PROGRESS REPORT

SEPTEMBER 1, 1972 — FEBRUARY 28, 1973

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on the
Research Projects:

CALCULATIONS FOR CANCER RADIOTHERAPY WITH
NEGATIVELY CHARGED PIONS

and

A COMPARATIVE STUDY OF THE USE OF PHOTONS,
NEUTRONS, PROTONS, NEGATIVELY CHARGED PIONS,
AND HEAVY IONS IN CANCER RADIOTHERAPY

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Neutron Physics Division
and
Health Physics Division

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MARCH 1973

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A. CALCULATIONS FOR CANCER RADIOTHERAPY WITH
NEGATIVELY CHARGED PIONS

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INTRODUCTION

Very approximate estimates indicate that about 60,000 lives per year might be saved if new and improved radiotherapeutic techniques for cancer treatment were available. The use of negatively charged pions is one possible method of obtaining the needed improvement since these particles, because of their physical properties, make it possible, in principle, to deliver highly concentrated radiation doses to small localized regions. The calculational program described here is directed toward the following broad objectives: assessing the biological effect and radiotherapeutic value of negative-pion beams, ascertaining the influence of beam parameters on the dose, LET spectra, cell-survival probabilities, and oxygen enhancement ratios, and providing quantitative data to aid in planning and understanding biological and therapeutic exposures.

A.1. SPAR, a Computer Program for Calculating Stopping Powers and Ranges

*T. W. Armstrong and K. C. Chandler**

In order to evaluate calculationally the response of thin ($\sim 10 - 100$ microns) semiconductor detectors placed in phantoms exposed to negative-pion beams, it is necessary to have reliable estimates of the stopping powers and ranges of muons, pions, protons, and heavy (mass number > 1) ions. Although theoretical and experimental values for stopping powers and ranges are available from the literature for numerous cases, the needed information for stopping powers and ranges over a wide range of energies, materials, and particle types is not readily available. In particular, available stopping-power and range data at very low energies (which are important in studying thin detectors) are sparse and often in disagreement. Therefore, a computer program named SPAR (Stopping Powers And Ranges) has been written to calculate the stopping powers and ranges of muons, pions, protons, and heavy ions in any nongaseous medium at energies from zero to several hundred GeV.**†

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**Stopping powers provided by SPAR are also needed in calculating the LET spectra produced by π^- beams and in calculating cell-survival probabilities. SPAR has been programmed so that it can be used in these studies also.

†The writing of this code was partially funded by the National Aeronautics and Space Administration and by the U. S. Atomic Energy Commission.

Stopping powers are computed with SPAR using a different calculational procedure for each of three (β, z) regions, where β is the speed of the particle relative to the speed of light and z is the nuclear charge of the particle. At high energies ($\beta > 0.04 z^{2/3}$), where the particles can be considered to be completely ionized, Bethe's¹ theory with shell and density-effect corrections is used. At intermediate energies ($0.0046 z^{1/3} < \beta \leq 0.04 z^{2/3}$), where charge reduction is important but energy losses from elastic Coulomb collisions can be ignored, an empirical expression² for the charge reduction is used in conjunction with Bethe's theory. At low energies ($0 \leq \beta \leq 0.0046 z^{1/3}$), where both charge reduction and nuclear Coulomb stopping are important, the theory of Lindhard *et al.*³ is used. For $\beta < 0.04 z^{2/3}$, the range is computed by numerical integration of the stopping power. For $\beta \geq 0.04 z^{2/3}$, the range for protons is computed by numerical integration of the proton stopping power, and the ranges for other particle types are scaled from the proton range.

Stopping powers and ranges computed with SPAR have been compared in a few cases with the work of others. For example, Fig. A1.1 shows a comparison of the stopping powers of alpha particles in water.

A report describing SPAR has been written and is in press.⁴ A short description of SPAR will be submitted for journal publication, and the computer program will be made available to others through the Radiation Shielding Information Center of the Oak Ridge National Laboratory.

Fig. A1.1. Alpha-particle stopping power in water as computed by SPAR and as given by Northcliffe and Schilling,⁵ Steward,⁶ Caswell and Berger,⁷ and Tisljar-Lentulis *et al.*⁸

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A.2. Modification of the Code HETC to Include Range Straggling

*T. W. Armstrong and K. C. Chandler**

In previous pion-dose calculations using the computer code HETC,¹ the effects of energy-loss fluctuations on the charged-particle ranges (i.e., range straggling) have either been ignored² or taken into account in an approximate manner.³ Since for certain pion beams range straggling can be an essential factor in determining the spatial distribution of the π^- captures and, consequently, the spatial distribution of the absorbed dose and biological damage, the transport code HETC has been modified to include range straggling for all primary and secondary pions, protons, and muons.

The straggled range distribution is taken to be Gaussian about the mean range with a variance given by:⁴

$$\sigma_{iR}^2(E \rightarrow E') = 4\pi e^4 Z_i^2 n \int_{E'}^E \frac{(1 - \frac{1}{2}\beta^2) K(E)}{(1 - \beta^2)[1 + (2m_e/m_i)\gamma]} [S_i(E)]^{-3} dE ,$$

where

$\sigma_{iR}^2(E \rightarrow E')$ = the variance of the range distribution for a particle
of type i slowing down from kinetic energy E to E' ,

e = the electron charge,

Z_i = the charge of the particle slowing down,

n = the electron density of the stopping medium,

K = the binding correction factor,

$\beta^2 = [(E^*+1)^2 - 1]/(E^*+1)^2$,

$E^* = E/m_i c^2$,

m_e = the electron mass,

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$$\gamma = (1-\beta^2)^{-\frac{1}{2}},$$

S_i = the stopping power.

The factor K takes into account the binding effect of the atomic electrons at low E . Since K depends upon the effective ionization potentials and oscillator strengths of the individual electron shells of the atoms in the stopping material, it is laborious to evaluate in general. However, K has only a small influence on the value of the integral at the energies of interest here.⁵ Therefore, approximate values for K are sufficient and these are obtained for all stopping media by extrapolation and interpolation of the values given by Sternheimer⁴ for Be, Al, and Pb.

