BIOLOGICAL AND MEDICAL RESEARCH WITH ACCELERATED HEAVY IONS AT THE BEVALAC 1974—1977

Prepared for
Division of Biological and Environmental Research
U.S. Energy Research and Development Administration

April 1977

NOTICE
This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Energy Research and Development Administration, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

Prepared by
Division of Biology and Medicine
Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720

✓
Edited by
Sheryl Elam, Biomedical Division
and
Technical Information Department Staff

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

.

.

.

.

TABLE OF CONTENTS

Staff Associated with Biomedical Heavy-ion Research at Lawrence Berkeley Laboratory

Overview	1
1. Current Status and Planned Improvements of the Bevalac	
<i>Jose Alonso</i>	3
2. National Biomedical Heavy-ion Research Program at the Bevalac	
<i>Edward Alpen and Fred Lothrop</i>	13
3. Biomedical Research Facilities and Dosimetry	
<i>John T. Lyman and Jerry Howard</i>	26
4. Nuclear Physics of Accelerated Heavy Ions	
<i>Stanley B. Curtis and Walter Schimmerling</i>	36
5. Fundamental Radiological Physics and Radiation Chemistry of Heavy Ions in Models of Chemical and Biological Effects	
<i>John L. Magee and Alope Chatterjee</i>	49
6. Radioactive Beams	
<i>Alope Chatterjee and Cornelius A. Tobias</i>	59
7. Cellular and Molecular Radiobiology	
<i>Cornelius A. Tobias, Eleanor A. Blakely and Ruth J. Roots</i>	76
8. Tissue Radiobiology: Acute and Chronic Effects	
<i>Edward Alpen</i>	111
9. Tumor Radiobiology with Bevalac Heavy-ion Beams	
<i>Tom S. Tenforde and Stanley B. Curtis</i>	127
10. Space Radiobiology	
<i>Tracy C. H. Yang and Cornelius T. Gaffey</i>	140
11. Heavy-ion Radiation Genetics	
<i>Michael Freeling and Tracy C. H. Yang</i>	154
12. Heavy-ion Radiography	
<i>Cornelius A. Tobias and Eugene V. Benton</i>	164
13. Brain Research with Heavy-ion Beams	
<i>T. F. Budinger, J. A. Linfoot, B. R. Moyer, J. T. Lyman and J. L. Pelletier</i>	187
14. Heavy-ion Therapy	
<i>Joseph R. Castro et al.</i>	198
15. Design of Future Biomedical Accelerators	
<i>Herman A. Grunder and Christoph W. Leemann</i>	219

STAFF ASSOCIATED WITH BIOMEDICAL HEAVY-ION RESEARCH
AT LAWRENCE BERKELEY LABORATORY

Edward Alpen, Ph.D.*
Director, Donner Laboratory and Biology and Medicine Division, Associate Director
Lawrence Berkeley Laboratory

Joseph R. Castro, M.D.,[†] Chairman, Bay Area Heavy Ion Association (BAHIA)

Edward Lofgren, Ph.D., Director Accelerator Division, Associate Director, Lawrence Berkeley Laboratory

Cornelius A. Tobias, Ph.D.,* Leader, Radiation Biophysics Group, Lawrence Berkeley Laboratory

Jose Alonso, Ph.D. (Accelerator Design)

Edward Alpen, Ph.D.* (Tissue Radiobiology)

Eugene V. Benton, Ph.D., Professor, University of San Francisco (Physics and Radiography)

Eleanor A. Blakely, Ph.D. (Cellular and Molecular Radiobiology)

James Born, M.D. (Medicine)

Thomas F. Budinger, M.D.,* Leader, Research Medicine, Lawrence Berkeley Laboratory

M. Paul Capp, M.D., Chairman, Department of Radiology, University of Arizona Medical School (Radiology)

Joseph R. Castro, M.D.[†] (Radiology and Therapy)

Aloke Chatterjee, Ph.D. (Physics)

George T. Y. Chen, Ph.D. (Therapy)

Karen Crabtree, B.S. (Tumor Radiobiology)

Laurie Craise, B.S. (Space and Cellular Radiobiology)

Stanley B. Curtis, Ph.D. (Physics and Tumor Radiobiology)

Sue Daniels, M.S. (Tumor Radiobiology)

Robert Force, Operations Head, Accelerator Division

Michael Freeling, Ph.D.* (Radiation Genetics)

Cornelius T. Gaffey, Ph.D. (Space Radiobiology)

Grant Gauger, M.D.[†] (Neurosurgery)

Harry Genant, M.D.[†] (Radiology)

Hermann A. Grunder, Ph.D., Bevalac Group Leader (Accelerator Design)

Virginia Havens, M.A. (Histology)

Richard Henke, M.A., Research Physicist, University of San Francisco (Physics and Radiography)

William R. Holley, Ph.D. (Physics and Radiography)

Jerry Howard, M.S. (Physics Support, Bevalac Biomedical Operations)

Leal Kanstein, M.S. (184-inch Cyclotron Crew Operations)

Christoph W. Leeman, Ph.D. (Accelerator Design)
John A. Linfoot, M.D. (Brain Research and Therapy)
Fred H. Lothrop, Ph.D. (Bevalac Biomedical Operations)
John T. Lyman, Ph.D. (Dosimetry and Instrumentation)
John L. Magee, Ph.D., on leave from Notre Dame University (Radiation Chemistry)
Mara McDonald, A.B. (Tissue Radiobiology)
Howard Mel, Ph.D. (Membrane Biophysics)
Victor Montoya, B.S. (Space Radiobiology)
Jeanne M. Quivey, M.D.[†] (Radiology)
Edward Sickles, M.D.[†] (Radiology)
Graham Sommer, M.D.[†] (Radiology)
Walter Schimmerling, Ph.D. (Radiation Physics)
Karen Smith, B.S. (Cellular and Molecular Radiobiology)
Patti Smith (Tissue Radiobiology)
Laurie Stein, Radiotherapy Technician
Tom S. Tenforde, Ph.D. (Tumor Radiobiology)
Marsch Tekawa (Bevalac Operations)
Cornelius A. Tobias, Ph.D.^{*} (Radiobiology, Physics and Radiography)
Robert Walton, Radiotherapy Technican and Technical Associate
Graeme Welch, Ph.D. (Physics)
Kay H. Woodruff, M.D.[†] (Pathology)
Tracy C. H. Tang, Ph.D. (Radiobiology)

^{*}Staff, Division of Medical Physics, University of California, Berkeley.

[†]Staff, University of California, San Francisco, Medical School

OVERVIEW

The Bevalac, a versatile high-energy heavy-ion accelerator complex, has been in operation for less than two years. This report was prepared to report the progress that has been made in biomedical and supporting research and to project a program for the future.

The first successful acceleration of heavy ions to high energies at Princeton and Berkeley and even more the completion of the Bevalac generated interest and excitement in not only the biomedical staff of Lawrence Berkeley Laboratory but in many other laboratories among the more than 200 users of the facilities. Interest came from other countries whose scientists participate in the studies here or are planning their own heavy-ion accelerators (Chapters 1 and 2).

Heavy-ion beams have been useful for some time in nuclear chemistry, particularly for creation of transuranium elements and the study of nuclear excited states. At first, the interest among physicists was only moderate, but now that they realize that heavy ions behave like "hadrons," there is a strong nuclear science program with heavy ions ranging from low energy levels through spallation and fission to attempts to create for the first time with heavy ions conditions such as may exist in the interior of stars. Recently, it was even suggested that heavy-ion beams might be more efficient initiators of controlled fusion energy, and a national program for this purpose is in its inception.

A major purpose for which the Bevalac was constructed was to explore the possibility of heavy-ion beams for therapy for certain forms of cancer. Significant progress has been made in this direction. The National Cancer Institute has recognized the advantages that these and other accelerated particles offer, and heavy ions have been included in a long-term plan for particle therapy that will assess by means of controlled therapeutic tests the value of various modalities. Since accelerated heavy ions became available, the possibility of other contributions, not planned, became apparent. We are developing a new diagnostic method known as heavy-ion radiography that has greatly increased sensitivity for soft-tissue detail and that may become a powerful tool for localizing early tumors and metastases (Chapter 12). We have discovered that radioactive beams are formed from fragmentation of stable deflected beams. The use of these autoradioactive beams is just beginning; however, we know that these beams will be helpful in localizing the region in the body where therapy is being delivered. In addition, it has been demonstrated that instant implantation of the radioactive beam allows direct measurements of blood perfusion rates in inaccessible parts of the body, and such a technique may become a new tool for the study of fast "hot atom" reactions in biochemistry, tracer biology and nuclear medicine (Chapter 6). The Bevalac will also be useful for the continuation of previously developed methods for the control of acromegaly, Cushing's disease and, on a research basis, advanced diabetes mellitus with vascular disease. The ability to make small bloodless lesions in the brain and elsewhere with heavy-ion beams has great potential for nervous-system studies and perhaps later for radioneurosurgery (Chapter 13).

With regard to the main study of heavy ions in relation to cancer therapy, rapid progress is being made to understand and control the physical interactions of the beam (Chapters 3, 4 and 5). Experimental studies are in progress on the actions of heavy particles on normal tissues including chronic effects (Chapter 8). Major justification for future therapy is based on the effects of heavy ions on cellular systems (Chapter 7) and on tumor model systems in small rodents (Chapter 9), combined with the superior ability to deliver advantageous depth-dose patterns (Chapter 7), which are much superior to those that can

be produced by exponentially absorbed beams (gamma rays and neutrons). The versatility of heavy-ion accelerators lies in the fact that it will be possible to deliver optimal beams for a variety of purposes -- argon and neon beams for shallow tumors requiring low oxygen effect, neon beams for deep-seated tumors, carbon and helium beams when the body region affected by cancer is very large, carbon beams for producing small, well localized radiolesions.

Heavy-ion medicine is being approached with excellent support from the community. The Bay Area Heavy Ion Association (BAHIA) was formed of members from more than 10 northern California hospitals plus participants from the Los Angeles area and neighboring states. The head of this group, Joseph Castro, M. D., has joined our staff and is spearheading a group that has commenced helium-ion therapy at the 184-inch cyclotron and that will soon be in a position to use heavier ions (Chapter 14).

Heavy ions, when they cross the retina, can be seen as streaks and light flashes, as was demonstrated by our staff (Chapter 13); this phenomenon had been reported by astronauts. Helium ions, when they affect the olfactory apparatus, cause a distinct odor as reported by one of our patients. The ability of the Bevalac to accelerate nuclei of iron, an important component of cosmic radiation in space, has increased the importance of our facility as an adjunct to NASA's effort to make spaceflight safe (Chapter 10).

At the cellular and molecular level we are finding that heavy-ion beams can help to identify some basic molecular lesions in DNA and in membraneous structures that may lead to a better understanding of such diverse effects as lethal effects of radiation, mutation and cell transforamtion.

In another field, basic and applied genetics, it has been demonstrated that the heavy-ion beams produce copious chromosome deletions and other rare mutations. Not only fundamental genetics but agriculture may also benefit from the eventual results (Chapter 11).

The Bevalac is a very expensive research tool. Can the nation afford to apply the fruits of heavy-ion research on a greater scale? We have an able study group planning possible future applications (Chapter 15). Future machines will be more compact than the Bevalac and will have highly reliable operation. As to cost, the rapid progress in technology shows promise for reducing both size and price when several machines will be used. The Bevalac ushers in a somewhat new concept in radiation diagnosis and therapy, that of cooperating medical teams and fairly large central therapy establishments. The concept is not entirely new; much of cancer medicine is already concentrated at a few large and respected medical establishments. Given a large center with many patients, the Bevalac concept can mean financial savings. Because the beams are quite intense, multiport operation is feasible; a single heavy-ion machine might do the equivalent work of several of today's diagnostic and therapeutic units. In the minds of the Berkeley group, it is not the cost but rather the cost benefit ratio that is important. We feel that we have a good change to demonstrate tangible benefits from the use of our methods-- improved early detection of cancer and prolonged useful life from heavy-ion therapy. Should these results be achieved in a demonstration project, the benefits of heavy-ion medicine would in the future far outweigh foreseeable costs.

CHAPTER 1

CURRENT STATUS AND PLANNED IMPROVEMENTS OF THE BEVALAC

Jose Alonso

INTRODUCTION

The Bevalac, shown in Fig. 1, is operated by the LBL Accelerator Division, E. Lofgren, Division Leader, H. Grunder, Bevalac Group Leader, R. Force, Operations Head. It is a high-energy heavy-ion accelerator complex created in 1974 by the joining of the older SuperHILAC and Bevatron accelerators. The SuperHILAC is an Alvarez-type linear accelerator which has produced beams of ions as heavy as xenon at energies up to 8.5 MeV per atomic mass unit. This energy is eminently suited for nuclear-reaction studies, but tissue penetration at this energy is insufficient for biological work on anything other than exceedingly thin samples. It was noted in 1971 by Albert Ghiorso¹ that the pulse and energy characteristics of the SuperHILAC beam were ideally suited for injection into the Bevatron, where energies up to 2.1 GeV per nucleon would be possible, affording tissue penetration ranges of up to a meter or more. Earlier acceleration of heavy ions in the Bevatron, injected by the Bevatron's 20-MeV linac, had demonstrated the feasibility of producing high-energy heavy-ion beams, but intensities from this local injector were insufficient to contemplate active radiobiology and therapy programs. Thus, the use of the SuperHILAC as a high-intensity injector would greatly expand the horizons of the Bevatron's beam repertoire, both in intensity and mass number.

To bring these beams to the Bevatron, a transfer line was built to cover the 800-foot distance between the two machines (including 148 feet of vertical drop).² This line uses 12 bending magnets and 30 quadrupole magnets to shepherd the beam along its rather convoluted passage, but a sophisticated computer-monitoring and control scheme allows for rapid and efficient tuning of this line so that close to 100-percent transmission is generally achieved.

The Bevatron was built in the mid 1950's as a pioneering machine in high-energy particle acceleration.³ Much of the early fundamental work in particle physics was done with this machine. Over the years constant improvements have been made, and the most recent landmark is the acceleration of heavy ions. To date, ions as heavy as iron have been accelerated to 2 GeV per nucleon,⁴ injected with the SuperHILAC and transfer line. Plans are now well under way for increasing the mass number of the accelerated ions to range over the entire periodic table.⁵ These plans will be discussed further later in this chapter.

The Bevatron is a weak focusing synchrotron that accepts particles into its circular ring for a period of several hundred microseconds and then bunches them and accelerates them while the confining magnetic field is increased so that the particles remain in basically the same circular orbits. When the desired energy has been obtained, the guide field is held steady ("flat-topped") while the beam is extracted from the ring. This extraction is accomplished by an excitation of one of the natural resonances of the beam; the growth of the amplitude of this resonance is carefully controlled so that at one point beam particles will "jump the septum," that is, will enter a region of high magnetic field separated from the main circulating orbit by a very thin wall. The beam is kicked out of the machine by this septum magnetic field and is then transferred to the desired experiment through the magnet switchyard beam-delivery system known as the External Particle Beam (EPB). The whole acceleration process from injection to extraction requires less than two seconds so that, allowing for magnet ramp-down and resetting, pulses can be delivered at a rate of one every four or six seconds depending on the final energy. The extracted beam-pulse (spill) width can be varied from a few milliseconds to about a full second by an elaborate

Fig. 1. Area Plan of SuperHILAC/Bevalac.

(XBL 764-1024A)

feedback mechanism that controls the growth of the extraction resonance. Energies at which the beam can be extracted are continuously variable from about 100 MeV per nucleon to 2.1 GeV per nucleon, covering tissue penetration ranges from 2.5 to 300 cm for carbon ions. The ion species and beam currents that are routinely provided to the Biomedical facility are summarized in Table I.⁶ This list is only an indication of the beams that have been delivered, the different ion species and the different energies that can be easily provided if the demand exists.

The beam time of the Bevalac is divided so that one third is for biomedical use and two thirds are for nuclear-science experiments. Nuclear-science experiments cover a wide range of fields including elementary-particle production with heavy ions, nuclear fragmentation, cosmic-ray simulation (with the recently acquired iron beam), and atomic physics (electron capture and loss of relativistic ions). These varied and active programs along with the vigorous biomedical research efforts place great demands on available accelerator time. As a consequence, machine reliability and beam-on-target times are constantly monitored and improved whenever possible. Our present reliability figures, which will be discussed further in the next chapter, are commendably high and have been improving at a very good rate. The rate of progress has been quite remarkable, considering the complexity of the operation and that the SuperHILAC is completely time-shared, providing different ions at different energies to its own experimenters while at the same time sending required pulses to the Bevalac.

BIOMEDICAL FACILITIES

Beam Lines

The extracted beam is run through a magnet switchyard that can direct the beam to any of the ten nuclear-science experimental areas or three biomedical areas. The layout of the beam delivery system is shown in Fig. 2. The use of septum magnets and pulsed magnets allows the beam to be shared between two or more different areas. This feature was used extensively when high-intensity protons were accelerated, but beam-splitting with heavy ions is not widely used because of contamination of the beam due to fragmentation of projectile nuclei on the septum walls.

The beam lines that access the main biomedical research area take off to the west from Channel II and are capable of delivering beams of energies as high as 1 GeV per nucleon. Higher-energy beams cannot be bent by the present magnets, nor are they of much interest owing to their exceedingly long range. Both beam lines are designed achromatically so that small energy variations in the beam will not affect the location of the beam spot. These energy variations are very small, typically less than 0.1%, but are detectable by small but measurable range changes (a few tenths of a millimeter) in certain experiments.⁷

The beam in both Cave I and Cave II can be made as small as about a one-centimeter circle, and, by means of scattering foils, uniform Gaussian circular spots of up to 30 to 40 cm in diameter have been obtained. Dose rates for very large spot sizes are considerably reduced, but intensities are adequate for certain low-level work such as radiography. Dose rates for 3-cm-diameter beams are summarized in Table I.

The third biomedical area is known as the "Minibeam" facility.⁸ It is located on top of the shielding roof directly above Channel II. The beam is brought up through a hole in the roof blocks at an angle of 27° and runs parallel to an inclined optical rail system inside the Minibeam house. This facility is designed for low-energy, low-intensity operation with extremely finely collimated beams for microscopic radiobiological work and perhaps microsurgery. The main vertical bending magnet strength limits the beam energy to a maximum of 200 MeV per nucleon (8-cm range in tissue), and the minimal radiation shielding in the Minibeam house limits the particle flux to 10^7 particles per pulse. For small spot sizes, this flux will still allow dose rates of several thousand rads per minute.

Irradiation Areas

Figure 3 shows the layout of the beam lines and facilities for the two principal irradiation caves. At present, all of the biomedical work is performed in Cave II, which is fully instrumented. Proximity to the preparation rooms and animal storage facilities has made this a particularly convenient setup. A detailed description of the cave and the dosimetry instrumentation in the beam line will be given in Chapter 3.

Beam dosimetry equipment for Cave I is presently being constructed and will be installed in the next few months. In the meantime, this cave has been used for physics experiments, primarily studies of beam composition and energy spectra after passage through layers of different types of materials. These measurements are important in radiological work to correlate biological effects of beams passing through variable water columns with measured beam compositions. These experiments are discussed at greater length in Chapter 4.

The immediate plans for the Cave I area call for development of the area into a patient treatment facility for diagnostic radiography and therapy. These plans will be discussed in the next section of this chapter.

The layout of the Minibeam facility is shown in Fig. 4. The beam emerges through a hole in the floor and is modulated in energy by the variable wedge assembly, monitored by the ionization and multiwire proportional chambers, and brought to a focus at the sample located on the microscope stage. Individual cell response to radiation can be monitored by time-lapse cinematography, and the extremely high degree of RF shielding of the Minibeam house allows for nerve-response monitoring during irradiation.

Beam-dynamics studies have been completed that indicate that the desired beam sizes and intensities can be delivered to the Minibeam facility but that helium bags must be used to prevent an increase in beam size due to scattering from the air between the end of the vacuum pipe and the target position. In all, the Minibeam facility is ready to operate; it requires only the approval of experiments and assignment of beam time.

CONTINUING AND FUTURE PLANS FOR BEVALAC IMPROVEMENTS

Beam Delivery

(Bevatron Operations Staff: R. Force, D. Rondeau, J. Alonso, J. Howard, J. Lyman, M. Tekawa)

Several areas are being developed to improve the beam quality and delivery efficiency to the biomedical facilities.

Beam Flattening

A system of scattering foils and occluding rings is being developed to produce large-field (approximately 20×20 cm or larger) beam sizes of uniform dose profile over the entire field. The system designs are similar in concept to the beam flattening scheme employed at the 184-inch cyclotron⁹ but differ in detail because of the different beam optics at the Bevalac. It is anticipated that we can at least match the performance of the 184-inch system, namely, ± 2 -percent uniformity over the entire field, with approximately 50-percent beam loss. This beam loss compares very favorably with losses incurred by taking only the central position of an overly enlarged Gaussian-shaped beam.

Improved Monitoring

To facilitate tuning of the beam lines, beam monitoring information available only on the biomedical dosimetry equipment will be transmitted from the biomedical control room to the main Bevatron control room, thus allowing the machine operators to precisely steer and focus the beam through to the target.

Rapid Beam Cutoff

Intensity variations from one machine pulse to the next can be bothersome for certain crucial experiments. Also in some cases, required exposures can be delivered in a very few pulses or even a fraction

Fig. 3. Biomedical Beams B1 and B2.

(XBL 773-7883)

Fig. 4. Minibeam Facility.

(CBB 772-1307)

of a pulse. To achieve accuracy in intensity delivery and to ensure that the beam is interrupted when the precise dose has been delivered to the sample, a rapid beam-cutoff system is being constructed. This system will be triggered by the dosimetry-controlled computer and will send a signal to the Bevatron extraction system to stop sending beam to the experimenter. This signal might be activated during the spill of a particularly intense beam bunch to either preserve the average flux level or accurately terminate an exposure. The response time of the system is expected to be less than one millisecond.

Rapid Beam Switching

When the Cave I area is ready for biomedical work (see next section), more efficient utilization of beam time can be obtained by irradiating in one cave while setup for the next experiment is proceeding in the other cave. To accomplish this, control of one of the main bending magnets (BOM2 in Figure 3) must be modified to allow for bipolar operation. A small amount of degaussing current is required when the magnet is off to cancel its residual field and allow a straight-through beam passage into Cave II. A small supply is being installed to provide this reverse current, and the control system is being modified for the use of two different supplies for the same magnet. This system will allow switching of the beam between caves between beam pulses so that, in principle, complete continuity of beam usage will be possible.

Preparation of Cave I for Therapy

(Bevatron and Biomedical Operations: R. Force, J. Alonso, A. Glichsman, J. Lyman, J. Howard, F. Upham, R. Walton)

Work has been initiated to convert the Cave I area into a patient treatment facility. A commercially manufactured treatment couch, the Philips/MEL Ram-type therapy couch, has been ordered and will provide the basis for the patient support systems to be used. Platforms, chairs and head-holding devices will be constructed in our shops and interfaced with this assembly, satisfying essentially all foreseeable patient-locating and holding requirements. Dosimetry, x-ray and laser-alignment equipment is being purchased, constructed and installed. A movable optical-bench system is being constructed to allow the

placement of collimators close to the patient. The cave itself is being remodeled by erecting stud walls, carpeting, constructing storage cabinets, etc., to bring the area up to the standards of a medical treatment facility. A patient area, including waiting, changing, examination and preparation rooms, is being constructed just outside of the treatment room to streamline operations in view of the expected, very heavy patient load. Work is progressing well on these projects, and we expect to have the facilities operational by mid to late fall of this year.

Uranium Capability for the Bevalac

(Accelerator Division: E. Lofgren, H. Grunder)

A long planned upgrading program for the Bevalac to accelerate high-intensity uranium beams to relativistic energies will be carried out in this next two years.¹⁰ The project includes the building of a third injector for the SuperHILAC, including a pre-accelerator linac section that will produce very high currents of low-charge-state, very heavy ions. These ions will be accelerated through the existing SuperHILAC, transported down an upgraded transfer line and injected into the Bevatron through a new injection system.

To accelerate these partially stripped ions, the vacuum in the Bevatron must be improved from its present 10^{-7} Torr to 10^{-9} Torr. This will be accomplished by the installation of a cryo-pumped vacuum liner that will create a high-vacuum area within the confines of the present vacuum enclosure. Acceleration, extraction and beam delivery will proceed with only minor modifications to the existing running conditions.

This project will open up an entirely new area of physics to exploration by nuclear scientists. It will influence design studies on the very exciting prospects of pellet fusion driven by intense heavy-ion beams instead of lasers. Although the very heavy ions will perhaps not find many immediate uses in the Biomedical program, the general upgrading of the accelerators will provide significant increases in beam intensities for all ion species. These increases, by perhaps as much as a factor of 100, will have particularly great effects on large-field radiotherapy, where very significant shortening of treatment times can be anticipated.

The impact of the project on Bevalac operation will be minimal since most of the preliminary construction work need not interfere with existing accelerator components. The only exception is the installation of the Bevatron vacuum liner, which will require a two-month shutdown, anticipated for late 1978 or early 1979.

Beam-sharing Studies

(Bevatron Operations: H. Grunder, R. Force)

The anticipated expansion of biomedical usage of Bevalac time when full-scale clinical trials are underway will cut heavily into the nuclear-science research program. In view of the relatively modest requirements on beam time for therapy (several minutes of treatment time with possibly half an hour of setup time for each patient), however, it is well worth the effort to investigate possible ways of beam sharing to satisfy other experimenters. The mode of operation would be that a standby experiment would receive the beam whenever it was not actually being used for therapy.

The simplest system, namely a rapid switching capability, would be satisfactory only if the backup user could use the ion type and beam energy provided for therapy. This might be the case for many biomedical experiments where the effects of therapy beams are specifically studied, but the average nuclear-science user would not find this arrangement satisfactory, especially if uranium beams were available.

The next level of sophistication would be to provide the same ion type but at different energies to different users. The existing Bevatron motor-generator systems can be made to operate in this mode by

using multiple "flat-topping" during each phase, thus providing different energy capabilities but with a possible loss of pulse repetition rate. Modifications are being considered that can overcome this difficulty. One possible application of this capability is combined heavy-ion radiography and therapy. A patient would be located on the positioner and radiographed with a high-energy beam that will penetrate through the patient into detectors placed behind him or her. Then the radiographs would be analyzed, and the beam energy would be lowered for treatment without moving the patient.

The most flexible beam-sharing system provides the capability of accepting different ions on different pulses and accelerating each ion type to a different energy. This system requires rapid setup changes for the full set of transferline magnets and for all of the injection, acceleration and extraction parameters for the Bevatron. These problems are not as formidable as they at first appear, considering the sophistication of the computer control systems currently running the accelerators and the complete success of the time-sharing system now in operation at the SuperHILAC.¹¹ This system allows for changing all critical machine parameters within a few milliseconds to accept pulses from either of the two injectors and to route them through the accelerator to different experimenters. Duplicate control consoles tune each set of parameters (through the computer) independently as if each console had complete control of the entire machine.

Our experience has demonstrated that the most elaborate beam-sharing scheme envisioned for the full Bevalac can be achieved; although effort is indeed required, the technology and experience are available in our laboratory to gauge and carry out the job.

New Biomedical Facilities

(Medical Accelerator Study Group: Ch. Leeman, E. Lofgren, H. Grunder, J. Staples, J. Alonso)

Plans are being considered for possible expansion of the biomedical facilities to include a third cave that would incorporate new ideas in beam-delivery systems. Such a cave would have, at least, static horizontal and vertical beam-delivery capabilities and perhaps a gantry system. The gantry is being extensively studied by the Medical Accelerator Study Group at LBL (many of the findings of the group are summarized in Chapter 15), and, although present layouts of a gantry system for therapeutic carbon beams appear large and unwieldy, these designs have not yet been fully optimized, nor have design alternatives been exhaustively examined.

A second beam-delivery innovation to be tested is the beam scanning system in which a pencil beam is scanned under computer control over the desired treatment volume, thus allowing for greater freedom in treatment planning for difficult tumor sites. A prototype magnet is currently being constructed, and experience gained with it may lead to a model that can be used in therapy within a year or two.

The third cave would serve as a testing area for these new concepts and is expected to be the forerunner of Tomorrow's radiotherapy facilities.

In summary, new developments and plans for steady improvements of the Bevalac are constantly evolving, and, if past history can be used as a yardstick, the level of operation and facilities available will continue to improve at a highly satisfactory rate for some time to come.

TABLE I

Ion and source	Energy (MeV/amu)	Rate (particles/pulse; rads/min)	Range to Bragg peak (cm)
${}^4_2\text{Helium}$ (Bevatron)	225	3×10^8 to 1×10^9 p/pulse 10 to 50 rads/min	30.4
${}^{12}_6\text{Carbon}$ (Bevatron)	400	5×10^7 to 2×10^8 p/pulse 20 to 80 rads/min	25.9
${}^{12}_6\text{Carbon}$ (Bevalac)	400	5×10^8 to 2×10^9 p/pulse 350 to 1,500 rads/min	25.9
${}^{20}_{10}\text{Neon}$ (Bevalac)	400	2×10^8 to 1×10^9 p/pulse 250 to 1,200 rads/min	14.6
${}^{40}_{18}\text{Argon}$ (Bevalac)	500	2×10^7 to 5×10^7 p/pulse 200 to 500 rads/min	12.3

Note: Dose rates are given for a beam diameter at the 80% level (assuming a Gaussian distribution). Nitrogen and oxygen have been accelerated at low intensities from the Bevatron, but Bevalac beams of these ions have not been accelerated to the biomedical area as of this writing.

REFERENCES

1. Ghiorso, A., H. Grunder, W. Hartsough, G. Lambertson, E. Lofgren, K. Lou, R. Main, R. Mobley, R. Morgado, W. Salsig and F. Selph. The BEVALAC -- an economical facility for very high energetic heavy particle research. *IEEE Trans. Nucl. Sci.* NS-20, 155 (1973).
2. Avery, R., G. Behrsing, R. Morgado, D. Rondeau, W. Salsig, F. Selph, J. Staples and R. Yourd. The BEVALAC beam transport system. *IEEE Trans. Nucl. Sci.* NS-22, 1529 (1975).
3. L. Smith. The Bevatron. *Sci. Amer.* 184, 20-25 (1951).
4. The first iron beam. *Research/Accelerators* 1, 3-4 (1976), Lawrence Berkeley Laboratory Report LBL-4874.
5. High intensity uranium beams from the SuperHILAC and BEVALAC. Lawrence Berkeley Laboratory Proposal No. 32 (1975).
6. Bevatron/Bevalac User's Handbook: Biology and Medicine. p. IV-1 (1977).
7. C. A. Tobias, private communication.
8. Schimmerling, W., J. Alonso, R. Morgado, C. A. Tobias, H. Grunder, F. T. Upham, A. Windsor, R. A. Amer, T. C. Yang and J. T. Gunn. The BEVALAC minibeam facility. Lawrence Berkeley Laboratory Report No. LBL-6162 (1977).
9. Crowe, K., L. Kanstein, J. Lyman and F. Yeater. A large field medical beam at the 184-inch synchro-cyclotron. Lawrence Berkeley Laboratory Report No. LBL-4235 (1975).
10. High intensity uranium beams from the SuperHILAC and BEVALAC, conceptual design report. Lawrence Berkeley Laboratory Pub 96 (1976).
11. Grunder, H., and F. Selph. Status of the SuperHILAC. *Proceedings of the 1976 Proton Linear Accelerator Conference, Chalk River, Ontario*, AECL-5677.

CHAPTER 2

NATIONAL BIOMEDICAL HEAVY-ION RESEARCH PROGRAM AT THE BEVALAC

Edward Alpen and Fred Lothrop

Research programs in biology and medicine began on a small scale in August 1971. Nine experiments were run with 250-MeV/nucleon nitrogen and carbon beams during the first four months for a total of 141 hours. Activity increased in 1972 when 33 experiments were run for a total of 350 hours. During 1973 nearly 500 hours were devoted to 35 experiments. Meanwhile, the Bevalac was being built, and a dedicated beam line was designed for biomedical applications. The Bevalac system was commissioned in August of 1974, and the biomedical program began using high-intensity beams of carbon, neon and eventually argon in its new experimental area.

Early experiences with the Bevalac for both biology and medicine and nuclear science were dramatic and at times traumatic as the operating staff learned to fuse two independent accelerators into one unit with high operating efficiency as a goal.

Data for 1975 reflect the difficulties encountered upon entering the new Bevalac research mode; the total number of hours and experiments were about the same as for 1973, but because available beam intensities were 10 to 100 times the 1973 levels, more research per accelerator hour was obtained almost immediately in spite of an operating efficiency of about 60 percent during 1975. The array of ions at practical intensities was greatly enlarged, and comparative studies of radiobiological effectiveness could be undertaken with confidence. Table I lists the ions and intensities currently available. Iron is now available at low intensities, and, if demand is adequate, further improvements will be made.

Two important goals must be achieved for the beams to be of significance in biomedical and radiotherapeutic applications. The beam must be made available to the experimenter with a high degree of reliability in order for him or her to be able to design fractionation experiments and studies requiring precise timing of biological events. Furthermore, the efficiency of utilization of the beam must be so that eventual cost per unit of operating time will be within acceptable limits. Reliability of beam availability is of particular importance for the scheduling of radiotherapeutic treatment schedules because the patient will generally be treated daily or possibly five times per week until the total dose is accumulated. Unscheduled interruption of the treatment plan should be avoided.

Very careful attention to problems and their long-term solutions and to synthesizing the most useful operating schedule consistent with the operating budget gave rise to an overall operating efficiency in 1976 of about 70 percent for the Bevalac, peaking at 94 percent in November when the first extended fractionation runs were done. This seven-day run involved several three- to seven-day daily fractionation experiments. The second run included a set of daily fractionations in a five-day period. The operating efficiency was 84 percent for that operation. An average operating efficiency of at least 85 percent with the present accelerator configurations is the goal that we hope to achieve in the near future. There were 52 ongoing biomedical experiments in 1976 approved by the Program Advisory Committee. These experiments accumulated a total of about 1,050 hours operating time.

From the beginning of Bevalac operation, it has been recognized that the facility is a unique national resource. To realize its greatest benefits requires both an efficiently run accelerator complex and a properly balanced research program. Consequently, the Program Advisory Committee, formed many years ago for physics and nuclear-science program advice, was expanded to include eminent scientists in the var-

ious biomedical disciplines. At present, the two panels of the Program Advisory Committee, nuclear-science and biomedical, operate independently but closely to insure the best possible use of Bevalac resources. Members of the biomedical panel at present are E. Alpen (LBL), V. Bond (BNL), M. Elkind (ANL), J. Magee (Notre Dame), T. Phillips (UC San Francisco), H. Rossi (Columbia), and H. R. Withers (M. D. Anderson Hospital, Houston). They meet twice a year to review biomedical proposals, make recommendations to LBL's Director for approval and priority of individual experiments, and advise on the general direction of the entire program.

The Program Advisory Committee must review the scientific content of the research proposed by all prospective Bevalac users, both LBL staff and outside users. If the Advisory Committee believes that the research has scientific merit warranting the use of this expensive national facility, it is approved and assigned a priority. The experiment is also assigned to an appropriate experimental category. These categories are as follows:

- O - Fundamental Dosimetry
- I - Cancer-related Radiation Biology
- II - Medical Diagnostic Procedures
- III - Fundamental Effects, Chemistry and Physics
- IV - Fundamental Effects, Cellular and Mammalian Biology
- V - Exploratory Studies
- VI - Space-related Studies

Priorities are assigned within these categories, but the overall importance of some programs will give precedence to certain categories of research. At present, the program of overriding importance in the national plan for utilization of the Bevalac is radiotherapy. Second in overall priority is the category of Space-related Studies because NASA has immediate programmatic needs to examine the effects of heavy-particle bombardment of personnel operating in space.

After the Director of LBL approves the actions of the Advisory Committee, the experiments' approval and priority are transmitted to the Accelerator Research Coordination Office (ARC Office) for inclusion in the Bevalac operations schedule. The responsible investigator is informed by mail of the Committee's action.

The ARC Office staff includes members responsible for scheduling of specific biomedical and nuclear-science experiments as well as general research coordination and information. Specialists in the office are available for consultation on virtually any matter of concern to the accelerator user from general information about the Laboratory to specific questions on travel and lodging or accounting of accelerator time for a particular experiment or program. The Office has been designed as the major interface between the Bevatron/Bevalac and SuperHILAC facilities and the users.

The scheduling of an experiment at the Bevalac is handled in two stages. The first is the interpositioning of biomedical programs with others at the Bevalac and SuperHILAC and is concerned with the selection of ion, frequency of operation, and duration of a specific run. An overall operating cycle for the accelerator consistent with budget constraints is adopted for each operating year. To maximize the number of available research hours, a two-week cycle has been selected, 14 days of 8-hour shifts. Of the total of 42 shifts, a 4-shift block of time is assigned for maintenance; an average of two shifts are allowed for tuneup, and two shifts are assigned for accelerator improvement and development projects. The remaining 34 shifts are available for research. Twenty shifts are allotted to nuclear science, and fourteen are allotted to the biomedical program. The net scheduled time for biology and medicine is about 40% of the available research time. Because biomedical runs are generally short and by their nature not as efficient as are nuclear-science experiments in the use of Bevalac beam-on-target time, the over-

scheduling of biomedical time is a deliberate attempt to achieve the goal of one operational biomedical research hour for every two hours devoted to nuclear science. General scheduling seeks the optimum combination of biomedical and nuclear-science requirements for a given 34-shift period. Every attempt is made to work out these general schedules several months in advance.

Detailed scheduling, the second stage of Bevalac scheduling, is handled by the ARC-Office biomedical specialist who is in direct communication with the experimenters to ascertain their requirements and synthesize a schedule of 10 to 20 experimental runs in the 14-shift interval each two weeks. Detailed accounting of each run is maintained so that investigators have access to dosimetric information, ion species, and time consumed for their experiments.

Data on experiments operated at the Bevatron/Bevalac since 1971 are shown in Table II. These data have been extracted to show in concise form some interesting features of the biomedical program. LBL biologists played a significant role in establishing an experimental facility at the Bevatron as indicated by the 1971-1973 data. The balance of activity shifted dramatically to national use of the facility starting in 1974. We expect that the balance of the program will remain essentially as shown for the 1974-1976 period with perhaps slightly more emphasis on experiments from institutions other than LBL.

Some changes presently underway at the physical facilities in the biomedical beam area will significantly improve the overall effectiveness of beam utilization. At present, all activities are carried out in Experimental Area II (known as "Cave II"). Much experimental time is now lost during setup, dosimetry and animal-change periods. The highest-priority development for the coming year is the completion of Experimental Area I. As designed in the original plans, Area I will continue to be the patient treatment facility, but we intend to make the facility as multi-purpose as possible without interfering with its primary purpose as a patient treatment area. When complete, it will be possible to carry out a number of experiments more or less simultaneously by careful scheduling of experiments with similar requirements. Improved computer control and better planning and management of the facilities should increase real experimental time about 25% with the present beam-availability schedule.

SCIENTIFIC RESULTS

It would be virtually impossible to provide a complete description of the results of the research that has been carried out by outside users since the program began in 1971. Generally, our research can be classified as in Table II. There is a group of outside users who are pursuing their own goals unrelated to the ongoing programs at LBL. We, of course, have a strong continuing interest in the scientific content of their activities, and we provide support in both the planning and execution of the studies. A second group of outside users works in close collaboration with LBL staff members to carry out our specific assigned responsibilities in support of the national trial of heavy ions in radiation therapy. The results of this group of users have been incorporated into other chapters of this report.

Table III is a list of all Bevalac users since the Advisory Committee and coordinating activity was established in 1974. It can be seen that some authorized users have not yet started their experiments in spite of appreciable time lapse. These delays have generally not resulted from lack of beam time but rather from technical or administrative difficulties arising at the investigator's home institution.

Among space-related studies that are nearing a scientific conclusion is the NASA-supported work of the groups at Ames Laboratory, the University of San Francisco, Duke University, and Indiana University. The investigators are L. M. Kraft, M. A. Kelly, J. E. Johnson, E. V. Benton, R. P. Henke, D. E. Philpott, F. S. Vogel and W. Zeman. These groups have been investigating the proposition repeatedly put forward that the passage of a high-energy, accelerated heavy ion through tissue produces a column of lethally irradiated cells surrounded by a penumbra of sublethally irradiated tissue. If this proposition is found to be true, its significance to nonproliferating central-nervous-system tissues is enormous. The passage

of a single charged particle of high energy would presumably cause the death and functional loss of a large number of neurons. Other investigators had failed to observe this phenomenon at the SuperHILAC when D. melanogaster was irradiated with ^{40}Ar ions, but it was essential that the trial be repeated for mammalian systems with higher-energy particles. Kraft and coworkers used the 400-MeV/nucleon ^{20}Ne beam degraded through a water column so that the Bragg peak was localized 2 to 3 mm below the skin surface. The effective energy at entrance was 40 MeV/nucleon. Doses of 1,000, 100 and 10 rads were delivered to the brain of the pocket mouse, P. longimembris. The tissues of the brain were examined microscopically after recovery periods of up to two years. In the brain, necrotic neurons were seen predominantly in the regions of highest energy deposition where extensive damage resulted from the higher doses. In the eye, occasionally damaged retinal cells were seen at the highest doses. The investigators concluded that the likelihood of similar results in the human brain after spaceflight is not as high as predicted from theory. Damage was observed at generally higher doses than might be encountered in space flight, and they deliberately terminated the particle tracks in the brain, an unlikely occurrence in space. As an example, at a dose of 10 rads of ^{20}Ne particles, no necrotic neurons were observed among 200,000 neurons examined. These experiments should be extended to higher-Z particles that will more closely mimic space conditions. Studies with argon are underway, and the new iron beam could find immediate application in such studies.

An additional space-related study not reported in other chapters is that of Abrams, Malachowski, Leith and Tobias. These investigators have irradiated the retina of Necturus maculosus with x rays and helium, carbon and neon ions. Preliminary results suggest that the relative biological effectiveness of helium ions compared to x rays is essentially 1.0 for damage of the retinal cells of N. maculosus but that carbon and neon ions have significantly higher biological effectiveness than do x rays. G. E. Powers and J. T. Lett of Colorado State University have been carrying out extensive studies of the effects of heavy-ion radiation on the cells of the rabbit retina. Their studies are still in progress.

Excellent preliminary experiments have been performed measuring the DNA damage in nondividing photoreceptor cells of New Zealand White rabbit retinæ exposed throughout the Bragg curve of 400-MeV/nucleon neon ions having a penetration of approximately 14.2 cm in water. Both in vitro and in vivo repair studies demonstrate that complete repair of DNA damage is not obtained within repair time allotted in the preliminary experiments (up to 8 hrs). Based on three points, the strand-breaking efficiency of 400-MeV/nucleon neon ions is 120 keV/single-strand break.

All in vitro studies (of DNA damage due to exposure in the Bragg curve, in vitro repair in the pre-Bragg-peak region, and strand-breaking efficiency) have used a submarine culture vessel similar to that used at Berkeley for tissue-culture irradiations. The in vivo irradiations were accomplished by placing the restrained rabbit in front of the neon beam so that only the right eye was irradiated, leaving the left eye to serve as a control. An 8-cm column of water was used in front of the rabbit to shift the Bragg curve, allowing a direct comparison between in vivo and in vitro results.

These investigators have reported the expected strand breakage of DNA in the cells of the rabbit retina irradiated in vivo; the amount of breakage is dose-dependent, of course, but interestingly they did not observe more than a moderate increase in the amount of strand breakage in the Bragg-peak region of the depth-dose curve. They have measured the strand-breaking efficiency for x rays and ^{20}Ne ions for their system at 50 eV/break for x rays and 120 eV/break for neon ions, giving an estimated RBE of 0.4 for neon ions relative to x rays. These investigators have also gathered preliminary data on repair of damaged DNA in vivo.

A significant amount of beam time has been allocated in the past and continues to be made available for calibration efforts in support of various space missions. The various groups involved include those

of E. V. Benton at the University of San Francisco, W. Schimmerling of LBL, H. Bucher of the Space Agency of the Federal Republic of Germany, E. Schopper of the University of Frankfurt, R. Katz of the University of Nebraska, and G. Luxton of Stanford University. Dr. Katz has also carried out work on track structure and the theory of heavy-ion dose deposition in support of the radiobiological applications of heavy ions at LBL. In this work, his interests have been similar to those of A. Chatterjee, reported in another chapter.

McNulty and coworkers are using the heavy-ion beams at the Bevalac in their studies on the visual phenomena associated with the passage of heavy particles through the eye. Light flashes associated with heavy particles striking the retina were first reported during spaceflight some years ago, and the phenomenon was confirmed in the laboratory by Tobias and Budinger. McNulty and coworkers are investigating the possibility that the phenomenon results from Chernekov radiation rather than interaction with chemical phosphenes. They believe that their studies at the Brookhaven AGS and the Princeton Particle Accelerator support such a hypothesis. Their studies are just commencing at the Bevalac with oxygen, nitrogen, neon and argon beams.

Two new investigations of radiation carcinogenesis, unrelated to space research, have been started within the last year. C. J. Shellabarger of the Brookhaven National Laboratory has been working for a number of years on the model of mammary neoplasia in the Sprague-Dawley rat. This model has been particularly valuable for evaluating the effects of LET, dose, and dose rate on carcinogenesis. The system has been particularly useful for estimating RBE at low doses, an essential function of a model for evaluating the dual radiation-action theory for radiation damage. Shellabarger has irradiated rats at the Bevalac with neon, carbon and argon ions over a wide range of doses, including some very low doses. It will be some months before preliminary data become available.

Simultaneously with the Shellabarger experiment, a closely related study by H. Vogel of the University of Tennessee has been initiated. Vogel is using a system essentially similar to that of Shellabarger, i.e., mammary neoplasia in the Sprague-Dawley rat.

Vogel has established that fission neutron doses as low as 2 to 5 rads are sufficient for a high yield of tumors in the Sprague-Dawley rat. His objectives are similar to those of Shellabarger, but he is also evaluating the influence of genetic makeup and animal age on tumor incidence. He has irradiated rats with doses as low as 50 rads of 400-MeV neon ions and expects to continue the experiment with argon and carbon ions. If his preliminary data are interesting, he proposes to reduce the doses to as low as 1 rad.

In the category of Fundamental Studies, Chemistry and Physics, E. Benton, University of San Francisco, W. Schimmerling, LBL, A. Appleby, Rutgers University, J. Magee, Notre Dame, R. Katz, University of Nebraska, M. Daniels, Oregon State University, and R. Schuler, Carnegie Mellon Institute, in collaboration with M. Jayko, LBL, have been conducting studies of the effects of heavy-ion beams on chemical and physical systems. Results are generally not yet available.

FUTURE PLANS

The completion of Experimental Area I for patient treatment and biomedical-program experiments should have a significant effect on the available time for outside users during late 1977 and 1978. It is our hope that all investigators' requests that are found to have scientific merit will have beam time available.

Table I. Accelerated ions now available at the Lawrence Berkeley Laboratory Bevalac. Two ion sources are available, the conventional 20-MeV injector and the SuperHILAC. Energies up to 1.0 GeV/nucleon are available in the two biomedical exposure rooms.

Ion	Maximum Number of Particles/pulse	
	20-MeV Source	SuperHILAC Source
Proton	2×10^{12}	
Helium	5×10^{10}	
Carbon	2×10^8	2×10^9
Nitrogen	5×10^7	1×10^9
Oxygen		1×10^9
Neon		5×10^9
Argon		1×10^8
Iron		Under development

Table II. Bevatron/Bevalac Biomedical Program, 1971-1976

	LBL		Outside Institutions		LBL and Outside	
	Experiments	Hours	Experiments	Hours	Experiments	Hours
Pre-Bevalac (1971-1973)	54	744.50	11	133.75	9	93.50
Bevalac (1974-1976)	29	856.25	25	351.75	17	254.50
Total	83	1,600.75	36	485.50	26	348.00

Table III. Authorized Bevalac Users

2148	START DATE	9/75	FINISH DATE	BEAM HOURS	7.75
IRRADIATION OF DOG HYPOTHALAMUS WITH HEAVY IONS					
L B L		T. BUDINGER			
2158	START DATE	11/74	FINISH DATE	BEAM HOURS	69.25
EFFECTS OF HEAVY ION IRRADIATIONS ON THE LUNGS OF HAMSTERS					
L B L		K. WOODRUFF			
2158-1	START DATE	9/76	FINISH DATE	BEAM HOURS	6.25
DELAYED CARCINOGENESIS AND PULMONARY FIBROSIS IN HAMSTER LUNGS					
L B L		K. WOODRUFF			
2168	START DATE	6/76	FINISH DATE	BEAM HOURS	3.25
HEAVY ION IRRADIATION OF THE RETINA OF NECTURUS MACULOUS					
L B L		J. LEITH			

217B	START DATE 10/74	FINISH DATE	BEAM HOURS 12.25
SURVIVAL OF IN VITRO BRAIN TUMOR CELLS AFTER IRRADIATION WITH HVY IONS			
	UCSF	K. WHEELER	
	LBL	J. LEITH	
218B	START DATE 3/76	FINISH DATE	BEAM HOURS 14.00
IN VIVO DAMAGE/REPAIR TO GENETIC MAT'L IN RAT NORMAL AND TUMOR BRAIN			
	UCSF	K. WHEELER	
	LBL	J. LEITH	
220B	START DATE 9/74	FINISH DATE	BEAM HOURS 3.50
LEUKEMOGENIC EFFECTS OF HEAVY IONS ON RF MICE			
	LBL	L. KELLY	
221B	START DATE 9/76	FINISH DATE	BEAM HOURS 1.00
BONE MARROW STEM CELL SURVIVAL AFTER HEAVY ION RADIATION			
	LBL	J. SCHOOLEY	
222B	START DATE 10/74	FINISH DATE	BEAM HOURS 10.00
EFFECT OF HZE PARTICLES ON THE DYNAMICS OF DEVELOPMENT (INCLUDES 247B)			
	LBL	T. YANG	
233B	START DATE	FINISH DATE	BEAM HOURS 6.00
PARTICLE INDUCED VISUAL SENSATIONS (INCLUDES 262B)			
	CLARKSON COLL. TECH	P. MCNULTY	
	BNL	V. BOND	
	UNIV. OF HOUSTON	L. PINSKY	
242B	START DATE 2/76	FINISH DATE 12/76	BEAM HOURS 5.00
EFFECTS OF HEAVY IONS ON RED CELL MEMBRANES FOLLOWING IRRADIATION			
	LBL	M. JAYKO	
243B	START DATE 2/76	FINISH DATE 12/76	BEAM HOURS 11.00
IN VIVO REPAIR (INCLUDES 8-88) (CONTINUES AS 295B)			
	COLORADO STATE U.	G. POWERS	
244B	START DATE	FINISH DATE	BEAM HOURS 33.75
DEVELOPMENT OF MULTIWIRED PROPORTIONAL CHAMBERS FOR USE IN RAD. PHYSICS			
	LBL	W. SCHIMMERLING	
245B	START DATE 2/76	FINISH DATE 12/76	BEAM HOURS 39.50
HYDROGEN YIELDS AND CHEMICAL ISOTOPE EFFECTS			
	RUTGERS UNIV.	A. APPLEBY	
	LBL	M. JAYKO	
249B	START DATE 11/74	FINISH DATE	BEAM HOURS 5.25
PARTICLE IRRADIATION OF MAMMALIAN BRAIN CELLS			
	AMLS RESEARCH CNTR	W. HAYMAKER	
253B	START DATE 4/75	FINISH DATE	BEAM HOURS 1.75
IRRADIATION OF BIOSTACK-UNITS WITH HEAVY IONS			
	ARBTSGRPE BIOPHYS.	H. BUCKER	
254B	START DATE 1/75	FINISH DATE	BEAM HOURS 3.25
RESPONSE OF SPECIAL NUCLEAR EMULSIONS TO HEAVY IONS			
	UNIV. NEBRASKA	R. KATZ	

255B START DATE 11/74 FINISH DATE 12/76 BEAM HOURS 11.50
 SEARCH FOR RELATIONSHIP BETWEEN RBE AND LET IN MAMMALIAN RETINA
 LBL C. GAFFEY

256B START DATE 8/75 FINISH DATE BEAM HOURS 23.75
 MEASUREMENT OF RBE AND OER FOR ENT6 TUMOR CELLS IN VITRO
 U.C. SAN FRANCISCO T. PHILLIPS

257B START DATE 1/76 FINISH DATE 12/76 BEAM HOURS 3.75
 BLOOD CIRCULATION (CONTINUES AS 356B)
 LBL A. CHATTERJEE

256B START DATE 8/75 FINISH DATE BEAM HOURS 51.00
 RBE MEASUREMENT FOR MOUSE INTESTIN. CRYPT AND CLONOGENIC MARROW CELLS
 U C S F T. PHILLIPS

257B START DATE 1/76 FINISH DATE 12/76 BEAM HOURS 24.50
 RBE FOR ESOPHAGEAL LETHALITY IN LAF(1) MICE
 U C S F T. PHILLIPS

259B START DATE 2/76 FINISH DATE BEAM HOURS 11.50
 RBE MEASUREMENT FOR PULMONARY LETHALITY IN THE LAF(1) MOUSE
 U C S F T. PHILLIPS

272B START DATE 1/77 FINISH DATE BEAM HOURS 25.75
 EFFECT OF TRACK STRUCTURE ON RADIATION CHEMISTRY OF HEAVY IONS
 L B L M. JAYKO
 CARNEGIE-MELLON R. SCHULER

274B START DATE 11/75 FINISH DATE BEAM HOURS 10.25
 AEROBIC AND HYPOXIC CELL SURVIVAL AT PLATEAU AND PEAK OF BRAGG CURVE
 LOS ALAMOS SL M. RAJU
 L B L C. TOBIAS

275B START DATE 11/75 FINISH DATE BEAM HOURS 5.75
 CELL SURVIVAL VS. DEPTH FOR ONE- AND TWO- FRACTION EXPOSURES
 LOS ALAMOS SL M. RAJU
 L B L C. TOBIAS

276B START DATE 6/76 FINISH DATE BEAM HOURS 8.50
 EARLY AND LATE EFFECTS OF EXTENDED BRAGG PEAKS ON MICE FEET
 LOS ALAMOS SL M. RAJU
 L B L J. LEITH

278B START DATE 11/75 FINISH DATE BEAM HOURS 4.00
 RBE OF HEAVY IONS FOR BONE MARROW STEM CELL SURVIVAL
 L B L L. KELLY

280B START DATE 12/75 FINISH DATE BEAM HOURS 6.50
 CALIBRATION OF AND EXPERIMENTATION WITH SILVER CHLORIDE TRACK DETECTOR
 UNIV. OF FRANKFURT E. SCHOPPER
 USF E. BENTON

281B-2 START DATE 6/76 FINISH DATE BEAM HOURS 9.25
 EFFECT OF HYPERTHERMIA ON RBE AS A FUNCTION OF LET
 UNIV. OF ARIZONA E. GERNER
 L B L J. LEITH

288B	START DATE 2/76	FINISH DATE	BEAM HOURS	1.50
HEAVY ION RADIATION EXPOSURE OF BIOLOGICAL SYSTEMS				
	NORTHROP SERVICES	T. ROGERS		
	NASA/LBJ SPACE CENTE	G. TAYLOR		
299B	START DATE 8/75	FINISH DATE	BEAM HOURS	205.25
OER DETERMINATION IN HUMANT/ AND HAMSTER CELLS WITH HEAVY IONS				
	L B L	E. BLAKELY		
290B	START DATE 10/75	FINISH DATE	BEAM HOURS	120.50
HEAVY PARTICLE RADIOGRAPHY				
	USF	E. BENTON		
	L B L	M. CRUTY		
292B	START DATE 1/76	FINISH DATE	BEAM HOURS	18.75
HZE PARTICLE STUDIES OF MAMMALIAN BRAIN, EYE, AND ASSOC. HEAD STRUCTURES				
	NASA/AMES	W. HAYMAKER		
	USF	E. BENTON		
	INDIANA UNIVERSITY	W. ZEMAN		
293B	START DATE 8/75	FINISH DATE	BEAM HOURS	11.75
TIME-LAPSE CINEMATOGRAPHIC STUDIES OF EMT6 TUMOR CELLS IN VITRO				
	INST. GUSTAVE ROUSSY	R. GILET		
	L B L	S. CURTIS		
294B	START DATE 3/76	FINISH DATE	BEAM HOURS	7.50
CELL TRANSFORMATION AS A FUNCTION OF LET OF HEAVY IONS				
	L B L	T. YANG		
295B	START DATE 8/75	FINISH DATE	BEAM HOURS	40.25
EFFECT OF COSMIC RADIATION ON THE BRAIN				
	COLORADO STATE U.	G. POWERS		
296B	START DATE 12/75	FINISH DATE	BEAM HOURS	2.75
HEAVY ION LESIONNAL EFFECTS ON RAT ENCEPHALON<<<<WAS 213B>>>>				
	UNIV. OF PARIS	A. PFISTER		
297B-1	START DATE	FINISH DATE	BEAM HOURS	.75
RESPONSE OF SPECIAL NUCLEAR EMULSIONS TO HEAVY IONS				
	UNIV. OF NEBRASKA	R. KATZ		
	USF	E. BENTON		
312B	START DATE 12/75	FINISH DATE	BEAM HOURS	3.25
EFFECTS OF HEAVY IONS ON THE LIGHT-SENSING ELEMENTS OF THE RETINA				
	L B L	M. MALACHOWSKI		
314B	START DATE 10/76	FINISH DATE 10/76	BEAM HOURS	9.50
TUMOR INDUCTION IN RAT SKIN WITH HIGH LET RADIATION				
	N.Y.U. MED CENTER	F. BURNS		
315B	START DATE 1/77	FINISH DATE	BEAM HOURS	27.50
HEAVY ION DNA DAMAGE-REPAIR AND RELATIONSHIP TO MAMMALIAN CELL KILLING				
	L B L	R. ROOTS		
318B	START DATE 1/76	FINISH DATE 1/76	BEAM HOURS	16.50
DEPTH-DOSE STUDIES OF A 500 MEV/AMU ARGON BEAM				
	BROOKHAVEN NAT LAB	L. GOODMAN		

313B	START DATE 1/76	FINISH DATE 1/76	BEAM HOURS	50.25
OER, RBE, AND RELATED STUDIES WITH 500 MEV/AMU ARGON IONS				
BROOKHAVEN NAT. LAB			L. GOODMAN	
311B	START DATE 12/75	FINISH DATE	BEAM HOURS	10.75
NONCYTOKINETIC INJURY TO INSECT TISSUE				
UNIV. OF ILLINOIS			H. DUOFF	
312B	START DATE 12/75	FINISH DATE	BEAM HOURS	41.75
CHEMICAL MODIFICATIONS OF INACTIVATING ELEMENTS BY HEAVY IONS				
AEC. CANADA			J. CHAPMAN	
LBL			E. BLAKELY	
319B	START DATE 6/76	FINISH DATE	BEAM HOURS	11.00
EFFECTS ON RAT AND MOUSE KIDNEYS OF ACCELERATED HEAVY IONS				
STANFORD			E. GLATSTEIN	
LBL			J. LEITH	
325B	START DATE 1/76	FINISH DATE	BEAM HOURS	1.50
EFFECTS OF HEAVY ION IRRADIATION ON THE RETINA				
LBL			M. MALACHOWSKI	
321B	START DATE 1/77	FINISH DATE	BEAM HOURS	50.75
VELOCITY SPECTROMETRY OF HIGH ENERGY HEAVY IONS				
LBL			W. SCHIMMERLING	
323B	START DATE 1/76	FINISH DATE	BEAM HOURS	34.50
RBE AND TCD-50 DETERMINATION FOR EMT6 TUMOR WITH O, NE, AR IONS				
UCSF			T. PHILLIPS	
335B	START DATE 6/76	FINISH DATE 6/76	BEAM HOURS	16.25
HEAVY ION CARCINOGENIC POTENTIAL				
BNL			C. SHELLABARGER	
331B	START DATE 9/76	FINISH DATE	BEAM HOURS	10.50
MUTATIONS OF MAIZE GENE BY HEAVY IONS... GENE STRUCTURE AND DAMAGE				
U.C.B.			M. FREELING	
LBL			T. YANG	
332B	START DATE 6/76	FINISH DATE 6/76	BEAM HOURS	3.75
RBE FOR SOMATIC MUTATION INDUCTION IN TRADESCANTIA				
BNL			J. BAUM	
344B	START DATE 10/76	FINISH DATE	BEAM HOURS	44.25
RESPONSE OF RAT RHABDOMYOSARCOMA TO FRACTIONATED TREATMENTS				
LBL			S. CURTIS	
345B	START DATE 6/76	FINISH DATE 6/76	BEAM HOURS	6.50
RADIATION RESPONSE VARIATIONS OF MOUSE CRYPT CELLS THROUGH CELL CYCLE				
UNIV. OF TEXAS			R. WITHERS	
346B	START DATE 10/76	FINISH DATE 10/76	BEAM HOURS	22.00
HEAVY ION DOSE QUALITY AT DEPTH				
STANFORD			G. LUXTON	

359B	START DATE 1/77	FINISH DATE	BEAM HOURS	39.25
MICRODOSIMETRY OF THE 20 GEV ARGON BEAM				
	COLUMBIA UNIV.	P. KLIAUGA		
360B	START DATE 6/76	FINISH DATE	BEAM HOURS	110.25
RBE FOR TESTICULAR ATROPHY OF AR AND C IONS RELATIVE TO COBALT				
	L B L	E. ALPEN		
363B	START DATE 1/77	FINISH DATE	BEAM HOURS	9.75
HEAVY ION INDUCTION OF HARDERIAN GLAND TUMORS IN THE MOUSE				
	LBL	E. ALPEN		
	ARGONNE NAT. LAB	M. FRY		
364B	START DATE 2/77	FINISH DATE	BEAM HOURS	19.75
RBE OF HEAVY IONS AND HELIUM FOR CRYPT CELL SURVIVAL IN LAF1 MICE				
	LBL	E. ALPEN		
366B	START DATE 3/77	FINISH DATE	BEAM HOURS	7.75
THE INDUCTION OF MAMMARY CARCINOGENESIS IN FEMALE RATS				
	U. TENNESSEE	M. VOGEL		
369B	START DATE 11/76	FINISH DATE	BEAM HOURS	21.75
YIELDS OF BIOLOGICALLY RELEVANT CHEMICAL SPECIES IN WATER				
	LBL	A. CHATTERJEE		
376B	START DATE 2/77	FINISH DATE	BEAM HOURS	3.75
HZE RADIATION EFFECTS ON THE VASCULAR SYSTEM OF MAMMALS				
	AMES RES. CENTER	D. PHILPOTT		
345	START DATE 10/74	FINISH DATE	BEAM HOURS	81.25
R1 TUMOR CELL EXPOSURE				
	LBL-BIOMED.	S. CURTIS		
860	START DATE 3/73	FINISH DATE	BEAM HOURS	19.00
ACUTE SKIN REACTIONS IN MICE.				
	LBL-BIOMED.	LEITH		
368	START DATE 3/73	FINISH DATE	BEAM HOURS	8.50
USE OF WIRE CHAMBERS IN DOSIMETRY.				
	LBL-BIOMED.	SCHIMMERLING		
870	START DATE 3/73	FINISH DATE	BEAM HOURS	4.00
ACTIVATION CROSS SECTIONS FOR (11)C, (18)F, (24)NA.				
	LBL-BIOMED	SCHIMMERLING		
871	START DATE 9/73	FINISH DATE	BEAM HOURS	60.50
EXPOSURE OF MICE TO (12)C(6) BEAM.				
	LBL-BIOMED	KELLY		
372	START DATE 9/73	FINISH DATE 11/76	BEAM HOURS	6.50
HEAVY ION BEAMS IN ANIMAL EXPERIMENTS DEALING WITH EPILEPSY				
	LBL-BIOMED	C. GAFFEY		
373	START DATE	FINISH DATE	BEAM HOURS	17.00
ACUTE EFFECTS OF ACCELERATED OXYGEN IONS ON THE SKIN OF MICE.				
	LBL-BIOMED	J. LEITH		

376	START DATE 9/73	FINISH DATE	BEAM HOURS	11.50
MAMMALIAN RETINA RESPONSE.				
	LBL-BIOMED	BUDINGER		
377	START DATE 9/73	FINISH DATE	BEAM HOURS	90.00
OER OF R-1 TUMOR CELLS (IN VITRO) IN STOPPING HEAVY ION BEAMS.				
	LBL-BIOMED	S. CURTIS		
379	START DATE 9/76	FINISH DATE 9/76	BEAM HOURS	13.00
HEAVY ION RETINA STUDIES.				
	NASA-AMES LAB.	D. PHILPOTT		
380	START DATE 9/73	FINISH DATE	BEAM HOURS	29.75
AUTOACTIVATION STUDY OF STOPPED FRAGMENTS.				
	LBL-HEALTH PHYSICS	SMITH		
	LBL-BIOMED	TOBIAS		
385	START DATE 9/73	FINISH DATE	BEAM HOURS	22.50
RADIATION CHEMISTRY.				
	L B L BIOMED	CHATTERJEE		
386	START DATE 9/73	FINISH DATE	BEAM HOURS	27.00
HEAVY PARTICLE RADIOGRAPHY.				
	UNIV. OF SAN FRAN.	BENTON		
	L B L BIOMED	TOBIAS		
388	START DATE 9/73	FINISH DATE	BEAM HOURS	11.75
EFFECTS OF COSMIC RADIATIONS ON THE BRAIN (DNA DAMAGE).				
	COLORADO STATE UNIV.	POWERS		
389	START DATE 11/74	FINISH DATE	BEAM HOURS	3.25
CELL SURVIVAL VS DEPTH.				
	L B L BIOMED	KALOFONOS		
390	START DATE 9/73	FINISH DATE	BEAM HOURS	61.50
OER AND RBE OF CULTURED KIDNEY CELLS.				
	L B L BIOMED	KALOFONOS		
391	START DATE 9/73	FINISH DATE	BEAM HOURS	8.75
RBE OF HEAVY IONS FOR VITAL ORGAN FUNCTION DAMAGE.				
	L B L BIOMED	BUDINGER		
393	START DATE	FINISH DATE	BEAM HOURS	4.50
NANOMETER DOSIMETRY OF HIGH ENERGY HEAVY IONS.				
	BROOKHAVEN NATL LAB	BAUM		
394	START DATE 9/76	FINISH DATE	BEAM HOURS	8.50
RAT SKIN TUMOR INCIDENCE AFTER EXPOSURE TO HEAVILY IONIZING PARTICLES				
	LBL BIOMED	J. LEITH		
395	START DATE 11/74	FINISH DATE	BEAM HOURS	12.25
LONG TERM RAT SPINAL CORD EFFECTS AFTER HEAVILY IONIZING RADIATION				
	LBL BIOMED	J. LEITH		

CHAPTER 3

BIOMEDICAL RESEARCH FACILITIES AND DOSIMETRY

John T. Lyman and Jerry Howard

INTRODUCTION

A special area at the Bevatron has been designated as the Bevalac Biomedical Facility.¹ Within this area, three irradiation rooms are available and instrumented in an appropriate manner to allow the controlled irradiation of selected biological objects. Some nonbiological objects placed in the heavy-ion beam have been various radiation-detecting instruments and dosimeters such as nuclear emulsions, x-ray film, plastic track-detector sheets, thermoluminescent materials (e.g., lithium fluoride), chemical solutions (e.g., ferrous sulfate), proportional chambers, scintillator paddles, and ionization chambers. These detectors are exposed to the beam for calibration purposes or to help characterize a particular heavy ion or heavy-ion beam.

