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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14. Experiments comparable to those described in (*12*) indicate that T-1 cell survival profiles are quantitatively similar to those obtained for Chinese hamster M3-1 cells, for which cell survival parameters have not yet been computed.
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.

15 October 1971

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

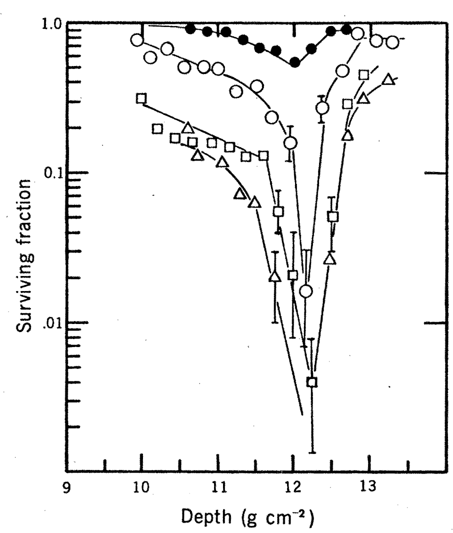

Fig. 1. Chinese hamster cell survival (colony formation) as a function of depth at the end of the 3.9-Gev nitrogen ion beam. The surviving colonies were counted in each 2.3-mm interval and compared with the number of colonies in the corresponding intervals in unirradiated control cultures. The doses 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

allowed to multiply for 5 days at 37°C, and the resulting individual colonies were stained with methylene blue. The number of colonies per 2.3-mm interval was counted. Unirradiated cultures with 10^4 cells in each flask were used as controls and were counted in the same manner. Survival was calculated as the number of colonies in a 2.3-mm band divided by the average number of colonies in the corresponding band in the control cultures. The resulting data give cell survival as a function of distance along the beam path. These are presented in Fig. 1 for four doses of nitrogen ions. It can be determined from the data that about 110 rads at the Bragg peak resulted in 55 percent cell survival on the uppermost curve of Fig. 1. Uncertainty in the dose estimation is about 15 percent.

Reference radiation (gamma ray) experiments were performed under the same conditions with dose rates of 0.16 and 350 rad/min. The doses required for 50 percent survival were 350 and 240 rads, respectively, so that the relative biological effectiveness of Bragg-peak nitrogen ions for this end point is between 2.2 and 3.0 at the dose rates used. The survival values are in quantitative agreement with predictions based on survival data for low-energy heavy ions (*1, 5, 12*).

These results confirm the favorable depth-dose profile and high efficiency of cell killing at the Bragg peak. An extensive experimental program to investigate the remaining relevant properties of high-energy heavy ions is necessary; however, the present evidence suggests that cancer therapy and other biomedical applications of high-energy heavy ions are distinct possibilities.

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15 October 1971

Acceleration of Heavy Ions at the Bevatron

Abstract. *Substantial beams of deuterons, α-particles, and nitrogen ions have been accelerated to high energies (nitrogen to 36 billion electron volts) in the bevatron. Beams of various energies were successfully extracted for experimental use. Modifications of the ion source, the injector, and the main acceleration system made the production of high-energy heavy ions possible. Our computer control system played an important part.*

The bevatron, a proton synchrotron of 6.2-Gev energy with a long history of having been used for research in elementary particle physics, has been modified to provide the additional capability of accelerating heavy ions to very high energies. We have verified its potential in several fields of physics, in biology, and in medical research. So far, deuterons, α-particles, and nitrogen ions have been accelerated and extracted from the machine; experiments with the nitrogen ions in radiobiology and in physics are under way (*1, 2*). Table 1 gives the energies and intensities of the extracted heavy ion beams. For comparison, the usual extracted proton beam is 3×10^{12} particles per pulse.

The duoplasmatron source normally used to produce protons could be used without difficulty in forming the $^2H^+$ and $^4He^{2+}$ ions. But since these ions have only one-half the charge to mass ratio of protons, they are not accelerated in the usual (1 $\beta\lambda$) mode in the injecting linear accelerator, which is designed for 20-Mev protons. Instead, they are accelerated in the 2 $\beta\lambda$ mode, which is only one-tenth as efficient, to 5 Mev/nucleon—or to one-half the velocity of protons. In the 2 $\beta\lambda$ mode, the ions take two radio-frequency periods to pass from one drift tube to the next; their lower velocity (compared with protons) requires that the starting frequency of the bevatron accelerating system be reduced by one-half. This capability had already been built into the original conservative design.

Particles can be accelerated in the bevatron to energies that are determined by the radius and magnetic field. For deuterons, this maximum is 5.2 Gev and for α-particles, 10.4 Gev. Lower energies can also be obtained, presently down to about 280 Mev/nucleon, a limit imposed by the design of the extraction system.

Getting a beam of nitrogen ions was much more difficult (see Fig. 1). Nitrogen ions are produced in the ion source in various charge states, in the ratio $N^{a+}:N^{(a+1)+} \simeq 0.1$ for charge states higher than $+3$. With a cold-cathode

Table 1. Intensities (particles per pulse) for various energies E (billion electron volts per nucleon) of extracted heavy ion beams. The letters ND mean not done.

Particle	$E = 2.1$	$E = 1$	$E = 0.28$
Deuterons	10^{11}	ND	2×10^{10}
α-Particles	5×10^9	5×10^9	10^9
Nitrogen ions	7×10^5	ND	1.4×10^3