mately 57 percent of that due to transmitted nitrogen ions. The computed contribution to the dose from the fast secondaries as measured in these experiments is about 1 to 2 percent of the contribution from the nitrogen peak; this is necessarily a lower bound, since we have counted only secondaries that go straight along the beam line.

We have observed the production of protons, deuterons, ^{3}He, tritons, and α-particles at a laboratory angle of 13° (*10*). We have also observed some evidence that neutral pi-mesons are produced by the nitrogen beam of 278 Mev/amu striking a copper target.

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10. These experiments were done in collaboration with W. Wales of the University of Pennsylvania.
11. We appreciate the help of E. Christman and the support of Professor M. G. White. We are grateful for the support of the Fannie E. Rippel Foundation and the cooperation of the Atomic Energy Commission.

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Prediction of the Spatial Distribution of Cell Survival in Heavy Ion Beams

Abstract. *The possible use of heavy ion beams for biomedical applications was examined through calculations of the physical beam properties and the spatial distribution of cell survival. Range straggling, creation of secondary particles, electron pickup, and the effects of inhomogeneous absorbers were analyzed in terms of cell survival. Depth-survival plots for typical irradiations provide substantial encouragement for the investigation of these beams for biomedical applications in which localized tissue destruction is desired.*

Calculations have been made that predict the occurrence of a localized zone of extreme tissue destruction at the end of the path of an energetic heavy ion beam (*1*). Such localized destruction is desirable in certain medical procedures, including the treatment of tumors (*1*, *2*). This report presents a detailed method for calculating mammalian cell survival as a function of position in the beam path; the method accounts for the known physical interactions of heavy ions with matter and utilizes the known radiation response of mammalian cells. The resulting computer program leads to confirmation of the predicted localized cell killing, and it provides a versatile method of predicting the biological consequences of varying the beam energy, composition, and intensity and the absorbing material.

The calculation follows the general outline of those undertaken by Tobias and Todd (*1*), who have indicated the potential of heavy ions in tumor therapy. The cell-survival predictions are based on the track-effect treatment of Katz and collaborators (*3*), which provides a good fit to representative data for irradiations with many different sources and cell specimens.

The present work extends that of the workers cited above in that it considers the physical properties of realizable (nonideal) beams in detail, including several effects that have not been treated before in a systematic fashion. Calculations are carried out by means of a Monte Carlo computer simulation of the irradiation process. A group of many heavy ions is mapped through the specimen while its dose and the dose of nuclear irradiation secondaries is recorded. The cell survival is computed from the accumulated dose at the end of each fraction of exposure. Following the prescription of Katz *et al.* (*3*), the dose is divided into two parts, namely "ion kill mode" and "gamma kill mode." The "ion kill" dose is that portion contributing to kills by single hits whereas the "gamma kill" dose contributes to processes requiring multiple hits. At each point in the target specimen, the cell survival is calculated with the survival parameters appropriate to the cell type. The only biological effect considered is the reproductive death of multiplying cells. The division of the ion path into many small segments (typically 0.1 cm) allows the analysis of complex targets made up of several cell types and materials of different density (for example, tissue cells and bones). Monte Carlo techniques for representing distribution functions with randomly selected independent variables are used to represent the various statistical processes that occur (such as nuclear interactions, straggling, and energy spread). Several hundred groups of particles are mapped through the irradiated area to smooth out statistical fluctuations in this procedure. Among the processes considered are the following.

1) The heavy ion beam is exponentially attenuated by nuclear interactions. The cross sections are assumed to be the geometrical areas of the nuclei. The computed attenuation for the nitrogen beam is in agreement with recent measurements at the Princeton Particle Accelerator (*4*).

2) As the heavy ions undergo nuclear interactions, they create secondary particles that contribute to the cell killing. The calculation of these effects is uncertain in view of the limited experimental data for the reactions; however, some fragmentation parameters are available from high-altitude cosmic-ray studies (*5*), and these allow us to estimate the flux of secondary particles, although no information is available on the energies or angles of emission. We have assumed that the heavy fragments maintain the beam velocity (*6*). The dose deposited locally is more difficult to estimate, and this measurement may be one of the most interesting experimental problems. However, averaged over the entire irradiation, the amount of energy deposited locally by nuclear interaction products along any given path segment (once the forward-traveling heavy ions are subtracted) is less than about 20 percent of the energy deposited by the primary beam. Thus, the final calculated cell survival is not inordinately sensitive to approximations used in estimating the dose of second-

