

REPORT OF THE VISITING COMMITTEE FOR THE MEDICAL DEPARTMENT

BROOKHAVEN NATIONAL LABORATORY

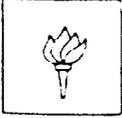
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Peter J. Quesenberry  
Norman C. Staub  
Henry N. Wagner, Jr.  
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September 13, 1984

Dr. Robert E. Hughes  
President  
Associated Universities, Inc.  
Suite 603  
1717 Massachusetts Avenue, N.W.  
Washington, D.C. 20036

Dear Dr. Hughes:

This is to report to you on the visit to the Medical Department, Brookhaven National Laboratory, by the Department's Visiting Committee, on April 16-17, 1984. Members of the Committee who participated in the visit were Drs. Samuel Hellman, Marvin Kuschner, Yale Nemerson, Emil A. Pfitzer, Peter J. Quesenberry, William H. Sweet, Norman C. Staub, Arthur C. Upton, and Henry N. Wagner, Jr. (Dr. William J. Schull was unable to attend).

At the outset of the visit, as you will recall, the Committee met with Drs. Victor P. Bond, Donald C. Borg, Nicholas Samios, several members of their respective administrative staffs, and yourself, at which time the budget crisis currently confronting the Department was reviewed. In brief, the Committee was informed that the FY'85 Presidential budget for the Department calls for a reduction in DOE funding of approximately \$3 million below the amount needed to maintain the program at the '84 level. This cut, which was unexpected, corresponds to a reduction of about \$4 million below the funding level projected as recently as December, 1983. The reduction would cause the following impacts on major program areas: 1) it would necessitate closing the in-patient research hospital in 1984; 2) it would withdraw all DOE support from the Inhalation Toxicology Facility (Drew); 3) it would reduce by more than 50 percent the budget needed to maintain the human pulmonary biology program (Chanana, Joel, Susskind); 4) it would terminate all DOE programs on radiation and chemical carcinogenesis in experimental animals (Shellabarger); 5) it would reduce support for research on mutagenesis (Bender, Tice, Carsten); and 6) it would reduce support for research on medical applications of nuclear technology ("nuclear medicine") (Brill, Srivastava, Mausner). In addition to the marked reduction in support from DOE, the support

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from other funding agencies (WFO) is projected to be reduced by about \$1,289,000 below the amount needed to maintain it at its FY'84 level. Altogether, the projected reductions correspond to a deficit of \$4,276,000 in FY'85, which could result in the loss of 65 of the Department's scientific, professional, and support personnel.

Such a drastic loss of staff and capabilities (closing of the in-patient research hospital facility has already been deemed to be a necessary response and has been accomplished) poses a threat to the survival of the Department in its present form. Hence the Committee was asked to consider whether changes in the organizational structure and mission of the Department were called for; e.g., should the Medical and Biology Departments be merged? In the same context, the Committee was asked to review the future plans for research programs that would be most severely impacted by the projected budget cuts, with an eye toward adjustments that might be warranted.

Also discussed with the Committee were issues relating to the appointment of successors to Dr. Bond, Associate Laboratory Director, and Dr. Borg, Department Chairman, neither of whom wishes to remain in office after the expiration of his present term. The Committee was informed that several qualified candidates had been interviewed for Dr. Bond's position, and that it may be possible to recruit one of them between now and August, 1984, when Dr. Bond wishes to return to full-time research.

The Committee was then briefed by a number of principal investigators of programs that would be heavily impacted by the projected budget cuts. The names of the investigators and the Committee's comments on their research plans are presented below.

On the second day, the Committee met in executive session to assess its findings and to formulate recommendations. These are presented in the following.

#### Organization and Leadership

First, as concerns the future status and mission of the Medical Department, the Committee unanimously recommends that the Department continue to exist as an organizational entity. The same conditions that have enabled the Department to achieve a distinguished record of research contributions in the past can be expected to persist into the foreseeable future; namely, the availability at BNL of unique resources relevant to the development of new methods for the application of nuclear technologies in medical diagnosis and treatment. The latter is an avowed goal of DOE's long-range research program. Hence there is a mission for the Medical Department at the Brookhaven National Laboratory which no other organizational entity can in principle better fulfill. In addition, of course, many other research activities exist at the

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interface between energy systems and human health, in which the Medical Department can continue to play a productive role.

Second, the Committee recommends vigorous action to assure the timely recruitment of capable successors for Drs. Bond and Borg, which cannot be accomplished without assurance of stable, long-term core support for the Department and sufficient flexibility in funding to allow for initiation of new programs with funds from various sources. The current budget difficulty, coming after a series of funding crises, is perceived by many as a sign that DOE is prepared to abandon medical research. To dispell the pervading gloom, recruit new leadership, and build for the future, the termination of key personnel and programs should be deferred, pending negotiation with the new Associate Director and Chairman. This is a crucial moment in the history of the Department which calls for far-sighted leadership. If the opportunity is not siezed upon, the future may be lost irretrievably.

