Title
Radiobiological Experiments with Heavy Ions at the Bevatron

Permalink
https://escholarship.org/uc/item/2dx7p9kr

Author
Tobias, Cornelius A

Publication Date
2023-09-06

REFERENCES

1. M. G. White, M. Isaila, K. Prelac, and H. L. Allen, Science 174, 1121 (1971).
2. H. A. Grunder, W. D. Hartsough, and E. J. Lofgren, Science 174, 1128 (1971).
3. M. V. Isaila, W. Schimmerling, K. G. Vosburgh, M. G. White, R. C. Filz, and P. J. McNulty, Science 177, 424 (1972).
4. E. Lofgren (private communication).
5. C. A. Tobias, J. T. Lyman, A. Chatterjee, J. Howard, H. D. Maccabee, M. R. Raju, A. R. Smith, J. M. Speridde, and G. P. Welch, Science 174, 1131 (1971).
6. T. F. Budinger, J. T. Lyman, and C. A. Tobias, Visual perception of accelerated nitrogen nuclei interacting with the human retina, in: Initial Radiobiological Experiments with Accelerated Nitrogen Ions at the Bevatron, LBL-529 (1971), p. 49-65.
7. W. J. Heinze, L. Craise, and J. Howard, Heavy-ion irradiation of Zea mays--a search for biological endpoints, in: Initial Radiobiological Experiments with Accelerated Nitrogen Ions at the Bevatron, LBL-529 (1971), pp. 93-107.
8. C. A. Tobias, J. T. Lyman, and J. H. Lawrence, Some considerations of physical and biological factors in radiotherapy with high-LET radiations including heavy particles, Pi mesons, and fast neutrons, Chap. 6 in: Progress in Atomic Medicine: Recent Advances in Nuclear Medicine, Vol. 3, (J. H. Lawrence, ed.), Grune & Stratton (1971), pp. 167-218.

ACKNOWLEDGEMENTS

The effort at Berkeley is carried on by a collaborative research group. A partial list of the individuals who have contributed to the scientific basis of this paper is as follows:

Radiological physics: J. Lyman; A. Chatterjee; G. Welch; H. Maccabee; S. Curtis; D. Palmer, W. Schimmerling; E. Benton.

Accelerator physics: E. Lofgren; H. Grunder; W. Hartsough; D. Evans; F. Lothrop; R. Morgado

Biology: J. Leith; B. Martins; R. Roisman; D. Kalofonos; W. Schilling; T. Yang; J. Risius R. MacGregor.

Medicine: J. H. Lawrence; J. Born; T. Budinger.

I am particularly grateful to Dr. A. Chatterjee for his help in preparing this paper. For a more thorough discussion of the topics raised here, please refer to PRETHERAPEUTIC INVESTIGATIONS WITH ACCELERATED HEAVY IONS, C.A. Tobias.

The work at Berkeley described here is carried out under the auspices of the Atomic Energy Commission, Contract No. W7405-eng-48, with some additional support provided through NASA-Ames Order W12792, Task #6.

LBL-1751

RADIOBIOLOGICAL EXPERIMENTS WITH HEAVY IONS AT THE BEVATRON

Cornelius A. Tobias

Summary

Penetration of heavy charged particles can be characterized by three basic physical facts: 1) almost no scattering; 2) abrupt increase of linear energy deposition (LET) close to the point where the particles stop; and 3) exact range-energy relationship.

These facts constitute the basis of very favorable depth-dose characteristics for heavy ions to be used in radiotherapy. Availability of accelerated high LET heavy ions in the Laboratory, though a recent development, has already provided us with much useful information in physics, chemistry, and radiobiology.