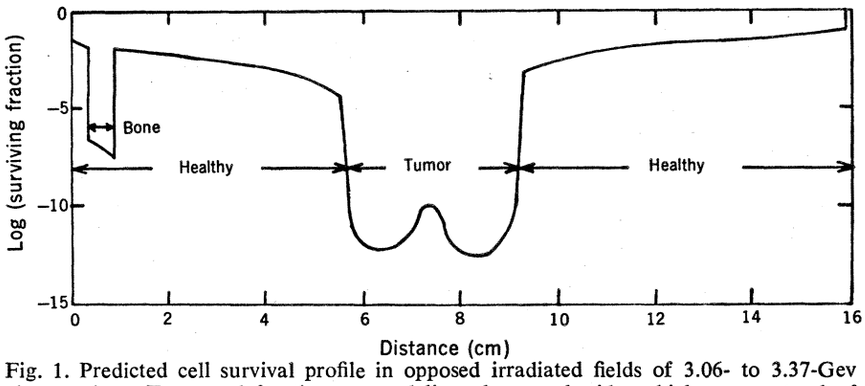

Fig. 1. Predicted cell survival profile in opposed irradiated fields of 3.06- to 3.37-Gev nitrogen ions. Ten equal fractions were delivered on each side, which gave a total of 8×10^8 particles. Zones marked "healthy" were assumed to be composed of aerated human kidney T-1 cells; the zone marked "tumor" was assumed to be composed of hypoxic human kidney cells. The survival parameters for these irradiation conditions were obtained from the work of Katz *et al.* (*3*), who fit the data of Todd (*13*).

ary particles. In the calculation, the particle types and energies are established, the local energy deposit is calculated, and the cell survival is calculated by the methods used for the primary beam.

3) Incident particles of the same energy penetrate different distances into the specimen (range straggling). An approximation to the Vavilov distribution for energy loss (*7*) has been used. The results of the calculation are not sensitive to this approximation, since the straggling of the beam is generally small relative to typical tumor or irradiation zone dimensions.

4) As a heavy ion slows down and reaches the end of its track, it captures electrons from the surrounding medium, and the specific ionization is decreased. This effect has been analyzed in two ways: first, by using the "effective charge" as given by Barkas (*8*), and second, by cutting off the track at an energy near the threshold for electron capture and ignoring the end of the track. These two methods gave comparable results.

5) Systems that include various cell types (for example, tumor cells, which might be hypoxic, may be surrounded by a region of healthy, oxygenated cells, which are more sensitive to radiation) are analyzed by changing the cell-survival parameters (*3*) and computing the survival directly at each point from the accumulated dose.

6) Variation in tissue density must be taken into account in calculating the dose and the beam attenuation by nuclear interactions. As an example, irradiation through bone causes a higher energy loss and a greater probability of nuclear interaction inside the bone than would occur in soft tissue. These effects are analyzed directly by changing the values of the local electron density (*9*) and the nuclear cross section at the location of the bone.

7) The effects of dose fractionation are analyzed by dividing the simulated particle dose into a number of segments and setting the accumulated gamma mode dose to zero at the end of each segment. It is assumed that the cell replication time is large compared with the interval between fractions.

8) In order to spread the region of high cell kill over a large area, an energy spread is introduced in the primary beam by choosing the initial ion energies in the Monte Carlo distribution according to the desired spectrum.

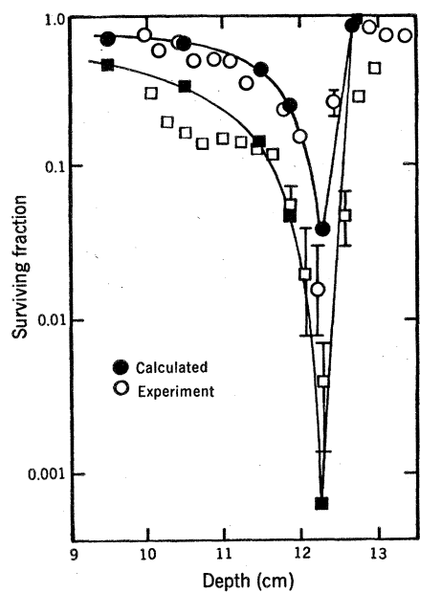

Fig. 2. Comparison of predicted cell survival profiles for exposures to 2.2×10^7 nitrogen ions per square centimeter (solid circles) and 4.5×10^7 nitrogen ions per square centimeter (solid squares) with experimentally determined survival profiles for the same incident exposures (open circles and squares) (*12*). The calculations were based on survival parameters (*3*) for human kidney T-1 cells, which survive irradiations similarly to the Chinese hamster M3-1 cells used in the experiment (*14*).

Test calculations have been performed, and several exposure situations have been considered. Survivals in both single field and opposed field irradiations have been computed. The calculated physical parameters of the beam (such as range and energy spectrum at the Bragg peak) are in good agreement with recent measurements (*4, 10*) and previous calculations (*11*).

Two examples of applications of the calculation are presented in Figs. 1 and 2. In Fig. 1 we consider that a zone in which we wish to destroy cells ("tumor") is centered 7.5 cm deep and beneath a bony structure on one side and 8.5 cm below the skin on another side. The presumed objective is the reduction of cell survival to less than 10^{-10} in all portions of the zone called "tumor," with minimum destruction of "healthy" tissue. To accomplish the survival profile of Fig. 1, 8×10^8 total nitrogen ions were delivered in ten equal fractions on each side. The beam energy was distributed between 3.06 and 3.37 Gev. Survival parameters for hypoxic cells were applied in the "tumor" zone, and survival prameters for aerated cells were applied in the "healthy" zone. The calculations show that substantial cell kill can be achieved in the "tumor" region even if the tumor cells are assumed to be hypoxic and that the region of extensive cell kill can be made quite large.

