy losses.

3. To develop methods by which physical data acquired using cyclotron accelerated protons may be used to predict the energy deposition patterns (macro and micro) in large animals or humans irradiated by specifically defined proton fields.

4. To collate radiobiological data which has been obtained using both whole animals and cells exposed to high-energy protons, so that tolerance levels for manned space flight may be generated.

A considerable period of time was required during the initial period of this grant to acquire and construct equipment necessary to continue the cyclotron work initiated when the principal investigator was at the Hughes Research Laboratories. A Nuclear Data 512 channel analyzer and most of the required associated electronics (preamplifiers, amplifiers, power supplies, single channel analyzer, etc.) were acquired with non-grant funds. The proportional counters were available from our previous work, as were large volume, small frontal cross-section, p-i-n silicon detectors, which are used as coincidence detectors. A flow system and other necessary auxiliary equipment had to be designed and built.

Two experimental runs were undertaken at the NASA Space Radiation Effects Laboratory cyclotron during the last year. These experiments were designed to test the Blunck-Leisegang theory of the statistical distributions of small energy losses for pathlengths corresponding to those of biological interest. Preliminary results were obtained at 600 MeV while inherent characteristics of the 300 MeV cyclotron beam prevented the experimental determination of such distributions for this energy.

A computer program was developed to produce isodose curves for high-energy protons using experimentally determined depth-dose data.[1] The

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1. R. L. Tanner, N. A. Baily, and J. W. Hilbert, "High-Energy Proton Depth-Dose Patterns," Rad. Res. 32, 861-874 (1967).

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details of this program and the results obtained were presented in the semi-annual report, and a paper presenting this material is now in press.[2]

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2. N. A. Baily and H. S. Frey, "The Measurement and Characteristics of Depth-Dose Patterns Due to Proton Beams," Health Physics (in press).

Results of experimental microdosimetry measurements for $\simeq$ 40 MeV protons were also presented in the last semi-annual report. These results included an investigation of the variation of the frequency distributions of energy deposition as a function of depth in tissue-equivalent plastic, as well as an extensive discussion and illustration of the method used to obtain the frequency distributions in arbitrarily shaped tissue microvolumes. This material has also been presented recently in a dissertation.[3]

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3. Jerald W. Hilbert, "Statistical Fluctuations of Energy Deposited by Protons in Thin Layers of Low Atomic Number Materials - Microdosimetric Applications," Doctoral Dissertation, University of California, Los Angeles, 1968.

A considerable amount of effort has been expended in a more detailed analysis of several sets of data obtained previously, in an attempt to realize the full implications, physical and biological, of these experimentally measured distributions. A computer program was devised to apply the Blunck-Leisegang correction to the Vavilov distribution of energy losses in order to compare the experimental data with an entire theoretical curve. A comparison shows some discrepancies between theory and experiment out in the high energy tail regions of the distributions, and several possible reasons for this discrepancy have been examined.

A computer program has also been written to examine more thoroughly the very important question of the number of individual pathlengths which must be simulated in order to give a sufficiently accurate approximation to the distribution in an entire microvolume when the distributions for individual pathlengths are convoluted. This program may be applied to microvolumes of arbitrary shape and size.

A student was employed to collate all available proton radiobiological data from the open literature, conference reports, and both the internal and contract reports of government laboratories and contractors. These have been compiled, edited, and presented as a function of biological sample and proton energy. Data for absorbed doses less than 25 rad and greater than 10^3 rad have been deleted. This material will eventually be analyzed for dose-rate effects and the influence of the geometrical distribution on both the macro and micro dose patterns existing within the irradiated material.

Frequency Distributions of Energy Deposition

A more extensive analysis of the data which was presented in a recent Physical Review[4] article was undertaken in order to include the biologically

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4. J. W. Hilbert, N. A. Baily, and R. G. Lane, "Statistical Fluctuations of the Energy Deposited in Low Atomic Number Materials by 43.7 MeV Protons," Phys. Rev. 168, 290-293 (1968).

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important high-energy tail. There are two important points to be investigated. The first is the agreement of this portion of the experimentally determined distribution with the Blunck-Leisegang corrected values of the Vavilov function. This correction for losses to bound electrons becomes very important for energy losses of the order of the binding energies of the various atomic shells. Second, from the point of view of radiobiological theories, the percentage of the macro dose delivered in single high-energy events is important, since information of this type will not only serve as a test for some existing theories and possibly guide their modifications but may aid in the formulation of entirely new ones. Also, this is probably the most pertinent and direct way to predict a meaningful RBE. Only the first of these questions has thus far been investigated in detail.

Previous comparisons between the experimental distributions and theoretical predictions have been only in terms of one parameter, the full width at half maximum of the peaks of the distributions. In order to compare the entire theoretical distributions with experimental data requires that a gaussian, whose width is determined by the Blunck-Leisegang parameter b and the quantity ξ, be folded into the Vavilov distribution.[5]

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5. U. Fano, "Penetration of Protons, Alpha Particles, and Mesons," Ann. Rev. Nucl. Sci. 13, 1 (1963).

If the Vavilov function is denoted by $f_v\ (\Delta,\ x)$, then the corrected function is given by

$$f\ (\Delta,\ x) = (\xi b \sqrt{\pi})^{-1} \int_{\infty}^{\infty} f_v\ (\Delta - U,\ x)\ \exp\left[-(U^2/\xi^2 b^2)\right] dU \qquad (1)$$

Birkhoff[6] used a four term series expansion of the relation represented

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6. R. D. Birkhoff, "Distribution of Energy Losses-Straggling," Handbuch Der Physik, XXXIV, 87 (1958).

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by equation (1) to calculate the distribution function. His results were reported as FWHM as a function of b^2. A previously reported[4] comparison between experimental data for 43.7 MeV protons and Birkhoff's results showed good agreement, indicating that the theory represented by equation (1) was valid in the region of the peak. In order to compare equation (1) with the experimental data in the region of the biologically important high-energy tail, a computer program was developed to perform the calculation in equation (1). Required values of $f_v\ (\Delta,\ x)$ were taken from Seltzer and Berger[7] or from Börsch-Supan[8]

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7. S. M. Seltzer and M. J. Berger, "Energy Loss Straggling of Protons and Mesons: Tabulation of the Vavilov Distribution," NAS-NRC, 1133, 205 (1964).

8. Wolfgang Börsch-Supan, "On the Evaluation of the Function $\phi(\lambda) = \frac{1}{2\pi i}\int_{\sigma - i\infty}^{\sigma + i\infty} e^{u \ln u + \lambda u} du$ for Real Values of λ," J. Res. Natl. Bur. Std.—B. Mathematics and Mathematical Physics 65B, #4, 245-50 (1961).

(depending on the value of κ). Comparisons of experimental data with theoretical spectra are given in Figures 1-4. The theoretical spectra were

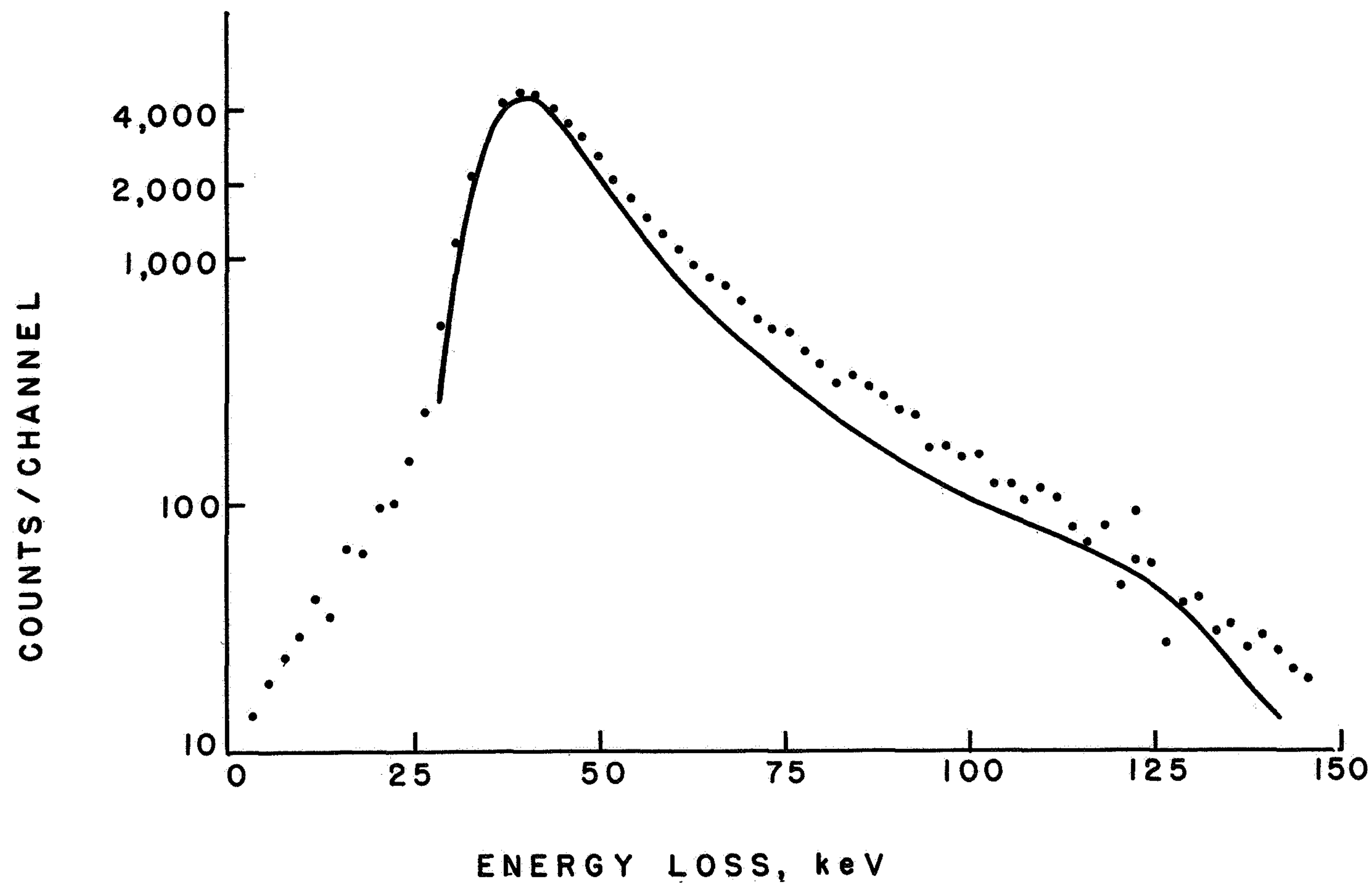

Figure 1. Distribution of energy losses by 43.7 MeV protons after passage through 4.00×10^{-3} g/cm^2 of low atomic number materials. The circles represent the experimental data, and the solid curve represents the Blunck-Leisegang corrected Vavilov distribution.

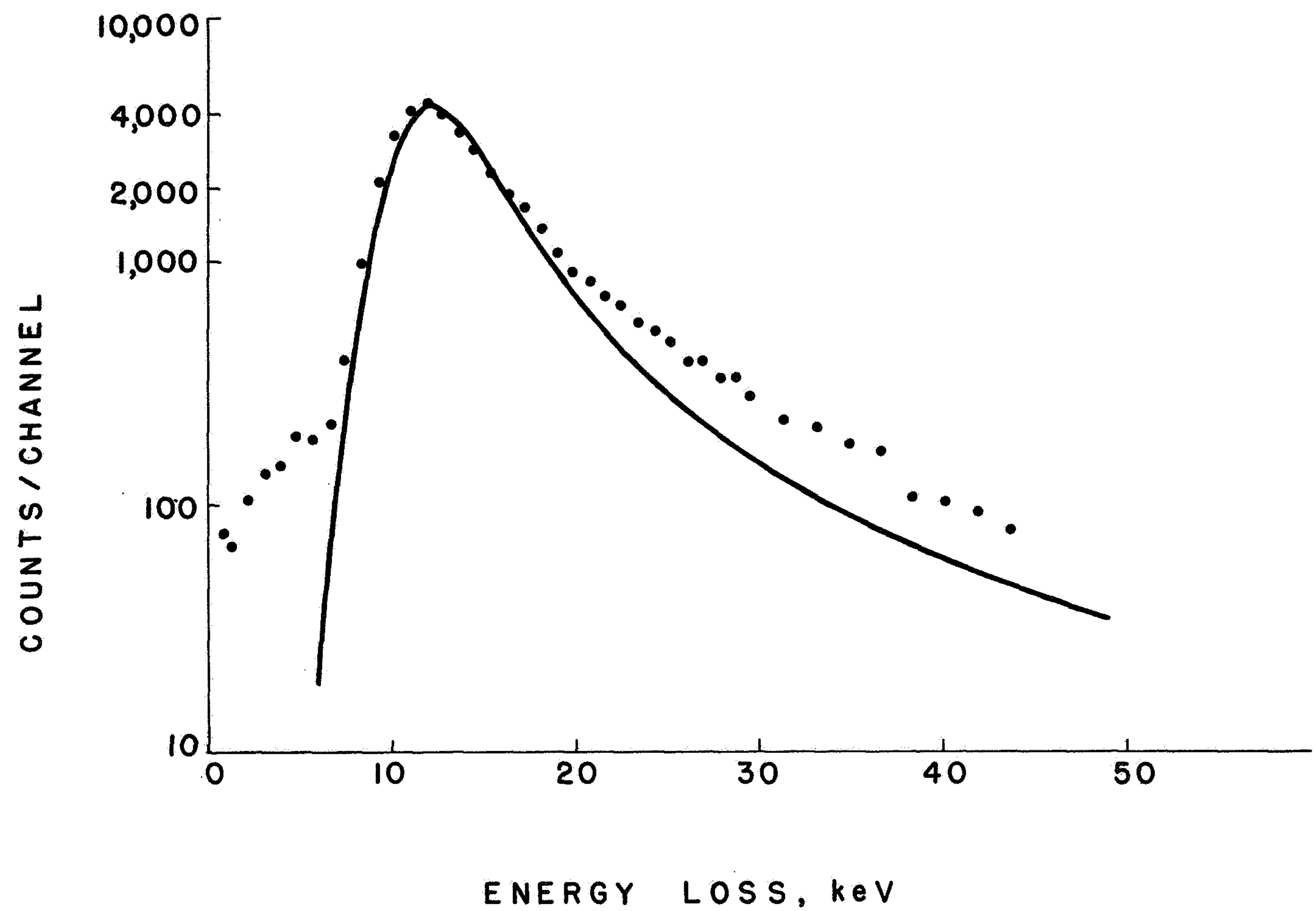

Figure 2. Distribution of energy losses by 43.7 MeV protons after passage through 1.33×10^{-3} g/cm^2 of low atomic number materials. The circles represent the experimental data, and the solid curve represents the Blunck-Leisegang corrected Vavilov distribution.

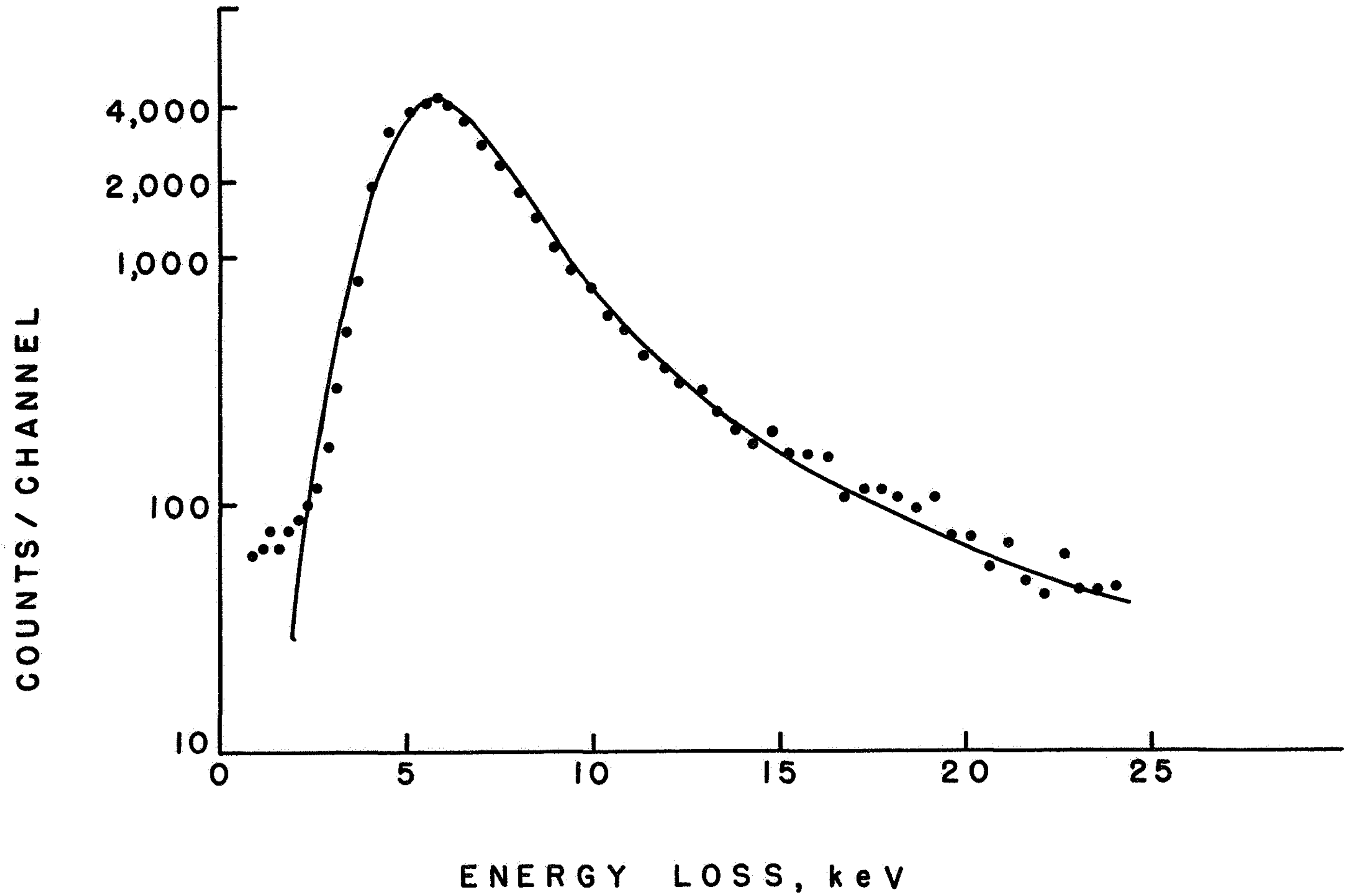

Figure 3. Distribution of energy losses by 43.7 MeV protons after passage through 6.66×10^{-4} g/cm^2 of low atomic number materials. The circles represent the experimental data, and the solid curve represents the Blunck-Leisegang corrected Vavilov distribution.

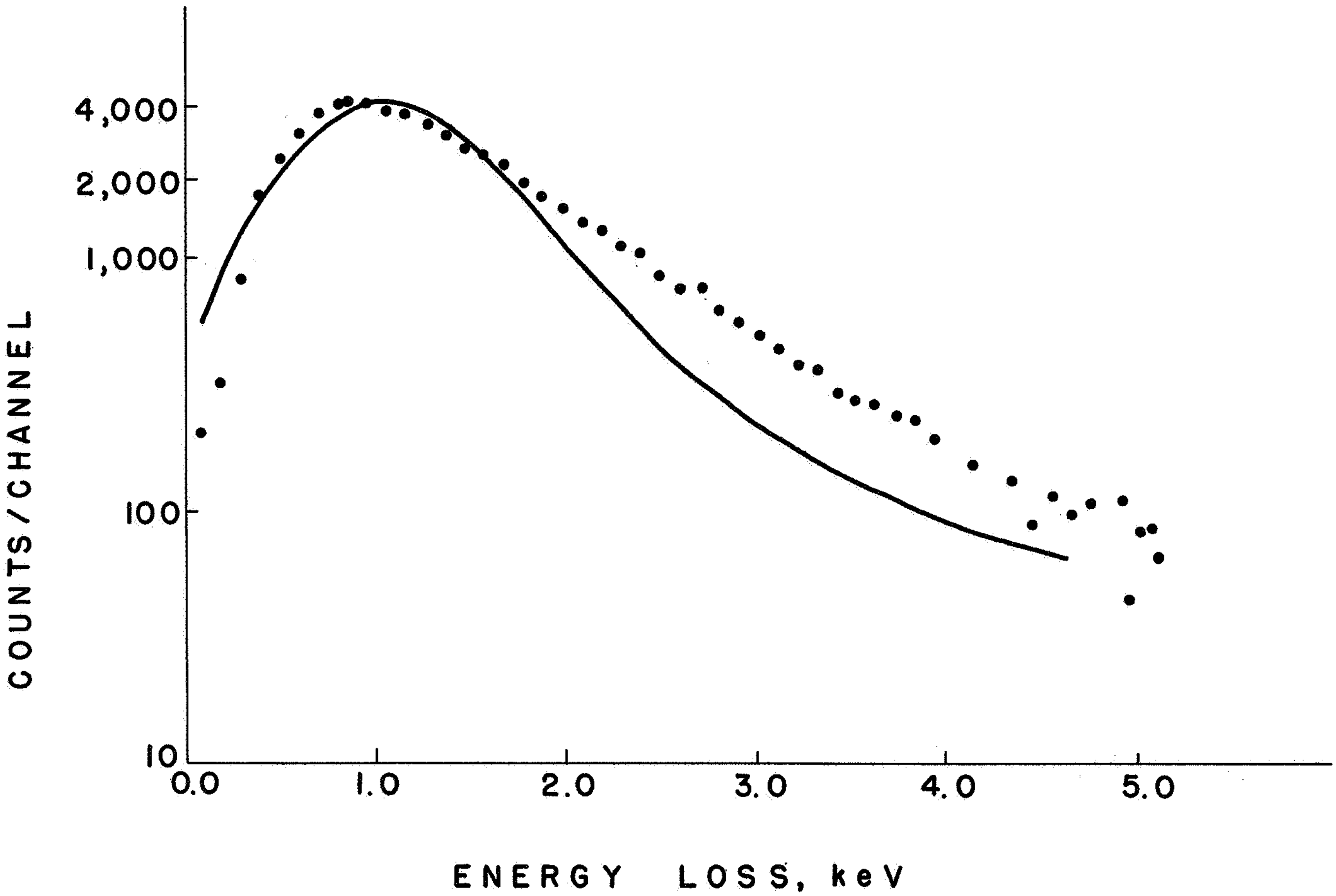

Figure 4. Distribution of energy losses by 43.7 MeV protons after passage through 1.33×10^{-4} g/cm^2 of low atomic number materials. The circles represent the experimental data, and the solid curve represents the Blunck-Leisegang corrected Vavilov distribution.

normalized to the experimental number of counts per channel, at the value of the most probable energy. Resulting curves represent relative probability, and it should be noted that this normalization point is arbitrary. For a path-length of 6.66×10^{-4} gm/cm^2 the agreement is good. However, for the other pathlengths there are more counts in the biologically important high-energy tail than predicted by theory.

Several possible explanations exist for these differences. First, the theory may be in error. Second, the differences observed may represent the difference between energy deposition (experimentally observed) and energy loss (theoretically calculated) as discussed previously.[9] Third, spectra distortion

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9. Summary Technical Report Contract No. NAS 2-2366 Research and Development Program for Radiation Measurements of Radiobiological Hazards of Man in Space, Hughes Research Laboratories, Malibu, California, 1 August 1966 through 31 July 1967.

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by the pile-up effect should be considered.

Experimental pulse height spectra are distorted by the effect of pulse pile up when count rates are high. This effect occurs when a pulse is generated in the detector during the time the height of the preceding pulse is being measured. The observed pulse height of the first pulse will be higher than its true value, and the recorded spectrum will therefore be in error.

Williamson[10] discusses a method of estimating the distortion of an

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10. J. H. Williamson, "Distortion of Pulse Height Spectra by Pile-Up Effect," Rev. Sci. Instr. 37, #6, 736-739 (June 1966).

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experimental pulse height spectra due to the pile-up effect. He first considers the effect of pile-up caused by one other pulse arriving during the processing time of the original pulse. Let us consider the true spectrum to be represented by P(y) and the distorted spectrum by D(y). Let the individual pulses have amplitude ys(t) where the shape function s(t) is normalized to unit peak value. Then the probability of the amplifier output being ys is P(y) g(s) where

$$g(s) = \left[\tau\left|\frac{ds}{dt}\right|\right]^{-1} \tag{2}$$

and τ is the pulse length. The weight g(s) is proportional to the time that the pulse amplitude stays between s and s + ds. Integrating over y gives the probability of the output being x from a single pulse,

$$B(x) = \int y^{-1} P(y)\, g(x/y)\, dy \tag{3}$$

If any portion of this signal is still present when the peak of the next pulse arrives, it will be recorded with the wrong amplitude. The probability that a pulse is processed correctly is $e^{-\alpha}$, where α is the product of τ and the mean rate of arrival of pulses, v. Thus the observed distribution contains a term

$$D_o(y) = e^{-\alpha} P(y) \tag{4}$$

Pile-up with only one other pulse has probability $e^{-\alpha}\alpha$ and yields

$$D_1(y) = e^{-\alpha}\alpha \int B(x)\, P(y - x)\, dy \tag{5}$$

Thus, the distorted spectrum is (neglecting third and higher order pile up):

$$D(y) = e^{-\alpha} P(y) + e^{-\alpha}\alpha \int B(x)\, P(y - x)\, dy \tag{6}$$

A computer program was developed at Emory to estimate pile-up effects based on equation (6). Because an accurate shape function, s(t), was not known, the following was assumed:

$$s(t) = t/\tau \quad \text{for} \quad 0 \le t \le \tau$$

$$s(t) = 0 \quad \text{for} \quad t < 0 \text{ and } t > \tau$$

This simplified shape function in conjunction with the approximate pile-up estimation represented by equation (6) was evaluated by comparison with experimental data obtained using alpha particles and a surface barrier detector. This combination produced a relatively sharp peak with no pile-up effects at low count rates (~ 0.7 counts/sec.). The maximum count rate available was about 5,000 counts/sec, at which point pile-up effects were observed. The distorted spectra were characterized by a relatively uniform distribution extending from the peak to twice the peak energy. The magnitude of this uniform distribution increased with count rate. The ratio of this magnitude to the peak height is useful in comparing the pile-up effect as a function of count rates. Results are listed in Table I. Calculations were also made using the computer code, and these results are listed in Table II. In order to compare the calculated values to those obtained experimentally, the pulse length, τ, is required. An accurate value of τ for this system was not available. Manufacturers of surface barrier detectors suggest values from one nanosecond to tens of nanoseconds for the pulse rise time. For a count rate of 163 c/sec, the experimental pile-up magnitude was 0.56×10^{-4} (see Table I). From the calculations, this pile-up magnitude is predicted for $v\tau = 2.15 \times 10^{-6}$. This indicates that the pulse length is $\tau = v\tau/v = 2.15 \times 10^{-6}/163$ c/sec = 13 nanoseconds. If the theory is accurate, using $\tau = 13$ nanoseconds would give correlation between the experimental and

Table I

Effect of Pile Up for Alpha Particles

Incident on a Surface Barrier Detector: Experimental

Count Rate (c/sec)	Amplitude at Peak	Amplitude at 1.5 Times Peak Energy	Pile-Up Magnitude*
63.3	12,400	0.286	0.23×10^{-4}
163.0	54,000	3.0	0.56×10^{-4}
433.0	109,000	12.0	0.11×10^{-3}
4,880.0	85,003	120.0	0.14×10^{-2}
5,400.0	58,000	130.0	0.22×10^{-2}

*Pile-Up Magnitude is the ratio of the amplitude at 1.5 times the peak energy to the amplitude at the peak.

Table II

Effect of Pile Up for Alpha Particles

Incident on a Surface Barrier Detector: Calculation

Count Rate Times Pulse Length x 10^6	Amplitude at Peak	Amplitude at 1.5 Times Peak Energy	Pile-Up Magnitude*
0.833	100.00	0.21×10^{-2}	0.21×10^{-4}
1.67	100.00	0.42×10^{-2}	0.42×10^{-4}
3.33	100.01	0.84×10^{-2}	0.84×10^{-4}
6.33	100.01	0.16×10^{-1}	0.16×10^{-3}
16.33	100.03	0.41×10^{-1}	0.41×10^{-3}
43.33	100.09	0.11	0.11×10^{-2}

*Pile-Up Magnitude is the ratio of the amplitude at 1.5 times the peak energy to the amplitude at the peak.

the theoretical results. A comparison is given in Figure 5. The largest deviation of the experimental data from the theoretical prediction is about 20%. The agreement is satisfactory considering that the comparison extends over two orders of magnitude.

An experimental spectrum for a low count rate is given in Figure 6. Also given is the experimental spectrum for a high count rate ($\sim$ 5,000 c/sec, $\nu\tau = 63 \times 10^{-6}$) and the theoretical spectrum for $\nu\tau = 44 \times 10^{-6}$. The predicted shape of the distorted spectrum is quite reasonable, and agreement for the energy at which pile-up with one other pulse becomes negligible is very good. However, experimental spectra at high count rates have a tendency to show a second peak at about twice the energy of the main peak, while theoretical calculations do not predict this. This discrepancy is caused by the assumed pulse shape. The assumed shape and the probable shape are shown in Figure 7. The assumed shape has a uniform probability for any pulse height. The probable shape, however, has a greater probability for higher pulse heights. This could cause a second peak in the pile-up spectrum. To illustrate this effect, the following approximation for the probable pulse shape was assumed:

$$s(t) = 1.6\, t/\tau \qquad 0 \le t \le \tau/2$$

$$s(t) = 0.8 + 0.4\,(t - \tau/2)/\tau \qquad \tau/2 < t \le \tau$$

$$s(t) = 0 \qquad \text{for } t < 0 \text{ and } t > \tau$$

and a pile-up spectrum was calculated. The results are compared with the experimental data in Figure 8. This agreement is very satisfactory.

For the purposes of this work, it is concluded that the predictions of the pile-up magnitude and the shape of the distorted spectrum are quite reasonable. Thus, these methods may be used to evaluate the effects of pile-up on experimental proton energy deposition spectra.

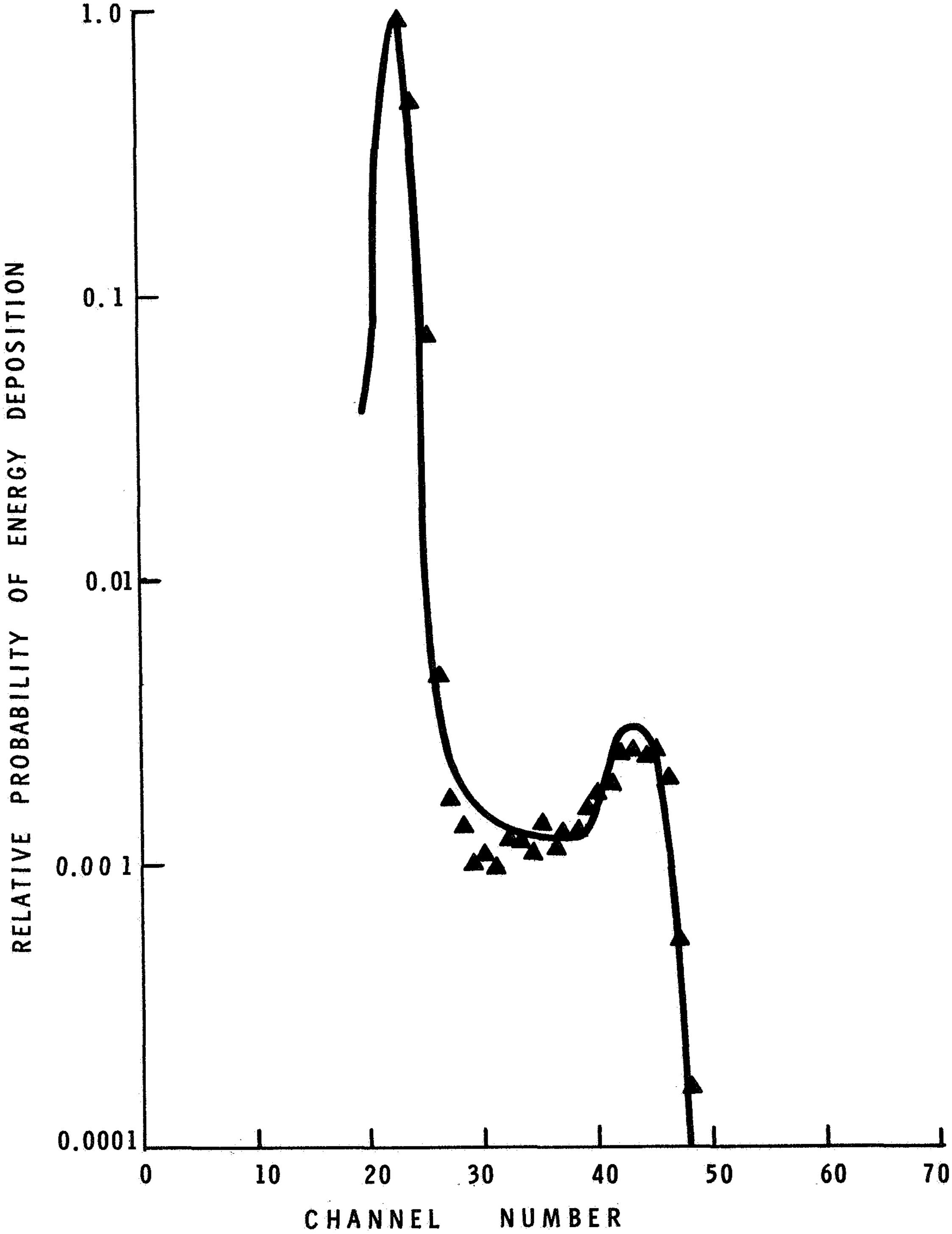

Figure 8. Experimental and theoretical pile-up spectrum with $\nu\tau = 63 \times 10^{-6}$. Triangles are the experimental points. The solid line represents the theoretical calculation with the following idealized pulse shape:

$s(t) = 1.6\ t/\tau$	$0 \le t \le \tau/2$
$s(t) = 0.8 + 0.4\ (t - \tau/2)/\tau$	$\tau/2 < t \le \tau$
$s(t) = 0$	for $t < 0$ and $t > \tau$

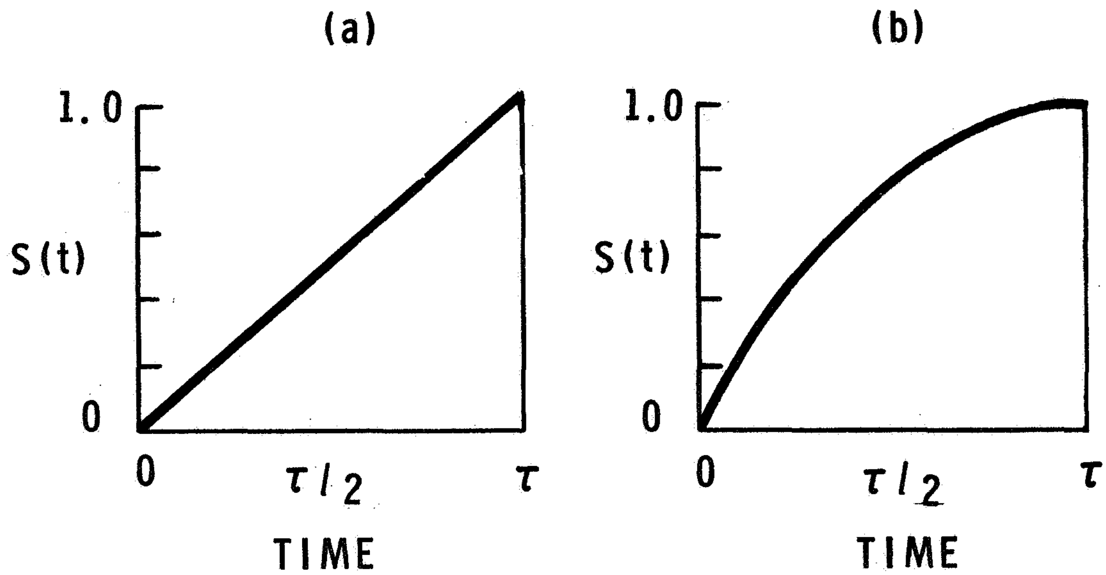

Figure 7. Normalized pulse shape (a) assumed, (b) probable.

