BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM 718315

DATE: September 30, 1993

TO: N.P. Samios

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

SUBJECT: **Response to the report of The Medical Department Visiting Committee, 1993**

INTRODUCTORY OVERVIEW

We would like to express our gratitude to the members of the visiting Committee for the considerable time and effort they put forth in critically evaluating the Medical Department's research programs. The Committee was requested by us to be rigorous in its review, and the well written, thorough report that was submitted clearly reflects that request. We are pleased that the reviewers were, in general, impressed with the high-quality of science and the overall progress made in the past two years. Nevertheless, we are especially appreciative of the criticisms and the excellent suggestions for strengthening ongoing research programs.

We agree with the Committee that there is a very real potential for establishing a comprehensive, advanced radiation therapy center at BNL, which would include proton (and possibly heavy-ion) therapy, neutron capture therapy, microplanar radiation therapy, photon activation therapy, and the conventional accelerator-based photon and electron therapies already in operation. This totally unique experimental radiation therapy complex would utilize existing major facilities at BNL, including the LINAC, the NSLS, and the Medical Research Reactor, however, heavy-ion therapy will require construction of the proposed Booster Application Facility. Implementation of these therapeutic modalities will obviously require guidance by an Advisory Committee to oversee planning of clinical trials, active participation by research-oriented radiation oncologists, and a close working relationship with SUNY (Stony Brook) and other major medical centers in the Long Island/Metropolitan area.

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DETAILED PROGRAM REPORTS

BODY COMPOSITION STUDIES USING IN VIVO NEUTRON ACTIVATION ANALYSIS

Within the multi-institutional NIH-sponsored program project, the research efforts of BNL scientists focus primarily on technical developments of the three analytical systems to assure precision and accuracy of elemental measurements in humans. Although refinements in these systems will continue, the program will now concentrate on the accumulation of patient data for the four clinical studies in progress. Results of these studies will be reported at the next Visiting Committee Meeting in 1995.

We agree with the reviewers that the long-term value of this unique facility will depend on its application to a better understanding of the pathophysiology of human disease. Although four clinical studies are ongoing, three of these are located in distant institutions causing a significant problem in patient transport. To most effectively utilize the facilities, relevant clinical projects need to be developed locally. We have recently established collaborations with the Department of Surgery, SUNY (Stony Brook) to study patients on chronic dialysis and patients recovering from major surgery who are known to suffer from protein malnutrition and significant changes in muscle mass/metabolism. In addition, Dr. A. Vaswani (Winthrop University Hospital), an endocrinologist who has studied osteoporosis using neutron activation for several years, will be given a part-time appointment in the Medical Department in order to develop a comprehensive regional clinical program.

The whole-body counter is a state-of-the-art system that could also be advantageously used to compliment the nuclear medicine program both for estimating internal radiation doses from systemically administered radionuclides and for tracer kinetic analysis. Data can be obtained with doses of radioisotope that are orders of magnitude below those required for PET or SPECT imaging. These studies will be initiated under the direction of Dr. L. Feinendegen who has been a consultant for this project and whom the Laboratory hopes to recruit full time.

SUNY/BROOKHAVEN RADIATION THERAPY FACILITY (RTF)

The RTF was established primarily to increase collaboration between the Medical School, SUNY and the Medical Department, BNL and to provide patient material for clinical trials. In addition to the clinical research projects mentioned in the Committee report, a pilot study evaluating functional changes of normal brain tissue in patients undergoing radiation therapy for brain tumors using PET has been initiated. Also, cell culture and animal experiments are being done at the RTF in support of the photon activation and neutron capture therapy (BNCT) projects.

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It is anticipated that the RTF will be upgraded to eventually include on-site simulation, computed tomography, advanced treatment planning, and conformal delivery of the photon beam. In the meantime these efforts will be carried out at SUNY and the data sent to the RTF by a new fiber optic cable system. As mentioned by the reviewers, these upgrades will also be necessary for support of BNCT and proton therapy. We fully agree with the recommendation (also the recommendation made by the reviewers for BNCT) that a full time research- oriented radiation oncologist on the staff would be highly desirable. However, none of the radiation therapy projects currently has sufficient funding to support such a position. Instead, this expertise will be provided by an external advisory committee and by the rotation to BNL of a radiation oncologist from a major medical center i.e. Beth Israel Hospital in New York City.

