

## BROOKHAVEN NATIONAL LABORATORY

718310

## M E M O R A N D U M

DATE: June 8, 1989

TO: N. P. Samios

FROM: A. D. Chanana and R. B. Setlow *R.B.*

SUBJECT: REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1989

I. Overview

We are pleased that the Committee was impressed with changes in research emphasis, ongoing research and the improved morale of the professional staff. We share the Committee's concern that, despite significant progress during the past 2 years, much more still needs to be done. We don't intend to relax our efforts. We are in agreement with the Committee's findings concerning personnel, budgets and programs which need either to be strengthened or revitalized. We will address these issues in response to the critique of the specific research programs.

The Committee recommends the installation of a dosimetry simulator, computed tomography unit and a versatile computerized treatment planning facility. We have been reviewing these matters with Dr. Meek and his colleagues at Stony Brook and the construction plans for the radiation therapy facility have been modified to provide for a simulator room as well as for the treatment planning facility. We are reviewing the various 'funding' options in order to obtain these additions to the radiation therapy facility.

The Committee will be pleased to know that you have approved our request to reactivate the Inhalation Toxicology Facility in collaboration with NSI-Technology Services, Inc. We intend to have the first collaborative project in place before the end of this calendar year. Reactivation of this facility will certainly help to maintain our excellent research animal facility. The long-term solution for the research animal facility and the ambulatory clinical research center is, however, to obtain core support for these facilities from DOE. The current system imposes too heavy a burden on programmatic budgets and as one of the bases of the issue to be brought up at the Annual Institutional Plan Meeting in July 1989.

Capital equipment funds remain grossly inadequate despite some recent increase. We shall continue to pursue this matter with DOE as a very high priority item.

We agree with the Committee's recommendation that, in addition to pursuing high priority funding issues with DOE, we should continue to explore other options.

REPOSITORY *Associated Univ Inc (Wash D.C.)*  
 BOARD OF TRUSTEES & ITS EXECUTIVE  
 COLLECTION *Committee's Mtg Minutes*

BOX NO. *locked filing cabinets in INTERNAL*  
*Aud. office*

FOLDER \_\_\_\_\_

1125027

**REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1989****II. Critique of Specific Research Programs****Medical Applications of Nuclear Technology**

This program, under Dr. Weber's leadership, was initiated 18 months ago and it took 6 months to provide Dr. Weber with minimum equipment and personnel. We are, therefore, pleased to note that the Committee was impressed by the quality of science. This program remains deficient in key personnel (technician, software specialist and nuclear medicine physician). We have recently discussed this matter with DOE staff and have proposed an approach which, if accepted, will not only strengthen collaborative PET research with the Chemistry Department but will also provide additional technical support for Dr. Weber.

We are fully cognizant of the need for more 'clinical' participation and we are pleased to inform you that in addition to Dr. Atkins and Dr. Oster from Stony Brook, Dr. Shreeve and Dr. Bateman from Veterans Administration Hospital have started to spend regularly scheduled time at BNL.

We object to the following statement "many of the commendable research projects underway could be done in many nuclear medicine laboratories". We feel that this statement fails to do justice to Dr. Weber and his colleagues who are continuing to replace routine work (almost 100% just 2 years ago) with innovative research programs as attested to by the Committee's report.

**Total Body Counting Systems**

We fully share the Committee's concern about this unique national resource. We have managed to keep the project intact without any DOE support and our plans will keep it intact at least to September 30, 1990. A program grant in collaboration with Winthrop University, Columbia University, Cornell University and Tufts University was submitted on June 1, 1989 to NIH. Funding of this proposal will assure long-term survival, major upgrades and increased utilization of this unique resource.

**Radionuclide and Radiopharmaceutical Development**

We are particularly pleased to see that the Committee is impressed by the quality of research of this group. The 3 younger scientists who are doing good work were recruited during the past 2 years. We share the Committee's concerns about staffing and BLIP operations. With regard to staffing, there are two full time research technicians and not one as stated by the Committee. We are now ready to hire two additional post-docs [Synthetic Chemistry (1) Radio- and labeling Chemistry (1)].

As far as the BLIP operations are concerned, it is very doubtful that DOE will provide additional BLIP operating funds for Radiopharmaceutical and Radionuclide programs even though it is clear that we need, at the minimum, BLIP operating time of 35 weeks/year. The current BLIP operating time of 18-20 weeks/year is certainly inadequate. Following the recommendations of the BLIP Users Committee and discussions with DOE Staff, we increased the prices of 'routine' radionuclides this year. We were informed by DOE Staff that the only way to provide for more research technicians would be to generate more income from sales. This first year has shown very uneven consequences of the sudden price increases and we expect that we will need to experience one more cycle before we can review the long-term impact of this policy. Of the three 'production' technicians, we have supported one with additional sales income generated this year.

## REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1989

The Report indicates that we have had difficulties with Au-199 incorporation into gold clusters. It was our inability to pursue this work. As a result of new funding decisions by DOE, both the ligand synthesis and gold cluster projects will now be expanded.

We were surprised to see the comment "*There is also need for an animal facility that can maintain athymic mice*". We do have such a facility and it is in regular use.

Head and Neck Computed Tomography (CT)

This project has now been approved for funding by DOE and we are searching for a young physicist to assist Dr. Dilmanian. We fully share the Committee's enthusiasm for this imaginative project.

Angiography

We agree that it is important to evaluate the degree of diagnostic advantage possible with monochromatic x-rays. A collaborative research proposal (BNL Medical and NSLS, North Shore University Hospital and Stanford University) was submitted to NIH on June 1, 1989.

Boron Neutron Capture Therapy

We are very pleased to note that the Committee was so impressed by our progress in the BNCT program that its attitude changed from skepticism to enthusiasm.

We are perturbed to see the following comments "*The long-term role of these investigators (Slatkin and Joel) in the BNCT project remains unclear, however, as both have other primary research interests and significant time commitments in other areas. For example, Dr. Chanana's presentations suggested that reactivation of the inhalation exposure facility might compete for the interests and time of both investigators*". At this time, the only active research interest of Drs. Joel and Slatkin is directly related to the BNCT program.

Their proposed role in the reactivated inhalation toxicology facility will be to assist in developing good research proposals, which if funded, will enable us to hire young scientists. We do not expect either Slatkin or Joel to devote more than 10-15 percent effort on these projects.

Dosimetry and development of epithermal neutron beam

The last two years have been devoted to the design, installation and testing of the present "optimized" epithermal neutron beam, in which reactor produced contaminating  $\gamma$  and fast neutrons have been reduced to negligible proportions. We fully share the Committee's concerns as they relate to the dosimetry. The epithermal beam was installed just a few days prior to the Committee's visit (April 1989). There was not much data to present at that time. Considerable progress has been made during the past 2 months and our approach is compatible with the Committee's recommendations. As pointed out by the visiting committee, isodose charts must now be constructed for the various mixed field components, for the various geometries which may be used in therapy. This is best done by Monte-Carlo calculations, by a computer program, MCNP. This part of the BNL NCT program is being done in collaboration with associates at SUNY-Stony Brook. We anticipate that the ability to formulate isodose charts for the mixed field components will be available in ~2 months. A one dimensional code (ANISIN) is now being used for current beam design problems, and the capability with MCNP will also be applied to

## REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1989

these problems. Conventional dosimetric techniques will be used to measure in phantom contributions from mixed field components, as has been done already in air, to check MCNP calculations.

RBE measurements (both in vitro and in vivo) have already been carried out for the  $^{10}\text{B}(n,\alpha)^7\text{Li}$  and  $^{14}\text{N}(n,p)^{14}\text{C}$  reactions, and for the fast neutron component of the present epithermal neutron beam (in vitro measurements). The effects of repair in the mixed radiation field are now being evaluated with V-79 cells using split-dose techniques, in a head phantom. Radiobiological (tolerance) studies will be carried out in pig-skin, and in the CNS of large animals. However, definitive experiments will depend upon the selection of the tumor-compound system and mode of administration, for clinical trials of NCT. The same argument obtains for the final selection of total irradiation dose, beam geometry and patient support devices, and fractionation schedule.

Evaluation of boron compounds for BNCT of malignant gliomas.

We welcome the Committee's opinion that Phase I permission for candidate BNCT compounds is needed, and we are pleased that our studies of the sulfhydryl borane monomer,  $\text{B}_{12}\text{H}_{11}\text{SH}$ , in two glioma-bearing patients are viewed as pointing the way to such work. In our terminally-ill patient, monomer-derived boron was concentrated in all microscopically discernible zones of glioma tumor tissue. In our neurosurgical patient monomer-derived boron was concentrated in the tumor and, more markedly, in peritumor edematous brain parenchyma. Isolated glioma cells in "peritumor" edematous brain parenchyma are thought to be the main source of locally recurrent gliomas after radiation therapy. Perhaps, unlike the Committee, we are being unduly optimistic in being encouraged by these distributions. Nevertheless we are working, in parallel with others in this field, toward FDA approval of a comparative phase I study of this monomer and its dimer,  $\text{B}_{24}\text{H}_{22}\text{S}_2$  in glioma patients before and during neurosurgical biopsy. However, until in vitro and in vivo studies with boronated compounds other than monomer, dimer and p-boronophenylalanine reach a more advanced stage than they have reached at present, we consider that only the former three boronated compounds are suitable for an FDA-approved Phase I study in humans in the immediate future. Indeed, the European Communities BNCT group, also plans to sponsor Phase I studies in 1990-91 using the same compounds.