Fast heavy ions could previously be studied only in outer space where they form important components of primary cosmic rays. Heavy ions in the Laboratory became available as early as 1957 at the Berkeley HILAC, but at very low energies. In August, 1971, two accelerators, the Princeton Synchrotron[1] and the Berkeley Bevatron[2] produced penetrating deflected beams of nitrogen nuclei. Since that time, carbon, oxygen and neon, as well as a few oxygen particles at Princeton, have been accelerated.[3, 4] Stopping-power curves as a function of range for various ions in water, as calculated theoretically, are shown in Figure 1. Various ion energies in units of Mev/nucleon are designated on each curve. The uniformly shaded area represents the stopping-power and associated ions accelerated at the HILAC and cyclotron. The BEVALAC (a compound accelerator formed from the HILAC and Bevatron) adds a new dimension, and initially it will be able to accelerate ions with atomic no. up to that of iron ($Z = 26$) to considerable energies. The hatched area in Figure 1 represents accelerated ions within the scope of accelerations projected for the BEVALAC.

A few aspects of the properties of accelerated heavy ions as they relate to radiobiology and radiotherapy will be discussed below.

Depth-dose Distributions

High-energy, heavy-ion beams have already been shown (at PPA and the Bevatron) to have physical characteristics useful for biomedical application, including a high sharp Bragg peak, good depth-dose characteristics and high LET. The entrance dose can be kept small and the exit dose insignificant. In contrast, it is possible to give significantly large doses to exceedingly small tissue volume inside the body, a desired therapeutic application not heretofore possible. One application of this will be exposure of small loci of the brain or the spinal cord.

The depth-dose distribution, measured as ionization behind a water phantom, for a nearly mono-energetic oxygen beam, is shown in Figure 2. A detailed description of the method is described elsewhere.[5] The oxygen beam has a kinetic energy of 260 MeV per nucleon. The Bragg ionization ratio (peak to plateau) is about 6. This beam is adequate to produce small lesions in brain or in spinal cord of 1.5 mm. or more in diameter.

Qualitative Effects

Visual perception

Visual phenomena in the form of streaks and flashes induced by accelerated nitrogen ions (10 to 20 particles per pulse) near the end of their range and passing through particular light-sensitive regions of the human retina, have been observed.[6] It is concluded from the experiments that accelerated nitrogen ions near the end of their range cause bright streaks and flashes. In order to cause light flashes, the particles must cross light-sensitive regions of the retina at the posterior portion of the eye. Ionization and excitation, and possibly fluorescent light quanta in the immediate vicinity of the particle tracks, cause light sensation. Light flashes and streaks caused by single particles are well localized and are different from the diffuse light sensations reported in the field of diagnostic X-ray machines, or in a mu-meson field. Some degree of dark adaptation is necessary for visual sensation. Similar results were obtained with 260 MeV/nucleon Neon particles.

Heavy-ion irradiation of hybrid maize seed

An attempt has been made to determine biological endpoints showing the effects of very low doses of nitrogen ions on corn seed, Zea mays.[7] Dose varied from 0.018 rads to 0.348 rads, and 97.18% of the seeds germinated, while 6% of the irradiated seeds showed developmental abnormalities. This particular endpoint seems quite promising.