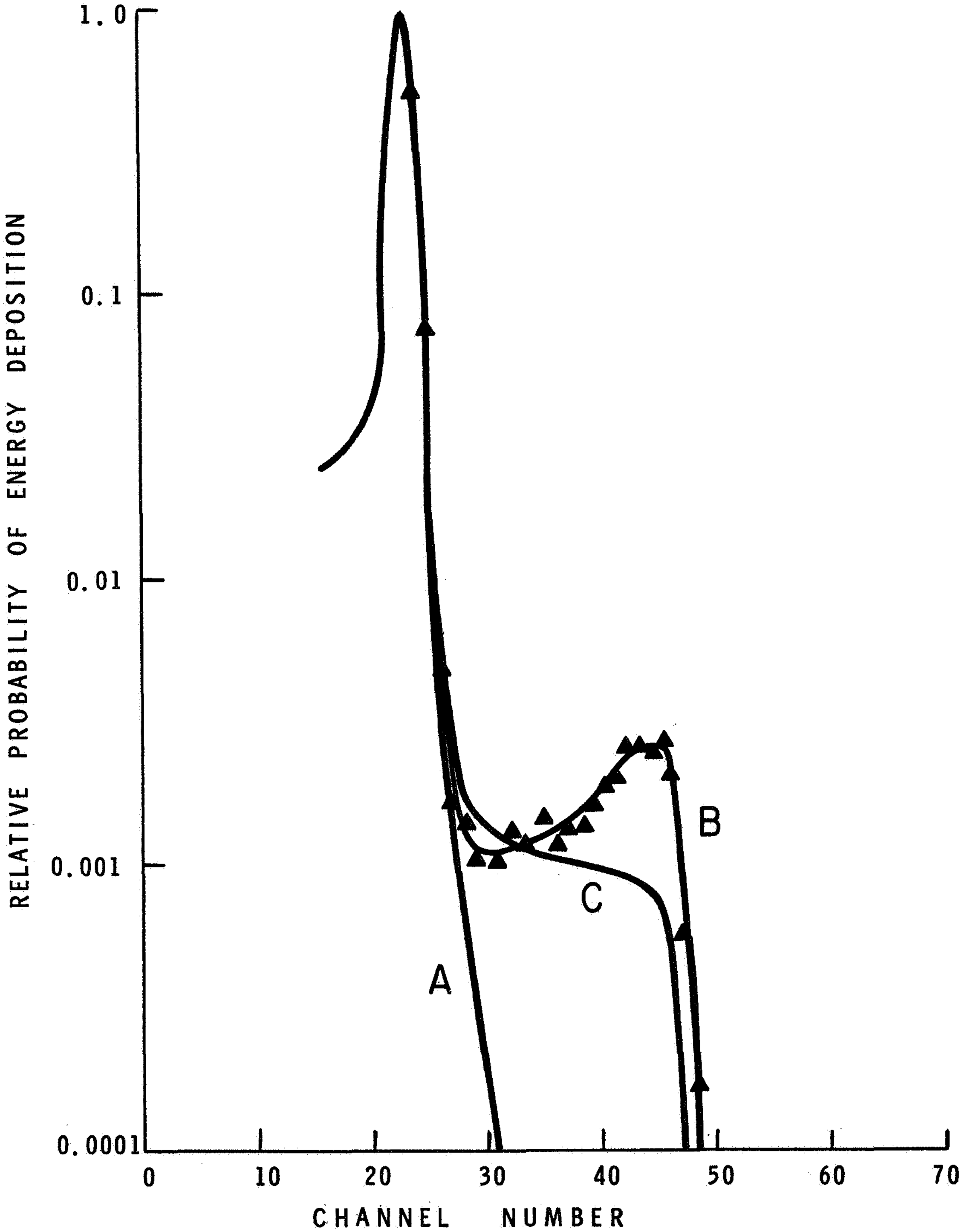

Figure 6. Alpha spectra obtained using a surface barrier detector and showing the effect of pulse pile up. A is experimental spectrum for a low count rate (~ 0.7 counts/sec); B is experimental spectrum at a high count rate (~ 5000 counts/sec, $\nu\tau = 63 \times 10^{-6}$); C is theoretical pile-up spectrum with $\nu\tau = 44 \times 10^{-6}$ based on the experimental spectrum obtained at the low count rate.

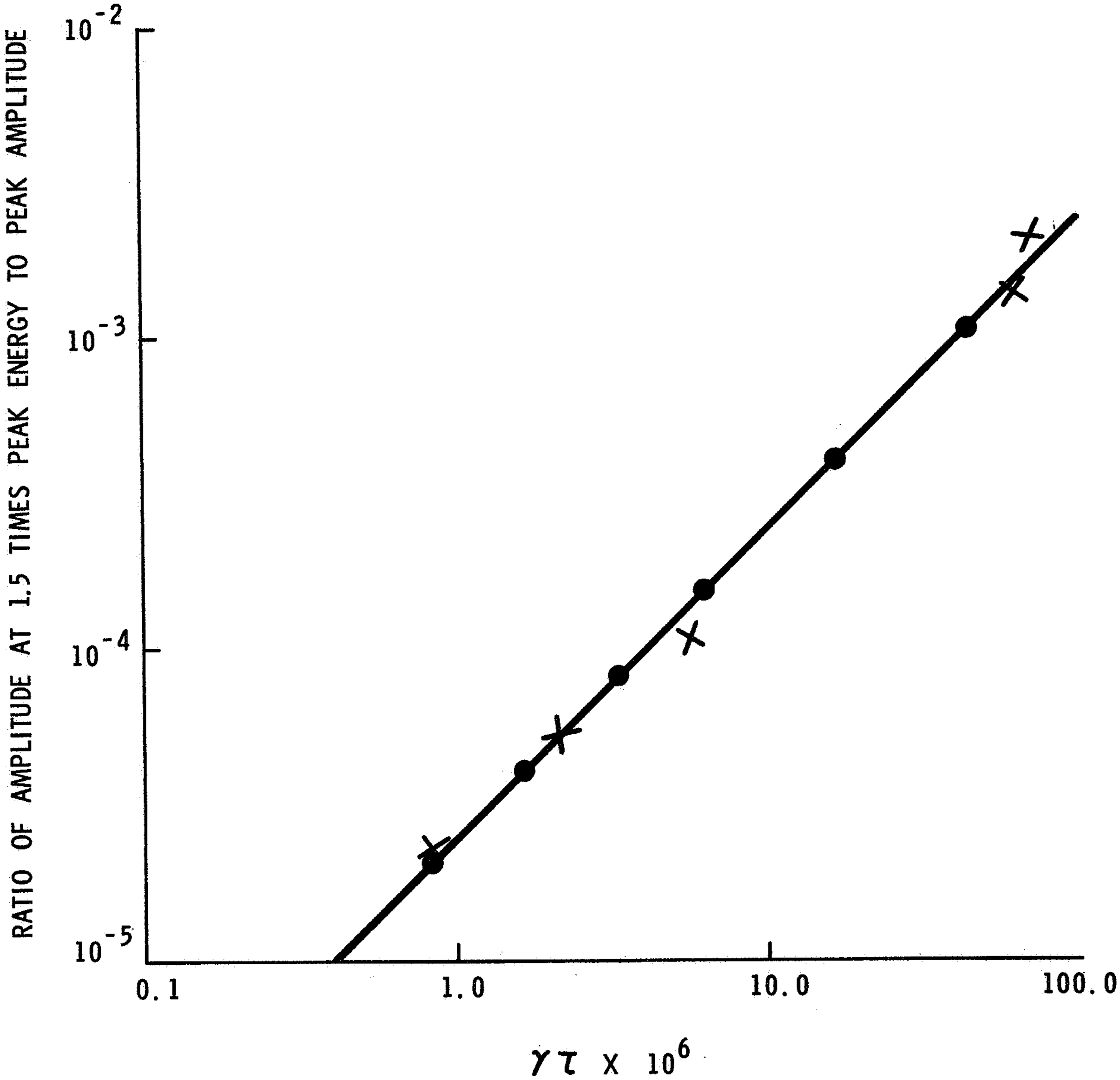

Figure 5. Theoretical and experimental pile-up magnitude as a function of the product of count rate and pulse length. O theory, x experimental (using τ = 13 nanoseconds).

Theoretical pile-up spectra using a linear pulse shape were calculated for 43.7 MeV protons and a pathlength of 1.33×10^{-4} g/cm^2. The results are compared with the experimental data in Figure 9. These spectra were normalized to the peak height at the most probable energy. For $v\tau = 10^4$ the calculated pile-up spectrum agrees with the experimental data. If τ were of the order of 1μ second, a count rate of 10,000 counts per second would produce a distorted spectrum in good agreement with the experimentally determined spectra. Note that the FWHM of the distorted spectrum is still in agreement with the FWHM of the theoretical spectrum without pile-up. The result of this analysis shows that pile-up cannot be eliminated as a possible explanation for the difference between the experimental results and the theoretical predictions. Further experimental work will be undertaken to investigate this point.

Cyclotron Experiments

Two experimental runs were undertaken at the NASA Space Radiation Effects Laboratory cyclotron during the last year. These were designed to test the Blunck-Leisegang theory of the statistical distributions of small energy losses for pathlengths corresponding to those of biological interest. The very high-energy protons available at SREL are of particular interest since the maximum energy transferable to an electron in a single collision is so very much greater than the average energy left in a tissue path of the order of cell sizes. For instance, the maximum energy delta ray produced by a 600 MeV proton is 1.7 MeV compared to an average energy loss of approximately 250 eV in a micron of tissue.[11] This large difference between the average

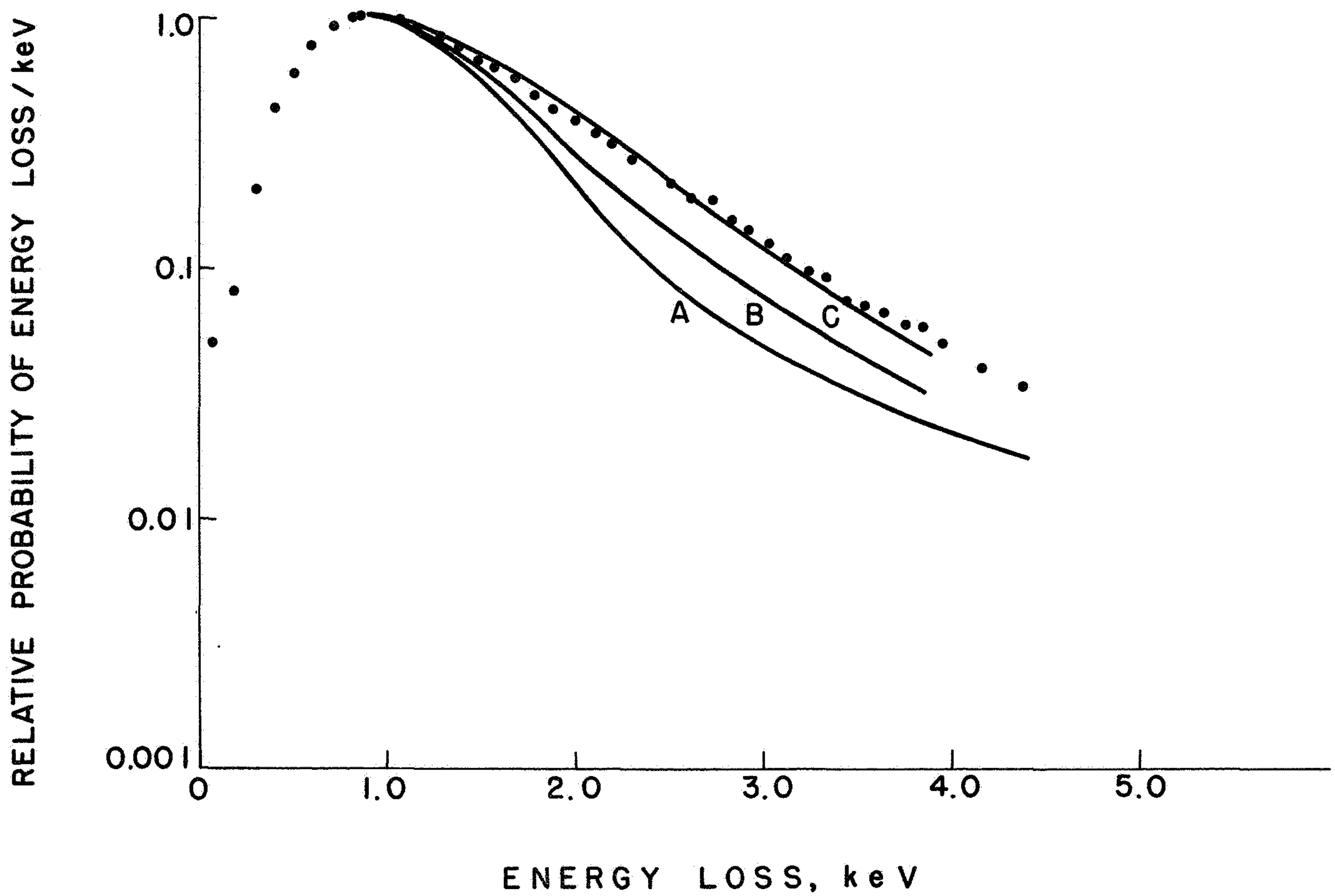

Figure 9. Distribution of energy losses by 600 MeV protons after passage through 1.33×10^{-4} g/cm^2 of low atomic number materials. The circles represent the experimental data. Solid lines represent theory showing the effect of pile-up. A. $v\tau = 0$, B. $v\tau = 10^3$, C. $v\tau = 10^4$.

11. J. F. Janni, "Calculation of Energy Loss, Range, Pathlength, Straggling, Multiple Scattering, and the Probability of Inelastic Nuclear Collisions for 0.1 to 1000 MeV Protons," AFWL-TR-65-150, Air Force Weapons Lab., New Mexico (1966).

energy loss and the maximum possible energy loss per collision makes the relative extent of the high-energy tail very large and thus extremely important in interpretation and formulation of radiobiological theories.

The first run consisted of six days of parasite time. The beam utilized at that time was a low-intensity stretched beam (for practical purposes essentially continuous) of 600 MeV protons obtained as a by-product during Meson production. A ΔE spectrum deposited by this beam in the $\simeq 1.5$ cm long silicon p-i-n detector is seen in Figure 10. The coincidence technique described previously was used to determine frequency distributions of energy deposition for pathlengths of 1.33×10^{-3} g/cm^2, 6.66×10^{-4} g/cm^2, 3.33×10^{-4} g/cm^2, 1.33×10^{-4} g/cm^2, 9.95×10^{-5} g/cm^2, 6.66×10^{-5} g/cm^2, and 3.33×10^{-5} g/cm^2 in the He-Co_2 gas mixture.

Rather poor agreement with the theoretical predictions was exhibited by all of the experimental distributions. The distributions for pathlengths of 1.33×10^{-3} g/cm^2, 1.33×10^{-4} g/cm^2, and 6.66×10^{-5} g/cm^2 are seen in Figures 11, 12, and 13, respectively. Also shown in these figures are the theoretical predictions, normalized to the same number of counts at the position of the peak. These distributions are, of course, rather preliminary at this point, but the same reasons for the discrepancy between theory and experiment discussed in detail for the 43.7 MeV distributions may be advanced here. One rather unexpected aspect of the experimental distributions which should be pointed out is the fact that the resolution of the peak (expressed in % FWHM),

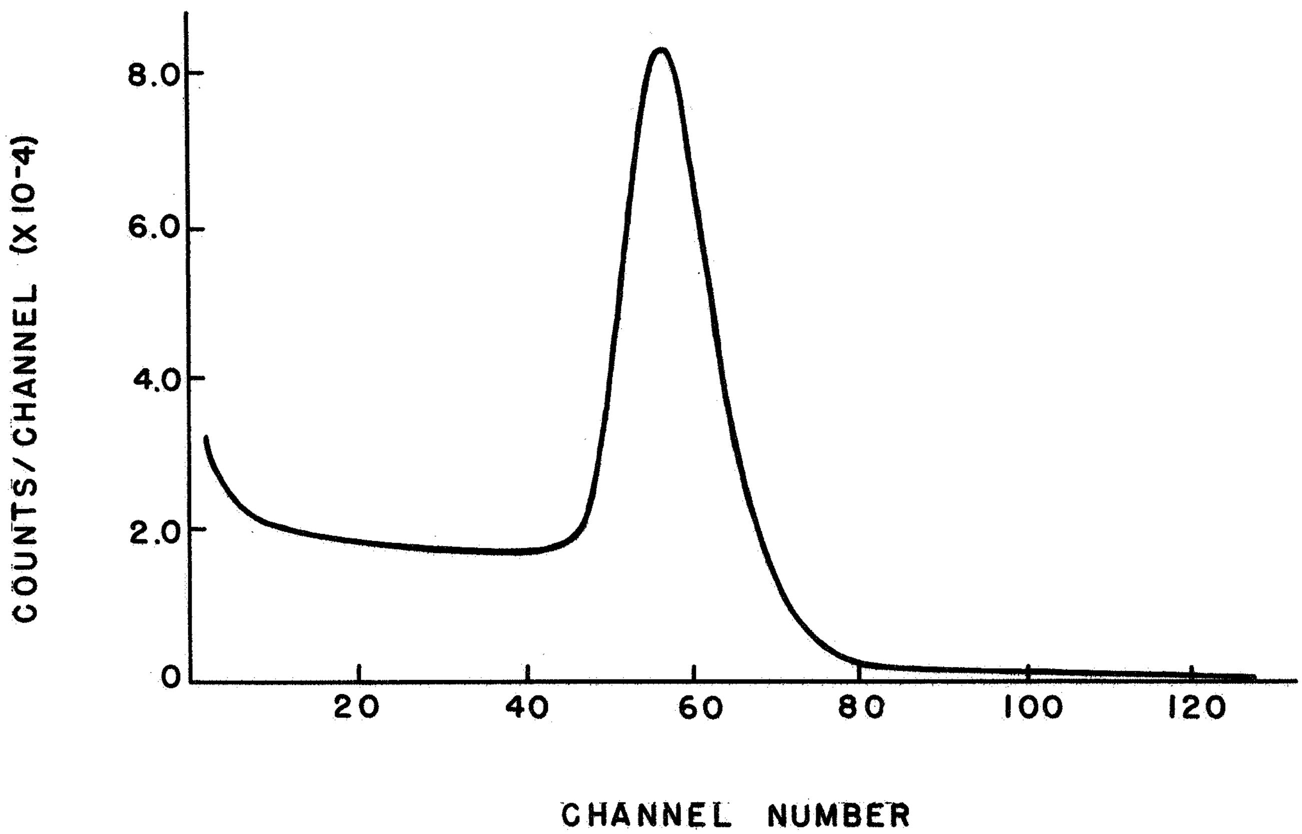

Figure 10. ΔE spectrum deposited by 600 MeV protons in our p-i-n detector.

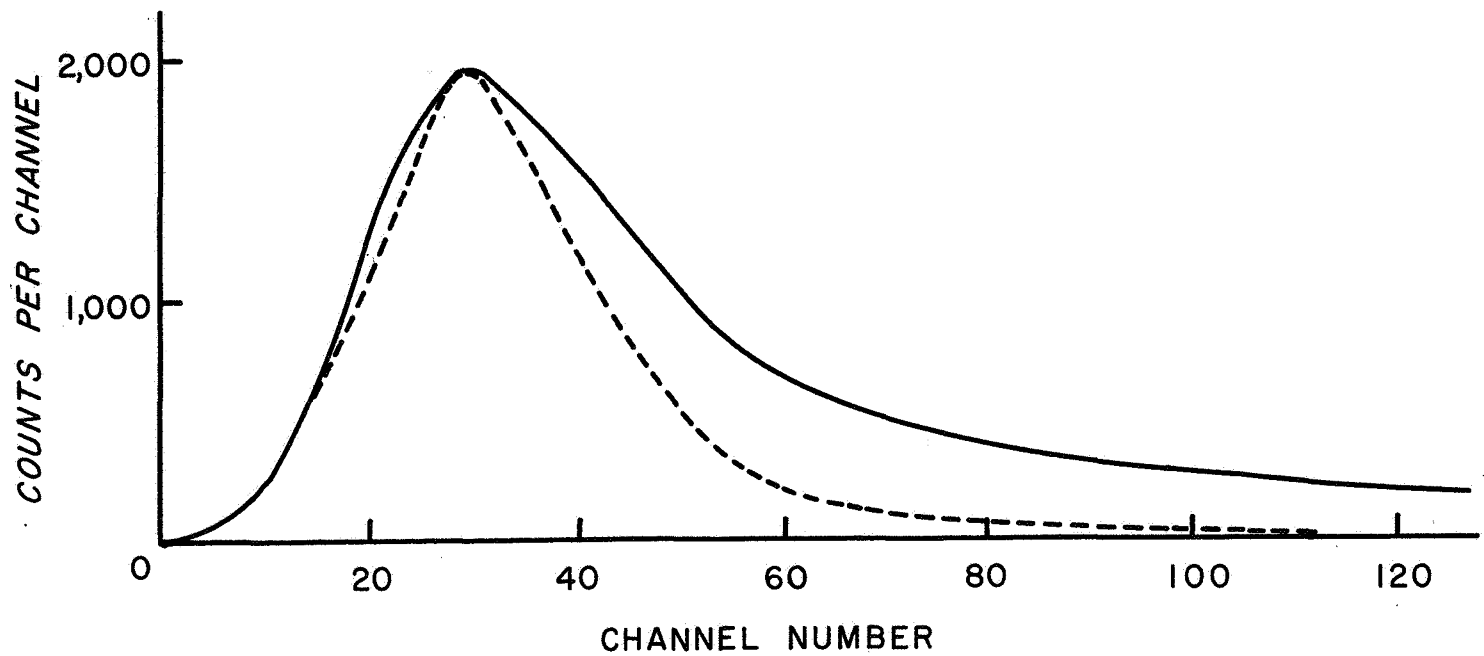

Figure 11. Distribution of energy losses by 600 MeV protons after passage through 1.33×10^{-3} g/cm^2 of low atomic number materials. The solid line represents experimental data. The dashed curve represents Blunck-Leisegang corrected Vavilov distribution.

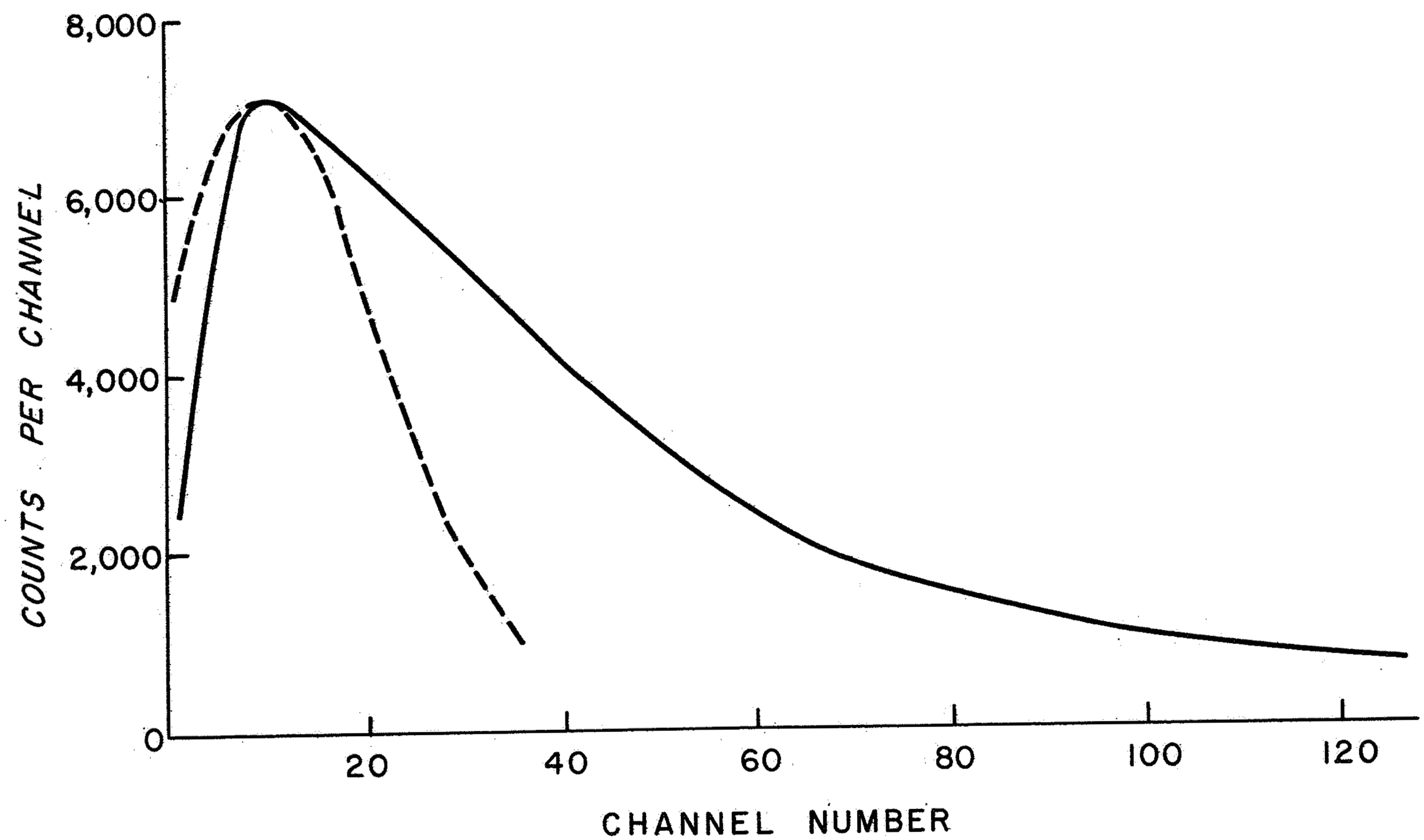

Figure 12. Distribution of energy losses by 600 MeV protons after passage through 1.33×10^{-4} g/cm^2 of low atomic number materials. The solid line represents experimental data. The dashed curve represents Blunck-Leisegang corrected Vavilov distribution.

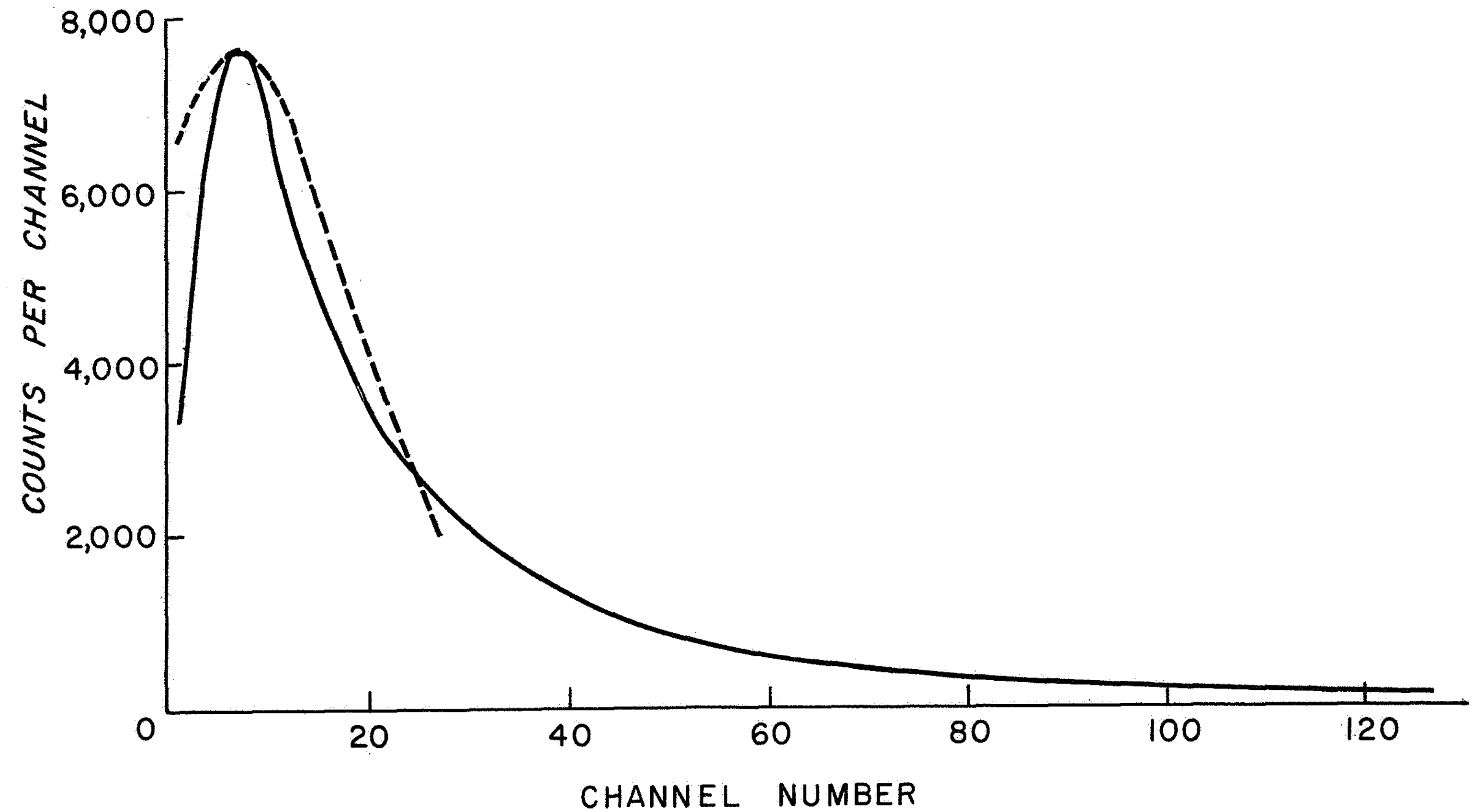

Figure 13. Distribution of energy losses by 600 MeV protons after passage through 6.66×10^{-5} g/cm^2 of low atomic number materials. The solid line represents experimental data. The dashed curve represents Blunck-Leisegang corrected Vavilov distribution.

which increases to $\simeq$ 400% for a pathlength of 1.33 x 10^{-4} g/cm^2, subsequently decreases for the three smaller pathlengths. However, theoretical predictions of the effect of pile up on distributions of this type can lead to such a result for reasonable combinations of resolving times and count rates.

The pile-up effect for the proportional counter and associated electronics used in these experiments was demonstrated using ~ 5 MeV alpha particles. The simulated pathlength was 1.33 x 10^{-4} g/cm^2, and the count rate was about 125 CPS. The experimental curve is given in Figure 14. The characteristic second peak is present at about twice the peak energy and the expected sharp drop in counts per channel beyond twice the peak energy is observe. The pile-up magnitude is between 1% and 2%, which indicates a strong pile-up effect considering the very low count rate.

A second run was planned in order to confirm the experimental data at 600 MeV and extend the investigation to 300 MeV, and we were assigned 16 hours of cyclotron time at each of these energies late in August. Unfortunately, however, the characteristics of the proton beams which the SREL group was able to provide at that time were such that it was impossible for us to measure meaningful energy distributions. The protons, at both 600 MeV and 300 MeV, were delivered in bursts of only a few microseconds duration, 55 times per second. Since the resolving time of our instrumentation is of the order of a microsecond, more than 2 or 3 protons per pulse would cause unacceptable pile-up problems, and the cyclotron could just not be run at proton flux rates approaching these. This problem could normally be alleviated at 600 MeV by "stretching" the length of time during which protons are extracted, but the equipment necessary to accomplish this was not functioning during our run. There is presently no comparable "stretching" equipment for the 300 MeV beam.

