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APPENDIX

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PROTECTION OF HUMAN SUBJECTS: RESEARCH STUDY ON
THERAPEUTIC USE OF HELIUM AND HEAVY IONS IN HUMAN CANCERS

Principal investigators: Joseph Castro, MD; Cornelius Tobias, PhD

Location: Donner Laboratory, Lawrence Berkeley Laboratory

In charge of
human subjects: Joseph Castro, MD; James Born, MD; Thomas Budinger, MD;
Theodore Phillips, MD; Max L.M. Boone, MD; David Pistenma, MD

This research project will evaluate the use of helium and heavy ions in the radiotherapeutic treatment of human cancers. The Donner Laboratory of Lawrence Berkeley Laboratory has long experience in the use of proton and helium-ion beams and the treatment of pituitary tumors and Cushing's Disease. Primarily, these techniques have involved the use of small-field, low-fraction-number, high-dose treatments. This expertise makes the Donner Laboratory the leading facility for evaluation of the use of helium and heavy-ion beams for other human tumors, utilizing the extended Bragg peak in multifraction, large-field, treatment techniques. Both helium and heavy-ion beams have the ability to better localize the irradiation dose by making use of the extended Bragg peak and finite range of the particle beam. In addition, the heavy-ion beams have the potential for significantly lower oxygen enhancement ratio. This biological fact may be useful in overcoming the radioresistance of certain human cancers which thus far have a very low rate of local control by conventional radiotherapy techniques.

Thus with helium ions the potential advantage lies in better localization of dose with sparing of normal structures; the same advantage plus the radiobiologic advantage of overcoming hypoxic radioresistant tumor cells exists with the heavy-ion beams. These radiation beams, if successful in improving local control of tumors, will significantly affect the chance of curing an additional one-third of patients currently dying each year from cancer. Nationally, this could represent the theoretical potential of approximately 60,000 additional lives being saved yearly.

Previously, radiobiologic evaluation in the laboratory and with test animals has been done with the helium-ion beam in order to study its biological effectiveness. Sufficient data, as noted in Section V, page 88, of the proposal regarding the relative biological effectiveness and oxygen enhancement ratio are available to proceed immediately to large-field, fractionated treatment with the helium-ion beam. The Radiobiological Committee of the Bay Area Heavy-Ion Association has recommended the use of an RBE of 1.2 initially for helium-ion therapy. With respect to heavy ions, pretherapeutic research, supported in part by the National Cancer Institute, is needed to evaluate the necessary radiobiologic data prior to human therapy.

Subjects for this study will all be adult, volunteer cancer patients able to give an informed consent in writing to participation in the research project.

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An association of community and university radiotherapists in collaboration with Donner Laboratory and Lawrence Berkeley Laboratory personnel are in the process of establishing protocol studies for various human tumor sites. As these protocols are developed, they will be submitted to the Campus Committee for the Protection of Human Subjects for approval. After approval, they will be open for patient accrual. A controlled study will eventually be developed, including helium-ion radiotherapy, heavy-ion radiotherapy, and conventional radiotherapy at collaborating facilities, as controls.

Initially, the helium-ion beam will be utilized with a relative biological effectiveness of 1.2. In addition, the first three to six patients in many of the protocols will be treated at approximately 20% reduction in dose. If no immediate untoward effects are noted and following the approval of the principal investigator, the dose will be raised to the planned level.

The diagnostic techniques, beam positioning and delivery include the most up-to-date techniques available. A special computer-controlled patient exposure device has been built in the laboratory. Isodose contours will be established in phantoms with the aid of ionization chambers and TLD dosimeters. During treatment the beam is monitored via externally-placed ionization chambers. When heavy-ion treatment is administered, the beam delivery will be checked by measuring the location of residual autoradioactivity.

The risks and discomfort of radiotherapy are well established for conventional X-ray treatment techniques. It is felt that sufficient information is available regarding the radiobiological effectiveness of the helium-ion beam to estimate that the risks and side effects will be similar to or less than with conventional techniques.

The side effects, discomforts, and risks of irradiation of each anatomic site will be explained to each volunteer patient and included in the informed consent form, so that he or she is well aware of these risks.

Medical records will be kept at Lawrence Berkeley Laboratory on each study patient. These will remain confidential unless consent is given in writing by the patient that such information may be identified as to name, etc. Each volunteer will, however, be asked to agree that data regarding his case may be included in analysis of the research project, so that valid conclusions can be drawn.

