use higher energies. The PPA is capable of accelerating fully stripped nitrogen, or any ion whose atomic number is half its mass number, to 1.2 Gev/amu. Still heavier ions with more neutrons than protons (for example, xenon) could be accelerated to 900 Mev/amu. To accomplish full stripping requires the development of new types of ion sources or the use of a two-step acceleration and stripping process (*5*).

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6. We thank the Fannie E. Rippel Foundation for its timely and generous support of this work. The support of Princeton University and the cooperation of the Atomic Energy Commission are also acknowledged. Finally, we are grateful to the entire Princeton Particle Accelerator staff for their unwavering loyalty and outstanding technical performance.

15 October 1971

Interaction of 3.9-Gev Nitrogen Ions with Matter

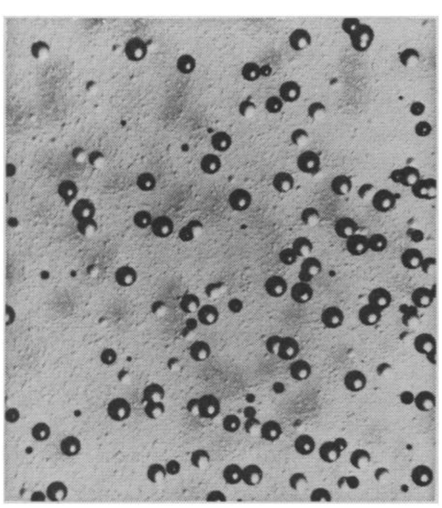
Abstract. *The interaction with matter of nitrogen ions in the 3.9-billion-electron-volt (Gev) beam of the Princeton Particle Accelerator has been studied. In polyethylene, the range of ions is 12.6 ± 0.2 grams per square centimeter and the mean free path for nuclear collisions is 15.4 ± 3.8 centimeters; the loss of energy by the ions passing through polyethylene agrees with that predicted by stopping-power theory. The production of secondary particles has been investigated. These data are useful for experiments and for evaluating the merits of nitrogen ions in biomedical applications.*

We have measured physical properties of beams of relativistic nitrogen ions made available by the Princeton Particle Accelerator (PPA) (*1*). Their interaction with matter was studied with the goal of obtaining accurate measurements that will be useful in planned experiments and in evaluating the predicted merits of nitrogen ions for cancer therapy and other biomedical applications involving localized tissue destruction (*2*).

The beam intensity was measured with an argon-filled ionization chamber (*3*) and scintillation-counter telescopes. The telescope counting rate was corrected for accidental coincidences and used for normalization in ionization chamber studies. The beam current, as measured by the ionization chamber, was found to be proportional to the corrected telescope counting rate and independent of the voltage applied to the chamber (indicating proper saturation). In the course of a test exposure of Lexan polycarbonate, consistent values for the number of particles were also obtained (*4*). Figure 1 shows the etched tracks in Lexan of stopping nitrogen ions from the beam. Particles other than nitrogen ions constituted less than 4 percent of the beam, as measured with nuclear emulsions (*5*).

The average energy needed to produce an ion pair in argon, W_{Ar}, can be calculated from the beam intensity measured by the counter telescope, the ionization chamber current, and the mass stopping power of the nitrogen ions. The last parameter was measured as described below. The preliminary result obtained for W_{Ar} is 29.2 ± 3 ev per ion pair. This is somewhat higher than but not inconsistent with the average value of 26.3 ± 0.1 reported for α-particles (*6*).

The ranges of nitrogen ions in polyethylene, aluminum, and lead were measured with the differential absorption scintillation-counter telescope shown in Fig. 2. Counters 1 and 2 detect the incident beam by registering only particles resulting in coincident signals. Counter 3 detects the beam transmitted through the variable absorber of thickness R (cm), which includes the scintillators, while counter 4 detects the beam transmitted through the incremental thickness ΔR of counter 3. The thickness of counter 3 affects the range resolution. The number of particles stopping in a depth of material between R and $R + \Delta R$ cm is defined by counter 4 in anticoincidence with counters 1, 2, and 3, designated $123\bar{4}$, and normalized to the total beam count, designated 12. This