Quantitative Effects

Relative biological effectiveness

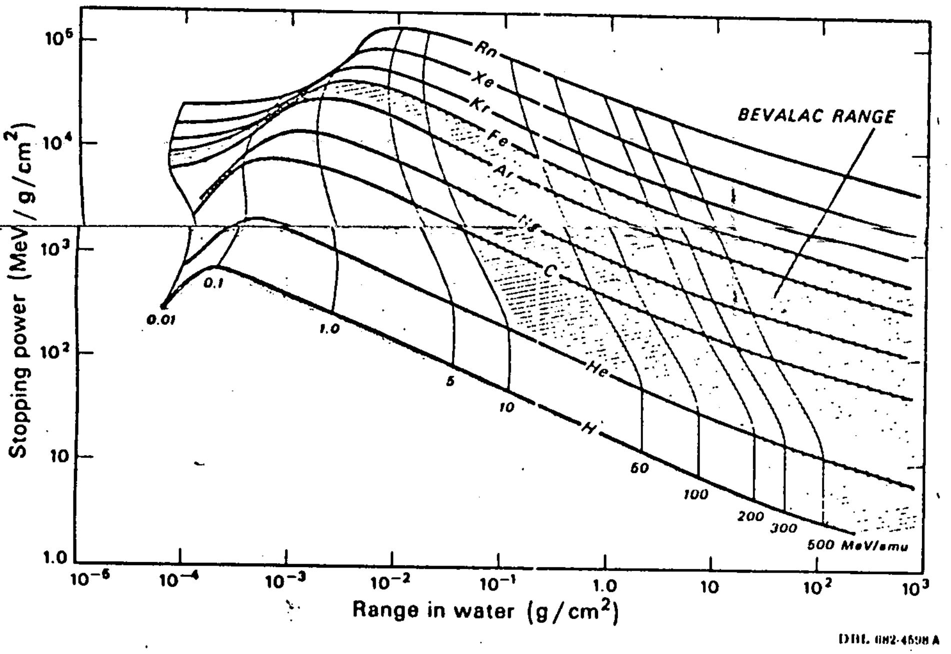
Since the radiation quality changes along the ionizing tracks, it is often possible to have those portions of the tracks that are more densely ionizing in the region of the tumor, with lower-density portions placed in the surrounding normal tissue. The relative biological effectiveness (RBE) of the end portions of the tracks of the particles is high; the tumor dose can be lower than it normally would be with low-LET radiations. As a result, normal nontumorous tissue in the beam path is spared. Since RBE is related to the oxygen effect, these two should be discussed together.

Oxygen effect

It is well known that anoxic cells are about three times as resistant to low-LET radiation than normally oxygenated cells. Evidence has also been accumulating that many tumors have anoxic cells, particularly tumors having necrotic portions. Since low-LET radiation allows preferential survival to anoxic tumor cells, the rationale for high-LET therapy of any kind includes the requirement that the oxygen effect should be reduced as far as possible. In fact, one of the main properties that differentiates heavy ions from protons and helium ions is the greater reduction of the oxygen effect by heavy ions. The study of the oxygen effect has become complex: we know that high-LET particles generally lower the OER (oxygen enhancement ratio); however, the actual value of OER depends also on the velocity of the particles. Generally, at the same LET, the OER is assumed to be higher for a higher-speed particle. In addition, OER seems to be related to the physiological state of cells and to their ability to repair radiation lesions. Finally, different strains of cells exhibit different OER ratios.[8]

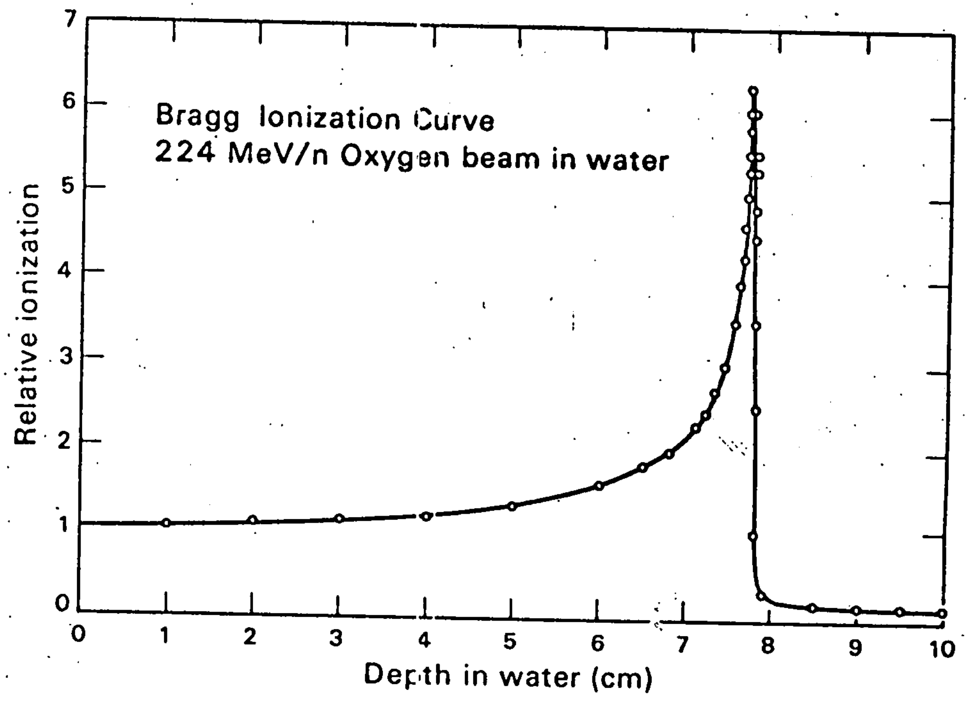
For heavy ions the OER values along the tracks of the particles is of crucial interest: the eventual choice of atomic number of the particles to be used in therapy may depend greatly on the practically attainable OER. It will be necessary to perform additional experiments with the BEVALAC on each of the beams in order to fully understand the diluting effect of delta-ray production.

