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RADIATION TRANSPORT CODES FOR POTENTIAL
APPLICATIONS RELATED TO RADIOBIOLOGY
AND RADIOTHERAPY USING PROTONS,
NEUTRONS, AND NEGATIVELY CHARGED PIONS

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MASTER

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Neutron Physics Division

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Table of Contents

	<u>Page</u>
Abstract	v
I. INTRODUCTION	1
II. RADIATION TRANSPORT CODES	4
III. THE CODE HETC	7
IV. COMPARISONS WITH EXPERIMENTAL DATA	10
Incident Protons	10
Incident Neutrons	10
Incident Pions	14
Cell-Survival Probabilities	16
V. DISCUSSION	20
References	21

Abstract

In connection with long-term programs in space-vehicle, accelerator, and reactor shielding, the Oak Ridge National Laboratory has developed rather sophisticated calculational methods for determining the transport in matter of protons, neutrons, pions, muons, electrons, and photons. This work has resulted in several Monte Carlo radiation-transport computer codes which are quite general with respect to allowable source-particle descriptions, geometries, material compositions, etc. Recently, a limited study has been directed toward applying some of these computer codes to predict quantities of interest in the fields of radiotherapy and radiobiology, such as depth-dose patterns, and toward assessing the accuracy of the codes for applications in these fields. In this paper, the calculational methods are described and comparisons of calculated and experimental results are presented for dose distributions produced by protons, neutrons, and negatively charged pions. Comparisons of calculated and experimental cell-survival probabilities are also presented.

I. INTRODUCTION

Currently about one-sixth of all deaths in the United States are due to cancer, and it is estimated that more than one in every four persons now living in the United States will develop some form of cancer during their lifetime.¹ Since there are many types of cancer requiring a range of treatment methods, efforts must proceed along multiple fronts in order to obtain a significant reduction in cancer fatalities. Radiotherapy, which may be used alone or in combination with surgery and/or chemotherapy, is an important treatment modality, and about one-half of all cancer patients receive radiotherapy at some stage during their illness.¹ Of those that receive radiotherapy, about one-half have little chance of cure because of late diagnosis or previous failure of other treatment methods, although radiotherapy is often able to relieve distressing symptoms in these cases.² Thus, radiotherapy presently plays an important role in cancer treatment, and this will probably remain true for many years to come even if there are significant breakthroughs in chemotherapy.

While it is apparent that many cancer patients are cured or relieved of distressing symptoms by present radiotherapy techniques, failure is too often the end result. Very approximate estimates³ indicate that some 60,000 lives per year might be saved by improvements in radiotherapy. A narrow margin exists between tumor control and the production of complications, and a major reason for radiotherapy failures for many types of cancer is the inherently large ratio of normal tissue dose to tumor dose delivered by those radiations (x-rays, gamma rays, and electrons) conventionally employed. By applying advanced accelerator technology, other radiations (protons, neutrons, π^- mesons, and heavy ions) can be produced

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which allow a better localization of the dose and improved biological effectiveness, and by combining these radiations with advanced dosimetry, diagnostic techniques, and computerized treatment planning, the potential exists for substantially reducing radiotherapy failures. Some patient irradiations with neutrons⁴ and protons^{5,6} have been carried out and it is expected that more extensive clinical studies using these particles, particularly neutrons,⁷ will be made in the future. In addition to these particles, there is evidence that negatively charged pions^{8,9} and heavy ions¹⁰ have properties which make them very desirable for use in radiotherapy, and with the completion of the Los Alamos Meson Physics Facility now under construction, a pion beam of sufficient intensity for radiobiological experiments and clinical trials will be available.

There are then many different particle species -- neutrons, protons, negatively charged pions, and heavy ions with various masses and charges -- which may ultimately be used in radiotherapy. To estimate the actual impact that each of these radiations might have on reducing cancer fatalities, many factors must be considered, including the basic physical and biological effects, the cost of producing and administering the radiation, and the types of cancer most suitable for treatment. Although the data needed for a complete assessment must be acquired through extensive radiobiological studies and clinical trials, it is the purpose of the present paper to indicate the potential for readily obtaining much useful information on the basic physical characteristics and biological effects of the proposed radiations by means of calculations.

In connection with long-term programs in space-vehicle, accelerator, and reactor shielding, the Oak Ridge National Laboratory has developed

rather sophisticated calculational methods for determining the transport in matter of protons, neutrons, pions, muons, electrons, and photons. This work has resulted in several Monte Carlo radiation-transport computer codes which are rather unique in their detailed treatment of the physics of the interaction processes and are quite general with respect to allowable source-particle descriptions, geometries, material compositions, etc. Recently, work has been directed toward applying one of these computer codes, the high-energy transport code HETC,¹¹ to predict quantities of interest in the fields of radiotherapy and radiobiology, such as depth-dose patterns, and toward assessing the accuracy of the HETC code for applications in these fields. In this paper, the calculational method used by HETC will be described and comparisons of calculated and experimental results will be presented for dose distributions produced by protons, neutrons, and charged pions. The applicability of the code for cell-survival calculations is also discussed.

