BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

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DATE: June 10, 1991

TO: N. P. Samios

FROM: D. D. Joel and R. B. Sclow

SUBJECT: RESPONSE TO THE REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1991.

I. General Overview

We thank the members of the Visiting Committee for the considerable time and effort put forth in critically evaluating the Department's research programs and for preparing a clear and thorough report of their findings. We are particularly pleased with the generally positive tone of the report and that the Committee was impressed with the high-quality of science and the overall progress made in the major research programs during the past two years. In spite of this progress, we are in agreement with the Committee for the need to further strengthen some ongoing programs and to develop new and innovative areas of research in conjunction with the coming on-line of the Inhalation Toxicology Facility (ITF) the Radiation Therapy Facility (RTF) and the *In Vivo* Neutron Activation and Analysis (IVNAA) facility for total body composition. Further, the expected construction of a heavy ion radiation facility at the AGS Booster will lead to an expansion of the radiobiological sciences in the Department.

The reviewers correctly point out that the operation of the RTF will not only enhance the collaborative research efforts between SUNY and BNL but will also bring to the Medical Department expertise in the treatment planning, delivery and quality control of radiotherapy. These capabilities will be essential for the implementation of other experimental radiotherapy programs, particularly boron neutron capture therapy.

Because of limitations in the review process the Committee made two suggestions; (1) a brief progress report covering a further year be prepared by the Department for Committee members and (2) site visits by Committee members be appropriately arranged to review different projects. We are supportive of these suggestions.

II. Critique of Specific Research Programs

Radiation Biology

We are pleased with the Committee's view that the Radiation Biology Program, although small, is important to the Medical Department. They expressed concern, however, as to how the Department intends to eventually replace the expertise of Drs. Cronkite and Bond as they approach the end of their illustrious careers. Proposals have been submitted to DOE to study, in collaboration with the Biology Department, the molecular biological events associated with the development of radiation induced leukemia in mice using the consistent change in chromosome 2 as a focal point. This

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type of study is directly responsive to DOE's recent initiative to utilize modern molecular technology in radiation effects studies. Support of this proposal as well as the establishment of a heavy ion radiation facility would provide the means to recruit young radiobiologists, however, to replace the scientific caliber of Drs. Cronkite and Bond clearly will be difficult.

Body Composition Program

Although facilities development will be a continuing process, it is anticipated that the project will actually begin patient studies about the middle of July, 1991. This project is funded primarily by NIH, however, we will seek additional support from DOE for upgrading capital equipment.

Clinical SPECT Program

We are pleased with reviewers assessment that this program has made good progress with well-chosen, scientifically sound projects. There was agreement between the Committee and BNL scientists that the sensitivity and specificity of results would be improved by the acquisition of a three headed camera. We will pursue this possibility.

Clinical PET Program

We agree with the Committee's view that this is "a strong program which is getting even better and which deserves strong continuing support". Since the site visit in April, an additional scientist, specializing in computer data processing and imaging, has been recruited and will join the program before the beginning of FY-1992.

Multiple Energy Computed Tomography (MECT) Program

The reviewers are correct in stating that a MECT apparatus is sophisticated and that the MECT concept is an original one that has not been tried previously. That the MECT images may not uncover "new basic information concerning cerebral structure or function" is reasonable, however, the likelihood is high that such instrumentation will be useful in individual patients with acute, vaguely diagnosed or undiagnosed neurological problems. Because of the increased (~ 10-fold) detectability of iodine (and even larger increases for higher-Z contrast elements), many more slices of the brain can be taken at more frequent intervals within a given limit of radiation safety. This represents a significant advantage over existing CT techniques. The likelihood of obtaining comparable information with much less radiation risk to the patient could restore some of the competitiveness of CT vis-a-vis MRI. Insofar as expense is concerned, the criticism is justified on the premise that an NSLS-like installation is required. Future developments in electrical engineering may, however, make the economical construction of narrow energy band x-ray sources possible. With such an apparatus, it would seem technically no more difficult to image the entire brain than it would be using existing CT and MRI instruments, which image the brain, as indicated clinically, slice by slice.