In order to approach the oxygen problem by measurement, two kinds of experiments are being carried out at Berkeley. Using a conventional method, we have obtained survival curves for mammalian cells in culture placed behind various thicknesses of absorbers. In addition, we have designed a special container, the "submarine," on which individual samples of tissue culture cells are suspended on thin glass slides behind one another, so that each is simultaneously exposed to the same particle beam. Although the work is still in progress, an early example of such "Bragg survival" curves is shown in Figure 3 for a single dose of 140 rads of 3.6-BeV oxygen particles. Although the oxygen-beam OER is lower than 1.9 everywhere along the track and only 1.25 near the Bragg peak, we expect to find still lower OER values for heavier beams (e.g. neon), when it becomes feasible to test these at the BEVALAC.



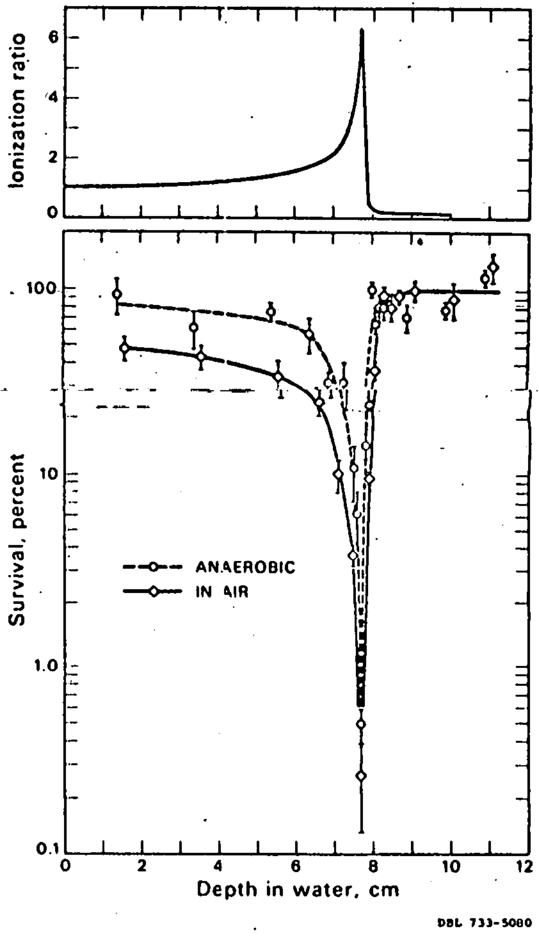
DBL 682-4598 A

Fig. 1. Stopping-power curves as a function of range for various ions in water, as calculated by the computer program. Various ion energies in units of MeV/amu are designated on each curve. The Ne-C and Xe-U crossovers at low energy although possibly a physical reality occur in regions of low confidence. DBL 682-4598A.



DBL 731-5035

Figure 2. Bragg ionization curve for a 3.6-GeV oxygen beam absorbed in water. The ratio of peak ionization to plateau ionization is about 6:1. The primary particles stop at a depth of about 10 cm. Ionization beyond that distance is due to secondary particles and rays generated within the beam. DBL 731-5035



DBL 733-5080

Figure 3. "Bragg survival" curves of human kidney cells exposed to a mono-energetic oxygen beam. The high RBE of the slow oxygen ion causes very low survival at the Bragg ionization peak. Exposure in air and nitrogen environments is shown. DBL 733-5080.