It might be pointed out, for future reference, that the pile-up problem is particularly troublesome at these high energies for two reasons. First,

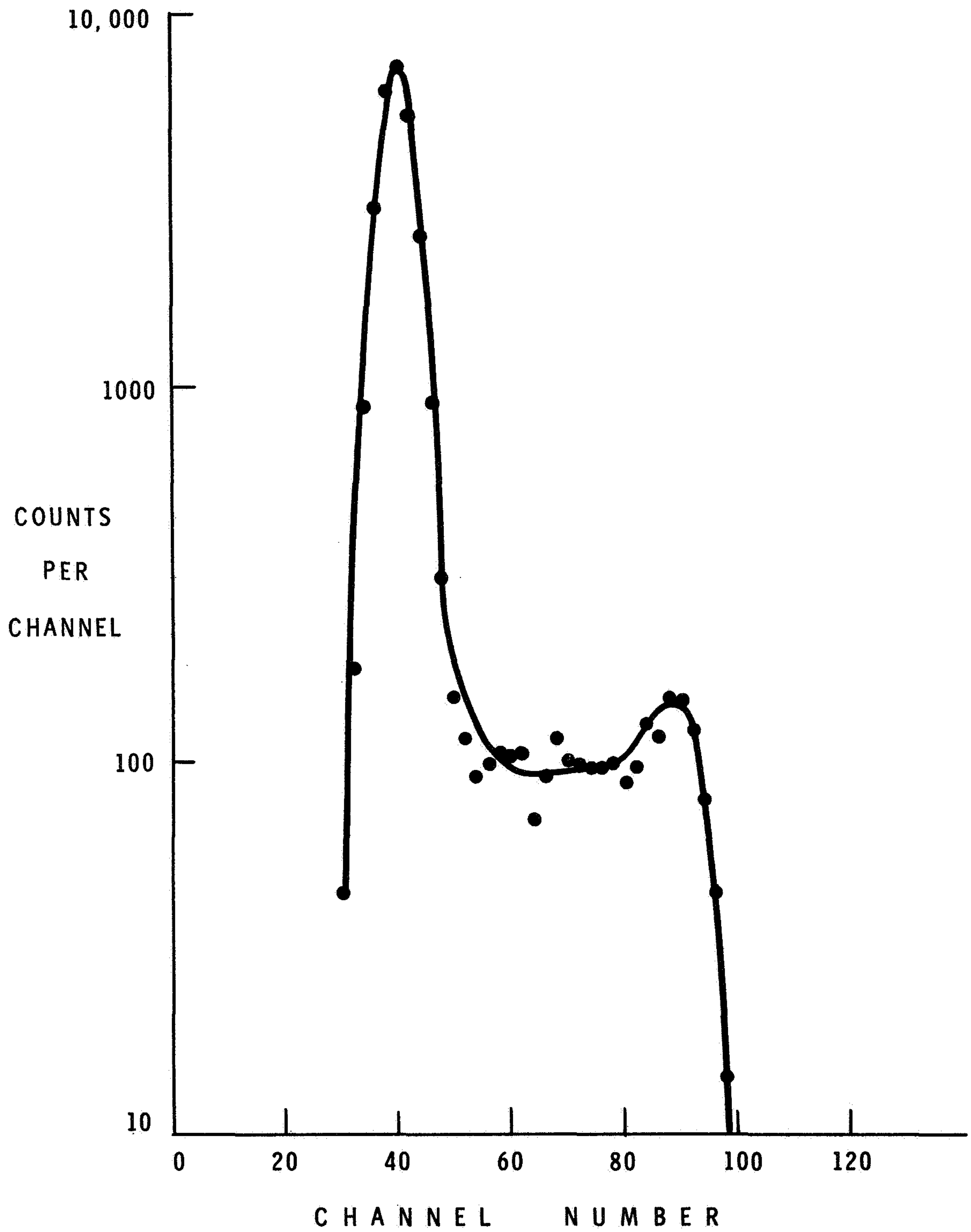

Figure 14. Pile-up effect for proportional counter and associated electronics used in 600 MeV experiments.

there is no satisfactory method of shielding the large portion of the proportional counter not being utilized, due to the high secondary production in any collimating material. Second, after a period of irradiation, the brass walls of the proportional counter itself become activated, leading to an extremely large background count rate of pulses comparable in size to those of interest.

Proton Radiobiological Data

A student was employed to collate all available proton radiobiological data from the open literature, conference reports, and both the internal and contract reports of government laboratories and contractors. These have been compiled, edited, and presented as a function of biological sample and proton energy. Data for absorbed doses less than 25 rad and greater than 10^3 rad have been deleted. This material will eventually be analyzed for dose-rate effects and the influence of the geometrical distribution on both the macro and micro dose patterns existing within the irradiated material. Because of the inherently rather special organization of this material, it has been included in this report as a coherent unit in Appendix A.

Publications

1. R. L. Tanner, N. A. Baily, and J. W. Hilbert, "High-Energy Proton Depth-Dose Patterns," Rad. Res. 32, 861-874 (1967).

2. N. A. Baily, W. M. Akutagawa, R. J. Andres, and H. L. Montano, "Some Characteristics of Lithium Drifted Silicon Structures," J. Appl. Phys. 38, 3907 (1967).

3. N. A. Baily, "New Developments and Recent Experience," Proc. Internat. Symposium on the Biological Interpretation of Dose from Accelerator-Produced Radiations, Berkeley, Calif., 329, Conf-670305, TID-4500 (1967).

4. N. A. Baily and G. D. Robertson, "Physical Factors Governing the Performance of Spherical Silicon Detectors as In Vivo Secondary Proton Spectrometers," Rad. Res. 31, 619 (1967).

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Appendix A

SUMMARY OF RADIOBIOLOGICAL DATA USING PROTONS AS THE IRRADIATION SOURCE.

The data summarized in the following sections represents all results of either animal or cellular radiation studies using protons as the source of incident radiation published either in the open literature or in laboratory reports receiving regular distribution and covering a time span ending June, 1968. The report is of necessity almost in outline form and organized primarily as a function of proton energy. All material represents the author only and no attempt at editorializing, or evaluation has been made.

Proton Energy - 13 Mev

Data Source - SAM-TR-68-16-2/68[1]

TABLE I

Harris rats irradiated with 13 Mev protons, neoplasms in long-term surivivors.

Dose in rads	Number surviving eight months postirradiation	Rats with tumor
101	1	None
202	2	One rat, basal cell carcinoma; the other, sebaceous gland adenoma.
300	3	None
406	2	None
500	3	Squamous cell carcinoma
607	2	
700	5	
800	1	
900	3	
1,001	2	
1,100	1	
1,200	5	
1,400	0	None
None	2	None

Cells in irradiated skin showed a broad flagstone appearance, multiple pseudopodia, and cornification. The latter was found particulary in cell cultures taken from epithelial tissues. There was no recovery of viability for at least 60 days.

In animals irradiated to a level $>$ 100 rads, many neoplasms were observed. These occurred mainly; posteriorly to the scapula, and over the spinous processes between scapulae and the thoracic region. That is, mainly over bony prominences where the skin was continually stressed by the animal's movement. In contrast, where less stress is applied; for example, over heavily-muscled areas, these did not occur. The author postulates varied rates of breakdown -vs- repair as a function of stress.

At levels $>$ 400 rads, epilation and hyperplasia occurs.

Above 500 rads, carcinoma was observed in all groups having 8 month survivors. These did not involve dermal tissues and involved only epidermal cells.

Proton Energy - 16 Mev

Rad. Res. Supl. 7, 1967, p. 325[2.]

Rhesus Monkeys

Dose: 125 - 4×10^3 Rads.

Irradiated in right eye from front, left eye used as a control.

Immediate iridocyclitis was evident in all irradiated eyes.

An erythema developed after 15 days in all groups.

No epilation at any level; however, the group receiving 4,000 rads showed desquamation after 15 days.

The RBE seemed lower than that for 730 Mev protons when compared on a LET basis.

32 Mev - Protons

SAM-TR-65-43[3.]

Primates

Dose - 560, 990 rads

Blood samples taken prior to and 1, 2, 4, 7, 15, 30, 60, and 90 days post irradiation.

Tests performed:

a. serum assay
b. enzyme assay
c. hemotology

TABLE II

Iron-59 ferrokinetics after irradiation

Dose (rads)	Number of animals	Plasma disappearance half-time (min.)		7-day % RBC reappearance		10-day % RBC reappearance	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
280	4	68 ± 11*	83 ± 32	84 ± 12	69 ± 10	87 ± 6	68 ± 11
560	4	83 ± 10	114 ± 19	73 ± 5	75 ± 21	78 ± 9	78 ± 12
990	4	69 ± 10	96 ± 19	89 ± 11	85 ± 11	94 ± 9	86 ± 10
1,880	4	81 ± 8	89 ± 19	80 ± 12	80 ± 17	82 ± 4	80 ± 16
2,800	4	65 ± 18	68 ± 18	94 ± 9	91 ± 9	91 ± 10	90 ± 15

The variations shown above are all within normal limits.

TABLE III

Total white cell count (per mm.^{3})

		Days after irradiation							
	Baseline	1	2	4	7	15	30	60	90
Controls	11,020	13,210	9,180	11,990	11,590	10,190	9,730	9,604	9,060
560 rads	10,740	10,190	11,225	10,460	11,240	8,950	13,275	12,430	14,925
990 rads	9,816	9,816	7,590	8,308	9,191	7,800	9,417	11,325	14,300
1,400 rads									
All animals	8,625	10,267	7,008	6,800	6,440	7,417	12,892	---	---
Survivors	9,263	8,938	7,113	7,325	6,925	6,375	10,238	13,388	15,950
Nonsurvivors	7,350	8,125	6,800	5,750	5,475	9,500	18,200	---	---
1,880 rads									
All animals	10,533	9,500	9,316	8,666	7,200	9,933	18,783	No	---
Survivors	12,575	11,800	10,275	11,650	10,275	11,975	12,100	samples	16,750
Nonsurvivors	9,512	8,350	8,838	7,175	5,663	8,912	22,125	taken	---
2,350 rads									
Nonsurvivors	9,560	8,950	8,330	7,416	6,725	11,400	16,170	---	---
2,800 rads									
Nonsurvivors	11,450	12,425	9,150	11,025	7,850	8,100	12,900	---	---
3,310 rads									
Nonsurvivors	9,683	8,017	7,117	9,700	8,116	9,480	20,075	---	---
4,250 rads									
Nonsurvivors	11,717	13,516	10,350	15,233	11,250	10,325	20,050*	---	---
5,200 rads									
Nonsurvivors	9,917	14,383	12,183	30,200*	13,000*	12,100*	15,050†	---	---

The entries in the table are the average counts of the bled animals.

*One animal.

† *In extremis* at day 28.

TABLE IV

Neutrophils (per mm.^{3})

	Days after irradiation								
	Baseline	1	2	4	7	15	30	60	90
Controls	3,674	4,254	3,255	3,522	3,741	2,509	1,517	2,500	1,712
560 rads	3,532	6,439	6,450	4,688	4,435	2,877	6,177	3,879	3,395
990 rads	2,630	4,454	2,951	2,722	2,648	1,822	2,803	2,486	2,563
1,440 rads									
All animals	2,557	7,121	3,730	2,501	1,897	2,509	7,230	---	---
Survivors	2,391	7,742	3,682	2,591	2,004	1,519	5,410	4,163	6,910
Nonsurvivors	2,888	5,880	3,825	2,320	1,684	4,490	10,868	---	---
1,880 rads									
All animals	2,859	6,576	4,841	3,875	2,037	4,085	10,042	No samples taken	---
Survivors	1,853	7,658	4,283	6,372	2,625	3,313	5,180		4,340
Nonsurvivors	3,530	6,035	5,120	2,626	1,744	4,471	12,472		---
2,350 rads									
Nonsurvivors	2,555	6,549	4,920	2,725	2,892	5,597	9,805	---	---
2,800 rads									
Nonsurvivors	3,022	9,135	5,806	6,639	2,506	3,682	8,885	---	---
3,310 rads									
Nonsurvivors	2,561	5,172	3,971	4,279	3,090	4,507	10,709	---	---
4,250 rads									
Nonsurvivors	2,954	9,099	7,584	12,093	7,990	4,481	12,630*	---	---
5,200 rads									
Nonsurvivors	3,627	11,268	8,142	26,576*	7,140	6,413*	9,330†	---	---

The entries in the table are the average counts of the bled animals.

* One Animal.

† *In extremis* at day 28.

TABLE V

Lymphocytes (per mm.^{3})

	Days after irradiation								
	Baseline	1	2	4	7	15	30	60	90
Controls	7,200	8,636	5,854	8,028	7,706	7,322	7,960	6,521	7,290
560 rads	6,710	3,531	4,436	5,376	6,578	5,932	6,780	7,855	11,300
990 rads	6,866	5,048	4,505	5,480	6,392	5,854	6,348	8,373	10,980
1,440 rads									
All animals	5,991	2,917	3,114	4,158	4,375	4,773	5,431	---	---
Survivors	6,845	3,402	3,310	4,594	4,712	4,691	4,668	8,576	8,980
Nonsurvivors	4,284	1,946	2,720	3,284	3,700	4,937	6,958	---	---
1,880 rads									
All animals	7,405	2,817	4,193	4,572	5,059	5,631	8,673	No samples taken	---
Survivors	10,465	4,142	5,446	5,045	7,534	8,285	6,783		11,160
Nonsurvivors	5,366	2,155	3,567	4,336	3,821	4,304	9,618		---

(continued....)

TABLE V (continued....)

	Days after irradiation								
	Baseline	1	2	4	7	15	30	60	90
2,350 Nonsurvivors	6,606	2,287	2,846	4,491	3,738	5,622	6,227	---	---
2,800 rads Nonsurvivors	8,248	3,168	2,897	4,183	4,881	4,280	4,087	---	---
3,310 rads Nonsurvivors	6,895	2,396	2,752	5,184	4,593	4,606	7,470	---	---
4,250 rads Nonsurvivors	8,255	3,685	2,370	3,011	3,257	5,364	5,610*	---	---
5,200 rads Nonsurvivors	6,106	2,489	3,566	3,624*	5,590*	5,203*	4,665†	---	---

The entires in the table are the average counts of the bled animals.

*One Animal.

†*In extremis* at day 28.

No radiation induced leukopenia was observed.

In many animals, as a result of cutaneous infection and a resultant increase in lymphocytes and neutrophils, leukocytosis was seen with associated granulocytosis.

No effect on lasinophils and basophils was observed.

TABLE VI

Platelets ($\times 10^3/mm.^3$)

	Days after irradiation								
	Baseline	1	2	4	7	15	30	60	90
Controls	407	419	379	372	347	334	313	343	353
560 rads	362	308	331	330	316	391	370	413	375
990 rads	397	360	376	355	356	409	394	399	403
1,440 rads									
All animals	345	377	327	322	306	295	395	---	---
Survivors	330	313	292	293	282	327	301	344	356
Nonsurvivors	377	390	398	433	355	227	582	---	---
1,880 rads									
All animals	397	322	349	307	301	371	440	No	---
Survivors	391	388	366	357	220	436	354	samples	332
Nonsurvivors	400	289	340	283	341	340	483	taken	---
2,350 rads									
Nonsurvivors	392	326	326	287	367	456	571	---	---
2,800 rads									
Nonsurvivors	393	363	313	291	305	453	608	---	---
3,310 rads									
Nonsurvivors	392	264	350	322	395	420	343	---	---
4,250 rads									
Nonsurvivors	351	307	272	163	319	221	311*	---	---
5,200 rads									
Nonsurvivors	374	389	344	375*	418*	330*	561†	---	---

All values given above are within normal limits.
No thrombocytopenia noted.

The entries in the table are the average counts of the bled animals.

* One animal.

† *In extremis* at day 28.

TABLE VII

Hemoglobin (grams/100 ml. blood) and hematocrit (%)

	Days after irradiation																	
	Baseline		1		2		4		7		15		30		60		90	
	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT
Controls	13.4	42.5	13.9	44.6	12.1	38.0	12.0	37.4	12.3	38.2	12.4	39.0	13.4	43.0	13.6	43.6	13.0	41
560 rads	13.4	43.5	13.3	43.0	12.6	40.3	13.1	39.0	12.4	37.5	12.6	39.0	12.5	41.0	13.2	43.0	13.3	42
990 rads	13.4	43.3	12.5	39.9	12.1	39.2	12.5	36.7	12.0	36.7	12.5	38.0	12.4	41.0	13.3	42.3	13.3	41
1,440 rads																		
All animals	13.0	44.0	12.9	40.7	11.9	39.3	11.6	36.0	11.7	35.3	12.2	38.3	11.7	39.0	---	---	---	---
Survivors	13.4	45.0	13.4	42.0	12.4	40.8	12.1	37.3	12.1	36.5	12.6	39.0	12.7	41.3	13.4	44.0	13.2	43
Nonsurvivors	12.3	41.5	12.0	38.0	11.0	36.3	10.5	34.0	11.0	33.0	11.5	37.0	9.8	35.0	---	---	---	---
1,880 rads																		
All animals	13.3	43.7	12.7	42.0	11.9	39.5	12.1	36.5	12.0	36.0	12.6	39.1	11.3	39.5	No samples taken		---	---
Survivors	13.8	45.5	12.9	43.3	12.6	40.3	12.8	38.5	12.8	37.0	12.8	39.5	13.4	44.5			13.3	43
Nonsurvivors	13.1	42.8	12.6	41.1	11.6	39.1	11.8	35.5	11.6	35.2	12.5	39.0	10.2	37.0			---	---
2,350 rads																		
Nonsurvivors	12.7	42.0	12.3	40.0	11.7	38.8	11.2	34.0	11.0	34.0	12.0	38.0	10.2	36.0	---	---	---	---
2,800 rads																		
Nonsurvivors	13.8	45.3	13.4	42.8	12.2	40.1	12.4	36.3	11.6	35.3	12.5	39.3	10.4	35.0	---	---	---	---
3,310 rads																		
Nonsurvivors	14.2	42.0	12.0	38.0	11.8	38.0	10.9	35.0	11.6	37.0	12.0	38.0	10.3	34.0	---	---	---	---
4,250 rads																		
Nonsurvivors	13.0	40.0	12.5	39.0	12.5	40.0	10.3	32.0	9.5	29.5	10.3	33.5	9.0	30.0*	---	---	---	---
5,200 rads																		
Nonsurvivors	13.0	40.0	12.5	39.0	12.9	42.0	12.0	38.0*	10.4	34.0*	8.6	29.0*	10.7	35.0*†	---	---	---	---

The entries in the table are the average counts of the bled animals.

*One animal.

†In extremis at day 28.

The depression of both the hemoglobin concentration and hematocrit levels in groups irradiated to the highest levels occurred at a time (> 15 days) when skin infections were experienced.

SINGLE DOSE DATA

Those receiving 280 rads and 50% of those in the 560 rad group suffered no cutaneous changes.

50% of the 560 rad group showed edemic areas. These appeared after 8 weeks.

Those that received 990 rads (survivors) showed a transient tissue edema, pitting edema of the chest, fluid collection in the rectal sheath, abdominis, and peritoneal fluid.

TABLE VIII

Mortality after irradiation with 32 Mev protons

Dose (rads)	Dose rate (rads/min.)	Study	Number of animals	Number dead at 80 days	Percent dead at 80 days (all animals)	Mean survival time of nonsurvivors (days)
0		I*	5	0	0	---
280	100	II†	4	0	0	---
560	100	I	4	0	0	---
		II	4	0	0	---
990	100	I	6	0	0	---
		II	4			
1,440	100	I	6	2	33.3	41
1,880	100	I	6	4	80	46
		II	4	4		
2,350	100	I	6	6	100	32
2,800	100	I	4	4	100	26
		II	4	4		
3,310	1,000	I	3	3	100	33
4,250	1,000	I	3	3	100	21
5,200	1,000	I	3	3	100	11
6,700	1,000	I	10	10	100	‡

*PART I. The animals were bled for hematology and serum-enzyme assays.

†PART II. The animals were bled for Fe^{59} ferrokinetics.

‡Sacrificed between 2d and 3d postirradiation days.

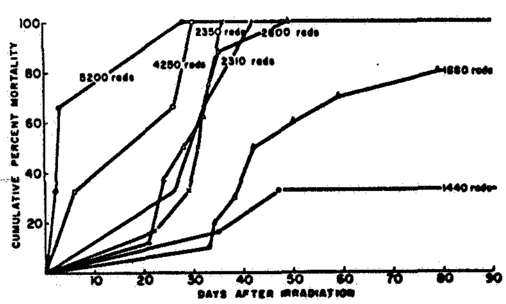


Figure 1. Cumulative percent mortality following irradiation. Since no deaths occurred after 280, 560, and 990 rads, these data have not been included on the plot.

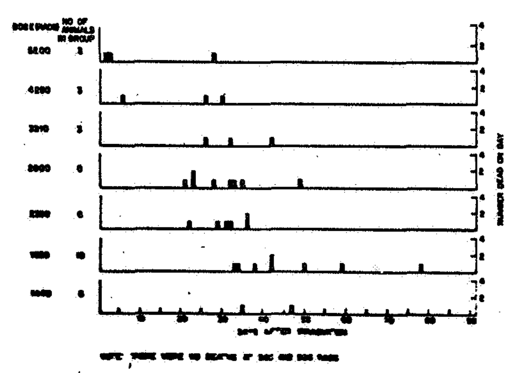


Figure 2. Frequency distribution of mortality following irradiation. Note the absence of deaths during the 10- to 20-day postirradiation period.

TABLE IX

Lactic dehydrogenase (LDH) (units/ml. serum)

	Days after irradiation								
	Baseline	1	2	4	7	15	30	60	90
Controls	407± 46	452± 108	295± 47*	638±125†	846± 365‡	519±152‡	530±104	434± 96	473±150
560 rads	363± 32	998± 240*‡	2,748±2,328‡	993±346‡	954± 270*‡	472± 68	506± 92	445± 92	368± 67
990 rads	465±173	847± 228†‡	1,021± 102*‡	676±249‡	998± 206*‡	568±101‡	564±134‡	471±107	801±320‡
1,440 rads									
All animals	419±143	785± 275‡	1,190± 233*‡	946±143*	1,533± 895‡	584±216‡	1,048±462†‡	---	---
Survivors	450±157	805± 230	1,122± 253	926± 80	1,131± 360	476± 75	770±296	653± 48†‡	560±253
Nonsurvivors	355	747	1,325	995	2,338	800	1,605	---	---
1,880 rads									
All animals	437± 93	1,822±1,775‡	1,000± 483‡	1,065±469†	1,546± 530*‡	506±126	1,271±463*‡	No samples taken	---
Survivors	260	3,550	752	1,021	1,408	405	1,061		279
Nonsurvivors	470± 60	957± 161	1,124± 208	1,087±500	1,614± 635	556±128	1,375±375		---
2,350 rads									
Nonsurvivors	398± 70	3,763±3,741‡	2,609±2,130‡	1,018±312*‡	1,123± 195*‡	893±326*‡	1,219±323*‡	---	---
2,800 rads									
Nonsurvivors	392± 65	2,257±2,370‡	1,276± 186*‡	999±346‡	1,615± 843‡	807±274‡	1,405±150*‡	---	---
3,310 rads									
Nonsurvivors	813±300	1,499± 850‡	810± 280	628±182‡	1,216± 73‡	554±185	1,540	---	---
4,250 rads									
Nonsurvivors	530± 14	1,127± 345‡	783± 290‡	375± 45*	4,660±2,600‡	643	1,270 §	---	---
5,200 rads									
Nonsurvivors	440± 85	3,851±4,350‡	3,243±2,700‡	580 §	3,760 §	663 §	4,630¶§	---	---
6,700 rads									
Nonsurvivors	*	3,430	10,410±11,500	---	---	---	---	---	---

The entries in the table are the means and standard deviation of the measurements of the bled animals.
*P < .001 compared with preirradiation baseline.
†P < .01 compared with preirradiation baseline.
‡P < .01 compared with pre-established normal range. Normal range based on 148 nonirradiated animals — 376+175 units.
§ One animal.
¶ In extremis at 28 days.

Increased enzyme levels are correlated with increased dose levels.

In the early postirradiation period, fluctuations of the LDH level appeared with an apparent periodicity.

TABLE X

Glutamic oxaloacetic transaminase (SGOT)
(units/ml. serum)

	Days after irradiation								
	Baseline	1	2	4	7	15	30	60	90
Controls	24 ± 5	15 ± 2+‡	34 ± 9‡	28 ± 4	36 ± 7‡	23 ± 4	21 ± 2	27 ± 3	26 ± 6
560 rads	22 ± 3	46 ± 16‡	76 ± 56‡	52 ± 31‡	33 ± 9	23 ± 8	22 ± 2	20 ± 2	26 ± 6
990 rads	23 ± 6	37 ± 17‡	38 ± 21*‡	26 ± 18	128 ± 136‡	21 ± 9	24 ± 5	22 ± 3	29 ± 6
1,440 rads									
All animals	25 ± 5	72 ± 65‡	57 ± 11‡	47 ± 10*‡	41 ± 7*‡	28 ± 4	27 ± 4	---	---
Survivors	25 ± 3	75 ± 40	57 ± 20	47 ± 11	43 ± 4	30 ± 2	26 ± 2	25 ± 4	26 ± 3
Nonsurvivors	26	67	57	47	36	23	29	---	---
1,880 rads									
All animals	24 ± 4	125 ± 98‡	66 ± 30+‡	35 ± 20‡	30 ± 8	22 ± 7	26 ± 8	No samples taken	---
Survivors	21	181	79	22	26	20	24		15
Nonsurvivors	26 ± 4	97 ± 83	60 ± 31	41 ± 21	32 ± 9	24 ± 6	27 ± 10		---
2,350 rads									
Nonsurvivors	23 ± 2	222 ± 187‡	160 ± 130‡	69 ± 35‡	47 ± 46‡	64 ± 75‡	44 ± 18‡	---	---
2,800 rads									
Nonsurvivors	22 ± 2	100 ± 72‡	58 ± 16*‡	108 ± 132‡	25 ± 8	20 ± 10	39 ± 10‡	---	---
3,310 rads									
Nonsurvivors	22 ± 5	117 ± 61‡	60 ± 16‡	25 ± 5	27 ± 2	32 ± 12	38	---	---
4,250 rads									
Nonsurvivors	24 ± 5	114 ± 77‡	34 ± 7	553 ± 272‡	212 ± 102‡	44	39¶	---	---
5,200 rads									
Nonsurvivors	20 ± 4	245 ± 265‡	160 ± 145‡	1,200 §	123 §	26 §	80¶	---	---
6,700 rads									
Nonsurvivors	*	167 §	500 ± 450	---	---	---	---	---	---

The entries in the table are the means and standard deviation of the measurements of the bled animals.

*P < .001 compared with preirradiation baseline.

+P < .01 compared with preirradiation baseline.

‡P < .01 compared with pre-established normal range. Normal range based on 201 nonirradiated animals – 26 ± 6.5 units.

¶ In extremis at 28 days.

§ One animal.

TABLE XI

Serum proteins (gm. %) after irradiation

Dose (rads)	Number of animals	Serum protein	Days after irradiation									
			Baseline	1	2	4	7	15	30	60	90	Remarks
		Total	8.5	8.2	7.7	7.5	7.3	8.4	7.0			
		albumin	4.7	4.6	4.1	4.1	3.6	5.0	3.6			
0	2	α	1.0	1.1	1.1	0.9	1.1	0.9	1.0	*	*	Alive at 150 days post-
		β	1.3	1.2	1.2	1.3	1.2	1.1	1.2			irradiation.
		γ	1.5	1.3	1.3	1.2	1.4	1.4	1.2			
		Total	7.7	7.6	7.8		7.7	7.7	7.6	8.7	8.8	
		albumin	4.5	3.9	4.0		4.4	4.5	4.3	4.6	4.8	Alive at 150 days post-
560	1	α	0.7	1.0	1.1	*	0.9	0.7	0.8	1.0	0.9	irradiation. No skin
		β	1.4	1.4	1.4		1.3	1.2	1.4	1.8	1.6	ulceration occurred.
		γ	1.1	1.3	1.3		1.1	1.3	1.1	1.3	1.5	
		Total	7.7	6.5	7.5	7.7	7.8	7.6	7.5	6.5	6.2	
		albumin	4.2	3.6	4.2	4.1	4.4	4.2	4.1	3.5	3.2	Alive at 150 days post-
990	1	α	0.9	0.8	1.1	1.0	0.7	0.9	0.9	0.7	0.7	irradiation. No skin
		B	1.1	0.8	1.0	1.1	1.2	1.2	1.0	0.8	0.8	ulceration occurred.
		γ	1.5	1.3	1.4	1.5	1.5	1.3	1.5	1.5	1.4	
		Total	7.1	6.9	7.3	7.1	6.8	5.9	7.5	6.6	5.8	Alive at 150 days post-
		albumin	3.7	3.9	3.9	3.7	3.9	3.0	3.0	2.8	2.8	irradiation. Moderate
1,440	1	α	0.7	0.7	0.8	0.9	0.7	0.9	1.1	0.8	0.6	skin ulceration occurred
		β	1.1	1.0	1.0	1.0	1.0	1.0	1.5	1.0	0.8	between days 15 and 30.
		γ	1.6	1.3	1.5	1.4	1.1	1.0	1.8	2.0	1.6	Subsequent healing complete by day 60.
		Total	8.1	8.3	8.0	7.3	7.5	8.1	7.2			
		albumin	4.7	5.0	4.8	4.4	4.4	4.5	2.1			Died on 35th post-
1,440	1	α	0.8	1.1	1.0	0.9	0.9	0.9	1.3	*	---	irradiation day with
		β	1.1	1.0	1.1	1.0	1.2	1.5	1.8			severe skin ulceration.
		γ	1.4	1.2	1.1	1.0	1.0	1.2	2.0			
		Total	7.8	7.3	7.7	7.7	7.8	7.1	8.2		7.3	Alive at 150 days post-
		albumin	4.0	3.5	4.1	3.5	3.5	3.0	3.4		3.1	irradiation. Moderate
1,880	1	α	1.3	1.3	1.4	1.4	1.4	1.6	1.6	*	1.2	skin ulceration occurred
		β	0.8	1.1	0.9	1.1	1.1	1.1	1.2		1.0	between days 15 and 30.
		γ	1.7	1.4	1.3	1.7	1.8	1.4	2.0		2.0	Subsequent healing complete by day 60.
		Total	7.6	7.5	6.8	5.9		6.4	8.2			
		albumin	4.5	4.0	3.5	3.0		2.8	2.1			Sacrificed in extremis on
1,880	1	α	1.3	1.5	1.4	1.3	*	0.7	1.8	*	---	the 79th postirradiation
		β	1.2	1.2	1.2	0.8		2.1	1.8			day. Severe skin
		γ	0.6	0.8	0.7	0.8		0.8	2.5			ulceration on days 20&40.

(continued....)

TABLE XI (continued....)

Dose (rads)	Number of animals	Serum protein	Days after irradiation									
			Baseline	1	2	4	7	15	30	60	90	Remarks
2,350	3	Total albumin α B γ	8.8 5.0 1.2 1.4 1.2	7.2 4.1 1.1 1.2 0.8	6.8 3.8 1.0 1.2 0.8	6.6 3.6 0.9 1.1 1.0	6.4 3.3 0.9 1.3 0.9	6.2 3.2 1.0 1.2 0.8	8.0 2.0 1.5 1.9 2.6	---	---	All died before day 60 postirradiation. Severe skin ulceration appeared between days 15 & 23.

When more than 1 animal is in a group, the table entries are the group means.

*No sample taken.

There were very few changes in the serum proteins as late as 90 days postirradiation.

In general, the following observations were noted:

1. Hyperemia and hyperplasia of germinal centers.
2. No splenic abnormalities except (1).
3. No destructive lesions although both the liver and kidney showed swelling.
4. Skin reactions ~ to third-degree burns.
5. Re-epithelization of the periphery of ulcers was abortive.
6. Serum protein changes were secondary to cutaneous destruction.

55- Mev Protons[4.]

Primates

The penetration (~2.6 cm. of soft tissue) is sufficient to irradiated much of the bone marrow.

TABLE XII

GROUP I: Cumulative Mortality After 55-Mev Whole-Body Proton Irradiation

Dose (rads)	Whole-body study	Number of animals	Number dead at 90 days (both subgroups)	Percent dead at 90 days (both subgroups)	Mean survival time of nonsurvivors (days)
1,000	A. Bled	4	6	43	15
	B. Nonbled	10			
800	A. Bled	4	4	28.5	45.5
	B. Nonbled	10			
600	A. Bled	4	0	0	---
	B. Nonbled	10			
400	A. Bled	4	0	0	---
	B. Nonbled	10			
200	A. Bled	---	0	0	---
	B. Nonbled	7			
0	A. Bled	4	0	0	---
	B. Nonbled	2			

Partial body irradiation (to abdominal area) of 750 rads had one survivor after 125 days.

Weight Loss (after whole-body irradiation)

30 days ~ 20%, $\simeq$ 32% for one animal irradiated to 10^3 rad.
60 days - (20 of 58 that survived) failed to regain pre-irradiation weight.
90 days - 45 had weight $>$ than pre-irradiation, 2 at pre-irradiation, and 8 below.

Weight Loss (partial body)

All lost weight rapidly.

See following graph.