The irradiation of a broad spectrum of biological objects is of paramount importance to the biomedical heavy-ion program; therefore, the facilities have been designed and constructed with the intent to provide the necessary work space to prepare specimens for irradiation, the equipment that is needed to monitor and control the exposure of the specimen, and, if possible, the equipment that will aid in the analysis of the results of a given exposure. The types of biological samples that have been irradiated (a noninclusive list) are seeds, plants, insects, mammalian cells in vitro, mammalian organs, and tissues in vivo. Human subjects have been used for space-radiation-related research and for cancer diagnostic procedures and will, in the near future, be used in cancer therapy trials.

The exposure of these objects has a multitude of requirements that place heavy demands on the space and funds available; therefore, the Biomedical Facility was designed with the intent to provide what was thought to be adequate support, space, and instrumentation so that the necessary irradiations could be accomplished with the minimum inconvenience to all persons involved. The Biomedical Facility has to be a radiation physics research laboratory, a radiobiology laboratory, and an outpatient clinic.

IRRADIATION ROOMS

Three areas are available for heavy-ion exposures. Each area is intended for a specific type or types of irradiation and is therefore supplied with different instrumentation and support devices.

Biomedical Beam B1

Cave 1, a 22- by 24-foot room (Fig. 1), is intended for use with human subjects and will be equipped with a positioner suitable for radiation therapy and with devices or attachments to adapt the positioner for heavy-particle diagnostic radiographic techniques. Prior to the installation of the human positioner, Cave I will continue to be used for selected radiological physics experiments.

Biomedical Beam B2

Cave II, a 20- by 30-foot room (Fig. 1), is designed as a general purpose radiobiological exposure area. It is possible to establish several noninterfering beam lines within this area to provide several long-term exposure facilities. Currently, only one beam line is equipped with beam-monitoring instruments and exposure devices. This beam line is supplied with two optical-type support benches, which are positioned in tandem. Most of the exposures are performed on the first bench. If a large radiation field is necessary (greater than 3 cm in diameter), samples can be placed on the second bench. The use of

Fig. 1. Biomedical beams B1 and B2.

(XBL 773-7883)

Fig. 2. Biomedical beam B3.

(XBL 773-7883)

scattering foils increases the angle of divergence of the beam, and the increased distance from the scattering foils results in a larger-diameter beam. There is, of course, a tradeoff; the larger beam is obtained at the expense of the dose rate, which is decreased proportionally to the beam area.

Biomedical Beam B3 -- Minibeam Cave

Located above the horizontal plane of the Bevatron is a third irradiation area known as the Minibeam Cave (Fig. 2). The beam is directed upward at a 30° angle to the horizontal along an inclined optical bench. This area is intended for direct observation via microscopy of cellular response to the passage of heavy ions and for possible in-vivo eye irradiations for vision studies or therapy. The minibeam facility was designed for particle energies less than about 200 MeV/nucleon and small beam diameters (0.1 to 1.0 cm). The exposure area has been RF shielded to allow measurements of low-level, high-impedance electrical signals.

Preparation Rooms

Adjacent to Cave I will be a patient waiting room, an examination room, a toilet facility, a consultation room for treatment planning, and a darkroom for processing diagnostic x rays used for patient alignment. Adjacent to Cave II are two preparation rooms designated as Room II and Room III (Fig. 1). These rooms provide the only wet laboratory space near the irradiation rooms. These rooms provide adequate space for most cellular and animal exposures that have been seriously considered. A small cell-culture laboratory is in Room III. Consequently, cellular experiments are customarily set up in Room III, and animal experiments use Room II. This arrangement does not, however, preclude other possible temporary usage.

Biomedical Control Room

The monitoring and radiation control of the majority of the exposures are performed in the Biomedical Control Room adjacent to Cave I (Fig. 1). This area and the adjacent Room I are used by the operations and support personnel and provide space for the PDP-11/45 computer and the associated peripheral devices used for display and data-recording functions. The control room can also be used for radiological physics experiments with limited and short-term space requirements. More extensive instrumentation of setups must be done in other locations, such as the control room annex (Fig. 1).

The computer facility, in addition to recording the dose delivered, stores measured and calculated data relating to such parameters as the range, size, position, and magnitude of the beam. The data are stored for an indefinite time on magnetic tape and can be furnished to the experimenter in printed form. The computer is available for complex radiological physics measurements such as pulse-height spectra in proportional chambers, velocity spectra of the primary and secondary beams, dE/dx measurements in solid-state detectors, and many other similar measurements.

INSTRUMENTATION

Alignment Benches

Support rails are constructed of two parallel, 2-inch diameter, precision-ground steel rods, 10 feet long with centers separated by 14.3 inches and mounted on a sturdy frame of welded channel iron. These rails are placed parallel to the beam axis, which is 15.25 inches above the intersection of the horizontal plane connecting the rail centers and the vertical plane midway between the centers. Precision mounting brackets are used to support the various instruments and sample holders on the rail assembly.

Some sample-holding devices can be prealigned outside the radiation room on a similar alignment bench and then moved into the treatment room for irradiation, with no further alignment to the beam necessary. X-ray equipment is provided to precisely align critical specimens with the beam. One unit is coaxial with the beam; the other is vertically perpendicular to it.

Ionization Chambers

The primary beam monitoring is best performed in a location that is unaffected by subsequent beam scattering, degrading, collimation, or other modification. The most useful monitor for such an application is a parallel-plate ionization chamber.² This chamber is oriented with its collecting field coaxial with the central ray of the particle beam. Such a beam monitor occupies a small distance along the beam path and presents a very small amount of absorbing material to the passing particles. A parallel-plate ionization chamber is useful over a wide range of beam intensities. Fortunately, this range includes the intensities needed by the majority of the biomedical experimenters. The electrode structure of the parallel-plate ionization chamber in the simplest case consists of a high-voltage electrode and a collecting electrode, the latter divided into two regions, a central region which is connected to a current integrating system and an outer guard ring which is connected to the electrical ground. A number of variations on this basic structure have been developed to fill particular measurement needs. To measure a quantity proportional to the total number of particles, the central portion of the collecting electrode is made larger than the beam diameter. If the central portion of the collecting electrode is further subdivided by a series of concentric rings, it is possible to monitor the beam intensity as a function of distance from the central ray.³ The addition of a second collecting electrode within the ionization chamber housing allows some degree of redundancy. This second electrode in our standard configuration is a quadrant electrode which aids in beam alignment.⁴ The three foils, mounted on lucite and nylon standoffs, are contained within a gas-tight aluminum housing. The housing is cylindrical and allows the undisturbed passage of a 20-cm-diameter beam. The outer diameter of the housing is 28.6 cm, and the thickness of the housing is 6 cm. The main collecting electrode has a collection area 17 cm in diameter. This collection area is further subdivided by a series of concentric circles of diameters 1, 3, 5, 9 and 13 cm. This foil is constructed of a 3-mil Kapton-H membrane stretched and glued to a lucite ring; it is opaque gold-plated on both sides, uniformly on one side and on the other side in a pattern providing electrical connections to the various parts of the foil. The quadrant electrode is similar except that the collecting side is masked by two cross wires to form four isolated sections. On both foils the areas not scribed or masked for collection regions or used to form connections to these areas are grounded. The high-voltage foil may take several forms from a double, aluminum-coated, $\frac{1}{4}$ -mil mylar foil to a double, gold-coated, 3-mil Kapton-H foil. The high-voltage foil is sandwiched between two lucite rings and constructed to eliminate high electrostatic fields in the gas at the edge of the high-voltage foil. The separation between each outer foil and the inner high-voltage foil is 1 cm. The ringed foil serves both as a beam-size-sensing device and a dose-measuring device while the quadrant foil is primarily for beam-position sensing.

The chamber is flushed with dry nitrogen gas, in most cases, with a low flow rate (0.1 cc/sec) and a minute over-pressure generated by a gas bubbler connected to the exit gas port on the chamber. Each collecting electrode is connected to a recycling integrator channel located within 3 m of the ionization chamber. These integrators, a modification of a LLL design,⁵ have a linear response over seven decades of current and are characterized by a transfer function of 10 picoamperes per hertz. The integrators do not require any operator action to initiate function or any operating range selection; they can measure a maximum current of approximately seven microamperes. The output of the recycling integrators is connected to scalers in a CAMAC crate located in the biomedical control room. If the ionization chamber is going to be used as a dose-measuring instrument, a calibration factor for each collecting area must be determined. This factor depends on the area of the collecting electrode, its separation from the high-voltage electrode, the energy required to make an ion pair (W) in the nitrogen gas, the density of the gas, and the relative mass stopping power of tissue to nitrogen. A value for W of 34.9 eV per ion pair has been assumed to be an appropriate value for heavy ions in nitrogen gas. When values of W have been experimentally measured, appropriate changes in the calibration factors will be made. The relative mass

stopping power of tissue to nitrogen has been assumed to be 1.125. The ionization chambers can also be used as a relative dose monitor; the chamber is calibrated by comparison with the output of a standard ionization chamber such as an EGG tissue-equivalent ionization chamber. Two chambers are generally used. One is placed in front of all other devices except a large defining aperture 15 cm in diameter. This chamber serves as a reference device since nothing is placed in front of it to modify its response. It is useful for beam-particle counts and as a reference cutoff for depth-dose measurements. The second chamber is placed as close as possible to the target to measure the dose received by the sample.

Variable Water Column

The variable water absorber or water column is a piston, cylinder, and reservoir arrangement that can be used to vary the range of the particles entering a target by introducing a measured amount of water into the beam path.⁶ Water columns are available with inside diameters of 15 and 20 cm. The maximum depth of water for the smaller water column is 30 cm, and that of the larger column is 40 cm. The water in the beam path is contained between a lucite window at the end of the cylinder and a lucite window on the movable piston. The total amount of water within the beam path is determined by the relative position of the two windows. The piston can be moved by computer or manual control of a stepping motor at a maximum speed of 0.5 cm/sec. The position of the piston is read by an encoder to the nearest 0.1 millimeter ± 1 digit.

Collimation

Some experiments require restriction of the beam to a target area with minimal irradiation of surroundings; this is usually done by passing the beam through an aperture. Most apertures in use are of brass, 5 cm long, and held in a sturdy prealigned holder on the alignment bench. Currently available diameters are from 0.2 to 3.8 cm. Larger-diameter apertures can be made and individually mounted on a stand.

Ridge Filters

Some biological samples are thick compared to the width of the Bragg peak; consequently, when irradiating with this part of the curve, the dose will vary substantially in different parts of the sample.^{7,8} The Bragg curve can be modified over a predetermined distance by interposing in the beam a filter of non-uniform thickness called a ridge filter,⁹ which results in the sample being irradiated with a series of Bragg curves of different penetrations. A computer program (SURFR) has been written for calculating the relative widths and thicknesses of these ridges so as to produce the desired dose distribution (Fig. 3).

Secondary Electron Chamber

The secondary electron chamber¹⁰ is constructed with a series of alternate collecting and high-voltage foils enclosed within a vacuum. This device, because it is operated in a high vacuum, does not have the problem of ion recombination encountered with ionization chambers.¹¹ The current that can be measured with the chamber placed in the radiation field is due to the transfer of electrons between the collection and high-voltage foils. Since the great majority of electrons that are emitted from the surface of a foil have low energies,¹² a modest voltage will suppress the electron current flow in the unwanted direction. The secondary electron chamber is less sensitive as a radiation detector than the ionization chamber, but, since its current is not limited by recombination, the secondary electron chamber is usable at very high beam levels. The response of the chamber is sensitive to the surface condition of the foils; therefore, to maintain a clean stable surface condition, the vacuum should be about 10^{-8} Torr or better.

DOSIMETRY

The most well known feature and one of the most necessary measurements of a heavy-ion beam is its characteristic Bragg curve. A Bragg curve is a plot of the relative ionization as a function of the

Fig. 3. Bragg curves for helium-, carbon-, neon- and argon-ion beams.
(XBL 768-9226)

Fig. 4. Bragg curve for the 400-MeV/u neon beam and a broadened depth-dose distribution in water.
(XBL 755-4910)

absorber thickness or penetration distance of the beam. A Bragg curve is characterized by a relatively flat plateau followed by a rapid rise to a peak known as the Bragg peak and then a very precipitous fall to decreasing values in the tail of the curve. The Bragg curve should include all contributions to the ionization at each penetration distance. Therefore, the ionization chamber should have a large collecting area relative to the cross-section area of the beam, or the beam should be very large and uniform in cross section relative to the detector. Measurements with a small collector and a small beam should probably not be called Bragg curves but more properly central-axis depth-dose curves since the numbers obtained are proportional to the doses in small volumes at the points along the curve. This type of curve is more sensitive to differences in geometry and beam size than is a Bragg curve. Bragg-curve measurements are typically done with a small beam (on the order of 1 cm in diameter) and a 17-cm-diameter collection electrode. With a monitor ionization chamber located upstream from the variable water column and a second ionization chamber at the exit window of the water column, the Bragg curve is measured by plotting the relative ionization in the second chamber as a function of the water-absorber thickness. The central-axis depth-dose distribution is simultaneously measured by plotting the relative ionization from the 1-cm-diameter collector as a function of the penetration distance. These measurements have been made and are shown in Fig. 4 for four heavy-ion beams (helium, carbon, neon and argon) and two energies for each beam. Energies were chosen to provide residual ranges between 11 and 15 cm and between 27 and 33 cm. The energies at extraction are listed in Table I. The data have been normalized to an initial value numerically equal to the linear energy transfer (LET) measured in $\text{keV}/\mu\text{m}$. The energy of the beam at the absorber thickness of the first data point is lower than the extraction energy because of energy loss in the windows of the water absorber, the vacuum windows, and the thickness of the various beam monitors. It should be noted that the low-energy beams have higher peak-to-plateau ratios and lower doses of secondary particles beyond the Bragg peak.

Independent dosimetry of the energetic argon ions performed by Goodman and Colvett¹³ from Columbia University has confirmed that depth-dose distributions measured in a water phantom and in a tissue-equivalent liquid phantom are essentially the same provided that the difference in the electron densities of the liquids is considered. The depth-dose distribution measured behind a water absorber is essentially the same as that measured in a water phantom, and reliable dosimetry for tissue can be performed by using air instead of tissue-equivalent gas in the cavity of a tissue-equivalent ionization chamber.

The dose contribution of the primary ions to the Bragg curve is well understood and can be predicted using a method developed by Litton.¹⁴ The difference between the dose of the experimental Bragg curve and the dose predicted for the primary heavy ions is, of course, due to the dose contribution of the secondary particles. To assess the importance to the total dose of the dose due to the secondary particles, it is necessary to know the number and types of particles present in the beam. Computer-calculated Bragg curves including the contribution of secondary charged particles are compared with the experimental Bragg curves, as shown in Fig. 5. Such a comparison allows a reasonable estimation of the number and types of secondary particles generated in interactions of the primary ions with the absorbing media. This analysis has made possible the calculation of the dose-weighted, average LET distributions as functions of depth for the various heavy-ion beams. Goodman has made LET-distribution measurements for the 500-MeV/nucleon argon-ion beam, and Luxton has made similar measurements for carbon- and neon-ion beams.¹⁵ The results of these measurements, when available, will be compared with calculated average LET values.

FUTURE WORK

Current plans for the future include the installation of a Phillips treatment couch in Cave I. A chair will be designed that can be connected to the translational mechanism of the couch. A support for a standing patient will also be designed. These additions will permit the choice of standing, sitting or reclining treatment positions.

TABLE I. Energies of selected heavy-ion beams.

Ion	Low Energy	High Energy
Helium	150 MeV/u	225 MeV/u
Carbon	250	400
Neon	400	594
Argon	500	900

Fig. 5. Bragg curve of the 500-MeV/u argon beam in water. Experimental points are compared with calculated curves for the total as well as the primary and secondary ionization. (XBL 768-9256)

Magnet power supplies will be supplied with the appropriate controls to facilitate a rapid change of the beam between Caves Ia-d and II. Then the beam can be used in Cave II while a patient is being set up in Cave I. When the patient is ready for therapy, the beam will be switched to Cave I. Following treatment, the beam can be immediately switched back to Cave II.

The data-acquisition system will be improved by the installation of more generalized software. This software will improve the ease of data acquisition for various experimenters; in particular, it will greatly help experimenters from other institutions who bring their equipment to the Bevatron/Bevalac and are using these instruments to augment the measurements that are customarily made by the operations crew.

REFERENCES

1. *Bevatron/Bevalac Users Handbook*. Division of Biology and Medicine, Lawrence Berkeley Laboratory (1977).
2. Raju, M. R., J. T. Lyman, T. Brustad, and C. A. Tobias. Heavy charged-particle beams. In: *Radiation Dosimetry*, Vol. III, 2nd Ed. (F. H. Attix, W. C. Roesch and E. Tochilin, eds.). (New York: Academic Press) pp. 151-99 (1966).
3. Lyman, J. T., J. Howard and A. A. Windsor. Heavy charged-particle beam monitoring with segmented ionization chambers. *Med. Phys.* 2, 163 (1975). (Abstract)
4. Lyman, J. T., and J. Howard. Dosimetry and instrumentation for helium and heavy ions. *Int. J. Rad. Oncology, Biology & Physics*, in press.
5. Shapiro, E. G. Linear seven-decade current/voltage-to-frequency converter. *IEEE Trans. Nucl. Sci.* NS-17, 335-44 (1970).
6. Tobias, C. A., J. T. Lyman, A. Chatterjee, J. Howard, H. D. Maccabee, M. R. Raju, A. R. Smith, J. M. Sperinde, and G. P. Welch. Radiological physics characteristics of the extracted heavy ion beams of the Bevatron. *Science* 174, 1131-4 (1971).
7. Raju, M. R., M. Gnanapurani, U. Madhvanath, J. Howard, and J. T. Lyman. Relative biologic effectiveness and oxygen enhancement ratio at various depths of a 910-MeV helium ion beam. *Acta Radiol. (Ther.)* 10, 353-7 (1971).
8. Raju, M. R., E. Blakely, J. Howard, J. T. Lyman, D. P. Kalophonos, B. Martins, and T. C. H. Yang. Human cell survival as a function of depth for a high-energy neon ion beam. *Radiat. Res.* 65, 191-4 (1976).
9. Karlsson, B. G. Methoden zur Berechnung und Erzielung einiger fuer die Tiefentherapie mit hochenergetischen Protonen guenstiger Dosisverteilungen. *Strahlentherapie* 124, 481-92 (1964).
10. Taufest, G. W., and H. R. Fechter. A nonsaturable high-energy beam monitor. *Rev. Sci. Instr.* 26, 229-31 (1955).
11. Boag, J. W. Ionization chambers. In: *Radiation Dosimetry*, Vol. II, 2nd Ed. (F. H. Attix, W. C. Roesch and E. Tochilin, eds.). (New York: Academic Press) pp. 1-72 (1966).
12. Oda, N., and J. T. Lyman. Secondary-electron distributions for heavy ions. *Radiat. Res., Supply*, 7, 20-32 (1967).
13. Goodman, L. J., and R. D. Colvett. PD-4 dosimetry of energetic argon ions. In: *Brookhaven National Laboratory Report Annual Report 1976* (ERDA DOC COD-3243-5 pp. 55-78).
14. Litton, G., J. Lyman, and C. Tobias. Penetration of high-energy heavy ions with the inclusion of Coulomb, nuclear, and other stochastic processes. Lawrence Berkeley Laboratory Report No. UCRL-17392 Rev. (1968).

CHAPTER 4

NUCLEAR PHYSICS OF ACCELERATED HEAVY IONS

Stanley B. Curtis and Walter Schimmerling

INTRODUCTION

High-energy heavy ions, traversing an absorbing medium, produce ionization by atomic and molecular collisions; in addition, they interact with the nuclei of the medium. The processes are qualitatively different. The former will be discussed in Chapter 5; the latter is discussed in this chapter.

One of the most important types of nuclear interaction is the production of lighter fragments of the incident particle. These fragments can penetrate past the stopping region ("Bragg peak") of the primary beam and alter its "radiation quality." For medical applications, the nuclear secondaries in a radiotherapeutic beam may alter the biological response from that expected in the absence of secondaries. In addition, the fragments will deposit energy outside of the treatment volume. If these secondaries are radioactive, however, it may be possible to image their stopping region and thus calculate the analogous information for the primary beam. The importance of the more sparsely ionizing secondaries in basic studies of chemical and biological mechanisms lies in the increased yield of chemical species and, at the same time, the decreased biological effect per unit of absorbed dose. Nuclear interactions of heavy ions, in the context of galactic cosmic radiation, are of importance for the evaluation of space hazards on long missions. Thus, knowledge of nuclear fragmentation processes is important in obtaining optimal application of heavy-ion beams for diagnostic and therapeutic use as well as a better understanding of the specific biological effects of these highly ionizing beams of radiation.

GENERAL FEATURES OF HEAVY-ION NUCLEAR INTERACTIONS

In general, products of nuclear interactions are fragments of the heavy-ion projectile, fragments of the target nucleus, and nucleons (or groups of nucleons such as alpha particles) produced in an interaction region where projectile and target overlap. The projectile fragments emerge from the interaction that created them in a direction very close to that of the incoming primary heavy ion and with little or no change in velocity from that of the primary. The target fragments are characterized by a broad angular distribution, relatively low energies, and high multiplicity. In the intermediate region (central or "head-on" collisions), intermediate energy products are produced by the de-excitation of "fire-balls" consisting of nucleons swept out of both the projectile and the target. In addition to these interactions involving nuclear forces, heavy ions are scattered slightly due to multiple collisions with the electric fields of the absorber nuclei (multiple Coulomb scattering).

PROJECTILE FRAGMENTATION

Projectile fragmentation, most commonly referred to simply as fragmentation, shows the following characteristics¹⁻⁷:

1. The reactions resulting in projectile fragments are due to grazing collisions.
2. The total reaction cross sections are generally independent of energy in the energy region above 300 MeV/nucleon.
3. The velocity of the fragments is close to the velocity of the incident projectile, and the fragments are emitted in a direction close to the direction of incidence. The momentum distributions of the fragments are Gaussian in the parallel and perpendicular components, showing that they are emitted isotropically in the frame of reference of the projectile. The standard deviation of this Gaussian shape

approximates a parabolic function of the beam and the fragment masses but is independent of the target mass.

4. The probability of producing a fragment is related to the target mass only through a *geometric scale factor*.

5. Geometric considerations have resulted in calculations of the cross section as two overlapping black disks with the overlap region subtracted.⁸ Saito,⁹ however, analyzed the available data for inelastic cross sections and concluded that an adequate fit is obtained by simply adding the areas of the two nuclei. A similar conclusion was reached in a calculation by Barshay.¹⁰

Fragmentation cross sections have been calculated by Bertini et al.¹¹ using an intranuclear cascade approach. Agreement with experimental data is poor, mainly because these preliminary calculations neglected depletion of nucleons in the nucleus and shadowing effects of one nucleus on another.

Various calculations exist for predicting the standard deviation of the Gaussian momentum distributions based on the internal energy of the projectile excited by a grazing collision,⁴ but, although the predicted parabolic function is found to be a reasonable approximation, unexplained nuclear structural effects persist.

TARGET FRAGMENTATION

The main features of target fragmentation are the following^{12,13}:

1. The distribution of reaction products is not significantly dependent on heavy-ion energy between 0.3 and 2 GeV/nucleon. This is in contrast with the yields from proton bombardment in the same energy range, which change by a factor of 100 due to the onset of meson production. The energy independence of the heavy-ion yield ratios seems to indicate that the mesonic degrees of freedom are opened at lower energies.

2. The distribution of reaction products is similar to that obtained with protons of the same *total* energy with the exception of lighter target fragments and neutron-deficient products which are favored. Target fragmentation is thus approximately independent of the projectile mass except for a scale factor to account for the larger total reaction cross section.

The projectile independence in target fragmentation is similar to the target independence in projectile fragmentation and is referred to as "factorization" while the approximate energy independence is referred to as "limiting fragmentation." Both characteristics are analogous to similar behavior of composite particles in high-energy physics.

Significant deviations from factorization for light fragments have been pointed out by Cumming,¹³ Lindstrom,¹ and Raisbeck and Yiou¹⁴ who used a kinematically equivalent experiment (production of Be in C and O targets by 2.8-GeV alpha particles). These deviations are generally ascribed to "central" collisions where both partners in the reaction collide "head-on" and the distinction between target and projectile is lost.

CENTRAL COLLISIONS

Nuclear reactions in the central region have recently attracted theoretical interest. These processes involve "head-on" collisions in which large amounts of energy and transverse momentum are transferred, as opposed to grazing collisions resulting in target or projectile fragmentation. In particular, the formation of nuclear shock waves has been postulated based on the fact that the velocity of sound in nuclear matter is about 20% of the speed of light, corresponding to an energy of 20 MeV/nucleon. Studies by Poskanzer et al.¹⁵ have failed so far to find evidence of the emission of fragments into the narrow cone expected if shock waves are produced in the target nucleus.

Pi-meson production,^{16,17,18} accounts for a very small fraction of the charged particles produced in high-energy, heavy-ion interactions. The angular distribution of pi-mesons is peaked in the forward direction.

Measurements of the angular distributions and multiplicities of hydrogen and helium isotopes produced by high-energy neon on uranium targets by Gutbrod et al.¹⁹ showed that these products were two and three orders of magnitude higher than those found for proton-induced reactions at comparable energies. These higher yields were explained in terms of final state interactions between the nucleons affected by the collision. In this coalescence model, it is assumed that there will be many nucleons to which energy is transferred in such a collision and that among these there will be pairs with small relative velocity, thus favoring their coalescence into a composite light fragment.

This model has been refined by treating the cluster of excited nucleons as a "fireball."²⁰ Geometrically, it is assumed that the target and the projectile are spheres and that they make clean cylindrical cuts through each other, leaving a spectator piece of the target and, if the impact parameter is large enough, a spectator piece of the projectile. These spectator pieces eventually lead to target and projectile fragmentation products. The swept-out nucleons originating from the interaction are heated by the energy transferred, leading to a quasi-equilibrated "fireball," which cools by emission of light fragments and even pi-mesons of low energy.

The predictions of these models agree quite well with experimental measurements of proton spectra for proton energies between 30 and 120 MeV. The spectra of composite hydrogen and helium isotopes can be calculated using the neutron and proton spectra only. Experiments are under way by several groups at LBL to study these collisions.

IMPLICATIONS FOR BIOMEDICAL RESEARCH

The above features affect biomedical studies in various ways. The most important effect is from projectile fragmentation. Fragments emitted into the forward direction cause a gradual change in the fraction of the beam having lower charge and longer range. These fragments contribute on the order of 15% of the dose at the Bragg peak for light ion beams (nitrogen and oxygen) and constitute the major part of the exit dose. This percentage will, in general, be larger for heavier ion beams. The depths at which many tumors must be treated require the initial energy of the beam to be such that the primaries will travel 20 to 30 cm in tissue. Absorption mean free paths in water for carbon, neon and argon beams, calculated from recently derived nucleus-nucleus cross sections given by Wilson and Costner,²¹ are 26, 21 and 15 cm, respectively. Since the nuclear mean free paths are on the same order as the necessary range of beam penetration, there will be a significant fraction of the incident beam that will undergo nuclear breakup. The fragmented ions continue as more sparsely ionizing radiation, altering the radiation quality and consequently the biological effects expected at depth. The extent to which this occurs for ions of different charge and mass must be quantitatively determined to provide the physical basis for understanding the resultant biological responses. A major effort of the Radiation Biophysics Program, as will be seen in the next section, has been and is presently directed toward this end.

Some of the fragments will be radioactive and can be used to visualize the stopping region, for instance, in the case of positron emitters, by the detection of the annihilation radiation from positron decay. Such radioactive fragments can also be used for noninvasive implantation of tracers into tissues, as discussed in Chapter 6.

Reaction products emerging at relatively large angles to the forward direction as well as multiply Coulomb-scattered primaries and secondaries will result in beam broadening and contribute to the dose received by lateral parts of the absorber, including nontarget tissues during therapy. In diagnostic radiography, these effects will reduce resolution. A discussion of such problems connected with heavy-ion radiography is presented in Chapter 12.

Radioactive target residues activated by the traversing beam will make only a small contribution to the absorbed dose delivered in the path of the beam. Such radioactivation, however, can be used for calibration and beam monitoring. The most useful reactions are the $^{12}\text{C}(\text{A},\text{Xn})^{11}\text{C}$ and $^{27}\text{Al}(\text{A},\text{X2pn})^{24}\text{Na}$ reactions due to the convenient target material and half-life as well as the easily identifiable decay radiation of the product (positrons resulting in two characteristic 0.511-MeV annihilation gamma rays for ^{11}C ; one 1.39-MeV beta ray and 1.37- and 2.75-MeV gamma rays for ^{24}Na). In the above notation, A denotes the incident heavy ion, and X is the unobserved residual product. The use of the ^{11}C reaction to calibrate ionization chambers for radiation dosimetry has been described.²²

High-energy heavy ions produce more neutrons and pi-mesons than do protons and neutrons at comparable energies. The production of neutrons is of special importance because of their penetrating nature and large RBE (Relative Biological Effectiveness), especially at low doses. It is possible that in some situations the neutron dose at large distances from the tumor site may limit the dose that can be safely given to the tumor.

DIVISION OF BIOLOGY AND MEDICINE STUDIES OF NUCLEAR PROJECTILE FRAGMENTATION OF HEAVY IONS

Initial calculations²³ showed that, on the basis of "pessimistic" (i.e., large) values for the fragmentation cross sections, the dose from secondaries would be only 15% of the primary dose in the Bragg peak region of a stopping neon-ion beam with a range of 10 cm in water. The full-width-at-half-maximum would be increased by only 15%. These predictions were borne out by subsequent experimental data. Maccabee and Ritter²⁴ studied fragmentation of high-energy oxygen-ion beams in water by measuring pulse height spectra in lithium-drifted silicon detectors. The mean free path for oxygen ions in water was found to be 19.4 ± 1.3 cm. The cross sections for fragment production were found to be 331 ± 140 , 324 ± 64 , and 102 ± 14 millibarns for nitrogen, carbon, and boron fragments, respectively. The measured cross sections and mean free paths are in agreement with values calculated from geometric models and cosmic-ray data. The mean fragmentation cross sections appear to be energy-independent in the 215- to 250-MeV/nucleon range and at higher energies. The interactions producing nitrogen, carbon, and boron fragments constitute approximately one half of the total interactions for oxygen ions in the energy range studies. Chatterjee et al.²⁵ have analyzed cosmic-ray, nuclear emulsion fragmentation data and have extrapolated the results to water and calculated integral fluence and absorbed doses as functions of distance for nitrogen and oxygen beams. Good agreement is obtained between their calculations and experimental fluence and absorbed-dose data obtained for nitrogen and oxygen ions at the Bevalac. Calculations were also made of the fluences and doses produced by the various secondary fragments in a nitrogen-ion beam.

DEVELOPMENT OF THE COMPUTER PROGRAM HZESEC

In order to study the "radiation quality" of a heavy-ion beam at depth in an absorber, a computer program was developed to calculate distributions of various physical quantities of interest.^{26,27} At present, the code can be used to calculate, at any depth, the distributions in LET_∞ , velocity, energy, or pulse height as well as the integral distributions of particle number, absorbed dose and total charge. The calculation includes the contributions from the primary ions and the nuclear secondaries produced along the beam path. The cross sections (probabilities) for the production of various secondary products must be input as well as the incident-ion identity and energy and the spread of the incident energy distribution (assumed to be Gaussian). The assumption is made that the secondary fragment continues in the same direction as the primary and has the same velocity at the point of interaction. The cross sections can be assumed constant, or energy dependence can be estimated using another code, COSMIC, which utilizes the analytical expressions developed by Silberberg and Tsao.²⁸ These authors have developed a semiempirical model by using analytical expressions derived from physical considerations and by fitting adjustable parameters to experimental data for proton-nucleus fragmentation cross sections. Agreement of these expressions with experiment is, in general, better than 30%. A modification of the procedure has

been made in the development of the program COSMIC²⁹ in which an empirical scaling factor is introduced to account for the increased cross section in going from protons to heavy ions. The scaling factor has been adjusted to agree better with the ratio of nitrogen-induced to proton-induced fragmentation, a ratio observed to be constant.³

LET DISTRIBUTIONS FOR EXTENDED-BRAGG-PEAK REGIONS

Another area of interest, particularly in the pretherapeutic studies, is the radiation quality of the beam in the extended peak of the depth-dose distribution that has been spread out by means of a "ridge filter" as described in Chapter 3. A modification of the above code is used to calculate LET distributions at any depth in such an extended-peak region.²⁷ In Fig. 1, a calculation for a neon-ion beam, assuming an initial energy per nucleon of 373.25 MeV, is compared with experimental data from the Bevalac for the unmodified peak (top graph) and for the curve modified with a ridge filter spreading the peak region to 3.9 cm (bottom graph). The lower curve in each graph shows the dose from the primary neon ions only; the upper curves include the dose from secondary fragmentation products. The arrows in the bottom graph denote positions where the LET distributions were calculated for this ion beam as well as for helium, carbon and argon beams with the same range and ridge filter.³⁰ Figure 2 gives the integral LET distributions, that is, the fractions of absorbed dose deposited at LET's greater than a given LET_{∞} , plotted against LET_{∞} for the four beams at the three depths indicated within the spread-peak regions. The variation in distribution is small except at the extreme distal ends of the heavier-ion beams.

COMPARISON OF CALCULATIONS OF VELOCITY SPECTRA BY HZESEC AND EXPERIMENTAL RESULTS FOR PPA

Velocity distributions of primary and secondary particles produced by 3.5-GeV nitrogen ions have been calculated as a function of depth in a polyethylene (CH₂) absorber, using an extended and modified version of HZESEC,²⁹ and compared with experimental data obtained at the Princeton Particle Accelerator using a direct measurement of the time of flight of emerging charged particles.²² In the calculation, secondary-particle production was computed using cross sections given by the semiempirical model of Silberberg and Tsao,²⁸ modified as described above in the program COSMIC. Detector time-of-flight resolution, multiple scattering in the detector telescope, and the energy spread of the incident beam were folded into the calculation. Qualitative agreement was obtained between the theoretical and experimental spectra as shown in Fig. 3. The experimental spectra are given by the histograms, and the calculated spectra are shown as continuous curves. The depths of polyethylene for panels a through h were 3.31, 4.42, 5.52, 6.63, 7.73, 8.84, 9.39 and 9.67 g/cm², respectively.

PRESENT EXPERIMENTAL MEASUREMENTS OF HEAVY-ION FRAGMENTATION IN THICK ABSORBERS

The original experimental design used at the Princeton Particle Accelerator has been modified for use at the Bevalac in the following ways:

1. The scintillation-counter, time-of-flight telescope has been replaced by a channel-plate telescope with a time resolution of approximately 100 psec developed at LBL.³¹ The need to place the flight path under vacuum also eliminates the large multiple-scattering corrections that limited the Princeton experiment.
2. A pulse ionization chamber has been designed and built to identify the charge and velocity of every recorded particle simultaneously. Ionization chambers have been used as charge identifiers in cosmic-ray studies³² and have the significant advantage of presenting a minimum of material to the beam.
3. A computer-based, on-line, data-acquisition system has been developed to multiply analyze the properties of single heavy ions, and a program for multiparameter experiments, HIIMEX, has been written.
4. Delay-line wire-chambers have been added for spatial resolution.

Data collection on this experimental program has begun, and a sample time-of-flight spectrum of a 500-MeV/nucleon argon beam after traversing 14.5 g/cm² of Lucite is shown in Fig. 4. Data analysis of such

Fig. 1. Unmodified and modified (with a 4-cm ridge filter) Bragg peaks for a neon-ion beam with incident energy of 373.25 MeV/nucleon. The experimental data were obtained with parallel-plate transmission ionization chambers. The arrows on the lower curve denote the depths for which LET distributions are presented in Fig. 2. (From Ref. 30).

(XBL 769-9266)

Fig. 2. Normalized integral LET distributions at 11.28, 12.84 and 14.4 cm of water for helium, carbon, neon and argon beams chosen to have equal ranges. The fraction of dose deposited above a given LET_∞ is plotted as a function of LET_∞ . (From Ref. 30).

(XBL 769-9265)

Fig. 3. Comparison of calculated velocity spectra (shown as histograms) with experimentally derived velocity spectra (shown as continuous curves) for primary and secondary particles produced by 3.5-GeV nitrogen ions. The depths of polyethylene for panels a through h were 3.31, 4.42, 5.52, 6.63, 7.73, 8.84, 9.39 and 9.67 g/cm².

(XBL 769-9277)

Fig. 4. Time-of-flight spectrum of a 500-MeV/nucleon argon beam after traversing 14.5 g/cm^2 of Lucite. (XBL 772-3114)

Fig. 5. Measurements of C-11 production for incident α particles³³ and N nuclei.³⁴ Circles represent published data. Crosses are preliminary, unpublished data from the Bevalac.³⁵ (XBL 772-3113)

spectra is in progress and will yield information on the spatial distribution of secondary fragments in biological absorbers. Detailed comparisons of calculated and measured velocity distributions will be made so that, eventually, accurate predictions of velocity and other distributions of interest to the radiobiologist and radiotherapist can be made. Basic physical data calculated with the computer program can then be used with confidence in estimating tumor response and checking the validity of models of cell killing and other important biological effects.

STUDIES OF TARGET FRAGMENTATION

From the point of view of biomedical applications, the most interesting target nuclear reactions are those of the lighter elements (C,N,O). Measurements of ^{11}C production have been made for incident alpha particles³³ and nitrogen nuclei.³⁴ The existing data are shown in Fig. 5 where the circles represent published data and the crosses are preliminary, unpublished measurements obtained at the Bevalac.³⁵ A least-squares fit to the published results leads to a target dependence, as shown by the full line, if the proton datum for the same total energy as the alpha particles (900 MeV) is used. The preliminary results obtained at the Bevalac show a discrepancy with the nitrogen result obtained by Skoski et al.³⁴ which has been confirmed by another, independent measurement²² and seems well established. On the other hand, it can be argued that reactions leaving most of the target carbon nucleus intact must be grazing reactions, in which case the area available for the reaction is a ring on the target periphery proportional to the target radius. Thus it is tempting on intuitive grounds to assume an $A^{1/3}$ dependence for the cross section. Such a dependence would be in agreement with the unpublished Bevalac data and would suggest that nitrogen is an anomalous target. This matter merits resolution in future investigations using the Bevalac beams because of the practical importance of the reactions involved.

STUDIES OF NEUTRON PRODUCTION BY HEAVY-ION BEAMS

The measurement of neutrons is of intrinsic interest in biomedical applications as well as in fundamental physics. Even though neutrons may constitute only a small fraction of the radiation dose, their effect on healthy tissue and their distribution throughout the body may restrain the maximum therapeutic dose. The problem is similar for heavy-ion and pi-meson irradiation, but in the case of high-energy heavy ions, the angular distribution of neutrons is not isotropic, and the highest-energy neutrons are peaked in the forward direction. Preliminary results²⁹ indicate that the flux of neutrons emitted in the forward direction by a stopping nitrogen beam is greater than or equal to the incident flux of heavy ions.

Neutron production by high-energy heavy ions will yield data needed to calculate doses to passengers in high-altitude aircraft. These doses are mainly due to neutrons produced in the atmosphere by cosmic rays. While the contribution of heavy ions to the cosmic-ray flux is small, the high energy of the neutrons produced and their preferential forward emission will make a significant contribution to the total neutron flux at greater depths in the atmosphere.

The relatively favorable properties of neutron production, especially their angular distribution, may make heavy-ion-produced neutrons attractive as a means of producing low gamma-ray background beams for comparative studies. An experimental program funded by NASA has been initiated to measure doubly differential, neutron-production cross sections by carbon, neon and argon beams.

EXPERIMENTAL PROGRAMS

Fragmentation Studies

The experimental apparatus for the study of time-of-flight and charge distributions of high-energy heavy ions as they come to rest in tissue-equivalent absorbers has been set up in an initial configuration.

Data have been taken for central-axis depth distributions of carbon, neon and argon. Plans call for the following extensions and additions to the experiment:

1. Continued data-taking with range studies for particle identification in order to identify the products emitted in the forward direction as a function of depth (central-axis distributions).
2. Data analysis to determine secondary particles (element distributions), limited isotopic identification, $(z^*/\beta)^2$ distributions, velocity distributions, stopping powers of some of the elements, and W-values as a function of velocity, all referred to the central axis.
3. Conversion of the channel-plate, time-of-flight telescope to a large-area, avalanche-chamber type of detector for off-axis studies followed by experiments similar to those described above (1) to obtain a spatial distribution of the quantities of interest.

Instrumentation Development

Instrumentation studies of the properties of the detectors are a natural part of the experimental program and will be pursued to explore the applications of the apparatus to other aspects of radiation physics such as imaging.

Neutron Production

An experimental program to measure neutron production by high-energy heavy ions has been funded by NASA and is being done in collaboration with the Physics Department at Kent State University of Ohio. A preliminary run using a tagged neutron beam produced by deuterons disintegrating on a uranium target has been performed to measure the neutron detection efficiency of our detectors. The program calls for complete measurements of the detection efficiency of the detectors followed by measurements of the double differential cross section (energy spectra and angular distributions) for production of neutrons by C, Ne and A beams on several targets.

THEORETICAL PROGRAM

The above data will be used to check the calculational approach developed to characterize the physical distributions of the beams. The appropriate distributions of physical characteristics as calculated by HZESEC, for instance, will be used as input for models of radiobiological action currently being developed. The calculational efforts will be refined as information is gained in order to increase confidence in predicting biological response in untried situations such as with different ions, at different energies, or at different depths. This program will also aid in optimizing fractionation schedules for radiotherapy, ridge-filter design, diagnostic procedures, and protocols for future radiobiological experiments.

REFERENCES

1. Lindstrom, P. J., D. E. Greiner, H. H. Heckman, B. Cork, and F. Bieser. Isotope Production Cross Sections; Lawrence Berkeley Report LBL-3650 (1975).
2. Heckman, H. H., D. E. Greiner, P. J. Lindstrom, and F. S. Bieser. Fragmentation of Nitrogen-14 Nuclei at 2.1 GeV per Nucleon. *Science* 174, 110 (1971).
3. Heckman, H. H., D. E. Greiner, P. J. Lindstrom, and F. S. Bieser. Fragmentation of ^{14}N Nuclei at 29 GeV: Inclusive Isotope Spectra at 0° . *Phys. Rev. Lett.* 28, 926-929 (1972).
4. Greiner, D. E., et al., Momentum Distributions of Isotopes Produced by Fragmentation of Relativistic C-12 and O-16 projectiles. *Phys. Rev. Lett.* 35, 152 (1975).
5. Jakobsson, B., R. Kullberg, and I. Otterlund. Transverse Momentum Distributions of Multiply Charged Fragments in O-16 Emulsion Nucleus Interactions at 2.0 GeV/nucleon. University of Lund, Cosmic Ray Physics Report LUIP-CR-75-02 (1975).

6. Kidd, J. M., P. Wefel, W. Schimmerling, and K. Vosburgh. The Fragmentation of 0.5-GeV/u ^{14}N Ions. *14th International Cosmic Ray Conference* 2, 510 (1975).
7. Wefel, J. P., J. M. Kidd, W. Schimmerling, and K. G. Vosburgh. A Measurement of Differential Forward Fragmentation Cross Sections for 7.3 GeV Nitrogen Ions Incident on Protons. In preparation.
8. Bradt, H. L., and B. Peters, The Heavy Nuclei of the Primary Cosmic Radiation, *Phys. Rev.* 77, 34-70 (1950).
9. Saito, T., The Nucleon-Nucleus Inelastic Cross Sections at Cosmic Ray Energies. *J. Phys. Soc. Japan* 38, 282 (1975).
10. Barshay, S., et al. Validity of Factorization Hypothesis. *Phys. Lett.* 51B, 5-8 (1974).
11. Bertini, H. W., T. A. Gabriel, and R. T. Santoro. Predicted Proton Spectrum at Forward Angles for 29.5 GeV N on C Collisions. ORNL-TM-4311 (1973).
12. Cumming, J. B., P. E. Haustein, R. W. Stoenner, L. Mausner, and R. A. Naumann. Spallation of Cu by 3.9 GeV ^{14}N Ions and 3.9 GeV Protons. *Phys. Rev. C* 10, 739 (1974).
13. Cumming, J. B., R. W. Stoenner, and P. E. Haustein. Spallation of Copper by 25-GeV ^{12}C Ions and 28-GeV Protons. *Phys. Rev. C* 14, 1554 (1976).
14. Raisbeck, G. M., and F. Yious. Production Cross Sections of Be Isotopes in C and O Targets Bombarded by 2.8 GeV Alpha Particles: Implications for Factorization. *Phys. Rev. Lett.* 35, 155 (1975).
15. Poskanzer, A. M., R. G. Sextro, A. M. Zebelman, H. H. Gutbrod, A. Sandoval, and R. Stock. Search for Fragment Emission from Nuclear Shock Waves. *Phys. Rev. Lett.* 35, 1701 (1975).
16. Schimmerling, W., K. G. Vosburgh, K. Koepke, and W. Wales. Measurement of Charged-Pion Production by 7.28-GeV Nitrogen Ions. *Phys. Rev. Lett.* 33, 1170 (1974).
17. Schimmerling, W., K. G. Vosburgh, K. Koepke, and W. Wales. Measurement of Charged-Pion Production by 7.28-GeV Nitrogen Ions. *Phys. Rev. D* 11, 1743 (1975).
18. Jaros, J., P. Papp, L. Schroeder, J. Staples, H. Steiner, and W. Wagner. In: *High Energy Physics and Nuclear Structure, Proceedings of the Fifth International Conference on High Energy Physics and Nuclear Structure, Uppsala, Sweden, 1973* (Tibell, G., ed.). (Amsterdam: North-Holland) p. 407 (1974).
19. Gutbrod, H. H., A. Sandoval, P. J. Johansen, A. M. Poskanzer, J. Gosset, W. G. Meyer, G. D. Westfall, and R. Stock. Final-State Interactions in the Production of Hydrogen and Helium Isotopes by Relativistic Heavy Ions on Uranium. *Phys. Rev. Lett.* 37, 667 (1976).
20. Westfall, G. D., J. Gosset, P. J. Johnsen, A. M. Poskanzer, W. G. Meyer, H. H. Gutbrod, A. Sandoval, and R. Stock. A Nuclear Fireball Model for Proton Inclusive Spectra from Relativistic Heavy Ion Collisions. Lawrence Berkeley Laboratory Report LBL-5072, *Phys. Rev. Lett.* , ().
21. Wilson, J. W., and C. M. Costner. Nucleon and Heavy-Ion Total and Absorption Cross Section for Selected Nuclei. National Aeronautics and Space Administration Technical Note NASA TN D-8107 (1975).
22. Schimmerling, W., K. G. Vosburgh, P. W. Todd, and A. Appleby. Apparatus and Dosimetry for High-Energy Heavy-Ion-Beam Irradiations. *Radiat. Res.* 65, 389-413 (1976).
23. Curtis, S. B. Secondary Particle Contribution to the Bragg Peak of a High-Energy Heavy-Ion Beam. Semiannual Report of Biology and Medicine, UCRL-18347, p. 171 (1968).
24. Maccabee, H. D., and M. A. Ritter. Fragmentation of High-Energy Oxygen-Ion Beams in Water. *Radiat. Res.* 60, 409 (1974).

25. Chatterjee, A., C. A. Tobias, and J. T. Lyman. Nuclear Fragmentation in Therapeutic and Diagnostic Studies with Heavy-Ions. *Spallation Nuclear Reactions and Their Applications* (Shen, B.S.P., and Merker, M., eds.), (Dordrecht, Holland: Reidel Publishing Co.) p. 169 (1976).
26. Curtis, S. B. Calculated LET Spectra from Heavy Primaries and Secondaries in Stopping Heavy-Ion Beams in Water. *Radiat. Res.* 55, 77 (abstr.) (1973).
27. Curtis, S. B. Dose Distributions in LET Through the Spread-Out Bragg Peaks of Heavy-Ion Beams. *Radiat. Res.* 59, 288 (abstr.) (1974).
28. Silberberg, R., and C. H. Tsao. Partial Cross Sections in High-Energy Nuclear Reactions for Targets with $Z \leq 28$. *Appl. J. Suppl.* 25, 315-334 (1973).
29. Schimmerling, W., S. B. Curtis, and K. G. Vosburgh. Velocity Spectrometer of 3.5-GeV Nitrogen Ions. Lawrence Berkeley Laboratory Report LBL-5602 (1976), submitted for publication.
30. Curtis, S. B. Calculated LET Distributions of Heavy Ion Beams. *Int. J. Radiat. Oncol.* (1977), to be published.
31. Gabor, G., W. Schimmerling, D. Greiner, F. Bieser, and P. Lindstrom. High Resolution Spectrometry for Relativistic Heavy Ions. *Nucl. Instr. Methods* 130, 65-71 (1975).
32. Epstein, J. W., J. I. Fernandez, M. H. Israel, J. Klarman, and R. A. Mewaldt. Large Area Pulse Ionization Chamber for Measurement of Extremely Heavy Cosmic Rays. *Nucl. Instr. Methods* 95, 77-85 (1971).
33. Radin, J. Cross Section for C-12 ($\alpha, \alpha n$)C-11 at 920 MeV. *Phys. Rev. C* 2, 793 (1970).
34. Skoski, L., M. Merker, and B. S. P. Shen. Absolute Cross Section for Producing ^{11}C from Carbon by 270-MeV/nucleon ^{14}N Ions. *Phys. Rev. Lett.* 30, 51-54 (1973).
35. Smith, A. R., Private Communication.

CHAPTER 5

FUNDAMENTAL RADIOLOGICAL PHYSICS AND RADIATION CHEMISTRY
OF HEAVY IONS IN MODELS OF CHEMICAL AND BIOLOGICAL EFFECTS

John L. Magee and Aloke Chatterjee

INTRODUCTION

The energy deposit that creates the track of a high-energy particle in a condensed phase such as water is established in a time of the order of 10^{-16} sec. The physical, chemical and biological effects initiated by the energy deposit are expressed over much longer periods of time. Track models are constructed to assist in the understanding of the various effects, and many models have been used. In this chapter we are most concerned with studies aimed at the construction of a model that has the potential for use in physical, chemical and biological applications.¹

The patterns of energy deposit are determined by the physical interactions of the particle with the medium. The two essentially different mechanisms of approximately equal importance* in the determination of stopping power, which in turn determines the energy deposit, are the following:

1. A resonant energy loss process which creates states of excitation between the lowest electronic excited state and about 100 eV
2. The creation of knock-on electrons with energies between 100 eV and a well understood maximum energy which depends only on particle velocity.

Any study of models must start with these two facts. Energy lost in the first mechanism is located initially in close proximity to the trajectory of the particle; energy lost in the second mechanism leads to delta rays and branch tracks. In track models, the first mechanism leads to the creation of a "core" and the second to a well-defined region of lower energy density, sometimes called the "penumbra."

A model that emphasizes explicit geometrical arrangements and development of tracks in time has been constructed by several authors.^{2,3,4} In the interval of time between 10^{-16} sec and 10^{-9} sec when the first important chemistry usually starts, there are many processes that must be treated in intuitive ways. This approach has been used to model in a satisfactory manner the chemistry for low-LET radiation and for low-energy protons and α particles.⁵ It would appear that this same approach can be used for heavy-particle radiation.

The fundamental nature of the problem is of interest, and much work remains to elucidate the nature of the initial energy deposition in condensed phases. There are probably early effects, not recognized at the present time, that continue on to determine the course of the chemical and biological actions of radiation. The early physical mechanisms have been studied by several authors.^{6,7,8} Although the details of treatments vary, the general features of track structure remain the same; along the trajectory of the particle is created a "core" or "infra track," and extending to larger distances is a "penumbra" or "ultra track."

The concept of using basic physics and chemistry in the interpretation of radiobiological effects has been understood for many years and was promoted by Lea.⁹ Recent work by Rossi and Kellerer¹⁰ attempted to use explicit space-time development of track effects in biology.

*The "equipartition rule" says that exactly the same amount of energy is lost by these two mechanisms.

MODEL OF PHYSICAL EFFECTS

The radius of the track core is given by

$$r_c = \frac{\beta_c}{\omega_p} \quad (1)$$

where ω_p is the plasma frequency of the medium. This equation gives the Bohr adiabatic criterion; matter that is farther away from the particle trajectory than r_c has time to follow the impulse adiabatically and does not absorb energy directly. The simplest model for energy density consistent with the equipartition rule is a uniform distribution of energy equivalent to half the value of LET_∞ in a cylinder of radius r_c .

The energy density within the penumbra is much more complicated than that of the core and is made up of energy deposited by the recoil electrons with energies extending from 100 eV to a maximum value of $2mc^2\beta^2/(1-\beta^2)$ where m is the rest mass of the electron and $\beta = v/c$. An analysis of this problem has led to the following reasonably good empirical formula for the penumbra radius⁴:

$$r_p = 396 v^{2.7} \quad (2)$$

where the particle velocity is in 10^9 cm/sec and r_p is in Angstroms. The distribution of energy within the penumbra is found to vary with r^{-2} .³ These facts were used by Chatterjee and Tobias⁴ to write for the energy density of the track

$$\rho_{core} = \frac{LET_\infty/2}{\pi r_c^2} + \frac{LET_\infty/2}{2\pi r_c^2 \ln(e^{1/2} r_p/r_c)}, [0 \leq r \leq r_c], \quad (3)$$

and

$$\rho_{pen} = \frac{LET_\infty/2}{2\pi r^2 \ln(e^{1/2} r_p/r_c)}, [r_c < r \leq r_p] \quad (4)$$

The energy density in the deposit is defined from $0 \leq r \leq r_p$ and the integral of $\rho(r)$ over the entire range of r as

$$2\pi \int_0^{r_p} r \rho(r) dr = LET_\infty. \quad (5)$$

The second term in ρ_{core} is to some extent arbitrary and was arranged to give the proper normalization. It is, of course, true that the core initially has more than half the energy because some of the energy deposit of the low-energy delta electrons is deposited in the core.

The energy deposit given by Eqs. 3 and 4 corresponds to a very early time. The core energy deposit is approximately valid at 10^{16} sec. In order to use this deposit explicitly we must consider the redistribution as it occurs with the progress of time. The energy density in the penumbra is a statistical distribution of the deposit of low-energy electrons. The value of $\rho(r)$ is the average value at an early (unspecified) time after the local deposit.

Values of $\rho(r)$ calculated using Eqs. 3 and 4 for neon at various energies in water are shown in Fig. 1. This figure shows that the core energy density is about an order of magnitude larger than the average energy density in the penumbra adjacent to the core. The energy density drops abruptly to zero at $r = r_p$, a phenomenon that results from the finite range of knock-on electrons.

Comparison with experiment has been made in a limited way. Data obtained in the gas phase can be scaled to give the energy density at distances on the order of Angstroms. In Fig. 2, calculated energy densities of the penumbra (Eq. 4) for He and H ions are compared with the experimental data of Wingate and Baum¹¹ and Menzel and Booz.¹² This figure shows that the calculated energy densities agree within experimental error with the few measured values available.

Fig. 1. A log-log plot of calculated energy density versus radial distance for neon particles in water. (XBL 772-3082)

Fig. 2. A log-log plot of calculated penumbra energy densities for α particles and protons compared with experimental points of Wingate and Baum¹¹ for α , and Menzel and Booz¹² for p. (XBL 772-3079)

MODEL OF CHEMICAL EFFECTS

The chemical actions of high-energy radiations occur through transient reactive intermediates created in the tracks. These transient species are formed on several time scales, and the entire process is rather involved. In this chapter we shall consider only one aspect of the problem and use one example, the oxidation of an aqueous solution of ferrous sulfate. This reaction is an important example in radiation chemistry and is used in a dosimeter (the "Fricke" dosimeter). We can assume that the reactive intermediates are H and OH radicals; they are formed in the tracks and react with each other and with the solute (Fe^{++} ions) as they diffuse away from their points of origin. A completely adequate treatment of the problem would require simultaneous solution of a set of partial differential equations,

$$\frac{\partial c_i}{\partial t}(r_i, t) = D_i \nabla^2 c_i(r_i, t) - \sum_j k_{ij} c_i(r_i, t) c_j(r_j, t) - k_{is} c_i(r_i, t) S, \quad (6)$$

$$i, j = 1, 2, \dots, p,$$

with an equation for each of the p reacting species. In Eq. 6, $c_i(r_i, t)$ is the time- and space-dependent concentration of the i^{th} species, D_i is its diffusion constant, k_{ij} is the reaction rate constant, and ∇^2 is the Laplacian operator. The rigorous solution is obviously impossible, and various approximations are used. Kupperman⁵ has carried out computer calculations on the set of equations with assumed initial conditions. Kupperman's solutions have given radiation chemists a basis on which to develop simpler approximations.

The motivation for one particular type of solution can be seen by the following reasoning: the terms on the right side of Eq. 6 have rapidly varying magnitudes as a function of time. In a typical case, the terms involving the squares of concentrations can dominate at first; then the diffusion term can dominate; and finally the scavenger term is most important. One type of approximation involves neglect of the diffusion term while the recombination of radicals is fast and later neglect of the recombination term when diffusion is more important.

The most useful type of approximation in track problems is "prescribed diffusion," which allows the partial differential equations to be written as ordinary differential equations. If, in addition, other reasonable assumptions are introduced, a complete zero-order solution of the problem can be obtained.

Consider the track of a fast heavy particle of charge Z , and assume that the core and penumbra can be considered separately. At first the core has a cylindrical distribution of energy, and we assume that at the time the radicals start to diffuse they have a concentration dependence

$$c(r, 0) = c(0) e^{-r^2/r_c^2} \quad (7)$$

where

$$c(0) = \frac{N(0)}{\pi r_c^2}. \quad (8)$$

Here r_c is the core radius, and $N(0)$ is the number of radicals formed per unit length of the track. If there were only diffusion of the radicals (i.e., no reaction), the concentration would change with time as

$$c(r, t) = \frac{N(0) e^{-\left[r^2/(r_c^2 + 4Dt)\right]}}{\pi (r_c^2 + 4Dt)} \quad (9)$$

"Prescribed diffusion" essentially says that, when reaction is also considered, a good approximation is to take the concentration as a function of time to be

$$c(r,t) = f(t) \frac{N(0)e^{-\left[r^2/(r_c^2 + 4Dt)\right]}}{(r_c^2 + 4Dt)} \quad (10)$$

Use of Eq. 10 and a one-equation approximation to the set of Eq. 6 yields the result

$$N(t) = \frac{N(0)}{1 + (kc_o t_o/2) \ln [1 + (t/t_o)]} \quad (11a)$$

where k is the recombination coefficient for the radicals and $t_o = r_c^2/4D$ is a time parameter determined by the rate of diffusion of the radicals. Another time parameter is $\tau_{\text{recomb}} = 1/kc_o$; if we write $t_o = \tau_{\text{diff}}$, Eq. 11a can be given as

$$N(t) = \frac{N(0)}{1 + (\tau_{\text{diff}}/2\tau_{\text{react}}) \ln [1 + (t/t_o)]} \quad (11b)$$

which calls attention to the fact that the ratio of the diffusion to recombination characteristic times is an important parameter.

The chemical mechanism of the aerated ferrous reaction is the following:

The radical diffusion model in its simplest form assumes that the only effect of the radiation is to create radicals (i.e., N_o per unit of track) and that these radicals react according to the above scheme to oxidize Fe^{++} . Combination of two OH 's leads to H_2O_2 which oxidizes Fe^{++} , whereas combination of two H 's leads to H_2 which is inert. The G value (yield per hundred electron volts) is given by

$$G(\text{Fe}^{+++}) = 3G_{\text{H}} + G_{\text{OH}} + 2G_{\text{H}_2\text{O}_2} \quad (12)$$

Here the yields of radicals that react, i.e., G_{H} and G_{OH} , are to be interpreted as those that survive the initial recombination and are given by Eq. 11a. If we assume that

$$N_{\text{OH}}(t) + 2N_{\text{H}_2\text{O}_2}(t) = N_{\text{OH}}(0), \quad (13a)$$

we can write

$$2N_{\text{H}_2\text{O}_2} = N_{\text{OH}}(0) - N_{\text{OH}}(t) \quad (13b)$$

and using Eqs. 11a and 12

$$G(\text{Fe}^{+++}) \propto N(0) \left[1 + \frac{3}{1 + (kc_o t_o/2) \ln [1 + (t'/t_o)]} \right] \quad (14)$$

The value of t' implied by this equation is that time when the reaction with a scavenger becomes important because at that time the latter reaction dominates recombination. In this case

$$t' = 1/k_s c_s \quad (15)$$

where c_s is the Fe^{++} concentration. The quantity c_o is given by Eq. 8 and is proportional to the stopping power. For a particular ion, Eq. 14 can be written as

$$G(\text{Fe}^{+++}) \propto N(0) \left[1 + \frac{3}{1 + \alpha(-dE/dx)} \right] \quad (16)$$

where α is made up of known parameters.