LBL-1751

RADIOBIOLOGICAL EXPERIMENTS WITH HEAVY IONS AT THE BEVATRON

Cornelius A. Tobias

Summary

Penetration of heavy charged particles can be characterized by three basic physical facts: 1) almost no scattering; 2) abrupt increase of linear energy deposition (LET) close to the point where the particles stop; and 3) exact range-energy relationship.

These facts constitute the basis of very favorable depth-dose characteristics for heavy ions to be used in radiotherapy. Availability of accelerated high LET heavy ions in the Laboratory, though a recent development, has already provided us with much useful information in physics, chemistry, and radiobiology.

Fast heavy ions could previously be studied only in outer space where they form important components of primary cosmic rays. Heavy ions in the Laboratory became available as early as 1957 at the Berkeley HILAC, but at very low energies. In August, 1971, two accelerators, the Princeton Synchrotron[1] and the Berkeley Bevatron[2] produced penetrating deflected beams of nitrogen nuclei. Since that time, carbon, oxygen and neon, as well as a few oxygen particles at Princeton have been accelerated.[3, 4] Stopping-power curves as a function of range for various ions in water, as calculated theoretically, are shown in Figure 1. Various ion energies in units of Mev/nucleon are designated on each curve. The uniformly shaded area represents the stopping-power and associated ions accelerated at the HILAC and cyclotron. The BEVALAC (a compound accelerator formed from the HILAC and Bevatron) adds a new dimension, and initially it will be able to accelerate ions with atomic no. up to that of iron ($Z = 26$) to considerable energies. The hatched area in Figure 1 represents accelerated ions within the scope of accelerations projected for the BEVALAC.

A few aspects of the properties of accelerated heavy ions as they relate to radiobiology and radiotherapy will be discussed below.

Depth-dose Distributions

High-energy, heavy-ion beams have already been shown (at PPA and the Bevatron) to have physical characteristics useful for biomedical application, including a high sharp Bragg peak, good depth-dose characteristics and high LET. The entrance dose can be kept small and the exit dose insignificant. In contrast, it is possible to give significantly large doses to exceedingly small tissue volume inside the body, a desired therapeutic application not heretofore possible. One application of this will be exposure of small loci of the brain or the spinal cord.

The depth-dose distribution, measured as ionization behind a water phantom, for a nearly monoenergetic oxygen beam, is shown in Figure 2. A detailed description of the method is described elsewhere.[5] The oxygen beam has a kinetic energy of 260 MeV per nucleon. The Bragg ionization ratio (peak to plateau) is about 6. This beam is adequate to produce small lesions in brain or in spinal cord of 1.5 mm. or more in diameter.

Qualitative Effects

Visual perception

Visual phenomena in the form of streaks and flashes induced by accelerated nitrogen ions (10 to 20 particles per pulse) near the end of their range and passing through particular light-sensitive regions of the human retina, have been observed.[6] It is concluded from the experiments that accelerated nitrogen ions near the end of their range cause bright streaks and flashes. In order to cause light flashes, the particles must cross light-sensitive regions of the retina at the posterior portion of the eye. Ionization and excitation, and possibly fluorescent light quanta in the immediate vicinity of the particle tracks, cause light sensation. Light flashes and streaks caused by single particles are well localized and are different from the diffuse light sensations reported in the field of diagnostic X-ray machines, or in a mu-meson field. Some degree of dark adaptation is necessary for visual sensation. Similar results were obtained with 260 MeV/nucleon Neon particles.

Heavy-ion irradiation of hybrid maize seed

An attempt has been made to determine biological endpoints showing the effects of very low doses of nitrogen ions on corn seed, Zea mays.[7] Dose varied from 0.018 rads to 0.348 rads, and 97.18% of the seeds germinated, while 6% of the irradiated seeds showed developmental abnormalities. This particular endpoint seems quite promising.