An experiment actually performed at the Princeton Particle Accelerator was simulated, and the calculated and experimental results are compared in Fig. 2. The depth-survival profiles are for nitrogen ions of 3.9-Gev initial energy, at fluences of 2.2×10^7 and 4.5×10^7 cm^{-2}. Details of the experimental results are given in (*12*). The calculation is shown to give results in quantitative agreement with the experimental data.

The experimental verification of this method for predicting cell survival after heavy ion irradiation lends support to

the validity of the method for predicting biological responses in heretofore untested situations. In particular, the proposed use of nitrogen beams for tumor therapy is supported.

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15. I am grateful to Dr. Walter Schimmerling and Dr. Paul Todd for their extensive contributions to this work. The support of Professors M. G. White, R. J. Plano, and P. Weiss is appreciated. This research was supported by the Fannie E. Rippel Foundation and the National Science Foundation.

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Spatial Distribution of Biological Effect in a 3.9-Gev Nitrogen Ion Beam

Abstract. *A beam of nitrogen ions obtained with the Princeton Particle Accelerator was used for the irradiation of Chinese hamster (M3-1) cells in monolayer culture. The 3.9-billion-electron-volt (Gev) beam passed along the monolayer, so that ions were stopped in the culture. A sharply defined zone of extensive cell destruction occurred in the last centimeter of the beam path.*

The possible use of high-energy heavy ions for the radiation treatment of cancer and for certain neurosurgical procedures has been discussed (*1–3*). Accelerated heavy ions have been predicted to possess the following desirable properties: favorable depth-dose distribution, localized enhancement of cell killing and little recovery at maximum depth (*4*), and small dependence of the radiation effect on oxygen (some tumors are known to contain hypoxic cells) (*4, 5*). Our experiments with accelerated nitrogen ions support the predicted favorable depth-dose distribution and enhanced cell killing.

Nitrogen ions were accelerated to a total energy of 3.9 Gev in the Princeton Particle Accelerator, as described previously (*6*). The measured properties of the beams used in our experiments are presented in Table 1. Dosimetry was performed with an argon-filled ionization chamber (*7*) calibrated against the absolute particle flux as measured with scintillation detectors. Ionization chamber measurements of the depth-dose profile indicated that the dose deposited at the Bragg peak was about three times that in the minimum ionizing region of the nitrogen ion beam.

Chinese hamster cells of line M3-1 F3, a derivative of M3-1 (*8*) adapted for growth into compact colonies in nutrient mixture F-12 (*9*) with 5 percent fetal calf serum (*10*), were seeded, after trypsinization, from a monolayer culture in the log phase of growth into plastic flasks (*11*) at a titer of 10^4 or 2×10^4 cells per flask. The cells were allowed to attach for 1 hour in 5 ml of medium, after which 20 ml of medium was added to nearly fill each flask. The flasks remained horizontal and tightly capped for the remainder of the experiment. After 14 hours at room temperature the cells were irradiated, with the flask inserted into an agar mold and lying horizontally in the beam; the bottom of the flask pointed into the beam so that the beam passed along the monolayer of cells on the flat surface of the flask. Thus, the beam was stopped in the cell monolayer. The average dose rates at the entrance to the cell culture were 1.0 and 3.0 rad/min.

Cell survival was determined as a function of distance along the last 3 cm of beam path. The cells were

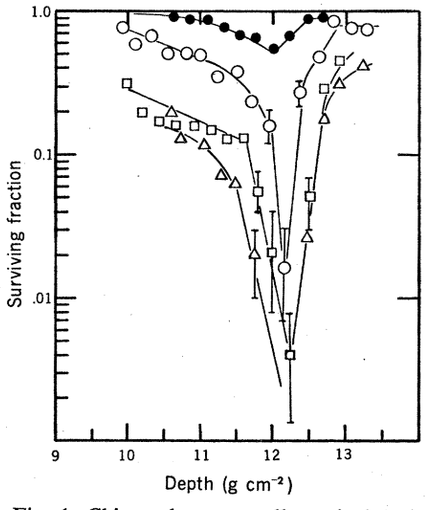

Fig. 1. Chinese hamster cell survival (colony formation) as a function of depth at the end of the 3.9-Gev nitrogen ion beam. The surviving colonies were counted in each 2.3-mm interval and compared with the number of colonies in the corresponding intervals in unirradiated control cultures. The doses at 10 g cm^{-2} were 44 rads (closed circles), 75 rads (open circles), 150 rads (squares), and 200 rads (triangles). The corresponding particle fluences were 6.9×10^6, 1.2×10^7, 2.4×10^7, and 3.2×10^7 particles per square centimeter, respectively.

Table 1. Measured properties of 3.9-Gev nitrogen ion beams, as used for cell culture irradiations.

Total range	12.6 g cm^{-2} in polyethylene
Minimum stopping power	190 Mev-cm^2/g
Maximum stopping power	~ 1200 Mev-cm^2/g
Beam diameter	3.5 cm
Uniformity of intensity	± 5 percent
Mean free path for nuclear collisions	15 ± 3 cm in polyethylene