It has been known for many years that Eq. 16 is valid for low-energy protons, deuterons and helium ions.¹³ The empirical equation

$$G(\text{Fe}^{+++}) = 3.6 + \frac{12}{1 + 0.45(-dE/dx)} \quad (17)$$

has been used for deuterons. It is clear that the physical significance of this equation is explained by the derivation of Eq. 16 given here.

The calculation of the G value for the cylindrical core is made with Eq. 16 using the appropriate parameters. Calculation of the penumbra yield is actually similar; although the energy is distributed tenuously over a large region (as given in Figs. 1 and 2), the actual deposit is made up of low-energy electrons, and the G values are calculated with Eq. 17. The recoil electron distribution is considered explicitly, and the G values are estimated as those of protons that have the same velocity as the electrons.

Calculations made by the methods described for carbon, neon and argon are summarized in Fig. 3. Experimental points are not indicated because the experimental results have not been evaluated. The calculation gives 11.7 for the carbon ion at 200 MeV/n, and the experimental value is 11.8 ± 0.12 ; the general shape of the calculated curves appears to be in agreement with the limited experimental data available.^{14,15}

The theoretical concepts sketched here make possible calculations of chemical yields from track structure. Comparison with experiment will allow us to check on the validity of the model and to construct a more refined model. One feature that is embedded in the track model is the dependence of effects (such as chemical yields) on both Z and $(-dE/dx)$. As an example, consider in Fig. 3 the calculated yields at an LET of 6 eV/A of the ions neon and carbon. The value for neon is 9.5, and the value for carbon is 8.7; the calculation explains the difference in terms of the separate contributions of the cores and penumbras.

MODEL FOR BIOLOGICAL EFFECTS

The explanation of biological effects is the most demanding requirement on a track model. For the most part, the physical phenomena of interest usually probe either the initial energy distribution or perhaps an electronic excited state which has a lifetime of a few nanoseconds. Chemical phenomena in the track are more complicated than the physical. The time scale of interest is longer, and more sequences of processes are involved. Biological phenomena appear to be still another order of magnitude more complicated. The very earliest chemical processes may be involved, such as the ion-molecular reaction at 10^{-14} sec

which is known to be influenced by high concentrations of chemicals, by all of the regular chemical reactions at the nanosecond time scale, and then by the chemical processes that activate enzyme systems on a still longer time scale. The nature of radiation effects on cells has been discussed by Tobias.¹⁶

Although mechanisms in radiation biology are, in general, complicated and involve interplay between chemical and biological processes, the suggestion that cell killing results from double-strand DNA breaks allows considerable simplification in a chemist's thinking about biology. A track model can be investigated on the postulate that a certain number of double-strand breaks (for example, one) cause the death of a cell.

Mechanisms of radiation damage to cells in suspension should be more understandable if radiation exposures are given in terms of the average number of particles that penetrate a cell rather than in rads. The two ways of measuring the exposure are proportional to each other. For Chinese hamster cells (CHV79) of nuclear area $4 \times 10^{-7} \text{ cm}^2$, the average number of particles, n , penetrating each cell nucleus is given by

Fig. 3. Model-calculated yield of ferrous oxidation (G values) for various particles plotted against particle energy in MeV/n. The values of LET_{∞} for neon and carbon are shown by the dashed curves and the scale on right.

(XBL 772-3081)

Fig. 4. Relative values of α (i.e., α/α_{max}) calculated from Eq. 28 with "best fit" of experimental data, the latter from Chapman et al.¹⁷

(XBL 772-3080)

$$n = \frac{D}{4LET} \quad (18)$$

where D is in rads and LET is in eV/A.

The distribution of particles penetrating a cell at any value of D is given by the Poisson distribution. Any treatment of cell survival must consider the probability distribution of cell fates resulting from various numbers of particle penetrations. Let us say that the kill probability for a single particle is p ($0 \leq p \leq 1$), the fraction of a cell that dies if one and only one particle penetrates it; of course, the survival is $(1-p)$.² From the fact that survival probabilities of cells sometimes depend on a higher power of the dose D, we know that tracks must interact in some way. Let us say that two tracks influence each other so that the survival probability is reduced from $(1-p)^2$ to $(1-p)^2(1-q)$ where q is the kill probability arising from the overlapping of two tracks. For penetration of more than two tracks, we assume that the intertrack influence is the same for each pair as if they were alone (this amounts to a neglect of higher than square dependence on D). This assumption allows us to write for the survival probability of a cell penetrated by j tracks

$$S_j/S_0 = (1-p)^j (1-q)^{j(j-1)/2} \quad (19)$$

The survival probability for any given exposure is obtained by averaging this expression over the Poisson distribution to get

$$S/S_0 = \sum_{j=1}^{\infty} \frac{1}{j!} n^j e^{-n} \frac{S_j}{S_0} \quad (20)$$

Consider the survival probability p for a cell penetrated by a single particle. As the particle goes through the cell nucleus, the probability that an event occurs that will ultimately lead to cell death is

$$-\frac{dS}{dX} = \kappa S \quad (21)$$

where κ is a constant that depends on the particle (charge, velocity, etc.). The survival probability is given by

$$\frac{S}{S_0} = e^{-\kappa L} = e^{-\rho} \quad (22)$$

where L is the average distance across the nucleus and $\rho = \kappa L$. The kill probability is $1-(S/S_0)$ or

$$p = 1 - e^{-\rho} \quad (23)$$

and $1-p = e^{-\rho}$.

The two-particle kill probability q can be obtained in the same elementary way

$$q = 1 - e^{-\sigma} \quad (24)$$

where $\sigma = \lambda L$ and $1-q = e^{-\sigma}$.

The quantities p and q are kill probabilities and are thus bounded between zero and unity. The quantities ρ and σ can be much larger than unity.

Equation 20 can be written in terms of the exponential expressions for p and q as

$$\frac{S}{S_0} = e^{-n} \sum_{j=1}^{\infty} \frac{1}{j!} (ne^{-\rho})^j e^{-j(j-1)\sigma/2} \quad (25)$$

This sum has simple closed-form expressions for various values of the parameters, in particular, for large n and small n .

A plot frequently used in evaluation of experimental data is $(\ln S/S_0)/D$ vs. D ; and, if survival is given by a quadratic expression in D as in the " α - β model," this plot becomes

$$-\frac{\ln S/S_0}{D} = \alpha + \beta D. \quad (26)$$

Using Eq. 25,

$$-\frac{\ln S/S_0}{D} \propto p + \frac{1}{2}n\sigma(1-p)^2. \quad (27)$$

Since D and n are related by Eq. 18, we can express p and q in terms of α and β as

$$p = 4\alpha(\text{LET}) \quad (28)$$

and

$$a = \frac{32 \beta (\text{LET})^2}{\{1 - 4 \alpha (\text{LET})\}^2}. \quad (29)$$

The analysis presented here allows track models to be used in the evaluation of radiobiological data, in particular, the survival of cells under heavy-particle irradiation. In general, the variation of p should be

$$p \sim 1 - e^{-a(\text{LET}) - b(\text{LET})^2} \quad (30)$$

where a and b are parameters to be determined from experiment and theory. Chapman et al.¹⁷ have presented α and β values for survival of CHV79 cells after various particle irradiations. Using Eq. 28 and a fit to the position of the maximum in the α curve, the solid curve is calculated (Fig. 4). The values of a and b obtained must be understood in terms of the track model.

CONCLUSIONS

The objective of track modeling is the interpretation of physical, chemical and biological phenomena. A successful model must be consistent with data of all three types, and we are developing a model that appears to have the required flexibility. It is important to test the model further with a broader range of physical, chemical and biological data.

REFERENCES

1. Cooper, R. D., and R. W. Woods, eds. *Physical Mechanisms in Radiation Biology*, Proceedings of CONF-721001, U. S. Atomic Energy Commission (1974).
2. Mosumder, A., A. Chatterjee, and J. L. Magee. Theory of Radiation Chemistry. IX. Model and Structure of Heavy Particle Tracks in Water. *Advances in Chemistry, Series 81*, 27-48 (1968).
3. Chatterjee, A., H. D. Maccabee, and C. A. Tobias, Radial Cutoff LET and Radial Cutoff Dose Calculations for Heavy Charged Particles in Water, *Radiat. Res.* 54, 479-94 (1973).
4. Chatterjee, A., and C. A. Tobias, *Radiation Res.*, forthcoming.
5. Kupperman, A., Ref. 1, pp. 155-176.
6. Brandt, W., and R. H. Ritchie, Ref. 1, pp. 20-46.
7. Ritchie, R. H., In: *Radiation Research, Biomedical, Chemical and Physical Perspectives* (O. F. Nygaard, H. I. Adler and W. K. Sinclair, eds.). (New York: Academic Press) pp. 315-324 (1975).
8. Fans, U., *Annual Review of Nuclear Science* 13, 1-64 (1963).

9. Lea, D. E., *Action of Radiation on Living Cells*. (Cambridge: Cambridge University Press) 1947.
10. Rossi, H. H., and A. M. Killerer, Ref. 1, pp. 224-243.
11. Wingate, C. L., and J. W. Baum, *Radiation Res.* 5, 1-19 (1976).
12. Menzel, H. G., and J. Booz. In: *Proceedings of the Fifth Symposium on Microdosimetry* (J. Booz, H. G. Ebert and B. G. R. Smith, eds.). pp. 61-75 (1975).
13. Schuler, R. H., and A. O. Allen, *J. Amer. Chem. Soc.* 79, 1565-1572 (1957).
14. Appleby, A., E. A. Christman, M. Jayko, and A. Chatterjee, forthcoming.
15. Appleby, A., and E. A. Christman, *Radiation Res.* 60, 34-41 (1974).
16. Tobias, C. A., Ref. 1, pp. 266-287.
17. Chapman, J. D., E. A. Blakely, K. C. Smith, and R. C. Urtasun, forthcoming.

CHAPTER 6

RADIOACTIVE BEAMS

Aloke Chatterjee and Cornelius A. Tobias

INTRODUCTION

Various classes of nuclear reactions have been identified and are understood to some extent for accelerated heavy particles of various energies. In the Biology and Medicine Division of Lawrence Berkeley Laboratory we are mostly concerned with projectile nuclear fragmentation through a mechanism called "grazing contact."^{1,2} According to this mechanism, there is an intermediate range of impact parameters for which the projectile nucleus comes into tangential contact with the target nucleus. During the short period of this contact ($\sim 10^{-23}$ sec), a nuclear bond may be formed between the nuclei, but the forward momentum is sufficient to break this nuclear bond. This reaction may result in single-nucleon as well as multi-nucleon transfer from one nucleus to the other. A general account of this nuclear fragmentation process is given in Chapter 4. In this chapter we will present a very special case of this general fragmentation process and its possible application in nuclear medicine.

As a result of "grazing contact" a variety of fragmented products are created from the same type of incident nucleus. When the beam particles are radioactive in nature, we call the phenomenon "autoactivation" and the fragments "autoactivated particles."³ We have studied their production, detection and physical characteristics with regard to their possible applications in medicine as described in this chapter.

There are various ways to study the problem of fragmentation. The differences in the various methods are due to different detection systems. For example, semiconductor detectors can identify fragments by observation of the energy-deposition characteristics of the main beam as well as of the fragments in these detectors and combine this information with known acceleration characteristics and cosmic-ray and particle-physics data. Such techniques have been used by Heckman et al.⁴ in a rather elaborate arrangement of semiconductors in series and by Maccabee⁵ in a somewhat simplified manner. On the other hand, in photographic emulsion studies a visual demonstration of the phenomenon of nuclear fragmentation and identification of the main beam particles as well as the fragments are made through grain-density studies.⁶ We have detected and identified the radioactive fragments by half-life determinations and the slopes of their decay curves. All of the incident nuclei studied so far have been produced at the Bevalac with beam energies between 240 and 500 MeV/n. At these energies the Coulomb barrier is of little importance, and the momentum of the fragments is predominantly in the forward direction. At low energies, however, deviations from this simple phenomenon have been observed. For example, at 10 MeV/n, Kaufman and Wolfgang¹ found that the fragments of O^{16} were distributed between 0° and 40° with respect to the initial direction of the projectile. Obviously, at these energies Coulomb potential is an important influence on the grazing phenomenon. Figure 1 is a diagram of the phenomenon of autoactivation for an individual oxygen particle colliding with resting nuclei in the absorber.

As a result of our studies, it is apparent that, after the fragmentation of an energetic beam produced in the Bevalac, it is possible to generate a clean beam of energetic radioactive particles. If these particles are obtained by stripping a neutron, positron-emitting ions result. Because the energetic radioactive particles have large atomic numbers, they also exhibit precise range-energy

NUCLEAR FRAGMENTATION

Figure 1. Schematic representation of the collision of a fast-moving $^{80}_{16}\text{O}$ particle with a resting $^{80}_{16}\text{O}$ nucleus in the target. In a glancing collision (top), radioactivity can be detected from two separate regions: (a) at the site of the collision producing target activity and (b) at the region where the parent beam stops, giving rise to "autoradioactivity." For a head-on collision (bottom), some of the possible products are indicated.

(XBL 7411-8134)

relationships. Thus, when this beam is focused on a precise location in the body, the initial result will be the highly localized injection of a positron-emitting isotope. The annihilation of the positrons generates two detectable 511-keV γ rays at nearly 180° and in time coincidence. The utilization of this localized initial distribution of positron emitters in studies related to nuclear medicine has generated considerable interest in our group, and the design and construction of an instrument to image the isotope distribution as a function of time have been initiated.⁷ When completed this instrument will find important applications in various diagnostic procedures.

EXPERIMENTAL DEMONSTRATION OF AUTOACTIVATION

Nearly parallel beams of energetic heavy nuclei were allowed to be stripped in various targets such as beryllium, lucite, polyethylene and aluminum. In each case, the targets were of sufficient thickness to stop the main beam and the different fragments under study so that they played the dual role of fragmenting the main beam and catching the fragments. The irradiation time was varied depending on the half-life of the particular fragment under study.

A preliminary experiment was done to determine whether cross sections for the multi-nucleon transfer process are large enough to permit detailed studies of their interactions and the approximate energy distribution of the products. A slab of spectroscopically pure beryllium metal (impurities less than 0.1%) was used to stop 250-MeV/n nitrogen (${}^{14}\text{N}$) particles. The slab was long enough to stop ${}^{11}\text{C}$ (half-life = 20.34 min) and ${}^{13}\text{N}$ (half-life = 10 min) particles produced in flight as a result of fragmentation of the main beam. Beryllium was selected as the target because its atomic number is lower than those of the products (${}^{11}\text{C}$ and ${}^{13}\text{N}$) under study and because it has generally low "target" radioactivity. These products are unstable and decay by positron emission. The annihilation of the positrons generates two 511-keV γ rays at nearly 180° . Activity from the beryllium catcher was analyzed by a scintillation spectrometer consisting of an 8-inch-diameter, 4-inch-thick NaI(Tl) crystal to generate the pulse height spectra shown in Fig. 2. No appreciable radioactivity was detected in the irradiated slab except in the channels set to measure annihilation radiation at 0.5 ± 0.01 MeV. Data obtained in these channels were analyzed into two components with half-lives of 20.34 and 10.1 min. These half-lives identified and confirmed the formation of ${}^{11}\text{C}$ and ${}^{13}\text{N}$ as a result of autoactivation. A typical example of the data for the decay of ${}^{11}\text{C}$ is shown in Fig. 3. The slope of the semi-log plot corresponds to the half-life of ${}^{11}\text{C}$.

We have also identified various other isotopes such as ${}^{15}\text{O}$ (half-life = 2.1 min), ${}^{17}\text{F}$ (half-life = 1.1 min) and ${}^{19}\text{Ne}$ (half-life = 17 sec) by the proper selection of incident beam particles and targets. Nevertheless, in each case these isotopes were produced in measurable quantities. In order to measure these short-lived isotopes, a special on-line counting technique was developed. It consists of an air-driven, remote-controlled device called a "rabbit" that can move the catcher in and out of the beam very rapidly. Within half of a second after irradiation is completed, counting can begin by moving the catcher into a lead-brick house and placing it between two NaI(Tl) crystals. For on-line counting, a coincidence mode is used to reduce the high background near the Bevatron.

ACTIVITY VERSUS DEPTH IN CATCHER

Our measurements of the activity at various depths in different absorbers agree with those made at low energies (10 MeV/n and less) by Kaufmann and Wolfgang.^{1,2} Autoradioactivity of accelerated particles appears as a localized peak in the region where the primary particles stop. For example, in one of the experiments performed at the Bevalac, the activity at various depths was measured with deposited ${}^{11}\text{C}$ fragments by directing a beam of ${}^{14}\text{N}$ particles toward a stack of 0.5-cm-thick beryllium discs. For each disc, the activity was measured, and the decay was followed over time to identify the

Figure 2. A typical pulse-height spectrum of an irradiated beryllium target-cum-catcher is shown. No appreciable (below background counts of 48/min) radioactivity was detected except in the channels set to measure annihilation radiation at about 511 keV.

Figure 3. A semilog plot of activity (counts/5 min) versus time (min) is shown. The slope of the line corresponds to ^{11}C activity resulting when 250-MeV/n nitrogen ions are stopped in a beryllium target. (XBL 721-2098)

fragments. As shown in Fig. 4, no measurable activity could be detected in the first 10 g/cm^2 of the beryllium catcher. Most of the activity was concentrated in a fairly sharp peak near the range of the ${}^7\text{N}^{14}$ particles. No activity was detected beyond 16.0 g/cm^2 of beryllium. The peak width arises mostly from the use of thick targets in which interactions can take place at various depths and hence at various energies.

In a similar experiment, a 220-MeV/n oxygen-16 beam was focused on a lucite (tissue-like material) target, and the activity of the fragmentation product, oxygen-15 (half-life = 2.1 min), was measured at various depths. The results are shown in Fig. 5. The location of the radioactivity peak can be compared with the Bragg peak for ionization produced by the main beam (dashed curve). In addition to the autoactivity peak, "target" radioactivity of oxygen-15 is also produced in the resting nuclei of the target, but such activity is much less than that produced in the incident nucleus. Using a 250-MeV/n oxygen-16 beam on lucite, all activity below the 5-cm depth is due to resting nuclei of the absorber (lucite contains oxygen-16).

The fragmentation of the neon-20 nucleus and the detection of autoactivated peaks of several positron-emitting isotopes were also studied. In Fig. 6, autoactivation peaks of neon-19 and fluorine-17 are shown for an incident neon-20 nucleus in beryllium. These peaks are well separated from each other even though they are adjacent to the stopping region of the neon-20 beam.

ESTIMATED CROSS SECTIONS

Through studies of the phenomenon of autoactivation, it has become apparent that if the incident nuclei are stripped of a neutron by an adequate nuclear reaction, a beam of positron-emitting ions can be generated. The energy of such a radioactive beam will depend on the thickness of the target. In order to develop a nearly monoenergetic beam, a thin target is needed. The choice of material for this target will depend on the cross section because a high-flux radioactive beam is necessary for diagnostic purposes. In addition, the dependence of the cross section on the energy of the incident nucleus will provide some important information on the fundamental aspects of nuclear fragmentation.

So far, we have obtained cross-section data that are averaged over a large path length and hence over a large energy range; however, such a cross section may not be too far from the thin-target cross section for the following reasons: (1) as the energy of the incident nucleus decreases, the cross section reaches a maximum, and hence the average cross section over a thick target is expected to be larger than the thin-target cross section; (2) fragments produced in the initial stage of the projectile's flight path are more likely to be further fragmented, hence reducing the thick-target cross section compared to the thin-target cross section. Because these two effects are in opposite directions, the actual cross section may not be too different. Further studies are needed to verify this conclusion.

As mentioned earlier, at present we have only thick-target cross sections. The cross-section values have been obtained by analysis of the activity data and incident flux. Table I gives the various thick-target cross sections for different incident particles and different products using beryllium as the target. At present, it is not clear why the cross section for ${}^7\text{N}^{13}$ is smaller than that for ${}^6\text{C}^{11}$. If it is associated with the fact that there is a loss of ${}^7\text{N}^{13}$ due to further fragmentation and subsequent production of ${}^6\text{C}^{11}$, the absolute cross sections for the production of ${}^{10}\text{Ne}^{19}$ and ${}^9\text{F}^{17}$ are puzzling. Obviously more experiments with both thick and thin targets are needed. If we confirm the present data, the problem of projectile fragmentation will become even more interesting from the fundamental point of view.

Figure 4. The distribution of ^{11}C activity at various depths in a beryllium target is plotted for an incident nitrogen beam of range 13 g/cm² in beryllium.
(XBL 754-1001)

Table I. Thick-target cross sections for the production of nucleon-transfer products* from $^7\text{N}^{14}$ and $^{10}\text{Ne}^{20}$ beams on beryllium targets. Listed in each case are the observed reaction product and the cross-section σ in millibarns.

Reaction Loss of Projectile	$^7\text{N}^{14}$ Beam [†]	$^{10}\text{Ne}^{20}$ Beam [‡]
(-n)	$^7\text{N}^{13}$, 6 ± 1.5	$^{10}\text{Ne}^{19}$, 23 ± 4
(-p2n)	$^6\text{C}^{11}$, 17 ± 4	$^9\text{F}^{17}$, 11 ± 2

* No attempt was made to investigate products that are formed by the pick-up of nucleons from the target.

[†] Range in beryllium = 7.03 cm.

[‡] Range in beryllium = 9.61 cm.

Figure 5. The distribution of radioactive fragments (^{15}O) at various depths in a lucite absorber for an incident ^{16}O beam (220 MeV/n) is shown by the continuous line in the diagram. In addition to the autoactivation peak, constant activity due to target activation is seen. The Bragg ionization curve is presented by the dashed line. (DBL 729-5497)

Figure 6. Autoactivation peaks for various fragments identified by decay curves are shown for an incident neon-20 nucleus in beryllium. The range of the beam in beryllium was 9.6 cm. (XBL 7411-8135)

DOSE DISTRIBUTION

In order to calculate LET distribution at various penetrating depths and to estimate dose due to nuclear secondaries, we need information on fluence distribution at these depths. We have made some theoretical estimates of the distribution of forward secondaries in monoenergetic heavy-ion beams. Because of their characteristic shape, we call these "dome distributions."

Let $\phi_p(x)$ denote the fluence of primary heavy ions at a penetration depth x . Through nuclear interaction some of the incident particles are removed from the primary beam. Let the macroscopic total cross section for removal of a primary from the incident beam be represented by σ_p (assumed constant with respect to energy). For a medium of mixed nuclear species, e.g., water,

$$\sigma_p^{H_2O} = N_H \sigma_p^H + N_O \sigma_p^O \quad (1)$$

where N_H is the number of hydrogen atoms present per unit volume and σ_p^H is the macroscopic total cross section for primary-beam interaction with hydrogen. Similarly, N_O is the number of oxygen atoms per unit volume, and σ_p^O is the primary-beam interaction cross section. The rate of removal of primary particles from the beam is given by

$$d\phi_p/dx = -\sigma_p \phi_p(x) \quad (2)$$

A solution of this equation,

$$\phi_p(x) = \phi_p(0) \exp(-\sigma_p x), \quad (3)$$

represents the primary fluence at a depth x . Owing to the loss of primary particles, secondary fragments are produced, and the rate of production of type- f fragments is given by

$$d\phi_f(x)/dx = \phi_p \sigma_{pf} \quad (4)$$

where $\phi_f(x)$ is the secondary fluence at a depth x and σ_{pf} denotes the macroscopic partial cross section for production of secondary fragments of type f .

In the event that the loss of secondary fragments through nuclear interaction can be neglected,* the solution of Eq. 4 can be given as

$$\phi_f(x) = \phi_p(0) [1 - \exp(-\sigma_p x)] [\sigma_{pf}/\sigma_p] \quad (5)$$

The ratio σ_{pf}/σ_p represents the frequency at which a fragment of type f is produced per collision, which removes a primary.

Because both the primary particles and the secondary fragments are charged particles, they interact very strongly with the medium electrons and hence lose energy to the medium. Thus, they have a definite range in a stopping medium depending on their charge and kinetic energy. If we neglect range straggling, which is not far from reality, primaries that survive nuclear interactions are finally removed at range R_p , i.e.,

$$\phi_p(x) = 0 \text{ for } x > R_p \quad (6)$$

* A more complete study considering the loss of secondary fragments through further nuclear interactions is in progress.

Secondary fragments are assumed to be produced at the same velocity that the primary particles have at the point of fragment production. These fragments can have greater or smaller ranges than the residual range of the primary beam. Generally, they will have a greater range than the primary because ranges of fast heavy charged particles (at the same velocity) scale as (A/Z^2) where A is the atomic mass and Z is the nuclear charge. In the case of a neutron-stripping interaction, the charge remains the same so the range of the secondary is less than that of the primary from the point of production.

If we denote the ratio of the range of the secondary fragment to the range of the primary as η_f , we have from the simple scaling law

$$\eta_f = R_f/R_p = (A_f/A_p)(Z_p/Z_f)^2 \quad (7)$$

Considerations such as these lead to the conclusion that there is a build-up in the secondary fluence by fragmentation of primaries up to range R_p where all of the primaries disappear. Then there is a continuous drop in the secondary fluence as they are removed at the end of their respective ranges. The maximum penetration of a type-f fragment is given by its own range. Fragments produced deeper in the medium will have smaller penetrations, the minimum penetration being that of a fragment produced just as the primary energy is less than the Coulomb barrier. Because a majority of the fragments will penetrate deeper than the primary, it is of interest to calculate the flux of such secondaries beyond the primary range.

The fragments of type f are produced at an arbitrary penetration depth x ; the range of these fragments is given by $\eta_f(R-x)$ where $(R-x)$ is the residual range of the primary particles at the point of their interaction. If we assume that the fragments are not lost through nuclear interaction (tertiary process), they will stop at a depth x' given by

$$x' = x + \eta_f(R-x) \quad (8)$$

Through a procedure similar to the one outlined above, for the secondary fluence at any depth beyond R , the range of the primary beam, it can be shown that

$$\phi_f(x) = \phi_p(0) [1 - \exp(-\sigma_p \eta_f(R-x)/(\eta_f-1))] [\sigma_{pf}/\sigma_p] \quad (9)$$

for $x \geq R$.

Equation 5, which is valid for $x \leq R$, and Eq. 9, which is valid for $x \geq R$, represent the theoretical analysis of the dome distribution. Several different types of fragments will be generated, producing a family of dome-distribution curves characterized by different values of the maximum range $\eta_f R$ and the maximum fluence proportional to the parameter (σ_{pf}/σ_p) .

From the flux distribution of secondaries, the dose distributions at various depths can be calculated easily by multiplying the fluence by the LET corresponding to their residual energy at any given depth. An example is shown in Fig. 7, which gives the dome distributions for various secondary fragments generated by a 275-MeV/n nitrogen-14-ion beam penetrating water. The range of such a beam is 12.55 cm. Dome distributions were computed using the fragmentation parameters (σ_{pf}/σ_p) and range ratios given in Table II. The distribution of momentum exchange between parent and daughter fragments and the angular distribution of fragments as well as the cross-section changes will modify the distributions in Figs. 7 by broadening them. Experimental and theoretical work is expected to be done along these lines. One cannot obtain specific data on various isotopes from the emulsion data. The fluence of each secondary component is plotted on the upper graph of Fig. 7 as a fraction (percentage) of the incident primary

Fig. 7. Calculated values for the dome-dose distribution due to secondary fragments in the ${}^{14}_7\text{N}$ beam are shown in the bottom panel; various peaks appear in close proximity to the Bragg peak of the primary beam. Estimated values for fluence distribution are shown in the top panel for fluence of nuclear secondaries generated in water by a ${}^{14}_7\text{N}$ beam of 12.5-cm range; heavy fragments stop near the range of the parent beam. (DBL 733-5078A)

Table II. Fragmentation parameters and range ratios used to compute the dome distributions of Figure 7 for various fragments.

	${}^{13}_7\text{N}$	${}^{13}_6\text{C}$	${}^{12}_6\text{C}$	${}^{11}_6\text{C}$	${}^{10}_5\text{B}$	${}^4_2\text{He}$	${}^1_1\text{H}$
$\sigma_{\text{nf}}/\sigma_{\text{p}}^*$	0.18	0.18	0.25	0.03	0.10	0.50	0.75
Range Ratio (η)	0.93	1.26	1.17	1.07	1.40	3.50	3.50

* Not normalized.

fluence versus depth of penetration in water. The arrow indicates the range of the incident primaries. The lower curves in Fig. 7 represent the composite dose distributions of the secondary nuclear components as a function of depth in water. Because it contains stopping particles of nitrogen, carbon and boron near the Bragg peak of the primary beam, the average LET is fairly high there. Dose contributions from head-on collisions are small because of the small cross sections of the particles, and dose contributions from local stars are also relatively small because these are distributed along the entire beam range.

An example of the application of the dome distribution to real data is shown in Fig. 8. The closed circles are experimental data measured by Maccabee et al.⁸ The ordinate is the number of carbon secondaries identified at a given depth of penetration in water normalized per 26,769 oxygen ions incident at 250 MeV/nucleon. The solid line is a theoretical fit to the data using the dome-distribution expression. No experimental results are currently available to verify the dome-distribution expression beyond the range of the incident particle.

BIOMEDICAL STUDIES WITH IMPLANTED RADIOACTIVE BEAMS ($^{19}_{10}\text{Ne}$ RADIOACTIVITY IMPLANTED IN THE BRAIN)

One simple initial experiment has been carried out to demonstrate the feasibility of the beam implantation technique in diagnostic procedures. A live rabbit was irradiated with a beam of $^{19}_{10}\text{Ne}$ (half-life = 17.2 sec). The beam was stopped in a selected portion of the brain (see Fig. 9a). The count rate of a coarsely collimated, coincidence gamma-ray detector was recorded as a function of time during and after the irradiation. As shown in Fig. 9b, the count rate increased with the time of irradiation. Irradiation was terminated at $t = 33$ sec, and the number of positron annihilations per unit time occurring in the region observed by the detector began to decrease as a function of time. A similar experiment was carried out with the same but sacrificed rabbit. The results of our study are shown in Fig. 9c. The radioactive decay of the short-lived isotope is quite evident in both curves, but in Fig. 9b (live animal) there is a well defined increase in the rate of decay between $t = 34$ and 40 sec. Such a rate is much faster than the normal radioactive decay. After $t = 40$ sec, the decay in activity seen in Fig. 9b is due to $^{19}_{10}\text{Ne}$ embedded in tissue as the slope corresponds to 17.2 sec. The faster drop is directly attributable to the blood flow from the region of the brain coarsely delimited by the geometry of the experiment.

Although preliminary, our studies do indicate the potential usefulness of the radioactive-beam implantation technique. More studies with such beams are needed before they will be useful for human patients. Dr. Grant E. Gauger, Assistant Professor of Neurological Surgery, University of California, San Francisco, participates in these experiments, and his enthusiasm is a key factor in the development of the technique. Al Smith of the LBL Health Physics Division is to be credited for the physics work with the rabbit exposures.

DISCUSSION AND CONCLUSIONS

It is clear that energetic radioactive beams can be generated through the process of nuclear fragmentation in measurable quantities. A good rule of thumb is that about one percent of the parent beam can be converted to a particular radioactive beam. With Bevalac intensities, the available radioactive-beam flux will be adequate for diagnostic studies.

Because the charge-to-mass ratio of radioactive fragments is often different from that of the parent nucleus, radioactive fragments can be separated from the main beam by deflection in appropriate magnetic channels. This principle has already been used by Heckman's group, and, with their help, a small deflected oxygen-15 beam (approximately 80-percent pure) was produced at the Bevatron before the Bevalac began operating. Using oxygen-16 from the Bevalac, a much higher-intensity oxygen-15 beam can be produced. The phenomenon of autoactivation thus provides a technique for obtaining high-energy radio-

Figure 8. One section of the dome-distribution curve representing the rise of carbon secondaries before the range of the parent 250-MeV/n oxygen ions in water is given. Solid curves represent the experimentally measured values obtained by Maccabee et al.⁸ (DBL 734-5149)

Figure 9. (a) Implantation of $^{19}\text{Ne}_{10}$ radioactivity beam in a selected position in a rabbit's brain. (b) Two components of the decay curve (after 33 sec) showing blood flow and natural decay. (c) Same animal but after being sacrificed showing one component corresponding to the physical decay process only.

[(a) XBL 773-634; (b) 773-635; (c) 773-636]

active beams not heretofore possible. Such beams will be extremely useful for diagnostic procedures in heavy-ion radiation therapy and nuclear medicine.

The lack of exact diagnostic knowledge of the position of the Bragg peak has hindered therapeutic procedures in the past. Exact calculations are impractical because of intervening bone, tissue, air, etc. By generating autoactive beams in a small thickness of absorber upstream from the exposure room, we will be able to determine the range penetration in a patient and hence the stopping power.

During the initial period of heavy-ion therapy, we anticipate that stable nonradioactive beams of, for example, $^{20}_{10}\text{Ne}$ or $^{38}_{18}\text{Ar}$ will be used. The autoradioactivity of accelerated particles appears as a localized peak of radioactivity in the region where the primary particles stop in an exact measurable relationship to the location of the Bragg ionization peak. Thus the Bragg peak of the therapeutic beam can be rather precisely localized.

Later in the program, it should be feasible to deliver therapy with pure autoradioactive beams if the primary nonradioactive beams can be increased to 10^{10} or 10^{11} particles per pulse. Such beams should become possible in the course of Bevalac development as a consequence of improved vacuum and HILAC ion sources.

In addition to localization of the Bragg peak with respect to heavy-ion therapy, radioactive beams will find important diagnostic applications. For example, a single pulse of a monoenergetic beam can be stopped in a small region inside the human heart. The time required might be as little as one millisecond. A radioactive bolus will be formed, some part of which will be carried with the streaming blood. An appropriate counting procedure for observing passage of the radioactivity will result in measurements of blood flow and heart-valve action. Such techniques could also be applied in the carotid artery to measure cerebral blood flow and perhaps elsewhere. The autoradioactive-beam technique might eliminate the necessity of arterial puncture catheterization and could reduce the injection time to less than that of currently used techniques.

We have already done some preliminary studies of cerebral blood-flow measurement using rabbits. Results show great promise for this technique and will be reported soon after further confirmation of the data is obtained.

FUTURE STUDIES

Variation of Cross Section with Energy

Using stable isotopes such as $^{12}_6\text{C}$, $^{16}_8\text{O}$, $^{20}_{10}\text{Ne}$ and $^{40}_{18}\text{Ar}$ from the Bevalac, we plan to measure thin-target cross sections. Measurements will be made on both short- and long-lived radioisotopes. For a given fragment, various incident beams will be studied with different targets. The targets will include elements with low and high atomic numbers. The energy distributions of the fragments will be determined.

Radioactive Beams

The above cross-section data will be useful in obtaining various radioactive beams. One of the requirements of such beams is no or very little spread in beam energy. This work will be done in collaboration with Hermann Grunder and Harry Heckman of LBL.

Localization of the Bragg Peak

We have just completed construction of a positron-emitter, beam-imaging device. With this device we will attempt to measure the range of an energetic heavy-particle beam in living specimens. In addition to range, we will obtain information on electron density along the trajectory of the particles, that is, stopping-power information for particles penetrating through nonhomogeneous matter such as in

a patient. This information will then be used for actual therapy with a predetermined beam. When the HILAC is able to accelerate particles up to uranium in sufficient flux, through the phenomenon of autoactivation we will be able to produce numerous long-lived radioactive beams. ^{19}F has already been identified in our studies.

Gamma-ray Camera

Over the past several months, we have been engaged in constructing a special gamma-ray camera for localization of the stopping region of a monoenergetic beam within the body. Dr. Jorge Llacer of the instrument research group at LBL has been collaborating with us on this project. The camera, which should be completed by April 1977, has two arrays of crystals arrayed in such a manner that they can detect the location of a point source with optimum efficiency. The camera is designed to acquire large amounts of data in times on the order of half a second each. The data are first held in the memory of a computer and later transferred to a disk. This apparatus will allow us to not only localize the distribution of stopping points but make accurate measurements of translocation of particles due to circulation and other forms of transport.

Measurement of Local Blood Circulation

Because of their precise range-energy relationships, energetic radioactive particles can be deposited at any desired position in the human body. The time required might be as little as one millisecond. A radioactive bolus will be formed; some part of this will be carried away with the streaming blood. The use of an appropriate counting apparatus to observe passage of the radioactivity could result in measurement of blood flow and biological functioning of the local region.

In one of our preliminary investigations of cerebral blood flow rate, ^{19}Ne particles were used to irradiate the brain of a rabbit. Elimination of these particles with the flow of blood could be easily separated from the physical decay process, thus enabling us to measure quantitatively the blood flow rate and the blood volume in the local region. Whereas use of ^{19}Ne may provide information on the diffusion effect, use of ^{15}O may lead to the determination of exchange effects with water molecules. Without the use of radioactive beams, no other technique is available at present that will provide information about the functioning of local regions in a living system.

Carotid Artery and Symmetry of Circulation

A burst of a radioactive beam can be made to stop in an appropriate region of the carotid artery. Radioactivity will flow into the two hemispheres of the brain, and under normal conditions the radioactivity should be identical in the two hemispheres. Any abnormality will result in asymmetrical behavior of the radioactivity in the two hemispheres and hence different count rates.

Arteries--Rate of Blood Flow

Local blocking of passage through an artery can be detected by depositing radioactive particles at one place and noting the arrival of activity in another place.

Elementary Interactions

Since 70 to 80 percent of the body is water, we can postulate the nature of elementary interactions as

If these reactions occur in pure water, they would be ready sources of formaldehyde and carbon monoxide. We plan to verify these processes and obtain appropriate yields by passing a radioactive C^{11} beam into a reaction vessel with pure water and analyzing the radioactive products.

Many other reactions are possible. For example, in the presence of oxygen, $^{11}CO_2$ may form directly. The free radical $^{11}C\cdot$ might also interact with the other free radicals, $H\cdot$ and $OH\cdot$, that are in the path of the ionizing track.

If ^{11}CO has formed by interaction with water, it will be an interesting opportunity to observe the intracellular reactions of this substance in cells. We know, for example, that myoglobin, cytochrome A_3 , and P450 interact with carbon monoxide. We might attempt to characterize various fractions of macromolecules that interact and to observe the partition of CO between these fractions. Eventually, it will be possible to observe the carbon monoxide generated in cells in the hemoglobin of the blood and in exhaled air.

$^{11}C\cdot$ will also interact with organic compounds in living cells.

The case of $^{13}N\cdot$ is equally interesting; we anticipate formation of $^{13}NO\cdot$ and an opportunity to trace the behavior of this toxic substance in tissues.

$^{15}O\cdot$ may participate in many processes. It might be possible to trace the autoxidation of lipid membranes and the removal of oxidized lipids, a process that is known to occur but where very little data are available.

^{19}Ne is an inert gas. It will diffuse freely through aqueous and lipid layers of cells and may allow the determination of some diffusion and transport coefficients.

Radiopharmacology

For a number of years it was of interest in nuclear medicine to synthesize rapidly compounds that contain the ^{11}C isotope, particularly nucleic-acid precursors. Whereas good progress has been made with target radioactivity, the relative slowness of synthetic steps has been a drawback. It is possible that the availability of "hot" radioactive free radicals might accelerate and facilitate the synthesis of some interesting compounds.

We can ask whether or not cyanide forms if we send a beam of ^{11}C into frozen or liquid ammonia

If labeled cyanide is easily available, as we already know from the work of Steinman and Calvin it can be a starting point for the production of a variety of compounds, for example, purines. This particular aspect of the project will be studied in collaboration with Dr. Bengt Langstrom, University of Uppsala. Dr. Langstrom is experienced in radiochemistry and is currently working with our group. Collaboration with Professor Larson, University of Uppsala, will be particularly profitable owing to his vast experience in this field.

REFERENCES

1. Kaufman, R., and R. Wolfgang. Nuclear transfer reactions in grazing collisions of heavy ions. *Phys. Rev.* 121, 192 (1961).
2. Kaufman, R., and R. Wolfgang. Single-nucleon transfer reactions of F^{19} , O^{16} , N^{14} , and ^{12}C . *Phys. Rev.* 121, 206 (1961).
3. Tobias, C. A., A. Chatterjee and A. R. Smith. Radioactive fragmentation of N^{7+} ion beam observed in a beryllium target. *Phys. Letters* 73A, 119 (1971).
4. Heckman, H. H., D. Greiner and P. Lindstrom. Fragmentation of nitrogen-14 nuclei at 2.1 GeV per nucleon. *Science* 174, 1130 (1971).
5. Maccabee, H. D. Composition of high-energy heavy-ion beams: Preliminary measurements. *Radiat. Res.* 54, 495 (1973).
6. Fowler, P. H., R. R. Hiller and C. J. Waddington. Interactions of the heavy nuclei of the cosmic radiation. *Phil. Mag.* 2, 293 (1957).
7. Llacer, J., A. Chatterjee, G. E. Gauger, C. A. Tobias and F. Goulding. Theory and design parameters for a positron-emitter beam-imaging device for biomedical research. In preparation.
8. Maccabee, H. D., and M. A. Ritter. Fragmentation of high-energy oxygen-ion beam in water. *Radiat. Res.* 60 409 (1974).

CHAPTER 7

CELLULAR AND MOLECULAR RADIOBIOLOGY OF HEAVY IONS

Cornelius A. Tobias, Eleanor A. Blakely and Ruth J. Roots

Contents

- I. Introduction
 - A. Statement of the Problem as Applied to Cancer Therapy
 - B. Statement of the Fundamental Problem
- II. Techniques and Overview of Work Completed
- III. Summary of Data
 - A. Monolayer Experiments
 - 1. Relative Biological Effectiveness (RBE)
 - 2. Oxygen Enhancement Ratio (OER)
 - B. Suspension Experiments
 - 1. Radiation Modifiers
 - 2. Synchrony
- IV. Analysis of Monolayer Data
 - A. Models
 - B. Interpretation of the Survival Data at the Extended Bragg Peak
- V. Additional Cellular and Molecular Experiments with Heavy Ions
 - A. Comparative Depth-dose Studies
 - B. Studies on the Argon Beam
 - C. Tumor Cells
 - D. Hyperthermia
 - E. Molecular Studies
 - 1. Results with Low-energy Ion Beams
 - 2. Results with High-energy (≥ 400 MeV/amu) Ion Beams
- VI. The Future - Summary of Plans
 - A. Survival Studies of Various Cell Strains
 - B. Continuation of Studies of the Age Response to Heavy Ions
 - C. Differences in Heavy-ion Radiosensitivity Between Normal and Tumor Cells
 - D. Mechanisms of Chemical and Physical Radiation Modifiers
 - E. Spheroids
 - F. Repair
 - G. Molecular Mechanisms
 - 1. Inhibition and Augmentation of Repair I
 - 2. Identification of Repair II
 - H. Lethal Effect: Double-strand Break or Misrepair?
 - I. Cytogenetics of Heavy Ions
 - J. Mechanism of Viral Transformation
 - K. Mechanism of Membrane Injury - Neurons
 - L. Epilogue

I. INTRODUCTION

A. Statement of the Problem as Applied to Cancer Therapy

The rationale for the use of heavy ions in cellular radiobiological research directed toward improved cancer therapy is based on a variety of findings gained from experiments at low energies including the following:

- Heavy ions decrease the radiobiological oxygen effect at the cellular level.
- Heavy ions decrease sensitivity variations during the cell division cycle.
- Heavy ions reduce repair.
- Cells of abnormally large nuclear cross section appear to have greater sensitivity to heavy ions than do normal cells; many varieties of cancer produce aneuploid cells of abnormal DNA content.
- Heavy ions retain most of the depth-dose advantages of protons and helium ions.

All of these parameters must be considered together in a realistic and complete evaluation of the therapeutic potential of each of the high-LET radiation modalities. Since the Bevalac was completed two years ago, a vigorous effort has been made to analyze radiobiological properties of cells in culture and to relate these properties to the requirements of therapy.

B. Statement of the Fundamental Problem

Heavy particles such as protons and higher-atomic-number elements have rather unique physical properties. They undergo very little scattering from their initial trajectory and have very precise range-energy relationships. The extent of interaction between matter and heavy penetrating particles increases with decreasing velocity and shows a maximum effect just before these particles are brought to rest. Compared to electrons, heavy particles have much higher values of linear energy transfer (LET) and are sometimes referred to as high-LET particles. In addition to these important advantages, heavy particles are expected to demonstrate desirable radiobiological advantages, which will make them especially attractive for radiation therapy. Before these high-LET particles can be used for such purposes with confidence, various relevant radiobiological parameters must be known for different therapeutic situations.

There are two aspects of the problem that we have addressed, and experiments at the Bevalac have been designed accordingly. One aspect is an understanding of the basic mechanism involved in cell killing by ionizing radiation, and the other aspect is the analysis of radiobiological properties of cells in culture with reference to high-LET particles and the relationship of these properties to the requirements of therapy. Obviously, these two aspects are interrelated with a common goal, namely, the optimal use of high-LET particles in therapeutic procedures.

It is well known that the distribution of energy in space by the passage of a heavy particle is rather nonuniform; hence the chemical stage that follows immediately after the initial absorption of energy has to deal with reactive species that are distributed in a nonhomogeneous manner (see Chapter 5). It is obvious that this distribution will be directly related to the energy and atomic number of a particle, and, therefore, it is important that a large variety of different heavy particles should be available for a reasonable understanding of the problem. Because heavy nuclei undergo nuclear fragmentation (see Chapter 4) and are thus diluted with lower-atomic-number particles, the problem becomes even more complicated. At present, however, a quantitative evaluation of the experimental data should form the basis of treatment planning as long as these data are obtained using a variety of heavy particles.

It is very seldom that a therapist would treat a patient with monoenergetic heavy particles. With such particles, the Bragg peak is very narrow, and hence either the treatment volume must be scanned with a monoenergetic beam or the beam must have adequate spread in energy (extended Bragg peak) to cover the whole tumor. With the Bevalac beams, efforts are being made according to the latter method. Thus, therapeutically relevant radiobiological data should be obtained with extended Bragg peaks.

Because of a possible role in therapy, external chemical modifiers of biological lesions are of great concern in the understanding of molecular mechanisms of damage. It is of interest to know whether the modifiers act on the initial fast radical reactions, on macromolecular long-lived states, or on the repair mechanism. The results of carefully planned experiments will help us evaluate this fundamental problem.

In accordance with the above-mentioned problems, we have been performing experiments with Bevalac ions. In this chapter, we report our data obtained with human kidney and Chinese hamster cells under various beam conditions. A complete analysis of the data will require more time, but we have already learned a great deal about the effectiveness of various high-LET particles. On the basis of our present analysis, we believe that RBE and OER at the 10-percent or any other survival level may not be very useful in evaluating the therapeutic potential of a given beam and that these should be replaced with other more appropriate parameters (see section IV below).

The Bevalac is a national facility, and therefore investigators from many groups across the country and abroad have taken the opportunity to study these unique high-energy, heavy-ion beams. A brief review of their cellular and molecular results is included here.

II. TECHNIQUES AND OVERVIEW OF WORK COMPLETED

Table I is a summary of cell experiments completed at the Bevalac since Fall 1974. Eight LBL staff members (E. A. Blakely, S. B. Curtis, J. T. Leith, A. Rodriguez, R. J. Roots, T. S. Tenforde, C. A. Tobias, T. C. H. Yang) and D. Chapman, on sabbatical leave from WNRE-AEC Canada, have conducted cell experiments with these particle beams. Eight graduate students have participated in thesis-oriented cellular research with heavy-ion beams (F. Abrams, D. Kalofonos, J. Risius, M. Ritter, P. Ross, R. Roisman, W. Schilling, M. Yezzi).

Investigators from six other institutions (University of California, San Francisco, Medical School, Colorado State University, Columbia University, Institute Gustave-Roussy in France, Los Alamos Scientific Laboratory, University of Arizona Medical School) have broadened the scope of studies to include loss of reproductive integrity in two additional mammalian cell lines (Chinese hamster ovary and EMT-6 mammary mouse tumor). Data from both in vitro and in vivo cell studies are included in the summary in Table I for completeness, but a more extensive description of in vivo results will be found in Chapter 9.

Six different cell systems (human kidney T-1, hamster V-79, rat brain tumor, rhabdomyosarcoma, tumor R-1, mouse 3T3 cells) have been used to assay radiation-induced effects including loss of reproductive integrity, the oxygen effect, the effects of radiation modifiers, effects on synchronized cells, enhancement of viral transformation, and the relationship of DNA strand breakage to cell lethality.

A variety of techniques have been used in the cellular investigations including the following:

- (1) Exposure of cells in *monolayers* contained in controlled-atmosphere chambers.^{1,2}
- (2) The use of cells *suspended in nutrient medium* of low calcium content and controlled atmosphere.³
- (3) Suspended cells in sealed vials in a state of hypoxia due to *metabolic depletion*.⁴
- (4) The *submarine*, a tissue phantom consisting of multiple stacks of cells mounted on monolayers and suspended in liquid medium with cells exposed to various parts of the Bragg ionization curve simultaneously.⁵
- (5) The *jello submarine* in which cells are suspended in a gelatin matrix.⁶
- (6) Measurement of DNA strand breaks by *sucrose-gradient centrifugation*.^{7,8}
- (7) Measurement of single- and double-strand DNA breaks by *mild alkaline uncoiling* combined with ion-exchange chromatography.⁹
- (8) Combined application of *drugs, hyperthermia, time delay, and radiation*.^{3,10}

TABLE I. Summary of cell experiments completed at the Bevalac since Fall 1974.

Cell System	Techniques	Assay	OER Data?	Ion	Ridged Filter?	References
<i>T-1 in vitro:</i>	Monolayer	Reprod. integ.	Yes	C,Ne,A	10-cm brass + 4-cm Pb	2
	Jello submarine	Reprod. integ.	No	C,Ne,A	10-cm brass + 4-cm Pb	3,27,29
	Monolayer	DNA SSB	No	C,Ne,A	No	42
<i>CH-V79 in vitro:</i>	Suspension (15mm wide)(sensitizers and protectors)	Reprod. integ.	Yes	C,Ne,A	4-cm Pb + 10-cm brass	3
	Sealed capsules (2-4mm wide)	Reprod. integ.	Yes	A	No	4
	Monolayer (synchr.)	Reprod. integ.	No	A	No	32
	Sealed capsules (2.5mm wide)	Reprod. integ.	Yes	C,Ne,A	10-cm brass	29
	Suspension (15mm wide)	DNA SSB	No	C,Ne	10-cm brass	42
<i>CHO in vitro:</i>	Monolayer (hyperthermia)	Reprod. integ.	No	C	No	38
<i>EMT-6 tumor:</i>	In vivo	Reprod. integ.	No	C,Ne,A	4-cm Pb + 10-cm brass	26
	In vitro (sealed capsules, 2ml size)	Reprod. integ.	Yes	C,Ne,A	4-cm Pb + 10-cm brass	36
	Monolayer	Division time	No	Ne	No	60
<i>Rat brain tumor:</i>	In vivo	Reprod. integ.	Yes	Ne	No	61
<i>R-1 rhabdomyo-sarcoma:</i>	In vivo (suspension - 15mm)	Reprod. integ.	No	C,Ne,	4-cm brass	65,66
	In vitro (suspension - 15mm)	Reprod. integ.	Yes	C,Ne,A	4-cm Pb + 10-cm brass	62
<i>Mouse 3T3 in vitro:</i>	Monolayer	Enhancement of viral transformation	No	Ne	No	63
<i>Rabbit retina:</i>	In vivo and In vitro	DNA SSB	No	Ne	No	43

III. SUMMARY OF DATA

A. Monolayer Experiments

Track-segment cell-survival studies in the Bevalac beams have to date been done chiefly with human kidney T-1 cells. We chose T-1 cells that originated in the laboratory of G. W. Barendsen for these investigations in view of their extensive use in studies of survival kinetics for x rays, neutrons, and low-energy heavy ions.^{1,2,11,12,57} Survival in air and in nitrogen of exponentially growing cells was measured at frequent points along the range of monoenergetic carbon-, neon- and argon-ion beams. Generally, survival curves at the "plateau," several centimeters from the Bragg peak, have an exponential component as well as "shoulders" and, therefore, at least two components of cellular inactivation. At the Bragg peak, survival is almost purely a simple exponential curve of the dose with the RBE rising monotonously from plateau to peak. As examples, survival curves are shown for a 400-MeV/amu carbon beam at the plateau and for a 500-MeV/amu argon beam near the Bragg peak in Fig. 1.

Fig. 1. Survival curves for oxalic and hypoxic exposures of T-1 human kidney cells to: (A) 400-MeV/amu carbon beam at the plateau; (B) 557-MeV/amu neon beam near the Bragg peak. OSR-dose plots accompany each set of curves. (XBL 773-3240)

Interpretation of survival data becomes complex because a beam that emerges from the Bevalac as a pure monoenergetic stream of particles fragments upon interaction with target nuclei. The heavy and light secondary particles that result are generally of lower linear energy transfer than the parent beam, and these fragments modify the biological effects. Figure 5 of Chapter 3 shows an argon Bragg curve with the secondaries included. The physics of the fragments is under intensive study (see Chapters 2 and 4), for our current description of these fragments is far from complete. In a monoenergetic neon beam of 15-cm range, fragments exert probably less than 10 percent of the biological effects. In an argon beam near the Bragg peak, nearly 40 percent of the biological effects can be attributed to the fragments.

When a given flux of particles impinges on a "submarine," the "depth-survival" relationship characteristic of the beam can be measured. In Fig. 2 we show depth survivals for T-1 cells in a beam of oxygen nuclei (A) and in a beam of 15-MeV neutrons (B) at the Lawrence Livermore Laboratory. The remarkably high effectiveness of oxygen particles is clearly evident by the sharp inverse lethality peak at the place where the oxygen particles stop. On the other hand, neutrons appear to be rather ineffective in killing cells at deeper penetration depths although many cells are killed near the surface.

1. Relative Biological Effectiveness (RBE)

The biological effectiveness of high-LET radiations is generally greater than that of low-LET radiations. The relative biological effectiveness (RBE) is defined here as the dose ratio of the standard 220-kVp x rays (A) to the tested beam (B) at the 10-percent survival levels as follows:

$$RBE_{0.1} = \frac{\text{Dose A}}{\text{Dose B}} \quad (1)$$

Fig. 2. Depth-dose cell survival for human kidney T-1 cells irradiated in a submarine phantom with an entrance dose of approximately: (A) 200 rads of 260-MeV/amu oxygen ions; (B) 400 rads of 15-MeV/amu neutrons.

(DBL 733-5080) (XBL 754-937)

Table II gives a summary of RBE's for kidney cells irradiated in air at positions depicted in Fig. 3. Figure 4 shows RBE's for cells irradiated in nitrogen. Both in air and in nitrogen, the RBE's rise with decreasing residual range of the heavy ions; however, the increase of RBE in nitrogen atmosphere is more dramatic than that in air. Neon ions at the Bragg peak have a hypoxic $RBE_{0.1}$ of 6.3, but in air the $RBE_{0.1}$ is only 2.4. If we eliminate the effects of fragments, it is clear that "pure" carbon and argon particles also have very high RBE's.

In order to effectively spread the effects of particle beams, it is necessary to use mixed rather than monoenergetic beams. Currently, we are using mixed beams that result when a rotating ridge filter, designed by J. T. Lyman, is interposed between the Bevalac and the cells to be irradiated. These filters are described in more detail in Chapter 3.

At the present stage of development, we are striving to develop filters that produce "isosurvival" over a certain depth interval and that decrease the oxygen effect as much as possible. During the last few months various ridge filters have been used by several investigators with several types of biological materials. The data show certain trends but are not always in complete agreement. Further development of filters and biological techniques is necessary before we have complete information for the radiotherapist.

TABLE II. Summary of relative biological effectiveness (RBE) values at the 50-percent and 10-percent survival levels as a function of depth for human kidney T-1 cells in monolayer experiments irradiated in air with helium, carbon, neon and argon beams (Blakely et al.).

Ion	Surviving fraction	Plateau → Bragg peak (see Fig. 3)										Range (cm H ₂ O)
		0	A	B	C	D	E		G	H	K	
Argon (500 MeV/amu)												12.2
	0.5	2.1	3.1	3.1	3.2	3.1	2.9		2.2	2.2	1.9	
	0.1	2.2	2.3	2.5	2.4	2.2	2.0		1.3	1.7	1.8	
Neon (400 MeV/amu)		0	A			D	E	F			K	14.4
	0.5	1.6	2.2			3.8	4.2	4.2			2.5	
	0.1	1.4	1.6			2.6	2.6	2.4			1.7	
Carbon (400 MeV/amu)		0	A		C	D		F	G		K	24.5
	0.5	1.0	1.2		1.3	1.8		2.6	2.8		1.0	1.1
	0.1	1.0	1.1		1.3	1.5		2.1	2.2		1.0	1.0
Helium (230 MeV/amu)			A				E	Prox.	Distal			25
	0.5		1.0				1.2	1.3	1.5			
	0.1		1.0				1.2	1.2	1.4

Fig. 3. A typical Bragg ionization curve depicting location of positions used in human kidney T-1 cell track-segment survival studies. All positions used are referenced from the peak position for each beam. (XBL 773-3235)

Fig. 4. Summary of relative biological effectiveness (RBE) values at the 10% survival level for human kidney T-1 cells irradiated in nitrogen as a function of depth for carbon (400-MeV/amu), neon (400-MeV/amu), and argon (500-MeV/amu) beams. (XBL 773-3276)

Fig. 5. Summary of oxygen enhancement ratios (OER) at the 10% survival level for human kidney T-1 cells as a function of depth for carbon (400-MeV/amu), neon (400-MeV/amu), and argon (500-MeV/amu) beams. (XBL 773-3175)

An important consideration in the use of extended Bragg curves is the distribution of stopping heavy particles. These can be directly calculated or measured. T. Yang measured the distribution of stopping neon ions in an extended Bragg peak of 10-cm width and 25-cm full range. In Fig. 6 we see that particles are stopping predominantly near the distal end of the distribution; therefore, we expect large biological effects and the lowest OER values in this region. Extended-Bragg-peak data are presented in Table III and discussed in section IV below.

Fig. 6. In the lower part of the figure, calculated depth-dose survival curves are shown for human kidney T-1 cells irradiated with an entrance dose of 688 rads of cobalt-60 gamma rays in air and nitrogen and for an entrance dose of 101 rads of 557-MeV/amu neon ions with a 10-cm extended Bragg peak in air and nitrogen. Doses for each modality were selected to give comparable survival at a depth of approximately 15 cm using a single-port exposure. At the top is shown a comparison of the number of neon particle tracks in plastic detectors along the extended Bragg peak. (XBL 773-3239)

In order to achieve uniformity in beam quality and obtain better isosurvival conditions, we have carried out some "cross firing" experiments with cell cultures in which the dose is given in two installations simulating equal doses from opposite directions. For particles this has the added advantage of further reducing by approximately a factor of 2 the dose delivered to "normal" tissues, i.e., outside the tumor region. Figure 7 compares the cross-fire experiments with a 38-cm phantom and 10-cm spread peak using gamma rays and neon ions. The gain factors are listed later in Table VIII.

Some years ago, it was shown in our laboratory that the cross section for inactivation for low-energy heavy ions is approximately equal to the geometrical cross section of the cell nucleus.^{13,14} If this finding holds true for high energies, it is important for therapy because many human tumor cells are aneuploid and have large nuclei. We have compared the survival curves of T-1 kidney cells (nuclear cross section = $140 \mu\text{m}^2$) and hamster V-79 cells (nuclear cross section = $50 \mu\text{m}^2$) near the Bragg peak of an argon

TABLE III. Experimental values and probable error of "X" and "Y" linear-quadratic coefficients best-fitted by least squares for human kidney T-1 cell survival in the plateau and extended Bragg peak. $OSR_{50\%}$ and $D_{50\%}$ values are also given (Blakely et al.).

		Dose factor	$X \times 10^{-3}(\text{rad}^{-1})$	$Y \times 10^{-5}(\text{rad}^{-2})$	$OSR_{50\%}$	$D_{50\%}^*$
Neon (557 MeV/amu, 25-cm range, 10-cm spiral ridge filter):						
Plateau (0 cm)	N ₂	1.00	0.70 ± 0.13	0.100 ± 0.009		
	Air		1.98 ± 0.28	0.839 ± 0.057	1.684	193
Proximal (14.5 cm) peak	N ₂	1.00	4.12 ± 0.14	0.017 ± 0.002		
	Air		7.17 ± 0.14	0.354 ± 0.045	1.584	101
Central (18.65 cm) peak	N ₂	0.85	3.00 ± 0.14	0.042 ± 0.018		
	Air		5.21 ± 0.21	0.645 ± 0.056	1.416	116
Distal (22.8 cm) peak	N ₂	0.71	5.39 ± 0.10	0.052 ± 0.013		
	Air		5.85 ± 0.32	1.190 ± 0.114	1.169	98.7
Cross-fire (14.5 and 22.8 cm)	N ₂	--	4.12 ± 0.14	0.017 ± 0.012		
	Air		7.17 ± 0.14	0.354 ± 0.045	1.365	92.4
Carbon (400 MeV/amu, 25-cm range, 10-cm spiral ridge filter):						
Plateau (0 cm)	N ₂	1.00	0.82 ± 0.03	0.048 ± 0.002		
	Air		2.26 ± 0.09	0.448 ± 0.014	1.64	215
Proximal (14.3 cm) peak	N ₂	1.00	1.21 ± 0.08	0.077 ± 0.005		
	Air		3.87 ± 0.23	0.467 ± 0.042	1.64	152
Central (18.8 cm) peak	N ₂	0.88	1.58 ± 0.09	0.053 ± 0.007		
	Air		3.19 ± 0.23	0.545 ± 0.045	1.51	169
Distal (23.3 cm) peak	N ₂	0.70	3.71 ± 0.17	0.115 ± 0.016		
	Air		5.06 ± 0.17	0.742 ± 0.042	1.28	117
Cross-fire (18.8 and 23.3 cm)	N ₂	--	2.37 ± 0.04	0.116 ± 0.003		
	Air		5.33 ± 0.14	0.500 ± 0.026	1.49	117

*Dose in rads for 50% survival.

Fig. 7. In the lower part of the figure, calculated depth-dose survival curves are shown for human kidney T-1 cells irradiated with an entrance dose of 350 rads of cobalt-60 gamma rays in air and nitrogen (based on experimental measurements of 220-kVp x rays) and for an entrance dose of 50 rads of 557-MeV/amu neon ions with a 10-cm extended Bragg peak in air and nitrogen. Doses for each modality were selected to give comparable survival at a depth of approximately 15 cm using dual-port (opposing) exposures. A depth-dose profile for each modality is shown at the top.

(XBL 774-3301)

beam. The ratio of geometrical cross sections was 1.6, and the ratio of inactivation cross sections was about 1.5. There may be other factors responsible for differences in sensitivity; nevertheless, kidney cells with large nuclear cross sections are significantly more sensitive to heavy ions than hamster cells with small nuclei. The difference in x-ray sensitivity between these two strains is less than 15 percent. We take this result as an indication that the factors determining x-ray response and response to very high LET are different.

2. Oxygen Enhancement Ratio (OER)

The oxygen effect is commonly expressed as the "oxygen enhancement ratio" (OER). This is a dose ratio, usually taken at the 10-percent survival level, as follows:

$$\text{OER}_{0.1} = \frac{\text{Dose}_{\text{nitrogen}}}{\text{Dose}_{\text{air}}} \quad (2)$$

Figure 5 shows $\text{OER}_{0.1}$ values for various unmodulated beams taken with the monolayer technique. The $\text{OER}_{0.1}$ near the Bragg peak reaches a level of about 1.1 for neon and about 1.2 for argon. At higher particle energies, the OER rapidly increases to a maximum value of about 3, which is very similar to that for x and gamma rays. As the particle becomes heavier, the depression in OER is expressed for several centimeters of the range, which is desirable if therapeutic uses are contemplated.

Table IV is a summary of OER data obtained from cell experiments in extended Bragg peaks by various investigators. Agreement is fairly good in most cases considering the various techniques and systems used. There is obvious lack of agreement at the distal end of the extended Bragg curve, especially for carbon. This discrepancy is understandable when we realize that the beam quality and dose are very rapidly changing in that region and that only monolayer techniques are able to measure the variation accurately.