BNCT of experimental rat gliomas

We appreciate the suggestions of the Committee that these studies would be strengthened by dose escalation experiments including a photon therapy group. Although it was not stated, we had initiated photon radiation at the time of the Committee's visit. One group of 10 rats bearing cerebral gliomas and exposed to 1500 rad in 4 minutes had a median survival of 14 days post-treatment. A second group of tumor-bearing rats has been given 2250 rad. BNCT has been escalated to 7.5 megawatt-minutes. This study will be repeated before starting a group of animals at 10 megawatt-minutes. We will include selected doses of BCNU for comparison.

Pre-clinical studies with p-boronophenylalanine as a melanoma seeking agent for BNCT.

We share the Committee's enthusiasm for this project. The Committee will be pleased to know that Dr. Coderre has received DOE funding for this project.

## REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1989

Summary and recommendations

As discussed above, we concur with these recommendations, are encouraged by the enthusiastic support of the Committee and plan to incorporate the constructive suggestions in our protocols.

Protons and Heavy Ions at BNL

We fully share the Committee view that BNL is in a unique position to carry on the U.S. effort in heavy particle as well as proton research. In response to the Committee's critique of our report to you concerning the possible biomedical application of heavy ions and protons, we would like to emphasize that the report was modified in order to accommodate a potential metropolitan medical center partner and did not entirely reflect the potential for the optimum approach to therapy and research. Our earlier discussions with regional medical centers had to be suspended due to sudden and severe budgetary constraints experienced by health care institutions.

We have, however, continued to explore these issues with NASA and have just submitted a proposal to NASA for a feasibility study. Phase 1 of this study, to be completed in FY-89, will establish the general requirements and parameters of a Radiation Health Research Facility at the AGS Booster. It will also establish support scenarios and infrastructure requirements for several modes of accelerator operation, including a primary dedicated mode, and a secondary mode in the context of other BNL research programs. Phase 2 of the study, to be completed in FY-90, will provide preliminary designs of a dedicated ion beam line and associated conventional facilities (tunnels, buildings, etc.), based on the parameters developed in Phase 1. We have been informed that the funds for FY 1989 (50K) have been authorized and that the FY 1990 funding (100K) is highly likely.

Health Effects Research

We share the Committee view that Drs. Bond and Cronkie are conducting important and exciting research and that their programs remain important assets to the Department. Like the Committee, we hope that DOE will continue to support Dr. Bond and will resume support for Dr. Cronkite.

The Committee's concerns as regards the leukemogenesis studies are noted and we are happy to inform you that a young scientist needed for this project has accepted our offer to join BNL effective September 1, 1989. We also agree that another young scientist is needed for Dr. Bond's studies, but RARAF is in financial difficulties and can't provide this individual.

We share the Committee's enthusiasm concerning the potential of the hemopoiesis studies of Dr. Cronkite designed to generate important and fundamental observations. Unfortunately, this project, initiated with support from the BNL Exploratory Research Program, will run out of funds in the very near future and DOE has terminated all support for Dr. Cronkite.

Molecular Cytogenetics

We fully share the Committee's recommendation that DOE should provide additional funds for a post-doc. We have continuously forwarded requests for additional funding to DOE but without any success thus far.

1125031

## REPORT OF THE MEDICAL DEPARTMENT VISITING COMMITTEE, 1989

Animal Facilities

As discussed above, the proposed reactivation of the inhalation toxicology facility will provide some help for the animal facility but 'core' support for this facility and the Clinical Research Center, is the only long-term solution.

Summary of the Major Current Problems and Most Pressing Needs of the Medical Department.

As mentioned above, we fully share the concerns of the Committee and shall continue to explore all possible avenues to achieve our goals.

In addition to the specific comments, as detailed above, it is extremely important to state that whereas the major focus of research in the Medical Department is to be the Medical Applications of Nuclear Technology and Experimental Radiotherapy, it is our considered opinion that for such an endeavor to thrive on a long-term basis, these programs must be underpinned by excellent programs in related basic sciences such as Radiation Biology, Molecular Hematology, Tumor Cell Biology and Immunology. We will continue to emphasize this viewpoint to the OHER Staff.

ADC/RBS:mas

1125032