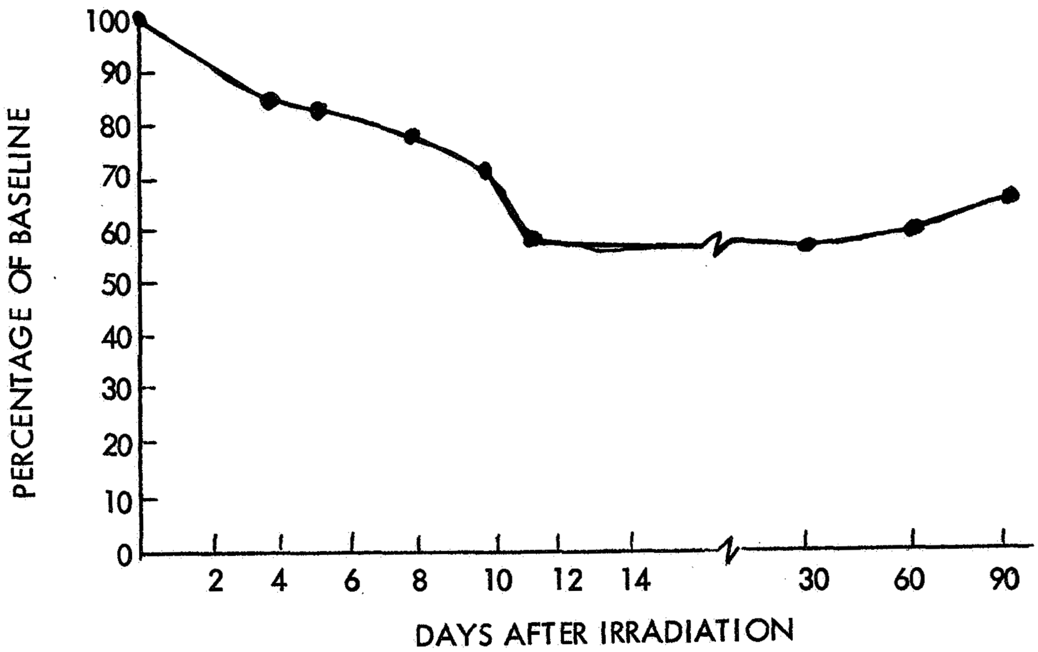


FIG. 3. Postirradiation weights of the group II animals exposed as percentage of preirradiation base-line weight after partial body irradiation of 750 rads.

Clinical

(a) Whole Body Irradiation

Early post-irradiation - malaise and inappetence
5th day - $>$800 rads; diarrhea
7th day - $>$ 600 rads; leukopenia
21st day - $>$ 600 rads; epilation and eczematous lesions of the face. Epilation was temporary.
90 days - $>$ 800 rads - epilation of frontal and temporal areas, buttocks and lower extremities. Facial edema.

Animals that died late (2 - 3 mos.) had sporadic diarrhea, gradual loss of condition, ragged coats, loss of activity until they assumed fetal position and died.

(b) Partial Body (abdomen) Irradiation

Massive diarrhea, inappetence, diarrhea continued until death for animals who died before 12 days.

Hematology

No significant effect on ferrokinetics.

TABLE XIII

Total White Cell Count[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	9,463	14,125	14,663	15,638	11,075	10,588	8,700	10,550	10,787
Group I: Whole-Body Exposure									
400 rads	8,850	6,475	4,738	6,375	3,975	5,387	9,412	9,025	8,287
600 rads	11,063	6,438	4,463	5,063	2,725	6,012	7,850	11,775	12,350
800 rads	9,088	6,563	4,463	6,100	2,688	4,888	6,100	9,463	10,125
1,000 rads									
A	10,463	10,563	3,225	4,388	2,563	5,575	14,116	14,083	17,533
S	11,117	9,817	3,183	4,850	2,866	6,450	14,116	14,083	17,533
NS[b]	8,500	12,800	3,350	3,000	1,650	2,950	---	---	---
Group II: Partial-Body Exposure									
750 rads									
A	7,150	7,525	6,350	5,275	4,850	5,300	8,675	12,900[b]	10,300[b]
S[b]	7,800	8,250	8,250	6,200	5,900	5,750	6,400	12,900	10,300
NS[b]	6,500	6,800	4,450	4,350	3,800	4,850	10,950	---	---

[a]entries are average counts per mm^3 of 4 bled animals in gr I and of 2 in gr II.
A = all animals
S = survivor(s)
NS = nonsurvivor(s)
[b]one animal

Platelets, Hemoglobin, and Hematocrits all showed no significant changes.

No leukopenia was observed after partial body exposure.

TABLE XIV

Neutrophils[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	2,619	4,920	3,659	4,480	3,550	3,221	3,258	3,095	2,197
Group I: Whole-Body Exposure									
400 rads	2,232	4,239	2,384	2,800	1,369	1,514	3,128	2,325	1,345
600 rads	2,504	4,473	2,205	2,850	841	1,973	2,176	2,271	4,750
800 rads	3,528	5,153	2,420	3,595	968	1,087	2,504	2,970	3,893
1,000 rads									
A	2,366	8,746	1,687	2,180	798	2,324	3,950	2,657	5,261
S	1,993	7,650	1,423	2,308	810	2,755	3,950	3,950	5,261
NS[b]	3,485	12,032	2,479	1,800	759	1,033	---	---	---
Group II: Partial-Body Exposure									
750 rads									
A	1,553	3,670	3,073	2,265	2,010	1,814	4,073	8,385[b]	4,429[b]
S[b]	1,872	4,620	4,455	2,790	2,690	2,415	3,328	8,385	4,429
NS[b]	1,235	2,720	1,691	1,740	1,330	1,213	4,818	---	---

A significant neutrophilia is shown after whole-body irradiation.

TABLE XV

Lymphocytes[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	6,550	8,967	10,862	10,775	6,698	7,028	5,171	7,286	8,105
Group I: Whole-Body Exposure									
400 rads	6,307	2,067	2,250	3,439	2,533	3,736	5,502	6,155	6,560
600 rads	8,164	1,766	2,194	2,118	1,844	3,742	5,153	8,621	7,086
800 rads	5,288	1,278	2,015	2,422	1,607	3,660	3,296	5,945	5,778
1,000 rads									
A	7,898	1,641	1,463	2,188	1,648	3,225	9,120	8,150	11,271
S	8,858	1,890	1,705	2,517	1,917	3,660	9,120	8,150	11,271
NS[b]	5,015	896	737	1,200	842	1,918	---	---	---

(continued....)

TABLE XV(continued....)

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
			Group II: Partial-Body Exposure						
750 rads									
A	5,395	3,690	3,150	2,905	2,700	3,409	4,172	4,515[b]	5,459[b]
S[b]	5,850	3,300	3,630	3,286	3,159	3,540	2,432	4,515	5,459
NS[b]	4,940	4,080	2,670	2,523	2,242	3,278	5,913	---	---

[a]Average counts per mm^3 of 4 bled animals in gr. I, and 2 in gr. II.
A = all animals.
S = Survivor(s)
NS - Nonsurvivor(s)
[b] one animal

TABLE XVI

Lactic Dehydrogenase (LDH)[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	632±88[b]	603±202	575±65	405±113	788±300[c]	379±22	651±97	398±71	325±21
Group I: Whole-Body Exposure									
400 rads	588±120	928±217[d]	850±96[d]	611±138	933±246[d]	473±159	749±336	735±121	485±77
600 rads	505±37	1048±148[d,e]	897±187[d,f]	721±97[f]	785±784	457±260	796±187[c]	884±282[d]	591±296
800 rads	518±172	1029±165[d,f]	795±103[c]	937±226[d]	1389±78[d,e]	667±256	859±193[c]	1025±320[d]	830±281[c]
1000 rads									
A	418±90	1179±174[d,e]	1077±140[d,e]	773±54[c,e]	871±252[d,f]	602±252	780±534	774±251	905±329[c]
S[g]	387±66	1195±191	1113±121	798±23	971±154	479±50	780±534	774±251	905±329
NS[g]	510	1130	970	700	573	973	---	---	---
Group II: Partial-Body Exposure									
750 rads									
A	570	556	666	413	873	405	863	853[g]	426[g]
S[g]	580	680	493	373	796	370	993[h]	853	426
NS[g]	560	433	840	453	950	440	733	---	---

[a]The entries are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals in group I (except the survivor and nonsurvivor subdivisions at 1000 rads) and the means of 2 bled animals in group II. A = all animals; S = survivor(s); NS = nonsurvivor. Normal range based on 198 nonirradiated animals, 540 + 146 units.

[b]Standard deviation.

[c]$p < 0.01$ compared with pre-established normal range.

[d]$p < 0.001$ compared with pre-established normal range.

[e]$p < 0.001$ compared with preirradiation base line.

[f]$p < 0.001$ compared with preirradiation base line.

[g]One animal.

[h]Hemolyzed sample.

TABLE XVII

Glutamic Oxalacetic Transaminase (SGOT)[a]

Group	Baseline	Days after Irradiation					
		1	2	4	7	15	30
Controls	32 ± 4[b]	35 ± 7	30 ± 3	21 ± 7	29 ± 3	24 ± 2	22 ± 1
25 rads	31 ± 12	50 ± 15	33 ± 1	29 ± 17	28 ± 5	25 ± 4	24 ± 2
50 rads	31 ± 10	62 ± 31[d]	33 ± 8	33 ± 9	32 ± 8	26 ± 3	36 ± 16
100 rads	27 ± 4	71 ± 60	35 ± 14	27 ± 6	32 ± 5	22 ± 2	25 ± 4
200 rads	31 ± 3	81 ± 77	38 ± 18[c]	39 ± 11[c]	40 ± 5[c]	28 ± 11	23 ± 2
400 rads	35 ± 7	59 ± 11[d]	36 ± 6	33 ± 4	40 ± 4[c]	32 ± 7	29 ± 7

TABLE XVIII

Serum Proteins[a]

Dose (rads)	Serum Protein	Baseline	Days after Irradiation					
			1	2	5	10	15	30
750	Total	8.3	8.0	7.9	8.2	6.5	5.3	4.6
	Albumin	5.1	4.8	4.5	4.6	3.4	2.9	1.8
	Globulin: α	0.8	1.1	1.1	1.1	0.9	0.8	0.7
	β	1.1	1.2	1.5	1.5	1.5	1.1	1.8
	γ	1.3	0.9	0.8	1.0	0.7	0.5	0.3

[a]gram % of measurement of 2 animals in gr. II, partial body irradiation.

TABLE XIX

Serum Electrolytes[a]

Dose (rads)	Animal Number	Baseline			Days after irradiation																	
					1			2			5			10			15			30		
		Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-
750	S-80	160	4.8	108	151	4.4	103	143	3.8	106	151	4.8	99	136	5.8	103	132	7.0	90	138	4.7	98
	R-61	144	4.0	106	145	4.8	104	142	4.4	108	147	5.2	103	132	5.9	103	137	6.7	100	---	---	110

[a]Electrolyte components are expressed in milliequivalents per liter of serum.

Animals having the most pronounced fall in serum proteins were observed to have the longest survival.

A progressive decrease in albumin concentration is associated with a steady increase in β-globulin level.

Those animals surviving 10 days or more showed a major fall in γ-globulin.

Mice[5.]

TABLE XX

Days after irradiation	350 rads, Co^{60} γ-radiation, initial dose			470 rads, 55-Mev portons, initial dose		
	Number of animals	$LD_{50(30)}$	Injury (rads)	Number of animals	$LD_{50(30)}$	Injury[a] (rads)
0[b]	144	735 + 18[c]	---	---	---	---
1	144	555 + 19	180 + 26	144	308 + 18[c]	427 + 25
2	144	582 + 20	153 + 27	144	256 + 26	479 + 32
4	144	607 + 18	128 + 25	144	358 + 28	377+ 33
8	144	753 + 31	-18 + 36	144	565 + 16	155 + 24

[a]In this context, injury is the difference between the single-dose $LD_{50(30)}$ for Co^{60} γ-radiation, 735 rads, and the $LD_{50(30)}$ on a given day after the initial exposure.

[b]Only single doses of Co^{60} were given to the mice to determine the $LD_{50(30)}$ of the normal population.

[c]Standard error.

102 Mev Protons[6.]

Guinea Pigs

Dose Administered: 22 - 170 rads.

Animals were irradiated for 10 days then challenged with bacteria (non-resident). These animals showed an increased lesion area of 30 - 40%.

For higher total dose levels ($\sim$ LD_{50}) and uniform total body irradiation, death was due to enteric G-I causes.

TABLE XXI

126 Mev Protons[7.]

Mice

INFLUENCE OF IRRADIATION BY PROTONS WITH ENERGIES OF 126 MEV ON MITOTIC ACTIVITY AND QUANTITY OF CORNEAL EPITHELIUM CELLS

Irradiation dose, rad	Time after irradiation, days	Mitotic index 10^{-3}	Relative quantity of cells in field of view of microscope	Relative content of pathological anaphases
200	1	5.81 ± 0.76	206.3 ± 3.1	0.164 ± 0.056
	1.5	13.61 ± 0.96	194.2 ± 3.0	0.091 ± 0.016
	2.5	9.05 ± 0.82	192.0 ± 3.0	0.063 ± 0.010
	3	9.59 ± 0.88	194.8 ± 2.5	0.031 ± 0.008
	4.5	8.36 ± 0.52	196.0 ± 2.8	0.028 ± 0.008
	5	10.63 ± 1.02	191.0 ± 2.6	0.047 ± 0.010
	6.5	11.40 ± 0.87	195.2 ± 2.7	0.028 ± 0.007
	7	3.41 ± 0.33	194.0 ± 2.9	0.020 ± 0.014
	8.5	12.28 ± 0.86	192.9 ± 2.8	0.022 ± 0.006
	9	5.25 ± 0.57	200.0 ± 2.9	0.020 ± 0.013
500	1	2.56 ± 0.29	188.0 ± 2.3	0.438 ± 0.056
	1.5	5.75 ± 0.50	188.1 ± 3.0	0.401 ± 0.033
	2.5	10.89 ± 0.81	185.0 ± 2.6	0.299 ± 0.026
	3	4.34 ± 0.49	192.5 ± 2.7	0.169 ± 0.045
	4.5	7.47 ± 0.58	198.7 ± 2.2	0.135 ± 0.020
	5	5.13 ± 0.26	200.1 ± 2.6	0.043 ± 0.013
	6.5	9.07 ± 0.69	199.7 ± 2.3	0.055 ± 0.010
	7	5.37 ± 0.48	202.2 ± 2.9	0.036 ± 0.014
	8.5	13.31 ± 0.43	203.0 ± 3.2	0.023 ± 0.006
	9	4.80 ± 0.53	201.8 ± 2.8	0.010 ± 0.005

Reduced rate of mitosis in corneal epithelium proportional to dose delivered. Repairability decreases with increased dose.

The genetic effect in this tissue was found to be dose dependent and given by;

$$F(D) = 8.7 \times 10^{-4}\ D$$

The RBE was found to be (for early genetic effects) = 0.67.

126 Mev Protons[8]

Rats, mice, and dogs

Small doses altered immunological reactivity (depressed phacocytic activity of neutrophils) in first dogs after irradiation.

Decreased oxidative processes. CO_2 liberation and oxygen consumption dropped 35 to 50% shortly after irradiation and remained this way until death or the disappearance of all radiation sickness symptoms.

RBE (dogs) based on % survival, duration of life, severity of symptoms, and laboratory tests; for multiple irradiations was 1.0 (19 exposures in 2-5 weeks).

RBE (dogs) - single exposure = 1.0.

RBE (White rats) based on $LD_{50/30}$ = 0.69.

RBE (White rats) based on $LD_{100/30}$ = 0.70.

RBE (mice) = 0.7.

130 Mev Protons[9].

Dogs

TABLE XXIII

THRESHOLD SENSITIVITY OF VESTIBULAR APPARATUS (°/sec) AFTER IRRADIATION OF DOGS BY PROTONS WITH ENERGIES OF 130 MEV WITH DOSE OF 500 RAD

Name of dog	Initial background			Days after irradiation					
	9/V	12/V	15/V	3	6	9	11	14	16
Shustrik	4	5	4	4	4	5	7	x	
Buyan	3	2	3	3	3	3	3	5	x
Lopushok	4	3	4	3	4	4	3	4	5

Dogs showed radiation sickness symdrome, but its severity did not correlate with changes in the threshold sensitivity of the vestibular apparatus.

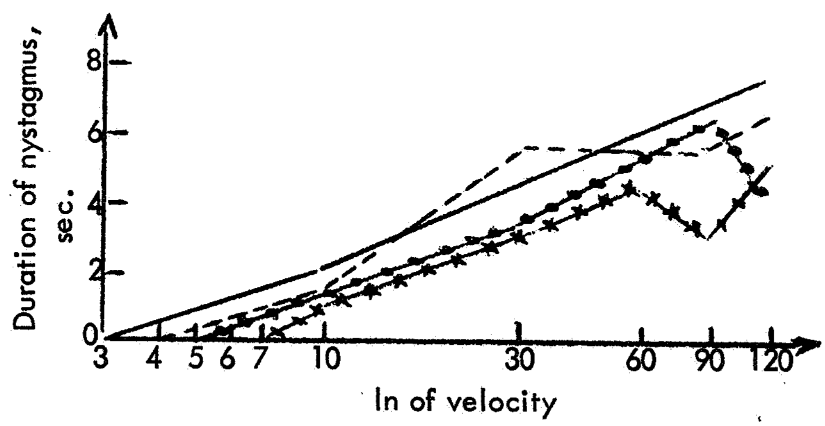


Figure 4. Curves of reaction of vestibular apparatus of dog Shustrik after irradiation with 500 rad: (1) curve for unirradiated animal; (2, 3 and 4) curves for 3d, 9th, and 11th day, respectively, after irradiation.

Figure 5. Change of duration of postrotational nystagmus after irradiation of dogs with dose of 500 rad: (1, 2, and 3) indices of dogs Lopushok, Buyan and Shustrik, respectively. Arrow indicates irradiation.

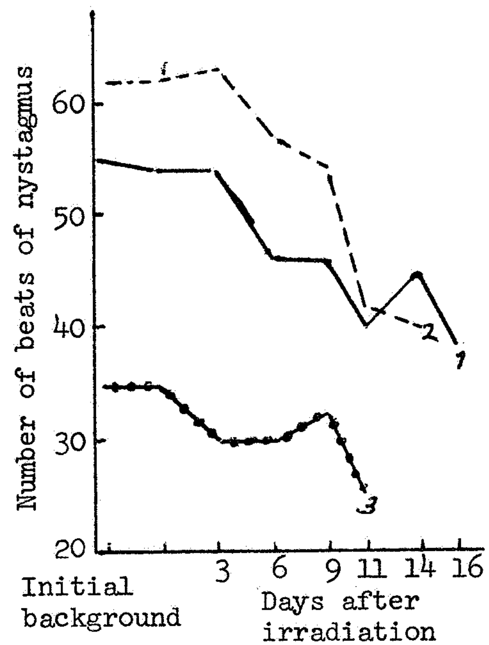


Figure 6. Change of number of beats of postrotational nystagmus after irradiation.

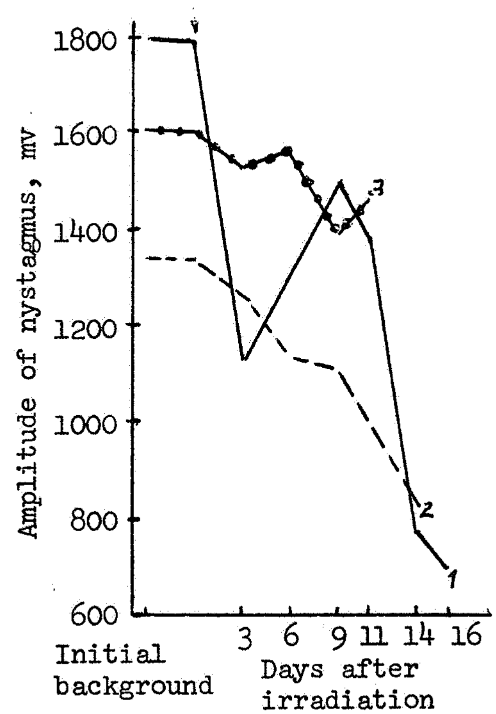


Figure 7. Change of the amplitude of postrotational nystagmus after irradiation.

TABLE XXIII

THRESHOLD SENSITIVITY OF VESTIBULAR APPARATUS (°/sec) AFTER IRRADIATION OF DOGS WITH PROTONS WITH ENERGIES OF 130 MEV WITH DOSE OF 350 RAD

Name of dog	Initial background			Days after irradiation								
	10/I	13/V	16/V	3	6	9	11	15	19	26	32	34
Driada	2	3	3	3	3	3	3	4	5	died on day-20		
Bezrodnaya	5	4	4	4	4	5	4	6	7	7	7	died on day-33
Pavlin	4	4	3	3	3	4	4	4	5	7	7	7

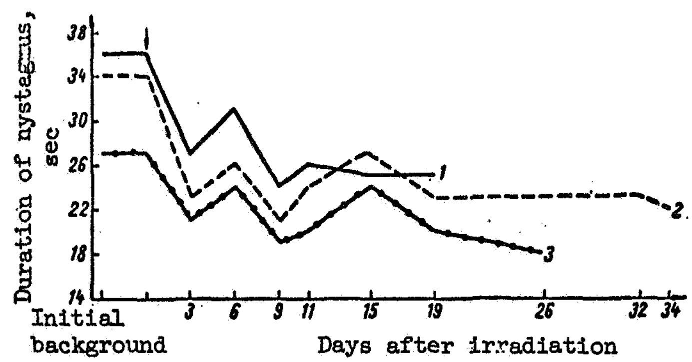


Figure 7. Change of duration of postrotational nystagmus after irradiation of dogs by protons with dose of 350 rad: (1, 2 and 3) data for dogs Driada, Pavlin and Bezrodnaya, respectively. Arrow indicates irradiation.

As a general pattern, at both levels of irradiation threshold sensitivity continued to decrease with time after irradiation together with a continuing decrease of reaction of the vestibular apparatus.

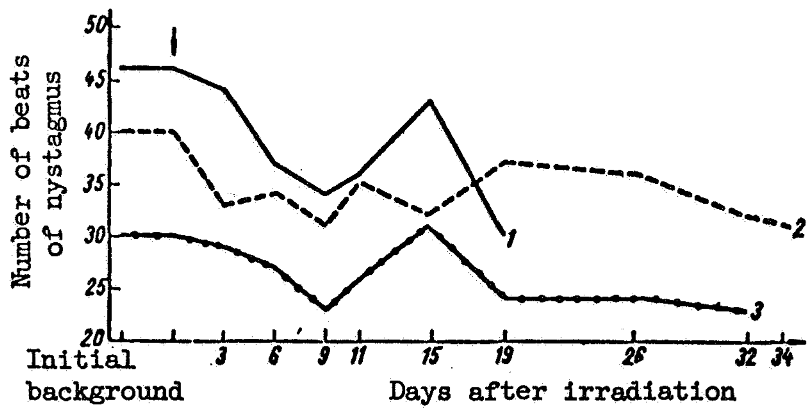


Fig. 8. Change of number of beats of postrotational nystagmus after irradiation.

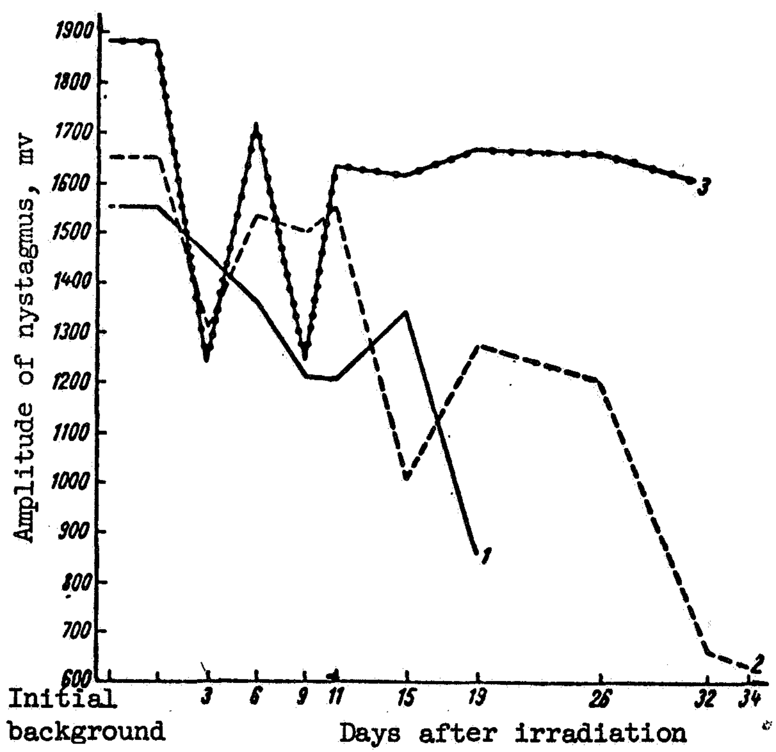


Fig. 9. Change of amplitude of postrotational nystagmus after irradiation.

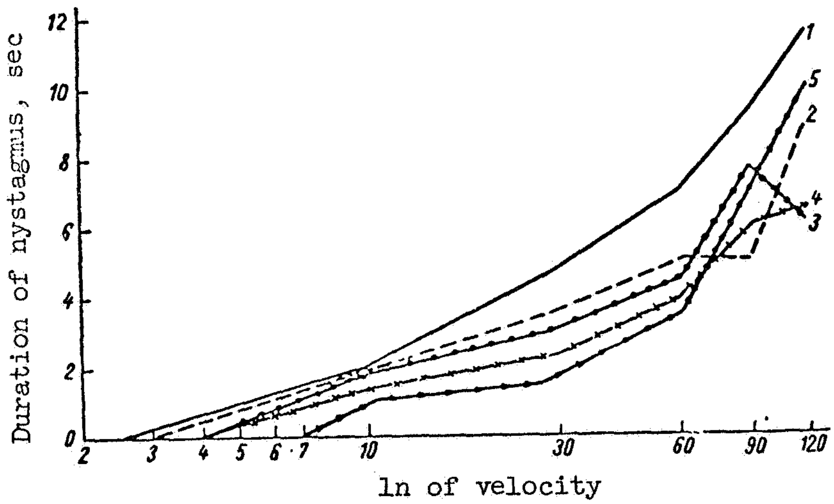


Fig. 10. Curves of reaction of vestibular apparatus after irradiation of dog Pavlin. (1) Curve before irradiation; (2, 3, 4 and 5) on the 3d, 9th, 11th, and 35th day, respectively, after irradiation.

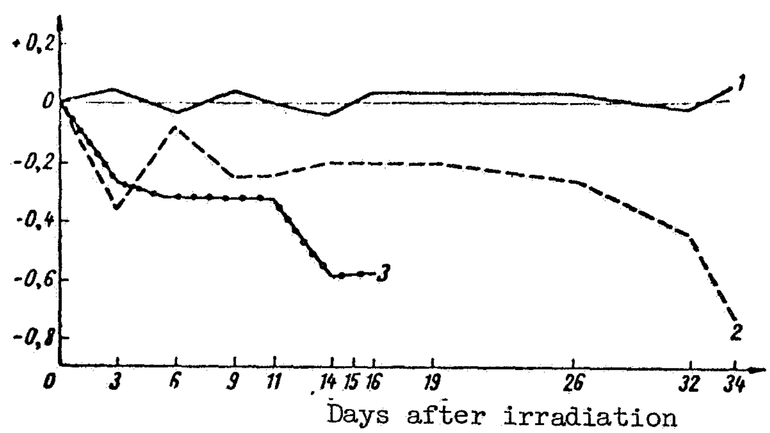


Fig. 11. Change (in relative units) of intensity of postrotational nystagmus after irradiation of dogs by protons with doses of 500 and 350 rad (mean indices in group): (1) data for 6 control dogs; (2) after irradiation with dose of 350 rad; (3) after irradiation with dose of 500 rad.

138 Mev - Protons [10,11]

Primates

TABLE XXIV

Cumulative Mortality After 138-Mev Proton Irradiation

Dose (rads)	Study	Number of animals	Number dead at 30 days (all groups)	Percent dead at 30 days	Mean survival time of nonsurvivors (days)
930	I - A. Bled[a]	4	14	100	10.4
	B. Nonbled	7	---	---	---
	II[b]	3	---	---	---
780	I - A. Bled	4	11	85	12.4
	B. Nonbled	7	---	---	---
	II	2	---	---	---
650	I - A. Bled	3	11	85	13.7
	B. Nonbled	7	---	---	---
	II	3	---	---	---
500	I - A. Bled	4	5	38	17.
	B. Nonbled	7	---	---	---
	II	2	---	---	---
360	I - A. Bled	4	2	15	20.
	B. Nonbled	7	---	---	---
	II	3	---	---	---
210	I - A. Bled	4	1	10	23.
	B. Nonbled	3	---	---	---
	II	3	---	---	---
105	I - A. Bled	3	0	0	---
	B. Nonbled	1	---	---	---
0	I - A. Bled	4	0	0	---

[a]Bled for hematological studies and serum enzyme assays.

[b]Iron-59 ferrokinetics.

$$LD_{50/30} = 516 + 31 \text{ rads}$$

Relatively more deaths occurred before postirradiation day 12 after 138 - Mev protons as compared with 2-Mev X-rays.

R.B.E. (relative to 2-Mev X-rays) = 1.

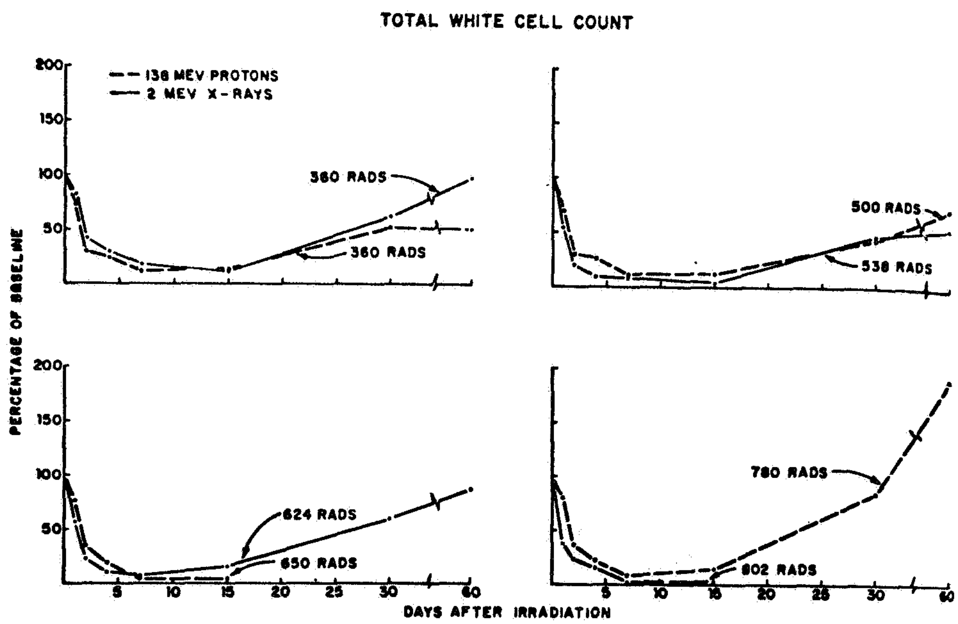
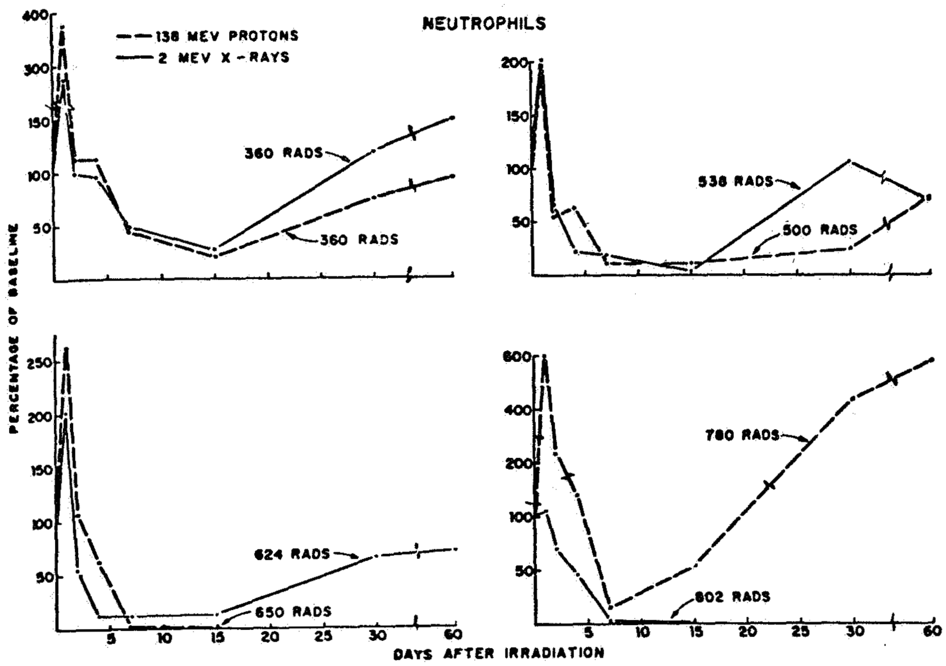


Fig. 12. Total white cell counts after 138-Mev protons and 2-Mev X-rays. There were no survivors past 15 days following 650 rads of 138-Mev protons and 802 rads of 2-Mev X-rays.



Neutrophil counts after 138-Mev protons and 2-Mev X-rays.

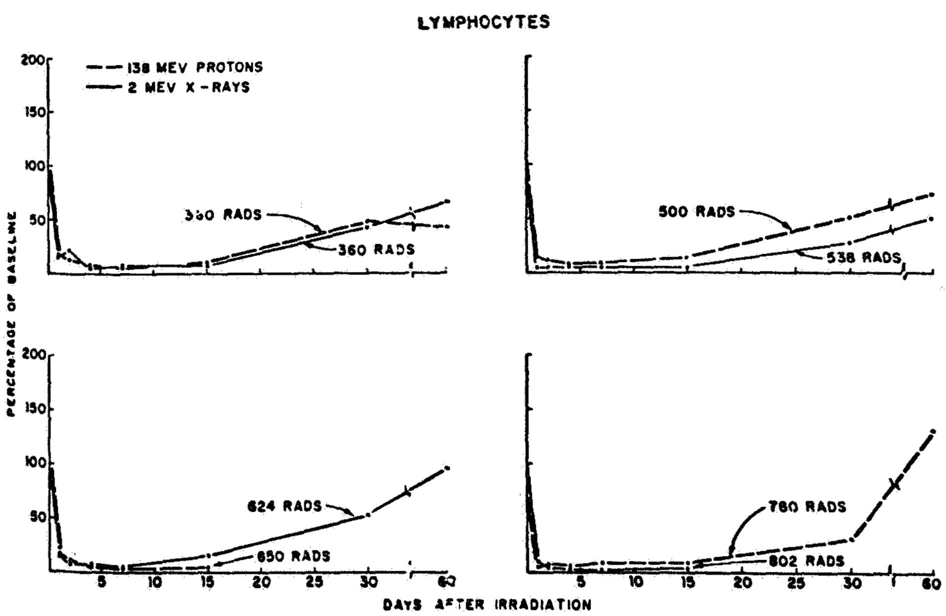


Fig. 13. Lymphocyte counts after 138-Mev protons and 2-Mev X-rays.