In short we feel the advantages of MECT over existing CT are not only the elimination of the beam hardening, but also increased sensitivity and increased precision of quantitative elemental measurement through use of the two energy-

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dependent methods of K-edge subtraction and dual-photon absorptiometry (DPA). In particular, K-edge subtraction is not possible with wide energy bands, and DPA with a monochrmatic beam is many times more sensitive to elemental composition than DPA with wide energy bands. As a result, lesions of about ten times less contrast than those detectable by conventional CT can be detected with the MECT system. The development of MECT at BNL will undoubtedly contribute to future advances in brain imaging by CT.

Radionuclide and Radiopharmaceutical Program

Although the Committee was enthusiastic about the high quality and productivity of the science in this program, some concerns were expressed relative to laboratory facilities and the availability of beam time for isotope production at both the High Flux Beam Reactor and the LINAC. We are currently putting together a proposal to DOE with the following objectives: (1) upgrade of the LINAC which would increase the number of operating weeks from 13-20 per year to 35-40 per year with an increase in average current; (2) upgrade of the isotope production facilities (BLIP) including new target and target cooling systems; and (3) upgrade of the hot laboratory with an additional 2 hot cells, improve hot cell ventilation and upgrade of the waste disposal system. We will pursue all available avenues to maintain adequate isotope production and the high-quality research in this program.

The High Flux Beam Reactor has been restarted and will probably be running at 30 megawatts in 6 to 8 weeks providing a source of neutrons for further radionuclide development.

Boron Neutron Capture Therapy (BNCT)

The reviewers were generally supportive of the BNCT program, however, several valid concerns were expressed.

There were little data presented to Committee on the physical characterizations of the epithermal beam at the Brookhaven Medical Research Reactor (BMRR) and treatment planning. This was in part due to the untimely death of Dr. Ralph G. Fairchild, the project leader and a recognized authority in epithermal neutron beam develop and characterization. Nevertheless these studies are not at a standstill. Currently, V. Benary, a visiting nuclear engineer, is conducting extensive measurements of the mixed field radiation doses in air and in phantoms as well as assessing the effects of shielding and collimator configuration on dosimetry. G. Shani, also a nuclear engineer, is developing a helium-3, solid state detector system for measuring the epithermal neutron spectrum at the port face. In addition, S. Fiarman, a nuclear physicist, will join the BNCT program for the summer to further develop MCNP modeling codes to assess collimator effects on dosimetry. He has previously worked on these problems and will further collaborate with Drs. Reinstein and Ramsey (SUNY) on the development of 3 dimensional treatment planning codes with MCNP.

Dr. Robert M. Brugger, a highly respected nuclear physicist, has accepted an appointment in the Medical Department and will lead the joint BNCT project with Ohio State and SUNY as well as coordinate the overall BNCT program at BNL. Therefore, we are confident that the justified concerns of the Committee as regards the physical aspects of the epithermal beam, treatment planning, patient monitoring and quality

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assurance, will be fully resolved.

The Committee also expressed reservations about the appropriateness of the rat transplantable brain tumor model employed to test the efficacy of BNCT since it may not be representative or predictive of human gliomas. Unfortunately this is true of nearly all animal models. The transplantable gliomasarcoma used at BNL is uniformly lethal within a narrow range of survival (22 ± 4 days) and is, therefore, useful to test various principles of BNCT and to compare effectiveness of different boron transport agents.

The Committee questioned the use of 'radiation resistant' when describing this tumor since we have observed tumor control in 30 percent of the rats treated with 30 Gy x-radiation. Since doses in excess of 30 Gy are not tolerated, we have been unable to achieve 50% tumor control with single doses of x-rays. In contrast, we have been able to obtain greater than 50% tumor control with BNCT using two different boron transport agent without causing observable damage to normal CNS tissues. 'Radiation-resistant' is clearly a relative term and probably should not be used. This tumor model is, however, used extensively in other laboratories to evaluate radiation therapy, with or without combined chemotherapy, and to our knowledge a 50% tumor control level has never been achieved. Furthermore, studies of the in vitro radio-sensitivity of cultured glioma cells removed at surgery to estimate the patient's ultimate response to standard radiation therapy concluded that a fractional cell survival of 0.6-0.7 after exposure to 200 rads x-radiation was indicative of radio-resistance. Similar in vitro exposure of rat gliosarcoma cells to 200 rads yields a fractional cell survival of ~ 0.9.