It should be understood that the calculation of even such basic quantities as depth-dose patterns for the particles that have been proposed for use in radiotherapy (neutrons, protons, negatively charged pions, and heavy ions) is a much more difficult problem than for those radiations conventionally used (x-rays, gamma rays, and electrons) because the proposed radiations undergo nuclear interactions, and in most instances secondary particles from nuclear interaction are very important contributors to the quantity of interest. The forte of the HETC code is its ability to account for the energy and angular distribution of all particles produced in nuclear interactions.

II. RADIATION TRANSPORT CODES

Table 1 lists some of the radiation transport codes that have been developed at Oak Ridge National Laboratory in connection with space-vehicle, accelerator, and reactor shielding studies.* All of these codes use Monte Carlo methods and are quite general with respect to allowable source-particle descriptions, geometries, material compositions, etc. The energy ranges shown in the table should be regarded as nominal -- in some cases the energy ranges can be extended without much difficulty whereas in other cases the energy ranges are rather inflexible. In addition to the codes listed in Table 1, other radiation transport codes developed at ORNL that might find some applicability in certain aspects of radiotherapy and radiobiology are the one-dimensional discrete ordinates code ANISN^{†16} [low energy (< 15 MeV) neutron and photon transport], the two-dimensional discrete ordinates code DOT^{†17} [low energy (< 15 MeV) neutron and photon transport], the weight-optimization code ASOP,¹⁸ and the Monte Carlo electron-photon cascade code of Zerby and Moran.¹⁹

The code HETC is basically an extension of the code NMTC to higher energies and in the energy range applicable to both codes the physics contained in the two codes is essentially the same. Therefore, in subsequent discussions where both codes would be applicable, only HETC will be referred to.

In the case of low-energy photons and neutrons, codes similar to those developed at ORNL exist at other installations. However, the nucleon-meson

* All of the codes listed in Table 1 are available upon request from the Radiation Shielding Information Center, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

† Available from the Radiation Shielding Information Center.

Table 1. Radiation Transport Codes

Code	Type of Source Particles Allowed and Approximate Energy Range	
HETC ¹¹	neutrons:	thermal to 1 TeV
	protons:	15 MeV to 1 TeV
	π^- , π^+ , μ^- , μ^+ :	1 MeV to 1 TeV
NMTC ¹²	neutrons:	thermal to 3.5 GeV
	protons:	15 MeV to 3.5 GeV
	π^+ , π^- , μ^+ , μ^- :	1 MeV to 2.5 GeV
05R ¹³	neutrons:	thermal to 15 MeV
OGRE ¹⁴	photons:	0.01 MeV to 100 MeV
MORSE ¹⁵	neutrons:	thermal to 15 MeV
	photons:	0.01 MeV to 10 MeV

code HETC is the only code available that can calculate the transport of neutrons, protons, and pions through matter taking into account the production of all of the various particles [neutrons, protons, pions, and heavy nuclei ($A > 1$)] that are produced by nuclear collisions. It is the ability of this code to predict the energy distribution of each type of particle as a function of position that makes it suitable for studies related to radiobiology and radiotherapy because this is precisely the information that is needed in conjunction with existing experimental biological data to predict such quantities as cell-survival probabilities. In the next section the calculational method used by HETC is discussed.

III. THE CODE HETC

A detailed description of the treatment of the various physical processes by HETC is given elsewhere,²⁰ so only a brief account of the calculational method will be given here. The Monte Carlo simulation of the particle transport involves selecting the energy, direction, and spatial coordinates of the primary particles from an input source description and computing the trajectories of the primary particles and the secondary particles produced by nuclear collisions and by pion and muon decay. Virtually arbitrary geometries and material compositions may be specified. The code takes into account charged-particle energy loss due to atomic ionization and excitation, multiple Coulomb scattering by the primary particles, elastic and nonelastic nucleon-nucleus and pion-nucleus collisions, elastic and nonelastic nucleon and pion collisions with hydrogen nuclei, pion and muon decay in flight and at rest, and negative-pion capture at rest. At each nonelastic nuclear collision, a calculation using a subroutine version of Bertini's latest intranuclear-cascade program²¹ and a subroutine version of Guthrie's evaporation program²² is performed to determine the identity, multiplicity, energy, and direction of the emitted particles and the charge, mass, and recoil energy of the residual nucleus.* The particles produced in the collision may be protons, neutrons, charged pions, and neutral pions from the intranuclear cascade, and protons, neutrons, deuterons, tritons, ³He's, and alpha particles from the evaporation. Each particle in the cascade is followed until it eventually escapes from the phantom, undergoes