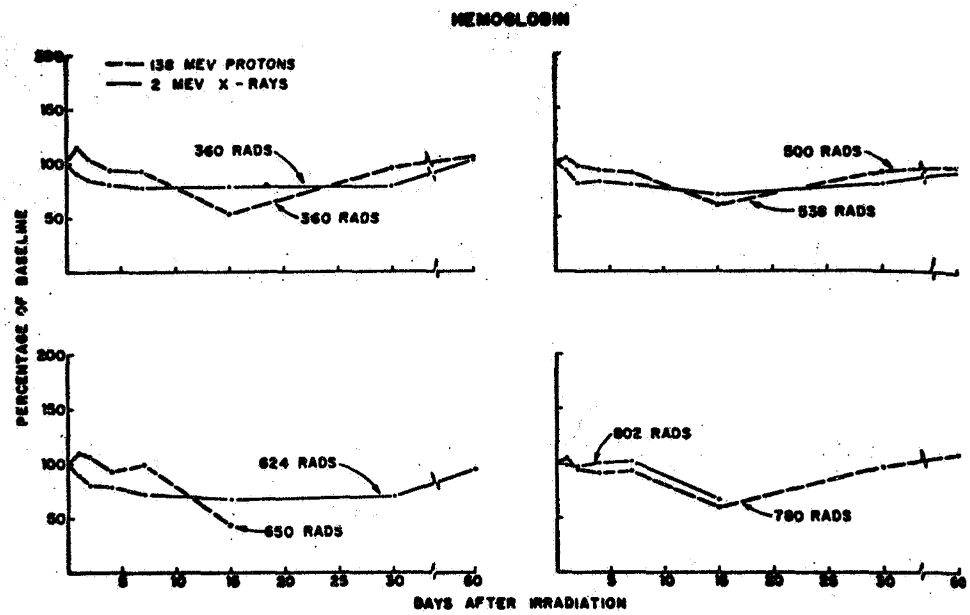


Fig. 14. Hemoglobin concentrations after 138-Mev protons and 2-Mev X-rays.

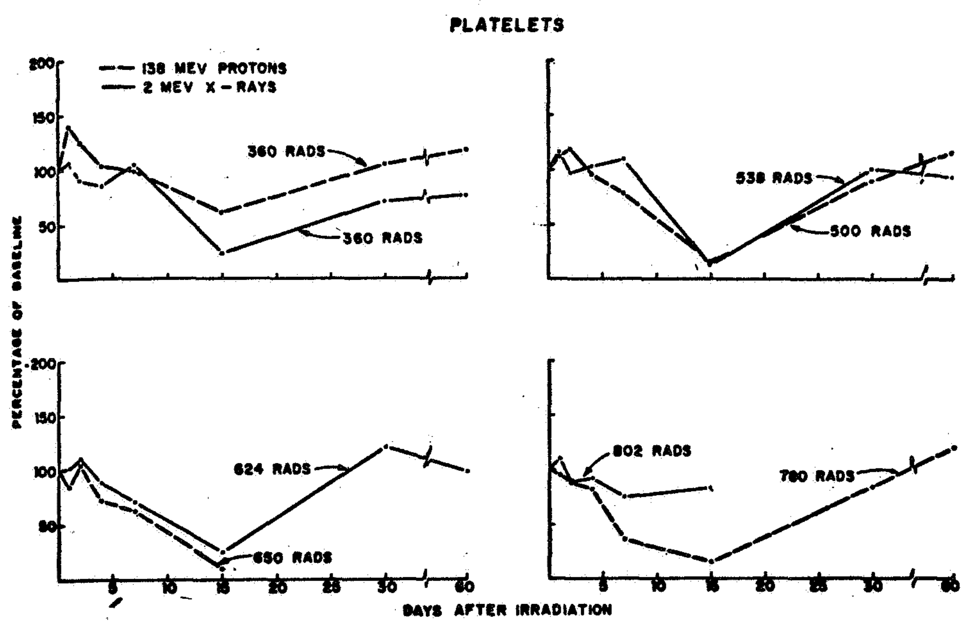


Fig. 15. Platelet counts after 138-Mev protons and 2-Mev X-rays. The somewhat unexpected high platelet count after 802 rads of 2-Mev X-rays occurred in a single animal in terminal status that was severely dehydrated. Our impression is that the dehydration caused hemoconcentration which produced a platelet count which was excessively high.

TABLE XXV

Lactic Dehydrogenase (LDH)[a]

Group	Base line	Days after irradiation								
		1	2	4	7	15	30	60	90
Controls	516 ± 88[b]	760 ± 150[c]	714 ± 103[c]	716 ± 162	410 ± 80	466 ± 157	572 ± 83	885 ± 292[d]	291 ± 46
105 rads	449 ± 130	416 ± 88	612 ± 200	999 ± 101[d,e]	917 ± 37[de]	347 ± 100	585 ± 93	1038 ± 364[c,d]	299 ± 41
210 rads	586 ± 195	1002 ± 252[d]	840 ± 281[d]	994 ± 290[d]	834 ± 249[d]	343 ± 42	646 ± 106	984 ± 92[d]	381 ± 41
360 rads									
A	472 ± 73	2691 ± 2810[d]	1382 ± 665[d]	1122 ± 825[d]	998 ± 410[d]	297	723	875	376
S	459 ± 81	3265 ± 3035	1544 ± 696	1284 ± 899	840	297	723	875	376
NS	510	970	893	633	316	---	---	---	---
500 rads									
A	593 ± 93	966 ± 204[d]	1025 ± 425[d]	1108 ± 364[d]	1008 ± 334[d]	338 ± 32	783	1188	698
S	653	1043	870	1351	1122	350	783	1188	698
NS	533	890	1180	865	895	326	---	---	---
650 rads all NS	633 ± 27	960 ± 119[cd]	1602 ± 610[d]	971 ± 238[d]	574 ± 133	1398 ± 1200[d]	---	---	---
780 rads									
A	692 ± 381[c]	1287 ± 349[d]	1594 ± 630[d]	1371 ± 374[d]	611 ± 222	564	690[f]	2600[f]	440[f]
S[g]	1283	1683	1566	1806	510	553	690	2600	440
NS	494 ± 197	1155 ± 302	1603 ± 728	1226 ± 321	644 ± 214	575[f]	---	---	---
930 rads all NS	446 ± 88	965 ± 190[cd]	1190 ± 270[de]	908 ± 174[cd]	398 ± 44	---	---	---	---
1080 rads all NS	523 ± 40	1063 ± 228[cd]	1255 ± 144[de]	945 ± 165[cd]	680	---	---	---	---

[a]The entries are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups). A = all animals; S = survivors; NS = nonsurvivors. Where no standard deviation is listed, less than three measurements were available. Normal range based on 124 examinations, 460 + 159 units.

[b]Standard deviation.

[c]$p < 0.01$, compared with pre-established normal range.

[d]$p < 0.001$, compared with pre-established normal range.

[e]$p < 0.01$, compared with preirradiation base line.

[f]One animal.

TABLE XXVI

Glutamic Oxalacetic Transaminase (SGOT)[a]

Group	Base line	Days after irradiation 1	2	4	7	15	30	60	90
Controls	25 ± 11[b]	26 ± 2	28 ± 5	27 ± 5	27 ± 1	17 ± 1	24 ± 6	31 ± 7	18 ± 3
105 rads	26 ± 8	23 ± 2	39 ± 11[c]	34 ± 3	29 ± 5	29 ± 5	23 ± 2	33 ± 7	18 ± 2
210 rads	35 ± 5[d]	56 ± 36[c]	46 ± 27[c]	45 ± 25[c]	32 ± 10	35 ± 6[d]	27 ± 16	37 ± 5[d]	19 ± 3
360 rads									
A	28 ± 7	363 ± 545	132 ± 156[c]	57 ± 50[c]	25 ± 14	32	22	32	23
S	29 ± 8	473 ± 592	169 ± 164	70 ± 53	33	32	22	32	23
NS[e]	26	35	21	20	10	--	--	--	--
500 rads									
A	28 ± 3	72 ± 39[c]	39 ± 9[c]	39 ± 24[d]	33 ± 8	35 ± 18	28	41	37
S	25	61	33	54	36	49	28	41	37
NS	30	82	45	24	30	21	--	--	--
650 rads all NS	31 ± 1	37 ± 3[d]	50 ± 12[c,f]	49 ± 33[c]	20 ± 2	119 ± 89[c]	--	--	--
780 rads									
A	32 ± 8[d]	99 ± 52[c,f]	64 ± 26[c]	42 ± 5[d,f]	24 ± 7	70	32[e]	68[e]	34[e]
S[e]	43	135	90	41	17	53	32	68	34
NS	28 ± 4	87 ± 55	55 ± 24	43 ± 6	26 ± 7	87[f]	--	--	--
930 rads all NS	26 ± 6	75 ± 61[c]	76 ± 37[c,f]	35 ± 17	18 ± 4	--	--	--	--
1080 rads all NS	33 ± 5	67 ± 18[c]	59 ± 26[c]	29 ± 10	24	--	--	--	--

[a]The entries are the means and standard deviations, in units per milliliter of serum, of the measurements of the bled animals (except for the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups). A = all animals; S = survivors; NS = nonsurvivors. Where no standard deviation is listed, less than three measurements were available. Normal range based on 202 examinations, 26 ± 7 units.

[b]Standard deviation.

[c]p 0.001, compared with pre-established normal range.

[d]p 0.01, compared with pre-established normal range.

[e] One animal.

[f]p 0.01, compared with preirradiation base line.

TABLE XXVII

FE^{59} Ferrokinetics After 138-Mev Proton Irradiation[a]

Dose (rads)	Plasma disappearance half-time (min)		8-Day RBC uptake (% of injected dose)		10-Day RBC uptake (% of injected dose)	
	Before irradiation	After irradiation	Before irradiation	After irradiation	Before irradiation	After irradiation
210	70 ± 12	263 ± 62	99 ± 1	6.3 ± .2	95 ± 6	9.5 ± 3.4
360	75 ± 8	259 ± 25	85 ± 1	1.4 ± 1.2	87 ± 4	2.4 ± 1.2
500	69	223	93	0.3 + 0.2	93	0
650	48 ± 7	237 ± 8	86 ± 15	0.67 ± 0.6	92 ± 8	0
780	78	265	86	0	89	0
930	62 ± 17	230 ± 28	97 ± 5	b	97 ± 4	b

[a]The entries are the averages and standard deviations of the measurements from either 2 or 3 animals at each dose level; where no standard deviation is listed, less than thr ee measurements were available.

[b]No sample taken.

Doses as low as 210 rad produce severe depression of bone marrow function.

In animals irradiated to levels >780 rads, malaise and depression of appetite was noted during the first few days. After the third day, severe G-I injury was observed accompanied by diarrhea. Stools were bloody and contained much mucous.

At the end of 12 days, the survivors showed hemorrhagic diathesis. Animals irradiated in the 360 - 650 rads range began to develop symptoms of G-I injury. Other symptoms appearing at this time were: hemopotysis, massive epistaxis, and extensive gingival hemotomata.

At necropsy, it was found that in those animals dying early, there was pronounced changes in the G-I tract with widespread destruction of the mucosa and many localized hemorrhages. Large clots of blood and tarry stool were often found in the lumen of the colen. Extensive hemorrhages were often found in the colen. In those animals surviving longer, the G-I epithelial damage was less. However, aplastic bone marrow was observed whose only residual elements were occasional reticular cells.

TABLE XXVIII

RBE As A Function Of Postirradiation Time

Days after irradiation	86 rads/min: LD_{50} on day, 138-Mev protons	86 rads/min: LD_{50} on day, Co^{60}	86 rads/min: RBE	256 rads/min: LD_{50} on day, 138-Mev protons	256 rads/min: LD_{50} on day, Co^{60}	256 rads/min: RBE	550 rads/min: LD_{50} on day, 138-Mev protons	550 rads/min: LD_{50} on day, Co^{60}	550 rads/min: RBE
6	1019	1202	1.18	1031	1088	1.06	1016	1285	1.26
8	916	1072	1.17	985	1050	1.07	951	1134	1.19
10	798	931	1.17	806	936	1.15	837	951	1.14
12	771	846	1.10	793	768	0.97	800	817	1.02
14	743	827	1.11	759	760	1.00	767	799	1.04
16	743	796	1.08	759	760	1.00	759	769	1.01
18	743	778	1.05	752	730	0.97	759	769	1.01
20	724	775	1.07	743	724	0.96	730	769	1.05
30	724	776	1.07	743	724	0.97	724	765	1.06

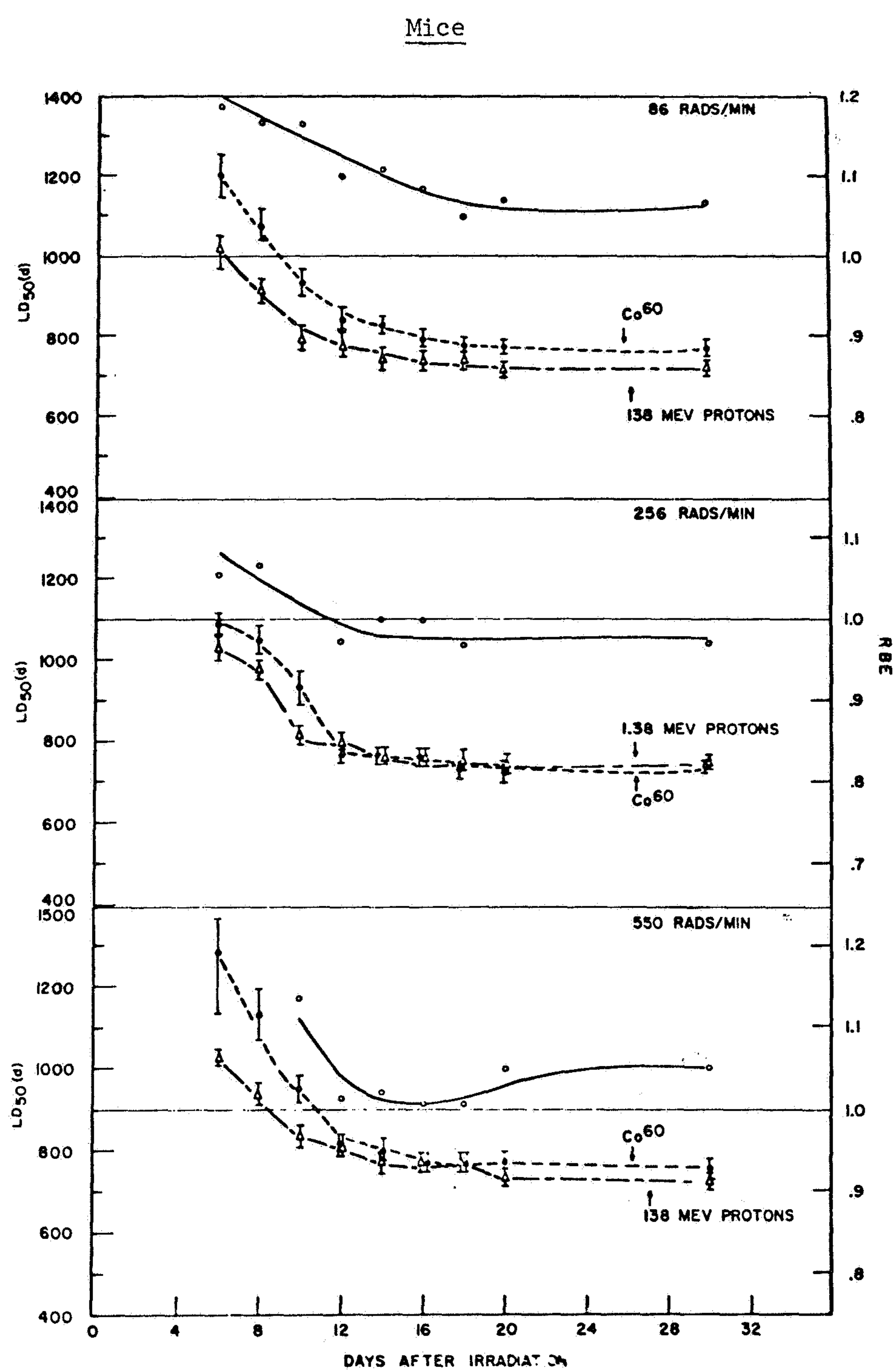


Figure 16. LD_{50}'s and RBE's after 138-MeV protons and Co^{60} γ-radiation delivered at 86 rads/min, 256 rads/min, and 550 rads/min. The open circles are the RBE's taken from the data given in Table II. Only those RBE's derived from parallel curves were plotted (see text). The triangles and the closed circles are the LD_{50}'s; the vertical bars are the standard errors.

157 Mev Protons[12.]

Mice

R.B.E. = 0.77 (compared to 250 Kvp X-rays). This value was obtained using a dose rate of 250 rad/min. and based on the LD_{50}.

185 Mev Protons[13.]

TABLE XXIX

Semi-quantitative comparison of the ability of protons and roentgen rays to cause microscopic regressive changes in Vx2 carcinoma. Each marking gives the results of observation of one tumour.

Experimental group	Dose	Time (in days) after irradiation					
		0.5	1	2	4	6	8
Tumours irradiated with protons	500 rad	c c	c	+ + c	+ +	++ +	++ ++
	800 rad	c	+	c c	+ +	++ +	+ +
	1 000 rad	c	+ c	+	++ +	++ ++	++
	1 200 rad	c c	c c	c	++	++ ++	++ + +
	1 500 rad	c c	c +	+	++ ++	++ ++ +++	++ + ++
	2 000 rad	c	c c	+ c +	++ + ++ +	++ ++ ++	++ +++ +++ +++
	3 000 rad	+ c	+ +	++	+++ ++	+++ ++	+++
	4 000 rad	c	c	++	+ +++	++ +++	+++ +++
Tumours irradiated with roentgen rays	500 r	c	+ +	+ c	+	+	+ +

(continued....)

TABLE XXIX (continued,,,,)

Experimental group	Dose	Time (in days) after irradiation					
		0.5	1	2	4	6	8
Tumours irradiated with roentgen rays	800 r	c +	+ +	+ + +	+	+ + ++	c ++
	1 000 r	c	c	+	++	c +	+
	1 200 r	c c	c c	c +	+ +	+ +++	+ c ++
	1 500 r	c	c	++	++ +	++ +++	+ +++
	2 000 r	c	c c	++	+++	++ ++	+++ +++

Grade c: Apparently viable carcinoma without regressive changes in the tumour cells.

Grade +: Apparently viable carcinoma with slight to moderate regressive changes in the tumour cells, mainly vacuolization of the cytoplasm, some abnormal mitoses and a few multinucleated giant tumour cells. Most of the carcinomatous tissue was, however, morphologically intact.

Grade ++: Regressive changes in the tumour cells were marked. Most of the cancer cells were swollen and vacuolated with distorted, intensely hyperchromatic nuclei. Multinucleated giant cells of grotesque appearance were numerous. The carcinoma was not split up by connective tissue.

Grade +++: Only sparse remnants of the carcinoma seen, small nests of tumour cells in newly formed cellular connective tissue, were found. The cancer cells showed marked regressive changes similar to those in grade ++.

200 Mev Protons [14].

Primates

The few instances of vomiting prior to and during irradiation is attributed to the anesthetic.

> 675 rads produced diarrhea in approximately 50% of the animals. This occurred 4 - 6 days postirradiation and continued until death.

Minimal lethal dose = 500 rads (air).

R.B.E. = 0.9 (compared to CO^{60} in air at midline).

Minimal lethal dose = 585 rads (tissue).

R.B.E. = 0.5 (compared to CO^{60} in tissue at midline).

Survival times 10 to 20 days.

Hypoplasia of bone marrow and arrested spermatogenesis were present in proportion to the dose delivered. These symptoms showed recovery in survivors.

Brain Damage

(a) Short survivors (10 - 19 days).

Abnormal forms seen in striatum, thalmus, cerebellar cortex, and inferior olivary nucleus. Microglial nodules were observed in the immediate vicinity of vessels, particularly in the cerebellar cortex and basal ganglia. No severe cell loss or vessel abnormality was observed.

(b) Long-term survivors (186 - 237 days).

The glial changes were similar to those observed in the short-term survivors; however, a great number of hypertrophic oligodendroglia were observed to be hypertrophic in both grey and white matter.

In all cases, the microglia cells were observed to have the greatest radiation sensitivity. No dose or time effects seemed evident.

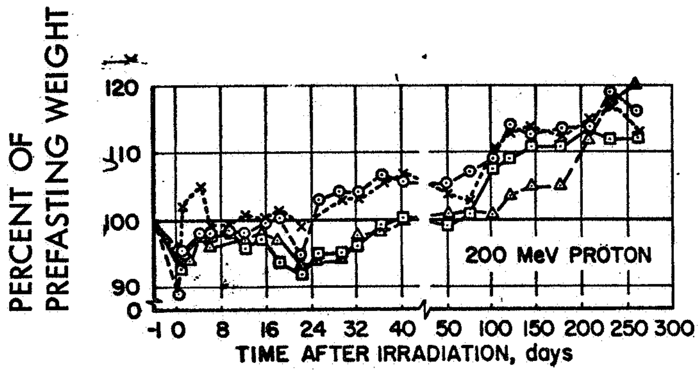
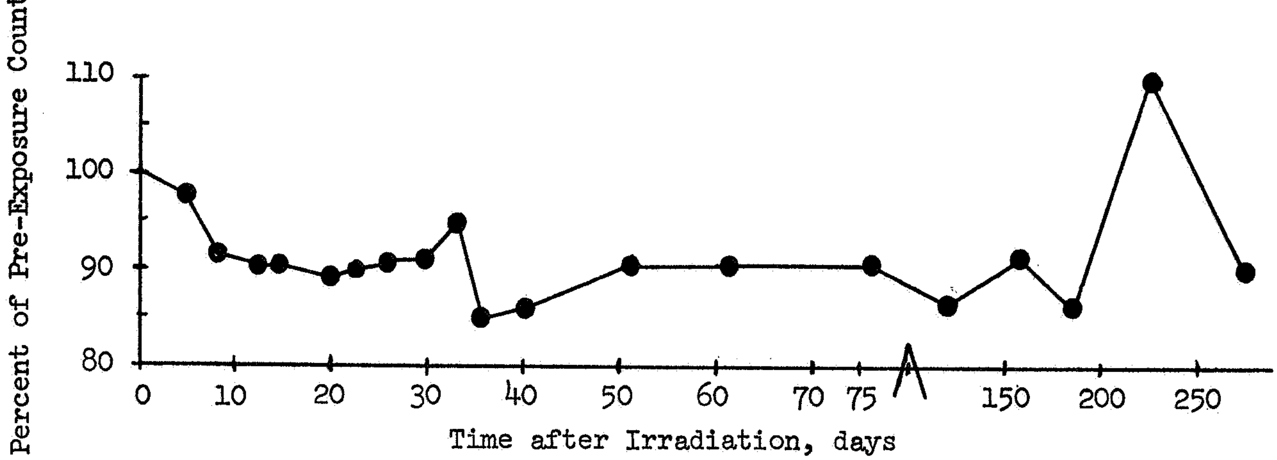


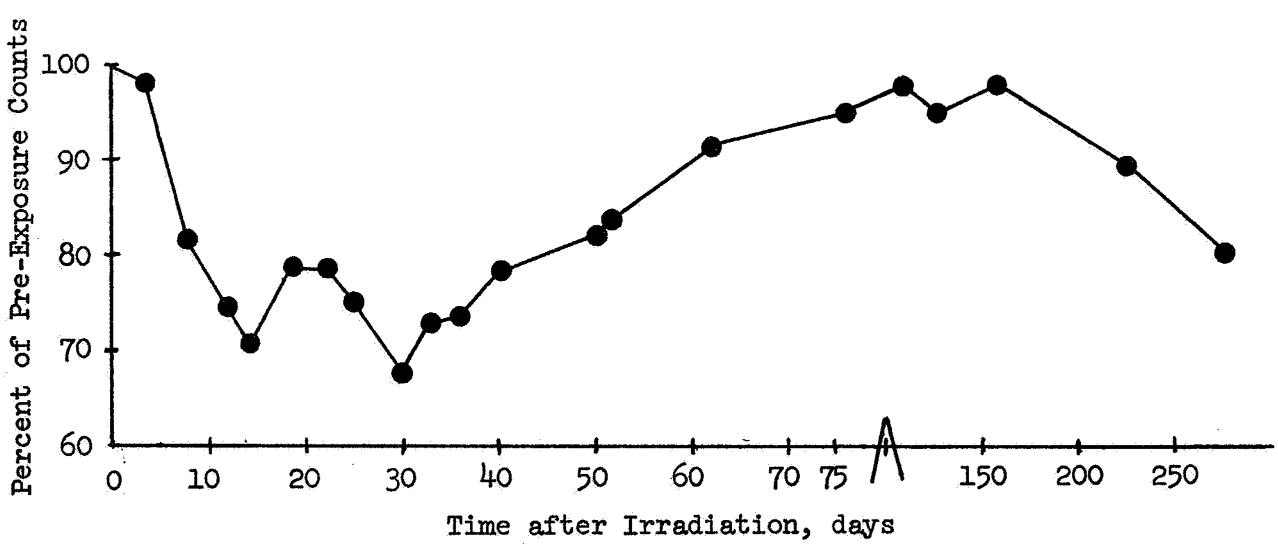
FIGURE 17

MTD, rads	Mad, rads
x- - - - -x 0	0
o———o 235	175 - 200
△———△ 410	300 - 350
□———□ 585	425 - 500

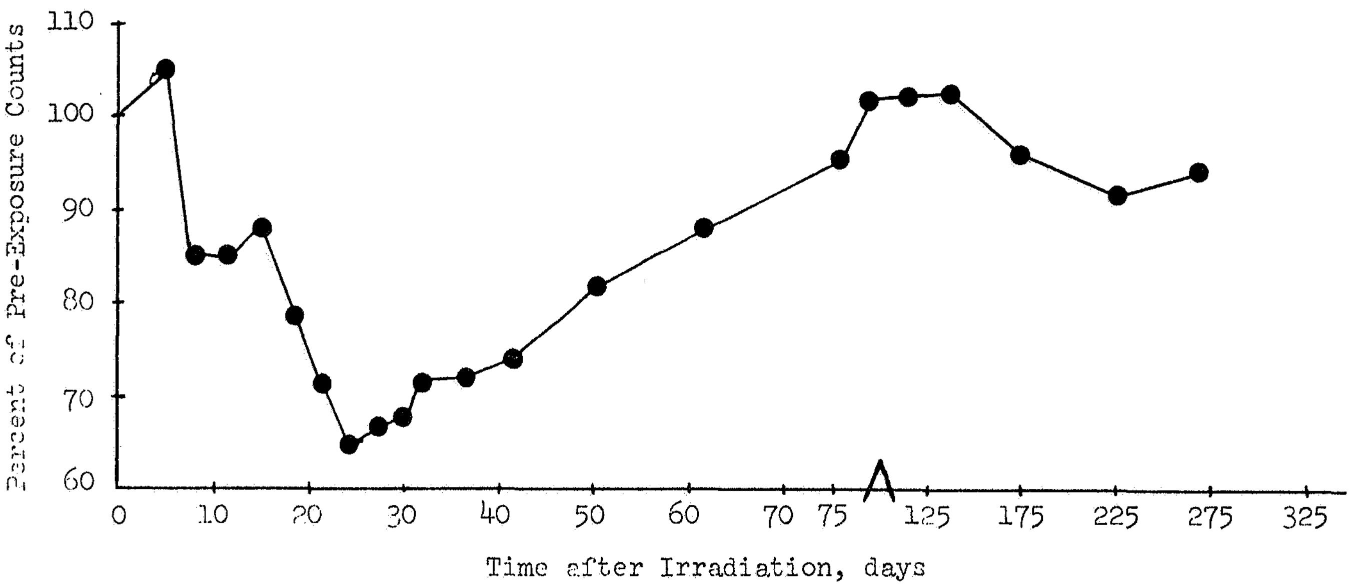
Figure 18. RBC Response As A Function of Time After Irradiation



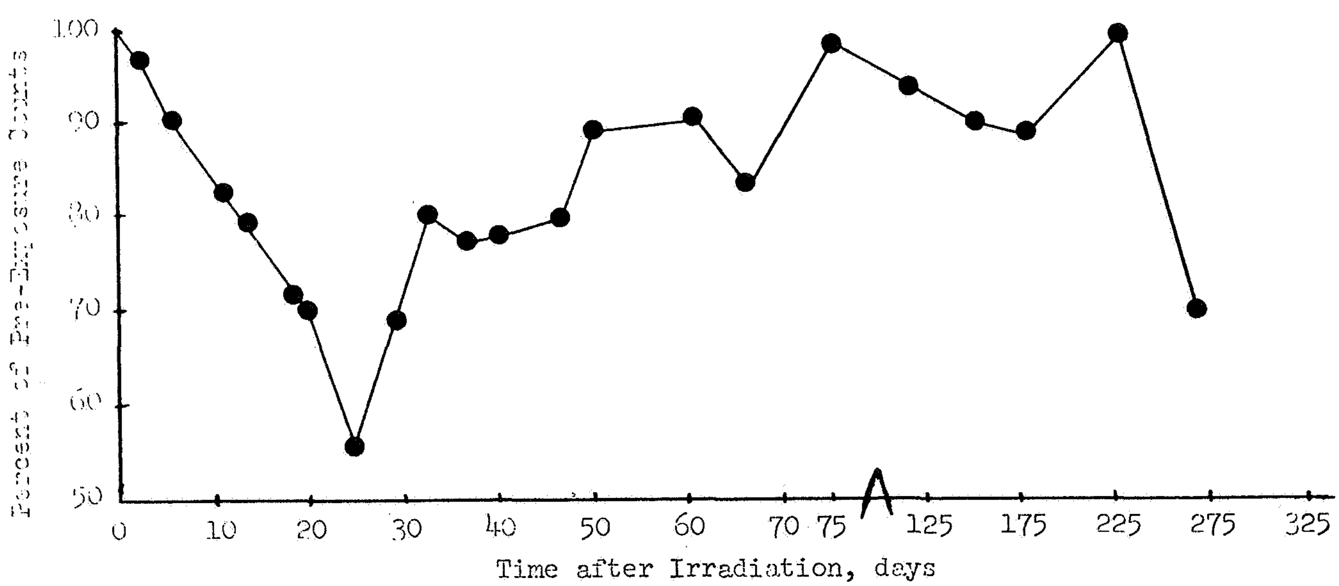
a. Controls



b. 175-200 rads MAD; 235 rads MTD



c. 300-350 rads MAD; 410 rads MTD



d. 425 - 500 rads MAD; 585 rads MTD

Figure 18. (Continued)

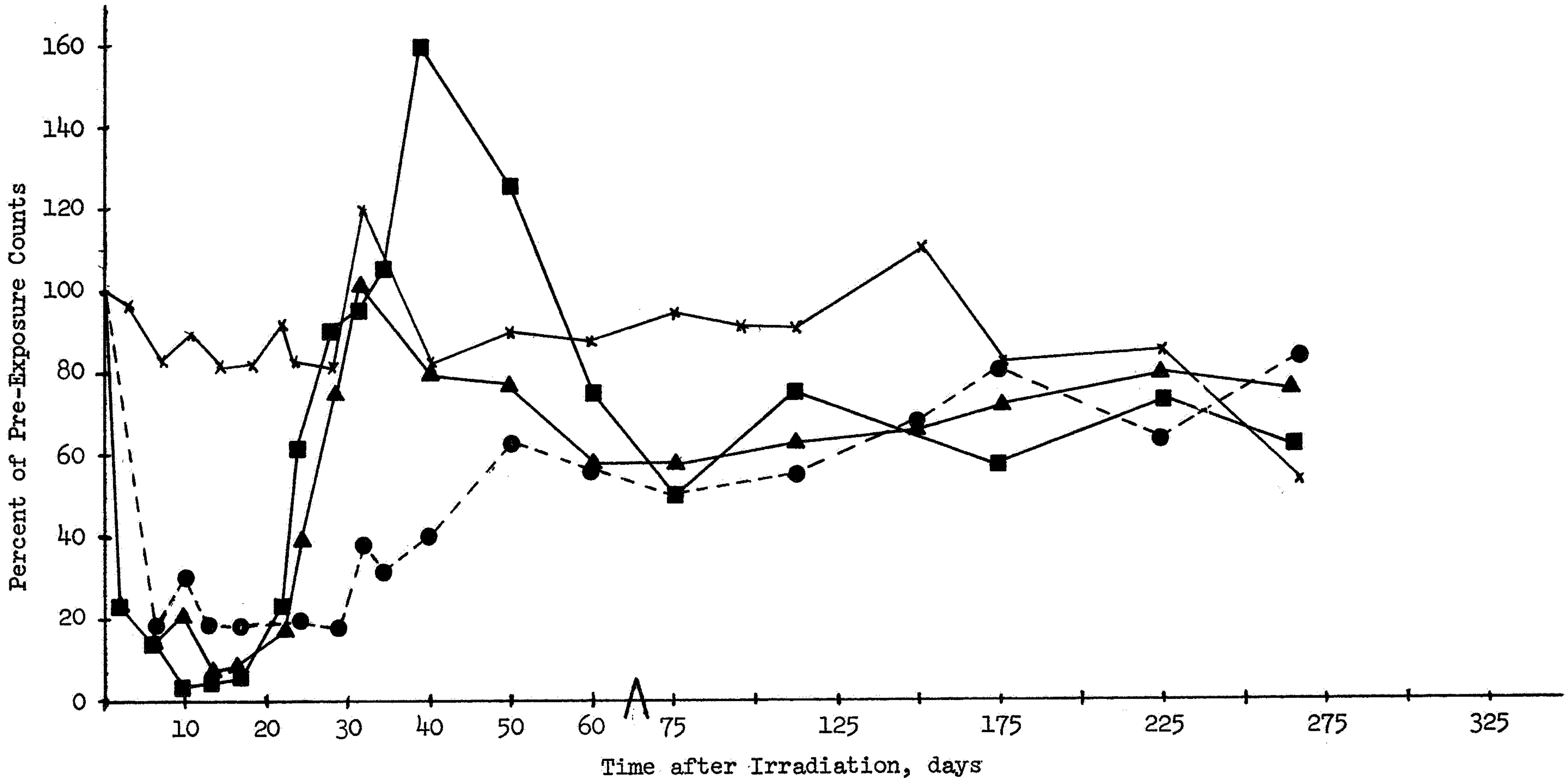


Figure 19. WBC Response As A Function of Time After Irradiation

MAD (rads)	MTD (rads)	
0	0	×———×
175 - 200	235	●- - - - -●
300 - 350	410	▲———▲
425 - 500	585	■———■

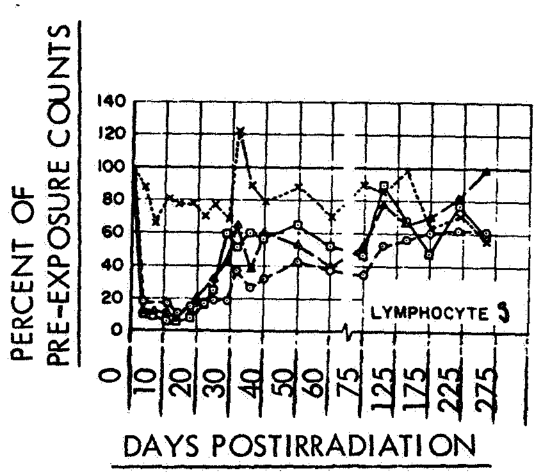


FIG. 20.

