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PRETHERAPEUTIC USE OF ACCELERATED HEAVY IONS:

PROJECTIONS FOR HUMAN RADIOTHERAPY

(currently supported by ERDA, pending award of NCI Grant #CA19138)

A. Progress to Date

A clinical radiotherapy group entitled the Bay Area Heavy-Ion Association has been formed to participate in the design and conduct of a co-operative trial of helium- and heavy-ion radiotherapy. This group consists of representatives from the radiotherapy sections of the three medical schools in Northern California, University of California at San Francisco, University of California at Davis and Stanford Medical School, as well as other radiotherapy facilities in the area. In addition to about twenty radiotherapist members, there are interested radiobiologists, physicists and other physicians in the group (see attached membership list).

This group has formulated physics, radiobiology, and protocol design committees to assist in preparations for clinical trial. Clinical protocols have been designed for the following tumors: carcinoma of the cervix uteri; carcinoma of the pancreas; carcinoma of the esophagus; malignant glioblastoma of the brain; carcinoma of the prostate; and for initial study, a miscellaneous group of advanced and/or recurrent tumors. Additional protocols are under design. It is planned that eventually approximately 20 tumor sites will be included in the clinical trial to allow as wide a participation as possible. The BAHIA group will also function to irradiate the control patients with conventional radiotherapy techniques. This group will seek assistance from the Radiation Therapy Oncology group and the Northern California Cancer Program in conducting the control clinical trial so as to assure statistical significance. Because of the existence of other high-LET clinical trials in the Northern California area, such as the Pion Radiotherapy Trial at Stanford Medical School, and the Neutron Radiotherapy Trial at the University of California at Davis, it is mandatory that the radiotherapists of this region draw together in order to assure the best possible utilization of the clinical patient resources in the region. By doing this and by spreading the patient referral over a large number of co-operating radiotherapists, we hope eventually to enter 400 patients per year in the clinical trial; 200 in the particle study group; and 200 in the control group per year. A request for support of the clinical portion of the study of heavy ions has been approved by the National Cancer Institute and is awaiting funding. In the interim, by a combination of support from ERDA; the National Cancer Institute (through the pretherapeutic study); and the volunteer efforts of a number of participating radiotherapists, physicists and biologists; it has been possible to begin the clinical irradiation pilot program utilizing the helium-ion beam available from the 184" Cyclotron. Initially, patients with malignant glioma of the brain, carcinoma of the pancreas, and other locally advanced and/or recurrent tumors will be irradiated. To date, four such patients have been treated. The knowledge gained from this pilot series will enable a smoother and more rapid increase in patient treatment once funds are available.

The overall plan is to begin the clinical irradiation program with the helium-ion beam from the 184" Cyclotron. It is expected that this phase of the clinical trial will be approximately 18 months underway before the BEVALAC is available for patient irradiation with heavy ions. Thus the techniques learned on the 184" Cyclotron will be immediately applicable to the BEVALAC heavy-ion human radiotherapy trial and will allow the initiation of the heavy-ion trial with the least amount of disruption. Currently it is expected that heavy-ion human irradiation would begin sometime in FY 1977.

To commence large-field irradiation of human cancers with the helium-ion beam from the 184" Cyclotron, it was necessary to convert from the small-field irradiation techniques previously utilized for pituitary irradiation to a larger beam. This has been accomplished through ERDA and NCI pretherapeutic support, resulting in a large irradiation field of 30-cm diameter, flatness, and homogeneity of ±2% over 92% of the field; an output of approximately 150 rads per minute at the treatment distance; as well as modification of ISAH to permit treatment of any portion of the patient, either in the lying, sitting, or standing position. A collimating system has been designed together with a Cerrobend shaping system to permit adoption of any shape of radiation field desired. Measurements have been made of the neutron background, which indicate a very small level of neutron contamination, thought to be within safe limits for patient treatment. Techniques for imaging of the treatment beam have also been developed.

The clinical protocols have been submitted to the Donner Laboratory Human Use Committee and the University of California, Berkeley Campus Committee for the Protection of Human Subjects. Approval of these two bodies is required before any clinical treatment protocol may be initiated.

B. Future Plans

As the pretherapeutic study of accelerated heavy ions proceeds, clinical irradiation techniques will be further developed utilizing the helium-ion beam from the 184" Cyclotron. It is planned that clinical protocols will be developed both for helium- and heavy-ion irradiation and compared to conventional control irradiation. The helium-ion study may therefore be continued for three to five years. When appropriate parameters have been evaluated in the pretherapeutic use of accelerated heavy ions, a pilot study of human radiotherapy with the appropriate heavy ions (to be identified) will be started. It is hoped that this study may begin in FY 1977. Initially patients with metastatic lesions causing skin or subcutaneous nodules will be irradiated in order to determine skin tolerance, tumor response, and some indication of acute and subacute radiation effects from heavy ions. In addition a clinical estimate of RBE may be obtained to compare with RBE studies done in the pretherapeutic investigation. Subsequently it is planned to proceed with a gradual development of a full-scale clinical trial of heavy ions, which is expected to require a minimum of five years in order to attain sufficient patients for statistical significance.

In order to accomplish this clinical trial, it will be necessary to refine treatment techniques with particles. This will require the development of techniques for assessment and correction of tissue inhomogeneities as well as development of computer techniques for radiation dosimetry. A clinical biomedical facility will be developed in a building adjacent to the BEVALAC in order to evaluate patients prior to treatment; to prepare patient contours and obtain tissue density information for treatment; and to follow patients post-treatment. A statistical center will be required in order to attain patients, randomize them, and assure proper control of the study. Techniques must also be developed to assure dosimetric consistency for study and control patients.