Ranges are chosen from the distribution

$$p(R_i) dR_i = \frac{1}{\sigma_{iR}^2 \sqrt{2\pi}} \exp \left[-\frac{(R_i - \bar{R}_i)^2}{2\sigma_{iR}^2} \right] dR_i,$$

where $\bar{R}_i$ is the mean range. HETC precomputes and stores the mean range and variance for protons as a function of energy for each medium in the system. Values of $\bar{R}_i$ and σ_{iR}^2 for pions and muons are obtained by scaling the stored proton values; i.e.,

$$\bar{R}_i(E_i) = (m_i/m_p) \bar{R}_p(E_i m_p/m_i)$$

and

$$\sigma_{iR}^2(E_i) = (m_i/m_p) \sigma_{ip}^2(E_i m_p/m_i).$$

If in slowing down the particle passes from one material to another, a new straggled range is chosen based on the material being entered and the energy at the medium boundary.

In determining the energy of the particle at any position during slowing down, a detailed treatment of the energy-loss fluctuations is not taken into account explicitly. Instead, the mean stopping power is modified so that the proper straggled range distribution and mean energy loss are obtained. To elaborate, consider a particle starting with energy E_0 and having straggled range R and mean range $\bar{R}$. After traveling a distance Δx , the energy of the particle is taken to be defined by

$$\int_E^{E_0} dE'/S'(E') = \Delta x , \quad (A2.1)$$

where $S'(E')$ is the stopping power which will result in a straggled range R when the particle loses all of its initial energy E_0 by ionization and excitation. Thus, S' is defined by

$$\int_{E_{\min}}^{E_0} dE'/S'(E') = R , \quad (A2.2)$$

where $E_{\min}$ is a cutoff energy at which the particle is considered to be stopped and the transport is terminated. ($E_{\min}$ is an input option to the code and is chosen sufficiently close to zero so that the residual range at $E_{\min}$ is negligible compared to R .) The mean range is given by

$$\int_{E_{\min}}^{E_0} dE'/\bar{S}(E') = \bar{R} , \quad (A2.3)$$

where $\bar{S}$ is the average energy loss per unit distance, i.e., the mean stopping power. From Eqs. A2.2 and A2.3,

$$S'(E') = \bar{S}(E') \bar{R}/R ,$$

and, substituting into Eq. A2.1,

$$\begin{aligned}\Delta x &= (R/\bar{R}) \left[\int_{E_{\min}}^{E_0} dE' / \bar{S}(E') - \int_{E_{\min}}^E dE' / \bar{S}(E') \right] \\ &= (R/\bar{R}) [\bar{R}_r(E_0) - \bar{R}_r(E)]\end{aligned}$$

or

$$\bar{R}_r(E) = \bar{R}_r(E_0) - \Delta x \bar{R}/R ,$$

where $\bar{R}_r$ is the mean residual range. Thus, the desired energy E can be retrieved from the stored tables of mean residual range vs energy.

The modifications to the code to include range straggling have been completed. The spatial distribution of the absorbed dose produced by an 82-MeV π^- beam incident on a slab of tissue has been computed using the modified code and compared with the dose obtained previously³ for this case in which range straggling was treated in a very approximate manner. The depth dependence of the absorbed dose from the two calculations differ by $\leq 10\%$. This small difference does not warrant redoing any of the previous calculations, but in all subsequent work the modified code will be used.

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A.3. Modifications of PION-1

R. N. Hamm, H. A. Wright, and J. E. Turner

Minor modifications have been made in the computer code PION-1, a Monte Carlo code developed in the Health Physics Division for the transport of pions, muons, and electrons with energies up to 125 MeV through water and other tissue equivalent material.¹⁻³ PION-1 could be considered as essentially a simulation, for the applicable cases, of the more general code HETC,⁴ developed by the Neutron Physics Division, in the sense that it samples from distributions generated by the cascade and evaporation models for nuclear interactions used in HETC.

Range straggling has now been included in PION-1. For each incident pion, a range is selected from a Gaussian distribution and the effective stopping power for that pion is adjusted to give it the selected range.

The treatment of multiple coulomb scattering, which was already in the code, has been improved. Originally a scattering angle was chosen from a distribution which would give the appropriate lateral displacements at a specified depth and the particle was transported in a straight line after its direction had been altered by the selected angle. This treatment has now been modified so that after traveling a specified distance (usually taken as 1 gm/cm^2) the direction of travel is altered by selecting an angle from the appropriate distribution. This allows the particles to more nearly simulate the actual paths that would be experienced. Both methods of treatment are available and

when the effects of the difference in the two methods of treatment are expected to be small, the former method can be used in order to save computing time.

Provision has now been made in the code for treating inhomogenities in the phantom, e.g., tissue, bone, or lungs.

The code PION-1 can be considered as an "intermediate" between the detailed code HETC and a simulation code that might be used on a small mini-computer by a radiologist in planning a therapy treatment. However, PION-1 is still a Monte Carlo code which treats each particle (nucleon, meson, electron, alpha, etc.) individually and enables the tabulation of LET distributions, the application of cell survival models, etc. Absorbed dose distributions calculated with PION-1 have been compared with results of experiments at CERN^{1,2} and good agreement has been obtained.

Results of the code PION-1 will be compared with those of the more detailed code HETC as time allows. It is expected that where the agreement is satisfactory, the code PION-1, which is faster and uses much less memory space, will be used.

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A.4. Isodata Contours

H. A. Wright, V. E. Anderson,* R. N. Hamm and J. E. Turner

In order to visualize the distribution of absorbed dose, cell survival, etc., it is helpful to have isodata contours. A computer program has been written for obtaining two-dimensional isodata contours for the data generated by the computer programs for pion transport and cell survival. These data are generated by Monte Carlo methods, and computer time limitations prevent the running of a sufficient number of particles to remove significant statistical fluctuations, particularly in regions where the dose is very low. Consequently, it is necessary to use a smoothing technique in order to reduce the effects of statistical fluctuations. The data are generated by assuming cylindrical symmetry about the axis of the pion beam and are given as a function of depth z of penetration and radial distance r from the beam axis. Typically about 50 values of z and 10 values of r are used. The procedure for obtaining the isodata contours will now be described briefly.