	MAD rads	MTD rads
X- - - - - -X	0	0
O— — —O	175 - 200	235
Δ—— —Δ	300 - 350	410
□———□	425 - 500	585

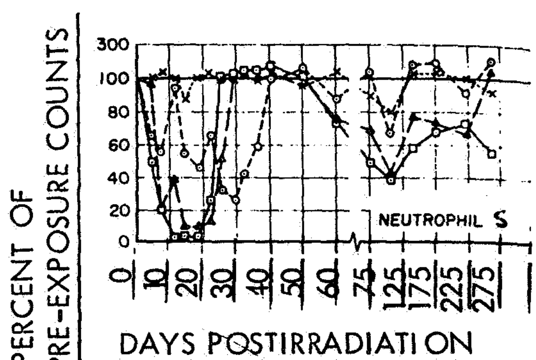


FIG. 21.

	MAD rads	MTD rads
X- - - - -X	0	0
O- - - -O	175 - 200	235
Δ— —Δ	300 - 350	410
□———□	425 - 500	585

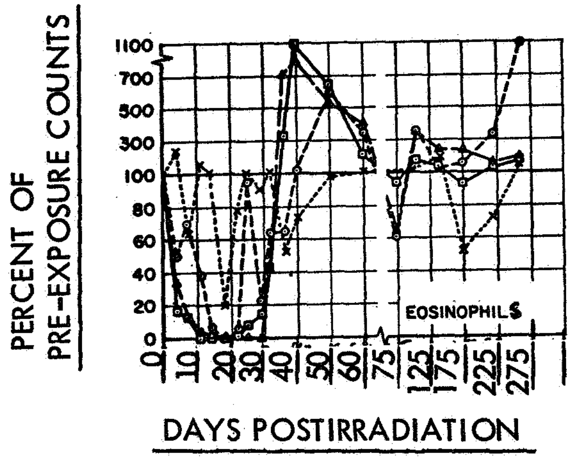


FIG. 22.

	MAD rads	MTD rads
X-----X	0	0
o- - - -o	175-200	235
Δ— —Δ	300-350	410
□———□	425-500	585

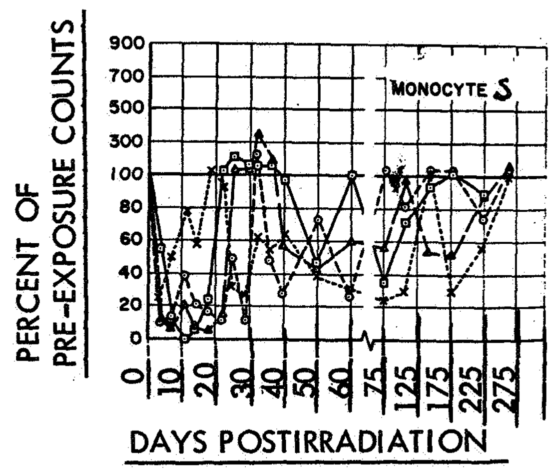


FIG. 23.

	MAD rads	MTD rads
X- - - -X	0	0
o- - - -o	175-200	235
Δ— —Δ	300-350	410
□———□	425-500	585

TABLE XXX

Relationship Between Radiation Dose and Maximum Depression of WBC

Midpoint dose (rads)		Maximum WBC depression (%)	
Air	Absorbed	Mean	(Incidence)
		^{60}CO gammas	
0	0	17	(16, 18)
175	120	68	(68, 68)
300	210	83	(79, 87, 84)
425	300	90	(90, 93, 86)
		200-Mev protons	
0	0	23	(14, 15, 40)
200	235	82	(79, 84, 80, 87)
350	410	92	(95, 93, 86, 93)
500	585	95	(95, 92, 97, 95)

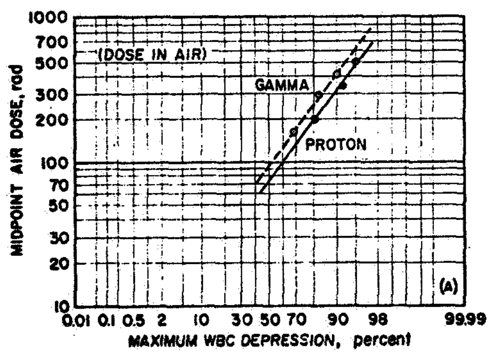


FIG. 24

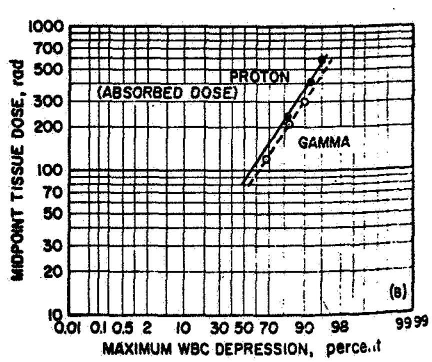


FIG. 25

250 Mev - Protons [5.]

Primates

In the 200 - 400 rad group, dermal petechiae and gingival hemorrhages were observed. In the 400 rad group, diarrhea was evident in 1 week. This was short lived, terminating in about a week. In those groups receiving $>$200 rads, dermal petechiae and gingival hemorrhages were seen after the cessation of diarrhea. Animals surviving (one death at 300 rad level) were clear of these symptoms after the 4th week.

Total white cell count dropped a factor of 2 after the 15th day in the 50 rad group (to low normal). After 100 - 200 rads, the count dropped to 3×10^3 - 4×10^3 cells/mm^3 in 7 - 15 days. 400 rads produced prominent leukopenia (2×10^3 cells/mm^3) starting after the 4th day postirradiation, becoming progressively more severe through 15 days. After 30 days, the count returned to the low normal range.

Lymphocytes were depressed after doses as low as 25 rads in as short a time as 1 day. This was followed (2nd day) by a definite lymphopenia which persisted for approximately 15 days. Moderate recovery was evident after 30 days.

50 - 100 rads did not disturb the platelet count. 200 - 400 rads produced a drop in the platelet count after 15 days. Recovery after 30 days.

Neutrophils rose for the first few days and then declined in the 7 - 15 day postirradiation period.

Dose levels of $<$200 rads produced no significant depression of the hemoglobin or hematocrit levels. 300 - 400 rads had a minimal effect which showed recovery by 30 days.

270-Mev - Protons 6.

Dogs

Whole Body Exposure

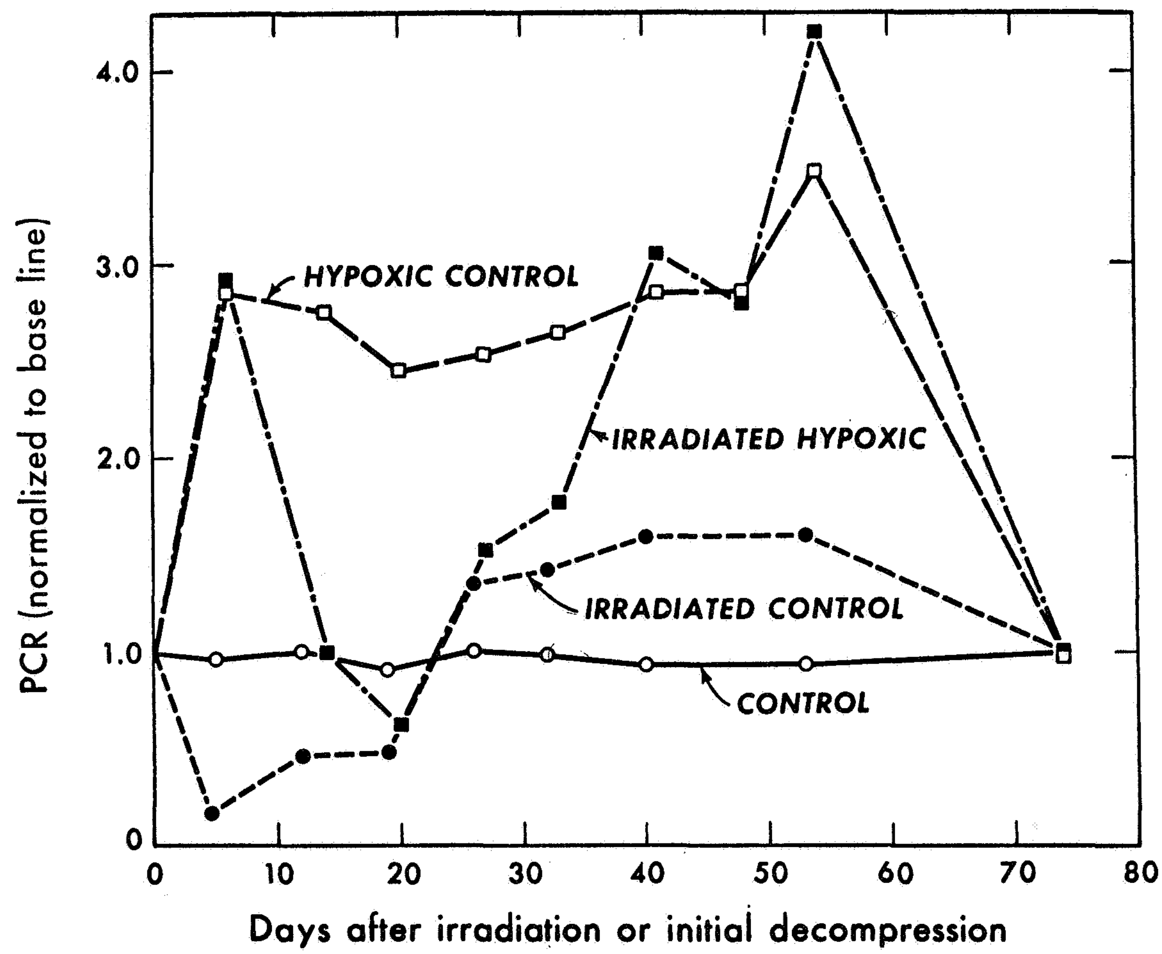


FIG. 26. Plasma clearance rate of beagles following radiation (200-rad) or hypoxia (18 000-ft altitude simulation) or both.

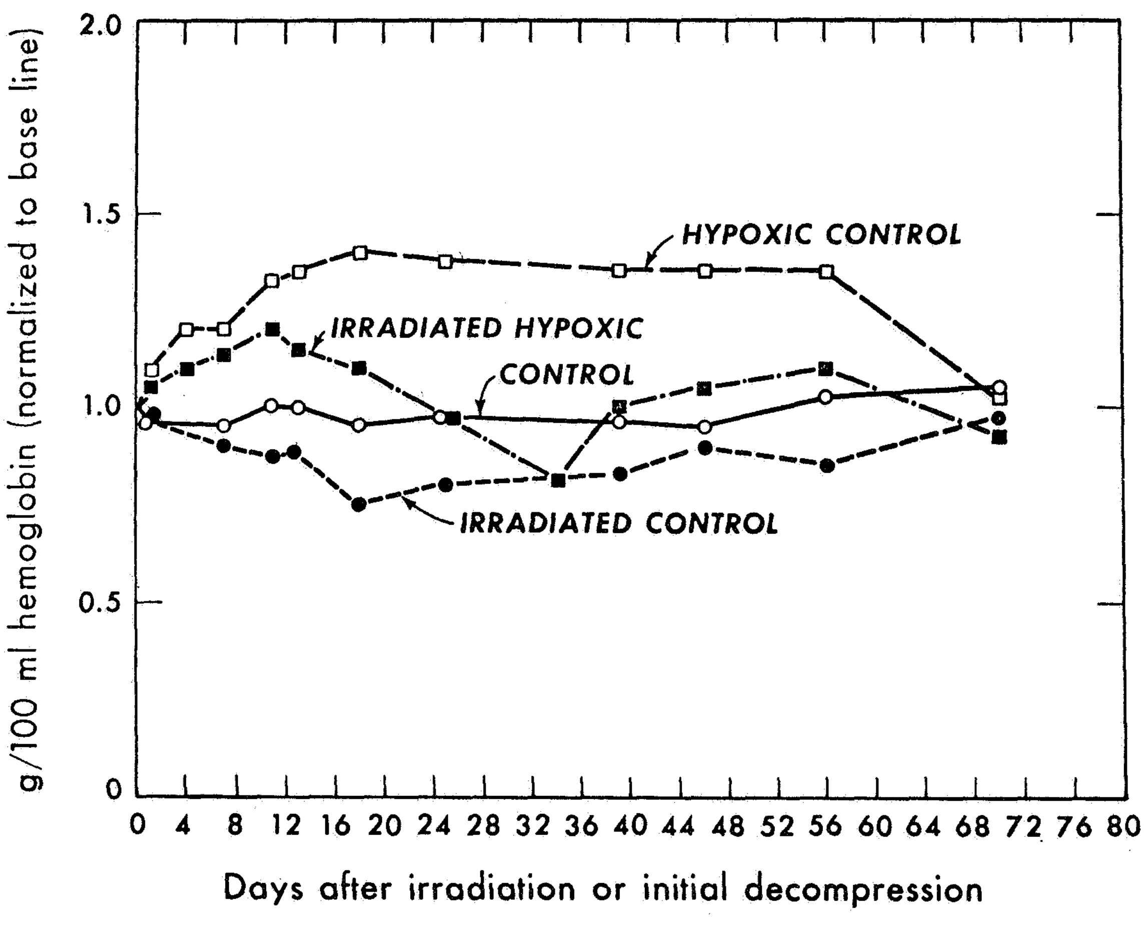


FIG. 27. Hemoglobin response of beagles following radiation (200 rad) or hypoxia (18 000-ft altitude simulation) or both.

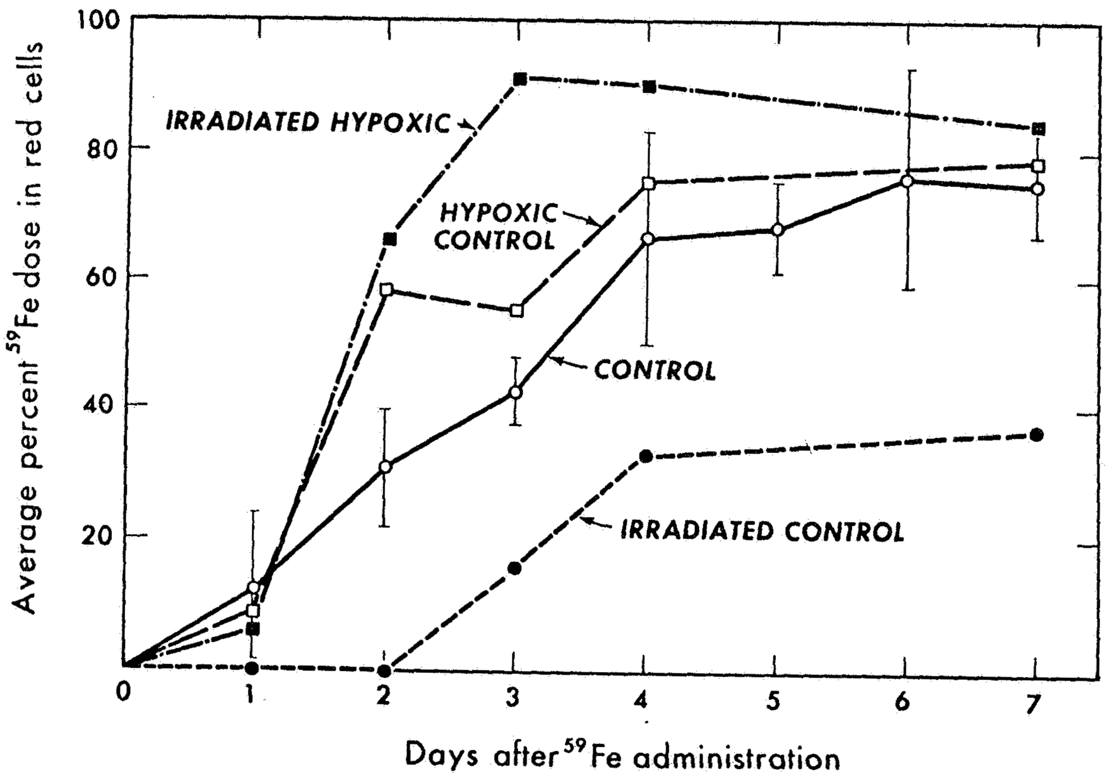


FIG. 28. Erythrocyte radioiron uptake response of beagles at 7 days postirradiation (200 rad).

400 Mev - Protons [15].

Primates

TABLE XXXI

Mortality After 400-Mev Proton Irradiation

Dose (rads)	Study	Number of animals	Number dead at 30 days (all groups)	Dead at 30 days (%)	Mean survival time of nonsurvivors (days)
800	I - A. Bled	4			---
	B. Nonbled	10	12	85.7	14
600	I - A. Bled	4	8	57	15.4
	B. Nonbled	10			---
400	I -A. Bled	4			---
	B. Nonbled	10	1	6	23
	II - (b)	3			---
200	I - A. Bled	4	0	0	---
	B. Nonbled	10			---
	II -	3			---
100	I - A. Bled	4			---
	B. Nonbled	10	0	0	---
	II -	3			---
50	I - A. Bled	4	0	0	---
	II -	3	0	0	---
25	II -	3			---

[a] Bled for hematological studies and serum enzyme assays.

[b] Fe^{59} ferrokinetics.

$$LD_{50/30} = 585 \pm 33 \text{ rads}$$

Greater than 800 rads produced severe G-I symptoms between the 3rd and 10th postirradiation days. These also appeared in the groups irradiated to the 400 - 600 rad levels but were less severe. Animals that survivied 10 days showed an abatement of these symptoms on the 12th day but exhibited hemorrhagic diathesis. Extensive dermal petechiae, hemorrhages, gingival hematomata then appeared.

TABLE XXXII

Total White Cell Count[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	12,138	14,433	9,600	5,933	9,116	7,766	8,350	10,850	9,338
50 rads	11,612	6,475	6,650	7,462	7,725	5,600	7,888	9,250	9,700
100 rads	10,588	4,500	2,787	3,800	3,900	5,075	4,925	7,663	9,525
200 rads	10,612	5,450	3,188	3,112	3,750	3,075	4,450	9,688	11,063
400 rads	9,725	4,250	2,212	2,125	1,412	975	5,613	5,625	9,975
600 rads									
A	9,850	5,488	1,525	2,275	2,150	750	12,666	14,066	10,617
S	5,513	5,733	1,433	2,033	2,550	933	12,666	14,066	10,617
NS[b]	12,600	4,750	1,800	3,000	950	200	---	---	---
800 rads									
A	11,550	7,188	4,050	2,437	1,425	400	4,500	11,300	6,500
S[b]	14,300	9,700	7,500	2,700	1,650	450	4,500	11,300	6,500
NS	10,633	6,350	2,900	2,350	1,350	350[b]	---	---	---
100 rads									
all NS	10,500	8,288	3,137	1,725	2,900	---	---	---	---

[a]The entries are the average counts, per cubic millimeter, of 4 bled animals (expect the survivor and nonsurvivor subdivisions of the 600-rad and 800-rad groups). A = all animals; S = survivors; NS - nonsurvivors.

[b]One animal.

TABLE XXXIII

Lymphocytes[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	8,168	6,117	6,300	2,838	6,264	5,033	6,153	9,017	7,289
50 rads	8,450	3,130	3,090	3,214	5,382	3,364	5,693	7,496	7,785
100 rads	6,412	2,714	1,579	1,717	2,027	3,639	2,399	4,051	6,951
200 rads	5,025	1,686	999	779	1,698	2,407	3,189	5,963	6,929
400 rads	6,880	1,072	610	438	710	707	4,213	3,013	6,636
600 rads									
A	6,219	1,176	422	852	1,254	663	8,073	8,812	8,052
S	5,268	1,283	383	735	1,520	840	8,073	8,812	8,052
NS[b]	9,072	855	540	1,200	456	130	---	---	---
800 rads									
A	8,901	1,534	870	609	977	264	2,475	6,554	2,665
S[b]	10,868	2,716	1,275	432	858	275	2,475	6,554	2,665
NS	8,246	1,140	735	668	1,017	252[b]	---	---	---
1000 rads									
All NS	7,206	1,479	473	506	1,418	---	---	---	---

TABLE XXXIV

Neutrophils[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	3,679	8,199	3,193	3,008	2,766	2,504	2,014	1,550	1,432
50 rads	2,957	3,169	3,483	4,155	2,294	2,140	2,084	1,683	1,433
100 rads	3,780	1,700	1,101	1,999	1,815	1,330	1,958	3,523	2,139
200 rads	5,408	3,627	2,048	2,314	2,028	650	936	3,515	3,248
400 rads	2,700	3,131	1,527	1,669	696	242	1,251	2,460	3,060
600 rads									
A	3,328	4,255	1,052	1,372	891	82	3,979	4,000	1,790
S	3,346	4,375	1,019	1,249	1,030	86	3,979	4,000	1,790
NS[b]	3,276	3,895	1,152	1,740	475	70	---	---	---
800 rads									
A	2,184	5,592	3,123	1,813	432	127	1,845	4,294	3,445
S[b]	2,717	6,984	6,225	2,268	729	162	1,845	4,294	3,445
NS	2,007	5,128	2,089	1,661	333	91[b]	---	---	---
1000 raas									
All NS	2,911	6,749	2,626	1,202	563	---	---	---	---

[a]The entries are the average counts (cells per cubic millimeter, X 10^3) of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600-rad and 800-rad groups). A=all animals; S=survivors; NS-nonsurvivors.

[b]One animal.

TABLE XXXV

Platelets[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	246	305	297	287	258	262	286	272	331
50 rads	370	270	203	243	279	263	256	261	321
100 rads	372	350	326	372	310	212	249	249	302
200 rads	353	308	265	366	340	151	304	231	260
400 rads	402	322	282	327	248	91	232	238	285
600 rads									
A	340	351	332	317	181	81	186	286	305
S	348	336	326	328	171	105	186	286	305
NS[b]	316	394	351	286	212	9	---	---	---
800 rads									
A	356	290	312	325	149	8	138	274	294
S[b]	334	269	278	321	139	4	---	---	---
NS[b]	363	297	324	326	152	12[b]	---	---	---
1000 rads									
all NS	327	329	377	328	142	---	---	---	---

[a]The entries are the average counts (cells per cubic millimeter, X 10^3) of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600-rad and 800-rad groups). A = all animals; S = survivors; NS = nonsurvivors.

[b]One animal.

TABLE XXXVI

Hemoglobin and Hematocrit Levels[a]

Group	Baseline		Days after Irradiation															
			1		2		4		7		15		30		60		90	
	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct
Controls	11.2	37	12.6	40	11.6	37	10.9	35	10.5	33	10.0	32	10.1	33	11.5	36	11.6	37
50 rads	12.4	40	11.7	37	12.6	38	12.3	39	10.6	34	10.0	33	12.6	40	12.2	38	12.6	39
100 rads	12.4	40	12.4	40	11.2	36	11.0	35	10.8	34	10.3	33	11.4	36	12.2	38	12.5	40
200 rads	12.5	42	11.9	38	11.1	36	10.8	35	10.5	34	9.9	32	10.3	33	12.3	39	12.0	39
400 rads	13.3	42	12.4	40	12.1	39	11.4	37	10.7	34	9.1	30	9.6	31	13.1	42	13.0	41
600 rads																		
A	11.7	38	12.0	38	11.5	37	10.9	36	10.0	34	6.4	22	9.0	30	11.5	38	11.9	38
S	11.2	36	11.9	38	11.2	36	10.8	36	10.2	34	7.2	25	9.0	30	11.5	38	11.9	38
NS[b]	13.1	41	12.4	38	12.2	39	11.1	35	9.7	33	4.0	15	---	--	---	---	---	---
800 rads																		
A	12.3	39	12.0	39	11.6	37	11.6	37	11.4	36	6.4	22	9.2	31	11.4	35	14.5	46
S[b]	14.1	43	12.4	40	11.5	35	10.8	35	10.6	34	7.7	27	9.2	31	11.4	35	14.5	46
NS	11.6	38	11.8	38	11.7	38	11.8	37	11.7	36	5.0[b]	18[b]	---	--	----	---	---	---
1000 rads																		
all NS	12.1	39	11.4	37	11.4	38	11.4	36	11.8	34	---	--	---	--	---	---	---	---

[a] The entries are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600-rad and 800-rad groups). A = all animals; S = survivors; NS = nonsurvivors. Where no standard deviation is listed, less than three measurements were available. Normal range based on 198 normal examinations, 31 ± 6 units.

[b] Standard deviation.

[c] $p < 0.01$ compared with pre-established normal range.

[d] $p < 0.001$ compared with pre-established normal range.

[e] $p < 0.01$ compared with preirradiation baseline.

[f] One animal.

TABLE XXXVII

Lactic Dehydrogenase (LDH)[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	518±33	413±41	476±56	430±81	595±137	497±55	732±200[c]	413±119	500±91
50 rads	580±34	643±290	419±27	588±151	807±129[g]	823±150[g]	417±106	385±45	466±51
100 rads	566±78	585±112	439±174	497±56	577±75	558±85	465±46	380±110	480±193
200 rads	605±113	896±163[d]	825±398[d]	676±154	598±142	400±86	542±132	469±63	424±64
400 rads	586±110	1003±326[d]	744±223[c]	715±187	509±52	417±107	642±180	355±92	400±83
600 rads									
A	593±82	1355±212[d,e]	1096±410[d]	759±308[c]	547±91	496±70	644±112	458±39	450±138
S	610±87	1443±174	1135±460	817±333	569±96	462±44	644±112	458±39	450±138
NS[f]	543	1090	977	583	480	600	---	---	---
800 rads									
A	546±119	1293±349[d,g]	1210±163[d,e]	905±284[d]	483±140	755	426	346	646
S[f]	556	1790	1376	763	396	430	426	346	646
NS	543±118	1128±107	1154±116	953±311	512±152	1080[f]	---	---	---
1000 rads									
all NS	528±89	1323±251[d,e]	1350±270[d,e]	1164±316[d,g]	611	---	---	---	---

[a] The entries are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600-rad and 800-rad groups). A = all animals; S = survivors; NS = nonsurvivors. Where no standard deviation is listed, less than three measurements were available. Normal range based on 198 normal examinations, 31 ± 6 units.

[b] Standard deviation.

[c] $p < 0.01$ compared with pre-established normal range.

[d] $p < 0.001$ compared with pre-established normal range.

[e] $p < 0.01$ compared with preirradiation baseline.

[f] One animal.

TABLE XXXVIII

Glutamic Oxalacetic Transaminase (SGOT)[a]

Group	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	33 ± 3[b]	27 ± 1	42 ± 19	36 ± 1	31 ± 6	28 ± 5	28 ± 4	28 ± 5	26 ± 4
50 rads	30 ± 7	34 ± 5	26 ± 5	34 ± 6	33 ± 7	30 ± 3	22 ± 2	22 ± 2	25 ± 3
100 rads	31 ± 2	32 ± 6	30 ± 5	34 ± 5	39 ± 12[c]	27 ± 1	23 ± 3	24 ± 4	28 ± 10
200 rads	29 ± 2	45 ± 16[d]	46 ± 21[d]	40 ± 7[c]	33 ± 6	24 ± 3	23 ± 6	25 ± 6	22 ± 3
400 rads	35 ± 8	68 ± 62[d]	42 ± 30[c]	33 ± 10	34 ± 5	26 ± 3	24 ± 2	23 ± 3	24 ± 2
600 rads									
A	28 ± 8	65 ± 17[e]	32 ± 8	29 ± 7	29 ± 9	28 ± 14	24 ± 6	30 ± 6	26 ± 2
S	27 ± 8	71 ± 16	34 ± 9	30 ± 7	30 ± 10	20 ± 5	24 ± 6	30 ± 6	26 ± 2
NS[f]	32	49	27	26	25	50	---	---	---
800 rads									
A	30 ± 2	98 ± 65[d]	80 ± 44	64 ± 44	24 ± 5	45	22	22	26
S[f]	28	211	150	52	25	18	22	22	26
NS	31 ± 0	61 ± 6	56 ± 21	67 ± 50	23 ± 6	71[f]	---	---	---
1000 rads all NS	31 ± 4	127 ± 72[d]	135 ± 88[d]	71 ± 45[d]	33	---	---	---	---

[a]The entries are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 600-rad and 800-rad groups). A = all animals; S = survivors; NS = nonsurvivors. Where no standard deviation is listed, less than three measurements were available. Normal range based on 198 normal examinations, 31 ± 6 units.

[b]Standard deviation.

[c]$p < 0.01$ compared with pre-established normal range.

[d]$p < 0.001$ compared with pre-established normal range.

[e]$p < 0.01$ compared with preirradiation baseline.

[f]One animal.

TABLE XXXIX

FE^{59} Ferrokinetics After 2-Mev X-Irradiation And 400-Mev Proton Irradiation

Dose (rads)	Plasma disappearance half-time (min)				10-day RBC uptake (% of injected dose)			
	400-Mev protons		2-Mev X-rays		400-Mev protons		2-Mev X-rays	
	Before irradiation	After irradiation	Before irradiation	After irradiation	Before irradiation	After irradiation	Before irradiation	After irradiation
0 (Sham-irradiated)	---	---	55	88	---	---	98	75
25	85 ± 19	116 ± 18	87 ± 13	101 ± 12	89 ± 4	87 ± 18	90 ± 13	75 ± 6
50	74 ± 26	111 ± 21	85 ± 9	163 ± 17	87 ± 11	92 ± 14	97 ± 4	61 ± 6
100	86 ± 23	221 ± 62	82 ± 16	176 ± 38	93 ± 7	56 ± 20	84 ± 5	53 ± 15
200	70 ± 14	211 ± 11	81 ± 23	215 ± 14	88 ± 12	34 ± 16	88 ± 11	18 ± 14
400	65 ± 22	335 ± 89	94 ± 14	267 ± 34	95 ± 9	0 ± 0	88 ± 5	2.2 ± 4

100 rads produced bone marrow injury with 200 rads producing clinical evidence of hemorrhaging (internal). At levels of 800 rads, death appeared due to the G-I syndrome which occurred prior to day 12 postirradiation. Platelet counts were normal and there was no clinical evidence of an increased tendency towards bleeding.

The only significant clinical departure from the experience with 2-Mev X-rays was an increased severity of gastrointestinal and hemorrhagic signs. RBE's based on 30-day mortality are approximately unity.

440 - Mev - Protons [16].

Mice

R.B.E. determined relative to 250 Kvp X-rays using the $LD_{50/30}$ as a criterion and dose rates in the 18 to 80 r/min. range.

R.B.E. = 0.7 ± 0.2.

480 - Mev - Protons [17]

Rabbits

TABLE XXXX

Changes in the Protein Fractions of the Plasma of Rabbits Exposed to the Action of High-Energy (480 Mev) Protons and X-Rays.

Animal No.	Dose, rep	Time after exposure, in days	Protein fractions, in per cent: albumins	globulins α	globulins β	globulins γ	Fibrinogen
	Normal (mean of 21 rabbits)		58,1±3,6	9,3±0,9	14,3±1,4	8,9±3,2	9,4±1,4
	Protons						
169	1 220	10	23,4	21,3	23,6	9,2	22,5
5	1 000	1	47,7	12,6	14,7	10,2	14,8
347	650	11	34,4	13,6	18,6	15,9	17,4
147	550	9	29,7	23,7	19,3	5,5	21,7
322	500	11	39,4	12,8	24,8	11,7	11,2
131	500	50	69,8	7,2	9,9	6,2	6,8
161	325	3	55,4	14,5	14,7	4,9	10,4
302	325	11	37,9	18,2	20,7	12,5	10,7
4	325	19	39,8	12,3	14,9	17,1	15,9
483	325	25	47,6	10,3	18,1	15,8	8,2
696	325	31	45,5	16,3	14,6	10,3	13,3
648	325	50	51,4	9,3	14,2	14,6	10,5
2	250	25	58,1	10,3	12,5	9,1	10,0
91	240	24	53,7	13,6	14,7	10,3	7,7
212	156	30	51,3	11,9	13,2	10,5	14,1
204	88	24	55,2	10,4	12,0	13,9	8,5
	x - Rays						
171	1 000	10	30,9	20,9	22,3	7,4	18,4
6	1 000	1	52,1	12,0	10,0	10,0	15,8*
22	1 000	1	52,3	12,1	12,7	9,8	13,1
6	650	11	57,3	10,6	14,9	8,8	8,4
1	500	11	58,5	13,0	13,0	12,4	8,1
43	325	3	47,4	14,5	13,6	13,6	10,9
42	325	3	54,7	15,3	13,1	6,3	10,5
42	325	11	60,6	7,8	12,8	11,1	7,8
43	335	11	59,0	9,8	11,4	12,0	7,7
43	325	19	44,4	12,5	16,3	13,7	13,0
42	325	19	60,2	9,8	12,6	8,4	9,0
42	325	40	51,4	13,0	14,1	11,4	10,2

EXPERIMENTAL RESULTS

The results of the analyses for the two groups of animals are given in the table.