There is a question, as yet not fully answered, relating to the origin of the oxygen effect in heavy-ion beams. Does oxygen interact with primary free radicals in the core of the track, or does it modify the biological effects in the penumbra, or does it interact with the secondary (DNA?) radicals and modify them? We have done some exposures in neon and argon beams at various oxygen concentrations at energies where the OER has been reduced to a value of 2. At the 10-percent survival level, already 0.1-percent oxygen modifies the hypoxic survival curve. Such data indicate that some of the oxygen effect for heavy ions does not originate in the fast radical reaction. For example, for neon ions of 0.6-cm range, 0.1-percent oxygen decreased the OER value from 2 for "pure" nitrogen to 1.5. Experiments such as these make us wonder what "relevant" oxygen concentrations are in various tumors. This information would help us plan in vitro experiments. It appears that starving cancer cells in tumors deprived of oxygen perish, causing necrotic centers to appear; living cancer cells might need a minimal oxygen concentration in order to proliferate.

B. Suspension Experiments

An extensive series of experiments were performed by D. Chapman et al.,^{3,15-20} which are only briefly reviewed here. Survival curves were generated with stationary-phase, Chinese hamster V-79 cells at various positions indicated for each beam in Fig. 8.³ The data were best-fitted to the linear-quadratic expression $S/S_0 = \exp(-\alpha D - \beta D^2)$ (see also Eq. 3), and the values of α and β are plotted versus the average LET in Fig. 9. The results indicate that the increase in RBE observed at high LET is predominantly the result of an increase in cell killing by the single-hit mechanism. This component of cell inactivation increases to a maximum value at an LET of 100 to 150 keV/ μm . In most suspension experiments, there is a large double-hit component of cell inactivation present. The double-hit component of cell inactivation is thought to result from the large delta-ray penumbras associated with energetic particle beams and, consequently, would have characteristics of low-LET radiations. The quadratic component is, however, most important at large doses and low survival levels; at "therapeutic" dose levels and high LET the linear effects dominate.

At the middle of the 4-cm spread-out Bragg peak, the RBE in air at 10-percent survival for stationary-phase V-79 cells increased from 1.9 for carbon to 2.1 for neon and to 2.2 for argon (see Tables V and VI for oxic and hypoxic data). The OER values under these conditions were 1.7, 1.6 and 1.4 for carbon, neon and argon beams, respectively.

Human kidney cells were also irradiated in stirred suspensions placed at various positions in the plateau and 4-cm extended Bragg peak of a 400-MeV/amu carbon-ion beam.¹⁷ Survival comparisons with stationary-phase and G_1 -phase populations of Chinese hamster cells showed that the absolute radiosensitivity of asynchronous human kidney cells is between the radiosensitivities of stationary-phase and G_1 -phase populations of Chinese hamster cells. The increases in radiobiological effectiveness observed as carbon

TABLE IV. Summary of OER_{0.1} values for 4- and 10-cm spread-out Bragg peaks of heavy-ion beams.

	4-cm extended peak	10-cm extended peak
<i>Carbon (400 MeV/amu, ~25-cm range):</i>		
Plateau	2.65, ^b 2.30 ^d	3.2, ^c 3.0 ^a
Proximal peak	--	2.4, ^b 2.7 ^a
Mid-peak	1.7 ^b	2.4, ^c 2.55 ^a
Distal peak	1.8 ^d	1.55, ^b 1.8 ^a 1.9, ^d 2.3 ^c
Cross-fire	--	2.1 ^a
<i>Neon (400 MeV/amu, ~14-cm range):</i>		
Plateau	2.4, ^b 2.4 ^e	2.3 ^c
Proximal peak	--	2.0 ^d
Mid-peak	1.6 ^b	2.0 ^c
Mid-distal peak	--	1.9 ^d
Distal peak	1.5 ^e	1.7, ^d 1.8 ^c
<i>Neon (557 MeV/amu, ~25-cm range):</i>		
Plateau		2.8 ^a
Proximal peak	analysis	2.5 ^a
Mid-peak	in	2.3 ^a
Distal peak	progress	1.6 ^a
Cross-fire		1.9 ^a
<i>Argon (500 MeV/amu, ~12-cm range):</i>		
Plateau	1.7, ^e 1.8 ^b	1.7 ^c
Proximal peak	--	--
Mid-peak	1.4 ^b	1.7 ^c
Distal peak	1.0 ^e	1.3, ^d 1.5 ^c

^aReferences 1, 2, 11, 64.^bReference 3.^cReferences 28, 29.^dReference 62.^eReferences 26, 37.

Reference radiation OER (x or gamma rays):

a, 2.8; b, 2.8; c, 3.0; d, 2.9; e, 2.8.

Fig. 8. Depth-dose distributions for the various particle beams studied showing the positions in each beam at which RBE and OER were measured.³

(XBL 768-9213)

Fig. 9. Values of α and $\sqrt{B}$ obtained by best-fitting the experimental data to the linear-quadratic expression and plotted against the average LET of the various particle beams studied.³ (XBL 768-9211)

TABLE V. Summary of relative biological effectiveness values (relative to 220-kVp x rays) at the 50% and 10% survival levels from cellular experiments at the Bevalac with irradiation in the plateau of the Bragg ionization curve under aerobic conditions.

	Helium ions (230 MeV/amu)		Carbon ions (400 MeV/amu)		Neon ions (400 MeV/amu)		Argon ions (500 MeV/amu)		
	Survival								
	50%	10%	50%	10%	50%	10%	50%	10%	References
<i>Unfiltered:</i>									
			1.2 ^a	1.1 ^a	2.2 ^a	1.6 ^a	3.1 ^a	2.3 ^a	1,2,11
							4.4	2.4	4
						1.6			61
						1.6			63
<i>Filtered:</i>									
4 cm Pb			1.5	1.3	2.2	1.6	3.8	2.5	3
4 cm Pb					1.7 ^b	2.0 ^b			26,37
					3.1 ^b	2.0 ^b	6.3 ^b	3.5 ^b	26,37
10 cm brass			1.0		2.1		2.3		28,29
8 cm brass	1.0	1.0							64
8 cm brass	1.0	1.0							3

^aSee Fig. 3, "A" position.

^bRBE values relative to ¹³⁷Cs rather than 220-kVp x rays.

ions slowed down and stopped in water were similar for the three cell populations at doses greater than 400 rads. At lower doses, the RBE was greater for the hamster cell populations than for the human kidney cells.

More recent survival measurements were made in the plateau and 10-cm extended Bragg peak of a 400-MeV/amu carbon-ion beam. Stirred suspensions of Chinese hamster cells were irradiated in these experiments. Across the 10-cm carbon peak, the OER at 10-percent survival was found to vary between values of 2.4 and 1.55 from the proximal to distal positions. The higher OER at the proximal peak is not unexpected because as the Bragg peak is spread to a width of 10 cm, the stopping particles are diluted further. The data from these studies indicate that a 400-MeV/amu carbon-ion beam in comparison with low-LET modalities exhibits each of the following desired properties: improved depth dose, increased RBE, and lower OER compared to gamma rays (see Fig. 10). Although at 300 rads there is a near isosurvival condition under the spread peak, at higher doses the killing at the proximal peak is emphasized, but at lower doses the distal peak is emphasized. It is obvious from the figure that the lethal damage produced in the first 12 cm of water by the ⁶⁰Co beam would be much greater than that produced by carbon ions.

1. Radiation Modifiers

Historically, it was believed that high-LET radiation damage was not modifiable; however, in 1964,

TABLE VI. Summary of relative biological effectiveness values (relative to 220-kVp x rays) at the 50% and 10% survival levels from cellular experiments at the Bevalac with irradiation in the Bragg peak under aerobic conditions.

	Helium ions (230 MeV/amu)		Carbon ions (400 MeV/amu)		Neon ions (400 MeV/amu)		Argon ions (500 MeV/amu)		References
	50%	10%	50%	10%	50%	10%	50%	10%	
<i>Unfiltered:</i>			1.8 ^a	1.5 ^a	3.8 ^a	2.6 ^a	3.1 ^a	2.2 ^a	1,2,11
			3.1 ^b	2.4 ^b	4.2 ^b	2.4 ^b	2.2 ^b	1.3 ^b	1,2,11
							2.9	1.5	4
<i>Filtered:</i>									
4 cm Pb (mid-peak)			3.0	1.9	3.4	2.1	3.6	2.2	3
4 cm Pb (mid-distal)					2.9 ^c	2.6 ^c			26,37
					3.6 ^c	2.2 ^c	4.2 ^c	3.2 ^c	26,37
10 cm brass (mid-peak)			1.3		2.4		2.3		28,29
(distal peak)			1.6		2.7		2.2		28,29
4 cm Pb				1.8					62
10 cm brass (distal peak)				1.9					62
8 cm brass (prox. peak)	1.3	1.2							64
(distal peak)	1.5	1.4							64
8 cm brass (mid peak)	1.3	1.1							3

^aSee Fig. 3, "D" position

^bsee Fig. 3, "F" position.

^cRBE values relative to ¹³⁷Cs rather than 220-kVp x rays.

Manney and Tobias²¹ showed that glycerol in large concentrations modified yeast-cell survival in a very wide LET range. D. Chapman and M. Yezzi used the radioprotector DMSO and found that, similarly to neutrons and x rays, high concentrations of this substance (on the order of 1 to 2 Molar) protect against both the single-hit and double-hit components of radiation damage in plateau ions. In the case of argon beams, even higher concentrations of DMSO lost their effectiveness, an indication of special radiation chemistry in the "track core."

Hypoxic cell radiosensitizers that mimic the effects of molecular oxygen may have special importance in radiation therapy; they can serve to decrease the OER coefficients of hypoxic cells. Three sensitizers were studied using the helium and heavy-ion beams — metronidazole, RO-7-0582 and RO-7-0741. The sensitizers were found to eliminate a significant proportion of the OER for each of the beams studied. Results with 5-mM RO-7-0582, for example, indicate a reduction in the 10-percent survival OER for the 4-cm spread-out Bragg peak of from 1.6 to 1.1. Preliminary experiments with cells irradiated in the spread-out helium

Fig. 10. Depth-survival distribution curves for carbon particles of 25-cm range and 10-cm spread-peak calculated for various entrance dose levels in a water phantom from experimental data with Chinese hamster cells. The cobalt gamma-ray relationship is shown at an 850-rad entrance dose.¹⁷ (XBL 773-619)

beam indicate that lower (more clinically useful) concentrations of RO-7-0741 can also eliminate 30 to 45 percent of the oxygen effect.

2. Synchrony Experiments

It was feasible to study the stationary G-1 phase and mitotic stage of V-79 hamster cells with heavy-ion beams. As with x rays, the mitotic stage proved to be the most sensitive. The differences in radiation sensitivity of the various phases were gradually reduced with the extended Bragg peak of the heavier ions.

IV. ANALYSIS OF MONOLAYER DATA

During the experiments described above, it became quite clear that orthodox descriptions of radiation quantity are insufficient to describe the biological effects of accelerated heavy ions. Traditionally, at least two quantities were necessary to describe radiation fields, including x rays, gamma rays and neutrons; these were "dose" (D) in terms of energy transferred to tissue per gram and "linear energy transfer" (LET) in terms of energy transferred per unit length of track.

While working with heavy ions, we encountered a number of situations where both D and LET were the same but the biological effects produced were different. There is a need for at least one additional physical parameter. We are proposing the following three: particle atomic number, particle flux density,

and particle energy. When these three parameters are given, dose, LET and radial energy distributions can be calculated, and thus the beam will be physically defined. It is of interest to note that, even in the absence of complete physical description, we find that three experimental parameters for any given mixed heavy-ion radiation field are sufficient to describe cell survival curves. These three parameters are the dose and X and Y of Eqs. 3, 4 and 5 (see below). Two parameters are not sufficient. For example, an RBE coefficient and an OER at the 10-percent survival level at each point across the extended Bragg peak by themselves will not describe the behavior of a mixed heavy-ion beam for therapeutic considerations.

A. Models

The data obtained on monolayers have been fitted by least-squares analysis to three different models of survival curves. Two of these models assume that survival curves are composed of a single-hit, exponential function of dose and a more complex multihit component. In the Chadwick-Leenhouts or *linear-quadratic* model,²² the second component has two-hit kinetics; the underlying assumptions include the supposition that a key injury in DNA is a double-strand scission and that two single-strand breaks, when they are not too far apart, can result in a double-strand break. A second *multihit* model²³ associates only the exponential or "direct" component with double-strand scission; the multihit form (usually 1 to 6 hits) has as yet undefined molecular origin; it is related to sublethal and potentially lethal lesions as well as repair. The third model is that of Green and Burki.²⁴ We have termed it the *repair-saturation* model. This model recognizes that the availability of repair enzymes might have a limiting influence.

There is considerable argument in the literature as to which of the above models is the "best"; many of the survival curves taken with heavy ions were fitted for each of the three models.* With the presently available accuracy, each of the models can describe the data rather well; additional data at high and low survival ratios and molecular work with the repair systems are necessary before a distinction between them can be made. As an example, some data for the neon beam are shown in Fig. 11 with "best fit" type curves for each of the three models. An important consideration is that the "inactivation constant" of the exponential part of the curve, "X", depends strongly on the kind of particles used and their kinetic energies. This coefficient related directly to the chemistry of the molecular species created in the core of the particle track.

Two distinct approaches have been made to predict the behavior of X. One approach is the *Katz model* elaborated by Robert Katz and associates and is based on the behavior of photographic emulsions and other substances in intense gamma-ray fields.²⁵ The second was developed from earlier studies on cross section variations as functions of LET by our group and is known as the *Chatterjee-Tobias diffusion model*.²³ The attractive feature of this model is that it has been modified to describe radiochemical as well as radiobiological interactions. The diffusion model allows us to differentiate between first-order and higher-order radical reactions. For example, it appears that the "shoulder" of the survival curve, the oxygen effect, and the action of most radiomodifiers is first-order whereas the "cross section" calculated for the exponential part of the anoxic survival curve rises nearly proportionally with the density of free radicals in the central track.

*The analytical forms of the three survival functions are as follows:

$$\text{Linear-Quadratic} \quad S = \exp(-XD - YD^2) \quad (3)$$

$$\text{Multihit} \quad S = [1 - (1 - e^{-YD})^m] \exp(-XD) \quad (4)$$

$$\text{Repair-Saturation} \quad S = Y + 1/Y + \exp(XD) \quad (5)$$

where S = survival fraction, D = dose, X and Y are functions of particle atomic number and energy, and m = multiplicity.

Fig. 11. Survival data for hypoxic exposures of human kidney T-1 cells to 557-MeV/amu neon ions in the plateau. Data are best-fitted to the following models of cellular inactivation: (A) $S = \exp(-XD - YD^2)$; (B) $S = [1 - (1 - e^{-YD})^m] \exp(-XD)$; (C) $S = (Y+1)/[Y + \exp(XD)]$.

(XBL 773-3236)

B. Interpretation of the Survival Data at the Extended Bragg Peak

Either with monoenergetic beams or when particle-beam therapy is performed with the "extended Bragg peak," the dose varies with location ℓ along the treatment axis. For a particle of atomic number z_i , let the dose be $D = D_i(\ell)$. The survival S_a in air and S_n in nitrogen can be expressed as follows:

$$\text{hypoxic} \quad S_{in} = S[X_{in}, Y_{in}, D_i(\ell)] \quad (6)$$

$$\text{aerobic} \quad S_{ia} = S[X_{ia}, Y_{ia}, D_i(\ell)] \quad (7)$$

where X_{in} , X_{ia} , Y_{in} , and Y_{ia} are inactivation constants of Eqs. 3, 4 and 5. The concepts and results presented here are independent of the survival model used. As an example we shall use here the form of

$$S_i = \exp[-X_i D_i(\ell) - Y_i D_i^2(\ell)] \quad (8)$$

The oxygen effect ratio for a chosen survival level S^* can be calculated as

$$[\text{OER}] = \frac{-\frac{X_{in}}{2Y_{in}} + \left[\left(\frac{X_{in}}{2Y_{in}} \right)^2 - \frac{\ln S^*}{Y_{in}} \right]^{1/2}}{-\frac{X_{ia}}{2Y_{ia}} + \left[\left(\frac{X_{ia}}{2Y_{ia}} \right)^2 - \frac{\ln S^*}{Y_{ia}} \right]^{1/2}} \quad (9)$$

Thus, the OER is a function of the chosen survival level S^* . For this reason, caution must be exercised when "therapeutic gain" calculations are made from a single OER value at the 10-percent survival

level. We have found that "therapeutic gain" depends on additional variables including dose schedules and relative biological effectiveness. In fact, the conditions for which OER has been defined, i.e., constant survival in hypoxic and aerated states at different dose levels, never occur in radiation therapy. Usually, anoxic cells are mixed with normal cells, and in the course of treatment these both receive the same dose. In order to enable us to make comparisons, we introduce two new ratios; one describes the difference in survival between hypoxic and aerobic cells at the same dose, the "oxygen survival ratio" (OSR); the other describes the survival differences in aerobic conditions of two different radiations i and j at the same location ℓ in the body, $[SRL]_{\ell}$. We designate [OSR] by Ω and $[SRL]_{\ell}$ by θ . For the linear-quadratic model

$$\Omega_i = [OSR]_i = \exp[(X_{ia} - X_{in})D_i + (Y_{ia} - Y_{in})D_i^2] \quad (10)$$

and

$$\theta_{ij} = [SRL]_{ij} = \exp[(X_{ia}D_i - X_{ja}D_j) + (Y_{ia}D_i^2 - Y_{ja}D_j^2)] \quad (11)$$

[OSR] is not a constant but a function that increases with dose for each of the radiations studied regardless of its $OER_{0.1}$. For illustration we have plotted OER values as functions of dose above the survival curves in Fig. 1. It turns out that the radiotherapist can, if he or she wishes, choose an appropriate daily dose with any radiation and obtain the same OSR obtainable with any other radiation. The dose to achieve such an OSR is, however, different for each type of radiation.

In order to compare the therapeutic efficiency of two different radiations, it is necessary that the therapist choose for each a *daily dose installment*. In the following example, we compare neon ions (j) to cobalt gamma rays (i). A neon beam of 25-cm range in water was chosen with a rotating spiral ridge filter to create a 10-cm extended peak. The dose installments were chosen so that in aerobic conditions, one installment from either radiation results in 50-percent survival. Arbitrarily, we have chosen this survival level at the *proximal* peak of the 10-cm extended Bragg curve, 14.5 cm from the body surface. It turns out that a single entrance dose of 688 rads of cobalt gamma rays or 101 rads of neon ions (557 MeV/n) are needed. Survival curves were calculated for each radiation with the experimentally determined X and Y coefficients; these curves are shown in Fig. 6. We see that in the "normal" tissue region gamma rays exert much more killing effect than neon ions whereas in the tumor region neon, both aerobically and anaerobically, exerts more killing than do gamma rays.

We can now define a *therapeutic particle gain* (TPG) for each location ℓ in the tumor as follows:

$$[TPG] = \frac{[OSR]_i}{[OSR]_j} \cdot [SRL]_{ij} \quad (12)$$

The TPG has two distinct components. SRL_{ij} is a survival advantage in air from the use of neon (i) versus gamma rays (j) due to geometric absorption and effectiveness factors. In our example we have chosen the entrance doses of neon and gamma rays so that at the proximal peak in air both cause a 50-percent lethal effect; consequently, for this "reference point," $SRL = 1$ (see Figs. 6 and 7). The second component is a ratio of the OSR values for the two radiations. Tables VII and VIII contain relevant numbers for our example. Everywhere in the extended peak region TPG is greater than one; that is, neon is "better" than gamma rays. Outside of the extended peak, where presumably normal tissue is located, TPG becomes less than one and is, in fact, quite small, indicating depressed survival in the gamma peak and less killing by neon, a great advantage for neon.

Table VII indicates that the SRL factor is equal to one at the reference point of 50-percent survival. It increases for the central and distal peak because the number of stopping particles is increasing. The TPG is greatest at the distal peak (1.36) and is 1.07 at the proximal peak. This difference is amplified greatly when the TPG factor is calculated for a sequence of 20 therapeutic irradiations. The TPG is now 468 for the distal peak and only 3.9 for the proximal. We believe that this effect is in part due to the

TABLE VII. Evaluation of therapeutic particle gain: oxygen survival ratios (OSR) and TPG therapeutic gain ratios compared to cobalt gamma rays for plateau and peak positions of a 557-MeV/amu neon-ion beam (25-cm range, 10-cm brass spiral filter). Data are from human kidney T-1 cell experiments using a single-port exposure. (Blakely et al.).

	Depth (cm of water)	Atmosphere N = Nitrogen A = Air	Cobalt Gamma Rays			557-MeV/n Neon Ions			SRL	TPG single dose	TPG therapy n = 20
			Dose (rads)	Survival (%)	OSR	Dose (rads)	Survival (%)	OSR			
Plateau	0.5	N A	689	54 5.4	10	101	92 75	1.23	0.07	0.57	1.3×10^{-5}
Proximal peak	14.5	N A	259	85 50	1.7	101	79 50	1.59	1	1.07	3.9
Central peak	18.65	N A	186	90 64	1.41	85.7	77 61	1.28	1.05	1.16	19.5
Distal peak	22.8	N A	139	92 73	1.27	71.6	68 62	1.10	1.18	1.36	468

TABLE VIII. Evaluation of therapeutic particle gain: oxygen survival ratios (OSR) and TPG therapeutic gain ratios compared to cobalt gamma rays for plateau and peak positions of a 557-MeV/amu neon-ion beam. Data are from human kidney T-1 cell experiments using a double-port (opposing) exposure. (Blakely et al.).

	Depth (cm of water)	Atmosphere N = Nitrogen A = Air	Cobalt Gamma Rays			557-MeV/n Neon Ions			SRL	TPG single dose	TPG therapy n = 20
			Dose (rads)	Survival (%)	OSR	Dose (rads)	Survival (%)	OSR			
Plateau	0.5	N A	448	71.5 22.2	3.23	54.1	96 87.7	1.09	0.25	0.74	2.4×10^{-3}
Proximal & Distal peak	14.5 22.8	N A	259	84.8 50	1.70	92.4	68 50	1.36	1.0	1.25	86
Central peak	18.65	N A	242	85.9 53.1	1.62	91.9	76 68	1.30	0.78	0.97	0.54

number of stopping particles at the distal peak being much greater than at the proximal peak. It appears desirable to devise methods whereby the proximal peak will also have more stopping particles. This can be done by cross-firing the beams, that is, by giving approximately half of the dose from each of two opposing ports in such a manner that the extended Bragg peaks overlap exactly. Figure 7 and Table VIII show the results. The advantage of this procedure is that it will equalize particle distribution at the proximal and distal peaks. Both of these now have a TPG of 1.25 in a single-dose installment and a TPG of 86 in a 20-dose therapy sequence. The central peak shows less of an advantage. This is an indication of the characteristics of the particular ridge filter used. Calculations of this type are extremely sensitive for the accuracy of the measured survival curves. The results stress the necessity to carry out experiments at low doses with high accuracy if these are to be used for predicting therapy results.⁵⁸

We cannot expect that acute experiments with cells can accurately predict survival levels and other factors in a therapy sequence. It is nevertheless of interest to extrapolate the above results. If n equal dose installments are given and if all radiobiological factors remain constant (e.g., no re-oxygenation, no cell division between treatments in the tumor, no accumulation of sublethal damage), survival for the therapy sequence S_T can be calculated by $S_T = S^n$. At the "proximal" peak in air, $S_T \approx 10^{-6}$ if $n=20$. The results are shown in Tables VII and VIII. Calculations of this type convinced us that at a 25-cm range neon is better than helium; both of these are much better than gamma rays and neutrons, chiefly because of the good depth-dose advantage. Neon becomes much better than helium if the depth of penetration is decreased and the width of the extended peak is smaller. For short ranges of penetration (of a few centimeters), argon gives good depth dose and lower OSR than any of the other extended beams. For very localized treatment, e.g., pituitary irradiation, or for producing small lesions in the brain, the carbon beam has an advantage. Considering monolayer techniques (mostly with T-1 cells, Blakely et al.) and suspension work (mostly V-79 cells, Chapman et al.), reasonably good agreement exists among the data allowing for peculiarities of the two systems.

V. ADDITIONAL CELLULAR AND MOLECULAR EXPERIMENTS WITH HEAVY IONS

Tables V and VI summarize recent RBE in vitro cell data in air obtained at the Berkeley 184-inch cyclotron and the Bevalac facility. Table V provides RBE data relative to 220-kV x rays measured for Bragg plateau exposures of helium, carbon, neon and argon ions. LET values are approximately 2, 11, 41 and 100 keV/n, respectively.

There is excellent agreement at the 10-percent survival level for the various cell systems in the plateau. The $RBE_{0.1}$ values range from 1.0 for helium, 1.1 to 1.3 for carbon, 1.6 for neon, and 2.3 to 2.5 for argon at the beam energies listed. RBE values from Fu and Phillips²⁶ are slightly higher due to their use of ^{137}Cs gamma rays as a reference radiation.

At the 50-percent survival level, there are some differences among RBE values obtained. Slight technical differences in experiments from plateau exposures would not be expected to cause these variations. Rather, these differences may reflect the disparity in statistical reliabilities with lower doses. It is important to note that these low doses may well be more clinically significant than the 10-percent survival level doses, and thus these difficulties must be resolved.

In Table VI, RBE_{oxic} values are summarized for the Bragg peaks of helium, carbon, neon and argon beams. Survival data accumulated without spreading the beam with a ridge filter are presented first. One would expect that RBE's at positions D (0.6 cm H_2O upstream from the peak) and F (0.25 cm H_2O upstream from the peak) would bracket the results obtained with the spread beams because the LET mixture obtained with the spread beams would approximately encompass the LET range of monoenergetic particles between these two positions. This does not, however, always appear to be the case.

Early cellular radiobiology of the spread particle beams has progressed as the prototype ridge filters have become available. RBE comparisons in the peak regions are more difficult to analyze than the plateau RBE values because differences in experimental technique in the peak can easily be significant.

Despite these difficulties, RBE_{oxic} values for the spread peaks at the 10-percent survival level range from 1.1 to 1.4 for helium, 1.8 to 1.9 for carbon, 2.1 for neon, and 2.2 for argon.

A. Comparative Depth-dose Studies

Raju et al.²⁷⁻²⁹ have completed an array of comparative radiobiological experiments with heavy particles that are of interest in radiotherapy. The particles include protons from the Harvard Cyclotron, neutrons from the Texas A&M University Cyclotron, π -mesons from the Los Alamos Meson Physics Facility, helium ions from the LBL 184-inch Cyclotron, and carbon, neon and argon ions from the Bevalac. For this study, the

Fig. 12. Cell survival as a function of depth for a neon-ion beam.⁶
(XBL 752-4685)

Bragg peaks of all heavy charged particles were transformed to widths of 10 cm except the helium spread peak was 8 cm wide. Cell experiments conducted included cell-survival measurements as a function of depth using the gel technique and T-1 human kidney cells (see for example Fig. 12) and aerobic and hypoxic cell-survival curves at the beam entrance, peak center and distal peak (1 cm from the dose fall-off) using V-79 cells. hypoxia was obtained by the metabolic depletion technique using plastic sealed capsules.

RBE values in air obtained at the 50-percent survival level (relative to 250-kVp x rays) were 1.0 for x rays and protons, 1.2 for 910-MeV helium ions and π -mesons, 1.3 for 400-MeV/amu carbon ions, 2.4 for 400-MeV/amu neon ions, and 2.3 for 500-MeV/amu argon ions at the center of the peak for each beam. RBE values in the plateau were 1.0 for x rays, protons, helium ions, π -mesons and carbon ions, 2.1 for neon ions, and 2.3 for argon ions.

Raju obtained OER values of 3.0 for x rays and at the peak center of the proton beam. The following OER values were measured at the peak center of the other beams studied: helium - 2.6, carbon - 2.4, π -mesons - 2.3, neon - 2.0, and argon - 1.7. Neutron work by Hall³⁰ shows a comparable RBE_{0.5} of 2.0 and an OER_{0.1} of 1.7. Thus Raju and his associates found that the OER values decreased with increasing mass of the heavy ion. RBE and OER values obtained by Raju and coworkers are summarized in Tables IV, V and VI.

B. Studies on the Argon Beam

A single set of experiments, rather extensive in their scope, was conducted by a group from Columbia University with the 429-MeV/amu argon beam.³¹⁻³⁴ Cellular experiments included OER and RBE measurements and determinations of the degree of variation in cell survival as a function of the cell's progress through the division cycle.

For the RBE determinations, Chinese hamster V-79 cells were irradiated while contained in small plastic vials with an internal diameter of 2.5 mm. These sealed capsules were placed at four positions in the depth-dose Bragg curve of the unmodulated argon beam. For a surviving fraction of 1/10, the RBE (relative to 250-kVp x rays) in air was 2.4 for the plateau, ascending region and tail of the depth-dose curve and had a lower value of about 1.5 at the peak.

For the OER experiments, the metabolic-depletion-of-oxygen technique was used.^{4,35} Sealed glass ampules containing V-79 cells at high and low concentration (hypoxic and aerated, respectively) were irradiated at four positions in the depth-dose curve (in a tank of T.E. liquid). The OER measured at the incident plateau was 2.1 and fell to about 1.3 near the Bragg peak (averaged over 4 mm at the Bragg peak); it was about 1.5 a few millimeters beyond the peak. Estimates of RBE at the 50-percent and 10-percent survival levels have been made for comparative purposes from the available argon plateau and peak survival curves and are included in Tables V and VI.

Hall and coworkers^{4, v} concluded that the RBE values appear to indicate that the nuclear diameter for V-79 cells is somewhat less than 8 μ m and that in the plateau region nuclear transversal without inactivation is a likely process. They feel that the oxygen results indicate that, because of the diffuseness of the track and perhaps also because of fragmentation, argon ions under these conditions do not deliver sufficient energy to the domain critical for the oxygen effect (perhaps a few nanometers in diameter) to overcome the effect of anoxia. By the time the Bragg peak is extended by energy modulation, they anticipate that the average OER would probably be no less than 1.5 or 1.6.

The characteristic of the argon-beam studies that makes them unique among all of the accelerated-heavy-ion-beam experiments is the finding that the RBE is lower at the peak than in the entrance plateau. This observation is due to the fact that the stopping argon ions are so densely ionizing that they are in the region of overkill. This factor will not, therefore, provide optimal "biologically effective" dose in the tumor region close to the Bragg peak compared to the normal tissue traversed by the incident plateau. Fundamental studies of the biological responses to this beam could, however, prove beneficial to our understanding of basic mechanisms.

Synchronized cell experiments were done by Bird using hydroxyurea.^{32,34} Cells were irradiated with the argon-ion beam while attached in monolayer to culture flasks. The flasks were positioned in the tissue-equivalent liquid phantom with the growth surface at the argon-ion Bragg peak. Results showed that for argon-ion irradiation there is a two-fold cell-cycle variation in survival. This variation is greatly diminished from the 17-fold x-ray response.

C. Tumor Cells

Single-dose studies have been completed for helium, carbon, neon and argon using EMT6 tumor cells in vivo and in vitro by T. Phillips, K. Fu et al. of the University of California, San Francisco.^{26,36,37}

Chapter 9 contains a complete description of the in vivo results. The chief goal of the EMT6 in vitro studies was to determine the OER in the peak and plateau regions and, in addition, to measure RBE's in these regions of the Bragg curve.

In these studies, EMT6 cells obtained from flank tumors were irradiated using the metabolic depletion technique.³⁵ Survival studies were completed with the 400-MeV/amu neon beam²⁶ modified with a ridge filter to yield a 4-cm spread-out Bragg peak. Results showed that the aerated RBE (relative to ¹³⁷Cs gamma rays) at the 10-percent survival level was approximately 2.2.

From a report of preliminary data,³⁷ estimates of $RBE_{0.1}$ at the plateau and at the distal end of the 4-cm spread-out Bragg peak of the 500-MeV/amu argon beam were approximately 3.5 and 2.2, respectively. OER values at 1-percent survival for EMT6 cells in vitro include 2.8 for cesium gamma rays, 2.7 in the plateau and 2.4 at the distal end of the 8-cm spread 910-MeV/amu neon peak, 1.9 in the plateau and 1.5 at the distal end of the 4-cm spread 400-MeV/amu neon peak, and a preliminary value of 1.5 in the plateau and 1.0 at the distal end of the 4-cm spread 500-MeV/amu argon peak. From the survival curves available, estimates of the RBE at 50-percent and 10-percent survival and OER values at the 10-percent survival level have been made and are included in Fig. 13 and Tables IV, V and VI for comparative purposes. EMT6 in vitro survival and OER data are not yet complete for the 400-MeV/amu carbon beam.

Phillips et al.³⁷ have done comparative survival studies with 15-MeV neutrons. They concluded that the OER values in the peak of neon and in the plateau of argon are slightly lower than the OER values they obtained for neutrons. In the plateau of neon, the OER is just slightly higher than that for neutrons. In summary, they state that the OER and RBE data from the 4-cm spread peaks of carbon and neon appear to be of equal efficacy for therapeutic application. In vivo results with the EMT6 tumor cells reveal, however, a hypoxic tail in the survival curves for cells irradiated in the plateau of carbon, suggesting that broadly spread carbon peaks may show high OER's in the mid-peak position. More work is needed to confirm this result.

D. Hyperthermia

The effect of hyperthermia on Chinese hamster ovary radiosensitivity to accelerated helium ions has been studied by Gerner and Leith.^{10,38} Pre-irradiation hyperthermic treatment (43°C for 1 hr) of cells irradiated with accelerated helium ions (initial energy = 910 MeV) changes the radiation survival-curve slope and the extrapolation number. Pre-irradiation heat treatment with 4-MeV x rays only changes the slope, not the extrapolation number.

In a single set of experiments, cell survival parameters have been measured after exposure to accelerated carbon ions (LET = 34.1 keV/μm) combined with exposure to thermal doses administered immediately before irradiation. The findings show that heating for 30 min to 43°C prior to carbon-beam exposure is sufficient to eliminate the shoulder of the survival curve and, presumably, the repair process. At still higher temperatures, heat alone reduces survival and also modifies the slope of the carbon survival curve (see Fig. 14). The authors concluded that only a small high-LET component may be required in combination with hyperthermia to eradicate the shoulder region of the single-cell survival curve.

E. Molecular Studies

The effects of heavy-ion irradiation of mammalian cellular DNA have been studied for in vitro tissue cultures of human and Chinese hamster cells and for in vitro and in vivo photoreceptor cells of rabbit retinæ. In these investigations, radiation injury was measured as the induction of an initial number of DNA breaks, which were then assayed for their repair capacity. Interpretations of the ability of cells to rejoin DNA breaks must be made cautiously, however, because there is no way of assessing faulty rejoining.

Fig. 13. Response of the EMT6 tumor to in vitro irradiation with: (A) ^{137}Cs in air (○) and under hypoxia (●); (B) neon ions in the plateau region in air (□) and under hypoxia (■); (C) neon ions in the spread-out Bragg peak in air (▽) and under hypoxia (▼). Symbols represent the mean survival of cells irradiated in 2 to 4 ampules and assayed separately; bars represent standard errors of the mean.²⁶

Fig. 14. Survival response of CHO cells treated for 30 min at 37° (▲), 41° (●), 42° (○), 43° (■), or 44°C (□) before irradiation with accelerated carbon ions near the Bragg peak. Standard errors of the mean are shown.³⁸

(XBL 773-3237)

1. Results with Low-energy Ion Beams

The induction and repair of DNA breaks was initially studied in Chinese hamster V-79 cells for the heavy ions p, ⁹Be, ¹²C, ²⁰Ne, and ⁴⁰A with energies of approximately 4 MeV/amu covering an LET range of about 30 to 1,950 keV/μm.^{7,8,40} In these experiments, monolayers of exponentially growing cells were irradiated with a dose of 20 to 40 krads, and the DNA scissions were assayed by the alkaline sucrose sedimentation technique. The results were the following:

- (1) as the LET increased, the efficiency of the production of DNA breaks decreased rather rapidly at first and then leveled off at the very high LET values;
- (2) the extent of nonrepairable DNA breaks increased from a few percent at 1 to 3 keV/μm for x rays, to about 20 percent at 150 keV/μm for the heavy ions;
- (3) RBE values for the induction of nonrepairable breaks peaked at about 150 keV/μm.

In comparison, literature values of RBE's for the inhibition of colony formation in a human cell line show an RBE peak of about 200 keV/μm for heavy ions with energies of about 6 MeV/amu.¹³

2. Results with High-energy (≥ 400 MeV/amu) Ion Beams

Similar studies with heavy-ion beams having energies from 400 to 557 MeV/amu that might prove advantageous in radiation therapy have been done for both the unmodified Bragg ionization curve and a 10-cm extended Bragg peak.⁴²

For the studies with the unmodified Bragg peak, monolayers of human kidney T-1 cells were irradiated with 2000 rads at various positions in the Bragg ionization curves of 400-MeV/amu carbon, 400-MeV/amu neon, and 400-MeV/amu argon beams. DNA breaks were assayed by the technique of controlled DNA denaturation followed by separation of single-stranded DNA from double-stranded DNA by hydroxylapatite ion-exchange chromatography. These data, in agreement with the results from the 4-MeV/amu ion beams, show that the extent of nonrejoined DNA breaks is greater than that remaining after low-LET irradiations. The data also indicate that the rate of rejoining is substantially lower than that for x rays as LET increases and that it probably varies with ion species.

Studies of DNA damage and repair capacity in cells exposed in the 10-cm extended Bragg peak have so far only been made for 400-MeV/amu carbon ions accelerated to provide a depth range of about 25 cm in water. In this case, suspensions of V-79 cells in a 1.5-cm wide glass vessel were irradiated with 2000 rads at the positions shown in Table IX. These data, in agreement with the work on the 4-MeV/amu ion energies, show that the number of unrepaired DNA breaks increases as the LET increases, i.e., at the distal end of the peak.

TABLE IX. Percentage of nonrejoined DNA breaks following 2000 rads of accelerated carbon ions (10-cm spread peak, 25-cm range) in a suspension of exponentially growing V-79 cells.

	Postirradiation Incubation (hours)		
	0	0.5	4.5
Unirradiated	5%	5%	5%
Irradiated in proximal peak	60%	20%	10%
Irradiated in distal peak	66%	22%	22%

The difference in the extent of unrepairable DNA breaks between the proximal and distal ends of the 10-cm spread Bragg peak correlates with the data on induced cell killing under identical conditions for 400-MeV/amu carbon-irradiated cell suspensions and similar conditions for human kidney cells in monolayer. For example, at a dose of 500 rads, the surviving fractions of stationary-phase V-79 cells are 0.06 and 0.02 at the proximal and distal ends, respectively.¹⁷ In the case of the T-1 monolayer irradiations, the surviving fractions were 0.05 and 0.013 at 500 rads for the proximal and distal positions, respectively.¹¹

Damage to and repair of DNA in the photoreceptor cells of rabbit retinae have been studied for in vivo and in vitro irradiations with 400-MeV/amu neon ions at the Bragg plateau region.⁴³ Initial and long-term alterations in the macromolecular structure of DNA were followed after doses of 100 to 1500 rads. The DNA damage (DNA breaks) was initially repaired at all doses used; subsequently, however, DNA degeneration was observed. This degeneration of DNA could be a cause of biochemical or physiological changes in the cell, perhaps brought about by faulty DNA replication.

In summary, after exposure to a given radiation dose at various positions in the carbon 10-cm spread Bragg peak, there is a differential in the degree of cell injury so that cell damage, whether measured

as cell killing or unrepaired DNA breaks, becomes maximal at the distal end of the peak. Because it is well known from studies of DNA breaks caused by low-LET radiations that almost all of the DNA single-strand breaks are rejoined, it is plausible that the unrepairable breaks observed with high-LET radiations are DNA double-stranded breaks.

VI. THE FUTURE - SUMMARY OF PLANS

A. Survival Studies of Various Cell Strains

The work is progressing at such a pace that the survival relationships and oxygen effect should be well documented for at least two cell strains, T-1 and V-79, within the next few months with a good measure of agreement between various investigators. Hopefully, modeling will be advanced enough to fully describe the responses of cells to monoenergetic beams in such a manner that results can be predicted for other cell strains of known general characteristics and for a variety of "extended" Bragg peaks.

Experiments on the extended Bragg peaks are well under way. Given these conditions and progress in other related fields (e.g., radiological physics and tissue radiobiology), there should be a basis for initial explorations of radiation therapy with any of the beams, perhaps neon or carbon.

Cell biologists will continue working on other problems of fundamental and practical importance. We will briefly list and discuss some of these areas for future work.

B. Continuation of Studies of the Age Response to Heavy Ions

The radiation sensitivity of low-energy carbon ions is reported to be independent of cell cycle,⁴⁴ and cells exposed to the Bragg-peak argon beam show only a small variation in cell-cycle sensitivity.^{32,34} Cell-cycle sensitivity is probably related to the mode of injury and repair; its relationship to the efficacy of therapy should be better understood. The oxygen effect might also depend somewhat on the cell cycle.⁵⁹

Many normal and tumor cells are in the stationary state in the body and have important metabolic and synthetic activities. The radiosensitivity of such states should be better understood.

C. Differences in Heavy-ion Radiosensitivity Between Normal and Tumor Cells

Such differences are exceedingly important, perhaps even more than the oxygen effect, because successful radiation therapy depends on conditions that make tumor cells more vulnerable than normal cells. We have identified at least two factors worthy of study - nuclear size and DNA content. There are probably others such as the role of the cellular systems responsible for ATP production and synthesis of repair enzymes, the ability of cells to communicate with other cells, and the genetic factors controlling repair enzymes. The mouse 3T3 cell strain in our laboratory has stable nontumor cell lines and transformed cells that generate fast- or slow-growing tumors.

D. Mechanism of Chemical and Physical Radiation Modifiers

We already have some data on the concentration dependence of the oxygen effect. These data must be expanded and considered in the light of chemical mechanisms. There is some need for having information on the actual oxygen concentrations in living tumors so that comparisons between in vitro and in vivo systems can be made at proper levels. Already much data on sensitizers exist; however, much work is necessary to have information on minimum toxicity and maximally effective levels and mechanisms. Temperature sensitization is also of continuing interest.

E. Spheroids

Recently, a great deal of interest has developed in the use of multi-cell spheroids as a model tumor system in vitro.⁴⁵ Spheroids of cells in culture often exhibit an anoxic core and an aerated periphery;

because of the depleted nutritional supply in the core, spheroids are regarded as good models for some in vivo tumors. A. Rodriguez and E. Alpen in our laboratory have some preliminary data with neon-ion exposures of V-79 spheroids that are indicative of the increased effectiveness of these beams.⁴⁶

F. Repair

Sublethal damage repair and potentially lethal damage repair are two known types of cellular recovery from low-LET radiation damage that may be significant in planning dose-fractionation schedules for cancer patients.^{39,41} Many investigators have shown that sublethal damage repair can be drastically reduced with high-LET radiation modalities.⁴⁷⁻⁵¹ Recent work has shown that there is no recovery from potentially lethal damage (PLD) after exposure to a high-LET mixture of alpha particles and x rays⁵² or to neutrons.⁵³ There is a report, however, of PLD repair after exposure of EMT6 tumor cells to 645-MeV helium ions.⁵⁴

An intensive examination of split-dose and hyperfractionation survival kinetics is planned with the Bevalac beams in order to look for evidence of sublethal damage repair in human and hamster, oxic and hypoxic cells. In addition, we will test for PLD repair. We would also like to correlate these recovery processes with the repair of DNA synthesis and the rejoining of DNA single-strand breaks.

G. Molecular Mechanisms

1. Inhibition and Augmentation of Repair I

In the repair of DNA breaks, there is an initial fast rate of rejoining with a halftime of 8 to 10 min (repair I). It has been shown⁵⁵ that the fast rejoining rate involves DNA breaks that carry 5'phosphate and 3'OH end groups and that an exonuclease, DNA polymerase and polynucleotide ligase are probably necessary. Further elucidation of this repair process will be very valuable, especially if some means can be found to selectively inhibit the action of this DNA polymerase function because of the fast-rate-of-rejoining process probably accounts for more than 50 percent of the repair.

2. Identification of Repair II

The initial rapid rate of rejoining of DNA breaks is followed by a slower repair continuing for several hours (repair II). It seems that some DNA breaks cannot be rejoined until the cell enters the G₁-S border. It also appears⁵⁵ that the radiation-induced alkali-labile breaks are not repaired quickly. Much work, therefore, remains to be done to understand the various repair mechanisms that the cell uses to handle the different types of molecular lesions in DNA.

H. Lethal Effect: Double-Strand Break or Misrepair?

It may be that both double-strand breaks and misrepair are important. In the slowly dividing cell, misrepair may be more detrimental, especially if it is rather widespread, as enzyme synthesis would suffer. In the rapidly dividing cell, the unrepaired break(s) may prove disastrous as the cell proceeds to divide although it appears that a cell can go through one or two cell divisions before reproductive death is manifested.

I. Cytogenetics of Heavy Ions

As our knowledge of molecular lesions increases, it will be highly desirable to establish correlations between these changes and effects at higher levels in cells, for example, synthesis of repair enzymes, the kinetics of breakage and rejoining of chromosomes, and other cytogenetic changes as they relate to residual injury and cell lethality.

J. Mechanism of Viral Transformation

Using accelerated heavy particles, experiments have been conducted to determine the relationship between high-LET radiation and viral transformation of cells in vitro (see Chapter 10). It was established that exposure of 3T3 mouse cells to plateau neon radiation sensitizes cells to viral transformation by SV 40 virus much more effectively than exposure to x rays does. The mechanism of viral transformation is not known; however, one suggestion is that strand breaks (single or double) produced by irradiation and the subsequent induced DNA repair play roles in the incorporation of viral DNA into DNA of the host. We plan to explore this and other possibilities.

K. Mechanism of Membrane Injury - Neurons

Cultured murine neuroblastoma cells have been studied in the laboratory of T. Yang for the past two years. This tumor cell line is radiation-sensitive in the proliferative state but is radioresistant in the differentiated state. The mechanism of radiation effects on nondividing cells is not understood but is certainly of interest because many cells of the body are differentiated. A second interest in the neuroblastoma system stems from a recent observation with x rays. Doses of 220-kVp x rays, which were lethal to cells in the proliferative state, resulted in rapid retraction of neurites and growth cones. This phenomenon was clearly seen in microcinematography and was accompanied by osmotic changes in the cell. "Tugging" on synaptic regions was also observed. Zeman at the University of Indiana, working with the Ames Laboratory group, independently corroborated these findings when he observed synaptic separation following heavy-ion irradiation of the mouse brain.⁵⁶

Experiments using accelerated heavy ions with their unique penetration properties are planned to investigate further this unusual response. Neutron experience at the Hammersmith Hospital in London has indicated that we must know more about the radiation response of neurons and the brain if extensive therapy trials are to be conducted on brain tumors.

L. Epilogue

Many of us who are doing heavy-ion radiobiology with cellular systems are impressed with the potential that this method has for answering questions that have long eluded scientists about basic initial molecular steps in radiobiology, about the nature of several molecular repair processes and transformations, and about quantitative differences between normal and cancer cells.

Preliminary data are presented in this report, but we are hopeful that through radiobiological investigations with energetic particle beams important new knowledge will be gained of cellular dynamics during proliferative and regressive stages.

REFERENCES

1. Blakely, E., T. Yang, J. Lyman, A. Chatterjee, and C. Tobias. Survival of human kidney cells and oxygen effect in oxygen, neon and argon beams. *Radiat. Res.* 67, 60 (1976). (Abstract)
2. Blakely, E., C. Tobias, T. Yang, J. Lyman, and K. Smith. Cellular radiobiology of the 400 MeV/amu ²⁰neon ion beam. In preparation.
3. Chapman, J., E. Blakely, K. Smith, and R. Urtasun. Radiobiological characterization of the inactivating events produced in mammalian cells by helium and heavy ions. In *Proceedings of the International Conference on Particles and Radiation Therapy, Berkeley, September 14-17, 1976*; *Int. J. Radiat. Oncology, Biology & Physics*, in press.

4. Hall, E. J., H. H. Rossi, R. Coffey, and J. Varga. Biophysical studies with high energy argon ions. II. Determination of the relative biological effectiveness and oxygen enhancement ratio. *Radiat. Res.* 67, 622 (1976). (Abstract) Paper in preparation.
5. Tobias, Cornelius A. Pretherapeutic investigations with accelerated heavy ions. *Radiology* 108, 145-158 (1973).
6. Raju, M., E. Blakely, J. Howard, J. Lyman, D. Kalofonos, B. Martins, and T. Yang. Cell survival as a function of depth for a neon ion beam. *Radiat. Res.* 65, 191-194 (1976).
7. Ritter, Mark A., James E. Cleaver, and Cornelius A. Tobias. High-LET radiations induce a large proportion of non-rejoining breaks in mammalian cell DNA. *Nature*, in press.
8. Ritter, M. A. DNA strand break induction and rejoining in Chinese hamster cells as a function of radiation quality. Ph.D. Thesis, University of California, Berkeley (1976).
9. Rydberg, B. The rate of strand separation in alkali of DNA of irradiated mammalian cells. *Radiat. Res.* 61, 274-287 (1975).
10. Gerner, E., J. Leith, and M. Boone. Mammalian cell survival response following irradiation with 4 MeV x rays or accelerated helium ions combined with hyperthermia. *Radiology* 119, 715-720 (1976).
11. Blakely, E. A., C. A. Tobias, T. C. H. Yang, K. Smith, L. M. Craise, I. A. Madfes, and F. E. Abrams. Survival of human kidney cells and oxygen effect in carbon and argon beams. *Radiat. Res.*, submitted for publication. (Abstract)
12. Tobias, C. A., E. Blakely, T. Yang, and A. Chatterjee. Analysis of mammalian cell experiments with accelerated heavy ions. *Radiat. Res.*, submitted for publication. (Abstract)
13. Todd, P. Heavy-ion irradiation of cultured human cells. *Radiat. Res.* 7, 196-207 (1967).
14. Todd, P. Reversible and irreversible effects of ionizing radiations on the reproductive integrity of mammalian cells cultured in vitro. Ph.D. Thesis, University of California, Berkeley; Lawrence Berkeley Laboratory Report No. UCRL-11614 (1964).
15. Chapman, J. Chemical modification of the inactivating events produced in mammalian cells by heavy charged particles. *Radiat. Res.* 67, 605 (1976). (Abstract)
16. Chapman, J. D., E. Blakely, K. Smith, and C. Tobias. Some biophysical studies with Chinese hamster cells inactivated with energetic heavy ion beams. *Biophysics J.*, submitted for publication. (Abstract)
17. Chapman, J. D., E. Blakely, K. Smith, R. Urtasun, J. Lyman, and C. Tobias. Radiation biophysical studies with mammalian cells and a modulated carbon ion beam. In preparation.
18. Chapman, J. D., E. Blakely, K. Smith, S. Curtis, and C. Tobias. Biophysical studies with mammalian cells inactivated in suspensions with heavy-ion beams. In preparation.
19. Chapman, J. D., E. Blakely, K. Smith, A. Chatterjee, and C. Tobias. The role of hydroxyl radicals in mammalian cell inactivation by heavy-ion beams. In preparation.
20. Chapman, J. D., E. Blakely, K. Smith, R. Urtasun, and C. Tobias. The effectiveness of hypoxic cell radiosensitizers in mammalian cells inactivated with heavy-ion beams. In preparation.
21. Tobias, C. A. and T. Manney. Some molecular and cellular effects of heavily ionizing radiation. *Ann. N.Y. Acad. Sci.* 114, 16-32 (1964).
22. Chadwick, K. and H. Leenhouts. A molecular theory of cell survival. *Phys. Med. Biol.* 18, 78-87 (1973).
23. Chatterjee, A. and C. A. Tobias. Relationships between track structure and biological effects of heavy charged particles. In *Radiobiological Experiments Using Accelerated Heavy Ions at the Bevatron*, Lawrence Berkeley Laboratory Report No. LBL-2016 (1973).
24. Green, A. and J. Burki. A note on survival curves with shoulders. *Radiat. Res.* 60, 536-540 (1974).
25. Katz, R. Track theory and radiation quality. In *Biophysical Aspects of Radiation Quality*, (Vienna: International Atomic Energy Agency) pp. 11-23 (1971).
26. Fu, K. and T. Phillips. The relative biological effectiveness and oxygen enhancement ratio of neon ions for the EMT6 tumor. *Radiology* 120, 439 (1976).

27. Raju, M. A comparison of variation of cell-survival with depth for heavy charged particle beams with a modified Bragg peak. *Radiat. Res.* 67, 605 (1976). (Abstract)
28. Raju, M., personal communication.
29. Raju, M. and T. Phillips. The potential for heavy particle radiation therapy. Los Alamos Scientific Laboratory Report No. LA-6588-MS (1977).
30. Hall, E. Neutrons: radiobiological intercomparisons in vivo and in vitro. *Int. J. Radiat. Oncology, Biology & Physics*, in press.
31. Hall, E. J., H. H. Rossi, R. Coffey, and J. Varga. Biophysical studies with high-energy argon ions. II. Determination of the relative biological effectiveness and oxygen enhancement ratio. *Radiat. Res.* 67, 622 (1976). (Abstract) Paper in preparation.
32. Bird, R. P. and E. J. Hall. Biophysical studies with high-energy argon ions. III. Chinese hamster V-79 cell-cycle response at the Bragg peak. *Radiat. Res.* 67, 622 (1976). (Abstract) Paper in preparation.
33. Geard, C. R. and H. H. Rossi. Biophysical studies with high-energy argon ions. IV. Chromosome aberrations in aerated and hypoxic Vicia faba root meristems. *Radiat. Res.* 67, 623 (1976). (Abstract) Paper in preparation.
34. Bird, R. Synchrony experiment at the Bevalac. In *Annual Report on Research Project COO-3243-5*. Radiological Research Laboratory, Columbia University (1976).
35. Hall, E., S. Lehnert and L. Roizin-Towle. Split dose experiments with hypoxic cells. Implications for fractionated and low-dose rate radiotherapy. *Radiology* 112, 425-430 (1974).
36. Phillips, T., K. Fu, and S. Curtis. Tumor biology of helium and heavy-ion beams. Submitted for publication.
37. Phillips, T., K. Fu, and J. T. Leith. Interaction of hyperthermia with radiations of different linear energy transfer. *Int. J. Radiat. Biol.*, in press.
39. Hetzel, F. W., J. Kruuv, and H. E. Frey. Repair of potentially lethal damage in x-irradiated V-79 cells. *Radiat. Res.* 68, 308-319 (1976).
40. Ritter, M. and J. Cleaver. Induction of non-rejoining DNA breaks in mammalian cells by high-LET radiations: the relationship to cellular inactivation. *Radiat. Res.* 67, 604 (1976). (Abstract)
41. Suit, H. and M. Urano. Repair of sublethal radiation injury in hypoxic cells of a C3H mouse mammary carcinoma. *Radiat. Res.* 37, 423-434 (1969).
42. Roots, R. J., E. A. Blakely, T. C. H. Yang, and C. A. Tobias. Repair of DNA breaks in mammalian cells induced by accelerated heavy ions. *Radiat. Res.*, Abstract submitted for publication.
43. Keng, P., G. Powers, and J. Lett. Damage to tissues of the central nervous system from heavy ions. *Radiat. Res.* 67, 604 (1976).
44. Bird, R. and J. Burki. Survival of synchronized Chinese hamster cells exposed to radiation of different linear-energy transfer. *Int. J. Radiat. Biol.* 27, 105-120 (1975).
45. Sutherland, R. and R. Durand. *Current Topics Radiat. Res. Quart.* 11, 87 (1976).
46. Alpen, E. and A. Rodriguez, personal communication.
47. Barendsen, G. W. Response of cultured cells, tumors, and normal tissues to radiations of different linear energy transfer. *Current Topics in Radiat. Res.* 4, 295-354 (1968).
48. Ngo, F., A. Han, H. Utsumi, and M. Elkind. Comparative radiobiology of fast neutrons: relevance to radiotherapy and basic studies. *Int. J. Radiat. Oncology, Biology & Physics*, in press.
49. Todd, P. Fractionated heavy ion irradiation of cultured human cells. *Radiat. Res.* 34, 378-389 (1968).
50. Schneider, D. and G. Whitmore. Comparative effects of neutrons and x-rays on mammalian cells. *Radiat. Res.* 18, 286-306 (1963).

51. Elkind, M. Damage and repair processes relative to neutron (and charged particle) irradiation. *Current Topics in Radiat. Res. Quart.* 7, 1-44 (1970).
52. Raju, M., J. Frank, E. Bain, T. Trujillo, and R. Tobey. Repair of potentially lethal damage in CHO cells by x and α irradiation. Submitted for publication.
53. Shipley, W., J. Stanley, V. Courtenay, and S. Field. Repair of radiation damage in Lewis lung carcinoma cells following in situ treatment with fast neutrons and x-rays. *Cancer Res.* 35, 932-938 (1975).
54. Malaise, E. and M. Guichard. Relative biological effectiveness, oxygen enhancement ratio, and repair of potentially lethal damage of helium ions (overview). In *Proceedings of an International Workshop on Particle Radiation Therapy*, (American College of Radiology, pp. 385-402, 1975).
55. Lennartz, M., T. Coquerelle, and U. Hager. Modification of end-groups in DNA strand breaks of irradiated thymocytes during early repair. *Int. J. Radiat. Biol.* 28, 181-185 (1975).
56. Zeman, personal communication
57. Tobias, C., E. Blakely, T. Yang, A. Chatterjee, K. Smith, L. Craise, I. Madfes, and F. Abrams. The effects of accelerated heavy nuclei of neon and argon on mammalian cells in culture. In *Proceedings of an International Symposium on Radiobiological Research Needed for the Improvement of Radiotherapy*, Vienna, Austria, November 22-26, 1976. (Vienna: International Atomic Energy Agency) in press.
58. Alper, T., ed. Cell survival after low doses of radiation: theoretical and clinical implications. In *Proceedings of the 6th L. H. Gray Conference*, Bedford College, London, September 16-21, 1974. (London: John Wiley & Sons).
59. Saponzink, M. D. Oxygen enhancement ratios in synchronous HeLa cells exposed to low-LET radiation. *Radiat. Res.* 69, 27-39 (1977).
60. Gilet. See Chapter 9.
61. Leith, J. T., V. Arcellara, J. T. Lyman, and K. T. Wheeler. Response of a rat brain tumor with irradiation with accelerated neon ions. *Int. J. Radiat. Biol.* 28, 91-97 (1975).
62. Schilling, W. A., S. Curtis, T. Tenforde, K. Crabtree, J. Lyman, and J. Howard. Comparison of the radiation response of rat tumor cells exposed at various positions in the extended Bragg peak of heavy ion beams. Abstract submitted for publication.
63. Yang, T. C. H., J. Risius, I. Madfes, C. A. Tobias, J. Lyman, and J. Howard. Enhancement of viral transformation of cells in vitro by heavy-ion radiation. Abstract submitted for publication.
64. Blakely, E., et al. Unpublished data.
65. Tenforde, T., S. Curtis, D. Parks, W. Schilling, and J. Lyman. RBE for radiation-induced growth delay in a rat rhabdomyosarcoma exposed to Bevalac neon ion beams. *Radiat. Res.* 67, 555 (1976). (Abstract)
66. Curtis, S., T. Tenforde, S. Daniels, W. Schilling, K. Crabtree, J. Lyman and J. Howard. Comparison of tumor growth delay in a rat rhabdomyosarcoma irradiated with carbon, neon, and argon ion beams: single dose and preliminary fractionated dose results. To be presented at the 25th Annual Radiation Research Society Meeting, San Juan, Puerto Rico, May 7012, 1977.

CHAPTER 8

TISSUE RADIOBIOLOGY: ACUTE AND CHRONIC EFFECTS

Edward Alpen

EFFECTS OF ACCELERATED CHARGED PARTICLES ON NORMAL TISSUE SYSTEMS

An essential part of a research program leading to the use of heavy charged particles in radiation therapy of malignant disease is the set of studies aimed at the establishment of tolerance thresholds for normal tissues that might be included in the radiation field. Information on the effects of high-LET radiation on normal tissues was essentially limited to the studies of neutron effects until the initiation of the studies reported here.

The approach has been to establish the damage, repair, and late consequences associated with the exposure of organ systems that are judged to be critical dose limiters to radiotherapy. The organs identified as being of primary importance in limiting radiation treatment through effects on normal tissues are the lung and the spinal cord.¹ The skin and gastrointestinal tract are also important dose-limiting tissues. Skin, although not often the critical limiting tissue, plays a significant role as a contributor to patient morbidity, both late and delayed. The skin is particularly useful in quantitative studies of dose-response relationships, fractionation effects, and late sequelae. For this reason, we have chosen skin as an important tissue system for evaluation, along with the spinal cord and lung. Other tissues that we have chosen to evaluate for their occasional roles as dose limiters in radiotherapy are the gastrointestinal tract and the kidney.

An important consideration in heavy-ion therapy is the relative effectiveness of these beams in the production of late lesions that appear months to years after exposure. Fortunately, the lung, spinal cord, and skin systems that we have chosen are particularly amenable to observation for late sequelae, including carcinogenesis. Our studies have been extended, wherever possible, to include observations of late effects.

This chapter will review the studies done to date on the organ systems cited above with 910-MeV helium ions generated at the 184-inch cyclotron and with carbon and neon ions from the Bevalac.

EARLY EFFECTS ON SKIN (J. T. Leith, P. P. Smith, J. T. Lyman, and J. Howard)

Helium-ion Irradiation of Skin

A significant amount of work has been done on the effects of heavy particles on skin. Several different animals have been used, including mice, rats and hamsters. The reactions of the skin of the mouse leg have been used to compare single doses of 23-kV x rays to single doses of helium ions in the plateau region of ionization and to single doses of helium ions in the Bragg-peak region of ionization after modification by a moving copper ridge filter, yielding a modified or "spread-out" Bragg peak.² Skin responses to split doses of x rays (equal-size fractions) given over a 24-hour period were compared to split doses of spread-out Bragg-peak helium ions given over the same period. The skin reaction curves were then compared, and skin reactions averaged over a period of 8 to 30 days postirradiation were used to obtain dose-response curves by using a numerical grading system as shown in Table I.³⁻⁵

Comparison of skin reactions following different radiation treatments requires that the response-vs-time curves have similar shapes in terms of the rate of development of reaction, the maximum response reached, and the rate of decrease of reaction after allowance has been made for relative biological effectiveness (RBE).³ Given this similarity, it can be assumed that the demand and recovery processes

Table I. Grading system for acute skin irradiation reactions.

Tissue Grades and Appearance In Acute Injury Phase		Tissue Grades and Appearance In Recovery Phase	
1.0	No difference from controls.	1.0	No difference from controls.
1.5	Slight erythema.	1.5	Limb appears normal except for presence of hair depigmentation.
2.0	Distinct erythema.	2.0	Hair is depigmented, and there is sparse regrowth.
2.5	Suggestion of dry desquamation.	2.5	Sparse regrowth of hair, probably no edema; skin does not appear as thin as in a 3.0 recovery state.
3.0	Dry desquamation; powdery appearance of skin on close observation with small cracks and flaking skin; usually edematous.	3.0	Marked epilation; skin appears thin and tight.
3.5	Dry desquamation with suggestion of incipient skin breakdown.	3.5	Skin very thin, shiny, and usually edematous.
4.0	Moist desquamation of moderate extent; patchy appearance.	4.0	Focal areas of moist desquamation with extensive scab formation.
4.5	Major portion of field involved in moist desquamation; possibly small areas of necrosis.	4.5	Small, nonhealing areas.
5.0	Significant amount of necrosis with loss of dermis, similar to a third-degree burn.	5.0	Open but nondraining wound.

in the irradiated tissues are also similar so that the area underneath the response curve can be taken as an index of the "average" skin reaction.