For each value of r , the data are first smoothed as a function of z by a procedure that amounts to successive averaging of adjacent values of z . An iterative unfolding technique,¹ which was developed for analyzing experimental data in which the apparatus itself performs a transformation on the data, is then applied to unfold structure that might be lost in the smoothing. Since there are only a few values of r , and since there is generally

* Mathematics Division.

a large radial gradient in the data, attempts at smoothing or curve fitting as a function of r , as well as two dimensional smoothing, have generally been unsuccessful. Consequently, data at intermediate values of r are obtained by exponential interpolation between the values obtained after smoothing on z .

Figure 1 shows an example of isodose contours obtained for data calculated by the code PION-1² for the case of a pion beam of mean momentum 175 MeV/c and momentum spread 2%, incident on a water phantom. As mentioned above, cylindrical symmetry has been assumed. Consequently, the curves are symmetric about the beam axis and give the contours that would be seen in a plane containing the beam axis. The program is being modified to permit the option of having smooth contours to be drawn rather than points as in this figure.

One check that can be used to test the reliability of the fitting procedure is to compare the integral of the dose determined by the contours to the integral of the raw data. This integration has been performed over r for each z interval and agreement has generally been to within 10 percent for the cases tried so far. This agreement is considered very good in view of the statistical fluctuations in the raw data.

Fig. 1. Isodose contours at the levels of 0.9, 0.8, 0.5, 0.2, 0.1, 0.02, 0.01, 0.005, and 0.001 of the maximum.

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A.5. Calculation of Spatially Dependent Cell-Survival Probabilities

*T. W. Armstrong and K. C. Chandler**

A computer program that reads the particle transport data generated and stored on magnetic tape by the code HETC and computes spatially dependent (r and z) cell-survival probabilities, RBE, and OER using the model of Katz *et al.*¹ has been written and is operable. The program is applicable for incident pions, protons, and neutrons.

Cell-survival calculations have been made for the case of a broad beam of monoenergetic (82 MeV) negatively charged pions incident normally on a 30-cm-thick slab of tissue. In checking out the program, this case was chosen as a matter of convenience (the transport data generated by the code HETC for this case were available from previous work²), and, since the incident pions are all of the same energy, it does not represent a pion beam that would be of primary interest in treatment planning.

The depth dependence of the absorbed dose is shown in Fig. A5.1, and Fig. A5.2 shows the depth dependence of the cell-survival probabilities for both T-1 human kidney cells and leukemia cells. The cell-survival probability for T-1 kidney cells was computed using the latest model parameters (which differ somewhat from the published values¹ for T-1 cells) provided by R. Katz. Model parameters for leukemia cells have recently been obtained by R. Katz and coworkers and communicated to us, and these parameters have been used to compute the cell-survival probability for leukemia shown in Fig. A5.2. The incident-pion intensity (6.038×10^9 pions/cm²) was chosen to obtain 50% cell-survival probability for T-1 cells at the surface

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Fig. A5.1. Depth dependence of the absorbed dose in tissue for 82-MeV incident negatively charged pions.

Fig. A5.2. Depth dependence of the cell-survival probability for T-1 human kidney cells and leukemia cells under anoxic conditions for 82-MeV incident negatively charged pions.

(zero depth). Figure A5.2 shows that the ratio of the cell-survival probability at the surface to the cell-survival probability in the pion-stopping region (around 20 cm) is very large ($\sim 10^7$). For a beam more representative of the type that would be used in radiotherapy where a distribution of incident pion energies would be used, this ratio would still be expected to be very large but somewhat less than that obtained here for a monoenergetic beam where the incident pions stop in a relatively small depth interval. The depth dependence of the cell-survival probability is similar for kidney and leukemia cells except in the pion-stopping region where the kidney cells are killed much more efficiently. The depth dependence of the RBE and OER at various survival levels has also been computed.

At present experimental data on the spatial dependence of cell survival are not available to test the validity of the calculations. Experimental data on the spatial dependence of the cell survival of T-1 kidney cells for incident pions³ and incident neutrons⁴ are expected in the near future. These data should provide a definitive test of the calculations, and comparisons will be made as the data become available. In the interim, we have compared calculated and measured cell-survival probabilities for two cases which do not involve any spatial dependence. Barendsen and Broerse⁵ have made measurements of the survival of T-1 kidney cells exposed to 14-MeV neutrons. We have used HETC to compute the energy spectra of secondary charged particles produced by 14-MeV neutron bombardment of tissue nuclei. These spectra and the Katz *et al.* model were used to calculate the cell-survival probability, and excellent agreement⁶ with the experimental data was obtained. Also, Raju *et al.*⁷ have placed T-1 cells in the stopping region of a pion beam and measured the cell survival. We have calculated

the cell-survival probability in the peak dose region (19.8 - 20.0 cm) for the 82-MeV pion beam discussed above, and a comparison with the Raju *et al.* data is shown in Fig. A5.3. The agreement is good, although the calculated survival is slightly lower. However, the experiment was performed using an incident beam with a moderately wide momentum distribution and the calculations are for a monoenergetic beam. Thus, the difference in the incident beams is probably sufficient to account for the small difference in cell survival shown in Fig. A5.3. In subsequent cell-survival calculations, pion beams with a distribution of incident energies will be considered, and these calculations will allow a more definitive comparison with the Raju *et al.* data. Computed values for the RBE and OER of T-1 cells in the peak dose region have also been compared with the measurements of Raju *et al.*,⁷ and good agreement is obtained.

The program for calculating cell-survival probabilities seems to be working properly, and the program will now be used to compute the radial and depth dependence of cell survival, RBE, and OER for incident proton and neutron beams, as well as for other pion beams.

Fig. A5.3. Comparison of calculated and measured⁷ cell-survival probabilities in the pion-stopping region for T-1 kidney cells under anoxic and aerobic conditions.

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A.6. Calculation of LET Spectra

*T. W. Armstrong and K. C. Chandler**

A subroutine that will calculate spatially dependent LET spectra from the transport data generated by the code HETC is being written. This subroutine will be added to the present HETC analysis program that calculates absorbed dose and cell-survival probabilities, and will be applicable for incident pions, protons, and neutrons.