BORON NEUTRON CAPTURE THERAPY (BNCT)

The BNCT program was thoroughly reviewed and the issues well documented in the Committee's report. As noted by the reviewers, excellent progress has been made in the past two years and we are well-situated to begin a focused effort to bring this unique treatment modality to therapeutic trials, hopefully within 2 years.

Since the review in May, an additional (and perhaps the best) proposal to upgrade the Brookhaven Medical Research Reactor (BMRR), by installation of uranium fission plates (available from the JANUS reactor, ANL) directly into the shutter assembly, has been drafted. Calculations with this configuration indicate the epithermal neutron flux would be ~25 times the current flux with a corresponding 75% relative reduction in fast neutron contamination. With fluxes of this magnitude, patient exposure times for BNCT may be as short as 2 minutes as compared to previous estimates of 30 to 50 minutes. This completely changes the approach to patient therapy, i.e. no sedation will be required, and eliminates concerns about changes in tumor boron concentration during the course of treatment. Preliminary estimates indicate these modifications could be made for less than $500K.

Although we will continue to evaluate different boron compounds for BNCT, our efforts will now focus on boronophyenylalanine-fructose complex (BPA-F) as the compound of choice for the first clinical trials in patients with malignant brain tumors. Since the original FDA-approved investigative new drug (IND) was for the oral administration of BPA, a new IND is required for intravenously administered BPA-F. Conditional approval of this IND was verbally forward to the sponsor (M. Chadha, M.D., Beth Israel Medical Center) on September 30, 1993. Animal studies have shown that systemically administered BPA-F is well tolerated and significantly more effective for BNCT that oral BPA. With this exposure regimen, we have achieved a high percentage of cures (>90%) in animals bearing malignant brain tumors. The Phase 1 toxicity/distribution studies with BPA-F will be done primarily in collaboration with neurosurgeons in the major medical centers in New York City so that the availability of an adequate number of patients for study will not be a problem.

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The treatment planning system (hardware and software) has been transferred from SUNY to BNL. This will facilitate the coordination of beam characterization, dosimetry, and treatment planning in preparation for initiating clinical trials at the BMRR.

It is our plan that clinical trials of BNCT will begin at Brookhaven within the next two years. Progress toward this goal will be facilitated and, more importantly, will be improved in quality by establishing a formal Advisory Board of Physicians to oversee planning for clinical trials. Several radiation oncologists and neurosurgeons have been identified to serve on this Advisory Board and Dr. T. Phillips, an eminent research-oriented radiation oncologist and a member of the Visiting Committee, has agreed to assume a leading role in these efforts.

NUCLEAR MEDICINE (SPECT) PROGRAM

The reviewers were impressed with the progress made on methods for Compton scatter correction, and on new initiatives in autoradiographic imaging with conversion elections, and particularly, in the development of pin-hole SPECT for high resolution in small animals.

Nevertheless, the Committee saw the clear need for this group to be tied more closely to hypothesis-driven clinical research and to have closer interactions with the nuclear medicine PET and the radionuclide/radiopharmaceutical development groups. We fully agree with this assessment and are in the process of reorganizing nuclear medicine (SPECT) in the Medical Department with the objective of achieving an integrated developmental/clinical research program of a quality equivalent to the PET project. A plan recently presented to programmatic managers at DOE (OHER) received their enthusiastic support. The successful implementation of this new initiative will be required in order to fully regain the drastic cuts from the FY92 programmatic support. Nevertheless, it is essential that additional funds be obtained now for a state-of-the-art SPECT system that allows for rapid, sequential acquisition of data for quantitative kinetic analysis of new metabolic tracers.

To facilitate collaboration/interaction within the nuclear medicine program we are exploring the possibility of relocating the radionuclide/radiopharmaceutical (R/R) group from building 801 to the Medical Department (Building 490). Space has been identified, and although significant modifications would be required, this would provide a modern research facility which in the long-run would be far less costly than renovating the archaic laboratories in Building 801. A major additional advantage is that the R/R scientists would be in constant contact with all other Departmental researchers, including those in nuclear medicine.