* HETC uses an extrapolation model²³ to treat high-energy (≥ 3 GeV) nuclear collisions, but since collisions in this energy range are not of interest for present purposes, this model will not be discussed here.

nuclear absorption, or comes to rest. The deuterons, tritons, ^3He 's, and alpha particles are assumed to slow down and come to rest at their point of origin since, for the low energies involved, the range of these particles is very small and the probability of undergoing nuclear interaction before coming to rest is very small. The intranuclear-cascade-evaporation model is used to treat nonelastic pion-nucleus collisions at all energies and nonelastic nucleon-nucleus collisions at energies ≥ 15 MeV. Protons with energies ≤ 15 MeV are assumed to come to rest without undergoing nuclear interaction. Neutron collisions in the energy range from 15 MeV to thermal are treated by using experimental cross-section data¹² in conjunction with an evaporation model²² to determine particle production from neutron-nucleus nonelastic collisions. Positively charged pions that come to rest are assumed to decay. Negatively charged pions that come to rest are assumed to undergo nuclear capture, and the nucleons and charged pions produced are included in the transport calculations. The electron-photon cascade initiated by the photons from neutral pion decay and by the electrons and positrons from muon decay are not transported by HETC, but it is often adequate to treat the transport of these particles in an approximate manner.²⁴ Photons from all nonelastic nucleon-nucleus and pion-nucleus collisions are assumed to deposit their energy at their point of origin. A complete description of each "event" (nuclear interaction, stopped charged particle, etc.) that occurs during the transport calculation is stored on magnetic tape. The history tapes are then analyzed to obtain the results of interest. Thus, a single transport calculation provides not only the energy, angle, and spatial dependence of all particles but also much useful ancillary information.

In the next section, calculated results obtained using HETC are compared with experimental data for several cases. In addition, other comparisons to check the validity of the calculational method have been made for a variety of accelerator and space-radiation sources, and in general good agreement with experimental data has been obtained (e.g., refs. 20, 25). Also, the ability of the Bertini intranuclear-cascade-evaporation model for predicting the secondary particles produced in nuclear collisions has been investigated extensively.²¹

IV. COMPARISONS WITH EXPERIMENTAL DATA

Incident Protons

Figure 1 shows the depth dependence of the absorbed dose produced by 592-MeV protons incident on one end of a cylindrical phantom of tissue-like composition. The experimental results are those of Baarli and Goebel,²⁶ and the calculated results are from Armstrong and Bishop.²⁷ The calculated results for 25-cm radius correspond to the experimental configuration; the infinite radius results are shown for comparison purposes only. The experimental absorbed dose is not available in absolute units, and thus only the shapes of the calculated and experimental distributions can be compared. The initial increase in the depth-dose curve is due to the effects of secondary particles and the peak at ≈ 150 cm is the Bragg peak of the primary protons as they reach the end of their range.

Figure 2 shows the contributions to the absorbed dose due to various kinds of particles. The sum of these contributions corresponds to the total dose curve shown in Fig. 1 for the 25-cm case. Figure 2 indicates the importance of secondary particles in predicting the dose from high-energy protons.

Incident Neutrons

Figure 3 shows a comparison of experimental²⁶ and calculated²⁷ absorbed doses for the case of high-energy neutrons incident on a semi-infinite slab of tissue. In the experiment, the incident neutrons were generated by bombarding a thin Be target with 580-MeV protons which produces neutrons over a wide energy region with a peak in the energy spectrum at about 525 MeV. The calculated curve denoted "525-MeV spectrum" was