The output will consist basically of the absorbed dose deposited in various LET intervals as a function of position (r and z). As a particle loses energy by ionization and excitation, the energy deposition in the appropriate LET and spatial intervals will be computed using the SPAR program** to relate the kinetic energy of the particle to a specified LET grid. The contributions to the LET spectra by various particle types (pions, protons, deuterons + tritons + ^3He 's + alpha particles, recoil nuclei, muons, and electrons + positrons + photons) will also be obtained. In addition, the integral LET spectra, i.e., the energy deposited by particles with LET greater than specified values of LET, will also be computed as a function of position.

The computer programming for calculating LET spectra is in progress and is about 80% completed.

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**See Section A.1.

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A.7. The Effect of Bone in the Use of Negatively Charged Pions in Cancer Radiotherapy

R. T. Santoro
R. G. Alsmiller, Jr.
*K. C. Chandler**

When negatively charged pions are used to irradiate a tumor, the pions may or may not pass through bone before coming to rest and being captured in the vicinity of the tumor. Since the composition of bone is considerably different from that of tissue, it is necessary to know how the presence of bone along the pion path should be taken into account in treatment planning.

To answer this question, calculations have been carried out with the high-energy transport code HETC¹ for cases with bone both present and absent. The model used is that of a zero-width beam of monoenergetic (53 MeV) negatively charged pions normally incident on a slab of thickness 30 g cm^{-2} . In the first case, the slab was composed entirely of tissue, while in the second case the slab was composed of tissue except that a 1.08-cm ($= 2 \text{ g cm}^{-2}$) thick slab of bone was inserted at a depth of 1 g cm^{-2} ; i.e., the bone began at a depth of 1 g cm^{-2} and ended at a depth of 3 g cm^{-2} . The case considered here for tissue only is one of the cases discussed in detail in ref. 1, and the method of calculation is the same as that described in ref. 1. The composition of bone was taken from ref. 2.

The absorbed dose integrated over the indicated radial intervals is shown in Fig. A7.1 as a function of depth in the slab. Note that the absorbed doses in the figure are expressed in $\text{ergs cm}^{-1} (\text{incident pion})^{-1}$ to avoid any ambiguity about density, and the depth is expressed in g cm^{-2} . For all depths and all radial intervals considered, the differences between

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Fig. A7.1. Absorbed dose integrated over the indicated radial intervals vs depth in g cm^{-2} . (The tissue-bone configuration is described in the text.)

the solid and dashed histograms are within the statistical accuracy of the calculations. Thus, insofar as absorbed dose is concerned, the presence of bone near the surface of the tissue and well removed from the region where the pions are stopping and being captured may to a good approximation be taken into account by measuring depths in g cm^{-2} .

The absorbed dose may not be an accurate measure of the biological damage and therefore may not be a satisfactory basis for treatment planning with negatively charged pions. Work is in progress to compare cell-survival probabilities and LET spectra as a function of depth and radius for the two cases considered in Fig. A7.1, but results are not yet available.* In the interim, some conclusions may be drawn from the energy-deposition spectra of the various types of charged particles.** In Fig. A7.2 the energy depositions per unit depth, i.e., the energy depositions per unit volume integrated over all radii, by various charged particles in the depth interval of 9.2 to 10.4 g cm^{-2} , i.e., in the vicinity of the maximum absorbed dose, are compared for the two cases considered in Fig. A7.1. When the dashed line does not appear, it is covered by the solid line. The differences between the corresponding spectra when bone is both present and absent are quite small. This is also the case in several other depths and radial intervals that have been considered and are not shown. On the basis of this information, it seems likely that the presence of bone near the surface of the tissue and well removed from the region where the pions are stopping and being captured may, when biological damage is considered, be to a good

*See Sections A.4 and A.5.

**See Appendix B of ref. 1 for a discussion of the manner in which energy-deposition spectra may be used in conjunction with weighting factors to assess biological damage.

Fig. A7.2. Energy deposition per unit distance vs energy in the indicated depth and radial interval by various types of charged particles.

approximation taken into account by measuring depths in g cm^{-2} , but this conclusion must remain tentative until the cell-survival-probability calculations are available.

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A.8. Calculations Related to the Application of Semiconductor Detectors in Pion Radiobiology

*T. W. Armstrong and K. C. Chandler**

At the request of C. Richman of the Los Alamos Scientific Laboratory, calculations are in progress to determine the extent to which silicon and germanium detectors may be used to obtain dosimetry information in the vicinity of a stopping negatively charged pion beam. Initially, the calculations will be directed toward two main objectives: The first is to relate the measured energy deposition in the detector to the actual absorbed dose in a water phantom at the measurement location. In addition, it is of interest to know to what extent the difference between the measured and actual doses can be attributed simply to the different range and stopping-power values for the detector material vs water and to what extent the difference in doses is due to the difference in the products from π^- captures in the detector vs water. Secondly, calculations are to be made to determine the expected contributions of various types of particles (pions, protons, alpha particles, and heavy-recoil nuclei) to the measured pulse-height distribution and to determine if, from the measured distribution, the absorbed dose due to particular particle types can be inferred. There are numerous other aspects of the problem - such as the influence of detector thickness, silicon-vs-germanium response, response in the plateau region vs pion-stopping region, etc. - which are also of interest.

At present no results have been obtained, partly because the emphasis in the program up to this time has been mainly on code development rather than on applications. Also, since the problem requires reliable estimates

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of the stopping powers and ranges of various particles at low energies for a variety of materials, it was necessary to first write a computer program* to generate this information. This preliminary work is essentially finished, and since from extensive discussions with C. Richman the details of the problem, basic approach, and results needed have been well defined, initial results are expected within a few weeks.

*See Section A.1.

A.9. Effects of Various Beam Parameters on Depth-Dose Patterns

J. E. Turner, R. N. Hamm, and H. A. Wright

The distribution of dose as a function of position in a target irradiated by a beam of pions can be varied by adjusting certain parameters that characterize the beam. Foremost among these are the mean momentum of the pions, the width of the momentum distribution, beam size, and the degree of uniformity.

Studies of the effects of a number of beam parameters on both axial and radial depth-dose distributions have been started. Preliminary calculations have been made with PION-1 for a number of beams, having different shapes, sizes, degrees of uniformity, momentum distributions, and degrees of contamination. Figure 1 shows, as an example, the way in which the calculated depth-dose distribution in water changes for a typical beam when the percent momentum spread is held constant and the mean momentum is varied from 130 to 205 MeV/c. The other beam characteristics remained the same as in Ref. 1 with the contamination eliminated. (As in Ref. 1, a cylindrical detector of radius 3 cm was assumed.) These calculations are being compiled for a number of beam configurations. This work is expected to be completed during the second half of the current contract year.