The results obtained show that as the disease developed, the relative proportion of albumins fell, the α- and β-globulin fractions and the plasma fibrinogen rose, while the changes in the γ-globulin fraction were not characteristic. The most considerable changes were found in animals irradiated with massive doses of protons.

In rabbit No. 169, for instance, on the 10th day after exposure to a dose of 1200 physical roentgen equivalents, a well-marked dysproteinemia was evidently found in the agonal period of the disease. An appreciable fall in the albumin fraction was detected in the first few days after exposure to protons in a dose of 1000 physical roentgen equivalents (see table).

Sublethal doses of protons (650, 550 and 500 physical roentgen equivalents) also caused well-marked variations in the composition of the plasma protein fractions. Analyses carried out on the 9th and 11th days after exposure to protons in the doses mentioned showed significant dysproteinemia (see figure, a and b).

510 - Mev - Protons [19.]

Rats

Single doses of up to 400 rads produced only light illness and no early fatalities. All external symptoms such as listlessness, loss of appetite, and drop in weight increase disappeared before the end of the observationa period.

TABLE XLI

Injury To Rats As Function Of Dose For
Protons With Energies Of 510-Mev - Single Irradiation

Group	Dose, rad	Total number of animals	Number of dead animals	Mean life span of dead animals, days
I	330	21	0	All survived
II	440	49	0	All survived
III	420	21	1	16
IV	470	25	7	12
V	520	21	7	20
VI	620	22	20	6
VII	730	25	24	5
VIII	850	10	10	3.5
IX	920	15	15	3.5
X	950	15	15	3.5

Note. Total number of animals does not include control animals or those killed for pathologic-morphological investigations.

420 - 620 Rads - salivation, ichorous discharge from mouth and subconjunctional hemorrhages followed by diarrhea. These symptoms then disappeared.

Above 620 Rads - symptoms progressed until death.

Dogs

TABLE XLII

Single Irradiation Of Dogs By 510-Mev - Protons

Dose, rads	Number of animals	Number which died	Average life span days
550	5	5	7.6
400	5	5	11.4
250	5	2	14.2
690	1	1	4.0
550	1	1	9.0
520	1	1	9.0
495	1	1	9.0
440	1	1	9.0
330	1	1	9.0

TABLE XLIII

Clinical Symptoms Of Sickness And Time When Observed After Single Dose
(Mean Data For Each Group Of Animals)

Symptoms	Group I (550 rad)		Group II (400 rad)		Group III (250 rad)	
	Time of occurrence (Days)	Frequency of occurrence	Time of occurrence (Days)	Frequency of occurrence	Time of occurrence	Frequency of occurrence
Decrease of motor activity	4.6	All dogs	7.6	All dogs	11.4	All dogs
Decrease of alimentary excitability	2.6	All dogs	6.0	All dogs	9.6	All dogs
Blanching of mucous membranes	3.6	All dogs	6.8	All dogs	9.9	All dogs
Increase of body temperature	5.0	All dogs	7.6	All dogs	13.4	All dogs
Gingivitis	6.1	4 dogs	9.8	4 dogs	12.5	2 dogs
Necrotic angina	7.2	4 dogs	11.0	3 dogs	14.0	3 dogs
Diarrhea	6.8	4 dogs	11.0	4 dogs	14.0	2 dogs

(continued....)

TABLE XLIII (continued....)

Symptoms	Group I (550 rad)		Group II (400 rad)		Group III (250 rad)	
	Time of occurrence (days)	Frequency of occurrence	Time of occurrence (days)	Frequency of occurrence	Time of occurrence (days)	Frequency of occurrence
Hemorrhages in mucous membranes	6.6	4 dogs	11.0	1 dog	15.0	2 dogs
Hemorrhages in skin and subcutaneous cellular structures	7.6	2 dogs	7.0	2 dogs	15.0	2 dogs
Hemorrhages in gastrointestinal tract	6.3	All dogs	11.0	3 dogs	14.0	1 dog

Time of occurrence is in days postirradiation; 18 of the 21 dogs died between the 7th and 14th day postirradiation. The three survivors (250 rad group) showed the symptoms of severe radiation sickness.

TABLE XLIV

Repeated Irradiation Of Dogs With 510-Mev Protons

Dose, rads	Number of animals	Number which died	Average life span (days)
650	6	6	43.3
690	6	6	22.8
550	5	0	---
649	1	1	41.0
661	1	1	45.0
632	1	1	41.0
637	1	1	41.0
657	1	1	49.0
660	1	1	43.0

TABLE XLV

510-Mev Protons; Total Body Irradiation

Dose (rads)	Animal (dog or rat)	Number of animals	Number of animals which died	Life span days
250	dog*	5	2	14.2
330	rat* dog*	21 1	0 1	All survived 9.0
400	rat* dog*	49 5	0 5	All survived 7.6
420	rat*	21	1	16.0
440	dog*	1	1	9.0
470	rat*	25	7	12.0
495	dog*	1	1	9.0
320	dog* rat*	1 21	1 7	9.0 20.0
550	dog[a] dog*	5 5	0 5	All survived 7.6
620	rat*	22	20	6
632	dog	1	1	41.0
637	dog	1	1	41.0
649	dog	1	1	41.0
650	dog[b]	6	6	43.3
657	dog	1	1	49.0
660	dog	1	1	43.0

(continued....)

TABLE XLV (continued....)

Dose (rads)	Animal (dog or rat)	Number of animals	Number of animals which died	Life span days
661	dog	1	1	45.0
690	dog[c] dog*	6 1	6 1	22.8 4.0
730	rat*	25	24	5.0
750	rat	29	--	---
850	rat*	10	10	3.5
920	rat*	15	15	3.5
950	rat*	15	15	3.5

* Single irradiation. Rest are fractional irradiations.

[a]17 irradiations in 4 weeks.

[b]19 irradiations in 5 weeks.

[c]8 irradiations in 2 weeks.

Total dose, 550 rads; - no effect during first 25 - 30 days. After entire irradiation cycle (30-40 days), symptoms started appearing. These disappeared in about 1.5 to 2 weeks.

Total dose, greater than 650 rads; - first appearance of symptoms after 500 rads had been reached at the 35th or 36th day. After 600 rads (37-38 days), there was a sharp deterioration in the general state of all animals.

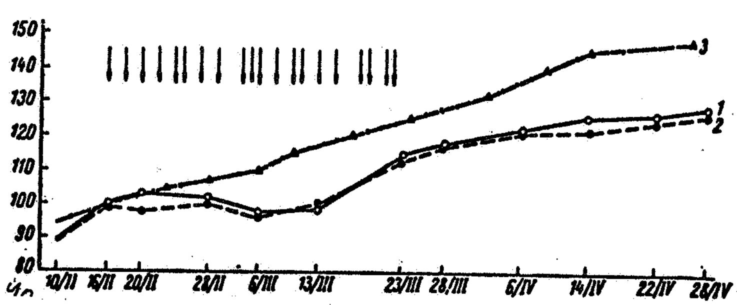


Figure 29. Change (in percent of initial level) of weight of rats in case of irradiation with dose of 750 rad (1) and 1,015 rad (2), control data (3).

Rats

TABLE XLVI

Content Of Erythrocytes (Millions Per 1 MM^3) In
Peripheral Blood Of Rats Subjected To Single Irradiations
By Protons With Energies Of 510 Mev

Group	Dose, rad	Number of erythrocytes before irradiation	Number of erythrocytes after irradiation, days							
			1st	3rd	5th	10th	15th	20th	30th	45th
I	330	7.30	7.20	6.32	6.29	6.57	5.89	6.85	5.35	6.68
II	400	6.61	7.33	6.98	5.18	5.21	5.53	5.56	5.78	6.49
III	420	6.87	8.00	7.54	6.20	6.10	6.84	6.32	6.28	6.10
IV	470	5.93	7.80	7.45	5.50	3.60	4.10	6.00	5.70	6.35
V	520	7.50	7.31	8.31	6.65	4.96	4.87	6.80	5.90	5.81
VI	620	7.20	7.54	7.35	6.15	---	---	---	---	---
VII	730	6.93	6.65	6.56	5.90	---	---	---	---	---
X	950	8.20	---	8.64	---	---	---	---	---	---

Figure 30. Change of quantity of erythrocytes (percent) in blood of rats in first month after irradiation and much later (months): (1) 850 r; (2) 750 r; (3) 275 r; (4) 100 r.

These animals showed anisocytosis, an increase in the number of polychromatophylic erythrocytes, and erythroblasts appeared in the peripheral blood.

TABLE XLVII

Content Of Leukocytes (Thousands Per 1 MM^3)
In Peripheral Blood Of Rats Subjected To Single Irradiations
By Protons With Energies Of 510 Mev

Group	Dose, rad	Number of leukocytes before irratiation	After irradiation, days							
			1st	3rd	5th	10th	15th	20th	30th	45th
I	330	13.80	3.96	2.74	2.98	4.37	5.40	6.40	12.40	15.80
II	400	15.00	3.60	1.36	2.40	2.30	5.80	10.10	9.96	10.10
III	420	16.00	4.20	1.24	4.90	7.00	7.30	13.30	12.00	16.30
IV	470	16.50	4.43	1.14	0.54	0.60	6.58	14.80	10.10	14.10
V	520	13.30	2.40	0.93	0.44	1.80	3.30	4.00	11.70	11.40
VI	620	14.30	2.0	1.04	0.90	---	---	---	---	---
VII	730	16.80	2.3	0.9	0.4	---	---	---	---	---
VIII	950	16.30	---	0.6	---	---	---	---	---	---

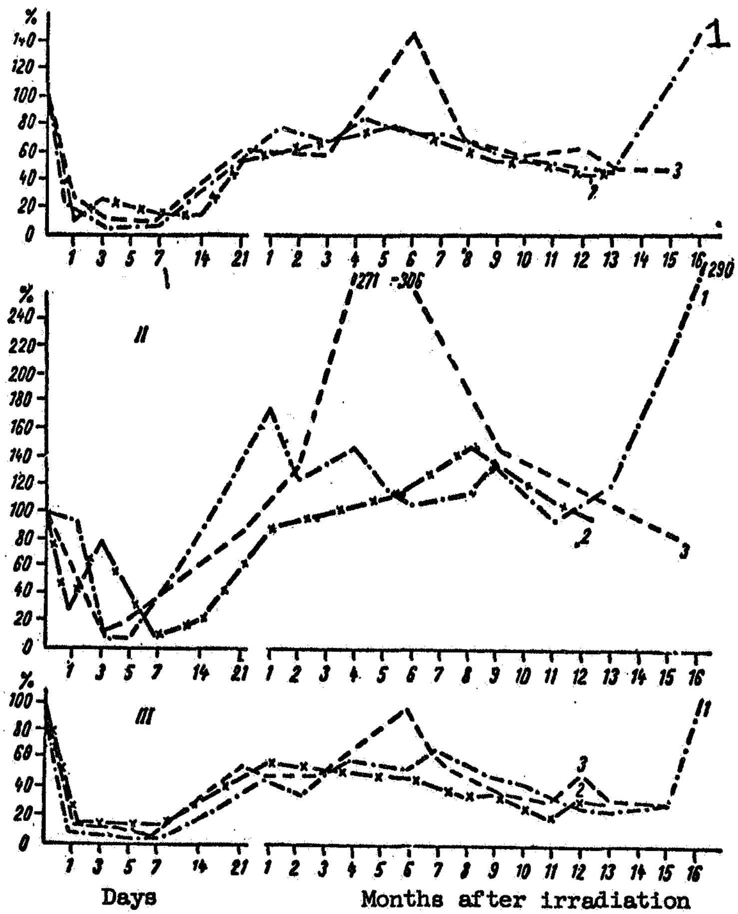


Figure 31. Change (percent) of total quantity of leukocytes (I), neutrophils (II) and lymphocytes (III) during first month after irradiation and much later: (1) 420 rad; (2) 730-760 rad; (3) 850 rad.

For the first 90 days, the dose effect curve for erythrocytes is "S" shaped becoming linear after this time and has a very small slope. In contrast, the neutrophils have an initially linear dose effect curve.

TABLE XLVIII

Change Of Body Weight And Indices Of Peripheral Blood Of Rats In Group I (Total Dose: 750 Rad)

Date and time of examination		Weight, g	Number of erythrocytes millions per 1 mm^3	Number of leukocytes, thousands per 1 mm^3	Number of thrombocytes, thousands per 1 mm^3
Before irradiations	1 Feb.	192 ± 6.1	9.01 ±0.23	17.75 ± 1.4	187 ± 18
	10 Feb.	202 ± 4.5	7.80 ± 0.12	15.68 ± 1.2	---
In period of irradiations	16 Feb.	225 ± 5.5	8.15 ± 1.10	15.31 ± 0.7	---
	20 Feb.	232 ± 5.5	7.58 ± 0.15	8.14 ± 0.5	164 ± 34
	28 Feb.	229 ± 4.0	7.78 ± 0.22	8.52 ± 0.5	147 ± 8
	6 Mar.	221 ± 4.1	7.73 ± 0.20	6.92 ± 0.8	139 ± 56
	13 Mar.	224 ± 4.8	7.14 ± 0.19	6.96 ± 0.7	195 ± 24
After irradiations	23 Mar.	259 ± 5.6	6.44 ± 0.12	6.21 ± 0.5	156 ± 18
	28 Mar.	267 ± 4.7	6.94 ± 0.13	7.66 ± 0.4	184 ± 14
	6 Apr.	275 ± 6.3	7.05 ± 0.12	16.50 ± 1.4	264 ± 69
	14 Apr.	283 ± 6.1	6.46 ± 0.12	12.20 ± 0.7	313 ± 28
	22 Apr.	286 + 8.3	6.47 + 0.13	11.45 + 0.9	124 + 14
	28 Apr.	290 ± 8.6	6.30 ± 0.12	14.25 ± 1.0	159 ± 18
	5 May	302 ± 9.0	6.28 ± 0.28	15.57 ± 1.2	135 ± 16
	12 May	313 ± 11.0	6.83 ± 0.26	16.37 ± 0.8	135 ± 16
	22 May	314 ± 11.0	6.37 ± 0.15	17.88 ± 0.4	201 ± 53

Unlike the results in dogs, the changes in thrombocyte concentration are small and variable.

TABLE XLIX

Results Of The Use Of Protective Agents In Rats With Acute Radiation Sickness Caused By Single Irradiations By Protons With Energies Of 510-Mev

Name of agent	Dose mg/kg	Irradiation dose, rad	Number of rats	Survived to 60th day
S-beta-aminoethylisothiuronium BrHBr + para-aminopropiophenone (AET + PAPF)	(PAPF) 50 (AET) 100	555	15	0
5-methoxytryptamine	75	508	15	0
Cystamine + amygdalin	(Ts) 360 (A) 20	508	9	2
Cystamine	300	430	4	0

(continued....)

TABLE XLIX (continued....)

Name of agent	Dose mg/kg	Irradiation dose, rad	Number of rats	Survived to 60th day
5-oxytryptamine (serotonin)	50	430	10	5
Para-aminopropiophenone (PAPF)	100	412	10	4
S-beta-aminoethylisothiuronium BrHBr (AET)	200	412	10	5
Control		430-555	20	0
Control		412	8	2

Note. All agents with the exception of 5-oxytryptamine and 5-methoxytryptamine were introduced orally 1 hour before irradiation; 5-oxytryptamine and 5-methoxytryptamine were introduced intramuscularly 10-15 minutes before irradiation.

Only minimal changes in the blood-generating system were induced by prophylactic injection of S-beta-aminoethylisothiuronium BrHBr and cystamine with amygdalin.

Genetics

Males were irradiated then mated. The females were sacrificed on the 14th - 16th day of pregnancy. All deaths (embryo) were a result of dominant lethals. The frequency was a function of the administered radiation dose.

Irradiation dose	Number of investigated females	Number of yellow bodies of pregnancy	Number of places of implantation	Number of live embryos	NUMBER OF DEAD EMBRYOS					
					Before implantation		After implantation		Total number	
					In fractions of dead embryos in relation to yellow bodies	In fractions of unit, with control taken into account	In fractions of dead embryos in relation to yellow bodies	In fractions of dead embryos in relation to yellow bodies with control taken into account	In fractions of dead embryos in relation to yellow bodies	In fractions of dead embryos in relation to yellow bodies with control taken into account
Control	21	271	243	220	0.1033	---	0.0749	---	0.1882 ± 0.0763	---
55 (44-66)	29	361	327	290	0.0992	---	0.0975	0.0105	0.1967 ± 0.0488	0.0105 ± 0.0388
200 (180-227)	11	119	102	71	0.1429	0.0441	0.2605	0.2210	0.4043 ± 0.0822	0.2651 ± 0.0597
360 (346-382)	27	352	305	209	0.1335	0.0337	0.2728	0.2349	0.4063 ± 0.0330	0.2686 ± 0.0388
520	15	192	145	91	0.2448	0.1578	0.2813	0.2584	0.5261 ± 0.0552	0.4162 ± 0.0477
780 (744-822)	20	254	200	88	0.2126	0.1219	0.4016	0.4028	0.6142 ± 0.0550	0.5247 ± 0.0402
1030	17	201	75	13	0.6269	0.5839	0.3084	0.3464	0.9353 ± 0.0165	0.9303 ± 0.0216

TABLE L

Chromosomal rearrangements were of two types: single breaks and multiple breaks dependent upon the dose.

$$LD_{50} = 565 \pm 21 \text{ rad}$$

$$\text{RBE (relative to 180 Kvp X-rays)} = 0.7$$

Lung Pathology (330 - 950 rads) - Perivascular edema, swelling of vessel walls, parenchymtous hemorrhages, iron-bearing pigmentation of cells along capillaries. In the later stages: plasmatic impregnation of walls of vessels, destruction of small arteries, increase in size of lymphoidal casing, intermediate pneumonia, grains of hemosiderin in vessel walls.

Heart - Edema of myocardium, expansion and plethora of vessels, swelling of vessel walls. In the 520 - 620 rad group hemorrhages near the aorta, destruction of the atrium corditis and interventricular septum and small agglomerations of lymphocytes were found in the myocardium.

Liver - Changes did not develop until after the 7th day postirradiation. These were: pyknotic nuclei, basophilously-colored cytoplasm containing large basophilic lumps and fatty inclusions in the cells. Necrotic foci were observed in the lobes. In the later period (30 - 45 days), the liver became flabby, there was dystrophy of the parenchyma, expansion of the intralobular capillaries and veins, massive parenchymal hemorrhages and disintegration of the hepatic ligaments. Adiposity developed. The intact cells had gigantic nuclei and were enlarged with vacuolated cytoplasm.

Kidney - Plethora and dilation of vessels in cortical and medullary layers, dilation of blood vessels, hemorrhaging in cortex and medulla near the renal pelvis and under the capsule. Dystrophy changes were observed in the epithelium of the tubules. The cavity of Bowman's Capsule was expanded and contained an albuminous effusion. There was also a plasmatic impregnation of the vessel walls.

Spleen - Large number of grains of hemosiderin, brown pigmentation, and general disintegration of the erythrocytes. Plethora appeared after the 3rd day. In the high dose groups, there was almost complete devastation of the lymphatic follicles. After 7 days, there was some tendency towards cellular regeneration. In the later stages (30 - 45 days), anemia set in and the size increased due to hyperplasia of reticular stroma with organ erosion. There was diffusely scattered lymphocytes and tiny foci of hemorrhaging.

Stomach, Large and Small Intestines - Changes in these organs only appeared after 30 - 45 days. Detachment of mucous membranes, granules of hemosiderin in the cells of the stroma of villi of the gastric mucosa and large intestine and prolonged impairment of vascular permeability.

Lymph – Almost total destruction of the lymph follicles, plethora, and distention of reticular stroma. After a month, there was partial restoration of the lymph apparatus. However, the follicles were more numerous and larger. The stroma was diffusely infiltrated by a considerable number of lymphocytes. Plethora was of a congestive character. Cells showed a large quantity of hemosiderin and brown pigment.

Testes - During the period immediately following irradiation, there were no clearly expressed changes in the seminific epithelium of the sperm ductiles. Some pathologic mitosis was seen (agglutination of chromosomes, irregular divergence toward poles, and gigantic multinuclear cells). At later times (approximately 1 month), there was total destruction of the sperm ductiles.

Dogs

Pathological and Morphological

Hemorrhages - Multiple in internal organs and tissues, also in subcutaneous cellular tissues of torso and neck. There were extensive hematomas in the lungs, heart, and G-I tract. In the kidney, they were mainly in the cortical layer and capsule and in the urinary tract. There was aplasia of the spleen, atrophy of the lymphoid mechanism, and almost total devastation of the active bone marrow. The marrow was almost entirely replaced by a bloody fluid.

Liver - Flabby, poor definition of its configuration, swollen. Impairment of both blood and lymph circulatory systems.

Kidneys and Heart Muscles - Destruction of boundary between cortical and medullary layers. Impairment of blood circulation, parenchymatous and perivascular hemorrhages, mottling, atelectasis, vessel wall distention, adventitia along vessels, cell cytoplasm filled with iron-containing pigment, desquamation of endothelium of the vessels and bronchi, accumulation of albuminous exudate and erythrocytes in alveolar regions, necrosis of pulmonary tissues.

Lymphoidal Tissue - The predominant form of cells found in the G-I tract and spleen were reticular and plasmatic, grouped in small clusters around the central arteries and trabeculae. There was considerable erythrophagia. Hemorrhages, edema, plethora of vessels. Loss of lymphoidal tissue.

Lumph - Frequent signs of incipient edema.

Tonsils - Amygdalitis.

Testicles - Decreased size, flabby, hemorrhages beneath capsule, enlarged capsule vessels, parenchymatos atrophy.

Bone marrow - Extreme devastation.

G-I Tract - Loss of lymphoidal tissue. Lymph spaces were distended, and erythrocytes and macrophagia were found in the lumen. Edema and plethora. Necrobiosis of mucous layer. Hemorrhage and edema of submucosa.

Spleen - Lymphoidal tissue destruction with the organ having a red pulpish appearance. It was poor in cellular elements, edematous, and plethoric. There were both young and mature lymphocytes scattered diffusely through it.

Heart - Distention and opacity of muscle fibres. Small foci of adipose dystrophy. Shrivering, vacuolization, and plasmatic impregnation of the endothelium and vessel walls. Dystrophic changes in the myocardium.

Endocrine Glands - Degeneration and atrophic changes. Depression of function. In the thyroid, there was a thinning of the colloids. Destruction of insular tissue.

Urinary Bladder - Hemorrhaging led to diffuse impregnation of all membranes by blood. Necrobiotic changes of epithelium and exfoliation.

Stomach - Hemorrhaging. Autolysis of tegmented epithelium. Necrobiotic changes of main and parietal acid cells.

Central Nervous System - Fibrous thickening in the pia mater of the brain and spinal cord. Disintegration of cerebral white matter. Lysis of nerve fibres in the white matter of the spinal cord and of the perivascular medulla in the grey matter of the medulla oblongata. Edema under ependyma, pyknosis and necrobiosis of ependymal cells. Edema of soft meningis with separation into fibres. Distention of perivascular spaces. Gross destruction of veins with periveinous hemorrhaging. Small hemorrhagic foci in all parts of the brain. Massive necrosis with disintegration of tissue in cortex of temporal region and cerebral tissue.

Lymph and Blood System - Edema of tissue at base of all cerebral ventricles. Focal disintegration of ependymal lining of ventricles and cerebral aqueduct. Shriveling and atrophy of corticospinal cells of motor apparatus. Hyperchromatosis of nuclei. General cell damage. Disintegration of astrocytes.

Peripheral Nervous System - All nerve ganglia had characteristic changes of nucleolar apparatus of neurons. Nucleoles were increased in size, stained poorly, and were vacuoleous. Chromatolysis of nerve cells, distention of nuclei of neurons. Polymorphism of nuclei of the peripheral glia was observed.

TABLE LI

Multiple Exposures

Irradiation of Dogs With Protons Having An Energy Of 510-Mev

Group of animals	Number of animals in group	Single minimum, maximum and mean irradiation dose (in sequence) (Rads)	Total minimum, maximum and mean irradiation dose (in sequence) (Rads)	Mean duration of period of irradiation, days
Treated	9	17.1 57.2 34.3	642.6 652.2 651.2	43
Control	6	11.9 63.0 34.5	622.0 667.0 646.2	41-43

TABLE LII

Survival Rate And Lifespan Of Control And Treated Dogs
Multiple Irradiations By Protons With Energies Of 510-Mev

Group of animals	Number of animals	Survived to 65th day	Mean lifespan, days
Treated	9	7	51
Control	6	0	43

Peripheral Blood:

(a) Control - Sharp decrease in number of thrombocytes. Total disappearance of reticulocytes. Leukocytes decreased to between 500 - 2,000 per mm^3. Hemoglobin and erythrocytes decreased by 25%.

(b) Treated - Same symptoms. Some restoration after 65 days. 6 of 7 developed severe aplastic anemia after 100 days. These 6 died by 110 days.

The bone marrow changes were similar for both groups. There was a stable decrease in erythroblastic or myeloid cells.

Serotonin behavior was also similar in both groups. In the controls, the content had decreased to zero by 35-45 days and coincided with death.

TABLE LIII

Periods Of Decrease Of Content Of Serotonin In Blood Of Dogs

Number of dogs	Group of animals	Period of decrease of serotonin content to zero, days	Lifespan after decrease of serotonin content to zero, days
6	Control	38th	3
1057	"	39 - 40th	2
1128	"	39 - 40th	2
1049	"	43rd	2
1062	"	38th	5
1084	"	43rd	6
883	Treated	39th	10
963	"	43rd	11

Prior to decrease, some dogs showed a considerable increase. Those showing the maximum increase easily withstood the acute phases of the radiation syndrome.

Pathology (Treated Animals)

Hemorrhaging was not as wide spread and had small foci. Severe anemia. Dystrophic changes of liver, kidney, myocardium and other organs.

Central Nervous System - Massive hemorrhages under dura mater localized at the base of the brain and cerebral hemispheres. Severe anemia of medulla. In the soft meninges there was: edema at the surface and base of the brain; edematous seperation into fibres; distoria of vessels with perivascular edema; slight growth of collagenic tissue; vessel lumens filled by hemogeneous albuminous mass; and cortex and subcortical stem formations.

Vascular System - The effects on cellular structure was mixed. In some animals, the structure was preserved; while in others, it was shriveled and atrophic. The lumens of small vessels were, in some cases, filled with pyknomorphic cast-off epithelium. The severest changes took place in the subcortical stem formations, with a gross impairment of vascular tone, resulting in wall collapsing and a devastation of the fine vessels. Cerebral fluid accumulations were found in the perivascular spaces. Edema propagated to a great part of the cerebral matter which appeared spongy and porous.

Brain - Gross disintegration in white matter of subcortical stem section, edematous softening and disintegration of nerve fibres. There was pyknosis and necrobiosis of ependyma cells, and proliferation of collagenic fibres of the stroma in the ependyma of the cerebral ventricles.

Nerve Cells - In the treated animals, there were clearer manifestations of polymorphism of the nerve cells in the cortex of the hemispheres and a greater intensity and extent of cellular pathology.

Cortex - Distention and degeneration of nuclei, with disintegration and dissolution of cytoplasms, with pathologically modified nucleoles. Cytolysis of nerve cells. There was shriveling and atrophy of large nerve cells along with ischemic modification.

Hemispheres - Pericellular edema, small foci of cellular obliteration. In the region of the motor apparatus, there was necrobiosis and an extraordinary distention of the appendices of pyrimidal Betz Cells.

Subcortical Gray Nodes - Distention of nuclei, hyperchromia and dissolution of cytoplasm. Foci of shedding of nerve cells in caudate nucleus.

Hypothalmus - All cells showed deviations. Different stages of change were clearly distinguishable in the supraoptical and periventricular nuclei.

Cerebellum - Cytolysis, shriveling, and necrobiosis of Purkinje cells. Pyknosis of nuclei of granular cells.

Astroglia - Focal proliferation in gray matter of subcortical stem formations, in caudate nucleus, tissues surrounding the aqueduct and at the base of the 4th ventricle. Hyperplasia and hyperthrophy of astrocytes. In the subthalamic region, there was hyperplasia of the perivascular astrocytes. Gross disintegration in the olivas of the medulla oblongata with hyperchromia. In the frontal cortex, there were drainage forms of oligodendroglia with edema of white matter.

In general, both treated and untreated animals reacted similarly with the exception of certain differences in the CNS caused by impairment of cerebral blood circulation in the treated group. This group showed severe vascular dystonia and extensive perivascular edema. In the untreated group, hemorrhagic foci were encountered in almost every part of the brain and spinal cord. Therefore, the therapeutic agents utilized prevented at least temporarily the destruction of cerebral vessels.

TABLE LIV

Changes Of Indices In The Peripheral Blood Of Dogs After Single Proton Irradiations With A Dose Of 250 Rad (510 Mev)

Time of analysis (days)	Quantity of leukocytes 1,000/mm^3	Quantity of erythrocytes 1 million/mm^3	Hemoglobin content Sali method	Reticulocyte content, %	Thrombocyte content 1,000/mm^3
Before irradiation	11.15 ± 1.23	7.54 ± 0.48	90 ± 5.5	5	189 ± 17
3rd	5.35 ± 1.01	6.44 ± 0.49	86 ± 6.8	0	249 ± 31
7th	2.31 ± 0.18	6.60 ± 0.36	73 ± 3.6	0	123 ± 12
10th-12th	2.95 ± 0.67	6.01 ± 0.20	73 ± 3.4	0	15 ± 5
19th	1.33 ± 0.37	3.69 ± 0.74	50 ± 12.7	3	9 ± 4
30th	5.41 ± 0.70	4.54 ± 0.67	53 ± 6.9	31	---
45th	12.61 ± 0.80	6.03 ± 0.23	75 ± 6.2	31	207 ± 88

TABLE LV

Changes Of Indices Of Peripheral Blood In Dogs Of Group III - 250 Rads

Date and time of examination, days	Number of erythrocytes, in 1 mm^3	Hemoglobin content, Sali method, %	Number of Reticulocytes, %	Number of thrombocytes, thousands in 1 mm^3	Number of leukocytes, thousands in 1 mm^3
Before irradiation					
23/II	7.50 ± 0.33	95 ± 6.1	5	174 ± 11	11.08 ± 1.49
26/VI	7.62 ± 0.93	86 ± 4.5	6	217 ± 25	11.45 ± 1.01
28/VI	7.51 ± 0.63	89 ± 3.8	3	---	12.16 ± 1.13
Mean before irradiation	7.54 ± 0.48	90 ± 5.5	5	189 ± 15	11.15 ± 1.23
After irradiation					
1st	7.08 ± 0.42	87 ± 4.1	0	263 ± 13	7.36 ± 0.67
3rd	6.44 ± 0.49	86 ± 6.8	0	248 ± 31	5.35 ± 1.01
5th	6.34 ± 0.35	78 ± 4.7	0	206 ± 32	3.51 ± 0.34
7th	6.60 ± 0.36	73 ± 3.6	0	123 ± 12	2.31 ± 0.18
10th	6.01 ± 0.20	73 ± 3.4	0	15 ± 5	2.95 ± 0.67
16th	4.74 ± 0.67	53 ± 8.6	0	4 ± 2	1.98 ± 0.60
19th	3.69 ± 0.74	50 ± 12.7	0	9 ± 4	1.33 ± 0.37
30th	4.54 ± 0.67	53 ± 6.9	31	62 ± 11	5.41 ± 0.70
45th	6.03 ± 0.23	75 ± 6.2	31	207 ± 88	12.61 ± 0.80

TABLE LVI

Changes Of Indices In The Peripheral Blood Of Dogs - 400 Rads

Time of analysis days	Quantity of leukocytes 1,000/mm^3	Quantity of erythrocytes 1 million/mm^3	Hemoglobin content (Sali Method)	Reticulocyte content %	Thrombocyte content 1,000/mm^3
Before irradiation	11.75 ± 1.19	7.65 ± 0.35	85 ± 2.5	6	171 ± 19
3rd	3.78 ± 0.52	6.86 ± 0.10	83 ± 1.4	0	257 ± 45
7th	0.93 ± 0.24	6.49 ± 0.40	68 ± 6.6	0	84 ± 19
10th - 12th	0.26 ± 0.09	4.91 ± 1.25	58 ± 3.4	0	14 ± 8.5

TABLE LVII

Changes Of Indices In The Peripheral Blood Of Dogs
Group II - 400 Rads

Date and time of examination, days	Number of erythro-cytes, in 1 mm^3	Hemoglobin content, (Sali method) %	Number of reticulo-cytes, %	Number of thrombocytes thousands in 1 mm^3	Number of leukocytes, thousands in in 1 mm^3
Before irradiation					
23/VI	7.81 ± 0.85	85 ± 3.8	5	190 ± 35	11.99 ± 1.44
26/VI	7.45 ± 0.44	87 ± 2.3	11	153 ± 40	11.95 ± 1.58
28/VI	7.70 ± 0.15	84 ± 3.3	3	---	11.32 ± 1.07
Mean before irradiation	7.65 ± 0.35	85 ± 2.5	6	171 ± 19	11.75 ± 1.19
After irradiation					
1st	7.10 ± 0.94	83 ± 5.6	0	167 ± 56	9.87 ± 2.41
3rd	6.86 ± 0.10	83 ± 1.36	0	257 ± 45	3.78 ± 0.52
5th	6.69 ± 0.30	72 ± 2.5	0	183 ± 24	1.36 ± 0.12
7th	6.49 ± 0.40	68 ± 6.6	0	84 ± 19	0.93 ± 0.24
10th	4.91 ± 1.25	58 ± 3.4	0	14 ± 8	0.26 ± 0.09

In rats irradiated to 400 rads, along with the decrease in erythrocytes, there were seen anisocytosis and an increase in the member of polychromatophylic erythrocytes with the appearance of erythroblasts in the peripheral blood.