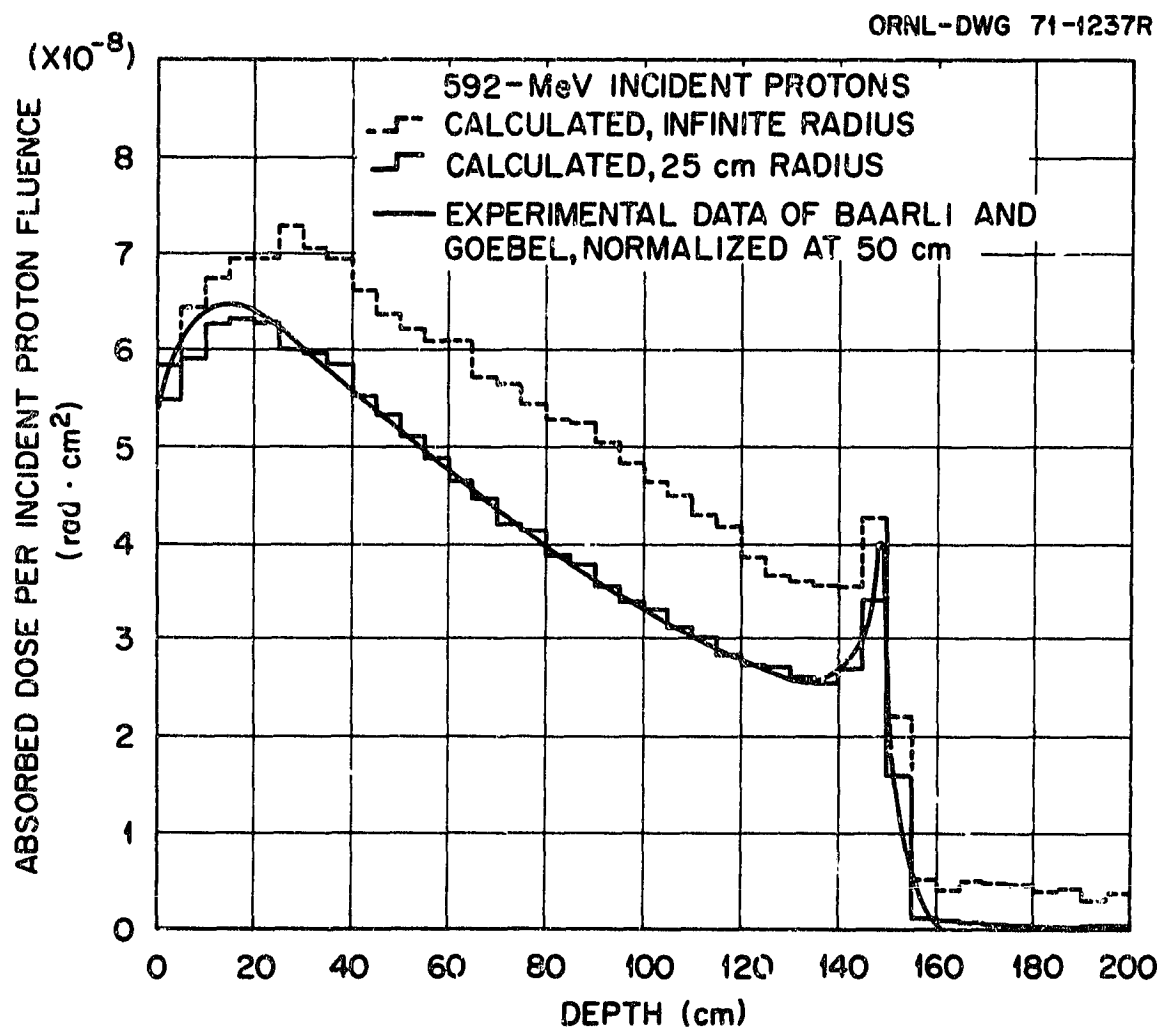


Fig. 1. Depth dependence of absorbed dose for 592-MeV incident protons.