Fig. 1. Variation of absorbed dose with mean momentum for a typical pion beam (Ref. 1) with fixed momentum spread of 2%.

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A.10. Contribution to Studies of Cell Survival*

H. A. Wright, J. E. Turner, and R. N. Hamm

Various models for estimating cell survival have been proposed, e.g., those of Katz,¹ Todd,² and the Berkeley group.³ Studies have been initiated to compare the predictions of these models for pions.

To estimate RBE for the survival of T-1 human kidney cells exposed to negative pions, calculations have been performed⁴ with the computer code PION-1 for a typical beam⁵ used in radiobiological experiments. The distributions of secondary products from the absorption of pions in water have been analyzed and the resultant doses weighted by the RBE values of Todd⁶ for T-1 kidney cell survival, at a level of 10%, after irradiation by heavy ions. The variation of the estimated RBE with depth in the water target for various momentum spreads is shown in Fig. 1, together with the depth-dose distributions for reference. In each case the RBE is a maximum at some distance behind the position of maximum dose. The most efficient position for killing cells is not that of maximum dose but at a somewhat greater depth, where the reduced dose is more than compensated by the increased relative number of pions absorbed.

These studies, which were begun prior to NSF funding, will be continued at a level consistent with the primary objectives of this contract. Special attention will be given to the distribution of dose from different secondary products in the immediate vicinity of the capture site.⁷

*This work is partially funded by the Division of Biological and Environmental Research, U. S. Atomic Energy Commission.

ORNL DWG.72-4131 R

Fig. 1. Variation of D and $\overline{\text{RBE}}$ with momentum spread of π^- beam. Mean momentum is 175 MeV/c and beam cross section is that of Ref. 5. Momentum spreads of 1, 2, 3 and 5% were used.

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B. A COMPARATIVE STUDY OF THE USE OF PHOTONS, NEUTRONS,
 PROTONS, NEGATIVELY CHARGED PIONS, AND HEAVY
 IONS IN CANCER RADIOTHERAPY

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INTRODUCTION

Radiotherapy, which is an important aid in the treatment of cancer, is used on about one-half of all cancer patients. Very approximate estimates indicate that about 60,000 lives per year might be saved if new and improved radiotherapeutic techniques were available. To obtain these needed improvements, a variety of particle types - neutrons, protons, negatively charged pions, and heavy ions - has been proposed for use in radiotherapy. The purpose of the program discussed here is to carry out calculationally an objective comparative study of the therapeutic value of these various particles and the commonly used ^{60}Co gamma rays. The calculational techniques and cross-section data that are being utilized will be verified insofar as possible by comparisons with available experimental data.

B.1. A Comparison of the Absorbed Dose from Negatively
Charged Pions, Protons, and Neutrons

R. G. Alsmiller, Jr.
R. T. Santoro
*J. Barish**

It is reasonably well established that negatively charged pions have physical properties that make them very favorable for use in cancer radiotherapy. The actual extent to which negatively charged pions are more suitable than protons or neutrons, however, is not well established. To obtain a partial answer to this question, calculations have been carried out with the high-energy transport code HETC¹⁻⁴ for beams of negatively charged pions and protons incident on tissue and with the OSR⁵ code for a beam of neutrons incident on tissue. In all cases, the tissue was taken to be a slab 30-cm thick.

For both pions and protons, the incident beam was assumed to have a circular cross section with a radius of 1 cm and the particles in the beam were assumed to be normally incident on the tissue. The energy distributions of the incident pions and protons were determined so that the absorbed dose integrated over all radii would be approximately a constant over the depth interval of 14 to 16 cm. The numerical procedure used to determine these energy distributions is discussed in Appendix C of ref. 4. The actual energy distributions used in obtaining the results presented here are shown in Fig. B1.1.

The energy of the incident neutrons was assumed to be 15 MeV and the neutrons were assumed to emanate from a point 100 cm in front of the tissue;

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Fig. B1.1. Energy distribution of incident negatively charged pions and protons that will produce an absorbed dose that is approximately constant in the 14- to 16-cm depth interval in a 30-cm-thick tissue slab. Both distributions are normalized to unity.

i.e., a source-to-skin distance of 100 cm was assumed. It was further assumed that the neutrons are emitted isotropically from the point source and only those neutrons in a solid-angle element with polar angle θ_s are incident on the tissue; i.e., it was assumed that all other neutrons are removed by a collimator. The tangent of the angle θ_s was taken to be $(115)^{-1}$; i.e., the incident beam was taken to have a radius of 1 cm at a depth of 15 cm into the tissue slab.

The calculated absorbed doses integrated over the indicated radial intervals are shown in Fig. B1.2 as a function of depth in the tissue slab for incident pions, protons, and neutrons. For comparison purposes, the proton and neutron absorbed doses have been normalized to be equal to the pion absorbed dose at the surface in each radial interval. To obtain absolute results in units of $\text{rad cm}^2 (\text{incident particle})^{-1}$, the values given in Fig. B1.2 must be multiplied by the appropriate factor given in Table I.

TABLE I

Normalization Factors

(The absorbed dose values in Fig. B1.2 must be multiplied by the appropriate value of N to obtain absorbed dose in units of $[\text{rad cm}^2 (\text{incident particle})^{-1}]$.)

Radial Interval	N for Pions	N for Protons	N for Neutrons
0 - 1.0 cm	1	1.81	0.115
0 - 2.5 cm	1	1.78	0.117
0 - 5.0 cm	1	1.70	0.117
0 - ∞	1	1.48	0.119

Fig. B1.2. Absorbed dose integrated over the indicated radial intervals vs depth in tissue for incident negatively charged pions, protons, and neutrons. (The beam parameters and geometry are described in the text.)