Figure 1 shows the average 8- to 30-day dose-response curve for irradiation in the distal region of the spread-out Bragg peak vs the comparative x-irradiation response. It is evident that there is an increased effectiveness in producing skin reactions by the helium ions, and estimated RBE values have been indicated for various levels of effect with an average RBE of about 1.3. The average 8- to 30-day skin reactions after irradiation in the plateau region of ionization were not significantly different from the x-ray-produced reactions (i.e., the RBE is 1). The LET value for helium ions of 910-MeV initial energy is about 1.6 keV/ μ , a value similar to the modal LET in water for x rays of 230-kV energy.⁶

Kellerer and Brenot⁷ have suggested a method of presenting subjective grading system data involving the use of nonparametric analysis, in particular, the Mann-Whitney rank-order or U test.^{8,9} This approach allows estimation of the similarity of doses of a standard radiation (in this work, x ray doses) to doses of another radiation (for example, helium or neon ions). To make such comparisons, the total skin reaction score for each mouse in each experimental condition is used. For example, a group of mice, given a single x ray dose of 750 rads, have their individual, total 8- to 30-day postirradiation skin-reaction scores ranked from lowest to highest. This ranking of effect can then be compared to a similar ranking for another situation (e.g., 750 rads of spread-out Bragg-peak helium ions); the U test will test the null hypothesis that there is no difference between the two sampled populations. If this is true, the effects are not significantly different, and the ratio of doses for the effects produces an RBE estimation that is statistically acceptable for the two dose levels. Conversely, if the comparison of effects rejects the null hypothesis, this ratio of doses for the effects produces an RBE estimation that

Fig. 1. Dose-response curve for early skin reactions in mice after irradiation with helium ions in the spread-out Bragg curve. RBE values are indicated for various levels of effect as compared to 230-kV x rays. Error bars indicate the standard deviations of the mean values. (XBL 7311-1454)

is statistically acceptable for the two dose levels. Conversely, if the comparison of effects rejects the null hypothesis, this ratio of doses (and therefore RBE) is excluded from the range of possible RBE's implied in the null hypothesis. The 5-percent level of significance has been chosen for discrediting the null hypothesis.

In Fig. 2, graphs are shown of RBE vs size of dose for both plateau and spread-out Bragg-peak helium ions using the U test as an estimator of RBE. It is clear from Fig. 2A that the effectiveness of plateau helium ions is not different from that of 230-kV x rays. In Fig. 2B it can be seen that spreadout Bragg-peak helium ions are more effective than 230-kV x rays with an RBE of 1.3 being a reasonable estimate of this increased effect; however, as the 95-percent confidence limits of the RBE estimation include an RBE of 1, in eight of the ten dose-level comparisons the RBE of 2.3 could be lower. In Fig. 2B the RBE may decrease with increasing dose of helium ions.

The dose-effect curves for the 24-hour split-dose experiments are shown in Figs. 3 and 4 for x rays and helium ions, respectively, in the spread-out Bragg-peak region of ionization. In both figures, the recovery dose $(D_2 - D_1)/(n - 1)$ in rads is given for various levels of effect. D_2 is defined as the total dose given in the two dose fractions separated by 24 hours that is needed to produce the same effect as the single-dose exposure (D_1); n is the number of fractions used, in this case, two. For the x-ray, 24-hour, split-dose experiment, the average amount of dose recovered is about 515 rads. For the spread-out Bragg-peak helium ions, the amount of dose recovered within 24 hours is about 390 rads, a decrease in the 24-hour repair capacity of about 25 percent, a value similar to the percentage increase in RBE. The values found for 24-hour recovery between split doses for the skin of mice after x-irradiation are similar to other values listed in the literature.¹⁰

Fig. 2. RBE versus dose level for production of early skin reactions for either helium ions in the plateau region of ionization (A) or helium ions in the spread-out Bragg-peak region of ionization (B) as compared to 230 kV x rays. The heavy solid bars indicate RBE values that are excluded at the 95% level of confidence. The direction of the wedges indicates the direction in which the true RBE is thought to lie. (XBL 7311-6803)

Late skin reactions as estimated using Table I are shown in Fig. 5. As in the case of early RBE values for single doses of plateau-region helium ions vs x rays, there appears to be no difference between the two types of radiation for late damage (to about 200 days postirradiation, Fig. 5A). There still appears, however, to be a greater effectiveness for single doses of spread-out Bragg-peak helium ions vs x rays for late effect as indicated in Fig. 5B for various levels of effect, the an RBE of 1.2 being a good estimate of this increased effect. In Fig. 5C, the late reactions after 24-hour split doses of spread-out Bragg-peak helium ions and x rays are shown. There is no difference between the two curves.

Neon-ion Irradiation of Skin

For the last 18 months we have extended our studies with mouse skin to neon-ion beams accelerated at the Bevalac. For these first studies, a neon beam was chosen that had a maximum penetration in tissue-

Fig. 3. Dose-response curves of the early postirradiation average skin reactions for mice irradiated with either single doses of 230-kV x rays or with the same total doses given in two equal fractions separated by a 24-hour period. The recovery dose ($D_2 - D_1$) in rads for various levels of effect is indicated. Error bars are the standard deviations of the mean values. (XBL 7311-1456)

Fig. 4. Dose-response curves of the early postirradiation average skin reactions for mice irradiated with either single doses of spread-out Bragg-peak helium ions or with the same total doses given in two equal fractions separated by a 24-hour period. The recovery dose ($D_2 - D_1$) in rads for various levels of effect is indicated. Error bars are the standard deviations of the mean values. (XBL 7311-1453)

Fig. 5. Dose-response curves of the late average skin reactions (95 to 105 days postirradiation). In A, late effects after helium-ion irradiation in the plateau region of ionization are shown. In B, late effects after helium-ion irradiation in the spread-out Bragg peak are shown. RBE values for various levels of effect are shown in A and B. In C, late effects for the 240-hour split-dose experiments using x rays and spread-out Bragg-peak helium ions are shown. Error bars are the standard deviations of the mean values (Leith et al., 1975b). (XBL 7311-6823)

equivalent material of about 14.5 cm. This penetration was achieved by using a 400-MeV/nucleon initial energy. The Bragg peak was modulated by an appropriate lead ridge filter to give the dose distribution in tissue shown in Fig. 6. Also shown is the modulated helium-ion peak utilized in these studies as described in the preceding section. The shape of the modulated peak has been determined on the basis of theoretical estimations of the LET distribution and the potential RBE to give essentially equally effective biological doses over the 5-cm spread-out peak. Arrows in the figure show the relative position of the mouse leg to the dose-distribution curve for both the helium-ion and neon-ion irradiations. Also shown is the dose-effect curve for irradiation of the skin of the mouse leg with plateau neon ions. As previously described, the area beneath the curve of graded skin reaction vs time is a measure of acute response.

Figure 7 shows the dose-response curves for hamster skin, using the same grading and exposure procedures as for the mouse. In the case of the hamster, the ventral thoracic skin was irradiated in the course of the lung irradiation experiments described later. X-ray curves are shown for both animal species. The RBE's for both animals range from 1.4 to 1.6 for the plateau-region irradiation. The average LET for this region of the neon depth-dose curve is about 32 keV/ μ m. The RBE's for the typical level of effect shown in the curve are 1.4 for mice and 1.6 for hamsters. The RBE is, to some extent, dependent upon dose (or conversely, level of effect).

Fig. 6. Depth-dose profiles for the modulated (spread-out) helium-ion, neon-ion and carbon-ion Bragg curves used for the irradiation of mouse skin. The positions of the mouse leg in the spread-out regions of the curves are indicated by arrows.
(XBL 773-3209)

Fig. 7. Dose-response curves of the early postirradiation, average skin reactions for mice (dashed lines) and hamsters (solid lines) irradiated with either x rays or neon ions in the plateau region of ionization. RBE values at specific levels of effect are indicated in the figure.

Figure 7 also shows data for the response of mouse skin to divided doses (two equal fractions in 24 hours). The average amount of dose recovered within the 24-hour period is 485 rads for the x-ray-treated animals and 140 rads for the neon-treated animals. If this latter dose is corrected for the RBE for the acute effect, the "effective x-ray equivalent recovery" is approximately 300 rads (140×2.2). The recovery adjusted for RBE appears to be approximately 70 percent of the x-ray recovery for the peak neon ions compared to 230-kVp x rays.

Figure 8 shows the acute response data for mouse skin irradiated in the spread-out Bragg peak in the position shown earlier. Comparison is to 230-kVp x rays as before. The mouse leg is about 0.5 cm thick; therefore, one would approximate the decrease of physical dose to be about 5 percent across the thickness of the leg. It should be noted, however, that the modulated peak is adjusted to give what would be predicted to be equally effective biological doses across the whole 4-cm region. From the figure, it can be seen that the RBE for the modulated Bragg peak is approximately 2.1 to 2.3 for the moderate response level (score of 2.5). This is compared with an RBE of 1.5 for the neon plateau.

Fig. 8. Dose-response curves of the early postirradiation, average skin reactions for mice irradiated with neon ions in the spread-out Bragg-peak region of ionization. A typical RBE value is indicated for a specific level of effect as compared to the 230-kV x-ray response. Also, the dose response curves of the early postirradiation, average skin reactions for mice irradiated with 2 equal fractions of x rays or spread-out Bragg-peak neon ions are shown. The recovery dose in rads for a specific level of effect for x rays and neon-ion irradiation is indicated in the figure.

Carbon-ion Irradiation of Skin

The most recent studies with skin have been carried out with accelerated carbon ions. The maximum penetration of the carbon-ion beam was 26 cm, achieved with an energy of 400 MeV/nucleon. The spread-out Bragg peak was approximately 4 cm across and was achieved in the same manner as for the neon-ion beam. The depth-dose distribution and the location of the mouse leg for irradiation are shown in Fig. 6. Studies were conducted with irradiations performed with the modulated Bragg peak as mentioned and with the plateau region of the depth-dose curve. For the plateau, the RBE was essentially 1.0 compared to the x-ray standard. For the modified Bragg peak, the RBE for the same level of response as before (an average severity score of 2.5) was 1.2. As yet, no comparative recovery studies have been carried out with the carbon-ion beam. The data for mouse skin at high doses are summarized in Table II.

Table II. The relative responses of mouse skin to accelerated helium ions, neon ions and carbon ions. The reference radiation in all cases is 230-kVp x rays.

Ion Beam	Beam Position of the Mouse Skin	RBE at Moderate Response Level	Relative Repair
⁴ Helium	Plateau	1.0	not studied
	Bragg Peak (6 cm)	1.3	same as x ray
¹² Carbon	Plateau	1.0	not studied
	Bragg Peak (4 cm)	1.2	not studied
²⁰ Neon	Plateau	1.5	not studied
	Bragg Peak (4 cm)	2.3	70% of x ray

Note: Studies with hamster skin in the neon plateau gave results essentially the same as for the mouse.

CHRONIC EFFECTS OF HELIUM- AND NEON-ION IRRADIATION ON THE LUNG (K. H. Woodruff, J. T. Leith, P. P. Smith, V. Havens and M. McDonald)

Irradiation-induced, delayed pulmonary fibrosis is of great significance as an undesirable side effect of radiation therapy that includes significant portions of the lung in the radiation field. Finding a suitable model for the study of this process has been difficult; however, the golden Syrian hamster has proven to be particularly valuable in this regard and has been used extensively by others.^{11,12}

The exposure conditions and locations in the Bragg peak were the same for the hamster-lung exposures as for the mouse-skin exposures described in the previous section. Figure 6 shows the location of the animal relative to the spread-out Bragg peak. The results, using standard morphometric techniques, are as follows:

The volume densities of pulmonary parenchyma and nonparenchyma are unchanged at two weeks and one month postirradiation for all types of irradiation and dose levels (Table III). The individual components of these two parameters (alveoli, septa, airways, blood vessels, and collagen) also remain constant.

In contrast, the cellular composition of the lungs undergoes change after irradiation, and the different types of treatment show different degrees of change. At two weeks, there is an influx of inflammatory cells into alveolar septa and spaces. The differences in volume density of inflammatory cells between controls and animals given the following treatments

Table III. Volume densities* of pulmonary parenchyma and nonparenchyma at 2 weeks and 1 month after irradiation.

Type irradiation	Dose (rads)			
	500	1000	1500	2000
Parenchyma, 2 weeks, control = 0.762 ± 0.022				
X-ray	0.789 ± 0.030	0.777 ± 0.013	0.794 ± 0.018	0.776 ± 0.024
Helium Bragg peak	0.843 ± 0.019	0.780 ± 0.015	0.777 ± 0.013	0.780 ± 0.027
Helium plateau	0.794 ± 0.026	0.797 ± 0.018	0.796 ± 0.027	0.790 ± 0.025
^{20}Ne plateau	0.784 ± 0.013	0.780 ± 0.035	0.807 ± 0.028	—
Parenchyma, 1 month, control = 0.804 ± 0.014				
X-ray	0.795 ± 0.023	0.785 ± 0.015	0.794 ± 0.014	0.796 ± 0.033
Helium Bragg peak	0.781 ± 0.011	0.797 ± 0.016	0.786 ± 0.015	0.809 ± 0.008
Helium plateau	0.796 ± 0.011	0.787 ± 0.016	0.783 ± 0.019	0.826 ± 0.006
^{20}Ne plateau	0.801 ± 0.022	0.814 ± 0.032	0.786 ± 0.004	—
Nonparenchyma, 2 weeks, control = 0.238 ± 0.022				
X-ray	0.211 ± 0.030	0.223 ± 0.013	0.203 ± 0.018	0.224 ± 0.024
Helium Bragg peak	0.197 ± 0.019	0.220 ± 0.015	0.223 ± 0.013	0.220 ± 0.027
Helium plateau	0.206 ± 0.026	0.203 ± 0.018	0.204 ± 0.027	0.210 ± 0.025
^{20}Ne plateau	0.217 ± 0.013	0.226 ± 0.035	0.173 ± 0.028	—
Nonparenchyma, 1 month, control = 0.196 ± 0.014				
X-ray	0.205 ± 0.023	0.215 ± 0.015	0.206 ± 0.014	0.204 ± 0.033
Helium Bragg peak	0.219 ± 0.011	0.203 ± 0.016	0.214 ± 0.015	0.191 ± 0.008
Helium plateau	0.204 ± 0.011	0.213 ± 0.016	0.217 ± 0.019	0.174 ± 0.006
^{20}Ne plateau	0.199 ± 0.022	0.186 ± 0.032	0.214 ± 0.004	—

* Volume density = mean of the number of hits per 1000 total points of three hamster lungs plus or minus one standard deviation.

Table IV. Volume densities of inflammatory cells* at 2 weeks and 1 month after irradiation.

Type irradiation	Dose (rads)			
	500	1000	1500	2000
Two weeks, control = 0.009 ± 0.001				
X-ray	0.010 ± 0.001	0.012 ± 0.001	0.016 ± 0.003	$0.023 \pm 0.004\uparrow$
Helium Bragg peak	0.016 ± 0.004	$0.028 \pm 0.001\uparrow$	$0.031 \pm 0.006\uparrow$	$0.037 \pm 0.004\uparrow$
Helium plateau	$0.018 \pm 0.002\uparrow$	$0.023 \pm 0.003\uparrow$	$0.026 \pm 0.004\uparrow$	$0.033 \pm 0.005\uparrow$
^{20}Ne plateau	$0.031 \pm 0.006\uparrow$	$0.035 \pm 0.007\uparrow$	$0.039 \pm 0.006\uparrow$	—
One month, control = 0.007 ± 0.001				
X-ray	0.016 ± 0.004	0.020 ± 0.005	$0.026 \pm 0.004\uparrow$	$0.025 \pm 0.002\uparrow$
Helium Bragg peak	$0.025 \pm 0.004\uparrow$	$0.034 \pm 0.004\uparrow$	$0.046 \pm 0.003\uparrow$	$0.050 \pm 0.003\uparrow$
Helium plateau	$0.030 \pm 0.005\uparrow$	$0.033 \pm 0.001\uparrow$	$0.039 \pm 0.001\uparrow$	$0.043 \pm 0.004\uparrow$
^{20}Ne plateau	$0.033 \pm 0.006\uparrow$	$0.039 \pm 0.005\uparrow$	$0.053 \pm 0.006\uparrow$	—

* Within each time group, significantly different from control values at $p = 0.05$.

Table V. Volume density of capillary lumina at 2 weeks and 1 month after irradiation.

Type irradiation	Dose (rads)			
	500	1000	1500	2000
Two weeks, control = 0.062 ± 0.005				
X-ray	0.079 ± 0.005	0.076 ± 0.002	0.075 ± 0.001	0.073 ± 0.002
Helium Bragg peak	$0.096 \pm 0.011^*$	$0.099 \pm 0.008^*$	$0.099 \pm 0.003^*$	$0.097 \pm 0.003^*$
Helium plateau	$0.091 \pm 0.006^*$	$0.095 \pm 0.008^*$	$0.085 \pm 0.003^*$	$0.104 \pm 0.010^*$
^{20}Ne plateau	$0.116 \pm 0.018^*$	$0.131 \pm 0.016^*$	$0.152 \pm 0.014^*$	—
One month, control = 0.056 ± 0.010				
X-ray	0.080 ± 0.008	$0.096 \pm 0.003^*$	$0.103 \pm 0.012^*$	$0.105 \pm 0.013^*$
Helium Bragg peak	$0.106 \pm 0.001^*$	$0.092 \pm 0.007^*$	0.081 ± 0.008	0.061 ± 0.006
Helium plateau	$0.094 \pm 0.007^*$	$0.087 \pm 0.006^*$	0.089 ± 0.010	0.080 ± 0.009
^{20}Ne plateau	$0.081 \pm 0.002^*$	0.075 ± 0.004	0.070 ± 0.008	—

* Significantly different from the control at $p = 0.05$.

are statistically significant: x-irradiation at 2,000 rads; helium in the Bragg peak, 1,000 rads and above; helium in the plateau region, 500 rads and above; and neon at doses of 500 rads and above. At all doses, the volume density changes resulting from neon compared to x-irradiation are statistically significant. No statistical significance can be demonstrated between the values resulting from the two types of helium irradiation and the neon ions. The helium irradiations result in values that show statistically significant differences from values resulting from x-irradiation at doses of 1,000 rads and above (Table IV).

At one month after irradiation, the increase in the number of inflammatory cells remains. At all doses, the volume density changes resulting from neon irradiation are statistically different from the control values and the values resulting from x-irradiation but not from those values resulting from helium-ion irradiation. X-ray values are different from control values at 1,500 and 2,000 rads; helium irradiation values show increases at doses of 500 rads and above. Helium values are statistically different from x-ray values at 1,500 and 2,000 rads. These numerical data are presented in Table IV. The individual components of the inflammatory response consist almost exclusively of neutrophils and macrophages. At two weeks, the majority of the response is neutrophilic; by one month, most inflammatory cells are macrophages.

The second parameter that undergoes significant change is the volume density of capillary luminae. Two weeks after irradiation, at all dose levels, the values from lungs irradiated with neon ions showed increases from the control values and values from animals receiving x-irradiation. In addition, neon values are significantly different from the values resulting from both types of helium irradiations at 1,500 rads. Volume density changes resulting from irradiation with helium in the Bragg peak of ionization are statistically different from the changes resulting from x-irradiation with doses of 1,000, 1,500, and 2,000 rads. Volume density changes resulting from irradiation with helium in the plateau region of ionization are statistically different from the changes resulting from x-irradiation at 1,500 and 2,000 rads (Table V). By one month, however, the morphometric data (Table V) illustrate that the capillaries in the helium- and neon-irradiated animals show a return toward control values while the x-irradiated lungs demonstrate increases in density of capillary luminae with increasing dose.

The volume densities of septal cells (Table VI) show no clear correlation with dose level or time period postirradiation although the decrease in septal cells in lungs at two weeks after neon-ion irradiation may reflect the increased capillary dilation. Table VII demonstrates that the numbers of alveolar Type-2 cells are unchanged at two weeks and one month after irradiation.

In addition to the morphometric analysis, both lungs and the heart, thymus, and thoracic skin of each animal were evaluated morphologically. One bronchial papilloma was identified in a hamster sacrificed two weeks after irradiation with 2,000 rads of accelerated helium ions in the Bragg peak of ionization. This was interpreted as a spontaneous occurrence. Pulmonary dysplasia and malignant tumors were not seen. In general, the morphologic findings were subtle, and differences resulting from the various doses and types of irradiation would have been obscured without the morphometric data.

The hearts showed no identifiable effects from any of the irradiations. The thymuses were small with mild cortical lymphocyte depletion. No differences in thymic damage were identified among the various types of irradiation, probably because, by two weeks after irradiation, repopulation of cortical lymphocytes occurs. The gross skin reactions have been reported elsewhere in this report.

Table VI. Volume density of septal cells at 2 weeks and 1 month after irradiation.

Type irradiation	Dose (rads)			
	500	1000	1500	2000
Two weeks, control	0.161 ± 0.004			
X-ray	0.149 ± 0.004	0.152 ± 0.012	0.153 ± 0.012	0.153 ± 0.010
Helium Bragg peak	0.138 ± 0.012†	0.142 ± 0.012	0.142 ± 0.001†	0.143 ± 0.028
Helium plateau	0.138 ± 0.012	0.153 ± 0.017	0.126 ± 0.010†	0.127 ± 0.015
²⁰ Ne plateau	0.112 ± 0.005†	0.110 ± 0.015†	0.116 ± 0.015†	—
One month, control	0.162 ± 0.015			
X-ray	0.150 ± 0.007	0.152 ± 0.006	0.165 ± 0.014	0.142 ± 0.015
Helium Bragg peak	0.121 ± 0.013	0.140 ± 0.015	0.137 ± 0.010	0.131 ± 0.016
Helium plateau	0.117 ± 0.001†	0.121 ± 0.002†	0.131 ± 0.008	0.131 ± 0.009
²⁰ Ne plateau	0.142 ± 0.016	0.142 ± 0.022	0.139 ± 0.007	—

* Significantly different from controls at p = 0.05.

Table VII. Volume density of alveolar type 2 cells at 2 weeks and 1 month after irradiation.

Type irradiation	Dose (rads)			
	500	1000	1500	2000
Two weeks, control = 0.026 ± 0.004				
X-ray	0.024 ± 0.002	0.022 ± 0.002	0.022 ± 0.002	0.021 ± 0.005
Helium Bragg peak	0.026 ± 0.001	0.028 ± 0.003	0.026 ± 0.001	0.021 ± 0.003
Helium plateau	0.028 ± 0.007	0.030 ± 0.002	0.033 ± 0.002	0.008 ± 0.004
^{20}Ne plateau	0.034 ± 0.004	0.034 ± 0.002	0.034 ± 0.004	—
One month, control = 0.021 ± 0.006				
X-ray	0.022 ± 0.002	0.025 ± 0.007	0.042 ± 0.005	0.035 ± 0.007
Helium Bragg peak	0.039 ± 0.006	0.040 ± 0.006	0.035 ± 0.007	0.036 ± 0.005
Helium plateau	0.035 ± 0.003	0.036 ± 0.003	0.037 ± 0.008	0.034 ± 0.004
^{20}Ne plateau	0.030 ± 0.005	0.037 ± 0.004	0.033 ± 0.002	—

In contrast to the skin, where it has been relatively easy to establish a quantitative model based on scoring of injury, it has been extremely difficult to do the same for the lung. Quantitative morphometric methods have been established by us and applied as described.

Clear evidence has been demonstrated of a dose-related change in the volume density of capillary luminae and in inflammatory cells in the hamster lung two weeks and one month postirradiation. It is also clear that plateau-region neon ions produce these lesions with significantly increased effectiveness.

At this point, it does not appear to be useful to try to estimate quantitative RBE values for the several radiations used.

So far, the incidence of radiation-induced carcinogenesis is still low. It is certainly expected, however, that as further experiments are performed we will accumulate significant data on tumor induction.

Data will soon become available on the effects of carbon-ion irradiation of the hamster lung. In October 1976, single-dose, Bragg-peak, carbon-ion exposures were completed as well as fractionated exposures--with two fractions separated by 24 hours and five fractions, each exposure separated by 24 hours. It is expected that data analysis on the carbon-ion exposures will begin producing useful results in the second half of 1977.

Additional studies are now underway to develop further quantitative endpoints beyond the morphometric studies described above. These endpoints include cumulative mortality from pulmonary insufficiency, analysis of enzymes of the lung, chest x rays accomplished in conjunction with the Department of Radiology, University of California, San Francisco, and electron transmission and scattering microscopy.

EFFECTS OF HELIUM-ION IRRADIATION ON THE GASTROINTESTINAL TRACT (E. L. Alpen, P. P. Smith, V. Havens, and M. McDonald)

All of the studies described here have been carried out using the Withers gut microcolony method,¹³ which has found wide application as a clonogenic assay for survival of the intestinal crypts. The standard assay, as modified by us, consists of irradiation of at least the whole abdomen of the LAF₁ female mouse with graded doses of the irradiation to be evaluated. In the case of x rays, the whole body is irradiated. In the case of accelerated heavy particles, a 3-cm by 5-cm collimator is used, and the radiation field is adjusted to cover the mouse from well above the diaphragm to the lower end of the body. Four days after irradiation, the animals are sacrificed, and a 2-cm segment of the jejunum is collected and fixed in Bouin's fluid. After the usual processing, the cross section of the small intestine is examined microscopically; the surviving crypt cells that show signs of regeneration at this time (using the criteria established by Withers) are counted.

Only the data on helium ions are complete enough for tentative conclusions. In the plateau portion of the Bragg curve for helium ions, where the average LET is approximately 1.5 keV/ μm , the D_0 was 197 rads

compared with a value of 160 rads for x rays. The proximal Bragg peak has an LET of approximately 2.0 keV/ μ m, and the proximal peak has an LET of 10 keV/ μ m. The D_0 values for these two positions were 201 and 182 rads, respectively. These values are in the expected order of effectiveness; the plateau and proximal peak, where LET is not significantly different from 230-kVp x rays, are essentially equal whereas the distal peak is significantly lower. We cannot at this time, however, explain why all values are higher than those for 230-kVp x rays.

The differences in D_0 are not significant at this time, and more data are being collected in replicate experiments. The curves, however, are not parallel, and at the higher survival fractions the distal peak is more effective than x rays.

Exposures have been completed for the same system using the plateau and the proximal and distal peaks of the neon-ion, carbon-ion and argon-ion beams.

We are now in the initial phases of two experiments; the first is a straightforward, two-fraction experiment to measure the 24-hour recovery potential for the three heavy-ion beams, and the second is an examination of the effects of five daily fractions on the response of the intestinal crypt cells. Another experiment planned for the immediate future is the measurement of the in vivo OER in gut crypt cells of anoxic animals following exposure. We are also examining the possibility of measuring the long-term, irreversible recovery of the gastrointestinal tract by using repeated smaller fractions of irradiation followed by a prolonged period of recovery (on the order of 2 to 3 months) before a test exposure to measure the D_0 for the previously exposed and recovered cells of the intestinal crypt.

SPINAL CORD EFFECTS (J. T. Leith, P. P. Smith, K. H. Woodruff and B. S. Lewinsky)

We have investigated the effects of ionizing radiation on the spinal cord as a model for the chronic effects of radiation. In this work, CF-1 rats have been irradiated at both the Lawrence Berkeley Laboratory 184-inch cyclotron using helium ions in both the plateau and spread-out Bragg-peak regions of ionization and at the Bevalac using 375-MeV/nucleon neon ions in the plateau region of ionization. The spinal cords were exposed over the region of the twelfth thoracic to the first lumbar vertebrae. For the helium-ion irradiations, both single and fractionated exposures were given. The fractionated exposures consisted of 10 equal fractions given over a 22-day period (10F/22D). After irradiation, the number of rats showing signs of partial myelopathy was assessed. It was found that, for both the plateau and spread-out Bragg-peak regions of ionization, the percent incidence of myelopathy was small (about 20 percent) at a single dose of 2,000 rads and rose to 100 percent at about 3,000 rads. There appeared to be no difference between the plateau and spread-out Bragg-peak regions of ionization for the production of myelopathy. Combined data for both positions on the Bragg curve appear to indicate a threshold tolerance dose for production of myelopathy of between 1,900 and 2,000 rads, with complete paralysis occurring at a dose level of about 2,600 rads or more.^{14,15} The latency periods for production of paralysis are the same for both the plateau and Bragg-peak regions of ionization, about 20 weeks.

Histological studies of the spinal cords showed few abnormalities in rats without overt paralysis; however, as early as 4 months postirradiation in paralyzed animals receiving doses of 3,500 rads, there was focal symmetrical demyelination and axonal degeneration in the anterolateral columns of white matter. With increasing time, the demyelination and necrosis became more extensive both anteriorly and laterally. The demyelination extended distally into the distal (sacral) cord, while the proximal cord remained histologically normal.

In the helium-ion fractionated-dose experiment, paralysis was found only in the group irradiated with the highest total dose (6,530 rads), and at this dose level only a few animals became paralyzed (about 10 percent). These data indicate that the threshold tolerance dose for production of paralysis in these rats is between 5,220 and 6,530 rads for the total dose given in 10 fractions over 22 days. If the

10-percent level of production of partial paralysis is used to evaluate dose effects, 2,000 rads administered in a single dose and 6,530 rads given with this fractionation schedule appear roughly comparable. The amount of dose recovered per interval is then about 500 rads; that is, about 77 percent of each radiation dose is completely repaired.

For irradiation with neon ions in the plateau region of ionization, only single doses have been studied. These data are shown in Fig. 9. At a level of production of partial paralysis of 50 percent, an RBE value of 1.3 is obtained. This value agrees relatively well with RBE values for mouse and hamster skin of about 1.5.

In Fig. 10 we have plotted the spinal-cord data from the work of Van der Kogel and Barendsen¹⁶ (who used x rays and 15-MeV neutrons) and Leith et al.^{14,15} (who used helium and neon ions) using the approach used by Douglas and Fowler¹⁷ in which the inverse of the total dose required to produce a given effect is plotted vs the dose per fraction. In this figure the multifraction skin data of Douglas and Fowler are included for reference. The low-LET, spinal-cord data (300-kV x rays and helium ions) have been fitted by a least-squares, linear-regression analysis (using the 10-percent level of myelitis for comparison). The intercept of the regression line occurs at a higher total dose than that of the curve for mouse skin. This suggests that the "survival curve" for the spinal cord (realizing that the target(s) at risk is not precisely defined) has a small initial shoulder. If one considers the line for the 15-MeV neutron data, it is clear that the intercept has changed greatly while the slope of the line has changed less dramatically. These changes may reflect the differences in repair of sublethal radiation damage with different radiation modalities. An interesting feature of such a plot is that, at any dose per fraction, the ratio of the total doses required to produce the effect is a measure of the RBE at that dose per fraction. As an example, we have indicated the RBE for neon ions vs the comparable point on the low-LET, spinal-cord curve yielding an RBE of about 1.5 (at 1,500 rads per fraction).

EFFECTS ON THE TESTES (E. L. Alpen, P. P. Smith, M. McDonald, and V. Havens)

The testes is certainly not generally considered to be a critical organ at risk in radiotherapy, but a broad range of reports have indicated that the testes is a valuable indicator of relative biological effectiveness across a broad range of LET values. The method consists of irradiation of the testes followed 28 to 35 days later by dissection of the testes and determination of the weight remaining. Other workers^{18,19} have shown that the weight loss of the testes has two components--a sensitive component, which has a D_0 for x rays of about 50 rads, and a radioresistant component, presumably the connective stroma, which has a D_0 variously estimated to be 1,500 to 6,000 rads.

Weight-loss analysis by the fitting of two first-order exponential relationships will provide estimates of both D_0 values. Because of the extremely shallow slope of the resistant fraction, the estimate of D_0 is highly variable.

We have completed exposures with x rays and helium, neon, argon and carbon beams in the plateau and proximal and distal peaks. As yet, not all of the data are analyzed, but the method has certainly proven to be highly precise. There is no shoulder in the dose-response curve, and the extrapolation number is 1.0. One study using five-fraction exposures has shown that weight loss is not sensitive to fractionation.

CARCINOGENESIS

Carcinogenesis studies are now beginning, but no data are yet available for analysis. As mentioned above, the animals exposed during both the skin acute-effects and lung studies will be followed for tumor induction. Another study whose sole purpose is the examination of the LET dependence of tumor induction has been initiated in collaboration with Dr. R. J. M. Fry of the Argonne National Laboratory.²⁰

Fig. 9. Production of partial myelopathy in rats after irradiation with neon ions in the plateau region of the depth-dose curve (closed circles) or with helium ions in either the plateau (open circles) or spread-out Bragg peak (closed triangles). The RBE for production of 50-percent myelopathy is indicated. (XBL755-4992)

Fig. 10. Plot of the reciprocal total dose to produce a given level of effect in rat spinal cord vs. dose per fraction. Multifraction mouse-skin data (dashed line) are included for comparison.

Dr. Fry has identified the Harderian gland of the mouse as a tissue with carcinogenic potential that is extremely sensitive to the LET of the radiation. His studies have shown that fission neutrons can induce tumors at doses at which gamma-ray controls as well as unirradiated controls have essentially zero incidence. We have repeated these studies using both plateau and Bragg-peak neon ions and we are presently scheduled to irradiate mice with helium and carbon ions. The tumors have a relatively long latent period (greater than 200 days), and we do not expect to have data for at least a year.

REFERENCES

1. *Cancer (Suppl.)* 37, 2046-1055 (1976).
2. Raju, M. R., M. Gnanapurani, U. Madhvanath, J. Howard, and J. T. Lyman. Relative biological effectiveness and oxygen enhancement ratio at various depths of a 910-MeV helium ion beam. *Acta Radiol.* 20, 353-357 (1971).
3. Denekamp, J., J. F. Fowler, K. Kragt, C. J. Parnell, and S. B. Field. Recovery and repopulation in mouse skin after irradiation with cyclotron neutrons as compared with 250 kV X-rays or 15 MeV electrons. *Radiat. Res.*
4. Leith, J. T., W. A. Schilling, J. T. Lyman, J. Howard, and D. G. Baker. Comparison of skin responses of mice after single or fractionated exposure to cyclotron-accelerated helium ions and 230 kV X-irradiation. *Radiat. Res.* 62, 195-215 (1975).
5. Leith, J. T., K. H. Woodruff, and J. T. Lyman. Early effects of single doses of 375 MeV/nucleon ²⁰neon ions on the skin of mice and hamsters. *Radiat. Res.* 66, 440-450 (1976).
6. Johns, H. E. Radiation fields and their dosimetry. In: *Radiation Dosimetry* (Hine and Brownell, eds.). (New York: Academic Press) pp. 391-594 (1965).
7. Kellerer, A. M., and J. Brenot. Nonparametric determination of modifying factors in radiation therapy. *Radiat. Res.* 56, 18-39 (1973).
8. Siegel, A. *Nonparametric Statistics*. (New York: McGraw Hill) 1956.
9. Tate, M. W., and R. C. Clelland. *Nonparametric and Shortcut Statistics*. (Danville, Illinois: Interstate Publishers) 1959.
10. Denekamp, J., M. M. Ball, and J. F. Fowler. Recovery and repopulation in mouse skin as a function of time after X-irradiation. *Radiat. Res.* 37, 361-370 (1969).
11. deVilliers, A. M., and P. Gross. Radiation pneumonitis: x-ray induced lesions in hamsters and rats. *Arch. Envir. Health* 15, 545-564 (1967).
12. deVilliers, A. J., and P. Gross. Morphologic changes induced in the lungs of hamsters and rats by external radiation (x-rays). A study in experimental carcinogenesis. *Cancer* 19, 1399-1410 (1966).
13. Withers, H. R., and M. M. Elkind. Microcolony survival assay for cells of mouse intestinal mucosa exposed to radiation. *Int. J. Radiat. Biol.* 17, 261-267 (1970).
14. Leith, J. T., B. S. Lewinsky, W. A. Schilling, K. H. Woodruff, and J. T. Lyman. Tolerance of the spinal cord of rats to irradiation with cyclotron-accelerated helium ions. *Cancer* 35, 1692-1799 (1965).
15. Leith, J. T., K. H. Woodruff, B. S. Lewinsky, J. T. Lyman, and C. A. Tobias. Tolerance of the spinal cord of rats to irradiation with accelerated neon ions. *Int. J. Radiat. Biol.* 28, 393-398 (1975).
16. Van der Kogel, A. J., and G. W. Barendsen. Late effects of spinal cord irradiation with 300 kV X-rays and 15 MeV neutrons. *Brit. J. Radiol.* 47, 393-398 (1973).
17. Douglas, B. G., and J. F. Fowler. The effect of multiple small doses of X-rays on skin reactions in the mouse and a basic interpretation. *Radiat. Res.* 66, 401-426 (1976).
18. Kalman and Kohn.
19. Krebs.
20. Fry, R. J. M. Radiation oncogenesis *in vivo*. In: *Particle Radiation Therapy, Proceedings of an International Workshop*, Oct. 1-3, 1975, Key Biscayne, Florida, pp. 304-330.

CHAPTER 9

TUMOR RADIOBIOLOGY WITH BEVALAC HEAVY-ION BEAMS

Tom S. Tenforde and Stanley B. Curtis

INTRODUCTION

Tumor radiotherapy using high-energy charged particles has several potentially advantageous features in comparison with conventional radiation modalities.^{1,2} First, the depth-dose characteristics of charged-particle beams (see Chapter 3) are well-suited for the irradiation of deep-seated tumors. By the use of Bevalac-accelerated heavy ions with energies less than 1 GeV/nucleon, tumors located as deep as 20 to 30 cm from the body surface can be irradiated within the Bragg-peak ionization region of the beam. Furthermore, by employing variable-thickness absorbers (ridge filters), the Bragg-peak ionization region of a high-energy beam can be spread to a width sufficient to encompass the entire tumor volume.

A second principal advantage of charged-particle beams with high linear energy transfer (LET) is a reduced oxygen effect. In the Bragg-peak region of stopping charged-particle beams, the oxygen enhancement ratio (OER) for cell killing is reduced relative to x rays, allowing a more efficient sterilization of hypoxic tumor cells.

A third major advantage is the large relative biological effectiveness (RBE) for cell killing by high-LET charged particle beams in comparison with low-LET x- or gamma-radiation. The high RBE in the Bragg-peak ionization region is expected to substantially increase the tumor cure probability for a given integral absorbed dose. In addition, the lower RBE in the plateau relative to the Bragg-peak ionization region should prove therapeutically advantageous because of the resultant sparing of normal tissues overlying the tumor.

Two other potential advantages of charged-particle radiation are the decreased repair of sublethal cellular damage³ and the reduced cell-cycle dependence of radiosensitivity.⁴ These factors are expected to be especially pronounced in the high-LET Bragg-peak ionization region and may allow tumor cures to be achieved with limited numbers of dose fractions compared with the treatment schedules used for conventional radiation modalities.

Since the completion of the Bevalac facility in 1975, extensive experiments have been carried out with three animal tumor systems in order to evaluate the therapeutic efficacy of high-energy charged-particle beams. The tumor systems employed in these studies and the participating principal investigators are listed below:

EMT6: A mammary tumor transplantable in Balb/c female mice.⁵ *Theodore L. Phillips, M.D., and Karen K. Fu, M.D., Division of Radiation Oncology and Laboratory of Radiobiology, University of California, San Francisco.*

9L: A rat brain gliosarcoma, originally induced by N-nitrosomethylurea and transplantable in Fischer 344 rats.⁶ *John T. Leith, Ph.D., Department of Radiation Oncology, University of Arizona Medical School, Tucson, and Kenneth T. Wheeler, Ph.D., Cancer Center, University of Rochester Medical Center, Rochester, New York.*

R1: A rhabdomyosarcoma transplantable in WAG/Rij rats, originally isolated from the mandibula of a rat radiation chimera.⁷ *Stanley B. Curtis, Ph.D., and Tom S. Tenforde, Ph.D., Lawrence Berkeley Laboratory, University of California, Berkeley.*

The results of the studies on the radiobiological responses of these tumor systems to Bevalac-accelerated neon ions are now available. These experiments have yielded information on both the RBE and

the oxygen effect for tumors positioned in the plateau and the Bragg-peak ionization regions of a neon-ion beam. A detailed discussion of these data follows, along with some initial results on the response of tumors to high-energy carbon- and argon-ion beams.

EMT6 MOUSE MAMMARY TUMOR

The survival of EMT6 tumor cells was measured following exposure *in vivo* to Bevalac-accelerated carbon, neon and argon ions.⁸⁻¹⁰ In these experiments, the Bragg peak was spread to a width of 4 cm using a lead ridge filter as shown in the Bragg curve reproduced in Fig. 1 for 400-MeV/n neon ions. Tumors implanted in the flanks of Balb/c mice were irradiated in either the plateau or the distal Bragg-peak ionization regions at the positions indicated by brackets in Fig. 1. Following irradiation, tumors were excised and dissociated to a single-cell suspension by trypsinization. The cells were then grown in tissue culture in order to assay the fraction of clonogenic cells. The resulting survival curves for EMT6 tumors exposed to carbon, neon and argon plateau and spread-out Bragg-peak radiation are reproduced in Fig. 2 along with a survival curve for tumors exposed to cesium-137 gamma radiation.

Fig. 1. The Bragg curve is shown for Bevalac-accelerated neon ions with initial energies of 400 MeV/n. The Bragg-peak ionization region has been spread to a width of 4 cm by means of a variable-thickness absorber. Positions of tumors irradiated in the plateau and distal Bragg-peak regions are shown by brackets. (XBL 7411-8146)

Fig. 2. Cell survival curves are shown for EMT6 tumors irradiated in the plateau and distal Bragg-peak ionization regions of carbon-, neon- and argon-ion beams. A survival curve is also plotted for EMT6 tumors exposed to cesium-137 gamma radiation. (The survival curve data were kindly provided by Dr. T. L. Phillips and Dr. K. K. Fu.) (XBL 772-3133)

The survival curve for EMT6 tumors irradiated *in vivo* with cesium-137 exhibits a shoulder region up to 600 rads, followed by a linear region extending to 1000 rads and characterized by an extrapolation number of 18 and a D_0 of 160 rads. A second linear portion of the curve with a D_0 of 360 rads appears at doses above 1000 rads and is attributable to the presence of radioresistant hypoxic cells. With carbon, neon and argon ions, the survival curves for EMT6 tumors exposed to either plateau or Bragg-peak radiation exhibit smaller shoulder regions, indicating a reduced accumulation of sublethal damage. With the exception of plateau carbon ions, which have the lowest median LET of the various charged-particle beams used in these experiments, the heavy-ion survival curves exhibit only a single linear region. The absence of a second linear region in the low survival range indicates the effectiveness of high-LET neon-ion radiation in killing the hypoxic cell fraction of *in vivo* tumors.

From the EMT6 survival curves of Fig. 2, RBE values relative to cesium-137 have been calculated at the 10% and 1% survival levels. As shown in Table I, the RBE values for carbon and neon ions are similar, both in the Bragg-peak and plateau ionization regions. The RBE values for carbon and neon Bragg-peak radiation range from 1.8 to 2.2; for plateau radiation, the RBE values are in the range of 1.4 to 1.6. The RBE values measured for both plateau and Bragg-peak argon-ion radiation are higher than those for carbon and neon ions and range from 2.6 to 3.1.

TABLE I. RBE values for cell killing in EMT6 tumors exposed to Bevalac heavy ions *in vivo*.

Ion	Initial energy	Tumor position*	RBE _{10%} [†]	RBE _{1%} [†]
¹² C	400 MeV/n	Bragg peak	2.2	2.0
		plateau	1.6	1.4
²⁰ Ne	400 MeV/n	Bragg peak	2.0	1.8
		plateau	1.5	1.5
⁴⁰ Ar	500 MeV/n	Bragg peak	3.1	2.6
		plateau	3.1	2.6

*Tumors were irradiated in either the plateau or the distal spread-out Bragg-peak ionization regions shown in Fig. 1; with each ion, a ridge filter was used to spread the Bragg peak to a 4-cm width.

[†]RBE values were calculated at the 10% and 1% survival levels relative to cesium-137 gamma radiation; the survival curves from which these data were obtained are plotted in Fig. 2.

Measurements of RBE and OER were also carried out for cultured EMT6 cells irradiated in either the plateau or Bragg-peak ionization regions of a neon-ion beam.⁸ In these *in vitro* experiments, EMT6 cell suspensions were placed in glass ampules and either exposed to room air for irradiation under oxic conditions or sealed after gassing with nitrogen for irradiation under hypoxic conditions. Compared with survival curves for cesium-137 irradiation, the survival curves for cultured EMT6 cells exposed to both plateau and Bragg-peak neon ions exhibit a reduced shoulder region and a smaller D_0 . For irradiation under oxic conditions, the extrapolation number and D_0 decreased from 13.5 and 139 rads, respectively, for cesium-137 to 1.4 and 132 rads for plateau neon ions and to 1.1 and 124 rads in the distal end of a 4-cm spread-out Bragg peak. For hypoxic irradiation conditions, the extrapolation number and D_0 varied from 6.5 and 490 rads for cesium-137 to 6.7 and 194 rads for plateau neon ions and to 1.3 and 171 rads in the spread-out Bragg-peak region. The values of RBE and OER calculated from these survival curves are given in Table II. At the 10% survival level, the OER decreased from 3.1 for cesium-137 irradiation to 2.5 for plateau neon-ions and to 1.4 for neon ions in the distal Bragg-peak region.

TABLE II. RBE and OER values for EMT6 tumor cells exposed to Bevalac neon ions *in vitro*.

	Bragg-peak position*	Plateau position*
$RBE_{10\%}^{oxic\ddagger}$	2.2	2.0
$RBE_{10\%}^{hypoxic\ddagger}$	4.8	2.5
$RBE_{1\%}^{oxic\ddagger}$	1.7	1.6
$RBE_{1\%}^{hypoxic\ddagger}$	3.9	2.5
$OER_{10\%}^{\ddagger}$	1.4	2.5
$OER_{1\%}^{\ddagger}$	1.4	2.0

*The Bragg peak of a neon-ion beam of initial energy 400 MeV/n was spread by a ridge filter to a 4-cm width; cell suspensions in glass ampules were placed in the plateau and the distal Bragg-peak positions used for *in vivo* tumor irradiations as shown in Fig. 1.

[†]RBE values were calculated at the 10% and 1% levels relative to cesium-137 gamma radiation.

[‡]The OER for EMT6 cells exposed to cesium-137 gamma radiation was 3.1 at both the 10% and 1% survival levels.

Studies of the effects of neon-ion irradiation on the cell population kinetics of cultured EMT6 cells were undertaken in 1976 by Dr. Roland Gilet at the Lawrence Berkeley Laboratory.¹ Using the technique of time-lapse cinematography, he observed a mitotic delay of 4 hrs per 100 rads of neon ions at the central position of a 4-cm spread-out Bragg peak. With cobalt-60 gamma radiation, the mitotic delay was 0.9 hr per 100 rads, giving an RBE of 4.5 for Bragg-peak neon-ion radiation. The decrease in division probability for the irradiated cells and for their progeny in the three subsequent generations was also studied by time-lapse cinematography. A comparable effect on division probability was observed for 1000 rads of cobalt-60 radiation and for 300 rads of Bragg-peak neon-ion radiation, which indicates that the RBE of 4.5 for mitotic delay is considerably larger than that for division probability. This observation implies that different mechanisms may be operative in these two effects.

9L RAT BRAIN GLIOSARCOMA

Cell survival parameters were measured for intracerebral 9L tumors exposed to a 400-MeV/n neon-ion beam in either the plateau or spread-out Bragg-peak ionization regions.^{12,13} In these experiments, the Bragg peak was spread to a width of 4 cm using a ridge filter, and 9L tumors were positioned at the midpoint of the spread-out peak region. Following *in situ* irradiation of 9L tumors, they were assayed *in vitro* for colony-forming ability by a procedure comparable to that described above for EMT6 tumors. From the cellular survival curve measured for 9L tumors exposed to 230-kV x rays, it appears that this tumor system does not have a measurable fraction of hypoxic cells. The x-ray survival curve for tumors in air-breathing rats lacks the radioresistant tail characteristic of an hypoxic cell compartment, and the fraction of hypoxic cells has been estimated to be less than 1.5%.^{12,14}

The cell survival curves for 9L tumors irradiated *in vivo* in the plateau and the spread-out Bragg-peak regions of a neon-ion beam are shown in Fig. 3. Similarly to the results described above for EMT6

Fig. 3. Cell survival curves are plotted for 9L gliosarcoma tumors exposed to Bevalac-accelerated neon ions in the plateau ionization region (a) or in the middle of a 4-cm spread-out Bragg-peak (b). Survival curves are shown for tumors irradiated under oxidic and hypoxic conditions. (The survival curve data were kindly provided by Dr. J. T. Leith and Dr. K. T. Wheeler and were taken in part from references 12 and 13 and are reproduced with the permission of the authors and the editors of the International Journal of Radiation Biology.) (XBL 773-3216)

tumors, the 9L tumors exposed to either plateau or Bragg-peak neon ions exhibited a reduced shoulder region and D_0 relative to 230-kV x rays. The D_0 values for 9L tumors irradiated in air-breathing rats were 295 rads for x rays, 205 rads for plateau neon ions, and 120 rads for Bragg-peak neon ions. Under hypoxic conditions established by asphyxiation of tumor-bearing rats with nitrogen gas prior to irradiation, the corresponding D_0 values were 625, 335 and 205 rads, respectively.

The RBE values determined from cell survival curves for 9L tumors exposed to x-ray and neon-ion radiation are summarized in Table III. For both plateau and Bragg-peak neon ions, the RBE for killing of hypoxic cells is significantly greater than for oxidic cells. Because the survival curves for x rays and neon ions contain only a single linear region, it is possible to obtain an *in vivo* OER for the 9L tumor system. The OER for tumors exposed to 230-kV x rays was found to be 2.1 at both the 10% and 1% survival levels. For plateau neon-ion radiation, the OER was reduced to 1.6 at both of these survival levels. A further reduction in the oxygen effect was not observed for 9L tumors irradiated in the spread-out Bragg-peak ionization region; the OER values were 1.6 and 1.5 at the 10% and 1% survival levels, respectively.

R1 RAT RHABDOMYOSARCOMA

The *in vivo* responses of R1 tumors to graded single doses of Bevalac-accelerated carbon, neon and argon ions have been analyzed by means of tumor volume measurements during the postirradiation period.^{15,16} From the resulting regression and regrowth curves for tumors exposed to heavy ions and to 220-kV x rays, a calculation has been made of the radiation-induced growth delay, i.e., the difference in time required for irradiated and control tumors to grow to twice their volume at the time of irradiation. In Fig. 4,

TABLE III. RBE and OER values for 9L tumors exposed to Bevalac neon ions *in vivo*.

	Bragg-peak position*	Plateau position*
$RBE_{10\%}^{oxic\dagger}$	2.5	1.4
$RBE_{10\%}^{hypoxic\dagger}$	3.2	1.8
$RBE_{1\%}^{oxic\dagger}$	2.6	1.4
$RBE_{1\%}^{hypoxic\dagger}$	3.5	1.9
$OER_{10\%}^{\ddagger}$	1.6	1.6
$OER_{1\%}^{\ddagger}$	1.5	1.6

*The Bragg-peak ionization region of a neon-ion beam of initial energy 400 MeV/n was spread with a ridge filter to a 4-cm width; 9L tumors were positioned either in the middle of the spread-out Bragg peak or at the position in the plateau ionization region indicated in Fig. 1.

[†]RBE values were calculated at the 10% and 1% survival levels relative to 230-kV x rays.

[‡]The OER for 9L tumors exposed to 230-kV x rays was 2.1 at both the 10% and 1% survival levels.

the radiation-induced growth delay is plotted as a function of absorbed dose for R1 tumors exposed to carbon, neon and argon ions at the distal position in a 4-cm spread-out Bragg peak (see Fig. 1). From these curves, the RBE for 50-day radiation-induced growth delay has been calculated as the ratio of the x-ray to heavy-ion doses necessary to produce a 50-day growth delay. The resulting RBE_{50} data for carbon-, neon- and argon-ion beams are summarized in Table IV. The RBE_{50} values in the distal Bragg-peak region were 2.3, 2.5 and 2.5 for carbon, neon and argon ions, respectively, indicating that a similar tumor volume response is obtained following irradiation with these three heavy-ion beams. The measurement of cellular survival curves for R1 tumors irradiated *in situ* with Bragg-peak heavy-ion beams is currently being carried out using the *in vitro* assay procedure described above for EMT6 and 9L tumors. These studies should provide additional RBE data for comparing the therapeutic efficacy of Bragg-peak carbon-, neon- and argon-ion beams.

On the basis of radiation-induced growth-delay data, a comparison has also been made between the RBE values for plateau and Bragg-peak neon-ion radiation. The RBE_{50} was found to be 2.5 in the distal region of a 4-cm spread-out Bragg peak and 1.8 in the plateau ionization region.

An initial study has been carried out to analyze the *in vivo* response of R1 tumors to fractionated doses of heavy-ion radiation. The growth-delay curve obtained for tumors given six daily doses of Bragg-peak carbon-ion radiation at 250, 350 and 500 rads per fraction is plotted in Fig. 3. Upon comparison of the radiation doses producing 50-day growth delay in the single-dose and six-fraction treatment schedules, calculations indicate that approximately 13% of the fractionated daily dose is recovered.

In vitro experiments have also been undertaken by Wolfgang A. Schilling to analyze the response of R1 cells to Bevalac-accelerated carbon-, neon- and argon-ion beams.¹⁷ In these studies, R1 cells were irradiated in suspension under both oxic and hypoxic conditions using a unique apparatus recently developed at the Lawrence Berkeley Laboratory by Dr. J. D. Chapman.¹⁸ With this technique, a cell suspension contin-

Fig. 4. Radiation-induced growth delay is plotted as a function of absorbed dose for R1 rhabdomyosarcoma tumors exposed to carbon-, neon- and argon-ion beams in the distal region of a 4-cm spread-out Bragg peak. The effect of dose fractionation (6 doses in 6 days) is shown for Bragg-peak carbon ions (a). The growth delay curve for plateau neon ions is shown in (b). (XBL 772-3132)

TABLE IV. RBE values for heavy-ion radiation-induced growth delay of R1 tumors *in vivo*.

Ion	Initial energy	Tumor position*	RBE ₅₀ [†]	RBE _(TCD 50/180) [‡]
¹² C	400 MeV/n	Bragg peak	2.3	--
²⁰ Ne	400 MeV/n	Bragg peak	2.5	3.1
²⁰ Ne	400 MeV/n	plateau	1.8	--
⁴⁰ Ar	500 MeV/n	Bragg peak	2.5	--

*Tumors were positioned in either the plateau or the distal spread-out Bragg-peak ionization regions shown in Fig. 1; with each ion, a ridge filter was used to spread the Bragg peak to a 4-cm width.

[†]RBE values were calculated as the ratio of 220-kV x-ray dose to heavy-ion dose required to produce a growth delay of 50 days.

[‡]The RBE_(TCD 50/180) value was calculated from the ratio of 220-kV x-ray dose to neon-ion dose required to produce 50% tumor cures in 180 days.

uously gassed with either air or nitrogen is first subjected to a prescribed radiation dose; an aliquot is then removed, diluted to an appropriate concentration, and plated onto tissue-culture dishes for determination of colony-forming ability. An OER value of 3.0 has been obtained in this manner for R1 cell suspensions irradiated with 225-kV x rays.¹⁷ In these experiments, the Bragg-peak ionization region was spread either to a width of 4 cm using a lead triangular ridge filter or to a width of 10 cm using a brass spiral ridge filter.

RBE and OER data for R1 cell suspensions exposed to Bevalac-accelerated carbon-, neon- and argon-ion beams are summarized in Table V. Several statements can be made on the basis of these preliminary results. First, the OER of 1.8 obtained in the distal region of a 4-cm spread-out Bragg peak of a carbon-ion beam was significantly lower than the value of 2.3 obtained in the plateau ionization region. Second, in the most distal region of a 10-cm spread-out Bragg peak, the OER decreases from 1.9 for carbon ions to 1.7 for neon ions and to 1.3 for argon ions. It must be pointed out, however, that because of the small number of studies carried out to date, the limits of experimental error for the OER values listed in Table V

TABLE V. Response of R1 cells *in vitro* to Bevalac-accelerated heavy ions.

Ion	Initial energy	Ridge filter	Position	RBE _{10%} ^{oxic*}	RBE _{10%} ^{hypoxic*}	OER _{10%} [†]
¹² C	400 MeV/n	4 cm	plateau	1.4	1.7	2.3
		4 cm	distal [‡]	1.8	3.0	1.8
		10 cm	1 [§]	1.8	2.9	1.9
²⁰ Ne	400 MeV/n	10 cm	1 [§]	1.5	3.4	1.7
		10 cm	2 [§]	1.4	2.9	1.9
		10 cm	3 [§]	1.4	2.6	2.0
⁴⁰ Ar	500 MeV/n	10 cm	1 [§]	2.0	4.6	1.3

* RBE values were calculated at the 10% survival level relative to 225-kV x rays; the x-ray dose giving 10% survival for oxyc cells was 460 rads, and for hypoxic cells it was 1380 rads.

† Values of OER were calculated at the 10% survival level; the OER obtained with 225-kV x rays was 3.0.

‡ The distal position in the 4-cm spread-out Bragg peak corresponded to the positioned labeled "1" for the 10-cm Bragg peak as shown in the inset of Fig. 5; this position was nearly identical to the distal portion used for *in vivo* tumor irradiation.

§ The positions in the 10-cm spread-out Bragg peak labeled "1," "2" and "3" are shown in the inset of Fig. 5.

are on the order of 0.2; consequently, it is not as yet clear whether the difference in OER values for carbon- and neon-ion beams is significant. Third, as shown by data presented in Table V and Fig. 5, the OER value of 1.7 for R1 cells irradiated at the most distal position in a 10-cm neon-ion Bragg peak is substantially lower than the OER of 2.0 obtained at the proximal end of the peak region. The lower OER in the distal region appears to result primarily from a significantly higher RBE for hypoxic cell killing as indicated by the RBE values given in Table V for oxyc and hypoxic cells.

Fig. 5. Survival curves are plotted for cultured R1 cells exposed to neon ions at three positions in a 10-cm spread-out Bragg peak. At each position, survival curves are shown for cells irradiated under oxidic and hypoxic conditions. (XBL 772-3130)

DISCUSSION

In order to choose the optimal accelerated-ion species to be used in tumor radiotherapy, it is important to determine for both tumor and normal tissues the therapeutic ratio, $\text{RBE}(\text{spread-out Bragg peak})/\text{RBE}(\text{plateau})$. At this time, the only *in vivo* tumor system for which sufficient data have been obtained to calculate the therapeutic ratios for all three ions is the EMT6 mammary carcinoma. With the RBE values determined at the 10% survival level for EMT6 tumors irradiated in air-breathing mice (see Table I), the RBE ratios are 1.4, 1.3 and 1.0 for carbon, neon and argon ions, respectively. For this tumor system, it thus appears that carbon- and neon-ion beams would be more advantageous than argon ions to maximize the therapeutic ratio. This observation is consistent with that of Chapman et al.¹⁸ who obtained RBE therapeutic ratios for cultured V79 cells of 1.6, 1.4 and 0.9 for carbon-, neon- and argon-ion beams, respectively. When evaluating the various accelerated heavy-ion species, however, one should bear in mind that the therapeutic ratio can vary considerably with different biological systems. For example, with the 9L tumor, the neon-ion therapeutic ratio calculated from RBE values at the oxidic 10% survival level

is 1.8 (see Table III). With RBE values determined from the radiation-induced growth delay in R1 tumors, the therapeutic ratio for neon ions is 1.4 (see Table IV).

Another approach to calculating the RBE therapeutic ratio for different ions is to use the ratio of the RBE for tumor tissue in the Bragg-peak treatment zone to the RBE for a normal tissue (e.g., skin) positioned in the plateau ionization region. From an analysis of skin reactions resulting from high radiation doses, Leith¹⁹⁻²¹ has obtained RBE values of 1.0 and 1.5 for plateau carbon- and neon-ion beams, respectively. With these plateau RBE values for skin and the Bragg-peak RBE values for EMT6 tumors, the therapeutic ratios for carbon- and neon-ion beams are 2.2 and 1.3, respectively. If Bragg-peak RBE values for the R1 tumor system are used, the carbon and neon RBE ratios become 2.3 and 1.7, respectively. This difference in the peak-to-plateau RBE therapeutic ratios for carbon and neon ions is further increased if the RBE ratio for each ion is multiplied by the peak-to-plateau physical dose ratio, which is significantly higher for carbon ions than for neon ions with the same residual range. From the preliminary data presented here, it would therefore appear that the "overall therapeutic ratio" (defined as the RBE ratio multiplied by the physical dose ratio) is greater for carbon ions than for the other ions currently under study. Other experimental evidence indicates, however, that this conclusion based on tumor data may not be applicable to all other types of tissue. With mouse skin, for example, the RBE peak-to-plateau ratio for neon ions is 1.6, which is higher than the value of 1.2 obtained for carbon ions. It therefore appears that additional studies should be carried out, both with *in vitro* cell lines and with normal and tumor tissues *in vivo*, in order to assess more fully the relative therapeutic ratios for different heavy-ion species.

A second factor of major importance in radiotherapy, for which a preliminary analysis can be carried out with the existing data, is the magnitude of the oxygen effect for tumor cells exposed to heavy-ion radiation in the plateau and Bragg-peak ionization regions. For *in vivo* tumors, the only data currently available on the oxygen effect were obtained for the 9L gliosarcoma exposed to neon-ion radiation under oxic and hypoxic conditions. In this system, the *in vivo* OER was reduced from 2.1 for 230-kV x rays to 1.6 in both the plateau and Bragg-peak ionization regions of a neon-ion beam. The oxygen effect gain factor is thus $2.1/1.6 = 1.3$ for both plateau and Bragg-peak neon ions. The value for Bragg-peak radiation is considerably lower than the values obtained by other workers with cell-culture systems. For example, with cultured EMT6 tumor cells, the oxygen gain factor at the 10% survival level in the neon-ion Bragg-peak was $3.1/1.4 = 2.2$; in the plateau region, the factor was $3.1/2.5 = 1.2$. With R1 tumor cells *in vitro*, the oxygen gain factors at the 10% survival level for carbon-ion beams were $3.0/1.8 = 1.7$ and $3.0/2.3 = 1.3$ in the Bragg-peak and plateau regions, respectively. The higher oxygen gain factors obtained *in vitro* in the Bragg-peak ionization region indicate the need for additional *in vivo* studies with the 9L and other tumor systems.

The data for cultured R1 cells permit an initial evaluation of the relative magnitudes of the oxygen effect with various accelerated heavy-ion species. In the most distal region of a 10-cm spread-out Bragg peak, the OER values obtained at the 10% survival level for carbon-, neon- and argon-ion beams were 1.9, 1.7 and 1.3, respectively. As stated above, the difference between carbon and neon OER values cannot as yet be regarded as significant. These data do indicate, however, that a substantial reduction in OER is obtained with argon ions compared to the lower-Z ion species. This conclusion is supported by the *in vitro* studies of Chapman et al.¹⁸ with V79 cultures positioned in the middle of a 4-cm spread-out Bragg peak. With this system, the OER values obtained at the 10% survival level were 1.7, 1.6 and 1.4 for carbon, neon and argon ions, respectively. In selecting the optimal ion for therapy, however, one must consider that the advantageous oxygen effect observed for argon ions is offset by their relatively low RBE therapeutic ratio and peak-to-plateau physical dose ratio.

FUTURE DIRECTIONS

Several aspects of the tumor research with accelerated heavy ions will be expanded to obtain further information relating to both therapy and the basic cellular radiobiology of charged-particle beams. Studies that will be conducted in depth with one or more experimental tumor systems include the following:

1. Further comparisons will be made between carbon, neon and argon ions to assess the most advantageous ion species for therapy. It will be important in this regard to determine the RBE and OER for each ion in both the plateau and Bragg-peak ionization regions and to analyze these parameters across the entire Bragg-peak region when it is spread to various widths in the therapeutically useful range of 4 to 12 cm. Similar experiments will be conducted with heavy-ion beams accelerated to different energies. These studies are of interest for two reasons. First, as the energy of an accelerated heavy-ion beam is decreased, the peak-to-plateau physical dose ratio increases; this effect would clearly be advantageous in tumor radiotherapy. Second, when the energies of heavy-ion beams are changed, radiobiological parameters for carbon, neon and argon ions can be compared under conditions where they have the same range in tissue. Such conditions have not been met in the experiments conducted to date where the respective ranges of carbon-, neon- and argon-ion beams have been approximately 26, 15 and 12 cm.