In animals irradiated to greater than 600 rads, there was no evidence of bone marrow destruction or disappearance of leukocytes from the peripheral blood up to 2 - 3 days before death. In this dosage range and for as low as 550 rads, there were:

1. A decrease in the absolute number of cells in the marrow.

2. A decrease in the erythroblastic and myeloid series of cells.

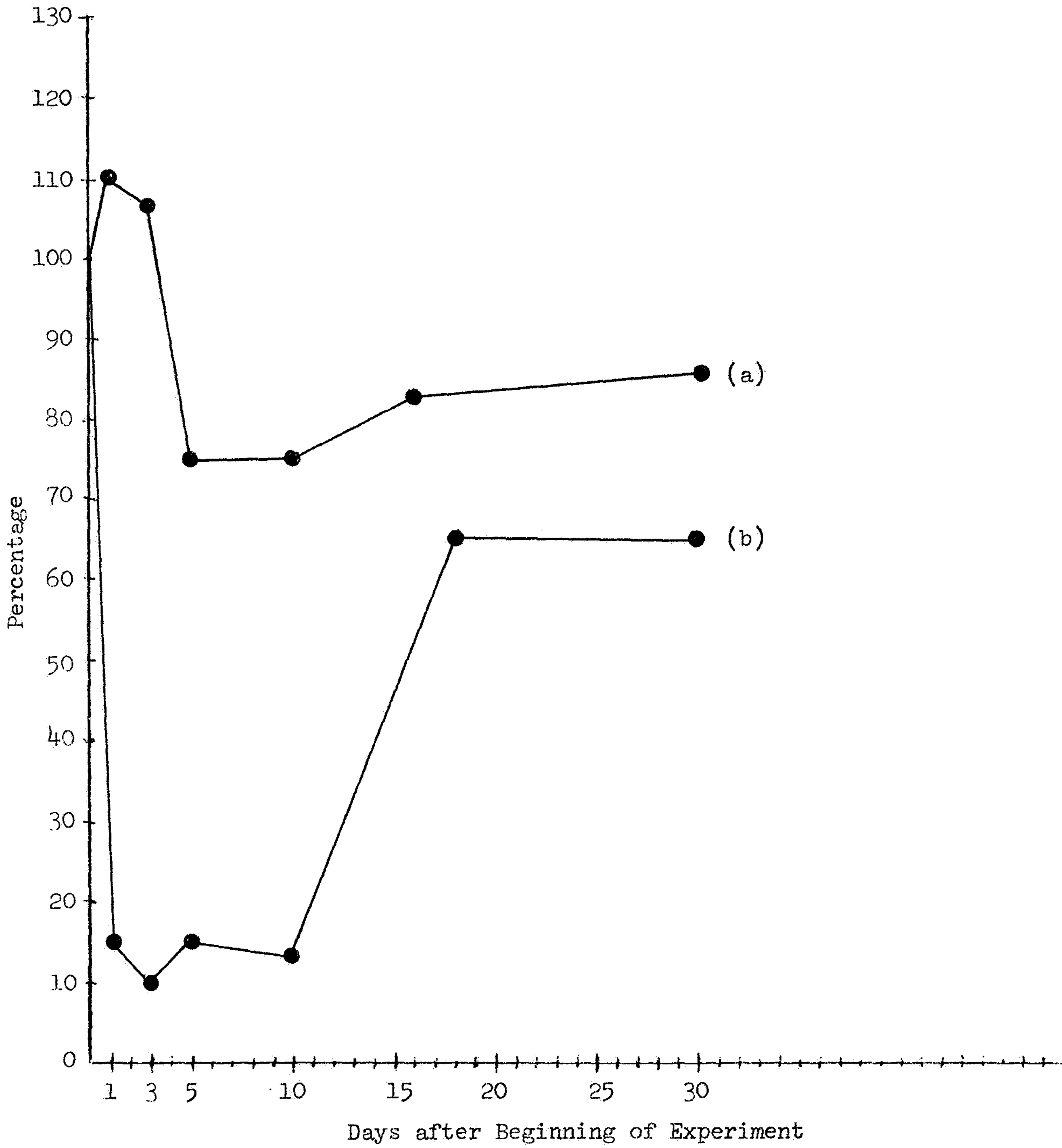


Figure 32. 400 Rad - Rats.
Change of quantity of (a) erythrocytes and (b) leukocytes in the blood of rats during first 45 days after irradiation.

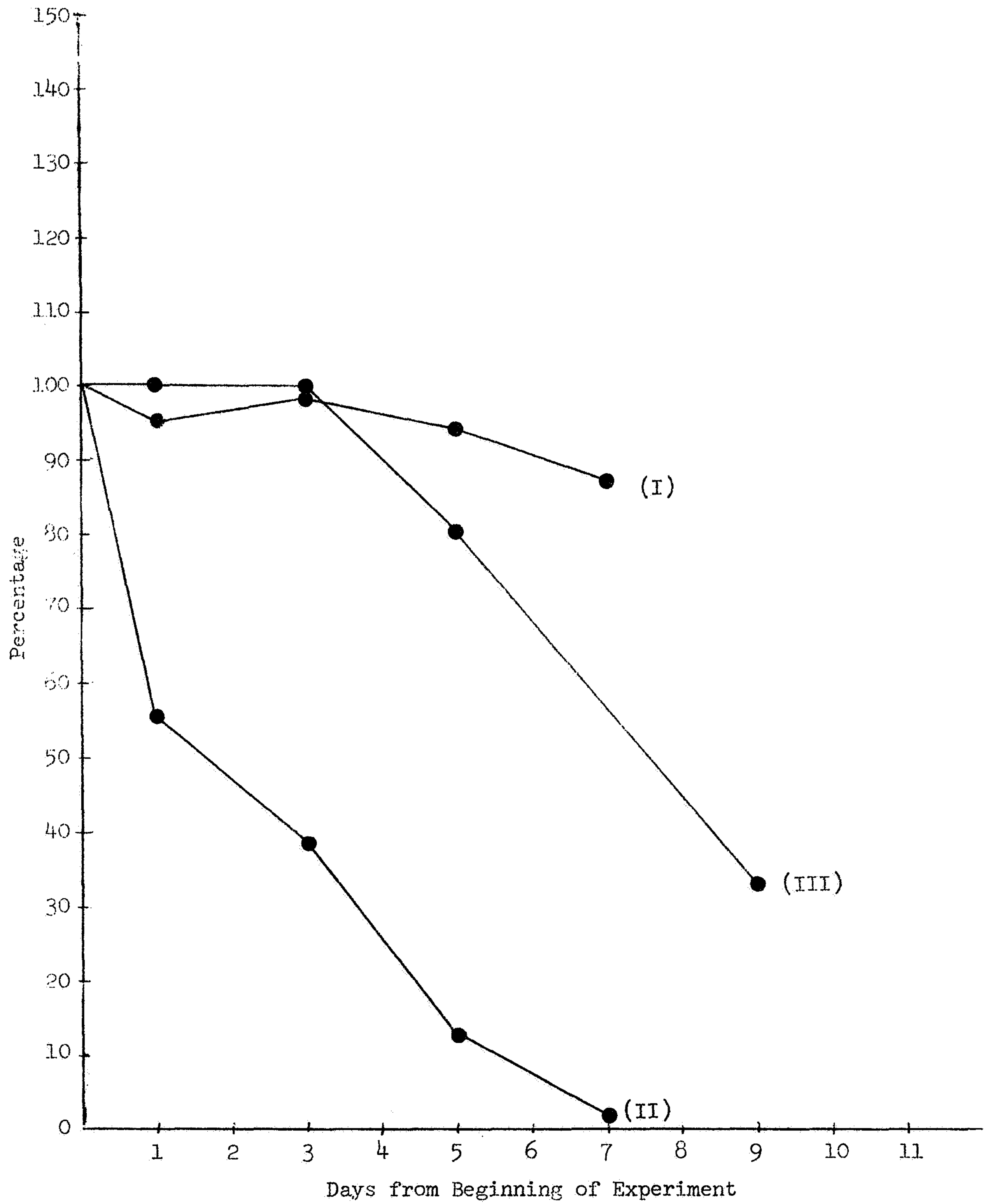


Figure 33. Change of quantity of erythrocytes (I), leukocytes (II), and thrombocytes (III) in dogs irradiated to 500 rads.

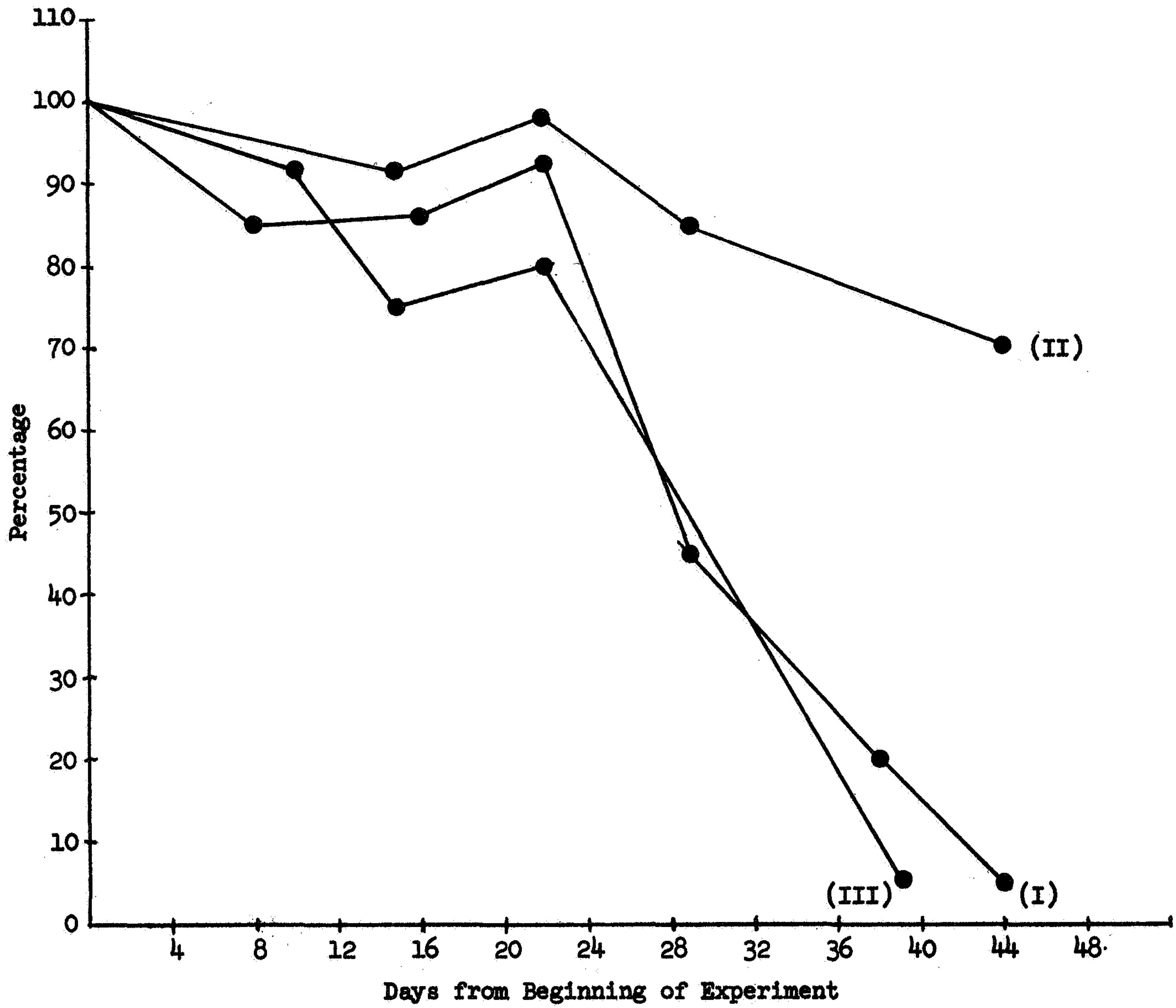


Figure 34. Dynamics in the change of number of leukocytes (I), erythrocytes (II), and thrombocytes (III) in dogs during fractional 510 MeV proton irradiations to a dose of approximately 600 rads.

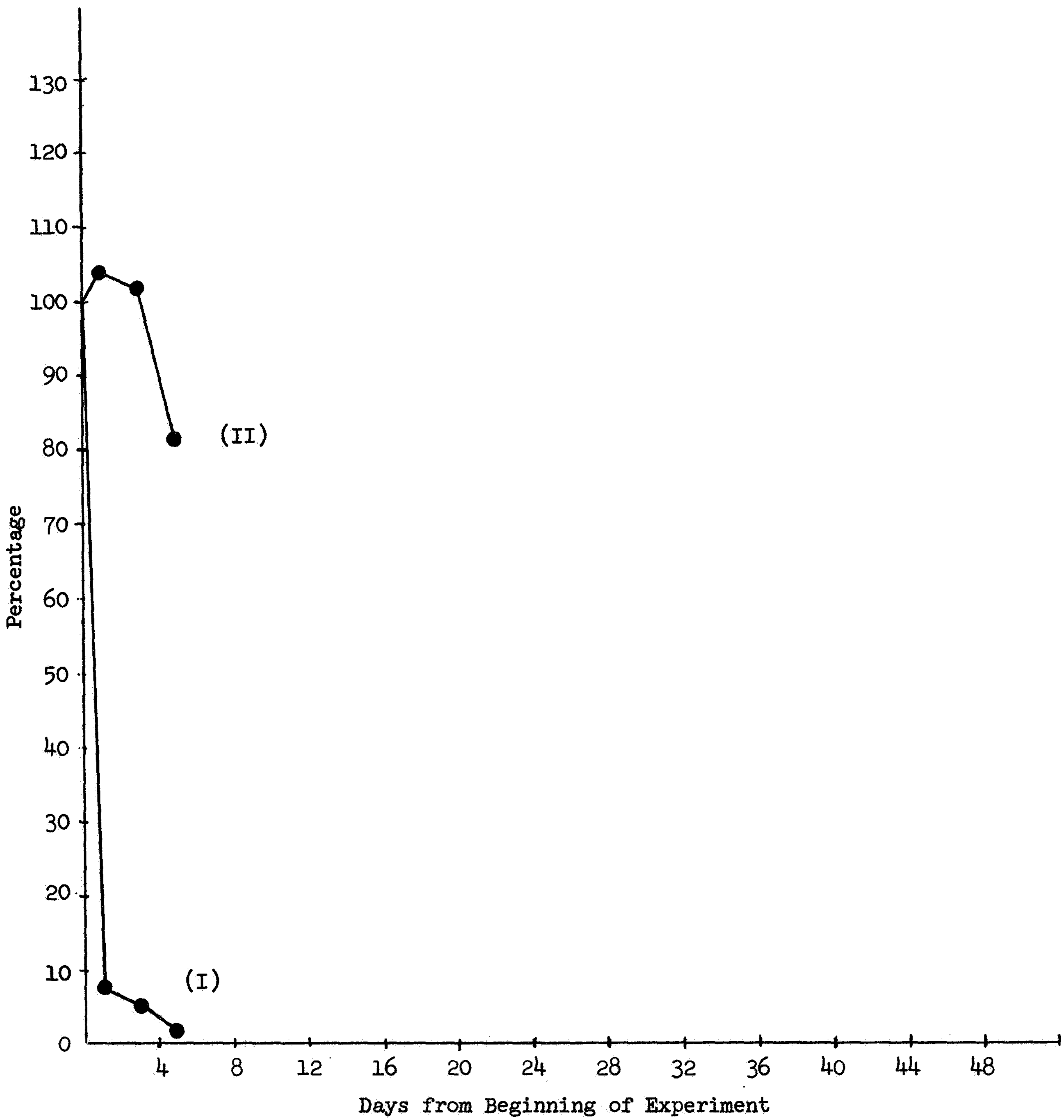


Figure 35. Change of quantity of leukocytes (I) and erythrocytes (II) in the blood of rats during first 45 days after irradiation by 510 MeV protons to a dose of 620 rads.

3. A decrease in the early generation of erythroblastic and granulocytic portions of the marrow.

4. A decrease in the number of erythroblasts in mitosis and in the number of monocytes.

5. An increase in the number of poorly differentiated reticuloendothelial cells.

6. An increase in the number of lymphocytes and plasmacytes with an appearance of fibroblasts.

7. Degenerative cell forms in the marrow with pyknosis, chromatinolysis, and fragmentosis.

TABLE LVIII

Changes In The Indices Of The Peripheral Blood In Dogs After Single Proton Irradiations To A Dose Of 550 Rads

Time of analysis	Quantity-leukocytes: 1000 per mm^3	Quantity-erythrocytes: 1 million per mm^3	Hemoglobin content (Sali method)	Reticulocyte content %	Thrombocyte content 1000 per mm^3
Before irradiation	9.52 ± 1.65	7.03 ± 0.46	97 ± 4.2	7 ± 0.8	276 ± 30
3rd	3.38 ± 1.29	6.85 ± 0.34	98 ± 3.6	0	279 ± 58
7th	0.38 ± 0.06	5.92 ± 0.30	87 ± 6.9	0	90 ± 22

TABLE LIX

Mean Data On Change Of The Indices In The Peripheral Blood Of

Dogs Irradiated To 650 Rads

Time of examination of dogs, days	Number of erythrocytes, millions per 1 mm^3	Hemoglobin content g %	Number of thrombocytes, thousands per 1 mm^3	Number of reticulocytes, %	Number of leukocytes, thousands per 1 mm^3	RBE mm/hour
Before irradiation	6.40 ± 0.22	14.2 ± 0.3	452 ± 23	9.6 ± 1.7	12.3 ± 0.4	2
"	6.90 ± 0.16	14.1 ± 0.2	320 ± 56	6.0 ± 2.0	9.7 ± 1.3	3
"	6.38 ± 0.36	13.8 ± 0.2	311 ± 29	6.8 ± 1.6	12.3 ± 1.5	3
Mean before irradiation	6.56 ± 0.24	14.0 ± 0.4	361 ± 30	7.4 ± 1.1	11.4 ± 0.8	3
At time of irradiation						
8th	6.38 ± 0.20	12.9 ± 0.3	336 ± 12	4.0 ± 0.9	9.8 ± 1.0	4
15th	6.10 ± 0.13	16.6 ± 0.4	277 ± 25	3.6 ± 0.9	9.9 ± 0.9	6
22nd	6.40 ± 0.26	15.1 ± 0.5	287 ± 14	1.3 ± 0.3	10.7 ± 1.7	9
29th	5.65 ± 0.15	12.9 ± 0.5	162 ± 13	0.1 ± 0.1	5.4 ± 0.6	10
38th	5.14 ± 0.08	13.3 ± 0.5	170 ± 34	0.0	1.9 ± 0.4	15
43rd	4.10 ± 0.17	10.9 ± 0.0	-	-	1.00 ± 0.6	22

TABLE LX

Mean Data On Content Of Different Forms Of Leukocytes Found

In The Peripheral Blood Of Dogs Irradiated To 650 Rads

Time of examination (days from beginning of irradiation)	Number of leukocytes, thousands per 1 mm3	Number of neutrophils, thousands per 1 mm3	Number of lymphocytes, thousands per 1 mm3	Leukocytic formula, %						
				Eosinophils	Young	Rod-shaped-nuclear	Segmented-nuclear	Lymphocytes	Monocytes	Plasmocytes
Before irradiation	11.4	8.35	1.63	7.2	-	2.6	70.7	14.3	6.2	1.2
8th	9.8	7.21	1.21	5.9	-	2.7	70.9	12.4	9.8	0.7
15th	9.9	7.60	1.08	4.4	3.0	3.3	73.5	11.0	6.3	1.1
22nd	10.7	9.03	0.93	2.6	5.5	4.8	79.6	8.7	6.4	3.5
29th	5.4	4.24	0.42	6.5	-	3.7	75.0	7.8	4.7	1.3
38th	1.9	1.48	0.32	7.0	-	7.2	70.9	17.0	4.0	1.0
43rd	0.5	0.27	0.15	11.0	-	10.0	45.0	32.0	2.0	-

The blood contained degenerative cells, there was chromatinolysis and fragmentation of the nuclei, an increase in cytolysis, and the appearance of toxic granularity in the protoplasm of the neutrophils was observed.

TABLE LXI

Mean Data On Change Of Indices In The Peripheral Blood Of Dogs Irradiated To 690 Rads

Time of examination	Number of erythrocytes, millions per 1 mm^3	Hemoglobin content, %, (Sali method)	Number of thrombocytes, thousands per 1 mm^3	Number of leukocytes, thousands per 1 mm^3
Before irradiation	6.23	92	244	14.1
Before irradiation	6.22	88	254	9.6
Before irradiation	6.39	90	168	11.3
Mean before irradiation	6.28	90	222	11.6
Days from beginning of irradiation: 4th, 12th, 19th	5.75 5.56 3.60	84 82 54	132 21 11	6.8 3.2 1.1

Cardiovascular System

TABLE XLII

Change Of Maximum And Minimum Arterial Pressure In Dogs

	Group I (550 rad)		Group II (400 rad)		Group III (250 rad)	
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
Before irradiation						
26/VI	120 ± 1.9	69 ± 3.8	120 ± 4.8	70 ± 0	115 ± 4.7	68 ± 2.8
28/VI	120 ± 3.8	64 ± 3.8	116 ± 6.0	64 ± 3.6	119 ± 4.7	62 ± 0.9
Mean before irradiation	120 ± 2.8	67 ± 3.8	118 ± 5.4	77 ± 3.6	117 ± 4.7	65 ± 1.7
After irradiation						
1st	117 ± 6.7	61 ± 3.8	120 ± 7.3	57 ± 3.6	122 ± 3.8	57 ± 2.8
3rd	110 ± 6.7	51 ± 3.8	107 ± 4.9	51 ± 6.0	109 ± 7.6	59 ± 11.2
5th	120 ± 3.8	57 ± 0.9	102 ± 1.2	60 ± 3.6	115 ± 5.7	64 ± 2.8
10th	-	-	108 ± 10.9	54 ± 2.4	124 ± 5.7	61 ± 2.8
16th	-	-	-	-	98 ± 12.0	48 ± 3.4
19th	-	-	-	-	85 ± 8.7	23 ± 8.6

TABLE LXIII

Change Of Some Indices Of Condition Of The Peripheral Vascular System Of Dog Stelka After Single Irradiation By Protons With Energies Of 510 Mev To A Dose Of 690 Rad

Days	Tone		Pressure, mm Hg		Blood flow rate, mm3/sec	Pulse rate, beats/min	Ear skin temperature, °C
	Arterial mm-1	Venous cm-1	Arterial	Venous			
Before irradiation	0.40	0.66	--	--	5.3	100	35.5
"	0.28	0.58	--	--	7.3	80	36.3
"	0.50	0.50	--	--	8.2	78	37.0
"	0.50	0.40	--	--	6.5	68	34.6
"	0.33	0.50	--	--	7.1	68	35.0
"	0.40	0.58	--	--	6.3	84	35.7
"	0.33	0.66	--	--	6.5	80	36.4
"	0.33	0.66	--	--	4.5	100	38.9
"	0.33	0.62	80	4	4.3	96	35.0
"	0.33	0.52	75	0-2	4.5	108	35.6
After irradiation							
0	0.50	0.66	100	20.0	3.8	124	35.0
1st	0.66	2.00	55	13.5	2.0	80	33.4
2nd	0.40	0.38	--	5.0	4.3	72	32.3
3rd morning	0.47	0.80	80	11.0	4.2	120	33.3
3rd evening	2.00	5.00	58	0-2	0.8	124	23.0

NOTE. Recording of background indices of condition of peripheral vascular system was carried out for 2 weeks before irradiation.

TABLE LXIV

Mean Data On Change Of Arterial Pressure And Other Hemodynamic Indices In Dogs

Group I (650 rads)		Time of examination of dogs of groups II and III, days after first irradiation	Group II (690 rads)			Group III (550 rads)		
Time of examination, days	Maximum arterial pressure, mm Hg		Maximum arterial pressure, mm Hg	Rate of propagation of pulse wave, m/sec	Pulse beats/min	Maximum arterial pressure, mm Hg	Rate of propagation of pulse wave, m/sec	Pulse beats/min
Before irradiation	--	Before irradiation	117	5.12	103	121	--	101
" "	110	" "	112	4.60	102	116	4.55	111
" "	112	" "	115	4.80	103	119	4.90	92
Mean before irradiation	111	Mean before irradiation	115	4.83	103	119	4.72	96
Period of irradiation		Period of irradiation						
8th	115	4th	115	5.66	97	136	5.33	95
15th	117	12th	97	5.66	102	140	5.05	100
22nd	91	19th	95	4.80	124	128	5.45	100
29th	100	26th	--	--	--	--	5.00	107
		After irradiation						
38th	104	34th	--	--	--	126	4.90	99
43rd	87	42nd	--	--	--	120	5.17	80
		49th	--	--	--	122	5.17	86
		57th	--	--	--	128	4.77	90
		64th	--	--	--	110	4.77	83
		100th	--	--	--	129	5.00	72

On the 22nd day, the indices of vascular tone were appraised as angiospasm. The blood flow rate had a tendancy to decrease on the eve of death. In at least two animals, there was angiospasm of the auricle.

After two weeks in animals given more than 650 rads, there were changes in the EKG reflecting functional and organic injury of the myocardium and circulatory system. At the height of the radiation syndrome, there was a splitting of the R wave, a decrease in amplitude, and in some cases, an inversion of the T wave. These occurred at a later time in the 550 rad group. There were also changes in the ST segment and the PQ interval.

Both oxygen consumption and the expiration of CO_2 decreased 35 - 50 per cent following irradiation and continued until death. These also manifested themselves in survivors (3 dogs) in the 550 rad group. In some cases, however, initial increases were observed.

There were bacterial changes in other tissues than the skin. Studied were the quantity of coccal flora, the bactericidal change of serum and the change in phagocytal activity of the neutrophils. In general, an impairment of nonspecific resistance to infection was found.

TABLE LXV

Protein Composition Of Blood Serum In Dogs Irradiated To A Dose Of 550 Rad (Mean Data For 5 Animals)

Date and time of examination, days	Total protein, g %	Serum mucoids mg % tyrosine	Relative content of protein fractions, %				
			A	α_1	α_2	β	γ
Before irradiation							
26/VI	7.4	2.4	55.2	5.6	7.8	21.7	9.0
28/VI	7.5	3.6	55.2	6.0	7.9	20.5	10.1
After irradiation							
1st	6.1	4.5	51.2	5.8	9.7	19.0	13.9
2nd	7.7	4.1	50.6	6.3	10.7	18.8	14.6
5th	7.1	4.8	46.5	6.7	13.2	20.2	12.9
7th	6.7	7.7	41.8	7.1	18.2	21.6	10.5

TABLE LXVI

Protein Composition Of The Blood Serum Of Dogs Irradiated To A Dose Of 250 Rad (Mean Data For 5 Animals)

Date & time of examination, days	Total protein, %	Serum mucoids mg % tyrosine	Relative content of protein fractions, %				
			A	α_1	α_2	β	γ
26/VI	7.3	2.4	57.00	5.90	7.30	20.9	8.50
28/VI	7.3	2.8	55.00	5.90	7.50	21.1	10.40
1st	6.6	3.4	53.55	5.87	8.51	21.8	10.77
3rd	6.1	2.4	52.02	6.66	8.00	20.7	12.48
5th	6.1	2.8	51.25	6.47	8.06	20.5	12.57
7th	6.3	3.0	47.70	8.20	9.00	21.4	12.30
10th	6.5	4.7	48.82	8.49	9.13	23.4	10.65
16th	6.5	4.5	50.83	6.35	9.82	21.7	11.11
19th	7.0	4.3	46.33	7.30	14.14	23.1	8.83
30th	6.6	4.0	44.63	7.03	11.70	25.7	10.51
45th	7.2	2.4	45.13	8.77	9.62	23.8	12.35
60th	6.4	2.3	50.80	7.60	7.90	22.3	10.80

TABLE LXVII

Protein Composition Of Blood Serum In Dogs Of Irradiated To A Dose Of 400 Rads (Mean Data For 4 Animals)

Time of analysis, days	Total protein, g %	Serum mucoids mg % tyrosine	Relative content of protein fractions, %				
			A	α_1	α_2	β	γ
Before irradiation							
26/VI	7.4	2.5	60.2	5.3	8.90	17.0	8.5
28/VI	7.5	2.9	57.7	6.4	7.50	18.4	9.4
After irradiation							
1st	7.0	9.0	54.7	5.7	10.16	16.9	10.8
3rd	6.1	3.2	50.9	5.9	12.70	19.1	11.5
5th	6.3	2.9	53.7	5.5	13.70	19.8	8.6
7th	6.1	6.7	43.5	7.0	14.40	23.6	11.6

TABLE LXVIII

Change Of Protein Composition Of Serum In Dogs Irradiated To 550 Rads - Fractional Irradiation

Time of examination, days	Total protein, g %	Serum mucoids mg % tyrosine	Relative content of protein franctions, %					
			Albumins	Globulins				
				α_1	α_2	β_1	β_2	γ
Before irradiation	7.4	2.5	57.7	6.6	8.4	17.8		9.2
" "	8.1	2.5	56.8	6.0	8.1	7.8	10.1	10.6
Period of irradiation 5th	6.5	2.2	53.2	6.5	9.9	9.2	9.8	11.1
Period of irradiation 12th	7.2	3.1	55.5	6.8	8.0	8.2	9.5	11.0
Period of irradiation 20th	7.0	2.0	53.8	6.3	8.4	9.6	10.1	11.7
Period of irradiation 27th	7.2	1.5	52.3	7.3	9.8	9.8	9.1	10.3
After irradiation 36th	6.9	1.3	57.6	6.1	10.2	8.4	8.3	9.8
After irradiation 44th	7.2	1.2	53.8	7.1	11.2	9.3	8.6	9.6
After irradiation 51st	6.6	2.1	55.5	7.4	9.0	8.2	9.9	11.2
After irradiation 62nd	6.9	1.9	50.7	6.8	9.2	10.0	11.6	11.7
After irradiation 74th	7.6	2.3	55.4	5.8	8.3	9.7	9.7	10.8

TABLE LXIX

Protein Composition Of Blood Serum Of Dogs Irradiated To
650 Rads - Fractional Irradiation

Time of examination, days	OB, g %	Serum mucoids mg % tyrosine	Relative content of protein fractions, %					
			Albumins	Globulins				
				α_1	α_2	β_1	β_2	γ
Before irradiation	7.3	2.6	59.5	5.4	6.5	9.1	12.2	8.7
Days from beginning of irradiation:								
9th	7.1	2.2	54.0	5.4	7.1	13.1	9.5	9.3
15th	7.8	1.8	55.6	5.1	7.1	9.3	9.8	12.4
29th	6.5	2.3	49.4	6.9	8.8	11.0	10.2	13.5
38th	6.7	3.0	49.7	8.4	10.0	9.6	10.2	11.5
43rd	5.5	3.0	43.5	10.6	10.4	11.4	11.0	13.3

TABLE LXX

Protein Composition Of Blood Serum Of Dogs Irradiated To
690 Rads - Fractional Irradiation

Time of examination (days from beginning of irradiation)	OB, g%	Serum Mucoids mg % tyrosine	Relative content of protein fractions, %					
			Albumins	Globulins				
				α_1	α_2	β_1	β_2	γ
Before irradiation	7.3	2.2	54.6	5.7	3.5	20.4		10.6
" "	8.2	2.3	55.2	5.5	8.8	9.2	10.7	9.3
5th	7.2	2.0	55.5	6.2	10.4	9.7	8.9	9.3
12th	7.1	3.5	57.5	6.0	8.3	10.3	9.1	8.3
20th	6.8	4.1	42.2	7.8	13.9	11.2	13.0	11.7

There were sharp and persistent decreases in the activity of cholinesterase of the blood serum which did not show recovery during the animals' life span.

592 - Mev Protons [18.]

Mice

R.B.E. (relative to 250 Kvp X-ray) based on $LD_{50/30} = 0.98$.

660 - Mev Protons [19.]

Mice and Rats

R.B.E. (relative to 180 Kvp) based on $LD_{50/30} = 0.55$ (mice); $= 0.65$ (rats)

730 Mev - Protons [2, 14, 20]

Primates

$LD_{50/30}$ = 338-468 rads (95% Conf. limits).

Deaths were due to G-I damage, although typical histological changes associated with this mode of death were not seen.

Mice

LD_{50} $<$ 700 rads. R.B.E. $<$ 1.

$LD_{50/6}$,	R.B.E.	$LD_{50/12}$,	R.B.E.	$LD_{50/30}$,	R.B.E.
940	0.96	790	0.81	730	0.75

R.B.E.'s are relative to 250 Kvp X-rays.

The peak death rate for a single irradiation of 940 rads occurred on day 4, while for a split dose (470/470), it occurred on day 11. The delay between courses of irradiation was found to effect the cumulative mortality curves. This time was varied between 0.5 and 8 hours.

The fertility response was identical to the X-irradiated group. However, the number of dominent lethals found in the protein irradiated group was approximately lower than that in the X-irradiated group for the first 60 days.

Using splenic atrophy as a criteria, an R.B.E. (relative to 200 Kvp X-rays) of 1.0 was found. The spleen weight went through a 50% decrease in those mice that died but remained essentially normal in the survivors.

Using weight loss (when compared with 200 Kvp X-rays), an R.B.E. of 1.0 was obtained. In contrast to surviving animals (600 - 800 rads), the lethals showed a consistent loss of weight (approximately 30-40%). The rapidity of this decrease in weight was proportional to the dose delivered.

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