For all radial intervals other than the 0- to 1-cm interval, the ratio of the maximum absorbed dose to the surface absorbed dose is larger for incident pions than for incident protons. In the 0- to 1-cm interval, this is not the case, but, in considering this, it must be remembered that the incident proton and pion beams were assumed to have a circular cross-sectional area with a 1-cm radius. The pion absorbed dose for the 0- to 1-cm radial interval decreases with depth up to 12 cm because the pions are being removed from the radial interval being considered by multiple Coulomb scattering. Protons are also being removed from this radial interval by multiple Coulomb scattering, but the effect is more apparent for pions than for protons. Beyond the region of peak absorbed dose, the absorbed dose from the incident-pion beam is considerably larger than the absorbed dose from the incident-proton beam for all radial intervals considered. The neutron absorbed dose is a monotonically decreasing function (except for statistical fluctuations due to the fact that the calculations were performed using Monte Carlo techniques) of increasing depth for all radial intervals considered. For the same surface absorbed dose, the neutron beam gives a higher exit dose in all radial intervals than does either the pion or proton beam. The results in Fig. B1.2 are, of course, dependent on the beam parameters used. In particular, the angle θ_s for neutrons is much smaller than that which usually will be used for patient treatment, and therefore the neutron results given in Fig. B1.2 are not realistic. Work is in progress to obtain results similar to those shown in Fig. B1.2 for a larger "tumor," and in this case the neutron-beam parameter will be more realistic.

The absorbed dose may not be an accurate measure of the biological damage and therefore may not provide a satisfactory basis for assessing the relative merits of the various particles for use in cancer radiotherapy. In

obtaining the results presented in Fig. B1.2, the type, energy, and angular distribution of all of the particles that are produced in nuclear interactions have been obtained as a function of depth and radius. This is the information that is needed to calculate cell-survival probabilities as a function of position in tissue for the various types of incident particles.* Work is in progress to obtain cell-survival-probability calculations for the cases considered in Fig. B1.2, and thus a comparison similar to that shown in Fig. B1.2 but based on cell survival will be available shortly.

The high-energy transport code HETC in its published form is not capable of treating incident alpha particles. However, the code has recently been modified, using an approximate model to predict particle production from alpha-particle-nucleus collisions,⁶ and may now be used for incident alpha particles.⁷ Calculations with this modified code are being carried out to obtain absorbed-dose and cell-survival-probability data for the case of an alpha-particle beam incident on a tissue slab. The beam parameters being used are similar to those used for incident pions and protons to obtain the results shown in Fig. B1.2; i.e., the alpha particles will be normally incident on the tissue and the beam will have a circular cross-sectional area with a radius of 1 cm. The energy distribution of the incident alpha particles will be such that the absorbed dose integrated over all radii is approximately constant over the 14- to 16-cm depth interval in the tissue slab.

Calculations of the absorbed dose and cell-survival probabilities for the case of ^{60}Co gamma rays incident on a tissue slab are also being carried out. The results in this case will be obtained with the photon transport code OGRE.⁸ The geometry being used for incident ^{60}Co gamma rays is the same

*See Section A.6.

as that used for neutrons to obtain the results shown in Fig. B1.2 except that the source-to-skin distance is taken to be 80 cm and the tangent of the polar angle defining the solid angle in which the photons are incident is taken to be $(95)^{-1}$.

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B.2. Cell-Survival Probabilities for Incident Heavy Ions
with Nuclear-Reaction Products Neglected

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J. Barish*

The major impediment to carrying out accurate calculations of the energy deposition and cell-survival probabilities as a function of position when high-energy (~ 300 MeV/nucleon) heavy-ion beams are incident on tissue is the lack of information on particle production from heavy-nucleus, heavy-nucleus collisions. If, however, the approximation is made that all nuclear-reaction products may be neglected, then it is possible to obtain estimates of such quantities as absorbed dose and cell-survival probability as a function of position when heavy-ion beams are incident on tissue. To carry out heavy-ion-transport calculations in the approximation that nuclear-reaction products may be neglected, a computer code, BRAGG, was written by Litton^{1,2} some time ago. This code treats the transport of any species of heavy ions through a homogeneous medium and gives the energy distribution of the ions as a function of depth in the medium. With these energy distributions and the cell-survival theory of Katz *et al.*,³ it is possible to estimate cell-survival probabilities as a function of depth in tissue for incident ion beams.

The calculated cell-survival probabilities are given in Table I as a function of depth for monoenergetic alpha particles of energy 116 MeV/AMU normally incident on a tissue slab. Results are given for T-1 kidney cells and for leukemia cells in both nitrogen and oxygen atmospheres. The cell-survival-model parameters used for both T-1 kidney cells and leukemia cells

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TABLE I
Cell-Survival Probability vs Depth for 116 MeV/AMU
Alpha Particles* Normally Incident on Tissue

Depth in Tissue (cm)	Cell-Survival Probability			
	T-1 Kidney Cells		Leukemia Cells	
	N ₂	O ₂	N ₂	O ₂
0	.50	.50	.50	.50
1	.50	.50	.50	.50
2	.49	.49	.49	.49
3	.48	.48	.48	.48
4	.46	.46	.46	.46
5	.43	.43	.44	.44
6	.39	.39	.40	.40
7	.34	.34	.35	.35
8	.25	.26	.27	.28
9	.12	.13	.15	.15
9.2	$.84 \times 10^{-1}$	$.94 \times 10^{-1}$	.11	.11
9.4	$.49 \times 10^{-1}$	$.58 \times 10^{-1}$	$.74 \times 10^{-1}$	$.77 \times 10^{-1}$
9.6	$.19 \times 10^{-1}$	$.24 \times 10^{-1}$	$.37 \times 10^{-1}$	$.40 \times 10^{-1}$
9.8	$.10 \times 10^{-2}$	$.22 \times 10^{-2}$	$.63 \times 10^{-2}$	$.75 \times 10^{-2}$
9.9	$.75 \times 10^{-6}$	$.13 \times 10^{-4}$	$.20 \times 10^{-3}$	$.42 \times 10^{-3}$
9.97	$.70 \times 10^{-14}$	$.15 \times 10^{-8}$	$.40 \times 10^{-6}$	$.69 \times 10^{-5}$
9.99	$.14 \times 10^{-14}$	$.30 \times 10^{-9}$	$.12 \times 10^{-6}$	$.42 \times 10^{-5}$
10.00	$.65 \times 10^{-15}$	$.27 \times 10^{-9}$	$.10 \times 10^{-6}$	$.48 \times 10^{-5}$
10.01	$.72 \times 10^{-15}$	$.42 \times 10^{-9}$	$.14 \times 10^{-6}$	$.73 \times 10^{-5}$
10.02	$.18 \times 10^{-14}$	$.10 \times 10^{-8}$	$.25 \times 10^{-6}$	$.14 \times 10^{-4}$
10.03	$.30 \times 10^{-14}$	$.84 \times 10^{-8}$	$.11 \times 10^{-5}$	$.50 \times 10^{-4}$
10.05	$.32 \times 10^{-11}$	$.19 \times 10^{-6}$	$.11 \times 10^{-4}$	$.31 \times 10^{-3}$
10.10	$.25 \times 10^{-3}$	$.11 \times 10^{-1}$	$.39 \times 10^{-1}$	$.74 \times 10^{-1}$
10.15	.23	.47	.59	.74
10.20	.92	.96	.97	.98
	(incident intensity = 1.51×10^9 No./cm ²)	(incident intensity = 5.64×10^8 No./cm ²)	(incident intensity = 1.17×10^9 No./cm ²)	(incident intensity = 5.04×10^8 No./cm ²)