2. Studies will be undertaken to analyze the effects of hypoxic cell sensitizers on the *in vivo* responses of animal tumors to heavy-ion radiation. Using hamster V79 fibroblasts *in vitro*, Chapman et al.¹⁸ have demonstrated that a significant reduction in OER occurs for carbon and neon ions in the presence of the sensitizers metronidazole, Ro 7-0582 and Ro 7-0741. Although the drug concentrations used in these studies were 5 to 10 times greater than those expected to be used clinically, the results nevertheless indicate the potential of chemical sensitizers in tumor therapy with accelerated heavy ions.

3. The effects of dose fractionation on the responses of animal tumor systems to heavy-ion radiation will be examined. The initial studies described above for six fractions of Bragg-peak carbon-ion radiation administered daily indicate that the recovered dose is small for high-LET charged-particle radiation. In order to provide data of clinical relevance, further experiments will be undertaken to determine recovery factors in more extended fractionation schedules.

4. Additional experiments will be carried out to analyze cellular radiobiological parameters in tumors exposed *in vivo* to heavy-ion beams. The repopulation of irradiated R1 rhabdomyosarcoma tumors will be studied by using the *in vitro* assay technique to determine the number of clonogenic cells present as a function of time postirradiation. Tritiated thymidine autoradiographic studies will be carried out by Dr. A. F. Hermens of the Radiobiological Institute REPGO/TNO in Holland to measure changes occurring in the cell-kinetic parameters of R1 tumors exposed to heavy-ion radiation. Extensive studies on the cell kinetics of R1 tumors exposed to x rays have previously been carried out,²² and an initial experiment with Bragg-peak neon-ion radiation was conducted in 1976. It is anticipated that this approach will yield valuable information on the effects of charged-particle beams on cell-kinetic parameters such as the cell cycle time, the growth fraction, and the cell loss factor in irradiated tumors.

REFERENCES

1. Tobias, C. A. Pretherapeutic investigations with accelerated heavy ions. *Radiology* 108, 145-158 (1973).
2. Raju, M. R. Pions and heavy ions in radiotherapy: a brief review. In: *Proceedings of the XIth International Cancer Congress, Florence, Italy, October 20-26, 1974, Excerpta Medica* (1975).
3. Todd, P. Heavy-ion irradiation of cultured human cells. *Radiat. Res. Supp.* 7, 196-207 (1967).
4. Bird, R. P. and H. J. Burki. Survival of synchronized Chinese hamster cells exposed to radiation of different linear-energy transfer. *Int. J. Radiat. Biol.* 22, 105-120 (1975).

5. Rockwell, S. C., R. F. Kallman, and L. F. Fajardo. Properties of a transplantable mouse mammary tumor and its tissue-culture-adapted derivative. *J. Nat. Cancer Inst.* 49, 735-749 (1972).
6. Schmidek, H. H., S. L. Nielsen, A. L. Schillel, and J. Messer. Morphological studies of rat brain tumors induced by N-nitrosomethylurea. *J. Neurosurg.* 34, 335-340 (1971).
7. Reinhold, H. S. Quantitative evaluation of the radiosensitivity of cells of a transplantable rhabdomyosarcoma in the rat. *Europ. J. Cancer* 2, 33-42 (1966).
8. Fu, K. K. and T. L. Phillips. The RBE and OER of neon ions for the EMT6 tumor. Presented at the 61st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November 30-December 5, 1975.
9. Phillips, T. L., K. K. Fu, and S. B. Curtis. Tumor biology of helium and heavy ions. In: *Proceedings of an International Conference on Particle and Radiation Therapy, Part II, Berkeley, California, September 14-17, 1976, Int. J. Rad. Oncology, Biology & Physics*, in press.
10. Phillips, T. L., personal communication.
11. Collyn, M., R. Gilet, S. B. Curtis, and E. P. Malaise. Influence of irradiation (high energy neon ions versus cobalt-60 gamma rays) on the kinetics of EMT6 cells: time-lapse cinematography. In: *Proceedings of an International Conference on Particle and Radiation Therapy, Part II, Berkeley, California, September 14-17, 1976, Int. J. Rad. Oncology, Biology & Physics*, in press.
12. Leith, J. T., V. Arcellana, J. T. Lyman, and K. T. Wheeler. Response of a rat brain tumor to irradiation with accelerated neon ions. *Int. J. Radiat. Biol.* 28, 91-97 (1975).
13. Leith, J. T., P. Smith, P. Ross, and K. T. Wheeler. Radiation response of an intracerebral rat brain tumor (9L gliosarcoma). *Int. J. Radiat. Biol.*, in press.
14. Leith, J. T., W. A. Schilling, and K. T. Wheeler. Cellular radiosensitivity of a rat brain tumor. *Cancer* 35, 1545-1550 (1975).
15. Tenforde, T. S., S. B. Curtis, D. L. Parks, W. A. Schilling, and J. T. Lyman. RBE for radiation-induced growth delay in a rat rhabdomyosarcoma exposed to Bevalac neon ion beams. *Radiat. Res.* 62, 555 (1976).
16. Curtis, S. B., T. S. Tenforde, S. J. Daniels, W. A. Schilling, K. E. Crabtree, J. T. Lyman, and J. Howard. Comparison of tumor growth delay in a rat rhabdomyosarcoma irradiated with carbon, neon, and argon ion beams: single dose and preliminary fractionated dose results. To be presented at the 25th Annual Radiation Research Society Meeting, San Juan, Puerto Rico, May 7-12, 1977.
17. Schilling, W. A., S. B. Curtis, T. S. Tenforde, K. E. Crabtree, J. T. Lyman, and J. Howard. Comparison of the radiation response of rat tumor cells exposed at various positions in the extended Bragg peak of heavy ion beams. To be presented at the 25th Annual Radiation Research Society Meeting, San Juan, Puerto Rico, May 7-12, 1977.
18. Chapman, J. D., E. A. Blakely, K. C. Smith, and R. C. Urtasum. Radiobiological characterization of the inactivating events produced in mammalian cells by helium and heavy ions. In: *Proceedings of an International Conference on Particle and Radiation Therapy, Part II, Berkeley, California, September 14-17, 1976, Int. J. Rad. Oncology, Biology & Physics*, in press.
19. Leith, J. T., K. H. Woodruff, and J. T. Lyman. Early effects of single doses of 375 MeV/nucleon ²⁰neon ions on the skin of mice and hamsters. *Radiat. Res.* 65, 440-450 (1976).

20. Leith, J. T., K. H. Woodruff, J. Howard, J. T. Lyman, P. Smith, and B. S. Lewinsky. Early and late effects of accelerated charged particles on normal tissues. In: *Proceedings of an International Conference on Particle and Radiation Therapy, Part II, Berkeley, California, September 14-17, 1976*, *Int. J. Rad. Oncology, Biology & Physics*, in press.
21. Leith, J. T., personal communication.
22. Hermens, A. F. and G. W. Barendsen. Changes of cell proliferation characteristics in a rat rhabdomyosarcoma before and after X-irradiation. *Europ. J. Cancer* 5, 173-189 (1969).

CHAPTER 10

SPACE RADIOBIOLOGY

Tracy C. H. Yang and Cornelius T. Gaffey

INTRODUCTION

Relatively long-term manned space flights have become reality since the successful Skylab program. Exploration and eventual colonization of the planets by man is probably only a question of time and no longer a mere fantasy. A thorough understanding of the effects of the space environment on man and on other biological systems is important to ensure the ultimate success of these long-term and long-distance space adventures. Among the many environmental factors in space, radiation is a challenging one and exists in a spectrum entirely different from that on the surface of the earth. There are vast belts of high-energy protons and electrons; there are spectacular solar events with protons, alpha particles and heavy ions; and there is primary cosmic radiation with light and heavy components and even far-ultraviolet and x-ray bursts. The biological effects of heavy charged particles of cosmic rays are least adequately measured and perhaps least understood in spite of the large amount of information available on the effects of x- and gamma-rays, neutrons and low-energy particles from radioactive isotopes. Because it is difficult to extrapolate with confidence from the experimental data on low-LET radiation to heavy-ion problems, the potential hazards of the cosmic rays to man can only be reliably determined by conducting biological experiments in space or with accelerated heavy ions on the ground. The completion of the Bevalac has provided a unique opportunity to conduct experiments with energetic heavy particles that are found naturally in cosmic rays.

For many years, a group of LBL researchers led by Dr. Cornelius A. Tobias has actively participated in space radiobiological research and conducted experiments both on the ground and in space. In this chapter, the experimental results obtained with the Bevalac and pertaining to space flight are presented.

SPACE-FLIGHT-RELATED HEAVY-ION STUDIES WITH *ZEA MAYS* SEEDS

In an early balloon-flight experiment, some developmental abnormalities, e.g., streaks and necrotic areas on maize leaves, were observed; these biological effects were attributed to the passage of single heavy-ion thin-down from cosmic-ray primaries.¹ Similar results were independently obtained by Curtis and Smith.² Both studies indicated that cosmic rays can be very effective in inducing biological damage because the heavy-ion particles absorbed by the corn seeds were probably few. A definite conclusion about the effects of cosmic rays on living organisms could not be reached, however, because at that time there were not enough quantitative data available and the technique of correlating observed biological effects with direct hits of primary cosmic rays was not used.

The success in accelerating heavy ions including carbon, nitrogen, oxygen, neon, argon and iron to very high energies (several hundred MeV/amu) at the Princeton accelerator and at the Bevalac provided an opportunity to check these earlier findings concerning heavy-ion radiation effects on the morphogenesis and development of corn seeds. Using accelerated oxygen particles (220 MeV/amu) at the Bevalac, experiments were performed with dry maize seeds containing a recessive lemon-white gene on the first chromosome; the results showed that seeds that received as little as 75 rads of oxygen ions developed large visible white stripes on the fourth leaves. Compared to ⁶⁰Co gamma rays, for leaf-growth retardation an RBE of about 9 is obtained for oxygen particles. For the depigmentation effect, oxygen-ion radiation appears to be more than eighteen times as effective as gamma radiation. That heavy ions were highly

effective in impeding corn-plant growth was also found independently at the Princeton accelerator by Todd et al.³

Because all results obtained at ground level were in agreement with earlier space-flight experiments, a corn-seed experiment was proposed as a more direct check and conducted as part of the Biostack III program in collaboration with Dr. H. Bucker of the University of Frankfurt. In order to correlate the flux, energy, atomic number and pathway of heavy nuclei in cosmic rays with a biological effect, dry hybrid corn seeds containing known gene markers, e.g., yellow green (yg_2) and shrunken (sh_1), were held in position in a lexan disc by solidified polyvinyl alcohol and sandwiched with many layers of plastic heavy-ion detector foils (e.g., cellulose nitrate) and lexan. At the end of the Apollo-Soyuz mission in 1975, both the flight package containing 156 corn seeds and the ground control package were successfully recovered. The plastic foils were etched, and the number, LET and charge of the heavy particles that had passed through the seeds were determined. The seeds were planted in individual pots in a light- and temperature-controlled greenhouse. Although no significant differences in germination rate and leaf size were found (for the first through the seventh leaves), a significantly higher frequency of yellow sectors was observed in the flight group; this finding is in agreement with observations made during earlier space-flight experiments. Among the germinated flight seeds, one matured into a plant with large yellow stripes from the second to the ninth leaves (Figs. 1a and b). A close check of the plastic dosimetry showed that the central region of the embryo of this particular seed had received two direct hits with LET in the range of 100 to 150 keV/ μ m and $Z = 26$. Since more than one leaf of this plant developed large yellow stripes, each particle must have produced a multicell lesion in the embryo.

In an earlier oxygen-ion experiment, some seeds that had received 1000 rads also developed large stripes on more than one leaf (Fig. 1c). Recently, a corn-seed experiment with accelerated argon ions was performed, and a seed exposed to 50 rads of argon particles with a residual range of about 3 mm in tissue grew into a plant showing stripes on the ninth and tenth leaves (Fig. 1d). It appears, therefore, that with an increase in the LET and Z number of heavy ions, the flux of particles needed to produce large stripes on leaves decreases. Although all results suggest that the observed effects in space-flight experiments are most likely due to heavy-ion radiation, more research with particles of higher atomic number, e.g., iron ions, should still be pursued to unequivocally demonstrate that a single direct hit of a heavy charged particle in the embryo can produce a severe biological effect. We would then have a final explanation for the results observed in earlier space-flight experiments.

DEVELOPMENTAL AND LATE EFFECTS OF HEAVY-ION RADIATION ON *TRIBOLIUM CONFUSUM*

One of the organisms chosen for space-flight studies to determine possible synergistic effects of radiation and the space environment in the Biosatellite II program was *Tribolium confusum*. A synergistic effect on pupal development was found, and it was suggested that weightlessness and/or heavy particles in cosmic rays might be responsible.⁴ Subsequent experiments were performed with heavy particles varying in charge and energy to determine their effects on embryonic development, late morphogenesis, adult mortality, and the radiosensitivity of F_1 eggs. The survival curves for eggs exposed to low-energy (10 MeV/amu) heavy ions and to high-energy carbon, oxygen and neon particles are shown in Fig. 2. In general, it appears that for particles of the same atomic number the lower the particle energy the higher the RBE; for ions with the same energy the higher the charge the higher the RBE. When the effect of heavy ions on embryogenesis is expressed as fluence (particles per cm^2), carbon particles (10 MeV/amu) are a thousand times more effective than protons (15 MeV/amu). This great effectiveness of heavy ions with high LET and high atomic number in damaging embryogenesis of animal eggs was also noticed and reported by some investigators involved in Apollo-16 and Apollo-17 Biostack experiments.^{5,6} For instance, only 10% of the *Artemia salina* eggs that were hit by heavy particles during space flight developed to the swimming larva stage (the nauplius) compared with 90% of the ground controls and 46% of the flight controls not hit. Similar effects

(a)

(b)

Fig. 1. (a) Corn plant developed from seed No. 2-31 exposed to cosmic rays during Apollo-Soyuz flight. Note yellow stripes on 4th, 6th and 7th leaves. Plant was photographed 33 days after planting.

(b) The fully grown plant of seed No. 2-31. Note the large stripe on the 9th leaf. Plant was photographed 96 days after planting.

(c)

(d)

(c) Stripe formation on leaves of corn plant irradiated as a seed with 1000 rads of oxygen ions.

(d) Depigmentation on leaves exposed to 50 rads of argon particles.

Fig. 2. Effects of various high- and low-energy heavy particles on hatchability of *Tribolium confusum* eggs (8 to 12 hrs old at 23°C).

(XBL 772-7752)

were found during the development of hit *Tribolium castaneum* and *Carausius morosus* eggs. Based on the finding that irradiation of *Artemia salina* eggs with 10-MeV/amu oxygen ions resulted in an exponential survival curve, the suggestion that the passage of a single particle of high-energy loss might damage a cellular area large enough to disturb embryogenesis was proposed to explain the results of the Biostack experiments. *Tribolium confusum* eggs irradiated with heavy ions also showed a significant decrease in the percentage of pupation and increases in abnormalities and the mortality rate at the adult stage compared with controls. Both hatchability and the radiosensitivity of F_1 eggs in the offspring of oxygen-ion-irradiated males changed significantly. For example, a dose of 900 rads of oxygen ions to male beetles caused a 50% decrease in hatching of F_1 eggs, about twice the effect of 220-kVp x rays; the radiosensitivity of eggs fertilized by males irradiated with 250 rads of oxygen ions (35 MeV/amu) showed a 10% increase.

STUDIES ON THE INACTIVATION CROSS SECTION OF HUMAN CELLS WITH HIGH-LET PARTICLES

Results from both space-flight experiments and Bevalac work strongly indicate that heavy ions are highly effective in producing various biological effects. Consequently, an important question arises. Can a single heavy particle kill a cell by passing through the non-nuclear region? This question is important not only in determining the potential hazards of cosmic rays to space travelers but in better understanding the fundamental aspects of cellular radiosensitivity and developing quantitative models for radiation response in human cells. To answer this question, the radiation responses of cultured human kidney cells (T-1) have been studied with very heavy particles accelerated at the SuperHILAC.^{7,8} The survival curve for asynchronous T-1 cells exposed in air to a 5.1-MeV/amu argon beam was found to be exponential with $D_0 = 210$ rads, and the calculated cell inactivation cross section was approximately $150 \mu\text{m}^2$, in close agreement with Todd's finding.⁹ An exponential survival curve with $D_0 = 720$ rads was also observed for asynchronous T-1 cells irradiated with 3-MeV/amu krypton ions in air, and an inactivation cross section of $145 \mu\text{m}^2$ was obtained. A linear plot of the inactivation cross section of T-1 cells against LET is shown in Fig. 3. It is evident that with LET greater than about $20,000 \text{ MeV}\cdot\text{cm}^2/\text{g}$ there is no further increase in the inactivation cross section. The maximum inactivation cross section for asynchronous T-1 cells may be 140 to $150 \mu\text{m}^2$, which agrees very well with the measured value for the nuclear area of T-1 cells. Whereas the inactivation cross section is comparable to the measured average nuclear size and does not appear to increase further with LET greater than $20,000 \text{ MeV}\cdot\text{cm}^2/\text{g}$, the nucleus of the cell is probably the only site sensitive to high-LET radiations; that is, a heavy ion passing through only the cytoplasmic membrane will not kill the cell. Although DNA lesions induced by ionizing radiation can lead to cell death, there might be other mechanisms for the lethal effect of heavy ions. The large ionizing track with a high energy density produced by high-LET heavy ions might be able to generate a hole in the nuclear membrane that could change the membrane permeability and consequently cause a disruption in nuclear structure and function. If the nuclear membrane is a predominant radiosensitive site, the very heavy particles with high LET will be equally effective in lethally damaging proliferating and nonproliferating cells as well as, for example, the cells of the nervous system. In fact, in a study on the microscopic changes in the brain of the pocket mouse (*Perognathus longimembris*) following irradiation of the head with a neon-particle beam (residual range = 2 to 3 mm) at the Bevalac, Kraft et al.¹⁰ found that fluences ranging from 10^5 to 10^7 particles per cm^2 (or 0.1 to 10 particles per $100 \mu\text{m}^2$) produced necrotic nerve cells one to two weeks after exposure.

TUMORIGENIC EFFECT OF HIGH-LET RADIATION

The effectiveness of cosmic rays in inducing tumors in living organisms is of great concern, particularly to space travelers. Using cultured golden Syrian hamster embryo cells, Borek et al.^{11,12} demonstrated that ionizing radiation, even at a very low dose, e.g., 1 rad, could directly induce cell transformation. This finding was later confirmed by Terzaghi and Little.¹³ Borek et al.^{14,15} found that 430-keV monoenergetic neutrons were much more efficient than x rays in producing transformation in hamster embryo cells *in vitro* and that the RBE of neutrons relative to x rays appeared to be no higher than 10 and varied little with dose over the range investigated, 1 to 200 rads. In regard to the carcinogenic potential of high-energy argon ions, it has been reported that argon ions do have oncogenic potential as judged by their ability to transform diploid mammalian cells *in vitro* and that in this system of diploid embryonic cells this potential does not seem to differ significantly from the oncogenic potential of 430-keV neutrons.¹⁵

In addition to its potential as an inducer, radiation has been found to be an effective promoter in carcinogenesis. Cultured mouse fibroblasts (3T3) irradiated with 1200 R of x rays before or after infection with SV-40 virus showed a seven-fold increase in transformation.¹⁶ Recently, experiments have been conducted to determine the relationship between high-LET radiation and viral transformation of cells in

Fig. 3. Inactivation cross section of T-1 cells for various LET. (XBL 765-1865)

vitro.¹⁷ Confluent monolayer mouse 3T3 cells exposed to 240-MeV/amu neon ions became more sensitive to SV-40 viral transformation. Neon particles were more effective than x rays in enhancing the viral transformation, and the RBE value varied from 1.7 for high doses to 3.0 for low doses. At 300 rads the transformation enhancement ratio for neon was about 45, and for x rays it was about 5. The kinetics of the enhancement by neon ions appear to have a linear as well as a quadratic dose component, and no plateauing was found up to 400 rads of neon particles as shown in Fig. 4.

Fig. 4. A comparison of enhancement of viral transformation of 3T3 cells exposed to x rays and neon particles. (XBL 7612-11040)

NEON-ION IRRADIATION OF THE CAT'S EYE

An assessment of the hazards of heavy-ion radiation to vision is needed for both manned space-flight projects¹⁸ and new therapeutic modalities using high-Z nuclei.¹⁹ Space radiation consists of protons trapped in the Van Allen belt, galactic radiation, and solar particles.²⁰ Galactic radiation is composed

of primarily protons and helium nuclei mixed with about two percent of relatively high-Z nuclei.²¹ Space fluxes of lead ($Z = 82$) and uranium ($Z = 92$) were reported by Fowler.²² Little is known about the ocular effects of high-Z radiation with the exception of the fundusoscopic lesions induced by 240-MeV/nuclear oxygen ions in the monkey.¹⁸ Some information on eye damage caused by low-Z nuclei has been reported by Momeni, Cahill and Horn²³ who studied the effects of proton irradiation on the eyes of beagles and by Constable and Koehler²⁴ who found that monkey eyes were compromised by proton exposures. Gaffey²⁵ found that helium-ion beams induced retinal blindness in cats. Since heavy nuclei are still unestimated risks on space missions^{26,27} more data are needed. If heavy nuclei can one day be used as an effective treatment for choroidal melanomas and retinal blastomas, the biological effects of these ions must be evaluated. The cat's eye is being used by one of the authors (C. Gaffey) to test the *in vivo* action of neon-ion radiation as a function of the absorbed dose. The electroretinogram is used as a physiological measure of vision, and fundusoscopic examinations are performed to index retinal vascular insult. These investigations are described below.

Irradiation Procedure

The Bevalac at the Lawrence Berkeley Laboratory can generate a beam of neon ions at the rate of 15 pulses/min. Each pulse contains 2×10^8 to 1×10^9 neon ions/pulse. The neon ions used in cat exposures have energies of 400 MeV/nucleon, charges of +10, and ranges of 14 cm in water. The plateau region of the beam used in these experiments has a linear energy transfer of 32 keV/micron of water. Circular beams 29 to 38 mm in diameter are obtained with absorption collimators. Lyman²⁸ has described the dosimetry for the biomedical facility at the Bevalac (see Chapter 3). The cats receive 140 to 478 rads/min as measured with parallel-plate ionization chambers. The relative biological effects of neon ions are compared with those of x rays. A therapeutic x-ray machine, operating at 200 kV and 15 mA with 0.5 mm Cu and 1.0 mm Al filtration, supplies a 4- by 6-cm field of x rays. One eye intercepts this irradiation field; the untreated eye serves as a control.

The Electroretinogram

The x ray doses required to suppress promptly and completely the electroretinogram (ERG) of ten cats ranged from 4000 to 4500 rads. The average inactivation x-ray dose was 4200 rad. If neon ions have the same relative biological effectiveness (RBE) as x rays, it would be expected that a minimum of 4200 rads of 400-MeV neon ions would have to be absorbed by the eye to inhibit the cat's ERG. This is not the experimental finding. The severe hazard of neon ions to vision is demonstrated by the fact that 1200 rads of neon nuclei fully attenuate the ERG. Hence, the RBE for neon ions is 3.5 with respect to x rays (assigned a relative value of one).

An eye that absorbs 1200 rads of x rays generates an ERG that is barely altered; 1200 rads of neon ions provoke blindness. Table I shows the effects of various doses of neon ions on the ERG of the cat eye. ERG loss has been confirmed to be equivalent to blindness by tests such as the eyelid blink reflex and the pupillary size to light reflex.

When the cat eye absorbs less than 1200 rads of neon ions, total blindness does not occur. Electrophysiological tests with double light flashes show that radiation as low as 360 rads of neon ions compromises vision. Figure 5 shows that the relative refractory period is adversely altered by heavy-ion radiation, suggesting that the recovery processes of the retina are the first sites of radiation damage.

Vascular Effects: A Delayed Response

Extremely fine retinal capillaries disappear by 28 days postirradiation when the cat's eye absorbs 1000 to 2000 rads of neon ions. Small blood vessels, slightly larger in caliber than capillaries, show thinning 14 to 28 days postirradiation with 2000 to 3000 rads of neon ions. Major arteries and veins (superior, nasal and inferior) become reduced to one fourth of their original caliber and eventually

TABLE I. 400-MeV neon-ion doses (rads) required to abolish the ERG of the cat eye.

ERG lost in 12 hrs.	ERG lost in 24 hrs.	ERG not lost
1200	1294	193
1600	1300	360
1800		381
1890		596
2200		720
2400		789
2500		1000
2800		1010
3000		
3100		
3400		
3700		
4000		
4300		
4500		

vanish after irradiation with 300 to 4000 rads of neon nuclei (Fig. 6). An eye exposed to 4000 rads or more of heavy ions shows marked retinal necrosis, hemorrhages and ultimately a dramatic stripping of the retina from the choroid coat. Optical imaging of the fundus, especially with doses near 4000 rads, is extremely difficult because of clouding in the vitreous humor and, to a lesser extent, in the aqueous humor. The loss of the richly detailed retinal surface is confirmed when clearing occurs. Corneal opacity, corneal scarring, superficial punctate keratitis, and cataract (lens) formation are very late postirradiation effects, i.e., they appear four to six months postirradiation.

Protein-dye leakage, a sign of loss of the semipermeable property of blood vessels, can be detected with fluorescein angiography two to five days after the absorption of 3000 to 4000 rads of neon ions. This defective permeability state is transient. Our findings, although limited, suggest that 1000 to 1200 rads of neon nuclei is the threshold dose for this effect. It is interesting that neon ions produce a vascular effect but x rays at 4200 rads do not. The RBE for the loss of capillaries is 3.5 (minimum) for neon ions compared with x rays.

Retinal Histology

Stained (H&E) sections of the retina show destruction of the pigmented epithelial cells and death of some astroglial elements. The light microscope can be used to show harmful effects in the pigmented epithelial cells with 1200 rads of neon nuclei. Neuronal elements such as bipolar, ganglion and horizontal cells maintain a tight laminar organization with no apparent change in the laminar structure with 1000 rads or less of radiation. Electronmicroscopic observations on this material are not available. Receptor cells (rods and cones) decrease in cellular density when the eye absorbs 2000 to 3000 rads of neon ions. Rod-cone spatial disorganization or loosening is found after 3000 to 4000 rads of radiation are absorbed by the eye.

Fig. 5. Neon ions suppress the relative refractory period of the retina. The five ERG traces on the left were recorded from an eye exposed to 569 rads of neon ions. ERG traces from the control non-irradiated eye are on the right. Each trace represents the retina's response to two light flashes closely paired in time. From top to bottom the interflash intervals (IFI) for these oscillographs are 100, 120, 140, 160 and 180 msec. The neon-exposed eye failed to produce 100- and 120-msec responses. Only attenuated potentials were generated at larger IFI by the neon-treated retina. The calibration bars for all ERG traces were 200 msec and 100 μ v (microvolts).

Fig. 6. Delayed radiation effect on the vascularity of the cat's retina as revealed by fundus photography. Neon ions (4000 rads) cause a decrease in the caliber of larger vessels and a disappearance of smaller vessels as seen in the bottom photograph. The top photograph is of the control nonirradiated retina. (BBC 772-817)

Late Effects as a Consequence of Neon Ions

Eyelid Reaction

Transient erythema and edema of the conjunctiva appeared four months after exposure to 720 rads of neon ions. Permanent eyelid closure followed the erythema-edema reaction with exposure to more than 2200 rads of neon nuclei.

Hair Depigmentation

The new hair on skin that intercepted the neon-ion beam during an eye exposure grew in grey (4 months postirradiation with 596 rads) or white (6 months postirradiation with 1000 rads). This bleached hair served as a "beam marker."

Hair Loss

Complete epilation occurred three to four months postirradiation with 2200 rads; partial epilation occurred with 1200 rads.

Neoplasms

The delayed effect of neon ions on the skin around the cat's eye involves severe fibrosis leading to eye closure, ulceration and, in cats receiving 2500 rads or more of radiation, the development of neoplasms. The carcinogenic potential of these neoplasms (Fig. 7) should be investigated.

SUMMARY AND FUTURE RESEARCH PLANS

Although interesting results were obtained in early space-flight experiments, no definite explanations could be given because of the limited experimental techniques used. The success in accelerating heavy particles to high energies at the Bevalac has provided a unique opportunity to systematically study on the ground the potential effects of cosmic rays on living organisms. Based on results obtained from experiments with accelerated heavy ions, it is suggested that some cosmic rays, probably very heavy particles, are extremely efficient in producing biological effects and may have been responsible for the early space-flight experimental results. Heavy particles with high LET may be able to produce local multicell lesions. Studies on the inactivation cross sections of human cells exposed to low-energy argon and krypton ions show that the whole nucleus of a cell is the target and that a single heavy particle passing through the nucleus can produce a lethal effect. These results indicate that nondividing cells, e.g., neurons, may be as sensitive to radiation as proliferating cells and that during space flight some loss of brain cells due to cosmic radiation can occur. The consequences of such neuron-killing by heavy ions in space may be quite different from the loss of nerve cells caused by the aging process. It is possible that the loss of nerve cells with aging is nonrandom and genetically programmed so that the vital functions of the brain can be maintained even at advanced age. The loss of nerve cells due to cosmic rays during space flight will, however, be random and of the local multicell-lesion type. A hit by a heavy particle on some specific area in the brain, e.g., the brain stem or nuclei in the hypothalamus, may change its function significantly. On long space flights, e.g., the Space Shuttle flights, the health hazards to astronauts caused by the heavy ions of cosmic rays could be serious. The responses of two major parts of the brain, the brain stem and the hippocampus, to heavy-ion radiation urgently need to be investigated. The brain stem is a small structure at the base of the brain and contains the nerve-cell groups that control movement of the face and neck and provide automatic control of respiration, blood circulation and digestive function. The hippocampus, located at the side and base of each cerebral hemisphere, is very active physiologically, influencing eating, emotion, sexual behavior and sleep. In addition to gross morphological changes, the effects of heavy ions on functional changes, including finely discernable changes and rates of change, should be examined for intercurrent assessment and prognosis for delayed effects. Cultured nerve cells, e.g., neuroblastoma cells, spinal ganglion cells and cerebellar cultures, can be

Fig. 7. Neoplasm of a cat's eye four months after this eye received 2500 rads of 400-MeV/nucleon neon ions.

good models to study the influence of heavy-ion radiation on neurite growth, membrane permeability, enzyme functions, etc., in neurons. Such studies should yield information on how cosmic rays affect synaptic structure, networks and the function of nerve cells as well as information on the fundamental problems of nerve function, structure and specificity.

As more and more travelers will be involved in the upcoming Space Shuttle flights, future NASA programs and SST flights, the carcinogenic effects of cosmic rays on man cannot be neglected. Present data show that 240-MeV/amu neon ions can be two to three times more effective than x rays in enhancing viral transformation of mammalian cells. Whether this enhancement effect of heavy ions will increase further with higher LET should be investigated. Since the mechanisms of initiation and promotion of cancer by radiation are virtually unknown, an investigation of the correlation between DNA breakage and repair and cancer induction by radiation of various LET should help us to better understand the mechanisms of carcinogenesis and to predict the radiation hazards to man in space.

The results of research with the cat's eye on the effects of radiation on vision suggest further studies. The susceptibility of the retina to other heavy ions should be investigated; argon, nitrogen and carbon are available at the Bevalac. The large RBE difference between neon nuclei and x rays suggests that the high linear energy transfer (LET) of heavy ions is an important factor in radiation damage; LET might be a means to predict the effects of these ions. In this regard, we are interested in establishing a possible RBE/LET relationship for heavy ions. The eye allows us to examine the action of radiation on nerves as well as non-neuronal elements including vascular elements and skin in an ordered system. How high-Z radiations alter the electrophysiology of excitable systems is not yet understood. The sensitivities of the optic nerve (ionic conductance mechanisms), lateral geniculate nucleus (chemical transmission of synapses), and visual cortex should be determined for high-Z radiations. A crucial factor in determining the tolerance dose, in order to appropriately limit the use of any new type of radiation treatment modality, is the po-

tential of normal tissue to be transformed into tumor tissue when caught in a radiation field. The delayed effect of neon ions on the skin around the eyes of cats involves severe fibrosis leading to neoplasms. It remains to be determined if these neoplasms are carcinogenic.

Because radiation in space is a mixture of neutrons, protons and heavy ions, knowledge of the delayed long-term effects of low-dose exposure to mixed radiation is vital. Since the iron particle is the most abundant heavy element in cosmic rays and may cause the most severe damage to biological systems, considerable research with this particle is needed and will be done when the intensity and energy of the new iron beam at the Bevalac become adequate.

REFERENCES

1. Slater, J. V., and C. A. Tobias. Effects of cosmic radiation on seed differentiation and development. *Radiation Research* 19, 218 (1963).
2. Curtis, H. J., and H. H. Smith. Corn seeds affected by heavy cosmic ray particles. *Science* 141, 158-160 (1960).
3. Todd, P., C. B. Schroy, W. Schimmerling, and K. G. Vosburgh. Cellular effects of heavy charged particles. In: *Space Research XIII; COSPAR Life Sciences and Space Research XI* (1973).
4. Slater, J. V., and C. A. Tobias. Effects of cosmic radiation on seed differentiation and development. *Radiation Research* 19, 218 (1963).
5. Bucker, H., and G. Horneck. Studies on the effect of cosmic HZE-particles on different biological systems in the Biostack experiments I and II flown on board of Apollo 16 and 17. In: *Radiation Research - Biomedical, Chemical, and Physical Perspectives*. (O. F. Nygaard, H. I. Adler, and W. K. Sinclair, eds.) pp. 1128-1151 (1976).
6. Planel, H., Y. Blanquet, J. P. Soleilhavoup, R. Kaiser, and B. Pianezzi. Effects of cosmic heavy ions on *Artemia* egg development. In: *Radiation Research - Biomedical, Chemical, and Physical Perspectives*. (O. F. Nygaard, H. I. Adler, and W. K. Sinclair, eds.) pp. 1152-1163 (1976).
7. Yang, T. C. H., E. Blakely, A. Chatterjee, G. Welch, and C. A. Tobias. Response of cultured mammalian cells to accelerated krypton particles. *COSPAR Life Sciences and Space Research XV* (in press).
8. Yang, T. C. H., E. Blakely, A. Chatterjee, C. A. Tobias, and G. Welch. Studies on inactivation cross section of cultured mammalian cells with very heavy ions. *Radiation Research* 67, 622 (1976).
9. Todd, P. W. Reversible and irreversible effects of ionizing radiation on the reproductive integrity of mammalian cells cultured in vitro. Ph.D. Thesis, University of California. Lawrence Berkeley Laboratory Report No. UCRL-11614 (1964).
10. Kraft, C. M., M. A. Kelly, E. V. Benton, and W. Haymaker. Effect of neon particle radiation on the brain and associated head structures of the pocket mouse. *COSPAR Life Science and Space Research XV* (in press).
11. Borek, C., and L. Sachs. In vitro cell transformation by x-irradiation. *Nature* 210, 276-278 (1966).
12. Borek, C., and E. J. Hall. Transformation of mammalian cells in vitro by low doses of x-rays. *Nature* 243, 450-453 (1973).
13. Terzaghi, M., and J. B. Little. X-radiation-induced transformation in a C3H mouse embryo-derived cell line. *Cancer Research* 36, 1367-1374 (1976).
14. Borek, C. Cell transformation in vitro by low doses of radiation. In *Particle Radiation Therapy*, pp. 284-301 (1976).

15. Borek, C., E. J., Hall, C. Pain, and H. Mason. Transformation in vitro by neutrons and argon ions. Annual Report on Research Project COO-3243-5, Radiological Research Laboratory, Columbia University, pp. 288-301 (1976).
16. Pollock, E. J., and G. J. Todaro. Radiation enhancement of SV-40 transformation in 3T3 and human cells. *Nature* 219, 520-521 (1968).
17. Yang, T. C., J. Risius, I. Madfes, C. A. Tobias, J. Lyman, and J. Howard. Enhancement of viral transformation of cells in vitro by heavy-ion radiation. To be presented at the 25th Radiation Research Meeting, San Juan, Puerto Rico (1977).
18. Bonney, C. H., F. N. Beckman, and D. M. Hunter. *COSPAR Life Sciences and Space Research XII*, 31-42 (1974).
19. Hunter, D. M., C. H. Bonney, J. E. Pickering, and J. H. Krupp. *Aeromedical Review* 6-7, 1-13, Report No. SAM-TR-75-36 (1975).
20. Curtis, S. B. *COSPAR Life Sciences and Space Research XI*, 209-214 (1973).
21. Benton, E. V., R. P. Henke, D. D. Peterson, J. V. Bailey, and C. A. Tobias. In: *Radiation Research* (O. F. Nygaard, H. I. Adler, and W. K. Sinclair, eds.). (New York: Academic Press) pp. 1164-1171 (1975).
22. Fowler, P. H. In: *Proceedings of the 13th International Cosmic Ray Conference* 5, 3627 (1973).
23. Momeni, M. H., T. A. Cahill, and P. L. Horn. *Radiation Research* 53, 15-23 (1973).
24. Constable, I. J., and A. M. Koehler. *Investigative Ophthalmology* 13, 280-287 (1974).
25. Gaffey, C. T. In: *Response of the Nervous System to Ionizing Radiation* (T. J. Haley and R. A. Smith, eds). (Boston: Little Brown and Co.) pp. 243-270 (1964).
26. Tobias, C. A., T. F. Budinger, and J. T. Lyman. In: *COSPAR Life Science and Space Research XI*, 233-246 (1973).
27. Forenko, B. S., and V. N. Lededev. In: *COSPAR Life Sciences and Space Research XI*, 225-232 (1973).
28. Lyman, J. T. In: *Particle Radiation Therapy*. (Philadelphia: American College of Radiology) pp. 151-154 (1976).

CHAPTER 11

HEAVY-ION RADIATION GENETICS

Michael Freeling and Tracy C. H. Yang

INTRODUCTION

The radiations available from the Lawrence Berkeley Laboratory's heavy-ion accelerator (Bevatron/Bevalac) have permitted an extension of studies within the traditional domain of radiation genetics. Now that larger ions such as argon are routinely accelerated to 500 MeV/amu, it is reasonable to anticipate that heavy ions can be used as tools to dissect fundamental biological processes and improve our food animals and plants. Listed below are six research areas where heavy ions are or will soon be useful. These areas are ordered from the conceptually difficult to the very difficult; areas 1, 2 and 3 involve heavy ions and their effects as important per se (radiation genetics); areas 4, 5 and 6 utilize heavy ions as tools applicable to high-priority genetic problems.

1. Relative Biological Effectiveness (RBE) for the induction of mutations and biological dosimetry.
2. RBE and qualitative studies at the chromosome level.
3. Qualitative studies on specific gene mutations.
4. Estimation of heavy-ion biohazard in terms of mutation and cancer.
5. Heavy ions as unique genetic "scalpels" to dissect complex biological processes.
6. Induced mutations for the genetic improvement of crop plants and food animals.

Each of the above research areas will be treated briefly and separately. Data from work in progress, including our own, are presented because they portend a unique and valuable contribution of heavy ions to the general field of genetics.

ASSESSMENTS

RBE for the Induction of Mutations and Biological Dosimetry

The fact that accelerated heavy charged particles can produce dense ionization tracks and may induce mutations qualitatively and quantitatively different from those caused by other mutagens has prompted several geneticists to study high-LET radiation genetics. Using low-energy heavy particles (10 MeV/amu), Nakai and Mortimer¹ studied the induction of a number of classes of genetic changes in yeast by high-LET radiation and observed that, for lethality, dominant lethality, mitotic segregation, allelic recombination and reverse mutation, densely ionizing particles are more efficient than sparsely ionizing radiation. At about the same time, Smith² determined the relative biological effectiveness of x rays, monoenergetic neutrons, muons, π -mesons and high-energy protons on a cytogenetic system in maize that is particularly favorable for analysis. Except for 7-GeV muons, all particle radiations yielded a higher mutation rate than did x rays. High-LET radiation can be highly mutagenic.

Since heavy ions have been accelerated successfully to very high energies (several hundred MeV/amu) at the Bevalac, experiments were conducted at LBL by one of us (T. Yang) to study the mutagenic effects of high-velocity oxygen particles.³ Dry seeds of a genetic stock of maize (*Zea mays* L.) heterozygous at the lemon-white locus (Lw_1/Lw_1) were irradiated with a uniform oxygen beam. The Bragg peak of the beam was placed 2 mm below the surface of the seeds so that the whole embryos would be irradiated in the Bragg peak region. After exposure, the seeds were planted in a greenhouse, and the length and width of the stripes appearing on the third leaves were measured. The results are given in Fig. 1. This figure clearly shows that both the total length and the total area of stripes (with respect to leaf length and area in oxygen-

Fig. 1. Irradiation of corn seeds with O^{16} . (XBL 736-773)

irradiated groups) are linear functions of dose. The ratio of stripe length to total leaf length increases at about 0.05 per rad. The third-leaf mutation rate as determined from the ratio of the stripe area to the leaf area was found to be about 2×10^{-5} mutations per rad. This value is about ten times as great as the value of 1.6×10^{-6} mutations per rad obtained by Smith² for x rays. A significant effect on the growth of the third leaf due to oxygen-ion irradiation was also observed, and a dose of 820 rads caused a 50% decrease in leaf area. The retardation in development of the leaf is evidently dose-dependent although a shoulder was found in the dose-response curve as shown in Fig. 2. The percentages of plants showing stripes on the third leaves corresponding to various doses were checked, and an exponential function was obtained. A dose of 300 rads produced stripes in 50% of the plants. This result suggests that a single hit by a heavy ion may be enough to cause a mutation and that cells in seeds may not be able to repair the radiation damage induced by high-LET oxygen ions. Comparison of the dose needed to produce stripes in 50% of the plants and the dose required for a 50% decrease in leaf area makes it clear that the oxygen-ion beam is about 2.7 times more effective in inducing mutation than in retarding plant growth.

Seeds irradiated with ^{60}Co gamma rays showed significant developmental changes at doses greater than 1000 rads. A dose of about 7600 rads was sufficient to produce a 50% decrease in the third leaf's area, and a dose of about 5550 rads was required for stripe formation in 50% of the plants as seen in Fig. 3. These results indicate that gamma rays can be only about 1.37 times more effective in inducing mutation than in inhibiting leaf growth. Oxygen ions are much more efficient than gamma rays in producing mutation for a given effect on leaf growth.

At present, all experimental results indicate that heavy-ion radiation can be highly effective in producing a large quantity, and most likely a great variety, of mutants in higher organisms. Further research is certainly needed in order to determine which particle velocity and charge are the most suitable for inducing desirable mutants. Heavy-particle radiation may prove to be a unique means for probing genetic secrets of higher organisms and for solving some agricultural problems.

The late A. H. Sparrow's group at Brookhaven National Laboratory has recently used the sensitive

Fig. 2. Irradiated corn seeds:
 O^{16} versus γ (^{60}Co).

(XBL 736-772)

Fig. 3. ^{60}Co irradiated corn seeds; effect on third leaf.
(XBL 749-1518)

Tradescantia stamen-hair, somatic-mutation system^{4,5} for RBE comparisons. Bevalac-accelerated neon-20 has also been included; L. Schairer provided the data given in Fig. 4.

RBE and Qualitative Studies at the Chromosome Level

Gross chromosomal mutations – reciprocal translocations, deletions of greater than 10 kilobases, etc. – are characterized by one or more of the following:

- 1) Shape of the dose curve using sparsely ionizing radiation (2 or more hits)
- 2) Occurrence of intensity and fractionation effects
- 3) Ion density dependence
- 4) Some proportion of inviable gametophytes (pollen) or inviability in the next generation
- 5) Cytogenetically characteristic homolog pairing configurations
- 6) Anaphase bridges, breaks and perhaps fusions
- 7) Morphologically altered chromosomes (e.g., isochromosomes, rings, and "gaps")
- 8) Impaired *intergenic* recombination
- 9) Restricted *intragenic* recombination
- 10) Nonrevertibility.

Items 1, 2 and 3 above were reviewed by Wolff,⁶ and the remainder are some of the common genetic tests originating with L. J. Stadler in maize and H. J. Muller in *Drosophila*. Densely ionizing particles are expected to generate some multiple-hit events with single-hit kinetics, and Wolff has shown this to be so.⁶ 450-MeV/amu ⁴⁰Ar ions have been used recently by Geard and Rossi⁷ to assess chromosomal aberrations in

Fig. 4. (From Brookhaven National Laboratory).

aerated and hypoxic *Vicia faba* root meristems. These workers found highly complex multiple aberrations involving groups of chromosomes, a condition apparently dependent on very dense ionizations.

Heavy ions provide an important tool for studying chromosome structure and mechanisms of chromosomal repair. In addition, complex chromosomal rearrangements induced by heavy ions have a wide variety of potential uses in fundamental biology. Examples are alteration of the regulation of a particular gene by transposing it to a new region of the chromosome (position effect), excision of "foreign" DNA insertional elements, and construction of chromosomally based male sterility systems.

Qualitative Studies on Specific Gene Mutations

All intragenic mutations are not alike. Unfortunately, the exact nature of radiation-induced lesions – especially in higher organisms – is poorly understood. "At a fundamental level, radiation genetics still suffers from our inability to give precise definition to radiation-induced mutagenic lesions."⁶ Wolff's statement is just as true today as it was a decade ago. At the root of our inability to understand intragenic radiation damage is our ignorance of the structure of the "gene" and its components in higher organisms. Since heavy ions leave behind them a track of dense ionization (core) and a penumbra of weaker ionization (δ rays), the quality of heavy-ion damage is expected to overlap that of x-ray damage. A particularly clear example of this overlap was found by Mortimer, Brustad and Cormack⁸ using particles accelerated from the HILAC and varying in LET to revert various mutations in yeast in either air or nitrogen environments. The oxygen effect decreased with increased LET except that one mutant showed an oxygen effect of 2 for Ne^{10+} (7 MeV/amu). It is likely that the δ rays were solely responsible for reversion of this mutant but not for the other ionization-induced reversions.

One of us (M. Freeling) has begun a qualitative study of the types of lesions induced by heavy ions at the *alcohol dehydrogenase-1* gene in maize. Maize was chosen to represent the typical "higher"-organism pattern of repeat/unique DNA interspersion. Mutants are selected via allyl alcohol-resistant gametophytes (haploid pollen grains) and recovered as rare, single F_1 seeds. Figure 5 diagrams our mutation recovery scheme and the electrophoretic methods used to confirm *Adhl*-mutant genotypes. Figure 6 shows examples of four classes of *Adhl*-pollen-deficient mutants as identified by F_1 allozyme profiles, a procedure that does not destroy the seed. Note that two of these classes, C and D, appear to be regulatory-type mutants. Table I gives the RBE for mutant recovery (not mutation rate) comparing that following irradiation with 400-MeV/amu neon ions and 250-kVp x rays with that arising spontaneously. In short, the RBE for Ne^{10+} mutant recovery is about 10. Using an arsenal of biochemical, genetic and cytogenetic tests, we are now analyzing each mutant to discover the exact nature of the lesion.⁹ For example, an *Adhl*-dysfunction mutant, Type A, might be a point mutant, a small insert/deletion, an inversion, a translocation or some other. These qualitative studies are yielding the first such data on heavy-ion-induced lesions in specific genes in higher organisms and should render all RBE data more meaningful.

Estimation of Heavy-ion Biohazard in Terms of Mutation and Cancer

Since the publication of the Ames group's recent mutagenicity data¹⁰ concerning 300 known carcinogens, there can be no doubt that mutagens in microbes often cause cancer in mammals. (This does not mean that somatic mutation is the only cause.) The safe use of heavy ions for medical diagnosis and therapy depends on adequate quantitative data on RBE and qualitative data on the nature of the induced lesions, specifically in the DNA of higher organisms. It is at least conceivable that heavy ions will induce "regulatory" mutants in DNA regions (intermediate repeat?) generally resistant to mutation by chemicals and sparsely ionizing radiations. The possibility that a single heavy ion can generate complex multihit *intragenic* aberrations (see next section) may place heavy ions in a special biohazard class. Considering the medical potential of heavy ions and the First World commitment to space exploration, continued assessment of heavy-particle (cosmic-ray) biohazard is vital.

We should also recognize that low-energy α particles from heavy elements such as Pu and U and their

Fig. 5. Step 1 of the approach: the chemical selection and recovery of radiation-induced *Adh1*-deficient mutants in pollen. The paternal and maternal *Adh1* alleles – variants *Adh1-S* and *Adh1-F*, respectively – are monitored via native starch-gel electrophoretograms stained specifically for ADH activity. ADH's are dimeric. Enzyme extracts are prepared from a small sliver of embryo (scutellum); the seed is not killed. Two of the many possible mutant allozyme profiles are diagrammed. (A) expected of a complete deletion of *Adh1-S*; (B) expected of a low-producing regulatory mutant of *Adh1-S* or a structural gene point mutant that lowers enzyme levels or ability to dimerize. This crude electrophoretic analysis is the first of many tests to which the mutants will be subjected. 0 is origin; + is anode.

daughters are a form of "heavy ion." Penetrating high-energy particle and meson fields near accelerators generate short-track, heavy-ion tracks. Thus biohazards from heavy recoils may exist in a variety of circumstances.

Heavy Ions as Unique Genetic "Scalpels" to Dissect Complex Biological Processes

Intuitively, it seems that heavy ions should generate a unique class of multi-hit, relatively small (0.1 to 10 kilobases) aberrations. Chatterjee, Maccabee, Tobias and Kobetch¹¹ and Christensen, Tobias and Taylor¹² have used LET, energy per amu, and the angular dependence of secondary electrons (δ rays) to estimate the expected length of single-hit deletions. They estimated that a particle at 10 MeV/amu would yield more than 50% of its deletions with 200 base pairs or less. More recent calculations (Chatterjee and co-workers, personal communication) have predicted penumbra diameters for high-energy ions; 400-MeV/amu ions yield an expected penumbra diameter of $3.12 \times 10^6 \text{ \AA}$ or 900 kilobases (a structural gene is about 1.3 kb).

Fig. 6. Electrophoretograms of F_1 scutellar extracts from four types of Ne^{10+} -induced mutants. (A) Dysfunction. (B) Low expression. (C) Over-expression. (D) ADH_2 subunits present. +'s denote wild-type $Adhl-F/Adhl-S$ profiles. (XBB 774-2774)

It is worthwhile to speculate on the chromosome effects of a fragmenting fast particle, a consequence of nuclear collisions, as pictured below:

If fragmentation occurs near a chromosome, the simultaneous interaction from two or more fragments might be able to produce not only deletions of significant base-pair length but other more complex chromosome effects as well.

In addition, a taut double helix of DNA at right angles to the track is clearly not the *in vivo* mutational target. Eukaryotic DNA is certainly coiled in some way into nu-bodies. The three-dimensional structure of the DNA target influences the sort of mutations recovered. The use of heavy ions to explore the shape of the gene is a possibility for the future.

As is commonly understood by geneticists working with higher organisms (in particular, with *Drosophila*), *intragenic* deletions are not available. Mutants induced by chemicals or sparsely ionizing radiations are either too small (<10 base pairs) or are chromosomal aberrations. Unfortunately, the method of deletion

TABLE I

A comparison of RBE for *Adhl-S-deficient* mutant recovery following x-ray and Ne^{10+} treatment to the pollen mother cells and subsequent selection with allyl alcohol. Types of mutants were electrophoretically catalogued. Mutation recovery strategy is diagrammed in Fig. 5.

Mutagen		None	x rays	Ne^{10+}
Mean dose in rads @ 50/rads/min		--	450	500
Number by type of <i>Adhl-S</i> mutant	A. Dysfunction	0	11	34
	B. Low balance	1	1	6
	C. High balance	0	2	2
	D. Up -- <i>Adh2</i>	0	2	8
	Total Number (A+B+C+D)	1	16	50
Percentage of ears with seeds*		17.2	23.6	16.9
Number of ears with seeds analyzed		153	161	30
Total number of ears analyzed		890	682	178
Estimated number of pollen grains @ 6×10^4 /ear ($\times 10^{-6}$)		53.4	40.9	10.7
Estimated percentage of viability†		50	45	60
Number of viable pollen grains ($\times 10^{-6}$)		26.7	18.4	6.4
Mutants/viable pollen ($\times 10^8$)‡		3.7	87.0	781.3
Mutants/viable pollen/rad ($\times 10^9$)		--	1.9	15.6

*Allyl alcohol concentrations were about equivalent for all mutagenic treatments. That these percentages of ears with seeds are about the same is reassuring.

†Pollen viability determined empirically. The unmutagenized pollen has such a low viability because it, unlike other pollen samples, was field-collected.

‡Note that these are mutant *recovery* frequencies, not mutation frequencies.

mapping¹³ to determine genetic fine structure depends on a series of short deletions. As argued previously, heavy ions may be uniquely suited to produce intragenic deletions.

H. H. Smith's group at Brookhaven^{14,15} has studied the RBE of x rays and various heavy ions in producing mutations, tumors, and growth inhibition in *Arabidopsis*. In addition to presenting data showing that the primary sites of damage that produce these three responses are probably the same, DNA, these studies are the foundation for the continued application of multitarget theory to cross-sectional analyses of dose-response data.

Since the 1930's, geneticists (notably *Drosophila* workers A. H. Sturtevant and C. Stern) have used somatic mosaics to dissect development and construct a fate map on the surface of the egg. Sexual mosaics, caused by spontaneous loss of ring chromosomes, have been most useful in *Drosophila*. High-energy heavy ions present a powerful tool for genetically marking cells at one stage of development and following their descendants in a clone. One of us (T. Yang) is exploring the cellular organization of the apical meristem in maize using heavy ions (see previous sections). Whereas sparsely ionizing radiations have been used for these purposes,¹⁶ high-energy heavy ions (e.g., 500-MeV/amu ^{40}Ar) are far more useful since their RBE is more than ten times as large; thus the exact path of a track through the biological material can be reconstructed by using cellulose acetate sheets and/or embedding materials. Aspects of such research were considered more fully in Chapter 10. Heavy ions should be of great value wherever genetic mosaic analyses are needed.

Finally, the use of heavy ions as tools to further our understanding of genetic phenomena may not be confined to DNA-mediated heredity. Sonneborn¹⁷ has pioneered, using the protist *Paramecium*, in a controversial area often called "structural heredity" where a pre-existing structure templates the assembly of further structure. What is apparently being inherited in such cases is architecture per se, not mediated by self-replicating molecules. The laser beam has been used to alter microns of cellular structure at the cortex of protozoans. We feel that heavy ions might be useful for targets about 10 to 100 mμ in diameter. The quest to reduce morphology to molecular genetic phenomena is just beginning. Heavy ions should prove invaluable.

Induced Mutations for the Genetic Improvement of Crop Plants and Food Animals

R. D. Brock¹⁸ has reviewed the general strategy of using induced mutations to generate quantitative traits of agronomic value. He concludes that, while further research is necessary, the evidence favors the traditional breeder's approach of using naturally occurring variation as opposed to induced mutation. For example, although male sterility (nonquantitative) can be readily induced in maize, high-lysine maize (e.g., *opaque-2*) is a natural variant (the high-lysine trait involves the balance between endosperm storage proteins).

Since heavy ions may induce intragenic chromosomal aberrations of possible regulatory significance, their use for crop improvement should be tested. Any new technology with potential to improve world nutrition via an improved gene pool would be a lasting contribution.

REFERENCES

1. Nakai, S. and R. Mortimer. Induction of different classes of genetic effects in yeast using heavy ions. *Radiat. Res. Suppl.* 7, 172-181 (1967).
2. Smith, H. H. Relative biological effectiveness of different types of ionizing radiations: cytogenic effects in maize. *Radiat. Res. Suppl.* 7, 190-195 (1967).
3. Yang, T. C., E. V. Benton, L. Craise, and C. A. Tobias. Studies of the development of *Zea mays* irradiated with accelerated oxygen ions. Lawrence Berkeley Laboratory Report No. LBL-2016, pp. 130-152 (1973).
4. Underbrink, A. G., L. A. Schairer, and A. H. Sparrow. The biophysical properties of 3.9-GeV nitrogen ions. V. Determinations of the relative biological effectiveness for somatic mutations in *Tradescantia*. *Radiat. Res.* 55, 437-446 (1973).
5. Underbrink, A. G. and A. H. Sparrow. The influence of experimental and points, dose, dose rate, neutron energy, nitrogen ions, hypoxia, chromosome volume, and ploidy level on RBE in *Tradescantia* stamen hairs and pollen. International Atomic Energy Agency Report IAEA-SM-179/31, pp. 185-214 (1974).
6. Wolff, S. Radiation genetics. *Ann. Rev. Genet.* 1, 221-44 (1967).
7. Geard, C. R. and H. H. Rossi. Biophysical studies with 450 MeV/amu ⁴⁰Ar ions: 4. Chromosome aberrations in aerated and hypoxic *Vicia faba* root meristems. Presented at the 24th Annual Meeting of the Radiation Research Society, 1976. (Abstract)
8. Mortimer, R. K., T. Brustad, and D. V. Cormack. Influence of linear energy transfer and oxygen tension on the effectiveness of ionizing radiations for induction of mutations and lethality in *Saccharomyces cerevisiae*. *Radiat. Res.* 26, 465-482 (1965).
9. Freeling, M. Intragenic recombination in maize: pollen analysis methods and the effect on parental *Adhl*⁺ isoalleles. *Genetics* 83, 641-654 (1976).

10. McCann, J., E. Choi, E. Yamasaki, and B. N. Ames. Detection of carcinogens as mutagens in the *Salmonella*/microsome test: assay of 300 chemicals (Part I). *Proc. Natl. Acad. Sci. U.S.* 72, 5135-5139 (1975).
11. Chatterjee, A., H. Maccabee, C. A. Tobias, and E. J. Kobetich. Radial energy deposition by heavy ions in water. *Radiat. Res.* 47, 335 (1971). (Abstract)
12. Christensen, R. C., C. A. Tobias, and W. D. Taylor. Heavy-ion-induced single- and double-strand breaks in X-174 replicative form DNA. *Int. J. Radiat. Biol.* 22, 457-477 (1972).
13. Benzer, S. On the topology of the genetic fine structure. *Proc. Natl. Acad. Sci. U.S.* 45, 1067-1620 (1959).
14. Hirano, Y., H. H. Smith, and J. T. Lyman. Tumor induction by heavy ionizing particles and x rays in *Arabidopsis*. *Radiat. Bot.* 8, 449-456 (1968).
15. Hirano, Y., H. H. Smith, J. T. Lyman, K. H. Thompson, and J. W. Baum. Relative biological effectiveness of heavy ions in producing mutations, tumors, and growth inhibition in the crucifer plant, *Arabidopsis*. *Radiat. Res.* 44, 204-223 (1970).
16. Steffenson, D. M. Reconstruction of cell development in the shoot apex of maize. *Amer. J. Bot.* 55, 354 (1968).
17. Sonneborn, T. M. Gene action in development. *Roy. Soc. Lond. B* 176, 347 (1970).
18. Brock, R. D. The role of induced mutations in plant improvement. *Radiat. Bot.* 11, 181 (1971).

CHAPTER 12

HEAVY-ION RADIOGRAPHY

Cornelius A. Tobias, Eugene V. Benton and M. Paul Capp

For almost 80 years, ever since Roentgen's discovery of x rays, the use of x rays has dominated the field of diagnostic radiological medicine, and one can say that the history of modern medicine parallels the history of diagnostic techniques.

The ability of x rays to differentiate among tissues depends on their absorption coefficients. The softer the x rays, the higher the absorption coefficient and the greater the ability to differentiate among structures of similar atomic compositions. When soft x rays are used, however, a great disadvantage develops because higher and higher absorption coefficients mean greater and greater absorption in tissues traversed and greater doses to the patient.

The involvement of the Lawrence Berkeley Laboratory in the potential use of heavy ions for radiography purposes began in about 1967 when we made an earlier proposal for a heavy-ion accelerator, the Omnitron. We had realized then that heavy ions might have an important role in both radiological diagnosis and microscopy (Fig. 1A).¹ This realization was, of course, preceded by the earlier elucidation of the ionization properties of heavy ions by Bragg in 1912 and by the recognition by Herbert Anderson, Professor of Physics at the University of Chicago, in 1960 that heavy ions can be used as delicate tools for the measurement of thickness.² In 1968, Andrew Koehler of Harvard University published his first remarkable proton radiographs obtained at the Harvard Cyclotron (Fig. 1B).³ Here the ability of protons for delicate density measurements was quite well demonstrated. In our laboratory, it was realized that various mathematical reconstruction procedures, then beginning to be used in x-ray crystallography and microscopy, could also be applied to helium-ion radiographs. John Lyman made 500 hand measurements of a tissue-like phantom using helium ions, and Michael Goitein, then at Berkeley, applied an algorithm based on a least-squares approximation. These efforts demonstrated that two-dimensional reconstruction was indeed practical.⁴ It was apparent, however, that the data must be very accurate and that a full-scale, "on-line," helium-ion reconstruction system would be quite expensive. We also recognized that neither protons nor helium ions would be ideal because heavy ions have greater resolution for detecting both small density differences and fine detail.

At about the same time, Hounsfield et al. published their first computerized tomography images,⁵ which allowed studies of the cross section of the body based on x-ray data. This technique became exceedingly popular and important so that now it is used in many radiology departments, and many different companies are now engaged in constructing such devices. The ultimate resolution of computerized tomography is, however, still limited by the absorption and scattering properties of x rays.

When the first heavy-ion beams were obtained at the Bevatron in 1971, we re-examined the possibilities for heavy-ion imaging. It became obvious that the use of a single photographic x-ray film was of only limited applicability as used with x rays and, up to that time, with protons because of the fact that the film could only respond to a very limited set of range differences. Other disadvantageous characteristics of the photographic film are the relatively large background fluctuations due to the graininess of the film, additional background due to secondary radiation in the proton field, and the logarithmic response of the film. We have devised a new method known as *heavy-ion radiography* that overcomes many of these difficulties (Fig. 3).⁶ The keys to this technique are the type of detectors used--plastic nuclear track detectors originally developed for research with heavy cosmic rays at high altitudes and in space--and the

Fig. 1. Various suggested methods for the use of heavy charged particles in radiography. (A) *Heavy-ion radiography*, Tobias et al.,¹; (B) *proton radiography*, Koehler³; (C) *scanned-beam radiography*, Steward et al.,⁷; (D) *scanned-beam radiography with location analyzer*, Koehler et al.,⁸; (E) *high-energy proton interface detector*, West and Sherwood⁹; (F) *proton-scattering analyzer*, Saudinos et al.,¹⁰. (XBL 773-3245)

manner in which the detectors are used. Several other new methods have been proposed for the utilization of heavy charged particles for radiographic purposes. Some of these methods are either still in the "idea" stage or in the process of being developed. We will briefly discuss some of these other ideas here.

SCANNED-BEAM RADIOGRAPHY

Investigators at the Argonne National Laboratory have performed preliminary investigations of a proton scanning radiography system.⁷ Pulses of the high-energy proton beam were scanned by a deflector system.

The residual range of the protons was measured in a large scintillation crystal, and the data were processed on line electronically (Fig. 1C).

SCANNED-BEAM RADIOGRAPHY WITH LOCATION ANALYZER

A version of the random-impact technique¹ was suggested by Koehler, Boyd and Gottschalk.⁸ The location of particles was diagnosed by a multiple-wire chamber upstream from the patient. Measurement of the residual range was done downstream by a large scintillation crystal. The two detectors were to operate in coincidence (Fig. 1D).

HIGH-ENERGY PROTON INTERFACE DETECTOR

It was gradually recognized (see below) that protons deflect in the object because of multiple scattering and that this deflection reduces resolution in a direction perpendicular to the beam. West and Sherwood⁹ successfully used higher-energy protons than those needed for stopping-power measurements alone, which scatter less, for imaging interface boundaries. At an interface, there is a slight anisotropy of scattering -- more protons are scattering away from the denser side than toward it. Unfortunately, at present this technique requires a relatively large dose (Fig. 1E).

PROTON-SCATTERING ANALYZER

Scientists in France and Switzerland are working on a proton scattering analyzer,¹⁰ taking advantage of known angular distributions between secondaries when protons scatter on protons, carbon or some other element. Coincidence analysis of the angular distribution from a given location inside the body can give information on the elemental composition of the object. The technique has had an experimental test. To keep the dose rate low, the spatial resolution is poor at present (Fig. 1F).