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FACILITIES AVAILABLE

Staff and Facilities of the Donner Laboratory/Lawrence Berkeley Laboratory

Donner Laboratory is the Biomedical Division of the Lawrence Berkeley Laboratory. The Lawrence Berkeley Laboratory is a National Laboratory operated under ERDA Contract W 7095 Eng. 48 with the Regents of the University of California. Donner Laboratory's interdisciplinary staff is engaged in a broad spectrum of biomedical studies. This spectrum ranges from biophysics and radiobiological studies to work on lipoproteins, metabolism and to hemopoiesis and nuclear medicine. The medical program covers the development of radionuclides and their use in clinical, diagnostic and imaging studies, as well as clinical studies with accelerated particles.

The Director of Donner Laboratory is Edward L. Alpen. The research of Donner Laboratory is divided into four groups: Environmental Physiology, headed by J. Schooley; Structural Biophysics, headed by R. Glaeser; Research Medicine, headed by T. Budinger; and Radiation Biophysics, headed by C. A. Tobias. Radiation Biophysics groups include the therapy program under J. Castro.

The staff and program of Donner Laboratory are housed in the following facilities:

a. The Donner Laboratory is a four-story building of 45,000 gross square feet, 29,700 net square feet; located on the Berkeley Campus and is a fully-equipped laboratory building with auditorium, conference rooms, library, the Donner clinic, a fully-equipped clinical laboratory with examining rooms with patient waiting rooms, machine shop, electronics shop, drafting room, electron and scanning electron microscopy laboratories with three instruments, a centrifuge laboratory, laboratories devoted to physiological, biochemical, medical, tissue culture and biophysical research. In addition there is the scanning facility with two Anger scintillation cameras, a positron camera, whole-body scanner, and tomoscanner developed by H. O. Anger, and computerized readout for the scanners and Anger positron cameras.

b. Donner Pavilion is a small hospital unit located in Cowell Memorial Hospital at the University of California containing a maximum of fifteen beds and associated laboratory space consisting of 3400 gross square feet and 2400 net square feet. It provides hospitalization beds and associated laboratory space for patients, both normal and in various states of disease, who, because either of illness or the complexity of studies desired, cannot be studied on an ambulatory basis. In addition to its own clinical laboratory, the metabolic ward provides space for those basic investigations which are closely allied to the clinical program.

c. Animal Radiobiological Laboratory of the Donner Laboratory, Building 74, Lawrence Berkeley Laboratory, is a 41,000 gross square feet, 28,000 net square feet, building containing facilities for housing rats, mice, monkeys, dogs, cats, rabbits, and pigs; quarantine facilities, washroom, sterilizers and rodent rooms are arranged with a clean-to-dirty concept of flow. In addition, there is a 1500-Curie cobalt source, Cesium source and a 250 kV X-ray machine.

There are specialized facilities: a fully-equipped surgery and a second surgery for handling animals to whom radioactive isotopes have been administered. There is general counting equipment in the building as well as liquid scintillation counters, low-background counters, and laboratory space for the

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associated investigations.

d. Space for Radiological Physics and Radiobiology. 7400 net square feet are allocated to Donner Laboratory use in Buildings 10 and 29, which are within walking distance of the Lawrence Berkeley Laboratory's five heavy-ion accelerators (the Hilac and Bevatron/Bevalac facility) as well as the 184" and 88" cyclotrons.

e. Lawrence Berkeley Laboratory is currently remodeling the BEVALAC Medical Building (Building 55) (12,573 gross square feet; 2985 net square feet, adjacent to the BEVALAC), in order to provide a suitable medical outpatient facility for patients to have pretherapeutic evaluation, helium/heavy-ion radiotherapy and follow-up. Building 55 has a separate patient entrance and patient waiting room with an attractive view of the San Francisco Bay; a Medical Conference Room; 4 physicians' offices and 4 patient examining rooms with a large room for a patient scanner and diagnostic X-ray unit (therapy simulator). This building will also provide space for pretherapeutic physics work which will be closely tied to Dr. Castro's therapy program to be carried out under a separate NCI proposal.

f. The BEVALAC facility consists of two accelerators (HILAC and Bevatron) joined together by a transfer line. The HILAC, heavy-ion linear accelerator, accelerates heavy ions up to 8.5 MeV*/nucleon. These are transferred by magnetic steering to the Bevatron, a proton synchrotron modified to accelerate heavy ions. The Bevatron uses the HILAC as heavy-ion injector and continues the acceleration process up to as high as 2.5 GeV**/nucleon. Beams with energies of the order of 200-300 MeV/nucleon will be adequate for our purposes. Fluxes of 10^{10} ions/pulse or 10^{11} ions/min are expected (12). This will yield uniform dose rates over 1 cm^2 in the 500-1000 rads/min range or above. The LET's expected in the "spread-out" Bragg peaks will vary over a wide range, but will average around 100 keV/µm in a ^{20}Ne beam.

g. The 184" Cyclotron presently accelerates ^4He ions to 225 MeV/nucleon. "Spread-out" Bragg curves are routinely produced here. Therefore, it will be possible to conduct comparison studies with ^4He ions. We will use this cyclotron instead of the BEVALAC for these studies because of the significantly lower cost of beam time for this accelerator. Also, the immediate availability of this beam allows us to proceed directly to these studies as soon as our colony is producing adequate animals for the experiments.

h. Computing Facilities. The Lawrence Berkeley Laboratory has a central Math and Computing facility with a staff of 100 mathematicians, statisticians, programmers and operators for the CDC-7600 and CDC-6600 computers. In addition, a PDP 11/45 has been recently purchased for biomedical studies at the BEVALAC and will be available for use by our group without charge.

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*MeV = million electron volts

**GeV = billion electron volts

PRINCIPAL INVESTIGATOR ASSURANCE

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

January 30, 1976
Date

Principal Investigator

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