Third, the proximity of the newly developing Health Science Center at Stony Brook constitutes a strategic resource. This academic center of growing excellence has already made possible many mutually complementary and beneficial collaborative interactions with the Medical Department. These can become increasingly important in the staffing and strengthening of the Department in the future, given appropriate opportunities for cooperation. In planning for the future of the Department, systematic consultation with the School of Medicine at Stony Brook will help to optimize the utilization of available talent and resources.

Fourth, there should be efforts directed toward further strengthening of the bonds among the various research groups at the Laboratory that are engaged in programs relevant to nuclear medicine. Stronger bonds would be of mutual benefit to the Medical Department and to the other groups concerned.

#### Comments on Specific Research Programs

##### Radiotherapy

Three radiotherapy approaches were discussed involving: 1) protons, 2) boron for neutron capture, and 3) photon activation/auger electrons.

Protons. Dr. Brill reported that the injector for the linear accelerator would be available for use as a proton source, and that a facility has been prepared for treatment of ocular melanoma, pending Blue Cross/Blue Shield approval. He also suggested that his group would be interested in using this source for treatment of intracranial arteriovenous malformations.

While proton therapy with the Harvard Cyclotron is being studied at Massachusetts General Hospital, as well as at the University of

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California, Berkeley, it is appropriate for this form of therapy to be studied at a third place. Nevertheless, it seemed from our discussions with Dr. Brill that this proposal was primarily an attempt to raise funds rather than a true investigative project. No evidence of the existence of a research team interested in this therapeutic application was presented. Such a research team would require a dedicated medical physicist, radiation oncologist, and neurosurgeon, who would meet regularly to decide what particular questions are most appropriate for exploration. Without such a team, the proposed program would not be feasible. To start such a program just for reimbursement would be a waste of Brookhaven resources, both intellectual and physical.

Neutron Capture. Approaches to neutron capture therapy were presented by Drs. Fairchild and Slatkin, which were based on the hypothesis that better ways of getting boron into tumors have become available. The approach described as most promising involved the use of a thymine analog containing boron. Studies are called for to prove that boron can thus be incorporated into tumors uniformly and in sufficient concentration to make capture therapy feasible. Experiments using tumors in situ are especially relevant.

Although boron capture therapy is an interesting idea, its success depends upon the levels and uniformity of boron incorporation in tumor cells. The critical data needed to decide this question were not presented.

Photon Activation/Auger Electrons. Studies of activation therapy were reported by Drs. Fairchild and Slatkin, based on evidence that <sup>127</sup>I-IdUrd incorporated into DNA can be stimulated to yield Auger cascades by irradiation with 32-to-50 keV photons. This is a clever idea; however, the energy of the photons is sufficiently low so that this approach may not be feasible unless implanted sources are used. It is also necessary to know how biologically effective such Auger cascades would be. Data were presented which indicated some improvement in effectiveness over the action of IdUrd as a radiosensitizer, but the data were not analyzed with reference to the respective D<sub>0</sub>'s as a function of thymidine replacement. Furthermore, the proposed use of SM-145 sources may pose problems, since their one-year half-life means that they may have to be removable. Although it was suggested that they would be used at low dose rates, the reduction of dose rate must be balanced against the proliferative activity of the tumor cells. Homogeneity in the distribution of the low-energy photons is another question that remains to be resolved.

In summary, the neutron capture therapy, as well as the photon activation therapy, are interesting ideas, but both ideas suffer from the lack of active involvement of a clinically oriented medical physicist and a radiation oncologist. If such people were on board or involved through appropriate collaborative arrangements, these projects would be worth pursuing.

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### Nuclear Medicine

Plans for renovation of the BLIP production facility, which are to be applauded, were presented by Drs. Srivastara and Mausner. The field of nuclear medicine is now at a stage where it can make major contributions to our understanding of human biology. Advances are being made in bioenergetics, receptor function, and body composition. BNL is in a position to continue to play a major role in these developments, because it is at the interface between technology and its applications to the solution of human problems. Much of the technology is based on exploiting properties of the nucleus and has been derived in the past largely from DOE-supported technology transfer to the biomedical research community, most often via extension of NIH-supported research. Drs. Brill, Mausner, Cohn, and Srivastara provide the necessary leadership in their subject areas to permit major advances to continue to be made in the areas of clinical research, radionuclide production, body composition, and radiopharmaceutical development. For example, iodine-123 is at the beginning of a log phase of growth in its use as a label for biomedically important compounds, an example being the labeling of ligands that bind to muscarinic cholinergic receptors. The nuclear medicine group should continue to be a major factor in the development and use of nuclear technology to increase our understanding of receptors and the effects of drugs in altering their behavior. With the prospect of similar advances in bioenergetics and body composition, it is important to exploit the use of this technology in biomedical research.