HELIUM RADIOGRAPHY WITH MULTIPLE-WIRE CHAMBERS

In our laboratory, Crowe and Budinger have built a helium-ion tomographic device that can operate "on line" by processing complex counting information.²⁴ Their device is shown schematically in Fig. 2A. The subject is exposed to a parallel stream of monoenergetic helium ions at the 184-inch cyclotron. The detection and measurement of residual range is done on individual particles by using multiple-wire chambers as range stacks. The multiple-wire chambers, initially developed for high-energy physics, consist of arrays of large ionization chambers arranged in such a manner that the charge is collected on sets of closely spaced wires mounted parallel to each other in planes perpendicular to the beam. Usually two chambers are next to each other with the direction of the collecting electrodes at right angles. Because a given collecting wire can sense the proximity of a passing particle, such wire chambers can measure the location of a crossing particle as well as its ionization. Stacks of wire chambers mounted behind each other can measure location, range, and, with appropriate circuitry, the directions of particles as well, thus giving opportunities for partially correcting blurring of the image due to multiple scattering.

The Crowe-Budinger technique was used with human patients for reconstruction of two-dimensional structures in the brain. At a helium-ion dose of only 1/50th the dose delivered by x-ray scanners, good reconstructions have been obtained; an example is shown in Fig. 2B. This technique, as most other tomographic techniques, is based on particle counting; for this reason, it is limited by the resolving time of the counting instruments. Counting sufficient amounts of particles usually takes several seconds; during this time, it is likely that the patient will move and the tomography might be distorted. With the improvements in fast counting techniques, however, the time needed for wire-chamber radiography will be reduced.

HEAVY-ION RADIOGRAPHY

Figure 3 shows schematically the technique of heavy-ion radiography. A nearly parallel stream of heavy particles crosses the object to be radiographed and stops in a stack of plastic foils. The foils are nuclear track detectors, originally developed as mentioned above to study heavy primary cosmic rays and to record tracks due to nuclear fission fragments.^{11,12} The stopping-point distribution in the plastic

(A)

EMI

1600 mrad :
180 VIEWS

(B)

HELIUM IONS

30 mrad
62 VIEWS

Fig. 2. Helium radiography with multiple-wire chambers. (A) Device used at the 184-inch Cyclotron. (B) Brain scan using this procedure (on the right) compared with brain scan using an x-ray scanner (on the left). (XBL 755-3024) and (XBL 752-1496)

Fig. 3. The principle behind the method of *heavy-ion radiography* with plastic nuclear track detectors. The beam passes through the object and comes to rest in a stack of thin plastic nuclear detectors (e.g., Lexan or cellulose nitrate) to detect the exact localization and depth of each stopping heavy ion. The particles of sufficient LET produce a latent lesion in the plastic that can be developed later by the application of concentrated NaOH to a microscopic tapered hole.

(DBL 736-5217)

detector stack corresponds to the residual-range distribution of the particles after crossing the object. Therefore, the plastic stacks indirectly measure the stopping power distribution in the object.

The plastic foils that we use have very special properties. They are insensitive to the passage of low-LET particles. High-LET particles cause a lesion in the plastic that can be developed by the application of concentrated sodium hydroxide until a tiny conical impression or hole forms. The plastics that we are using at present, lexan and cellulose nitrate, are only sensitive to stopping heavy particles; it is practical to use them for atomic numbers 6 through 10. A beam pulse produces patterns of small holes in each of the 25 to 50 stacked plastic sheets. The information on each plastic sheet can be photographed; alternatively, the information on location and residual range can be transferred by an optical scanning method to a computer for further quantitation and eventual display.

Compared to diagnostic x rays, heavy ions (e.g., carbon) are much more sensitive to small electron-density differences in the subject, which can be visualized with higher contrast and significantly lower doses. On the other hand, the lateral resolution of x rays (i.e., in planes perpendicular to the direction of the beam) appears to be better than that of heavy particles.

The "depth resolution," that is, the resolution for measuring the stopping power of the object, depends on the initial energy spread and straggling of the particles. The magnitude of straggling is nearly proportional to the range and to the inverse square root of the particle mass. Thus, carbon ions (mass = 12) are 3.5 times better in the resolution of depth than protons (mass = 1). The theoretical relationships as functions of range are shown in Fig. 4A.

Another quantity is the "lateral resolution," which depends on the deflection of the heavy particles caused by multiple scattering. The multiple scattering depends on approximately the inverse 0.6 power of the mass of the particles. Figure 4B shows the dependence of this factor on object thickness for a feature on the upstream edge of the object.

These properties have been measured in some detail for various particles using resolution phantoms. R. Henke, W. Holley, and formerly M. Cruty of our group have demonstrated experimentally a great advantage in the use of heavy particles, carbon and neon, compared to protons and helium ions. It was shown by Henke et al.,¹³ for example, that a 260-MeV/n carbon beam of 12 cm "useful" total range in water when delivered in a single beam pulse has a range straggling of 0.055 or less than 1% of the total range.

Fig. 4. Heavy ions have greater depth-resolution sensitivity and contrast than protons, alpha particles or x-rays. This is shown quantitatively here where the range straggling (A) and beam deflection (B) due to multiple small-angle scattering are drawn for protons and heavier particles as functions of the range penetration in water. In (B) the imaged feature is on the upstream side of the water. (DBL 741-4634A)

Working with line resolution phantoms, we obtained modulation transfer functions (MTF) for a variety of conditions. This measurement, often used in x-ray radiography, corresponds to the variation in density difference signals obtained in the x-ray image as a function of the frequency of line pairs to be resolved. Figure 5A shows comparative MTF curves for protons and carbon and neon ions of approximately the same range when the density of events on a single plastic foil is measured. It was feasible to resolve two line pairs/mm at an MTF of 0.1 with neon; this frequency was not resolved with protons or carbon ions. The

(XBL 773-3246)

Phantom Studies for Visualization of Tumors

The potential advantage of heavy-particle radiography over x rays lies in the superior density resolution attainable at a given dosage, which should permit better visualization of tumors differing little in density from surrounding tissue. To test the relative abilities of heavy-particle radiography and x rays in this regard, a phantom representing a body part containing a number of objects simulating tumors differing in density only slightly from their surroundings was constructed by Graham Sommer. This phantom is shown in Fig. 6A and consists of a rectangular lucite box 7.5 cm thick filled with water in which are suspended five 2.5-cm-diameter, very thin latex rubber spheres containing sucrose solutions varying in specific gravity from 1.005 (upper left) to 1.030 (lower middle). A sixth sphere at the bottom right contained a solution with a specific gravity of 1.030; this solution of monobasic potassium phosphate, a substance of mean atomic number very close to that of bone, was used to evaluate the effect of atomic-number difference on visualization by the two modalities. The phantom was radiographed using 250-MeV/amu carbon nuclei and a cellulose nitrate detector stack. The dose delivered at the middle of the phantom, an approximate value of the mean phantom dose, was 19 mR. A single sheet from the detector stack, shown in Fig. 6B, records the images of all six spheres. (The 1.005-specific-gravity sphere in the upper left had drifted laterally to the container wall just prior to the exposure.) The total change in stopping power through the thickest part of the phantom was equivalent to 0.0125 cm of water. At this very low flux level, considerable quantum "noise" or mottle is evident in the radiograph.

The phantom was then radiographed using a standard x-ray machine employing alpha-4 rare-earth screens and X-D film. An 8:1 grid having 130 lines/inch was used, and phantom entrance and exit doses were recorded using thermoluminescent dosimeters. A radiograph obtained at 60 kVp and 16 mAs, for which entrance and exit doses of 70 mR and 0 mR, respectively, were recorded, is shown in Fig. 6C.

For a further comparison, a CT scan of the phantom with the section passing through the six spheres was obtained using an EMI CT5000 body scanner. Such a scan is shown in Fig. 6D. Spheres containing sucrose solutions to specific gravity 1.015 are visible while the visibility of the 1.010 specific gravity sphere is equivocal and the 1.005 specific gravity sphere is not detected. Low-density regions above the spheres are due to small air bubbles. The dose delivered to the section of the phantom illustrated was approximately 1 rad.

The results of imaging this phantom with heavy-particle radiography and x rays indicate a very significant dose advantage of heavy-ion radiography over x rays in the resolution of tumor-like objects differing only slightly in density from their surroundings. The carbon radiograph taken at a 19-mR mean phantom dose was superior to the CT scan delivering 1 rad to the scan section and much superior to plain x-radiographs using 31-mR and 155-mR mean phantom doses in its resolution of spheres containing sucrose solutions of specific gravity close to that of the surrounding water. The relative ease of detection of the sphere containing a higher-Z salt is reflective of the dependency of x-ray absorption on photoelectric effect. Subject contrast for x rays is very largely dependent on atomic-number differences.

Specimen Radiography

It seems important to image with the new technique some normal tissues and tissues bearing a variety of tumors. We cannot hope to see soft-tissue tumors in vivo if these are not detectable in vitro. Furthermore, we wish to assemble information on the stopping power of a variety of tumors. The specimens used are either fresh unfixed human tissues removed in the course of previous surgery or fixed preparations. Because the fixation process causes some chemical changes, we cannot be sure that density differences in fixed specimens are identical with those in fresh specimens. The tissues were immersed in water for carbon radiography. Control x-ray pictures were often taken, but most of these failed to demonstrate the location of the tumor. A systematic study in specimen radiography is in progress by Professor Paul Capp

(A)

(C)

(B)

(D)

Fig. 6. (A) Photograph of a phantom representing tumors differing slightly in density from their surroundings. The spheres contain sucrose solutions with the following specific gravities: top row, left to right -- 1.005, 1.010, 1.015; bottom row, left to right -- 1.020, 1.030. The bottom right sphere contains KH_2PO_4 salt solution of specific gravity 1.030. (B) Carbon radiograph of the phantom taken at a dose level of 19 mR. (C) X-radiograph of the phantom taken at a mean phantom dose of 155 mR. (D) CT scan of the phantom taken with the EMI body scanner; the dose to the scan section was approximately 1 rad. (XBB 772-746)

of the Radiology Department of the University of Arizona Medical School and Graham Sommer of the University of California, San Francisco.¹⁴

Figure 7 is a photograph (top) and a carbon radiograph (bottom) of a fresh liver specimen containing numerous deposits of metastatic oat-cell carcinoma. The light region surrounding the area representing the full thickness of the tissue specimen is a consequence of the wedge-shape of this specimen. A number of small light areas within the specimen represent air trapped in vascular and ductal structures. Several metastatic deposits within the liver are easily identified on this detector sheet as light regions having indistinct margins.

Fig. 7. Photograph (top) and carbon radiograph (bottom) of a liver specimen containing metastatic oat-cell carcinoma. (XBB 772-1040)

Measurement of Stopping Power

Methods have been developed to accurately determine the stopping power in various portions of specimen. Using a fixed brain specimen, we calculated the stopping power values shown below relative to water.

White Matter	1.0307 ± 0.0019
Gray Matter	1.0290 ± 0.0013
Metastatic Melanoma	1.0451 ± 0.0012

We believe that the accuracy and resolution of stopping power at low doses is better for the heavy-ion method than for other methods. Eventually, such determinations should be routine from radiographs and reconstructions taken in vivo.

Studies with Humans

Heavy-ion radiography with human patients was initiated in June 1976 with mammography. Later in that year radiography of soft-tissue abnormalities in extremities was begun.

Mammography

Mammography is a generally used diagnostic procedure with soft x rays. The dose per picture varies between 0.5 and 2 rads. Xeroradiography of the mammary gland can be done with about 1 rad per exposure; 2 to 6 exposures are usually taken in each procedure. Although these procedures detect cancer with high reliability, they often do not show dense tumor tissues. There is also concern that repeat exposures for screening purposes give too high doses to the population. Our program with the participation of Edward Sickles, a mammographer, and Kay Woodruff, a pathologist, both of the University of California, San

Francisco, is an attempt to systematically compare diagnostic findings by various techniques with post-operative pathology findings.^{15,16} The experimental layout is shown in Fig. 8. The patient is lying on a stretcher; one of her breasts is hanging in a vessel with parallel walls and filled with lukewarm water; her breast is gently squeezed. The beam passes through a thin lead scatterer about 10 m upstream from the patient. A single beam pulse is used. We have found that a 100-millirem dose is sufficient to obtain a set of plastic films with a wealth of detail.

To date, 22 patients with previously diagnosed tumors or previous biopsies were radiographed. A comprehensive study is in progress. In these early cases, it is apparent that heavy ions may have an advantage when viewing "high-density breasts" with fibrocystic disease. Sometimes the radiologist is aided in diagnosis by comparing radiographs of both breasts of a patient and looking for signs of lack of symmetry. Such a pair of radiographs is shown in Fig. 9. The region of asymmetry was later proven to be lobular carcinoma.

Fig. 8. An overall view of the apparatus used for patient mammography. The water bath is locked into position perpendicular to the beam line, which is parallel to the optical bench rails. The couch, supported by the optical bench and semicircular track, can be rotated through 180° about the water bath. The ionization chambers used for dosimetry and the variable beam attenuator are shown in the foreground. Brass blocks used to shield the patient, located immediately upstream of the couch, are not shown. (CBB 757-5384)

Fig. 9. Heavy-ion radiographs of both breasts of a patient can be used to identify regions of asymmetry. Such a region in the left breast of this patient was later proven to be lobular carcinoma.

Skeletal Radiography

We are in the process of evaluating the potential usefulness of heavy ions for skeletal radiography. In this procedure, it is hoped that not only bone detail but soft-tissue detail (gray-scale differentiation) might be obtainable. Harry Genant of the Department of Radiology of the University of California, San Francisco, is our consultant in this work. Dr. Genant has done significant work in microfocal-spot radiography. We have done only two patients to date, the first patient had a giant-cell tumor of the distal femur. Direct examination of the series of plastic films in this case was not satisfactory because of the difficulty in synthesizing such a cumbersome amount of detail. Instead, an integral picture is prepared with a computer; the tumor of the femur is shown in Fig. 10. In this picture bone appears very black, and invasion of the joint structures by the soft tissues of the tumor is readily discernible.

The potential of skeletal radiography is great. Figure 11 is an example of the lateral exposure of a human foot (specimen). Not only skin and bones but several tendons are visible.

Fig. 10. Computer synthesized skeletal radiograph of a giant-cell tumor of the distal femur.

Computerized Analysis and Display

Before detailed quantification of electron densities and three-dimensional reconstruction of heavy-ion radiographs are practical, we must find methods for storing and analyzing the information on the plastic radiographs in a digital computer. We have made significant progress in this direction. Initially, the data obtained in a single radiographic procedure are present on 10 to 40 thin plastic sheets as small holes or conical indentations caused by the passage or stopping of individual heavy particles. The essential information at each point of the plane (X,Y) of the radiographs is the average depth Z to which particles penetrate at (X,Y). In addition, it is helpful to know the root mean-square deviation of Z. There is a variety of methods to extract this information including optical addition and subtraction and optical scanning followed by electronic processing. During the past two years, we have attempted some of these methods.

Much progress has been made recently by using an optical television scanner, the Quantimet 720, and a PDP-11 computer. A Vidicon television camera focuses on a single sheet of plastic. The plastic is illuminated obliquely from below so that the camera can see the scattered light coming from holes, conical indentations and imperfections in the plastic. This image is dissected into a number of picture elements, currently 204×156 or 31,824 elements, and the magnitude of scattered light signal is recorded on the memory disc attached to the computer. There are approximately 64 gray levels, and the information on a plastic stack takes about one fourth of the entire capacity of the disc (10^6 16-bit words). For each

Fig. 11. Skeletal radiograph of the lateral exposure of a human foot (specimen). Note that only skin and bones but several tendons are visible.

picture element (X,Y) the distribution of scattered signal is given. A bias is introduced to eliminate "background," and the scattered signal S_i at depth Z_i in each sheet is averaged to yield

$$\bar{Z}(X,Y) = \frac{\sum_i Z_i S_i(X,Y)}{\sum_i S_i(X,Y)} .$$

The distribution of stopping particles depends on beam purity, the homogeneity of the tissues and the number of particles per area element. Thus, a more accurate Z number results from a higher dose or a larger sampling-area element. Most of the background is not due to heavy particles but to optical imperfections on the surface of the plastic sheet.

The $\bar{Z}$ distribution then represents hills and valleys in Z on the plane (X,Y). This quantitative information is used either for final display or for computation of electron-density distribution patterns for thin specimens that are uniform in the Z direction.

The computer can also display quantitative variations in beam stopping points along any of the chosen coordinates. For example, in Fig. 12B we show a stopping profile along section s-s of a human

S - S →

(A)

(B)

Fig. 12. (A) Simulated three-dimensional display of the synthesized radiograph of a mastectomy specimen. (B) The stopping-point profile along section s-s of the specimen indicated in A; a = water; b = skin; c = subcutaneous lipid; d = tumor. (XBB 772-1038)

breast specimen, the radiograph of which appears in Fig. 12A. In Fig. 12B the increased density of skin, the lower density of lipid-containing subcutaneous tissue, and the higher densities of a tumor are readily discernible. The use of such computerized display methods for the interpretation of heavy-ion radiographs is in its initial stages.

Three-dimensional Reconstruction

Heavy-ion radiography is suitable for three-dimensional reconstruction by the methods of computerized tomography. Because of the high sensitivity for stopping-power measurements, we anticipate high-quality reconstructions at low dose levels.

Figure 13A shows our original conception of how two-dimensional reconstruction might be carried out. The beam is passed through a slit; as subsequent beam pulses are arriving, the patient is rotated to different angles of incidence while the plastic stack is moved vertically between beam pulses so that the images formed in the stack by a sequence of beam pulses do not overlap.

It is this method that has been used for the two-dimensional reconstruction of a section of a phantom. An actual photograph of the phantom is presented in Fig. 14A for comparison with the reconstruction shown in Fig. 14B. In Fig. 13B we show the patterns obtained in several films of the stack; the narrow bands are images of the phantom at specified angles of incidence. In this experiment a carbon beam of 12-cm range was used. A feature of 0.1-cm dimensions was well resolved. It is obvious that by increasing the width of each band a three-dimensional reconstruction will be possible. Preparations are being made now for computerized tomography of the human head by this method.

This technique depends on the frequency of beam pulses. At the Bevatron, 12 pulses/min are available. It will take several minutes to obtain sufficient data for reconstruction.

It may be possible to rotate a human patient over 180° in 1 or 2 seconds. We believe that the length of the beam pulses can be stretched to that length; however, motions of the internal organs will probably decrease resolution. In the future we hope to develop accelerator techniques that can take the necessary exposures without the need to rotate the human subject.

A possible scheme for a future diagnostic heavy-ion accelerator is shown in Fig. 15. The beam of partially charged carbon ions is circulated in a ring (accelerator or storage ring). This accelerator should be capable of about 30 beam pulses per second. Each beam pulse is inflected isocentrically through another beam port. Inflection is done by stripping the beam of all of its electrons. The patient would remain motionless for 2 to 3 seconds while the detector stack, downstream from the patient, is moved between each beam pulse.

Thin-specimen Radiography

The strict range-energy relationship holds for particles of short and long range equally well. Kay Woodruff and Graeme Welch have used the low-energy 88-inch cyclotron for thin-specimen radiography. We have tried cryostat-frozen sections of 6 to 11 micrometers in thickness. The frozen sections were applied directly to a stretched mylar filter in a specially designed holder filled with 70-percent alcohol. The sections were subjected to alpha-particle radiography using polycarbonated plastics of 10 to 13 micrometers etched up to two hours in sodium hydroxide as the detector. The sections were stained with hematoxylin and eosin directly on the mylar filter and then placed on glass slides, coverslipped and photographed. The photomicrographs were compared to photographs and direct microscopic impressions from the etched plastics. No comparable gamma radiographs have been taken because our available techniques will not image thin sections.

Fig. 13. (A) Method visualized for obtaining radiographs for two-dimensional reconstruction; the beam is passed through a slit, and, as subsequent beam pulses are arriving, the patient is rotated to different angles of incidence while the plastic detector stack is moved vertically. (B) Patterns obtained in several films of the detector stack used for two-dimensional reconstruction of the phantom shown in Fig. 14; the narrow bands are images of the phantom at specified angles of incidence. (DBL 736-5221, XBB 774-2824)

(A)

(B)

Fig. 14. (A) Photograph of a small phantom used to test the reconstruction procedure. (B) Radiograph of the phantom resulting from reconstruction of the data presented in Fig. 13(B).
(XBB 773-2678)

Fig. 15. A scheme for a future diagnostic heavy-ion accelerator in which a beam of partially charged carbon ions is circulated in a ring; each beam pulse is inflected isocentrically through another beam port.
(XBL 764-5439)

The particle radiographs yielded an image of breast tissue heretofore unseen. Ductal structures could be identified, but their appearance was different from that visualized by conventional microscopy. Figure 16A shows a duct etched in plastic; Fig. 16B shows a similar duct seen with light microscopy.

We do not know the significance of these experiments because little normal tissue has been analyzed, and there has been no effort to obtain increased resolution. It is a new method of imaging and has diagnostic potential that deserves further exploration.

(A)

(B)

Fig. 16. (A) An image of breast tissue produced by alpha-particle thin-specimen radiography showing a duct etched in plastic. (B) A duct similar to that in A but viewed with light microscopy.

(XBB 760-9186A) and (XBB 760-9185A)

HEAVY-ION MICROSCOPY

Heavy particles have great potential for microscopy. For a given velocity their wavelength is much smaller than that of electrons; hence these particles should ultimately be capable of higher resolution than is attained with ordinary electron microscopy. This property was recognized some time ago by Magnum.¹⁷ There have been sporadic attempts to do proton microscopy during the past 25 years^{18,19} including some in our laboratory.²⁰

Extension of the techniques of heavy-ion radiography to microscopic dimensions appears to be a promising initial step toward high-resolution, heavy-ion microscopy. The exact range-energy relationships hold to very small energies and range penetrations. Microradiography has the potential to image the distributions of electron densities and to respond to the atomic composition of the specimens. The relatively small deflection of heavy particles during their passage in matter is a great advantage; it allows us to image hydrated specimens with relatively small loss in resolution. In transmission electron microscopy, for high resolution one is usually restricted to the use of extremely thin dehydrated specimens. These are mounted in vacuum because air scatter in itself is also undesirable. Transmission electron microscopy of biological material in the normal hydrated state is technically difficult even with low-temperature frozen material. We should note that R. Glaeser et al.²¹ in this laboratory have recently succeeded in packaging thin hydrated samples for electron microscopy, and E. Kalman in Hungary is also experimenting with the electron microscopy of hydrated samples.²²

Preparation of Heavy-ion Replicas

We wished to take advantage of the ability of stopping heavy ions to produce microlesions in solid materials, which can be enlarged by etching and developed into a "replica." A monoenergetic parallel beam of heavy particles is allowed to pass through the specimen, and each particle comes to a stop in a plastic "thick target" mounted immediately behind the specimen (Fig. 17C). The contour envelope of all stopping points mirrors the stopping properties of the specimen; where the specimen thickness (as measured by electron density) is great the stopping points are near the surface, and where the specimen thickness is small the residual range of the particles is greater. Thus, by mapping the depths at which microlesions end, we should obtain an image of electron density distribution.

The measurement of residual range in plastic detectors can be accomplished in a variety of ways. We chose to etch the plastic detector in NaOH for varying lengths of time. Etching results in conical tracks with their apex at the stopping point. When sufficient numbers of particles are applied so that the etched cones overlap, one obtains a replica of the object in plastic. The replicas so obtained can be viewed either by light microscopy or by scanning electron microscopy.

A variety of heavy-ion-microscopy replicas were made with krypton ions at the HILAC, and some were made with alpha particles by T. Yang and G. Welch.²³ Figure 17B shows a wing from a fly by standard optical phase microscopy. Figure 17A shows the image of the same wing obtained by viewing the etched plastic detector after exposure of the wing to Californium alpha particles. These pictures were prepared by F. Abrams as part of his undergraduate thesis.

Scanning Electron Microscopy of the Replica

In collaboration with T. Hayes of Donner Laboratory, scanning-electron-microscopy images of the replicas were obtained in various stages of etching. In this procedure intensity of the electron beams was kept sufficiently low in order to avoid etching by the electron beam itself. Both standard and stereo pair scanning electron micrographs were obtained.

These initial results with heavy-ion microscopy are an example of new techniques and advances in other fields not anticipated in the originally planned Bevatron work. The first conception of heavy-ion

(A)

(B)

(C)

Fig. 17. (A) A wing from a fly shown by *heavy ion replica microscopy*; the image was obtained by viewing the etched plastic detector foil after exposure of the wing to alpha particles. (B) The same wing viewed with standard optical phase microscopy. (C) Setup for heavy-ion microscopy; a monoenergetic parallel beam of heavy particles is allowed to pass through the specimen and come to a stop in a plastic target behind the specimen.

(XBB 7610-9085)

microscopy followed from heavy-ion radiography with the more energetic beams. It appears that heavy-ion replica microscopy can be done quite well with low-energy protons or helium ions. In collaboration with F. Goulding of LBL, we are planning to use a Van de Graaf machine, which was given to the laboratory recently.

THE FUTURE

New patterns not heretofore visualized can be seen with heavy-ion radiography of soft tissues, and the sensitivity and accuracy of density measurements surpass the previous state of the art. We should be able to show that this technique can indeed discover and localize tumors and other structures in a manner useful to the physician. We believe that other techniques will follow for elemental analysis of tissues.

In addition, the beams might well have important industrial radiographic uses. The technique is potentially economical in accelerator time because one obtains a complete set of pictures with one fast beam pulse. A further advantage is that the dose is lower than the dose in routine x-ray exposures. It seems entirely feasible to build a "diagnostic" heavy-ion accelerator or to have diagnostic features in a therapy machine.

REFERENCES

1. Tobias, C. A., T. L. Hayes, H. D. Maccabee and R. M. Glaeser. Heavy ion radiography and microscopy. In: *Biomedical Studies with Heavy Ion Beams*. Lawrence Berkeley Laboratory Report No. UCRL-17357 (1967).
2. Anderson, H. L. U. S. Patent No. 3,193,680 (1960).
3. Koehler, A. M. *Science* 160, 303 (1968).
4. Goitein, M. *Nucl. Instrum. Methods* 101, 509 (1972).
5. Hounsfield, G. N. Computerized transverse axial scanning (tomography): Part I. Description of system. *Brit. J. Radiol.* 46, 1015-1051 (1973).
6. Tobias, C. A., and E. V. Benton. Additional techniques for heavy-ion radiography and laminography. Lawrence Berkeley Laboratory Report No. UCID-3593 (1972).
7. Steward, V. W., R. L. Martin, E. Parker and E. Colton. Progress report on proton beam studies. In: *National Cancer Program - Overview of Diagnosis Program*. U. S. DHEW, NIH, NCI (1975).
8. Koehler, Boyd and Goffschalk, personal communication.
9. West, D., and A. C. Sherwood. *Nature* 239, 157 (1972).
10. Saudinos, J., G. Charpak, F. Sauli, D. Townsend and J. Vinciarelli. Nuclear scattering applied to radioscopy. Submitted to *Physics in Medicine and Biology*.
11. Benton, E. V. A study of charged particle tracks in cellulose nitrate. USNRDL-TR-68-14 (1968).
12. Fleischer, R. L., P. B. Prince and R. M. Walker. *Nuclear Tracks in Solids*. (Berkeley: University of California Press) 1975.
13. Henke et al., in press.
14. Sommer, F. G., P. Capp, C. A. Tobias, E. V. Benton, K. Woodruff, A. Carlsson, R. Henke and H. K. Genant. Heavy-ion radiography: phantom studies of pathologic specimens. Use of heavy ions in tissue densitometry. To be presented at the Annual Meeting of the Association of University Radiologists, April 30-May 4, 1977, Kansas City, Kansas.
15. Tobias, C. A., E. V. Benton, M. R. Cruty, H. K. Genant, R. P. Henke, E. A. Sickles and K. H. Woodruff. Heavy-ion radiography and its application to mammography. Presented at the Annual Meeting of the Radiological Society of North America, Nov. 14-19, 1976, Chicago, Illinois.
16. Woodruff, K. H., G. Welch, M. Cruty, R. Henke, C. A. Tobias and E. Benton. Utilization of cyclotron-accelerated particle beams for human breast specimen radiography. Presented at the Meeting of the American Association of Pathologists, March 13-15, 1977, Toronto, Ontario, Canada.
17. Magnan, C. The proton microscopy. *Nucleonics* 4, 52-66 (1949).
18. Sasaki, N., M. Watanabe, T. Goto and T. Someya. Observation of element distribution in biological tissues using ion microscope. In: *Sixth International Congress for Electron Microscopy, Kyoto, Proceedings*. (Maruzen Co., Ltd.) p. 219 (1966).
19. Grivet, P. *Electron Optics*. (N.Y.: Pergamon Press) 781 pp. (1965).
20. Martin, A. R. The ion microprobe. Lawrence Berkeley Laboratory Report No. UCID-3573 (1972).
21. Taylor, K. A., and R. M. Glaeser. Modified airlock door for the introduction of frozen specimens into the JEM 100B electron microscopy. *Rev. Sci. Instrum.* 46, 985-986 (1975).

22. Kalman, E., S. Lengyel, L. Haklik and A. Eke. A new experimental technique for the study of liquid structure. *J. Appl. Cryst.* 7, 442 (1974).
23. Yang, T. C. H., G. Welch, C. A. Tobias, H. Maccabee, T. Hayes, L. Craise, E. Benton and F. Abrams. The feasibility of heavy-charged-particle microscopy. *N. Y. Acad. Sci.*, in press.
24. Crowe, K. M., T. F. Budinger, J. L. Cahoon, V. P. Elischer, R. H. Huesman and L. L. Kanstein. Axial scanning with 900 MeV Alpha Particles. *IEEE Trans. Nucl. Sci.* NS-22, 1752-1754 (1975).

CHAPTER 13

BRAIN RESEARCH WITH HEAVY-ION BEAMS

T. F. Budinger, J. A. Linfoot, B. R. Moyer, J. T. Lyman and J. L. Pelletier

OBJECTIVES

This chapter outlines the previous work in and future prospects for fundamental brain research using heavy-ion beams. The research program involves developing a method for ablating small regions of the mammalian brain (e.g., pituitary, hypothalamus, and amygdaloid complex) using the Bragg peak of a heavy-ion beam. The biomedical programs include investigation of nerve pathways in mammalian brains, investigation of the neurosecretory and behavioral importance of parts of the hypothalamus, amygdaloid nucleus and other areas of the brain, and development of techniques for treating pathological conditions of the brain by heavy-ion radiosurgery.

EARLY WORK ON THE USE OF CHARGED-PARTICLE BEAMS IN BRAIN RESEARCH

The use of the sharp peak in energy release at the end of the path of ionization of positively charged particles (the Bragg peak) for neurosurgery and tumor-destruction purposes was first described by Tobias and co-workers in the early 1950's.¹⁻⁵ Pioneering and continuing studies with helium beams for the treatment of pituitary disorders such as acromegaly, Cushing's disease, and other tumors were performed by Lawrence and co-workers at the Berkeley 184-inch cyclotron.⁶⁻²⁵

With high-energy particle beams of radiation it is possible to overcome the relative intensity of the pituitary gland to externally delivered radiations without irradiating large volumes of surrounding brain tissue. Currently, there are two centers in the U.S. that offer heavy-particle therapy for control of pituitary tumors. In 1954, treatment with the plateau portion of a beam of 340-MeV protons and a complex, multiplane rotation was initiated at Berkeley. A few years later, helium ions were used. Bragg-peak therapy with 910-MeV helium ions was performed in Berkeley in 1964 and 1965 in a limited number of cases. Proton-beam therapy using exclusively the Bragg peak was initiated in Boston in 1962.²⁶ Other studies with high-energy proton beams for pituitary tumors and other cerebral disorders have been done at the University of Uppsala in Sweden²⁷⁻³⁰ and at the Brookhaven 60-inch cyclotron.³¹⁻³³ Although the biological properties of the plateau portions of beams of protons and helium ions are identical, therapy with proton beams, which will not pass through the head or torso, must use the Bragg peak. Without precise knowledge of tissue heterogeneity, it was considered more prudent to use "plateau" ions for treatment of the pituitary if sufficient energy is available for head penetration.

Therapy is administered in four 4-minute treatments over a four- to five-day interval. In order to obtain the fine precision in beam placement required for heavy-particle therapy, plastic headmasks are individually fitted for each patient, ensuring that the head is rigidly fixed to the adjustable treatment table (Fig. 1). With the aid of diagnostic x-ray units and micrometer adjustments on the head holder, the head is accurately positioned prior to therapy. The specially designed treatment table and the head can be independently rotated during therapy. Thus a cone of tissue receives radiation with the greatest density of heavy particles concentrated in the sella turcica. A typical isodose curve is shown in Fig. 2. The brain and nasal pharynx are largely excluded from the radiation field. The optic chiasma, hypothalamus, and outer portions of the sphenoid sinus receive less than 10% of the nominal radiation dose. The amount of radiation to nonparasellar structures is small, as is the total body radiation dose. The unique headholder provides a noninvasive means of permitting no more than a millimeter of movement and makes it possible to fractionate treatment or vary alignment where desirable. Tumor size and configuration

Fig. 1. Schematic of patient positioned for pituitary irradiation with helium ions at the 184-inch cyclotron. (MU-13938)

PLATEAU DOSE DISTRIBUTION (Biaxial rotation)

18 mm CIRCULAR BEAM

Fig. 2. Isodose pattern for the 910-MeV helium ions (plateau dose distribution) for pituitary treatment using an 18-mm-diameter circular beam (elliptical collimator).

determine the beam aperture size, and each patient will require a different aperture. The central pituitary dose as well as the aperture size will determine the isodose curve and distribution to the cranial nerves and temporal lobes. At present, the upper dose limit to lateral brain tissue is 3,000 rads.

Diabetic retinopathy is part of the generalized vascular disease of juvenile diabetes and a leading cause of blindness. The sequelae of diabetes make this disease the third most common cause of death. Pituitary suppression by surgical excision or radiation ablation might alleviate the sequelae of juvenile diabetes. During the period from 1958 through 1969 a total of 169 diabetic patients were treated with helium-ion pituitary irradiation at Berkeley. Most of the patients (139) received between 8,000 and 15,000 rads to produce partial ablation by using the setup of Fig. 1. The most frequent change was a reduction in insulin requirement (50%). Basal human growth-hormone levels were significantly reduced after therapy, and in about 50% of the patients moderate vision was preserved in at least one eye.

The enthusiasm for heavy-ion beams as the method of producing discrete brain lesions is based on the fact that ion radiosurgery avoids the complexities of surgical procedures such as acute vascular damage³⁴⁻³⁸ and the poor spatial resolution and reproducibility of electrical-thermal lesions^{39,40} and x-irradiation.⁴¹ It has been found that doses of approximately 15,000 rads (peak dose), or 10^9 to 10^{10} particles per cm^2 of brain, constitute an effective range for producing a laminar lesion without apparently affecting overlying layers of neurons.⁴²

Unfortunately, with the exception of production of laminar lesions with a broad beam, it has not been possible to induce discrete lesions by using protons, deuterons, or helium ions. The reason is that the Bragg peak is spread out due to range straggling and multiple scattering. The relative importance of these factors decreases as the mass of the particle increases; thus, active investigations on brain research had to await the evolution of accelerator technology and the availability of heavier accelerated ions such as carbon (see Table I). Heavy ions with atomic numbers between 10 and 30 have distinct advantages for the production of deep, discrete lesions when compared with electrons, mesons, protons, and helium ions.⁴³

TABLE I

Atom	Z	A	Approx. T* (MeV/amu)		Bragg peak/plateau ratio†		FWHM Bragg peak (mm)‡		Multiple scattering at the Bragg peak (mm)‡	
			5 cm	10 cm	5 cm	10 cm	5 cm	10 cm	5 cm	10 cm
H	1	1	80	120	6.0:1	5.5:1	4.53	9.33	3.98	7.98
He	2	4	80	120	7.6:1	6.6:1	2.00	4.00	1.98	3.99
C	6	12	150	220	8.0:1	6.3:1	1.26	2.46	1.12	2.11
Ne	10	20	200	300	7.5:1	5.4:1	1.00	1.86	0.84	1.61
Ar	18	40	260	400	6.2:1	3.8:1	0.87	1.33	0.56	1.10

*Approximate T (MeV/amu) necessary to set the Bragg peak at 5 cm and 10 cm in water.

†Bragg peak full-width at half maximum; see Ref. 43.

‡FWHM for an infinitely small beam diameter; does not include nuclear fragments.

In 1971, the Bevatron facility at the Lawrence Berkeley Laboratory began accelerating ions heavier than protons and helium ions with sufficient energy to penetrate 10 to 15 cm of tissue-equivalent material with a Bragg-peak-to-plateau ratio of 6:1. These ions showed the expected reduced range straggling and low multiple scattering.⁴⁴

PRELIMINARY WORK WITH HEAVY IONS IN BRAIN RESEARCH

Light-Flash Phenomena Seen by Astronauts

Heavy ions interact with retinal cells to produce the sensation of light. During the last six Apollo missions, the Skylab flights, and the Apollo-Soyuz mission, crews made both scheduled and unscheduled observations of the frequency and character of brief, tiny star-like flashes of white light or pencil-thin streaks of light. After the first report of these visual phenomena by astronaut Aldrin, we recalled a prediction by Professor Tobias in 1952¹ that astronauts were likely to see flashes of light due to cosmic particles when away from the shielding provided by the magnetic fields of the earth.

In 1970, we undertook a series of experiments to show whether carbon, nitrogen, or oxygen ions of about 300 MeV/amu and other ions with equivalent ionizing characteristics could cause qualitatively the same phenomena seen by astronauts. These experiments were comprised of a series of eye and brain exposures using neutrons with energies of 630 MeV, neutrons with energies of ~ 8 MeV, helium ions from the 184-inch cyclotron at 230 MeV/amu, and nitrogen ions accelerated to 265 MeV/amu at the Bevatron (Fig. 3). The doses were extremely small (< 1 mrad). We learned that ionizing particles that have a stopping power in the range of 10 keV/ μ m or greater will cause phenomena similar to those seen by astronauts.⁴⁵⁻⁴⁸ These and additional quantitative experiments⁴⁹ demonstrated that ionization or electron excitation from cosmic particles can adequately account for the light-flash phenomena.

Radiosurgery of the Corpus Callosum

See Chapter 10 for the work of Dr. Cornelius Gaffey.

Production of Hypothalamic Lesions with Neon Ions

In late 1975 we initiated a pilot program with beagle dogs to evaluate the effectiveness of a neon-ion beam 2 mm in diameter for ablating small regions of the brain. These initial studies focused on the anterior hypothalamus, which is above the pituitary and known to mediate important neuroendocrine and vegetative functions including hormone release, appetite (weight control), blood pressure, and body temperature. Four adult male beagle dogs (weighing 12 to 15 kg each) were irradiated in the manner shown in Fig. 4. Each animal was anesthetized with pentobarbital (15 mg/kg; i.v.) and placed in an immobilization frame. Placement of the hypothalamic region in the beam line was accomplished by using a diagnostic x-ray unit with Polaroid film (settings of 50 kV, 4 mA, 10 sec, and 37 inches). The animal was moved to achieve a superposition of the hypothalamic region of interest with the ion-beam axis located by cross-hairs (Fig. 4). The alignment of the Bragg peak was accomplished by measuring the change in the particle range with the animal in and out of the beam. The water column was adjusted to bring the beam to the midline of the brain. This procedure is accurate to within a few millimeters for symmetrical targets.

The "plateau dose" before the final collimator for a beam of 400 MeV/amu neon ions was 6000 rads for each of two dogs and 18,000 rads (594 MeV/amu) for each of two other dogs. The peak-to-plateau ratio was estimated at 3:1 for these irradiations. The gross pathology and localization of the Bragg peak in the hypothalamus are shown in Fig. 5 for an animal that received the higher dose. The beam path in the brain was defined by cerebral tissue staining from hemorrhage. The Bragg-peak region was in the hypothalamus. The path through the temporal lobe from the plateau dose was faintly visible. There was no rotation of the animal to distribute the plateau dose over a larger area as is done for human patients. All animals were monitored for changes in water and food intake, behavior, weight, temperature, blood chemistries, and EEG recordings.

The two animals that received 18,000 rads were sacrificed ten days after irradiation, at which time they were having epileptic seizures. These animals demonstrated profuse salivation, improper mastication ("chewing-gum syndrome"), and irregular gait by the fourth day postirradiation. The body weights of both animals fell dramatically at this time.

Fig. 3. Setup for retina and cortex exposures using a few 250-MeV nitrogen or neon ions. (DBL 7112-6110)

Fig. 4. Set-up for heavy-ion irradiation of the anterior hypothalamus in a beagle dog. Upper left is an x-ray image for alignment of the hypothalamic region with the beam axis. (XBB 772-1353)

Fig. 5. A coronal cross section of dog brain irradiated (18,000 rads; plateau) in the region of the hypothalamus. Destruction of the hypothalamus with damage to the temporal lobe is evident. (SBB 772-1352)

Fig. 6. Rectal-temperature and body-weight changes in animals exposed to 6,000 rads and 18,000 rads. (XBL 772-3134)

The two animals given 6,000 rads in the plateau survived the treatment with one showing progressive weight loss over a three-month period. Comparative curves of body weight and rectal temperature are given in Fig. 6 for one animal given 18,000 rads and one animal given 6,000 rads. The thickness of the head of the other animal given 6,000 rads exceeded the beam range; hence, exact localization of the beam was not possible. This animal showed no weight changes over a one-year period and no shifts in rectal temperature.

The animals that received 6,000-rad doses were monitored for blood chemistries (SMA-12) and cortisol changes. Both dogs showed significantly lower than normal LDH serum levels at three days postirradiation. Cortisol levels remained at about 100 to 200 pg/ml serum over a two-month period. The EEG recordings showed epileptic syndromes in the two animals that received 18,000 rads and only marginal changes in the two animals given 6,000 rads.

POTENTIALS FOR FUTURE BRAIN RESEARCH

Heavy ions such as carbon have the ability to deposit 10,000 rads in a volume of 0.01 cm^3 (10 mm^3) with less than 5,000 rads to surrounding tissue. In addition, using methods of transverse section reconstruction, it is possible to localize the Bragg peak with a precision of 3 mm or less.^{50,51} Thus, we are now in a position to further develop this neuroscience tool. Results with the four animals are encouraging; however, our previous work required collimation of the beam, which resulted in difficulty in estimating the particle transmission through the collimator and the additional secondary particle production due to the collimator. These uncertainties make dose estimation at the Bragg peak questionable. One of the areas of further accelerator work involves development of a beam with a 2-mm FWHM and a fluence of 5×10^9 particles per minute. Because of the magnitude of straggling and multiple scattering, we do not expect to be able to induce lesions smaller than spheres 2 to 3 mm in diameter.

TABLE II. A partial list of potential neuroscience and radiosurgery applications of heavy-ion beams.

Region	Study or Therapy
Brain	Efferent and Afferent Fibers (Neuroanatomy)
Pituitary	Acromegaly Cushing's Disease Adenomas Nelson's Syndrome
Hypothalamus	Nelson's Syndrome Hypothalamic/Pituitary Communications
Temporal lobe	Epilepsy
Thalamus Pulvinar	Intractable Palsy Epilepsy
Cerebellum	Epilepsy
Corpus Collosum	Generalized Intractable Seizures
Hippocampus	Emotional Disorders
Pineal	Pinealoma
Mid-brain	Leiomyomas, Neuromas
Brain Parenchyma	Tumors

With this new tool, aspects of neuroanatomy can be explored in ways heretofore impossible due to the invasiveness in surrounding tissues from surgical excision or lesions. In addition, the neuroendocrinological responses of ablating various portions of the midbrain can be assessed without the need for difficult and unusual neurosurgical preparations. Table II gives some of the uses for heavy-ion beams in neuroscience.

REFERENCES

1. Tobias, C. A. *J. Aviation Med.* 23, 345 (1952).
2. Tobias, C. A., H. O. Anger, and J. H. Lawrence. Radiological use of high energy deuterons and alpha particles. *Amer. J. Roent. Rad. Ther. Nucl. Med.* 67, 1-27 (1952).
3. Lawrence, J. H., C. A. Tobias, J. A. Linfoot, J. L. Born, A. Gottschalk, and R. P. Kling. Heavy particles, the Bragg curve and suppression of pituitary function in diabetic retinopathy. *Diabetes* 12, 490-501 (1953).
4. Tobias, C. A., D. C. Van Dyke, M. E. Simpson, H. O. Anger, R. L. Huff, and A. A. Koneff. Irradiation of the pituitary of the rat with high energy deuterons. *Amer. J. Roent. Rad. Ther. Nucl. Med.* 72, 1-21 (1954).
5. Tobias, C. A., J. E. Roberts, J. H. Lawrence, B. V. A. Low-Beer, H. O. Anger, J. L. Born, R. McCombs, and C. Huggins. Radiation hypophysectomy with high energy proton beams. Lawrence Berkeley Laboratory Report No. UCRL-3035 (1955).
6. Lawrence, J. H., W. O. Nelson, and H. Wilson. Roentgen irradiation of the hypophysis. *Radiology* 29, 446 (1937).
7. Stone, R. S., J. H. Lawrence, and P. C. Aebersold. A preliminary report on the use of fast neutrons in the treatment of disease. *Radiology* 35, 322-327 (1940).
8. Lawrence, J. H. Proton irradiation of the pituitary. *Cancer Res.* 10, 759-798 (1957).
9. Lawrence, J. H., J. L. Born, C. A. Tobias, R. Carlson, F. Sangalli, and G. Welch. Clinical and metabolic studies in patients after alpha particle subtotal or total hypophysectomy. *Medicine in Japan* 5, (1959).
10. Born, J. L., et al. Biological and medical studies with high energy particle accelerators. *Progress in Nuclear Energy, Series VII*, 2, Medical Sciences, (New York: Pergamon Press, 1959), pp. 189-206.
11. Lawrence, J. H., C. A. Tobias, and J. L. Born. Acromegaly. *Trans. Amer. Clin. Climat. Assoc.* 73, 176-185 (1961).
12. Lawrence, J. H., C. A. Tobias, J. L. Born, C. D. Wang, and J. A. Linfoot. Heavy particle irradiation in neoplastic and neurologic disease. *J. Neurosurgery* 19, 717-722 (1962).
13. Linfoot, J. A., J. H. Lawrence, J. L. Born, and C. A. Tobias. Alpha particle or proton beams in radiosurgery of the pituitary gland for Cushing's disease. *New England J. Med.* 269, 597-501 (1963).
14. Lawrence, J. H., C. A. Tobias, J. L. Born, A. Gottschalk, J. A. Linfoot, and R. P. Kling. Alpha particle and proton beams in therapy. *JAMA* 186, 236-245 (1963).
15. Gottschalk, A., J. T. Lyman, and L. W. McDonald. Use of the Bragg peak for brain tumor therapy. *Semi-Annual Report, Biology and Medicine, Donner Laboratory, Lawrence Berkeley Laboratory Report No. UCRL-11184*, pp.121-127 (1963).
16. Lawrence, J. H. and C. A. Tobias. Heavy particles in medicine. *Progress in Atomic Medicine*, Chapter 6 (Grune and Stratton, 1965).

17. Linfoot, J. A., J. L. Born, J. F. Garcia, E. Manougian, R. P. Kling, C. Y. Chong, C. A. Tobias, R. A. Carlson, and J. H. Lawrence. Metabolic and ophthalmological observations following heavy particle suppressive therapy in diabetic retinopathy. In *Symposium on the Treatment of Diabetic Retinopathy* (M. F. Goldberg and S. L. Fine, eds.). (Warrenton, Virginia: Airlie House, 1968; Washington, D.C.: U.S. Government Printing Office, USPHS Publ. No. 1890, 1969), pp. 277-289.
18. Lawrence, J. H., C. A. Tobias, J. A. Linfoot, J. L. Born, E. Manougian, and J. T. Lyman. Heavy particles and the Bragg peak in therapy. *Annals of Intern. Med.* 62, 400-407 (1965).
19. Lawrence, J. H., C. A. Tobias, J. L. Born, J. A. Linfoot, and G. J. D'Angio. Heavy particles in experimental medicine and therapy. *JAMA* 196, 166-170 (1966).
20. Linfoot, J. A. Heavy particle irradiation of the pituitary. *Vascular Complications of Diabetes Mellitus* (S. J. Kimura and W. M. Caygill, eds), (St. Louis, Missouri: C. V. Mosby Co., 1967), pp. 219-226.
21. Manougian, E. Heavy particles in acromegaly. *Biomedical Studies with Heavy-Ion Beams*, Lawrence Berkeley Laboratory Report No. UCRL-17357, pp. 219-229 (1967).
22. Garcia, J. F. Growth hormone studies in acromegaly in patients receiving pituitary irradiation. *Biomedical Studies with Heavy Ion-Beams*, Lawrence Berkeley Laboratory Report No. UCRL-17357, pp. 213-218 (1967).
23. Linfoot, J. A., J. H. Lawrence, C. A. Tobias, J. L. Born, C. Y. Chong, J. T. Lyman, and E. Manougian. Progress report on the treatment of Cushing's disease. *Trans. Amer. Clin. Climat. Assoc.* 81, 196-212 (1970).
24. Linfoot, J. A., C. Y. Chong, J. F. Garcia, A. S. Cleveland, G. M. Connel, E. Manougian, M. D. Okerlund, J. L. Born, and J. H. Lawrence. Heavy particle therapy for acromegaly, Cushing's disease, Nelson's Syndrome, and non-functioning pituitary adenomas. *Recent Advances in Nuclear Medicine*, 3, Chapter 7 (J. H. Lawrence, ed.) (New York: Grune and Stratton, 1971) pp. 219-238.
25. Tobias, C. A., 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. *Recent Advances in Nuclear Medicine*, 3, Chapter 6 (J. H. Lawrence, ed.), (New York: Grune and Stratton, 1971) pp. 167-218.
26. Kjellberg, R. N., A. M. Koehler, W. M. Preston, and W. H. Sweet. Biological and clinical studies using the Bragg peak of the proton beam. Paper presented at the Second International Congress of Radiation Research, Harrogate, Yorkshire, England, August 11, 1962.
27. Larsson, B., L. Leksell, B. Rexed, P. Souerander, W. Mair, and B. Andersson. The high energy proton beam as a neurosurgical tool. *Nature* 182, 1222-1223 (1958).
28. Leksell, L., B. Larsson, B. Andersson, B. Rexed, P. Souerander, and W. Mair. Lesions in the depth of the brain produced by a beam of high energy protons. *Acta Radiol. (Stockholm)* 54, 251 (1960).
29. Falkmer, S., B. Fors, B. Larsson, A. Lindell, J. Naeslund, and S. Stenson. Pilot study on proton irradiation of human carcinoma. *Acta Radiol. (Stockholm)* 58, 33 (1962).
30. Larsson, B., L. Leksell, and B. Rexed. The use of high energy protons for cerebral surgery in man. *Acta Chir. Scan.* 125, 1 (1963).
31. Jannsen, P., I. Klatzo, J. Miguel, T. Brustad, A. Behar, W. Haymaker, J. Lyman, J. Henry, and C. A. Tobias. Pathologic changes in the brain from exposure to alpha particles from a 60-inch cyclotron. *Responses of the Nervous System to Ionizing Radiation*, (T. J. Haley and R. A. Snider, eds.), (New York: Academic Press, Inc., 1962), p. 382.

32. Malis, L. I., C. P. Baker, L. Kruger, and J. E. Rose. Effects of heavy ionizing monoenergetic particles on the cerebral cortex. I. Production of laminar lesions and dosimetric considerations. *J. Comp. Neurol.* 115, 219-242 (1960).
33. Malis, L. I., R. Loevinger, L. Kruger, and J. E. Rowe. Production of laminar lesions in the cerebral cortex by heavy ionizing particles. *Science* 126, 302-303 (1957).
34. Krey, L. C., W. R. Butler, and E. Knobil. Surgical disconnection of the medial basal hypothalamus and pituitary function in the rhesus monkey. I. Gonadotropic secretion. *Endocrinology* 96, 1073-1087 (1975).
35. Paxinos, G. and D. Bindra. Hypothalamic knife cuts: Effects on eating, drinking, irritability, aggression, and copulation in the male rat. *J. Comp. Physiol. Psych.* 79, 219-229 (1972).
36. Dunn, J. and A. Arimura. Serum growth hormone levels following ablation of the medial basal hypothalamus. *Neuroendocrinology (Switz.)* 15, (3-4): 189-199 (1974).
37. Starr, E., G. B. Makara, J. Morton, and M. Palkovits. ACTH release in rats after removal of the medial hypothalamus. *Neuroendocrinology (Switz.)* 13, (4-5): 224-233 (1973-74).
38. Lindholm, E., G. S. Shumway, D. V. Grijalva, T. Shallert, and M. Ruppel. Gastric pathology produced by hypothalamic lesions in the rat. *Psych and Behav. (Great Britain)* 14, 165-169 (1975).
39. Kokka, N., R. M. Eisenberg, J. Garcia, and R. George. Blood glucose, growth hormone, and cortisol levels after hypothalamic stimulation. *Amer. J. Physiol.* 222, 296-301 (1972).
40. Turlejska-Stelmasiak, E. Thermoregulatory responses to hypothalamic heating in dehydrated rabbits. *Experientia* 29, 51-52 (1973).
41. Caviness, W. S., A. I. Carsten, I. Roizin, and J. P. Strade. Pathogenesis of X-irradiation effects in the monkey cerebral cortex. *Brain Res.* 7, 1-117 (1968).
42. Kruger, L. Anatomical studies with laminar lesions. *Biomedical Studies with Heavy Ion-Beams*, Lawrence Berkeley Laboratory Report No. UCRL-17357, pp. 136-145 (1967).
43. Litton, G. M., R. W. Wallace, and C. A. Tobias. Penetration of high energy heavy ion beams into matter. *Biomedical Studies with Heavy-Ion Beams*, Lawrence Berkeley Laboratory Report No. UCRL-17357, p. 18 (1967).
44. Tobias, C. A., J. T. Lyman, A. Chatterjee, J. Howard, H. D. Maccabee, J. R. Raju, A. R. Smith, J. M. Spirende, and G. P. Welch. Radiological physics characteristics of the extracted heavy ion beams of the Bevatron. *Science* 174, 1131-1134 (1971).
45. Tobias, C. A., T. F. Budinger, and J. T. Lyman. Radiation induced light flashes observed by human subjects in fast neutron, x-ray and positive pion beams. *Nature* 230, 596-597 (1971).
46. Budinger, T. F., H. Bichsel, and C. A. Tobias. Visual phenomena noted by human subjects on exposure to neutrons of energies less than 25 million electron volts. *Science* 172, 868-870 (1971).
47. Budinger, T. F., J. T. Lyman, and C. A. Tobias. Visual perception of accelerated nitrogen nuclei interacting with human retina. *Nature* 239, 209-211 (1972).
48. Tobias, C. A., T. F. Budinger, and J. T. Lyman. Biological effects due to single accelerated heavy particles - problems of nervous system exposure in space. *Life Sciences and Space Research XI*, (P. H. J. Sneath, ed.) (Berlin: Academic-Verlag, 1973), p.233.
49. Budinger, T. F., C. A. Tobias, R. H. Heusman, F. T. Upham, T. F. Weiskamp, J. H. Schott, and E. Schopper. The results of the light flash experiment flown on ASTP mission, XXVII Congress International Astronautical Fed., Anaheim, California, October 10-16, 1976. Report No. IAF-76-032.

50. Crowe, K. M., T. F. Budinger, J. L. Cahoon, V. P. Elischer, R. H. Huesman, and L. L. Kanstein. Axial scanning with 900 MeV alpha particles. Presented at IEEE Particle Accelerator Conference, Washington, D.C., March 12-14, 1975 (also Lawrence Berkeley Laboratory Report LBL-3812).
51. Budinger, T. F., K. M. Crowe, J. L. Cahoon, V. P. Elischer, R. H. Huesman, and L. L. Kanstein. Transverse section imaging with heavy charged particles: Theory and applications. *Image Processing for 2-D and 3-D Reconstruction from Projections: Theory and Practice in Medicine and the Physical Sciences*, (New York: Optical Society of America and National Science Foundation, 1975) pp. MAL-1 to MAL-4.

CHAPTER 14

HEAVY-ION THERAPY

J. R. Castro, M.D., J. M. Quivey, M.D., J. T. Lyman, Ph.D., G. T. Y. Chen, Ph.D.
C. A. Tobias, Ph.D., L. L. Kanstein and R. E. Walton

A clinical trial to evaluate the use of helium and heavy-ion radiotherapy in the treatment of human cancers has been under way at the Lawrence Berkeley Laboratory since July 1975. The initial goals of the project were to develop the physical, radiobiological, and clinical bases to undertake helium ion radiotherapy as a direct lead-in to heavy-ion radiotherapy after appropriate pretherapeutic evaluation. Since July 1975 the following steps have been accomplished: 1) An organization of University and community radiotherapists, radiobiologists, and physicists has been developed to design and participate in a cooperative clinical trial of helium- and heavy-ion radiotherapy (BAHIA). 2) The 184-inch cyclotron and medical cave have been modified in order to permit large field, fractionated 934-MeV helium ion extended Bragg peak therapy. This has required modification of patient immobilization and support facilities, together with modification of the 934-MeV helium ion beam line, development of beam shaping techniques, improved radiation dosimetry and treatment planning, and development of techniques to assess and compensate for tissue inhomogeneities. 3) Treatment planning analyses have been conducted on a series of potential tumor sites for inclusion in the controlled cooperative trial. 4) A selected group of pilot patients has been treated with large field, fractionated Bragg peak therapy utilizing the helium ion beam at the 184-inch cyclotron. 5) The remodeling and outfitting of necessary clinical facilities for the heavy-ion trial adjacent to the Bevalac is under way. 6) Beginning studies have been made in the utilization of computer-assisted scanning techniques for tumor localization and for delineation of inhomogeneities within the beam path. 7) A request for support for the clinical phase of the project has been made to the National Cancer Institute, and funds have been awarded for an initial three year project period extending from 6/30/76 until 6/30/79. 8) Further evaluation of the radiobiologic parameters of the helium ion beam has been done to assist with planning and delivery of clinical radiotherapy.

At the present time work on the above tasks continues together with a concentrated effort to 1) improve treatment planning techniques, 2) acquire an on-site computer-assisted tomographic scanner in order to provide daily (if needed) patient scans for accurate tissue density assessment prior to treatment, 3) develop a system of ridge filters to modify the Bragg peak, utilizing physical and radiobiologic data to provide iso survival data across the peak width (our early planning experience has demonstrated that a family of such filters giving peak widths extending from 4 to 16 cm will be needed in order to provide optimal treatment dose distributions for a variety of anatomical sites), 4) continue radiobiologic studies to determine the most suitable heavy ion beam for clinical studies and 5) continue development and reinforcement of clinical referral patterns to insure sufficient patients for this study. This has included our participation in the development of clinical trials in cooperation with the Northern California Oncology Group (NCOG).

Close communication with other charged particle radiotherapy groups such as the proton beam radiotherapy project at Massachusetts General Hospital and the Harvard cyclotron (Doctors Herman Suit, Michael Goitein, and Andrew Koehler), and the pi meson radiotherapy projects at Los Alamos Meson Physics Facility (Doctors Morton Kligerman, Edward Knapp, and Charles Kelsey) and Stanford Medical Center (Doctors Malcolm Bagshaw, David Pistenma, and H. H. Schwettman) will continue to assist us in finding rapid solutions to common problems. We have also carefully followed the progress of clinical neutron trials in this country and abroad.

In addition to the staff of the Lawrence Berkeley Laboratory participating in the developmental and applied aspects of this project, a number of outside users have contributed both consultative advice and experimental data to the accomplishment of these goals. These include Doctors Theodore L. Phillips and Karen Fu of the University of California at San Francisco (pretherapeutic radiobiologic studies on the helium and heavy-ion beams and clinical consultation in the design and development of treatment protocols), Doctors David Pistenma and Eli Glatstein of Stanford University Medical School (assistance in design of clinical protocols, plus advice on treatment planning for radiation therapy, plus techniques of inhomogeneity correction), Mr. Phillip Purser, radiobiological physicist at the Zellerbach Saroni Tumor Institute (assistance with treatment planning and isodose distributions), Doctors Antolin Raventos and Saul Silverman of the University of California at Davis (clinical protocol design and liaison between the Davis neutron project and LBL heavy-ion radiotherapy project). Many members of the Bay Area Heavy Ion Association (BAHIA) have volunteered their time and constructive advice in many aspects of the design and organization of the project (see membership list later in this chapter).

RATIONALE FOR HEAVY-ION RADIOTHERAPY

Radiotherapy represents one of the most widely used modalities in cancer therapy today. It is primarily concerned with local and regional control, although it is also a potent tool for palliation in disseminated malignancies. Current conventional radiotherapy techniques are highly successful in the treatment of small localized cancers. This is often accomplished with preservation of the structural and functional integrity of adjacent tissues. However, larger tumors are less likely to be cured at doses of radiation that are still within the tolerance of adjacent normal tissues. In fact, it is the sparing of normal tissues that provides the therapeutic ratio that is the key to successful radiotherapy. Normal tissue sparing is enhanced when 1) the volume of normal tissues in the treatment volume is reduced and 2) the biologic effect on tumor cells is greater than that on surrounding normal cells. These two factors must be maximized to improve the probability of an uncomplicated cure. Heavy-ion radiotherapy offers an opportunity to improve both factors over conventional radiation techniques.

There is historical evidence to indicate that improved radiotherapy results have been accomplished with improved physical dose distributions. Poorly penetrating orthovoltage beams produced significant skin and subcutaneous skin changes, some leading to necrosis, in the early attempts to control deep-seated tumors. The availability of megavoltage beams of sufficient quality to spare the skin and subcutaneous tissues was associated with dramatic changes in these results. These beams are still limited by their exponential absorption with depth after the initial dose buildup. This latter fact limits the ability to avoid certain critical organs such as the kidneys, liver, bowel, lungs, spinal cord, and eyes, even when elaborate isocentric treatment plans are employed. Further improvements in the physical dose distribution by utilizing the Bragg peaks of heavy ions are expected to produce further improvements in the local and regional results. Volume considerations are also important to radiotherapists, who have empirically observed that a large volume treated with conventional techniques will limit the total amount of radiation that may be safely given. This observation is thought by many to be related to the integral dose of radiation given to both tumor and normal tissue. This volume limitation might therefore also be potentially decreased with the better dose distribution of heavy-particle therapy allowing the delivery of higher doses to the treatment volume.

In addition to the improvements of physical dose distribution, a biologic advantage is also expected. This advantage is small with helium ions and becomes more significant with the higher LET very-heavy-ion particles. The biologic interaction of radiations with tumor in normal tissues is complex. It appears to be dependent upon multiple factors, each of which must be optimized to produce maximum tumor killing with minimal tissue reaction. These factors include the oxygen effect, the variation of sensitivity according to cell cycle, and the capacity of damaged cells to repair and to repopulate.

Several experimental systems have been developed to assess the relative effects of these factors, and many have been applied to compare and contrast their relative importance with low- and high-LET radiations. In fact, an intercomparative study of heavy particles is currently in progress by Raju and his associates.

The first of these factors, the oxygen effect or oxygen enhancement ratio (OER), describes the two- to three-fold increase in the sensitivity of cells when they are exposed to low-LET radiations in an oxygen-rich environment rather than in an anoxic environment. If one postulates that all normal tissues are well oxygenated and there truly exist anoxic but viable tumor cells, a clear tumor protective effect would be operative. An illustration of this possibility by Fowler in 1963 showed that a fully oxygenated 75-mm-diameter tumor could be cured with a 90% probability with 5000 rads. However, if 1% of the tumor were hypoxic, a tumor even as small as 5 mm in diameter could not be controlled at this dose with the same probability. Many tumors are thought to have anoxic components which are reoxygenated during carefully fractionated doses of radiation. However, larger tumor masses are considered to be less likely to fully reoxygenate and therefore remain resistant to conventional radiation techniques.