*The mean range in tissue of an alpha particle with energy 116 MeV/AMU is 10.06 cm.

are the latest estimates of these quantities which have been communicated to us by R. Katz. In all cases, a single irradiation has been assumed and the normalization has been fixed by requiring that the cell-survival probability at zero depth be 0.5. The incident-particle intensity required to produce this cell-survival level at zero depth is given in the table for each case. The results shown in the table are unrealistic from the point of view of cancer radiotherapy because monoenergetic beams will not be used, but they do serve to illustrate the very rapid change in cell-survival probability that occurs in the vicinity of the Bragg peak.

The code BRAGG,^{1,2} which was used in obtaining the results in Table I, is not operable for an arbitrary energy distribution of the incident ions, and it does not give the radial distribution of ions as a function of depth when a narrow ion beam is incident. Work is in progress to revise the code in both of these respects. The revisions required to treat an arbitrary incident energy distribution are relatively straightforward and should be completed in the near future. The revisions required to treat the lateral spreading of a narrow beam are not completely determined as yet, and therefore it may be some time before a version of the code that will treat this lateral spreading will be available. Of course, results for incident heavy ions cannot be definitive as long as nuclear-reaction products are not considered.

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B.3. Fragment and Secondary-Particle Production from Heavy-Ion Collisions with Nuclei*

H. W. Bertini

T. A. Gabriel

R. T. Santoro

O. W. Hermann[†]

The energy values of interest for the application of heavy-ion beams to cancer radiotherapy are of the order of a few hundred MeV per nucleon. At these energies, it has been shown that the interaction of a single incident nucleon with a nucleus can be reasonably well represented by treating the nucleus as a gas of "free" nucleons, confined in space by a potential well, and by treating the nucleon-nucleus interaction as a series of two-body reactions with the individual nucleons of the nucleus,¹ thus generating a cascade of reacting nucleons within the nucleus.

A natural extension of this concept for the case of heavy ions is, in general terms, to treat the reaction of the incident heavy ion with a nucleus as though both incident ion and target nucleus consisted of free nucleons and to treat the nucleus-nucleus reaction as a series of two-body interactions among the nucleons of the projectile and target. It will be subsequently shown that this concept is not without merit because the comparisons of theoretical predictions from a preliminary version of the model with experimental data indicate a moderately fair agreement.

More specifically, the heavy-ion reaction is envisioned to take place as follows: during the passage of the incident heavy ion (projectile) through the target, those nucleons of the projectile that are in the region

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where the target and projectile overlap undergo quasi-free reactions with the nucleons of the target. A cascade is thereby generated simultaneously in both target and projectile. The nucleons that have been jarred free of the binding forces in either the target or projectile, and that also manage to survive capture during the development of the cascade, escape from the target and projectile. They are emitted as free nucleons in various directions with a variety of energies. The remaining fragments of the projectile and of the target move off in highly excited states emitting evaporation particles until sufficient excitation energy is lost, which thereby shuts off the evaporation process.

The present version of the model only approximates the feature of the simultaneous cascades in both projectile and target. To this end, the projectile is permitted to impinge upon a target that is stationary in the laboratory frame of reference, and cascades are allowed to take place only in the target. The remaining fragments of the projectile and target are allowed to recoil and evaporate particles. The target, moving with appropriate energy to correspond to the inverse reaction, is then made to move in the opposite direction from that of the incident projectile and is made to impinge upon a stationary projectile nucleus. Cascades are now permitted only in the projectile, and again the residual fragments of the target and projectile are allowed to recoil and lose their excitation energies by particle evaporation. The directions and energies of all particles thus calculated are transformed to their corresponding values in the original laboratory frame of reference. All of the results from the forward and inverse reactions are then weighted by one-half.

The details of the properties of the projectile and target nuclei that are simulated in the calculations are described elsewhere.¹ Those that are relevant to this discussion are briefly described here. The nucleons making up the nucleus are clustered closer together near the center of the nucleus than on the edges. The density distributions are thus approximations to measured, Fermi-type, charge-distribution functions.² The outer radius is taken to be that radius at which the measured charge-distribution function falls to 1% of its value at the center. The nucleons bound in the nucleus are in constant motion with zero-temperature Fermi-energy distributions, which are determined by their local densities. Attractive single-particle potentials are assumed to exist in the nucleus, and these are made to vary in strength with the Fermi energy.

Briefly, the calculation, which employs Monte Carlo techniques, proceeds as follows:

1. A center-to-center impact parameter, modified crudely for Coulomb effects, is randomly selected from a uniform distribution over the area of a circle whose radius is the sum of the target and projectile radii. The coordinate system of the laboratory frame of reference is located at the center of the target with the z axis in the direction of the incident projectile.
2. Each nucleon in the projectile is assigned a position inside the projectile and is given an internal energy. The positions and energies are randomly selected from the density and Fermi-energy distributions described above.