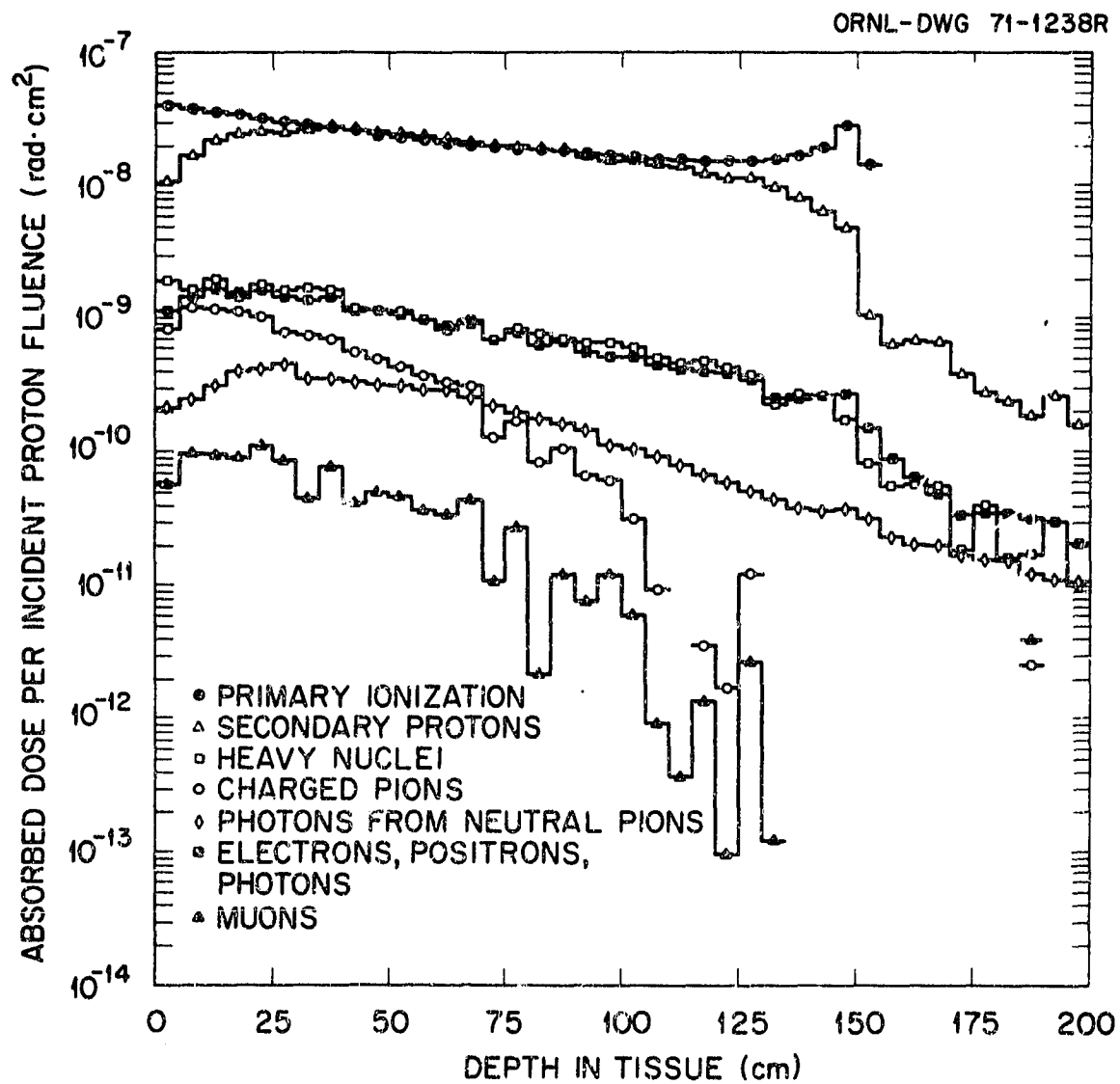


Fig. 2. Contribution of various particles to the absorbed dose for 592-MeV incident protons.

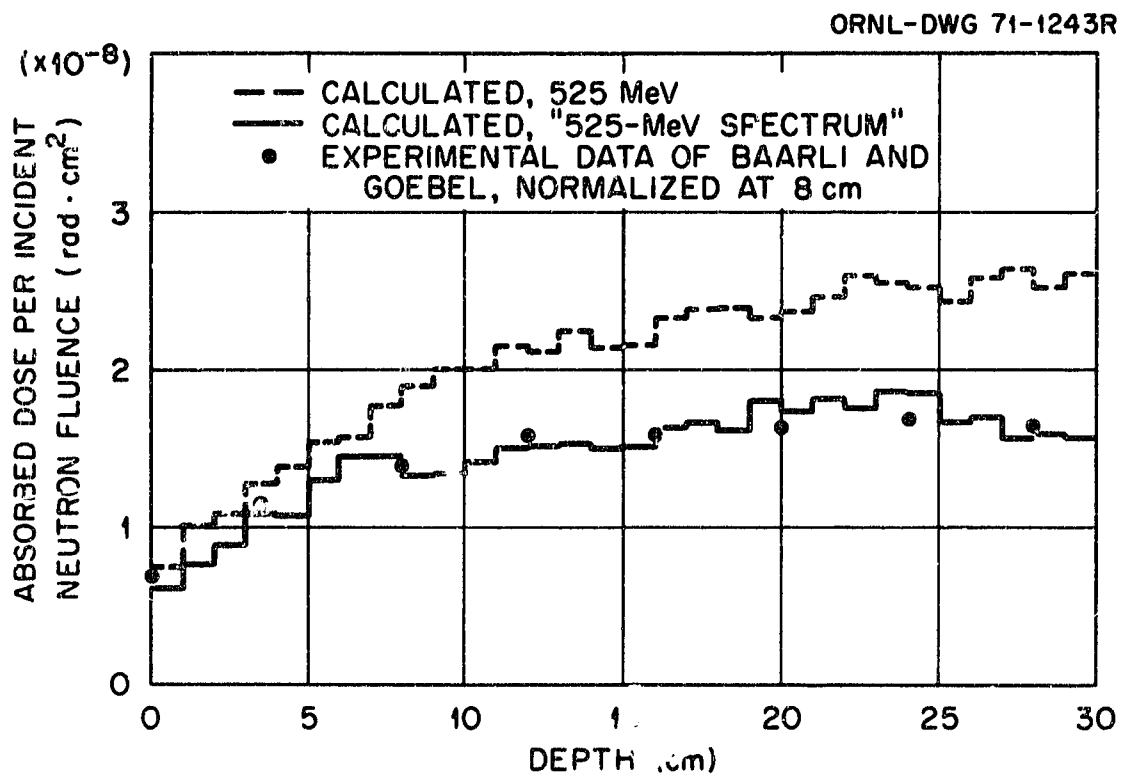


Fig. 3. Depth dependence of the absorbed dose for incident neutrons.

obtained by considering neutrons of all energies incident on the phantom and corresponds to the conditions of the experiment. For comparison, calculated results are also shown for monoenergetic 525-MeV neutrons incident. Since the absolute value of the experimental results is not reported, the experimental results have been normalized to the calculated results at a depth of 8 cm. In the case of incident neutrons, all of the energy deposition is, of course, due to secondary particles.