In summary, we are confident that, with the reorganization of nuclear medicine and facilitation of inter-group collaboration, a strong, high-quality research program that addresses current priorities of molecular medicine can be achieved.

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NATIONAL SYNCHROTRON LIGHT SOURCE (NSLS) PROJECTS

NSLS Transvenous Coronary Angiography Research Program

The reviewers recognized the technical competence and unique instrumentation of the angiography project, however, they were less clear about the objective advantages (other than reduced patient risk) of the system, the unlikely use of this kind of instrument for general clinical application, and the potential research applications.

Since two digital (not photographic) images are acquired, one above the iodine K-edge and one below, the amount of iodine in the image can be quantitated. This quantification of the image allows the relative thickness, and more importantly, the relative area of an artery to be determined, thus providing a more objective assessment of vascular function.

Although transvenous angiography is currently done only at large facilities such as the NSLS, a private company has designed and built a non-synchrotron-based prototype source (room-sized) to be used for digital subtraction angiography in a standard clinical setting. This company is presently seeking defense conversion funding to build a full-power source which will create an x-ray intensity comparable to our synchrotron source at wavelengths above and below the iodine K-edge. The cost and availability of such a system is expected to be similar to existing MRI systems. Efforts in compact synchrotron source design are also underway at a variety of institutions.

It is clear that transvenous angiography is best employed in longitudinal studies where serial images can be obtained without serious risk to the patients. We have now obtained images which are considered research quality and we are discussing with North Shore University Hospital (Manhasset, NY) and State University of New York (Stony Brook, NY) development of research programs taking advantage of these unique capabilities. Most likely the initial research project will focus on the progression of post-angioplasty coronary artery disease.

Multiple Energy Computed Tomography (MECT)

We agree with the Committee that MECT is an innovative application of the NSLS that should provide important information on image resolution limits, contrast and element identification.

The image resolution demonstrated for the prototype MECT system has been 0.3 mm, and not 3 mm as quoted in the report. The statement "Its finite time per slice will limit the size of its subject application." probably refers to the fact that MECT's K-edge subtraction of contrast elements can be applied only when the contrast agent distribution within the slice does not change considerably in a period of 5 to 10 seconds. However, the major contribution of MECT to neuroradiology is expected to stem from the dual photon absorptiometry (DPA) method.

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As with transvenous angiography, MECT is necessarily located at BNL. Its ultimate impact on clinical neuroradiology will depend upon the technology development of monochromatic x-ray scanners or compact synchrotrons as mentioned above.

Microplanar Radiation Therapy (MRT)

We are encouraged by the Committee's interest in MRT and fully agree that longer follow-up of animals is required to assure that the large doses of photon radiation delivered by this method will not result in delayed brain tissue damage. This concern is being addressed. One group of irradiated rats has now been followed for 11 months without any clinical evidence of brain damage. To further assess potential brain damage following MRT, analytical methods will be utilized including microdialysis to assess neurochemical function and computerized behavioral testing systems and MRI to assess neurologic function. The brains of all exposed animals are ultimately evaluated histologically by a neuropathologist.

The reviewers implied that, because of the low energy of the synchrotron radiation, multiple cross-fired beams will be required in order to achieve adequate dose to the tumor. However, our published calculations do not predict advantages to reducing the number of cross-fired microbeams in conjunction with increases in photon energy.

Preliminary studies indicate that MRT can be used to effectively control malignant brain tumors in rats. In these studies it was shown that cross-fired beams are significantly more effective in long-term tumor control than are unidirectional beams. Our research strategy will be to increase tumor doses within neurologically acceptable limits until significant concomitant normal brain tissue damage is observed.

Photon Activation Therapy With Iodine

The reviewers correctly point out that in order to take advantage of the increased cell kill observed with photon radiation energies just above the iodine K edge for clinical therapy, interstitial x-ray sources (brachytherapy) with the proper photon energies will be required. Samarium-145 emits photons with a suitable for activating iodine.

Samarium-144, encapsulated in titanium sources will be activated to samarium-145 by exposing the sources to a neutron fluence of -10^{20} neutrons. For therapy, the sources will be interstitially implanted directly into the tumor via brachytherapy techniques. We anticipate that this treatment will offer a significant therapeutic gain over conventional x-ray therapy.