3. Trajectories for each nucleon of the projectile are calculated, all parallel to the z axis, and with x and y positions determined by steps 1 and 2. Some of these nucleons will miss the target completely, while some will pass through the target but will not collide (because of target transparency). The fragment that remains of the projectile consists of all of these uncollided nucleons, and it also consists of holes interspersed throughout the fragment. The holes result from the removal of those nucleons of the incident projectile that have collided.
4. For each nucleon that collides, a cascade is developed in the target, and thus some of the cascade neutrons and protons (and also pions for sufficiently high incident projectile energies) escape with various energies and in various directions. The kinetic energy assigned to each nucleon of the incident projectile is the incident kinetic energy per nucleon of the heavy-ion reaction. The binding energy of each nucleon of the projectile that collides is subtracted from the reaction energy of the initial collision. The binding energies are calculated from the assigned internal energy of each nucleon.
5. The excitation energy remaining in the projectile fragment is calculated from the holes therein, while that for the target is calculated from the holes remaining in the target and from the number of cascade particles captured by the target.
6. Conservation of total energy and momentum is invoked in carrying out the relativistic kinematics calculations that determine the directions and kinetic energies of the fragments of the projectile

and target. Out of several similar distributions that were tried, the angular distribution for the projectile fragment that best represented experimental data was employed.³

7. As the excited projectile and target fragments move away from the interaction site, they are made to evaporate particles until their excitation energies are lost.
8. Steps 1-7 are repeated a sufficient number of times to reduce the statistical fluctuations in the resulting data to acceptable values.
9. The inverse reaction described above is calculated by repeating steps 1-8 while interchanging the roles of target and projectile, and the results are transformed back to the initial laboratory frame of reference.

The experimental data with which we can compare our preliminary results are meager, but samples of these comparisons are discussed. Table I illustrates a comparison of the predicted results vs the experimental data in one of the most stringent tests possible for heavy-ion calculations; i.e., the comparison is that of the absolute cross section for producing each of 14 fragments that are emitted into a very narrow angular range (0-4 mrad) and whose velocities are within 2% of the velocity of the incident projectile.⁴ Considering the preliminary nature of the model and the stringency of the test, the results are highly encouraging, even though there are significant discrepancies in a few of the cross sections. Comparisons between the theoretical predictions and experimental data for the reaction cross section for oxygen at two energies on a few targets are given in Table II. The agreement is fairly reasonable.

TABLE I
 Fragmentation Cross Sections for Fragments Produced in the Angular
 Interval 0-4 mrad from 29.4 GeV (2.1 GeV/nucleon) ^{14}N on Carbon

Fragment	Cross Section (mb)	
	Theory	Experiment ^a
^7_3Li	4 ± 1	9.1 ± 1.3
^7_4Be	2 ± 1	8.0 ± 1.0
^9_4Be	0	3.0 ± 0.3
^8_5B	0	5.1 ± 0.6
$^{10}_5\text{B}$	7 ± 2	14.4 ± 2.9
$^{11}_5\text{B}$	13 ± 3	10.7 ± 1.3
$^{12}_5\text{B}$	6 ± 2	1.9 ± 0.4
^9_6C	0	0.14 ± 0.02
$^{10}_6\text{C}$	1 ± 0.7	0.96 ± 0.12
$^{11}_6\text{C}$	11 ± 2	11.3 ± 1.1
$^{12}_6\text{C}$	74 ± 6	46.0 ± 9.0
$^{13}_6\text{C}$	53 ± 5	9.2 ± 1.8
$^{12}_7\text{N}$	1 ± 0.7	0.63 ± 0.13
$^{13}_7\text{N}$	52 ± 5	7.7 ± 1.5

- a. H. H. Heckman *et al.*, "Fragmentation of ^{14}N Nuclei at 29 GeV: Inclusive Isotope Spectra at 0° ," Phys. Rev. Letters 28, 926 (1972).

TABLE II
Theoretical and Experimental^a Total Reaction Cross Sections
for Oxygen at Two Energies on a Few Elements

Incident Particle	Energy (GeV)	Target					
		¹² C		⁶⁵ Cu		²⁰⁸ Pb	
		Theor.	Exp.	Theor.	Exp.	Theor.	Exp.
¹⁶ O	4 (0.25 GeV/nuc1.)	1090 ± 20	940 ± 179	2175 ± 30	2200 ± 550		
	33.6 (2.1 GeV/nuc1.)	1301 ± 49	935 ± 19	2228 ± 84	1820 ± 36	3534 ± 97	3100 ± 74

- a. H. H. Heckman, Lawrence Berkeley Laboratory, private communication, May 18, 1972.
The experimental cross sections are those for which the incident particles lost or gained at least one unit of charge.

A typical, predicted neutron spectrum at forward angles from 300 MeV/nucleon neon on carbon is illustrated in Fig. B3.1. It is important to note that the calculation yields neutrons at energies greater than the incident energy per nucleon. Physically, this corresponds to the situation where the incident projectile concentrates some of its kinetic energy on the individual nucleons of the target. It is worthy to note that all of the multiplicities and particle spectra relevant to cancer radiotherapy are generated from the calculation. For example, the correlated angle-energy spectra and the correlated fragment-nucleon multiplicities are readily obtained.

Of the many deficiencies in the model, there are four that can be resolved and that are consistent with the assumptions incorporated in the model. The first of these is the fact that the angular distributions of the projectile fragments are not determined by the model. These will be determined phenomenologically from experimental data as they become available.

The second is the neglect of high angular momentum transfers and the corresponding effect on the decay properties of the excited projectile and target fragments. Modifications to the model to include estimates of these effects are currently being studied.

The third deficiency is the omission of the development of a simultaneous cascade in the projectile and target during the course of the heavy-ion interaction. The inclusion of the simultaneous cascade represents a major revision in the coding, and it remains to be incorporated in the model. However, the approximation to the development of simultaneous cascades presently employed, i.e., the forward-backward reaction described above, is adequate and consistent with the other approximations used in this preliminary version.

Fig. B3.1. Neutron spectrum in the angular interval 0-15° from 6-GeV (300 MeV/nucleon) neon on carbon.

Finally, there is no account taken of nuclear depletion,* i.e., the reduction in the nuclear density of the projectile or target during the cascade due to the removal of bound nucleons when they are struck. Modifications in the model to include this effect represent a major undertaking.

*Work is in progress, as part of the AEC High-Energy Accelerator Shielding Program at Oak Ridge National Laboratory, to incorporate the effects of nuclear depletion in the existing intranuclear-cascade code which treats nucleon-nucleus and pion-nucleus collisions.

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