Quantitative Effects

Relative biological effectiveness

Since the radiation quality changes along the ionizing tracks, it is often possible to have those portions of the tracks that are more densely ionizing in the region of the tumor, with lower-density portions placed in the surrounding normal tissue. The relative biological effectiveness (RBE) of the end portions of the tracks of the particles is high; the tumor dose can be lower than it normally would be with low-LET radiations. As a result, normal nontumorous tissue in the beam path is spared. Since RBE is related to the oxygen effect, these two should be discussed together.

Oxygen effect

It is well known that anoxic cells are about three times as resistant to low-LET radiation than normally oxygenated cells. Evidence has also been accumulating that many tumors have anoxic cells, particularly tumors having necrotic portions. Since low-LET radiation allows preferential survival to anoxic tumor cells, the rationale for high-LET therapy of any kind includes the requirement that the oxygen effect should be reduced as far as possible. In fact, one of the main properties that differentiates heavy ions from protons and helium ions is the greater reduction of the oxygen effect by heavy ions. The study of the oxygen effect has become complex: we know that high-LET particles generally lower the OER (oxygen enhancement ratio); however, the actual value of OER depends also on the velocity of the particles. Generally, at the same LET, the OER is assumed to

Loretta/Joyce:
Accession
no.
only --
no copies
needed
for us.
- Della

be higher for a higher-speed particle. In addition, OER seems to be related to the physiological state of cells and to their ability to repair radiation lesions. Finally, different strains of cells exhibit different OER ratios.[8]

For heavy ions the OER values along the tracks of the particles is of crucial interest: the eventual choice of atomic number of the particles to be used in therapy may depend greatly on the practically attainable OER. It will be necessary to perform additional experiments with the BEVALAC on each of the beams in order to fully understand the diluting effect of delta-ray production.

In order to approach the oxygen problem by measurement, two kinds of experiments are being carried out at Berkeley. Using a conventional method, we have obtained survival curves for mammalian cells in culture placed behind various thicknesses of absorbers. In addition, we have designed a special container, the "submarine," on which individual samples of tissue culture cells are suspended on thin glass slides behind one another, so that each is simultaneously exposed to the same particle beam. Although the work is still in progress, an early example of such "Bragg survival" curves is shown in Figure 3 for a single dose of 140 rads of 3.6-BeV oxygen particles. Although the oxygen-beam OER is lower than 1.9 everywhere along the track and only 1.25 near the Bragg peak, we expect to find still lower OER values for heavier beams (e.g. neon), when it becomes feasible to test these at the BEVALAC.