### Medical Physics

Dr. Cohn reported studies implying that women prone to develop post-menopausal osteoporosis can be identified with an accuracy of up to 90 per cent by measurement of total-body calcium, using whole-body neutron activation analysis. He also reported projects involving similar measurements of total-body aluminum, iron and other minerals. The studies are of much scientific merit as well as practical importance, and they require facilities such as are available only at Brookhaven or similar laboratories. In our opinion, they strongly merit sustained support.

### Hematology

Dr. Cronkite reviewed three general research areas: one on benzene-induced leukemogenesis, another on the effects of low-dose radiation and neoplasia, and the third on a long-term stromal cell line and its production of various humoral factors. Dr. Cronkite's work has been independently funded by NIH, and he is clearly one of the leading scientists in the Medical Department. His work with the murine long-term marrow systems is innovative and exciting. The other projects are of some interest and will produce experimental data which will be useful; however, they are not highly innovative or at the cutting edge

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of research in the field. Hence it would appear that these projects may reflect the funding directions dictated by DOE rather than the natural preferences which Dr. Cronkite might follow. Dr. Cronkite presently works with Dr. Burlington but appears to have a few other individuals actively collaborating on the most promising work; namely, that involving the long-term Dexter cultures. A critical mass in hematology is lacking at present. This has been a long-standing problem but was severely accentuated by the recent departure of Dr. Miller. Although Dr. Cronkite remains an outstanding resource at Brookhaven, it is essential to the viability of the program that there be younger colleagues in hemopoiesis. The building of a critical mass in hematology should thus be a major goal for the Department.

#### Pulmonary Biology

Dr. Chanana summarized some of the technical developments and research in the large animal pulmonary biology program, which is reacting positively to the stated goals of the OHER Five-Year Research Plan and is fulfilling them in several important ways. The group provides extensive basic physiologic and sophisticated pulmonary function monitoring on large animals (mainly sheep) under baseline (normal) conditions and after exposures to specific energy-related substances. The techniques for controlled exposures are well-advanced and have the flexibility to permit studies of a wide variety of substances, as may be necessary. In addition, animals varying in age from newborn through senescence can be compared, thus permitting investigation of the effects of an important variable on lung responsiveness. The group is also able to produce controlled lung pathology of a type similar to the commonest form of chronic obstructive pulmonary disease in man (emphysema), so as to determine the effects of the interaction between stressful exposures and impaired lung function. In its studies, the group makes use of several nuclear medicine techniques which are available within BNL, for quantifying overall and regional pulmonary function. In several ways, their capabilities are unique.

The value of large animal investigations in biological research cannot be overemphasized. No matter how many cell culture dishes or tubes of chemicals are tested, there can be no successful extrapolation to man, except through the intermedicary of whole-animal investigations. There is no other way to understand the interactive controls, responses, and defense mechanisms that are involved. The specific value of large animal pulmonary biology includes the ease of manipulation of large animals (as opposed to mice and rats). These manipulations permit detailed measurements of organ and total-body responses (for example, pulmonary hemodynamics, ventilatory mechanics, control of breathing, lung defense mechanisms, and the sequence of lung injury and repair).

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Inhalation Toxicology

The Inhalation Toxicology facility headed by Dr. Drew includes a small staff to cover the areas of chamber operation, aerosol science, biochemical toxicology, small animal pulmonary function, behavioral toxicology, pathology, and electron microscopy. This group has been productive and innovative in their approach to problems of inhalation toxicology. It was hypothesized that DOE may have withdrawn its support from this group because of the funding of other inhalation toxicology facilities elsewhere. If so, this would appear to neglect the most important route of entry for environmental substances effecting human health. A core service facility to provide well designed inhalation exposures is a necessity for health researchers, and this cannot be made available from a remote location. Although the research involving the pulmonary system should not duplicate the work of other facilities, and the facility does not need to grow into a large unit competing with other available resources, some core support is essential to a significant health research department. The facility at present is in excellent working condition. During these times of economic hardship the facility should be sustained and allowed to find other funding sources, in order to remain functional and to maintain a critical mass of scientists.

Summary

In summary, the Committee finds scientific merit in the programs of the Medical Department, and it views with alarm the fiscal crisis that now threatens the Department's future. Without sufficient core support for key investigators and programs, recruitment of a new Associate Laboratory Director and Department Chairman will not be feasible. Hence the Committee strongly recommends that support be sustained at a level that will enable the continuity of leadership to be assured, thus safeguarding the future of the Department.

On behalf of the Committee, I would like to thank you for the privilege of reviewing the programs of the Department. If there is any further information you would like to receive from the Committee, or if there is anything further we can do to help you, please don't hesitate to let me know.

Sincerely,



Arthur C. Upton, M.D.

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