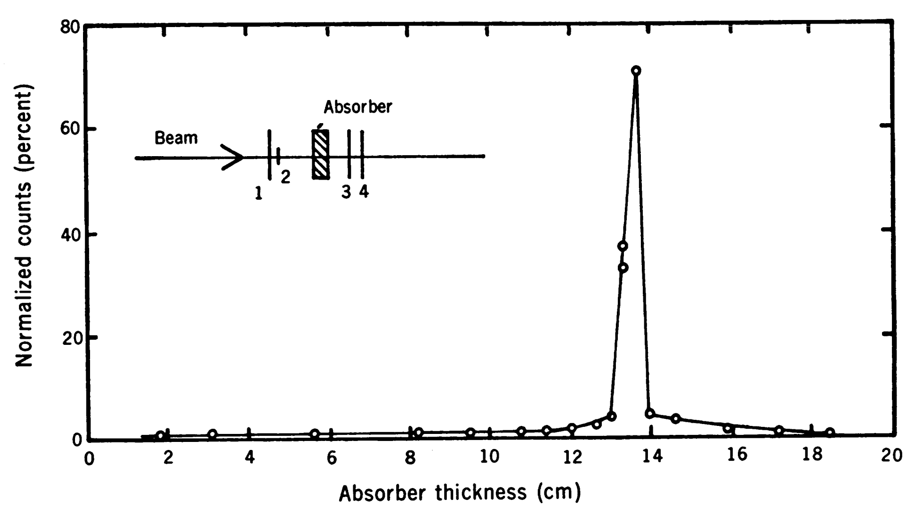


Fig. 1 (left). Nitrogen ion tracks etched in a Lexan polycarbonate sheet. Many of the nitrogen tracks in this photograph are overetched and appear as low-contrast depressions. Roughly the last 90 μm of the range of a nitrogen ion can be made visible in Lexan by etching; a suitable etchant is a mixture of equal volumes of 6.25N NaOH and ethanol, at 50°C. A 5-hour etch yields tracks with diameters up to 60 μm (*4*). Fig. 2 (right). Differential absorption curve for 3.9-Gev nitrogen ions in polyethlene. The mean range of the ions is given by the absorber thickness at the maximum. The inset shows the scintillation-counter telescope arrangement used for this measurement. The normalized counts refer to the ratio $123\bar{4}/12$ discussed in the text.

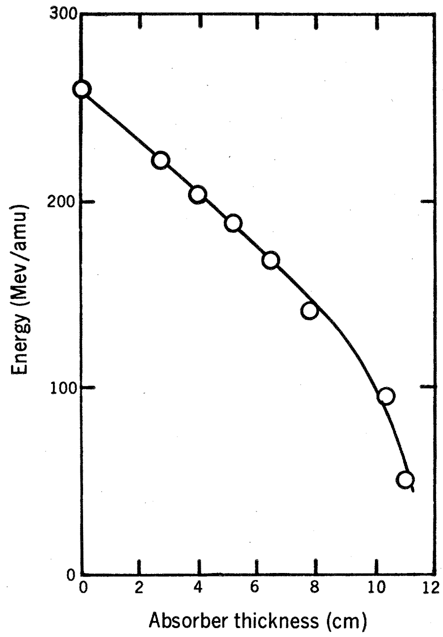


Fig. 3. Residual energy of the nitrogen ion beam after passing through the polyethylene absorber thickness shown in the abscissa. The energy was measured by the time-of-flight technique described in the text.

is an experimental differentiation of the number-distance curve, and it yields the mean range (*7*) as indicated by the maximum in Fig. 2.

The ranges obtained in different materials are shown in Table 1 and compared with predicted values calculated according to $R_N(v) = (A/Z^2)R_H(v)$ (*8*). In this formula, $R_N(v)$, A, and Z are, respectively, the range, atomic weight, and charge of a nitrogen ion with a given velocity v, and $R_H(v)$ is the range of a proton with the same velocity. The values of R_H were obtained from the tables of Janni (*9*). The agreement of our measured ranges with ranges calculated according to this prescription adds to the confidence with which such calculations can be applied to cosmic-ray nuclei.

A simple modification of the differential range telescope was used to obtain the energy loss of the nitrogen beam as a function of the absorber thickness. Counter 4 was removed to a distance of approximately 91 m from counter 3, and the time of flight of the transmitted nitrogen ions was determined over a measured path. The energy of the transmitted nitrogen beam thus obtained is graphed as a function of R for polyethylene in Fig. 3. Numerical differentiation of this curve yields the stopping power, dE/dx. Values of this parameter are shown in Fig. 4, together with a curve calculated from the proton stopping-power tables of Janni (*9*), scaled by Z^2. Again, it may be seen that agreement is good down to the lowest energies measured. At the lower energies the uncertainty in measurement due to absorption by the air in the flight path becomes large.