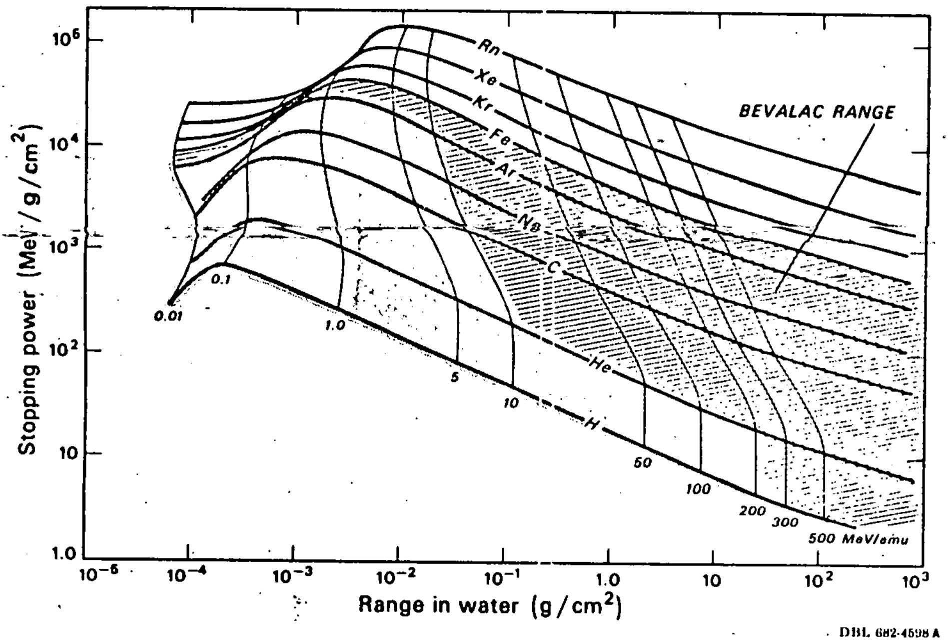


Fig. 1. Stopping-power curves as a function of range for various ions in water, as calculated by the computer program. Various ion energies in units of MeV/amu are designated on each curve. The Ne-C and Xe-U crossovers at low energy although possibly a physical reality occur in regions of low confidence. DBL 682-4598A.

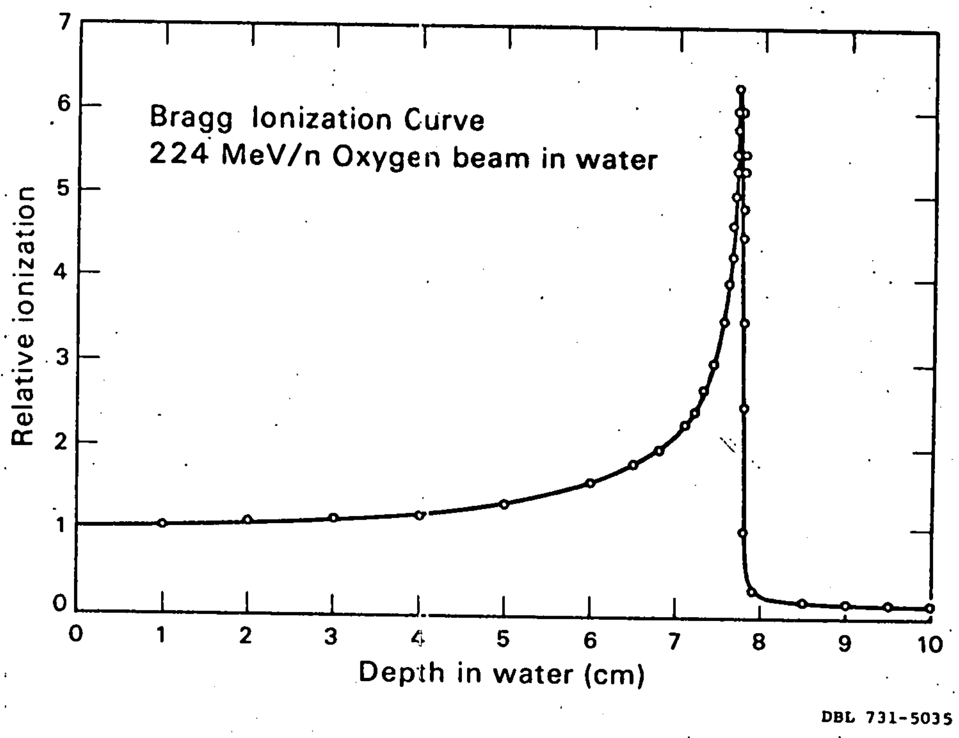


Figure 2. Bragg ionization curve for a 3.6-GeV oxygen beam absorbed in water. The ratio of peak ionization to plateau ionization is about 6:1. The primary particles stop at a depth of about 10 cm. Ionization beyond that distance is due to secondary particles and rays generated within the beam. DBL 731-5035