The oxygen effect has been studied by many investigators, including Chapman et al. in 1976, who noted values for helium ions (230 MeV/nucleon) in an 8-cm spread peak of 2.3; carbon ions (400 MeV/nucleon) 4-cm spread peak of 1.7; neon ions (400 MeV/nucleon) 4-cm spread peak of 1.6; and argon ions (500 MeV/nucleon) 4-cm spread peak of 1.4. These observations are consistent with the decreasing role of the oxygen effect for high-LET radiations. Chapman further observed the peak to plateau ratio of RBEs, utilizing these same beams, finding values of 1.15 for helium, 1.6 for carbon, 1.35 for neon, and 0.9 for argon. (See Table II.) This overkill noted with argon would suggest that carbon or neon might be more suitable for clinical trials. At least some of the improvement in the RBE of these particles is due to the decrease in the OER. Thus, it might be expected that a differential advantage on hypoxic tumor cells over normal cells might exist. Two other factors, i.e., cell cycle sensitivity and the repair of sublethal damage, are also decreased with the use of high-LET radiations. It is unclear whether these two factors will improve the therapeutic ratio with the use of high energy particles.

These potential physical and biological advantages must be tested in a clinical setting and remain to be of proven practical value. However, the very steep nature of the dose response curve of tumors to radiations allows that a very small gain, i.e., 10% to 20% in the tumor dose, can increase the cure or control from 20% to 80%. This observation has been documented in several head and neck sites by Shukovsky and Fletcher (1972). It has been estimated that approximately one-third to one-fourth of the 200,000 deaths from cancer each year occur in patients who do not have local and regional control of their tumors. Thus, the magnitude of the public health gain which could be achieved nationally by improved local and regional radiotherapy results is sizeable enough to suggest that a clinical trial of these heavy-ion beams be accomplished. A clearly significant improvement in treatment results must be demonstrated to justify the increased expenditures necessary to deliver heavy-ion radiotherapy to a large number of patients.

At the Lawrence Berkeley Laboratory, the utilization of helium ion beams for pituitary irradiation has been under way for many years. The first therapeutic human exposure to high energy deuterons was performed at the Lawrence Berkeley Laboratory in 1955, and since that time several hundred patients have been treated with small field, high dose, low fraction number helium radiation for pituitary tumors, acromegaly, and Cushing's disease. Most of these treatments were accomplished by complex isocentric rotations utilizing the plateau rather than the peak of the beam. A few patients were treated with small field, high dose, single fraction irradiation of small pulmonary metastatic nodules or brain malignancies prior to the onset of this trial.

We have utilized helium ion radiotherapy since July of 1975 in some sixteen patients with a variety of advanced or locally recurrent tumors, including malignant glioma of the brain, adenocarcinoma of the pancreas, para-aortic lymphatic metastases from carcinoma of the cervix, and nodal metastases of malignant melanoma. These patients have been treated in metastases of malignant melanoma. These patients have been treated in most cases with a combination of conventional photon irradiation and large field, fractionated Bragg peak helium ion radiotherapy. A list of the patients treated to date is shown in Table I. While no attempt has been made to utilize this group of patients for a comparative study of tumor response, valuable information has been gained with respect to treatment techniques, treatment planning, and biologic effects of helium ion radiotherapy on skin and mucosal membranes when possible.

As part of the pilot study we have also undertaken a re-evaluation of the RBE for helium ion fractionated radiotherapy. This analysis is still continuing, since detailed information at various positions within the plateau and Bragg peak will be of great value both in helium ion radiotherapy as well as indicating what information is needed for heavy-ion radiotherapy. Some information can be gained by an analysis of the distribution of LET under the expanded helium ion Bragg peak. This distribution has been calculated by Doctors Stand Curtis and John Lyman at the Lawrence Berkeley Laboratory, with some independent measurements being undertaken by Doctor P. Fessenden of Stanford University.

We have started our pilot helium ion radiotherapy series using a somewhat high estimate of the RBE with the intention to raise the equivalent dose where possible in a target volume while maintaining as low a dose to normal adjacent tissue as possible. As a goal, we have tried to establish that the dose to adjacent normal structures would be no greater than the equivalent conventional radiotherapy dose. Ultimately we hope to achieve doses to deep-lying tumors which are clearly biologically higher than conventional radiation. We believe we have had some success in doing that for certain tumor sites (see Table I). It is our plan to continue the helium ion study concomitantly with the heavy-ion radiotherapy study, so that we may evaluate the effects of physical dose distribution shown by helium ion radiotherapy in the effects of combined physical dose distribution advantages with biologic advantages (heavy-ion radiotherapy). Thus, it is expected that the helium ion radiotherapy will be of three years duration and the heavy ion radiotherapy project of five to ten years duration. This is necessary because a reasonable followup period will be required before statistically significant conclusions can be drawn from the controlled trial.

ORGANIZATION OF THE CLINICAL TRIAL

Initially an informal organization of interested radiotherapists and other scientists was organized (the Bay Area Heavy Ion Association) in order to provide 1) design of a cooperative clinical trial, 2) referral of sufficient numbers of patients for treatment at Lawrence Berkeley Laboratory, 3) participation of collaborating radiotherapists in the trial by assisting in treatment at Lawrence Berkeley Laboratory and by treating control patients in their respective clinical facilities. A broadened base for this study was sought in order to provide for a large pool of patient resources from whom a significant number of referrals could be drawn without seriously compromising the patient resources at any single institution. Additionally, this broad association has provided the ability to have close interaction and communication among a variety of scientific disciplines interested in the heavy-ion project in order to have the best available input in the design of the study.

During the past few years a parallel development in the region has occurred with the organization of the Northern California Cancer Program, a comprehensive cancer center without walls, organized by a consortium of some fourteen different institutions or facilities active in cancer care, including the five area medical schools, the American Cancer Society, major hospital cancer units, and foundations and organizations such as the Hospital Council of Northern California, the California Medical Association, etc. This organization has been partially funded by the National Cancer Institute and by private sources as

TABLE I.

Patient	Tumor Site	Conventional XRT Rads	Helium Ions Rads RBE	CRE*	Side Effects	Duration of Followup	
1 AM	Malignant Glioma, Brain	4440/25fx/31d (Total: 6870 CRE)	1736/10fx/13d	1.4	2430	Reddening of Skin: Alopecia	20 mos.
2 DC	Adenocarcinoma, Pancreas	3000/21fx/43d (Total: 5800 CRE)	2000/10fx/12d	1.4	2800	None	17 mos.
3 JI	Melanoma, Neck	1200/2fx/25d (Total: 4080 CRE)	2400/4fx/32d	1.1	2880	Reddening of Skin	Exp.
4 JC	Malignant Glioma, Brain (Recurrent)	3000/15fx/19d (Total: 4866 CRE)	1333/9fx/11d	1.4	1866	Reddening of Skin	Exp.
5 BM	Maxillary Sinus	2600/13fx/27d (Total: 6520 CRE)	2800/21fx/30d	1.4	3920	Reddening of Skin Radiation Conjunctivitis (4720 REM to eye)	LFU
	Mandible		2868/10fx/32d	1.4	4000	Minimal mucosal reaction	
6 CB	Brain (Recurrent)	1810/11fx/15d (Total: 4800 CRE)	2128/16fx/21d	1.4	2980	Partial Alopecia	8 mos.
7 CP	Recurrent Carcinoma of Colon, Retroperitoneum	3500/20/27d (Total: 6300 CRE)	2000/10fx/12d	1.4	2800	Reddening of Skin Slight Nausea	7 mos.
8 BH	Recurrent Carcinoma of Colon, Retroperitoneum	3990/22fx/49d (Total: 6500 CRE)	1800/9fx/12d	1.4	2520	Moderate Nausea	7 mos.
9 SF	Carcinoma of Pancreas	4000/20fx/42d (Total: 6200 CRE)	1570/10fx/14d	1.4	2200	None	3 mos.
10 LW	Recurrent Carcinoma of Nasal Cavity and Ethmoids		3560/25fx/44d 2710/25fx/44d	1.4 1.4	5000(max) 3550(min)	Skin Reddening, Conjunctivitis	3 mos.
11 BL	Multiple Skin Nodules (Carcinoma of Bladder)		1900/10fx/12d 2300/10fx/12d 2700/10fx/12d	1.3	2500 3000 3500	Skin Reddening, Dry Epidermitis	3 mos.
12 SA	Para-aortic Nodes (Carcinoma of Cervix Uteri)		3220/23fx/47d	1.4	4500	None	3 mos.
13 JG	Carcinoma of Pancreas	3000/17fx/24d (Total: 6000 CRE)	2100/15fx/25d	1.4	3000	None	3 mos.
14 CL	Para-aortic Nodes (Carcinoma of Cervix)		3200	1.4	4500	None	1 mo.
15 GvG	Carcinoma of Pancreas	2500/14fx/27d (Total: 6100 CRE)	2880/18fx/29d	1.25	3600	Mild Abdominal Pain	
16 JT	Carcinoma of Gall Bladder		4400/28fx/47d	1.25	5500		Under Rx

*CRE=Cohalt⁶⁰ Rad Equivalent

TABLE II

Beam	RBE Peak/RBE Plateau	OER (peak)
Helium ions (230 MeV/n, 8 cm peak)	1.15	2.3
Carbon ions (400 MeV/n, 4 cm peak)	1.60	1.7
Neon ions (400 MeV/n, 4 cm peak)	1.35	1.6
Argon ions (5 MeV/n, 4 cm peak)	0.90	—

TABLE III

Northern California Oncology Group (NCOG)

Stanford University

University of California, San Francisco

University of California, Davis

Lawrence Berkeley Laboratory

Kaiser Foundation Hospitals of Northern California

Letterman Army Hospital in San Francisco

U. S. Naval Medical Center in Oakland

U. S. Air Force Hospital, Travis Air Force Base in Sacramento

well as the component institutions and is directed by Doctor Stephen Carter. The chairman of the board of trustees is Doctor Saul Rosenberg of Stanford University. The clinical trial arm of the Northern California Cancer Program is the Northern California Oncology Group (NCOG) headed also by Doctor Stephen Carter. Lawrence Berkeley Laboratory has been accepted as a special member of the NCOG in order to facilitate interdigitation of its clinical high-LET protocols with other cancer protocols in the area. This is necessary in order to avoid competition for patient resources, since most of the major cancer facilities in the area will be participating in the NCOG.

It appears advisable to limit the heavy-ion clinical protocols to about five or six tumor sites, including carcinoma of the pancreas and stomach, malignant glioma of the brain, advanced tumors of the head and neck, advanced carcinoma of the uterus and bladder, and carcinoma of the esophagus. Adequate patient resources should thus be available in the Northern California area through the membership of the NCOG (see Table III) to assure reasonable patient accrual for our study. It has been the hope that we could treat approximately 200 patients per year at Lawrence Berkeley Laboratory, with perhaps an equal number of control patients being treated at collaborating facilities. In order to establish this mechanism, clinical protocols developed for use at Lawrence Berkeley Laboratory are being submitted to the Northern NCOG for evaluation and consideration as official NCOG protocols. In addition, NCOG protocols in existence will be modified in certain sites to include heavy-ion radiotherapy as one of the treatment arms.

Lawrence Berkeley Laboratory protocols will also remain in effect, allowing those physicians or facilities wishing to participate in the heavy-ion trial who are not members of the NCOG or who are outside the geographic region of the Northern California Cancer Program, to refer patients for treatment. Where possible we will also establish control arms at these collaborating facilities, if we can assure that the quality of the control irradiation is optimal, protocol techniques are scrupulously adhered to, and no statistical bias is encountered.

One of the distinct advantages of the participation in the NCOG will be the availability of their statistical services, which are specifically designed to support clinical trials. This should materially improve the standardization of our clinical trial, including forms development, patient accrual, randomization, collection of data, end result analysis and reporting, and quality assurance for control radiation.

A national cooperative trial group for radiotherapy studies, the Radiation Therapy Oncology Group, also may be considered for the above support services. Discussions are currently being held to see which organization will be the best group for the heavy-ion radiotherapy project.

The physical aspects of heavy-ion therapy are considered in the following sections. Theory of ridge filter design, production of large field scattering system, and improvements in patient setup and immobilization are discussed first. Following this, we describe efforts in charged particle treatment planning, including the use of computerized tomography data in these calculations, and a brief description of the present computer code used to generate isodose distributions. Finally, topics in clinical dosimetry are considered. An evaluation of dosimetry techniques suitable for high-LET radiations, the verification of dose distributions predicted by treatment planning codes, and fundamental dosimetry measurements on charged particle radiation quality and quantity are discussed.

All of the above developments and techniques are currently being refined during the helium ion trials, and will be directly applicable to the heavy-ion trials at the Bevalac.

Beam Development

Ridge Filter Design

The Bragg peaks of monoenergetic heavy-ion beams are narrow (less than 1 cm) and must be broadened

in order to produce a more useful therapeutic depth dose distribution. Modification of the dose distribution is usually obtained with the use of a range modulator such as a ridge filter. The design of such a filter to produce the ideal dose distribution depends on two factors: 1) the width of the spread peak, and 2) the variation of the RBE across the modified spread peak. The dose distribution of protons for therapy is usually flat over the modified peak, because the biological effectiveness of these particles for cell killing is essentially constant until the last fraction of a millimeter residual range. In contrast, our initial studies with the helium ion and very-heavy-ion beams indicated that ideally the physical dose should be a maximum at the entrance to the desired treatment volume (proximal peak) and should decrease in value until the remaining particles come to the end of their range at the far side of the treatment volume (distal peak). Thus, the physical dose must decrease as the RBE increases. Since the preliminary biologic experiments have been completed, data are available to evaluate the RBE of the various heavy-ion beams. With these data, it is now possible to design isosurvival depth dose distributions for therapeutic applications.

In order to calculate a physical depth dose distribution that will provide an isosurvival region, we use a beam model that allows us to calculate dose and average LET as a function of penetration distance. This beam model is a modification of the model used in the computer program BRAGG. The beam model used includes contributions of the primary and secondary particles to the dose and LET distributions. The model for cell killing is based upon the dual action theory developed by Rossi and Kelleher. This survival of cells is described as:

$$S = S_0 e^{-\alpha D - \beta D^2},$$

with the α and β components both being a function of the mean LET, as reported by Chapman et al. The isosurvival depth dose distributions that have been calculated are based upon biological data at the 60% survival level of cells per dose fraction. This is a survival level that is appropriate for typical daily fractions of 200 rads of photon irradiation. A set of isosurvival ridge filters is currently being fabricated based on these calculations. Beams with modified Bragg peak widths of from 4 to 16 cm, in 2-cm increments, will shortly be available for helium ion therapy.

Treatment planning is more complex because of the nonuniform physical dose distribution. One method to simplify treatment planning is to base it on a dose equivalent curve. The dose equivalent distribution is the distribution of a low-LET radiation that would be required to produce the same cell killing as a function of depth. The relationship between survival, dose, and dose equivalent, all as a function of depth, is illustrated in Fig. 1.

Large Field Scattering System

A double scattering system developed by Schneider et al. has been implemented in the biomedical beam at the 184-inch cyclotron. This system produces fields as large as 27 cm in diameter which are uniform to $\pm 2\%$. Secondary collimation of the expanded beam is accomplished by cerrobend collimators individually shaped for each patient. A similar scattering and beam shaping system will be installed at the Bevalac.

Patient Setup and Immobilization

The clinical trials with a fixed horizontal beam at the 184-inch cyclotron have yielded valuable experience in patient setup and immobilization which is directly applicable to future Bevalac trials. It is now clear that a majority of patients treated with a horizontal beam should be immobilized in an upright isocentric position. The major advantage of an upright position over a supine or prone patient orientation is the ability to deliver oblique fields accurately by rotating about an isocenter. This position also offers more patient comfort, ease of setup, and better reproducibility. Accessories have been built to attach to the cyclotron patient positioner ISAH to allow treatments to be given in either a seated or standing position.

Fig. 1. Per cent survival, relative dose, and relative dose in cobalt rad equivalent units as a function of depth. (XBL 772-3137)

Other techniques developed at the cyclotron which will be of use for heavy-ion trials include 1) development of a bite block head holder assembly available for head and neck irradiations, 2) the use of both line and spot lasers to facilitate patient setup, 3) the use of lightcast, a photosetting plastic resin, to make individualized girdle-like belts which help fix the patient contour and support bolus and compensators, and 4) application of a face mask technique previously developed for pituitary irradiations to immobilize the head.

Computerized Treatment Planning

Computerized treatment planning for charged particle therapy requires 1) a detailed knowledge of the inhomogeneities present in the beam path and 2) the development of a computer code to generate isodose and isoeffect distributions resulting from a proposed treatment plan. Computerized tomography (CT) is one method to obtain quantitative information about inhomogeneities. Other methods, such as heavy-ion radiography, are discussed elsewhere in this report.

Use of CT Data in Treatment Planning

The physical quantity relevant to charged particle treatment planning is the electron density (electron/cm³). This parameter predominantly determines both the relative stopping power for heavy charged particles and the photon attenuation characteristics at megavoltage energies. However, most CT scanners yield linear attenuation coefficients at diagnostic energies (about 80 keV), where the linear attenuation coefficient is a complex function of both the electron density and the effective atomic number, Z . The problem is to extract the electron density from such CT data. We are currently evaluating two solutions to this problem. In the first method, data from a single CT scan are extrapolated to give linear attenuation coefficients at megavoltage energies. The second method involves scanning the same body slice at two different energies. The single scan method is described first.

The linear attenuation coefficient of a CT pixel is written as follows:

$$\mu_x = \alpha \mu_1 + (1-\alpha) \mu_2, \quad (1)$$

where μ_1 and μ_2 are the linear attenuation coefficients of two reference materials, and define the upper and lower limits of all μ_x within a limited CT number range, and α is a mixing parameter. For example, CT numbers between 0 and 500 are modeled to be appropriate mixtures of soft tissue and compact bone. The interval -500 to 0 is represented as a combination of air and soft tissue.

The fraction α is determined at diagnostic energies by evaluating Eq. (1) at the effective energy of the CT scan. μ_x is determined by the equation

$$\mu_x = \frac{\text{CT NR} \times \mu_W}{500} + \mu_W, \quad (2)$$

where μ_W is the linear attenuation coefficient of water at the scan energy. With α known, Eq. (1) is re-evaluated with μ_1 and μ_2 assuming their values at high photon energies. Typically, this is done at 1 MeV, where the photon-electron interactions are dominated by Compton scattering. This yields a value for the linear attenuation coefficient at 1 MeV which is related to the electron density by the equation

$$\mu_{\text{Compton}}^{(E)} = N_e \frac{\text{KN}}{\sigma(E)}, \quad (3)$$

where N_e is the electron density and $\sigma(E)$ is the Klein Nishina cross section per electron at photon energy E .

Extrapolation calculations of this type have been made on a number of materials and the linear attenuation coefficient at high energies has been successfully determined with an accuracy of 3 to 4%.

The second method of extracting the electron density involves scanning the same body slice at two different CT energies. This dual energy scan allows for a rigorous calculation of the photoelectric and Compton fractions of the linear attenuation coefficient. One writes that the linear attenuation coefficient of a pixel is the sum of the Compton and photoelectric parts:

$$\mu_{\text{total}} = \mu_{\text{Compton}} + \mu_{\text{photoelectric}}. \quad (4)$$

The energy dependence of the photoelectric process has been parametrized in the diagnostic energy range by Cho as

$$\mu_{\text{pe}}(E) = \frac{K_p N_0 Z^{m-1}}{E^{3.1}}. \quad (5)$$

A set of simultaneous equations may then be written to describe the linear attenuation coefficient measurements at the different scan energies E_1 and E_2 :

$$\begin{aligned}\mu_1(E_1) &= \mu_c(E_1) + \frac{C}{E_1^{3.1}}, \\ \mu_2(E_2) &= \mu_c(E_2) + \frac{C}{E_2^{3.1}}.\end{aligned}\tag{6}$$

The ratio of the Compton linear attenuation coefficients may be calculated from the known energy dependence for the Compton process, as described by the Klein Nishina equations. The solution of Eq. (6) gives the linear attenuation coefficient for the Compton fraction, which is directly relatable to the electron density.

Experiments have been performed to test the accuracy of these two methods. Solutions of dibasic potassium phosphate (K_2HPO_4) and water were mixed in varying concentrations to simulate bones with different densities. Table IV gives the physical parameters of these solutions. The linear attenuation coefficients of these test solutions were then measured with narrow beam geometry experiments at an effective photon energy of 1.5 MeV. A comparison of the electron density predicted by the single scan method and measurements is shown in Fig. 2. A maximum difference of about 3% is seen. The dual scan method yielded differences between calculated and measured electron densities of about 1.5%.

The single scan method is attractive since it requires only one scan per slice and appears to give sufficiently accurate information on electron density. However, this technique is model-dependent and the choice of μ_1 and μ_2 is not arbitrary. Experiments on bone samples must be performed before the model is determined to be useful. The dual energy scan method gives an exact solution for both the electron density and effective Z. However, it may be sensitive to the effective scan energies and to inexact pixel registration present because of respiration and patient movement. The precision of the dual energy method is lower since fewer photons are used in the exact determination of the Compton fraction. Additional experiments to evaluate these two methods are planned.

The water equivalent range of a pixel will be predominantly determined by the electron density. However, the relative stopping power does have a small Z-dependent factor. The exact dependence of this factor will be experimentally determined. The water equivalent range has been measured as a function of CT number

TABLE IV

GM-%(K_2HPO_4)	CTNR 140 KVP	Electron Density $\times 10^{-23}$ e/cm ³	Specific Gravity	Effective Z
0	0	3.31	1.0	7.49
100	51	3.47	1.06	9.19
200	102	3.65	1.125	10.22
300	153	3.81	1.18	10.99
400	204	3.91	1.22	11.62
500	256	4.07	1.28	12.12
600	307	4.23	1.34	12.53
670	343	4.34	1.38	12.76
730	373	4.41	1.41	12.97

Fig. 2. Electron density as calculated for solutions of varying density by the single scan method are compared with measurement. (XBL 772-3116)

for the potassium phosphate test solutions and results are shown in Fig. 3. Note the nearly linear relation, again verifying that the water equivalent range is dominated by the electron density.

Treatment Planning Codes

Treatment plans for charged particle therapy are presently being calculated by the computer code DOSEM. This program is capable of computing a two-dimensional dose distribution in a transverse plane. At present, contours of pertinent inhomogeneities are obtained from CT scans, enlarged to life size, and digitized. Relative stopping powers are then assigned to the inhomogeneities and doses are calculated for a prescribed matrix of points. Output of the program is in the form of isodose contours superimposed on the patient outline. Isoeffect output may also be obtained by specification of the appropriate input dose equivalent curve. Treatment plans are typically generated for several transverse planes in order to assess the effects of the dose distribution along the longitudinal axis. A representative treatment plan is shown in Fig. 4.

Several important improvements to DOSEM are planned as a result of preliminary work on CT scans. An analysis of the distribution of CT numbers in vertebral bodies as seen in Fig. 5 shows that a simple assignment of an average relative stopping power to bones is not sufficient to describe its effects on dose distribution. In order to obtain a more accurate isodose distribution, the quantitative CT information in each pixel should be used. In the proposed version of DOSEM, the dose at a point is calculated by using the water equivalent range of each pixel in the beam path. In this case, localized CT artifacts, such as motion artifacts, will not give as accurate CT numbers as organ average values, and these differences must be considered in the proper use of the technique.

Fig. 3. Water equivalent range of K_2HPO_4 solutions are plotted as a function of CT number at a scan energy of 140 KVP. (XBL 772-3138)

Fig. 4. Representative treatment plan for helium ion therapy. The target is a pancreatic carcinoma. Isoeffect lines are shown in this plan. (XBL 771-7261)

Fig. 5. CT scan of a vertebral body as window level is raised. Note the non-uniform distribution of dense bone (white areas) as level is raised.
(XBB 772-1392)

Other current studies related to charged particle treatment planning include: 1) an evaluation of the need for multiple Coulomb scattering in dose calculations, 2) addition of the capability to calculate integral dose to tumor and non-tumor tissues, 3) development of a plan scoring system to evaluate the relative merits of different plans, and 4) a specification of features required for a CT scanner used for treatment planning.

The capability of conventional photon treatment planning is also important to implement for two reasons: 1) A limited number of patients have already received part of their treatment with photons. A knowledge of dose distributions and the accumulated dose to organs from a combined photon and charged particle course is necessary. 2) Realistic photon plans, which are calculated by using the quantitative information available from CT scans, must be compared with charged particle dose distributions to evaluate any potential benefit from dose localization. A photon treatment planning code is already in hand and only a modest effort is required to implement the code on the PDP 11/45. A version of the Memorial Hospital program has been selected for photon treatment planning, and a modified version will be generated to fully use the available CT information.

Clinical Dosimetry

A program in clinical dosimetry is currently under development. Its purpose and scope will be to 1) evaluate dosimetry techniques suitable for charged particles, especially high-LET radiations, 2) measure dose distributions from prescribed treatments in realistic phantoms and verify computer calculations, and 3) measure fundamental properties of therapeutic beams, such as LET spectra, and intercompare dose measurements with other charged particle therapy groups.

Several techniques presently used in photon dosimetry are directly applicable in the measurement of charged particle radiation. Ion chambers may be used for accurate charged particle dosimetry if W values

are well known. Relative measurements of sharp dose gradients in proton beams have been measured with silicon diodes by Koehler with high spatial resolution (0.1 mm). Intercavitary diode probes have been assembled and used in dose measurements on patients treated with helium ions. These techniques are available and accurate to 3 to 4% with current data available.

Thermoluminescent dosimetry (TLD) may be a convenient technique to routinely measure dose. Experiments are under way to determine the LET dependence of various phosphors. Powdered samples will be placed in carbon and neon beams at positions of known LET and their response measured. TLD capsules have already been placed in nasal and oral cavities of a head and neck patient treated with helium ions to measure reproducibility of dose. When a TLD phosphor with an acceptable LET dependence is found, it may be developed into a high-spatial-resolution dosimeter suitable for mapping two-dimensional dose distributions. Such a technique has been developed for photon dose measurements by Bjarngard and is described in the literature.

The response of photographic film to charged particle radiation is not linear with dose because of the complex LET and angular sensitivity of emulsions. However, photographic film may be used as a fluence detector, and the stopping point of beams may be determined with a film-plastic sheet stack. We have used a film stack to measure perturbations in penetration due to inhomogeneities such as vertebral bodies. An AP beam of helium ions was passed through the body and stopped in a film stack. A typical film set is shown in Fig. 6. Range shortening by transverse processes, edges of vertebral bodies, and gas are clearly visible. Film stacks have been converted to dosimeters with moderate success by placing intensifying screens behind films, or by replacing plastic sheets with scintillator. These methods are being refined to develop a convenient two-dimensional dosimetry technique.

An important application of the dosimetry methods developed will be the verification of dose distributions predicted by computer planning. By comparing the measured beam stopping points with calculations based on CT data, the accuracy of the calculation may be determined. An important tool in this evaluation is the unusually long range of the therapeutic helium ion beam. With a range of over 27 cm, this beam may be passed through thick body sections with enough residual range to obtain inhomogeneity information. Comparisons between predicted and measured stopping positions are under way. Respiration motion and other effects which smear dose distributions may also be measured by film stack studies. Potential over- and under-shoot due to bolus registration and multiple Coulomb scattering, as calculated by Goitein, may be measured and confirmed.

The final topic of clinical physics to be discussed is the fundamental measurements of beam quality and quantity. At our request, P. Fessenden (Stanford) has measured the LET spectra of the 5- and 8-cm helium beams. These measurements complement LET data taken at the Bevalac by Rossi (Columbia) and Fessenden, and will assist in the isoeffect ridge filter design and interpretation of cell survival as a function of LET.

In order to insure accurate absolute dosimetry, the radiotherapy physics group at LBL is participating in dose intercomparisons with other charged particle therapy groups under the auspices of the Charged Particle Physics Dosimetry Group (CPPDG) of the AAPM. Under this group, charged particle dosimetry protocols and procedures will be developed and standardized. This organization also serves as an information exchange on other common problems in clinical physics in charged particle radiotherapy.

Fig. 6. Film stack measurement through abdomen of a patient. Note visibility of transverse processes and gas in the bowel.
(XBB 772-1318,-1319)

Fig. 6. (Continued)

BAHIA Membership List

Lawrence Berkeley Laboratory Staff

Joseph R. Castro, M.D.
 Edward Alpen, Ph.D.
 Eleanor Blakely, Ph.D.
 Max L. M. Boone, M.D., Ph.D.
 James Born, M.D.
 Thomas Budinger, M.D., Ph.D.
 George T. Y. Chen, Ph.D.
 Claude Chong, M. D., Ph.D.
 Stan Curtis, Ph.D.
 Grant Gauger, M. D.

John Lawrence, M.D.
 John Leith, Ph.D.
 John Linfoot, M. D.
 John Lyman, Ph.D.
 Jeanne M. Quivey, M.D.
 Lisa Snow, M.D.
 Henry Stauffer, M.D.
 Cornelius A. Tobias, Ph.D.
 Kay Woodruff, M. D.

Collaborating Physicians and Physicists

Malcolm A. Bagshaw, M.D.
 Donald G. Baker, Ph.D.
 Joseph Beck, M.D.
 Richard Borrison, M.D.
 Barry M. Chauser, M.D.
 Irene Chino, M.D.
 William Connor, Ph.D.
 Roy Deffebach, M.D.
 H. Anthony Englebrecht, M.D.
 Karen Fu, M.D.
 Fred W. George, M.D.
 Eugene Germer, Ph.D.
 Eli Glatstein, M.D.
 Jerold P. Green, M.D.
 Delwin Hadel, M.D.
 Ralph Hanahan, M.D.
 Judith Harrison, M.D.
 William W. Helvie, M.D.
 Dennis Hill, M.D.
 William Johnson, M.D.
 David Karp, M.D.
 Joseph W. Kraut, M.D.
 Bernard Lewinsky, M.D.
 Kenneth Luk, M.D.
 Howard Maccabee, M.D.
 Lawrence W. Margolis, M.D.
 T. S. Meyler, M.D.
 Theodore L. Phillips, M.D.
 David Pistenma, M. D.
 Theodore Purcell, M.D.
 Philip Purser, M.D.
 Mudundi Raju, Ph.D.
 Aroor Rao, M.D.
 Antolin Raventos, M.D.
 Alan F. Schroeder, M.D.
 Glenn Sheline, M.D.
 Robert S. Sherman, M.D.
 Saul Silverman, M.D.
 Charles Sondhaus, Ph.D.
 Raul Urtasun, M.D.
 Ronald L. Van Roy, M.D.

Stanford University Medical Center
 Claire Zellerbach Saroni Tumor Institute
 Eden Hospital, Castro Valley
 El Camino Hospital, Mountain View
 St. Francis Hospital, San Francisco
 UC Irvine Medical Center, Irvine
 University of Arizona, Tucson
 Sequoia Hospital, Redwood City
 Peralta Hospital, Oakland
 UC Medical Center, San Francisco
 USC School of Medicine, Los Angeles
 University of Arizona, Tucson
 Stanford University Medical Center
 St. Francis Memorial Hospital, San Francisco
 Santa Rosa, California
 Santa Rosa, California
 St. Joseph's Hospital, Irvine
 Letterman Army Medical Center, San Francisco
 Franklin Hospital, San Francisco
 Peninsula Hospital, Burlingame
 U. S. Naval Hospital, Oakland
 Santa Clara Valley Medical Center, San Jose
 Los Angeles County Harbor General Hospital, Torrance
 Saroni Tumor Institute, San Francisco
 Berkeley, California
 Franklin Hospital, San Francisco
 Saroni Tumor Institute, San Francisco
 UC Medical Center, San Francisco
 Varian Associates & Stanford Medical Center
 Alta Bates Hospital, Berkeley
 Saroni Tumor Institute, San Francisco
 UC Los Alamos Scientific Laboratory, New Mexico
 U.S. Naval Hospital, Oakland
 UC School of Medicine, Davis
 Santa Rosa Radiation Therapy Center, Santa Rosa
 UC Medical Center, San Francisco
 Children's Hospital, San Francisco
 Radiation Oncology Center, Sacramento
 UC Irvine Medical Center, Irvine
 W.W. Cross Cancer Institute, Edmonton, Alberta, Canada
 Santa Rosa Radiation Therapy Center, Santa Rosa

REFERENCES

- Archambeau, J., Bennett, G. W., Levine, G. S., Cowen, R., and Akanuma, A. (1974). Proton radiation therapy. *Radiology* 110, 445-457.
- Barendsen, G. W., Walter, H. M. D., Fowler, J. F., and Bewley, D. K. (1963). III. Experiments with cyclotron-accelerated alpha particles and deuterons. *Radiation Res.* 18, 106-119.
- Barendsen, G. W. (1968). Response of cultured cells, tumors, and normal tissues to radiations of different linear energy transfer. In: *Current Topics in Radiation Research* 4 (Ebert, M., and Howard, A., Eds.). North-Holland, Amsterdam, pp. 295-354.
- Barendsen, G. W. (1972). Radiobiological dose-effect relations for radiation characterized by a wide spectrum of LET; Implication for their application in Radiation Therapy (October 2-5, 1972). Los Alamos Scientific Laboratory Report LA-5180-C, pp. 120-125.
- Barendsen, G. W. (1974). Characteristics of tumor responses to different radiations and the relative biological effectiveness of fast neutrons. *Eur. J. Cancer* 10, 269-274.
- Benton, E. V., Henke, R. P., and Tobias, C. A. (1973). Heavy-particle radiography. *Science* 182, 474-476.
- Bewley, D. K. (1968). Calculated LET distributions of fast neutrons. *Radiation Res.* 34, 437-445.
- Bewley, D. K., and Parnell, C. J. (1969). The fast neutron beam from the M.R.C. cyclotron. *Brit. J. Radiol.* 42, 281-288.
- Bjarngard, B. E., Chen, G. T. Y., and Maddox, B. J. (1976) High resolution dosimetry with stimulated phosphorescence. *Med. Phys.* 3, 39.
- Bond, V. P. (1971). Negative pions: their possible use in radiotherapy. *Amer. J. Roentgenol.* 111, 9-26.
- Booth, R., and Barschall, H. (1972). Tritium target for intense neutron source. *Nucl. Instr. Methods* 99, 1-4.
- Castro, J. R. (1976). Clinical experience and expectations: helium and heavy ions. In: *Proceedings of the International Conference on Particles and Radiation Therapy, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976)*. *International Journal of Radiation Oncology, Biology, and Physics, Part II*, to be published.
- Catterall, M. Rogers, C., Thomlinson, R. H., and Field, S. B. (1971). An investigation into the clinical effects of fast neutrons. *Brit. J. Radiol.* 44, 603-611.
- Catterall, M., Sutherland, I., and Bewley, D. K. (1975). First results of a randomized clinical trial of fast neutrons compared with x or gamma rays in treatment of advanced tumors of the head and neck. *Brit. Med. J.* 2, 653-656.
- Catterall, M. (1976) The results of randomized and other clinical trials of fast neutrons from the Medical Research Council cyclotron, London. In: *Proceedings of the International Conference on Particles and Radiation Therapy, Lawrence Berkeley Laboratory, Berkeley, California, (September 14-17, 1976)*. *International Journal of Radiation Oncology, Biology and Physics, Part II*, to be published.
- Chapman, J. D., Blakeley, E. A., Smith, K. C., and Uratsun, R. C. (1976). Radiobiological characterization of the inactivating events produced in mammalian cells by helium and heavy ions. In: *Proceedings of the International Conference on Particles and Radiation Therapy, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976)*. *International Journal of Radiation Oncology, Biology, and Physics, Part II*, to be published.
- Chen, G. T. Y., Private
- Cho, Z. H., Tsai, C. M., and G. Wilson. (1975). Study of contrast and modulation mechanisms in x-ray/photon transverse axial transmission tomography, *Phys. Med. Biol.* 20, 879.
- Constable, I. F., and Koehler, A. M. (1974). Experimental ocular irradiation with accelerated protons. *Invest. Ophthalmol.* 13, 280-287.
- Crowe, K., Kanstein, L., Lyman, J., and Yeater, F. (1975). A large field medical beam at the 184-inch synchrocyclotron. Lawrence Berkeley Laboratory Report No. 4235.
- D'Angio, G. J., Aceto, H., Nisce, L. Z., Kim, J. H., Jolly, R., Buckle, D., and Holt, J. B. (1974). Preliminary clinical observations after extended Bragg peak helium ion irradiation. *Cancer* 34, 6-11.

- Denekamp, J., Fowler, J. F., Kragt, K., Parnell, C. J., and Field, S. B. (1966). Recovery and repopulation in mouse skin after irradiation with cyclotron neutrons as compared with 250 KV x-rays or 15 MeV electrons. *Radiation Res.* 29, 71-84.
- Dzhelepov, V. P., and Ruderman, A. I. (1975). High energy protons and radiation therapy of malignant tumors. Dubna, U.S.S.R.
- Goitein, M., The measurement of tissue heterodensity to guide charged particle radiotherapy, to be published in *Int. J. Rad. Onc. Bio. Phys.*
- Gray, L. H. (1957). Oxygenation in radiotherapy. I. Radiobiological considerations. *Brit. J. Radiol.* 30, 403-406.
- Hall, E. J. (1973b). Radiobiology of heavy particle radiation therapy: cellular studies. *Radiology* 108, 119-129.
- Hewitt, H. B., and Wilson, C. W. (1959). Survival curve for mammalian leukemia cells irradiated *in vivo* (implications for the treatment of mouse leukemia by whole body irradiation). *Brit. J. Cancer* 13, 69-75.
- Hussey, D. H., Fletcher, G. H., and Caderao, J. B. (1974a). Experience with fast neutron therapy using the Texas A and M variable energy cyclotron. *Cancer* 34, 65-77.
- Hussey, D. H., and Fletcher, G. H. (1974b). Clinical features of 16 and 50 MeV d-Be neutrons. *Eur. J. Cancer* 10, 357-360.
- Hussey, D. H., Parker, R. G., and Rogers, C. C. (1975). A preliminary report of the fast neutron therapy pilot studies in the United States. In: *Proceedings of the International Conference on Particles and Radiation Therapy, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976)*. International Journal of Oncology, Biology and Physics, Part II, to be published.
- Kaplan, H. S. (1969). Potentialities of negative pi meson beams in radiotherapy of cancer. In: *Los Alamos Scientific Laboratory Report LA-4397-MS*, pp. 31-41.
- Kaplan, H. S. (1970). Radiobiology's contribution to radiotherapy: promise or mirage? *Radiation Res.* 43, 460-476.
- Kaplan, H. S., Schwettman, H. A., Fairbank, W. M., Boyd, D., and Bagshaw, M. A. (1973). A hospital based superconducting accelerator facility for negative pi meson beam radiotherapy. *Radiology* 108, 159-172.
- Kelleher, A. M., and Rossi, H. H. (1971) RBE and the primary mechanism of radiation actions. *Rad. Res.* 47, 15-34.
- Kelsey, C. A. (1975). Current status of DT targets for cancer therapy. *Med. Phys.* 2, 185-190.
- Kligerman, M. M., Sternhagen, C. J., Dobrowolski, F., Davis, H. T., Barnes, J. E., Lane, T. F., Bradbury, J. N., Knapp, E. A., and Petersen, D. G. (1976). Initial comparative response of metastatic superficial nodules and surrounding underlying normal tissue to peak pions and x-rays. *Amer. J. Roentgenol.* 126, 261-267.
- Kligerman, M. D. (1976). Clinical radiobiology studies with pi negative mesons. In: *Proceedings of the International Conference on Particles and Radiation Therapy, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976)*. International Journal of Radiation Oncology, Biology and Physics, Part II, to be published.
- Koehler, A. M. (1976). Dosimetry of proton beams using small silicon diodes. *Rad. Res. Suppl.* 7, 53.
- Lawrence, J. H., and Lawrence, E. O. (1936). The biological action of neutron rays. *Proc. Natl. Acad. Sci.* 22, 124-133.
- Lawrence, J. H., Aebersold, C., and Lawrence, E. O. (1936). Comparative effects of x-rays and neutrons on normal and tumor tissue. *Proc. Natl. Acad. Sci.* 22, 543-557.
- Leith, J. T., Woodruff, K. H., and Lyman, J. T. (1975a). Early effects of single doses of 375 MeV/nucleon ^{20}Ne ions on the skin of mice and hamsters. *Radiation Res.* 62, 195-215.
- Leith, J. T., Woodruff, K. H., Howard, J., Lyman, J. T., Smith, P., and Lewinsky, B. S. (1975b). Early and late effects of accelerated charged particles on normal tissues. In: *Proceedings of an International Workshop, Key Biscayne, Florida (October 1-3, 1975)*. *Amer. Coll. of Radiology*, pp. 361-384.

- Leith, J. T., Woodruff, K. H., Lewinsky, B. S., Lyman, J. T., and Tobias, C. A. (1975c). Tolerance of the spinal cord of rats to irradiation with neon ions. *Int. J. Radiat. Biol.* 28, 393-398.
- Leith, J. T. (1976a). Tissue biology of helium and heavy ions. In: *Proceedings of the International Conference on Particles and Radiation Therapy*, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976), *International Journal of Radiation Oncology, Biology and Physics*, Part II, to be published.
- Lyman, J. T., and Chong, C., (1974). ISAH: a versatile treatment positioner for external radiation therapy. *Cancer*, 34, 12.
- Malaise, E. P., and Guichard, M. (1975). Relative biological effectiveness, oxygen enhancement ratio and repair of potentially lethal damage of helium ions (overview). In: *Proceedings of an International Workshop*, Key Biscayne, Florida (October 1-3, 1975). *Amer. Coll. of Radiology* pp. 385-402.
- McCullough, E. E. (1975). Photon attenuation in computed tomography. *Med. Phys.* 2, 307.
- Phillips, T. L., and Margolis, L. (1972). Radiation pathology and the clinical response of lung and esophagus. *Frontiers Radiat. Ther. Onc.* 6, 254-273.
- Phillips, T. L., Fu, K. K., and Curtis, S. B. (1976). Tumor biology of helium and heavy ions. In: *Proceedings of the International Conference on Particles and Radiation Therapy*, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976), *International Journal of Radiation Oncology, Biology, and Physics*, Part II, to be published.
- Pisterma, D. A., Li, G. C., Fessenden, P., White, K., and Bagshaw, M. A. (1976). Treatment planning for negative pi meson radiation therapy: simultaneous multiport irradiation with the Stanford Medical Pion Generator (SMPG). In: *Proceedings of the International Conference on Particles and Radiation Therapy*, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976). *International Journal of Radiation Oncology, Biology and Physics*, Part II, to be published.
- Powers, W. E., and Tolmach, L. L. (1964). Demonstration of an anoxic component in a mouse tumor cell population by *in vivo* assay of survival following irradiation. *Radiology* 83, 328-335.
- Puck, T. T., and Marcus, P. I. (1956). Action of x-rays on mammalian cells. *J. Exp. Med.* 103, 643-666.
- Raju, M. R., Gnanapurani, M., Martins, B. I., Howard, J., and Lyman, J. T. (1972). Measurement of OER and RBE of a 910 MeV helium ion beam using cultured cells (T-1). *Radiology* 102, 425-428.
- Raju, M. R., and Phillips, T. L. (1977) Privileged communication.
- Raju, M. R., and Richman, C. (1972). Negative pion radiotherapy. Physical and radiological aspects. In: *Current Topics in Radiation Research 8* (Ebert, M., and Howard, A., Eds.). North-Holland, Amsterdam, pp. 159-233.
- Raju, M. R. (1974a). Negative pions in radiotherapy: a brief review. *Eur. J. Cancer* 10, 211-215.
- Raju, M. R., Blakely, E., Howard, J., Lyman, J. T., Kalofonos, D., Martins, B., and Yang, C. H. (1976a). Cell survival as a function of depth for a neon ion beam. *Radiation Res.* 65, 191-194.
- Raju, M. R., Amols, H., Bain, E., Carpenter, S., Dicello, J., Frank, J., Tobey, R., and Walters, R. (1976b). Biological effects of pi negative mesons. In: *Proceedings of the International Conference on Particles and Radiation Therapy*, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976). *International Journal of Radiation Oncology, Biology and Physics*, Part II, to be published.
- Rosen, L. (1972). The Los Alamos meson physics facility (LAMPF), a new tool for basic research and practical applications. *Peaceful Uses of Atomic Energy* 7, 167-181.
- Schneider, R., Schmidt, R. A., and Koehler, A. M. (1974). Physical preparations for cancer therapy at the Harvard cyclotron. *Bull. Amer. Phys. Soc.* 19, 31.
- Shukovsky, L. J. (1970). Dose, time, volume relationships in squamous cell carcinoma of the supraglottic larynx. *Amer. J. Roentgen.* 108, 27.
- Shukovsky, L. J., and Fletcher, G. H. (1972). Retinal and optic nerve complications in a high dose irradiation technique of ethmoid sinus and nasal cavity. *Radiology* 104, 629-634.
- Stone, R. S., Lawrence, J. H., and Aebersold, P. C. (1940). A preliminary report on the use of fast neutrons in the treatment of malignant disease. *Radiology* 35, 322-327.
- Stone, R. S., and Larkin, J. C., Jr. (1942). The treatment of cancer with fast neutrons. *Radiology* 39, 608-620.

- Stone, R. S. (1948). Neutron therapy and specific ionization. *Amer. J. Roentgenol.* 59, 771-785.
- Suit, H. D. (1969). Statement of the problem pertaining to the effect of dose fractionation and total treatment time in response of tissue to x-irradiation. In: *Time and Dose Relationships in Radiation Biology as Applied to Radiotherapy*, Carmel Conference. Brookhaven National Laboratory Report BNL-50203-(C-57), pp. vii-x.
- Suit, H. D., and Goitein, M. (1974). Dose limiting tissues in relation to types and location of tumors: implications for efforts to improve radiation dose distributions. *Eur. J. Cancer* 10, 217-224.
- Suit, H. D., Goitein, M., Tepper, J. E., Verhey, L., Koehler, A. M., Gragondas, E., and Schneider, R. (1976). Clinical experience and expectations: Protons and heavy ions. In: *Proceedings of the International Conference on Particles and Radiation Therapy*, Lawrence Berkeley Laboratory, Berkeley, California (September 14-17, 1976). *International Journal of Radiation Oncology, Biology, and Physics*, Part II, to be published.
- Till, J. E., and McCulloch, E. A. (1961). A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. *Radiation Res.* 14, 213-222.
- Tobias, C. A., Anger, H. O., and Lawrence, J. H. (1952). Radiological use of high energy deuterons and alpha particles. *Amer. J. Roentgenol.* 67, 1-27.
- Tobias, C. A., and Todd, P. W. (1967). Heavy charged particles in cancer therapy. In: *Radiobiology and Radiotherapy* (del Regato, J. A., Ed.). U. S. National Cancer Institute Monograph 24, 1-21.
- Tobias, C. A., Lyman, J. T., and Lawrence, J. H. (1971a). Some considerations of physical and biological factors in radiotherapy with high LET radiations including heavy particles, pi mesons, and fast neutrons. *Progr. Atomic Med.* 3, 167-218.
- Tobias, C. A., Chatterjee, A., and Smith, A. R. (1971b). Radioactive fragmentation of N^{+7} ion beam observed in a beryllium target. *Phys. Lett.* 37A, 119-120.
- Tobias, C. A. (1973). Pretherapeutic investigations with accelerated heavy ions. *Radiology* 108, 145-158.
- Todd, P. W. (1967). Heavy ion irradiation of cultured human cells. *Radiation Res. Suppl.* 7, 196-207.
- Todd, P. W., Martins, B. I., Lyman, J. T., Kim, J. H., and Schroy, C. B. (1974). Spatial distribution of human cell survival and oxygen effect in a therapeutic helium ion beam. *Cancer* 34, 1-5.
- Wilson, R. R. (1947). Radiological use of protons. *Radiology* 47, 487-491.
- Withers, H. R., and Elkind, M. M. (1970). Microcolony survival assay of cells of mouse intestinal mucosa exposed to radiation. *Int. J. Radiat. Biol.* 17, 261-267.
- Woodruff, K. H., Leith, J. T., Lyman, J. T., and Tobias, C. A. (1976). Morphologic and morphometric analysis of the early effects of x-ray and heavy ion irradiation of hamster lung. *Amer. J. Pathol.* 82, 287-298.

CHAPTER 15

DESIGN OF FUTURE BIOMEDICAL ACCELERATORS

Hermann A. Grunder and Christoph W. Leemann

INTRODUCTION

Today's biomedical studies and trials with neutrons, protons, π -mesons and heavy ions rely on accelerators designed for physics research. The design of these devices has been based on the priorities of the physics research community; performance in terms of beam energy, intensity and flexibility is often stressed at the expense of high reliability and ease of operation, which are crucial for a successful medical application.

In contrast, it is expected that by designing radiation sources strictly according to the medical requirements, cost-effective accelerators will result that will be suitable for routine, hospital-based, clinical operation with modest operation and maintenance crews.

Recognizing the need for a detailed investigation of the possibilities of present accelerator technology with respect to medical application, the Accelerator Division of LBL in collaboration with the University of Arizona Medical School obtained support from the National Cancer Institute to conduct a design study of a medically dedicated accelerator. Work began in September 1975 and will be concluded in September 1977. Essentially all of the following comments on future medical accelerators are based on this study.

The main effort is concentrated on the design of an accelerator complex for heavy-ion radiation therapy. In view of present uncertainties with regard to certain parameters (e.g., optimum ion species), an approach was adopted that is sufficiently broad and general to allow a valid extrapolation to slightly changed specifications at a later time. In addition, a number of secondary areas are under investigation. A protons-only machine, the generation of diagnostic beams, and the inclusion of neutron and/or isotope production are being studied.

It is understood that proven, established technology should be used unless new, novel technology is judged unavoidable to achieve the design goals. Specifically, the following steps were defined to achieve the goals of the study:

1. Clarify and define beam specifications (i.e., particle species, depth of penetration, dose, rate, treatment volume, and dose homogeneity).
2. Study special requirements of beam delivery.
3. Review existing accelerator technology and define most cost-effective solutions with emphasis on reliable and fail-safe operation.
4. Build component prototypes where novel concepts seem mandatory.
5. Produce conceptual designs and cost estimates of a complete facility.

OVERVIEW OF PRESENT RESULTS

A set of therapeutic beam requirements meeting the requirements of therapists has been arrived at and translated into accelerator specifications. The requirements of added neutron-generation capability have been studied and incorporated in designs. The problem of generating flat (or otherwise specified) dose distributions has been solved through a novel three-dimensional scanning scheme. Isocentric beam-delivery systems have been designed. Synchrotrons offer the most cost-effective and flexible solutions for helium

and heavier ions. Synchrotron design has been optimized with respect to design parameters. A preliminary design of a 250-MeV-proton cyclotron has been prepared. Several layouts of multi-treatment-room facilities have been studied, and construction of the components of a prototype scanning system is in progress. Below we will elaborate on some of these aspects.

BEAM SPECIFICATIONS

The choice of the optimal accelerator type as well as the size, complexity and cost of a radiation facility are largely determined by the required particle species, energy, and beam intensity. Details of the beam-delivery procedure might further dictate the accelerator's minimum acceptable duty factor. Beam energy is defined by range in tissue, atomic number Z and mass number A (Fig. 1). If, for example, we accept 27 cm as a desirable range, the beam energies will be 400 MeV/amu for C ions and 550 MeV/amu for Ne ions. Radiography with C and Ne beams requires somewhat higher energies; otherwise, it must be performed with lighter ions.

Fig. 1. Range-energy relationship for H, He, d, Ne and Ar ions in water.
XBL 769-10507

In order to calculate the required beam intensity, one should ideally start from quantitative radiobiological data using energy spectra yielding flat iso-effect distributions. At present, however, in estimating accelerator performance, physical dose and energy superpositions yielding flat depth-dose distributions have been used. Under these assumptions, the beam intensity for a given particle and an arbitrarily shaped volume are given by the product of the dose rate and treatment volume. A typical desired value is 600 rad-liter/min for which the beam intensities for two differently shaped volumes are listed below.

Particle	Beam Intensities (particles per second)	
	A = 400 cm ² L = 2.5 cm	A = 50 cm ² L = 20 cm
P	1.35×10 ¹⁰	4.5×10 ⁹
	3.4 ×10 ⁹	1.1×10 ⁹
C	6.7 ×10 ⁸	2.2×10 ⁸
Ne	3.0 ×10 ⁸	1.0×10 ⁸
Ar	1.1 ×10 ⁸	3.8×10 ⁷

A = cross section of volume perpendicular to beam

L = length of volume in beam direction

Another beam requirement formulated recently is 200 rad/min in a volume with dimensions of 30 cm × 30 cm × 15 cm. This translates into beam intensities close to those listed above for A = 400 cm². Typical intensity goals for extracted beams are, for example, 4 ×10¹⁰ protons/sec or 2 ×10⁹ carbon ions/sec, allowing for some inefficiency in beam transport and delivery.

Providing neutron-beam capability calls for intense proton or deuteron beams at energies between approximately 30 and 100 MeV. The yield from deuteron bombardment is typically six times greater than that from protons. In both cases, both the yield and the depth-dose distribution improve with increasing primary-beam energy. A typical required dose rate is approximately 100 rad/min at SSD of 124 cm. For 50-MeV deuterons, this rate requires a current of ~7 μA. As will be seen, such a capability is most economically included in an injector, not in the main accelerator.

BEAM DELIVERY

Questions of beam delivery are of high priority, and any impact on accelerator design must be established. Some problems were expected here, and two stand out--the irradiation of large volumes and the investigation of isocentric beam-delivery systems with high-rigidity beams.

The primary beams of accelerators have very good beam quality; they are economically transported without ever attaining very large diameters and can be easily focused to small spots allowing very precise localization but not meeting the requirement of irradiating large volumes. Such beams can be spread, flattened and shaped by the use of scattering foils, occluding rings, and collimators but at the expense of flexibility and precision. Furthermore, if included in an isocentric device or even a fixed vertical beam, this approach would tend to increase the size of the structure or would require large magnet apertures.

Three-dimensional scanning of a pencil beam appears to be an attractive alternative. In such a scheme, a small-diameter beam is swept over the treatment volume by scanning magnets bending the beam in orthogonal planes while its depth of penetration is adjusted by energy modulation. The beam intensity must be controlled simultaneously.*

Our present design calls for a fast scanning magnet, a slower (by about one order of magnitude) scanning magnet, and energy modulation on an even slower scale. All changes are to occur in discrete steps. Based on multiple-scattering calculations and the expected emittance of a modern accelerator, step sizes between 2 and 4 mm are envisioned. The time available to deliver the prescribed dose at any given point (X_o, Y_o, Z_o) depends on step size, treatment volume, and treatment time. Time allowances as short as 200 μ sec are planned. A fast beam switch ($\sim 2 \mu$ sec) completes the system and protects against sudden surges in beam intensity.

Energy variation can be achieved by changing the accelerator output energy or through degraders. In the latter case, we have shown that emittance increase is severe enough that the degrader system should be placed as close as possible to the patient. The technological limit for the speed of such a system is the power required to step the fast scanning magnet. Refinements of design bring peak power levels to a few tens of kW.

The scanning approach will allow irradiation of highly irregularly shaped volumes, minimizing irradiation of healthy tissue. Dose flatness of about 1 percent with sharp edges (90 to 10 percent in about 3 to 6 mm) is achievable as well as nonflat but otherwise prescribed dose distributions. Furthermore, tissue inhomogeneities can be compensated for to a degree impossible with a bolus.

We have completed several designs of an isocentric beam-transport system incorporating a scanning system. Such systems seem entirely feasible, costing approximately 25- to 30-percent more than a fixed horizontal and vertical beam system. Size seems to be the main objection, a cylindrical volume 15 m in length and 5.6 m in radius being required for a system rotating through 360° . The use of superconducting magnets has been investigated, but reduction in physical size is nominal compared to the complexity of superconducting technology.

CHOICE OF AN ACCELERATOR TYPE

Cyclotrons (isochronous or frequency-modulated), linear accelerators, and synchrotrons were considered. All can be designed to meet the intensity requirements; isochronous cyclotrons and linacs would indeed exceed them by orders of magnitude. Based on today's state-of-the-art technology and even some reasonable extrapolations, linacs are not economically competitive and so have been ruled out as

* Under the assumption that no time-dependent effects must be considered, that is, that the time structure of dose accumulation at any point during one treatment (~ 60 sec) is immaterial, the scanning process can be formulated as a Fredholm equation of the first kind:

$$D(X,Y,Z) = \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \int_{Z_1}^{Z_2} I(X_o, Y_o, Z_o) g(X, X_o, Y, Y_o, Z, Z_o) dX_o dY_o dZ_o.$$

The quantity $D(X,Y,Z)$ is the prescribed dose distribution, i.e., a mathematical representation of the treatment plan. $I(X_o, Y_o, Z_o)$ is the representation of the corresponding scanning procedure, i.e., the number of beam particles delivered in a pencil beam with centroid coordinates (X_o, Y_o) and range Z_o . The kernel $g(X, X_o, Y, Y_o, Z, Z_o)$ corresponds to the dose contribution at (X,Y,Z) resulting from such a beam; it describes the beam profile and all relevant interactions of the beam with the transversed matter. In order to obtain "exact" results, g must be found as the solution of a "transport" or "Boltzmann-type" integro-differential equation, a nontrivial task, at least in the presence of substantial inhomogeneities. For system-design purposes, a simple approach (closely realized for protons in a homogeneous medium) with $g = g_x(X-X_o) \cdot g_y(Y-Y_o) \cdot g_z(Z-Z_o)$ is used and yields answers to the important questions of spatial resolution and the required frequency response of the system.

main heavy-ion accelerators. The same holds true for conventional magnet cyclotrons (isochronous or FM). No isochronous cyclotron using superconducting coils has been built or designed yet for energies of ~ 400 MeV/amu, and hence substantial research and development efforts are anticipated. Thus, the superconducting FM-cyclotron and the synchrotron are the main contenders. Figure 2 summarizes the costs and capabilities of different circular accelerators.

Fig. 2. Cost versus maximum energy for circular accelerators.
XBL 769-10509

Cyclotrons are identified in the figure. Curves A through D correspond to the synchrotron options with the following capabilities:

Curve	Protons	Heavy Ions	Radioisotopes	Neutrons
A	X	X	X	X
B	X	X	X	
C	X	to mass 4	X	
D	X	to mass 4		

Considerable effort has been spent in studying the properties of a sector-focused, superconducting FM-cyclotron. At low field level, such a machine can operate in an isochronous mode, providing intense deuteron beams for neutron therapy; at the higher field settings required for the acceleration of C^{+5} ions from an internal source, FM-operation can be employed. A stripping extraction scheme, essentially 100-percent effective and with excellent beam quality, has been designed. Final cost estimates, however, show this machine to be more expensive than a synchrotron. Furthermore, it lacks the flexibility (energy and particle species) typical of the synchrotron, and the advantages of smaller floor-space requirements are largely offset by the need for a taller building.

SYNCHROTRON DESIGN AND OPTIMIZATION

To design a heavy-ion synchrotron, a considerable number of free parameters is available. The desired average beam intensity and the specified pulse repetition rate define the number of particles to be injected, captured, accelerated and extracted in each beam pulse. This number defines the required mag-

net aperture and therefore magnet size, stored energy, and power demand. For lighter ions, the aperture requirements for a given injection energy are given by space charge limitations; for the heavier ions, injector brightness determines the number of injected turns and therefore aperture. Further, injection energy determines the required synchrotron RF-frequency range. Injection energy, the known output of ion sources for various charge states, and the desired injector brightness thus determine the performance specifications for the injector.

All of these relationships, if formulated in an exact, quantitative way, presuppose a well defined synchrotron design. Using reasonable approximations and expected ranges of crucial variables, a quite general approach is, nevertheless, possible. For different injectors (linacs and cyclotrons, accelerating different charge states), an optimum repetition rate has been determined. Figure 3 shows an example. Optimal values of f_{rep} differ slightly for different injector options, but in all cases studied repetition rates much smaller than 1 Hz or faster than 5 Hz are quite uneconomical. All of these calculations were based on B_{max} values of $\sim 1\text{T}$. Increasing the peak magnetic field B_{max} will increase synchrotron cost but result in a smaller machine. It will be necessary, therefore, to consider building costs if an attempt at optimizing B_{max} is made.

Fig. 3. Repetition-rate-dependent synchrotron costs. XBL 769-10508

The most important features of a synchrotron designed on the basis of the above considerations will now be described. A cyclotron used as an injector results in a facility capable of also generating radio-isotopes and therapeutic neutron beams. In order to achieve a high brightness of the injected beam, C^{+2} is accelerated in the cyclotron. If only high-energy heavy ions are requested, a linac used as an injector might be slightly more advantageous, and several suitable injector linacs have been designed. Table I lists the injector parameters. Detailed beam dynamics calculations have been performed based on two synchrotron lattices, one of the combined and one of the separated function type. Table II compares their parameters. Both designs have a 3.0-m-long straight section in each period allowing for sufficient

Table I. Injector cyclotron parameters.

1. Ion source	Internal
2. Magnet	
Sectors	4
Spiral angle, max.	40°
K	130 (65-MeV deuterons, 2.9-MeV/amu C^{+2} & Ne^{+3} ions)
$\bar{B}$ (extraction radius) max.	1.5 T
B (hill) max.	1.8 T
B (valley) max.	1.2 T
Extraction radius	1.10 m
Magnet weight	227 tons
Main-coil power	173 kW
Trim coils	12 circular
Trim coil power	35 kW
Harmonic coils	2/valley, inner and outer
3. RF System	
Dees	2 @ 45° in valleys ($\theta_D = 45^\circ$)
Dee-ground voltage	50 kV
Frequency	33.2, 10.0 MHz
Harmonics	3,4,5
RF power	100 kW (H^+), 50 kW (C^{+2})

Table II. Representative synchrotron lattice parameters.

Parameter	Combined function	Separated function
Beam rigidity	6.5 Tm	6.5 Tm
Number of periods	6	6
Guide field	0.8 T	1.0 T
Sequence	DOFDOF'	MO'FO'MO'DOFO'MO'DO' (OFOD)
Mean radius	12.021 m	11.752 m
v_x, v_y	2.250	2.250
γ_{tr}	2.11	2.22
x-chromaticity	-4.9	2.7
y-chromaticity	-4.6	-2.3
Magnet gap	± 2 cm	± 2 cm
Magnet edge angle	0°	10°

room to incorporate injection, extraction and RF-components as well as requested correction elements. Modest β -functions ($\beta_{x,y} < 10\text{m}$) result in an efficient use of the magnet aperture. At a repetition frequency of 2 Hz multiturn injection is needed to meet the intensity requirements. Calculations simulating the stacking process have shown that 25 turns can be injected in a full radial aperture of 10 cm with 70-percent efficiency. RF-capture and acceleration using a single accelerating station operating on the first harmonic is envisioned, and corresponding RF-system requirements have been derived. A space charge induced ν -shift of 0.1 is expected after bunching, showing that the synchrotron is well matched to the injector brightness. Slow extraction at $\nu_x = 2-1/3$ will be used. Growth rates of $> 1\text{ cm/3 turns}$ will result in good extraction efficiency. Extraction quadrupoles and sextupoles, skew quadrupoles, correction sextupoles and octupoles fit well in the planned lattice structure.

OUTLOOK ON WORK IN PROGRESS

Two aspects of beam delivery are being investigated further. An effort is being made to reduce as much as possible the space requirements of isocentric beam-delivery systems. This might include approaches that involve translations of the patient. A subsystem of the three-dimensional scanning system--namely the demanding fast-scanning magnet together with its power supply and the associated control system--is scheduled for construction and subsequent testing at the LBL Bevalac.

We plan to investigate in more detail a 250-MeV-proton accelerator. Preliminary results indicate that a conventional, fixed-energy cyclotron might be the most cost-effective solution; however, this result is being questioned.

For heavy-ion accelerators, a detailed cost and reliability comparison will be made between combined and separated function machines.

Conceptual layouts of possible facilities have been made (Figs. 4 and 5), but a considerable amount of work remains. Most notably, an optimization of accelerator size and cost versus building cost is planned.

Fig. 4. Hypothetical facility, conceptual design. XBL 769-10434

Fig. 5. Compact hypothetical facility, conceptual design. (XBL 769-10433)

CONCLUSION

The described work constitutes the first detailed study in recent years of major accelerator facilities for exclusively medical use. This study is not tailored to the needs of a specific construction proposal but rather attempts to be broad enough to be of use in a variety of situations and to provide technical answers to a wide range of possible beam specifications. Our results indicate that proven, well established accelerator technology can meet the clinical demands of ion-beam therapy. A judicious choice of machine parameters has to be made, however, in order to arrive at the most cost-effective solutions, and careful engineering is required in the interest of high reliability.