The fraction of the incident beam that is transmitted through the absorber, designated 123/12 in the telescope arrangement, is also a measure of the nuclear attenuation in R. The fraction of particles transmitted decreased exponentially with increasing absorber thickness. A value of 0.37 at a depth of 15.4 ± 3.8 cm in polyethylene was obtained by extrapolation beyond the range of the nitrogen ions. This corresponds to the mean free path for nuclear interactions that remove nitrogen ions from the beam. This value is consistent with predictions based on the sizes of the nitrogen nucleus and the nuclei of the atoms in the absorber material (geometrical cross sections).

Table 1. Measured and calculated ranges of nitrogen ions.

Absorber	Measured range ($g\ cm^{-2}$)	Calculated range ($g\ cm^{-2}$)
Polyethylene	12.6 ± 0.2	12.25
Aluminum	16.2 ± 0.5	16.6
Lead	22.1 ± 4.0	25.8

The unique nanosecond pulse structure of the PPA beam permits measurement of the energies of neutral particles by time of flight. Figure 5 shows a graph of the time-of-flight spectrum obtained with and without a bending magnetic field positioned downstream from the absorber to sweep charged particles out of the beam. The total absorber thickness, including the air path, the scintillators, and the polyethylene neutron converter was 12.2 g cm^{-2}, or slightly less than the range of the nitrogen ions. The number of counts under the nitrogen ion peak, which is separated very clearly from the peaks of the higher velocity secondary particles, was integrated and corrected for counting losses due to beam divergence. The total number of counts due to secondary particles is approxi-

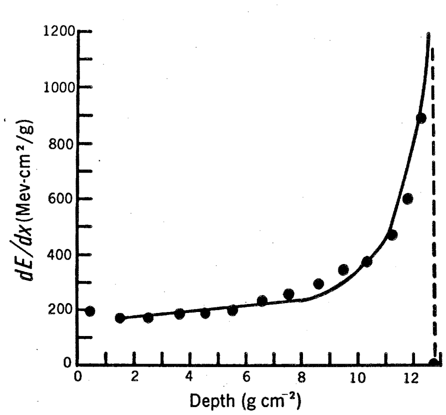
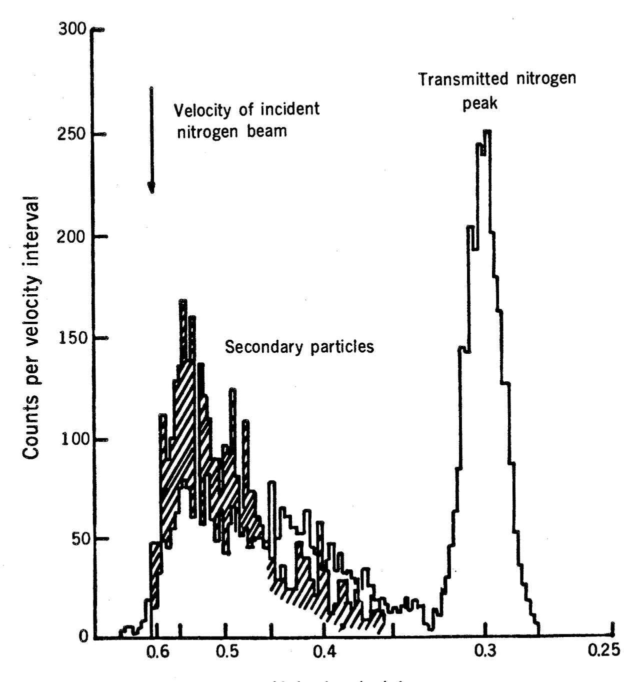


Fig. 4. Experimental dE/dx curve for 3.9-Gev nitrogen ions in polyethylene. The curve was obtained by differentiating the measured range-energy curve (plotted points), for which energy was determined by time of flight. The solid line was calculated from stopping-power theory. This dE/dx curve does not give the depth-dose profile, because nuclear collisions decrease the particle intensity.

Fig. 5. Time-of-flight spectrum obtained with (hatched area) and without sweeping charged particles out of the beam with a bending magnet. The total thickness of the absorber traversed by the transmitted nitrogen beam was 12.2 g cm^{-2}, or slightly less than the range. Velocity is given in terms of (v/c), where v is the particle velocity and c the velocity of light. The neutron counts have been multiplied by a factor of 10 in the graph for clarity of presentation. Analysis of these data is described in the text.



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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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.

15 October 1971

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-