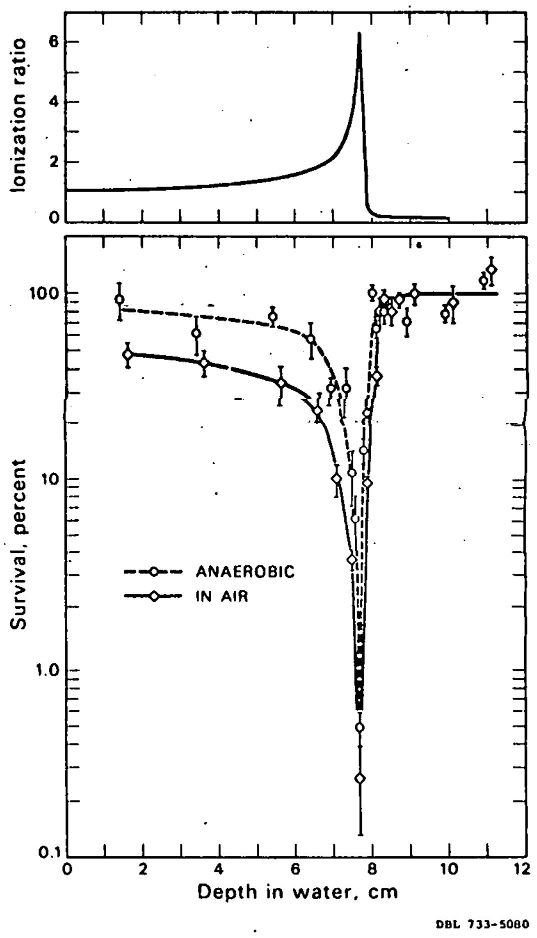


Figure 3. "Bragg survival" curves of human kidney cells exposed to a mono-energetic oxygen beam. The high RBE of the slow oxygen ion causes very low survival at the Bragg ionization peak. Exposure in air and nitrogen environments is shown. DBL 733-5080.

REFERENCES

1. M. G. White, M. Isaila, K. Prelac, and H. L. Allen, Science 174, 1121 (1971).
2. H. A. Grunder, W. D. Hartsough, and E. J. Lofgren, Science 174, 1128 (1971).
3. M. V. Isaila, W. Schimmerling, K. G. Vosburgh, M. G. White, R. C. Filz, and P. J. McNulty, Science 177, 424 (1972).
4. E. Lofgren (private communication).
5. C. A. Tobias, J. T. Lyman, A. Chatterjee, J. Howard, H. D. Maccabee, M. R. Raju, A. R. Smith, J. M. Speridde, and G. P. Welch, Science 174, 1131 (1971).
6. T. F. Budinger, J. T. Lyman, and C. A. Tobias, Visual perception of accelerated nitrogen nuclei interacting with the human retina, in: *Initial Radiobiological Experiments with Accelerated Nitrogen Ions at the Bevatron*, LBL-529 (1971), p. 49-65.
7. W. J. Heinze, L. Craise, and J. Howard, Heavy-ion irradiation of *Zea mays*--a search for biological endpoints, in: *Initial Radiobiological Experiments with Accelerated Nitrogen Ions at the Bevatron*, LBL-529 (1971), pp. 93-107.
8. C. A. Tobias, J. T. Lyman, and J. H. Lawrence, Some considerations of physical and biological factors in radiotherapy with high-LET radiations including heavy particles, Pi mesons, and fast neutrons, Chap. 6 in: *Progress in Atomic Medicine: Recent Advances in Nuclear Medicine*, Vol. 3, (J. H. Lawrence, ed.), Grune 4 Stratton (1971), pp. 167-218.

ACKNOWLEDGEMENTS

The effort at Berkeley is carried on by a collaborative research group. A partial list of the individuals who have contributed to the scientific basis of this paper is as follows:

Radiological physics: J. Lyman; A. Chatterjee; G. Welch; H. Maccabee; S. Curtis; D. Palmer, W. Schimmerling; E. Benton.

Accelerator physics: E. Lofgren; H. Grunder; W. Hartsough; D. Evans; F. Lothrop; R. Morgado

Biology: J. Leith; B. Martins; R. Roisman; D. Kalofonos; W. Schilling; T. Yang; J. Risius R. MacGregor.

Medicine: J. H. Lawrence; J. Born; T. Budinger.

I am particularly grateful to Dr. A. Chatterjee for his help in preparing this paper. For a more thorough discussion of the topics raised here, please refer to PRETHERAPEUTIC INVESTIGATIONS WITH ACCELERATED HEAVY IONS, C.A. Tobias.

The work at Berkeley described here is carried out under the auspices of the Atomic Energy Commission, Contract No. W7405-eng-48, with some additional support provided through NASA-Ames Order W12792, Task #6.