Incident Pions

Figure 4 shows a comparison of measured and calculated depth-dose distributions for a π^- -meson beam incident on a phantom of water. The experimental results are those reported by Turner et al.,²⁸ and the calculated results obtained using the code HETC are taken from Armstrong and Chandler.²⁹ In the experiment, the incident beam was contaminated with an unmeasured number of negatively charged muons and electrons, and the measured dose distribution included the contribution from incident μ^- and e^- as well as the contribution from incident π^- . In order to compare with the measured dose distribution, the dose distributions due to incident π^- , μ^- , and e^- beams were calculated separately, and portions of these individual contributions were then summed and normalized to the experimental curve at three different depths to determine the relative number of each type of particle incident. As a result of this procedure, the experimental and calculated curves in Fig. 4 necessarily coincide at depths of 20.5, 28.5, and 35 cm. The agreement between the calculated and dose distributions in Fig. 4 is quite good, although the comparison is not as definitive as desirable because the distributions had to be matched at three depths in order to obtain the beam contamination.

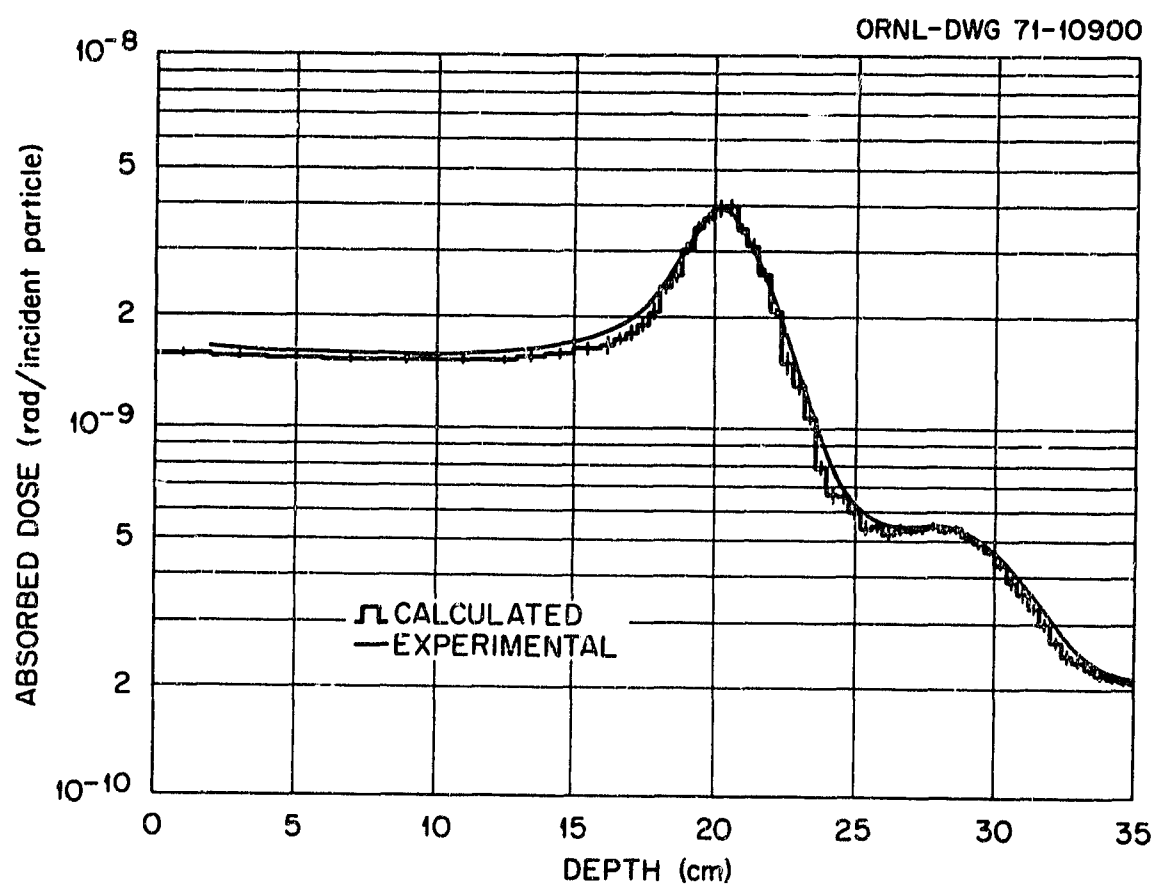


Fig. 4. Depth dependence of the absorbed dose produced by a contaminated π^- -meson beam.