NUCLEAR MEDICINE (PET) PROGRAM

We agree with the Committee's view that this is a high-quality, productive research program that focuses on relevant clinical problems. The success of the project is, to a great extent, the result of highly effective collaborations with investigators in the Chemistry

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Department and various Universities, particularly SUNY (Stony Brook) and NYU. A recently funded NIH grant will expand this group efforts to define the critical neurochemical changes associated with alcohol abuse. The PET program at BNL is viewed by program managers as an outstanding example of research responsive to missions and priorities of the Medical Applications and Biophysical Research Division.

RADIONUCLIDE/RADIOPHARMACEUTICAL PROGRAM

Although the reviewers were very supportive of the radionuclide production/ processing research efforts, concerns were expressed about the emphasis of the radiopharmaceutic program. In particular, the Committee felt the program would benefit by reducing its efforts on bifunctional chelating agents and focusing more on the development of "modern" protein-based radiopharmaceuticals. We fully agree that new directions in the design and labeling of receptor-specific probes will be essential if the program is to be responsive to the objectives of modern molecular nuclear medicine. To this end, additional personnel and increased collaborations with molecular and structural biologists at BNL would be extremely beneficial. However, we also feel that further refinement of bifunctional chelating agents, and their conjugation to monoclonal antibodies, is critical if these agents are going to be used effectively for the diagnosis and therapy of cancer. This is an active area of research, worldwide, to which the BNL group has already made significant contributions.

Clearly, the radionuclide/radiopharmaceutical program is in need of additional scientific personnel and support. The anticipated BLIP upgrade will require a substantial amount of developmental work in target design, processing, etc., if it is to achieve its stated production and delivery goals. It is important, however, to assure that this added effort does not substantially curtail ongoing research programs.

As previously stated, radionuclide/radiopharmaceutical research will be further integrated into the nuclear medicine program and the relocation of the group to Building 490 will help achieve this objective.

PROTON AND OTHER PARTICLE FACILITIES AT BNL

We agree with the Committee that protons are an exciting source of radiation for therapy and that currently there is an inadequate number of facilities in the U.S. The proposed BLIP upgrade, scheduled for completion in 1996, will result in the availability of protons from the LINAC for about 46 week/year, sufficient to be of interest for proton therapy. This upgrade, along with an already existing beam line to the neutral beam test facility, provides an economically sound basis for establishing a state-of-the-art proton therapy facility (PTF). An Adhoc Committee, charged with reviewing the feasibility of placing such a facility at BNL, has recently submitted a preliminary report to the Director strongly recommending that the Laboratory proceed with plans for developing a PTF. A

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review of the number of new cancer cases in Nassau and Suffolk counties alone indicated that from 700 to 1700 patients could benefit from proton therapy. The initial proposed facility would contain two treatment rooms, one room with a horizontal beam primarily for the treatment of head and neck tumors, and the second room with a vertical gantry of 360° for the treatment of tumors at all sites. The design of the facility will incorporate provisions for two additional treatment rooms in the future, if required.

The inclusion of a heavy ion therapy program at BNL is totally dependent upon construction of the Booster Application Facility (BAF) by NASA (or DOE) to study hazards associated with cosmic radiation exposure during extended space flights. Design of the BAF to incorporate a beam line(s) dedicated for therapy would then be feasible and cost effective.

RADIATION BIOLOGY/LEUKEMOGENESIS

As noted by the reviewers, Dr. Bond's work on low-dose radiation effects and the development of the hit-size-effectiveness-function (HSEF) addresses the need for new concepts in dosimetry that do not depend on absorbed dose and other restrictive concepts such as RBE, quality factor, and dose equivalent. The concept of HSEF continues to gain acceptance by scientists working on low-dose radiation effects.

Much of the data used in developing the HSEF was obtained during the past several years from large numbers of mice exposed to radiations of different quality. The program is now focused on the molecular changes in the development of leukemia. This is an important new direction in that; it will bring technical expertise to the Department that will be needed for establishing a modern, molecular medicine program, and; it will foster additional collaborations with the Biology Department.

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