The initial growth phase of the rat gliosarcoma is noninvasive and therefore not reflective of malignant brain tumors in humans. We have observed, however, that recurrent gliosarcomas following 22.5 or 30 Gy of x-radiation are highly invasive with isolated islets of tumor cells reminiscent of human malignant gliomas. We have recently initiated distribution studies and BNCT efficacy trials using this recurrent tumor model. Further, we are submitting a proposal (D. N. Slatkin, Principal Investigator) to use a transplantable dog glioma to study the distribution, toxicity and efficacy of BNCT using the two boron transport agents shown to be effective in the rat model. If funded, this would be the first well-controlled large animal study utilizing the optimized epithermal beam at the BMRR.

Although Dr. Slatkin's presentation focused on a review of clinical findings from the early BNCT trials, the conclusions he derived from those patients were new. Using data from animals injected with the boron compounds employed in the early clinical trials, he derived diffusion constants which were then used to estimate boron concentrations in the critical CNS tissues of those patients. From these estimates, coupled with known neutron fluences and CNS pathology, he concluded that the basal ganglia, not the cerebral cortex, were the most radiosensitive tissues and that a dose of about 10 Gy-Eq was the maximum dose that could be tolerated. This is important information for future clinical trials and has been recently published as a refereed article in the jounral Brain.

Contrary to what the Committee may have perceived, Dr. Slatkin, perhaps more than any other member of the group, has a clear understanding of both the physical and biological problems associated with BNCT, and is keenly aware of the information that will be required prior to resumption of clinical trials. Dr. Slatkin's

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administrative obligations will be less when Dr. Brugger arrives and he will be able to devote nearly full-time to the BNCT program.

We share the feeling of the Committee that methods for determining the microdistribution of ^{10}B are essential in order to predict efficacy of any potentially useful compound and to get a clearer understanding of the radiobiology associated with BNCT. We are currently developing an immunofluorescent technique using specific antibodies raised in rabbits against the sulfhydryl boranes (monomer and dimer) and boronophenylalanine. Synthesis of tritiated compounds with subsequent detection by autoradiography has been proposed. However, we do not currently have sufficient scientific personnel to perform this work. Determining the microdistribution of boron compounds will continue to be a major goal of the BNCT program. This will be particularly important as we proceed with Phase I compound distribution studies in patients.

The Committee also had some concerns with use of BPA-BNCT in the treatment of choroidal melanoma. Although the initial studies were done with tumors grafted into the anterior chamber of the eye, the current experiments are being done in rabbits bearing melanoma grafted in the posterior choroid. We feel that BNCT of choroidal melanoma offers the potential for tumor control with sight preservation. With the epithermal neutron beam, the tumor will receive nearly twice the thermal neutron fluence than the lids, cornea or lens. With BPA, the selective accumulation of ^{10}B in the tumor compared to the lids, glands, and cornea (3:1 tumor:normal tissue ^{10}B concentration ratio), combined with the thermal neutron profile will result in therapeutic gains (tumor-to-normal-tissue dose ratios) that range from 3.5:1 for critical tissues (lens) at a depth of 0.5 cm to as high as 8:1 - 10:1 for the cornea. These tumor to normal tissue dose ratios for BNCT should prove more effective than either plaques or particle beams with respect to achieving tumor control with preservation of sight in medium, and especially large, choroidal melanomas. With particle beams the normal tissue complication rate at 5 years is 50-80 percent.

In summary, we agree with the Committee that several issues relative to BNCT need to be addressed. We will, as advised, proceed cautiously as BNCT moves toward the resumption of clinical trials. In this regard, an external advisory committee, which will include experts in clinical radiation oncology, will be named to provide guidance and recommendations. The appointment of R. M. Brugger, a nuclear physicist, as coordinator will clearly strengthen the BNCT program. Additional expertise in the field of tumor biology will be sought as recommended by the reviewers.

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