It should be pointed out that the dose distribution produced by π^- beams is strongly dependent upon the momentum distribution of the incident beam. The dose distribution shown in Fig. 4 is for the special case of a beam having a mean momentum of $\bar{p} = 175$ MeV/c and a Gaussian shape with a standard deviation of $\sigma = 4.7$ MeV/c, and should not be regarded as typical of the dose distributions that can be attained for radiotherapy purposes.

Cell-Survival Probabilities

Katz et al.³⁰ have recently developed a model of cell inactivation which takes into account not only the density of the energy deposition along the path of the ion but also the spatial distribution of the energy deposited in directions transverse to the path produced by secondary electrons (delta rays). To compute cell-survival probabilities using the delta-ray theory of Katz et al. requires the evaluation of integrals of the type

$$\sum_Z \int dE \phi_Z(\bar{r}, E) R_Z(E; \kappa, \sigma_0, D_0, m)$$

where $\phi_Z(\bar{r}, E)$ is the fluence per unit energy at energy E of particles of charge Z at spatial point \bar{r} and $R_Z(E; \kappa, \sigma_0, D_0, m)$ is the response of the cell to particles of charge Z and energy E . The functional form for R_Z is arrived at by Katz et al. from theoretical relations describing the spatial distribution of delta rays produced along charged particle tracks and by considering the structure of tracks produced in emulsions. The radiosensitivity parameters, κ , σ_0 , D_0 , and m must be determined experimentally for each type of cell, and compactly represent the response of the cell to radiation.

The utility of the Katz et al. model is that once the radiosensitivity parameters have been evaluated for a particular cellular variety and kind of radiation, the model can be applied to obtain the response of this cellular variety due to other kinds of radiation. Thus, to predict cell survival requires only that the radiosensitivity parameters be available for this type of cell and that the charged-particle spectrum, $\phi_Z(\bar{r}, E)$, of the radiation be known. Since the HETC code can provide the charged particle spectrum, this code coupled with the cell-inactivation model of Katz et al. provides a convenient method of obtaining by means of calculation a quantity of significance in radiotherapy. For example, such calculations could be used to obtain the momentum distribution of the incident radiation beam which would produce a constant cell-survival probability over a tumor of specified shape and location. The shaping of the incident beam on the basis of constant cell survival over the tumor would appear to be a more realistic criterion than attempting to produce a uniform absorbed dose over the tumor. Although radiosensitivity parameters have thus far been evaluated for only a few biological materials, available parameters³⁰ such as those for T-1 human kidney cells should be adequate for at least initial beam parameter studies of this type.

The HETC code has been used to calculate the spectrum of charged particles produced by the interaction of 14.1-MeV neutrons with tissue nuclei (i.e., H, C, N, and O nuclei in the relative amounts found in tissue). These spectra were then used in the cell inactivation model of Katz et al.³⁰ based on delta-ray theory to obtain the cell-survival probability for T-1 human kidney cells. The results of the calculations are shown in Fig. 5, together with the measurements of Barendsen and Broerse^{31,32}