RISK/BENEFIT RATIO: With the data already available concerning helium-ion radiotherapy, the likelihood of increased risk over conventional radiotherapeutic techniques is minimal. The benefits to be gained in terms of better localization of dose outweigh the risks. It would be expected that local control could be raised in the various tumor sites where it might be possible to increase the dose from the low-LET radiation equivalent of 1,000 rads in five to six weeks to 7,000 rads in seven to eight weeks. Where this is possible, improved local control should be expected.

Where such tumoricidal doses already may be given with conventional techniques, local control may not be significantly improved, but morbidity may be decreased by a sparing of normal tissues. This also would be of sizeable benefit to the patient.

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The potential for improved local control with these beams is excellent. In the past, whenever radiotherapists have been better able to localize dose because of improved methods of physically distributing the dose, an increase in local control and survival rates has occurred. There is no reason not to be optimistic that a similar improvement can be achieved with these particle beams. In addition, the heavy-ion beam offers an improved biological effectiveness.

Joseph R. Castro

 Joseph R. Castro, MD

James L. Born

 James L. Born, MD

Cornelius A. Tobias

 Cornelius A. Tobias, PhD

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PATIENT CONSENT FORM FOR PARTICIPATION
IN A STUDY TO EVALUATE EFFECTS OF HELIUM
AND HEAVY-ION RADIATION ON HUMAN CANCERS

DONNER LABORATORY, LAWRENCE BERKELEY LABORATORY

Name of Institution

UNIVERSITY OF CALIFORNIA, BERKELEY, CA 94720

Address of Institution

Purpose of the study

Your physician has determined that you may be an eligible patient for participation in a study sponsored by the National Cancer Institute to compare the effects of helium or heavy-ion radiation with the effects of conventional X rays in the treatment of human cancers. The study is being conducted using equipment at the Lawrence Berkeley Laboratory and the Donner Laboratory, University of California, Berkeley. Researchers believe helium and/or heavy-ion therapy may offer significant advantages over conventional therapy, although this must be established. At present, we do not know which form of therapy is better.

Helium-ion radiotherapy has been successfully used to treat pituitary tumors for many years. However, we intend to use helium-ion therapy in a different way from the past pituitary treatments. Tests of heavy-ion radiation are just beginning. Our goal will be to test these new forms of radiation against conventional techniques of radiotherapy to see which is better. This may involve randomly assigning you to one or the other forms of therapy. Thus, your voluntary participation may help others who contract some forms of cancer in the future.

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Procedures to be followed

If you choose to enter the study, you must agree to spend the required amount of time at either your referring physician's institution or at Lawrence Berkeley Laboratory for treatment. You must also agree to return to the Lawrence Berkeley Laboratory for the required followup examinations.

If assigned to helium or heavy-ion therapy, you will receive radiation treatments at Lawrence Berkeley Laboratory for a period of 5 - 30 days and will need to remain in the area for approximately 30 days after the treatments and so that physicians can assess the short-term radiation effects. Treatments will ordinarily be given daily.

Standard preparatory procedures may be involved, including taking diagnostic X-ray pictures and nuclear medicine isotope scans.

There will be a prealignment exercise without administering radiation to familiarize you with the process and to ascertain that radiation during treatment will be delivered to the appropriate regions of the body. Plastic and flexible devices may be used for positioning and immobilization.

The treatments will be administered in the manner demonstrated to you during the prealignment exercise. There will be no pain or sensation from the beam during treatment. You will be alone in the treatment room; however, the treatment personnel can view you at all times on closed-circuit TV, and two-way voice conversation is possible anytime via intercom equipment. A nurse is stationed immediately outside the treatment room and is available if needed.

You will be asked to participate in a variety of standard medical tests in the postirradiation period: these will measure the progress and efficacy of the treatment.

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While you are taking part in the study, your physician is still responsible for your treatment and can change your treatment or remove you from the study at any time if he believes it to be in your best interest. Your well-being is his primary concern. While you are taking part in the study at Lawrence Berkeley Laboratory, your treatment will be managed in close co-operation with your physician, although he may not be administering the treatment himself.

Potential benefits

The potential advantage of helium/heavy-ion therapy is that it may be more effective in treating patients than standard management. The study is designed to try to compare the effects of the helium/heavy ions as closely as possible with those of conventional X rays, and evaluate which is better.

Possible discomforts and risks

We do not have complete information on the risks you may encounter due to helium/heavy-ion radiation. Preliminary biology tests indicate the procedure will not be unduly harmful, and the doses that will be given to you are designed to minimize the possibility of excessive discomfort or risk. Both helium/heavy-ion radiation and conventional radiation could result in some or all of the following types of discomfort and risks, depending on the area of treatment: (See insert appropriate to tumor site to be treated)