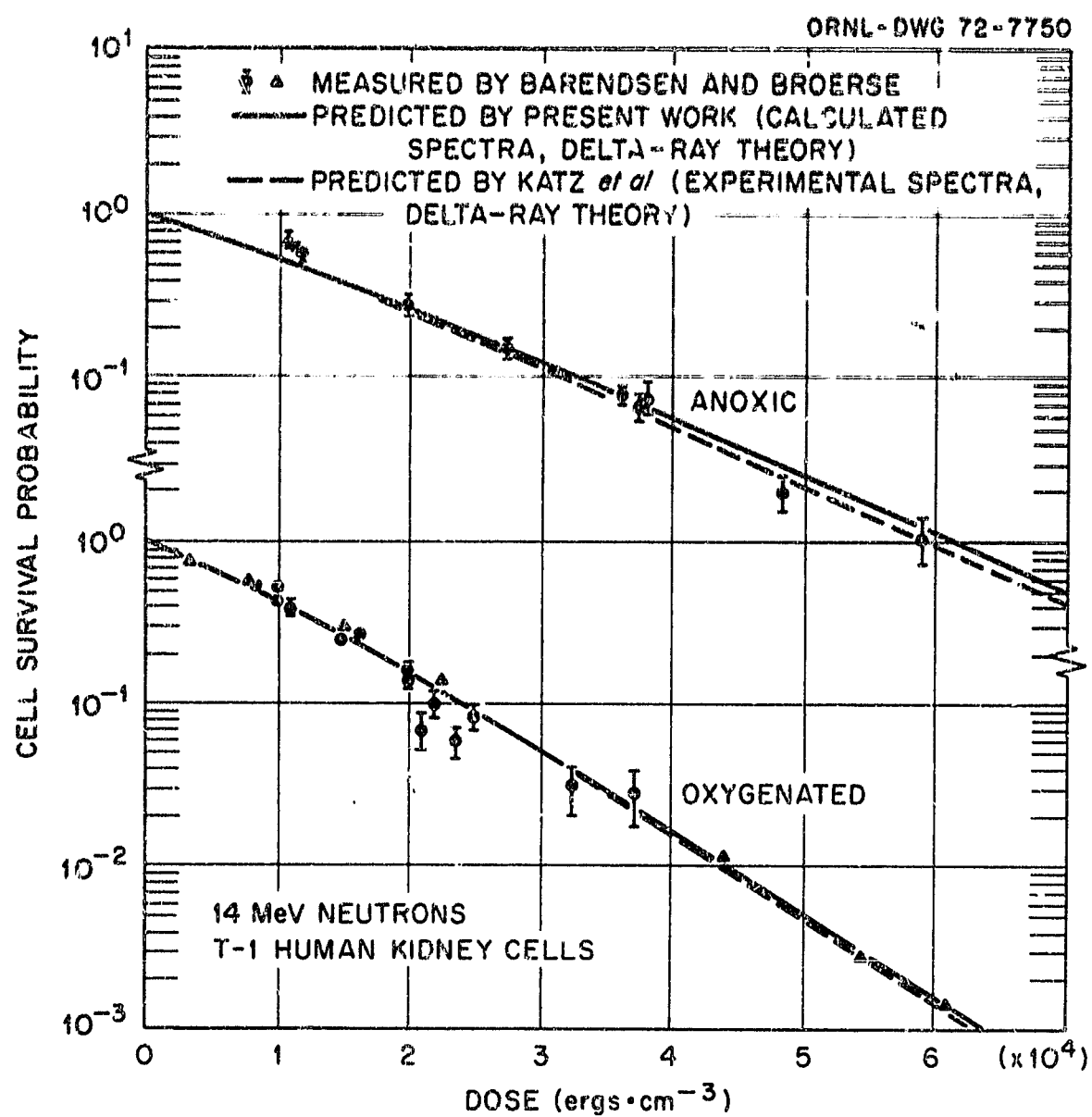


Fig. 5. Cell-survival probability vs absorbed dose for T-1 human kidney cells due to 14-MeV neutron bombardment.

for this case. Also shown in Fig. 5 are the results of Katz et al.³³ obtained using the charged-particle spectra of Caswell and Coyne,³⁴ which are based on experimental cross-section data. Since the same radiosensitivity parameters were used in converting the calculated and experimental charged-particle spectra to cell-survival probabilities, the differences shown in Fig. 5 between the present calculations and the predictions of Katz et al. are due to differences in the spectra calculated by HETC and the experimental spectra used by Katz et al.

The radiosensitivity parameters used in obtaining the results shown in Fig. 5 were evaluated by Katz et al.³⁰ from the experiments of Todd³⁵ in which heavy ions of various masses and charges from deuterium through argon were used. The application of these parameters to predict survival curves for 14-MeV neutron bombardment illustrates the applicability of the model of Katz et al. for treating mixed radiation fields for which experimental data are not available. It should be noted that Katz et al.³⁰ have also evaluated radiosensitivity parameters for T-1 human kidney cells using the experimental data of Barendsen et al.³⁶ for alpha particles and deuterons. These parameters result in survival curves considerably different from those shown in Fig. 5.³³

Since the response of cells to radiation is dependent upon the oxygen concentrations in the cells, Fig. 5 shows data for cells deficient in oxygen (anoxic) and for cells well supplied with oxygen (oxygenated). The ratio of the absorbed dose to anoxic cells required to produce a given cell-survival probability to the absorbed dose to oxygenated cells required to produce the same cell-survival probability is defined as the oxygen-enhancement ratio (OER), which is a quantity of considerable importance in practical radiotherapy.

V. DISCUSSION

A definitive assessment of the improvements in the eradication and palliation of cancer that can be achieved by using protons, neutrons, and charged pions in radiotherapy must, of course, await the results of extensive experimental studies. The calculated results presented here indicate the potential for obtaining by means of calculations much basic information related to the physical and biological effects produced by these particles. Thus, calculations can play an important role in providing data to effectively design radiobiological experiments and therapeutic tests that will determine the applicability of these particles for radiotherapy. Furthermore, such calculations can be carried out by specializing existing computer codes.

The few comparisons between calculated and experimental results shown here are the result of a very limited study of the applicability of the HETC code for predicting quantities of interest in radiotherapy. Although these comparisons give some indication of the validity of the calculational methods for a few source-geometry configurations for which experimental data are available, they do not illustrate the full versatility of the code nor do they indicate the accuracy of the code for source-geometry configurations that are representative of those of interest in radiotherapy.

Heavy ions also have properties which make them attractive for use in radiotherapy (e.g., ref. 10), but heavy ions have not been considered here because the HETC code is presently not capable of taking into account the production of secondary particles from heavy-ion-nucleus collisions. However, Bertini et al.³⁷ are presently developing a theoretical model to treat such collisions and, when available, this model can easily be incorporated into HETC.

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