

718287

Brookhaven National Laboratory  
Medical Department  
Report of Visiting Committee Meeting

May 3 and 4, 1977

George Brecher, Chairman  
Herman Suit  
Leon Miller  
Kenneth Sterling  
Gareth Green  
Louis Tobian  
David V. Bates  
James V. Neel

REPOSITORY Associated Univ. Inc (WASH D.C.)  
BOARD OF TRUSTEES + ITS Exec. Committee's  
COLLECTION Mtg Minutes  
BOX No. locked filing cabinets in Internal Audit Office  
FOLDER \_\_\_\_\_

1124804

## REPORT OF MEDICAL DEPARTMENT VISITING COMMITTEE FOR 1977

All members of your committee were able to participate in this year's annual visit on May 3 and 4. Your committee was gratified to find that the scientific programs have been successfully aligned with the goals of ERDA and that their excellence has been either maintained or further improved (as will be detailed under "Appraisal of Programs").

Your committee considered at length two major problems facing the Medical Department: the maintenance of the clinical research facility and the impending retirement of the chairman of the Medical Department, Dr. Cronkite.

### The Clinical Research Facility

Your committee was made aware that maintenance of a hospital facility is considered by ERDA to be outside its scope and its expense is believed to be excessive. Your committee finds, however, that a clinical research facility is actually indispensable to a meaningful functioning of the Medical Department. The Medical Department at BNL, thanks to its facilities and its cooperation with basic and applied divisions of physics and chemistry, has unique opportunities to advance knowledge of environmental hazards and to contribute directly to the reduction of such hazards. The whole-body-counter offers practically unique instrumentation for the measurement of body composition. Neutron activation and production of short lived isotopes carried out under an ERDA sponsored program continually offer new opportunities to measure body and organ composition and to make possible repeat physiologic measurements at

reduced radiation exposure. Research is also under way aimed at reducing the radiation exposure necessary for routine clinical x-ray or mammography examinations.

An on-site clinical research facility is essential (1) to test the practicability of new technological approaches critically before one can judge whether they are truly "feasible" and useful. (It should be noted that proximity is essential here because some of the new isotopes have so short a half life that they can only be used at present next door to the production facility); (2) to provide feedback for the research and development teams, e.g. to assess which of the new approaches merit further development with the goal of being used elsewhere (e.g. by developing portable production facilities of the new compounds); (3) to attract competent medical investigators who are anxious to restrict their clinical practice to a very small number of subjects that can be studied by the unique BNL facilities. (Your committee members were unanimous in the thought that no outstanding medical investigator could be attracted today in the absence of some clinical on-site facility which could utilize the new physical developments of BNL and thus shorten the transfer time of new technology.)

For these reasons, your committee urges the maintenance of at least a small clinical research facility as an integral and vital part of the Medical Department. The present single pavillion of eleven active beds should suffice for the needs enumerated above, including such clinical needs for the study of hematologic, pulmonary and possibly related metabolic diseases as could be

envisaged by your committee at present. In all instances a very intensive study using the special investigative tools of BNL is likely to involve only a small number of patients at any one time.

The possibilities of operating all 44 beds by assuming responsibilities other than those enumerated above and thus reducing the overhead to BNL were considered at length: (1) The possibility of the establishment of a clinical research center operated jointly with Stony Brook University and financed by HEW appeared attractive. The committee doubts, however, that Stony Brook and BNL could obtain financing for such an undertaking from NIH at this time. (2) The committee also expressed doubts that the use of beds in excess of eleven as a standby facility in case of a regional nuclear accident was practical. It was felt that casualties can be readily transported to existing acute care facilities; that acute care facilities are best situated in large hospital complexes where all laboratory and monitoring devices are routinely operative 24 hours a day, seven days a week. This would be a difficult task for the Medical Department at BNL (although it is recognized that the Medical Department maintains the training of its own nurses and doctors to be able to meet emergencies at a high level). (3) The possibility of making the other three pavillions available for psychiatric patients was discussed. The committee feels that this would be highly undesirable and unattractive to your committee.

It may be altogether unrealistic to hope that the overhead of the eleven-bed clinical research facility can be substantially

reduced by operating as part of an acute or chronic 44 bed hospital. The costs per bed per day do not appear grossly excessive by today's standards. It may be more realistic to recover some costs by attempting to include in appropriate NIH supported projects the bed costs for certain special patients.

In summary, while aware of the substantial cost, your committee finds that a small on-site research facility (eleven beds appears an appropriate size at this time) is essential to the ERDA goal of assessing the feasibility of new technology. New technology can only be developed to the point where it is truly "feasible" after some clinical trials and with continuous feedback from the clinical experience of the Medical Department to the divisions of applied science, chemistry and physics of BNL developing new technology. Closure of the minimum clinical research facility would jeopardize the mission of the Medical Department, reduce its attractiveness to investigators, and jeopardize its continued excellence.

#### Chairmanship of the Department

Dr. Cronkite will reach the mandatory retirement age of 65 in 2-1/2 years. He has carried out the duties of the position for eleven years with great distinction, continuing his own highly regarded research, and guiding the department through a series of difficult reorientations with great skill. His recent reorganization (abolishing separate divisions and creating four functional units under four program coordinators) appears to have been highly beneficial to the cohesion and productivity of the department.

The committee felt Dr. Cronkite's devotion to his fellow scientists and employees, and to the institution should not be misused, and that it would be unfair to him as well as an undesirable precedent to continue him as head of the department beyond 65. Two years appears a brief lead time to find and install a new chairman, and immediate appointment of a Search Committee is urged. Several members of the Visiting Committee are prepared to assist the Board of Trustees and the Search Committee by submitting their thoughts or actual names of possible candidates. The chairman of the Search Committee may wish to contact individual names of your Visiting Committee.

#### Appraisal of Programs

Committee members met individually with investigators in fields allied to their own research and interests. These sessions were followed by more formal presentations, question periods and executive sessions. The following represents your committees' joint appraisal of the programs reviewed.

#### Environmental Health Sciences

Hypertension: This program has been greatly strengthened by the recruitment of a geneticist, Dr. Haber, who has started an inbreeding program of the S and R strains of rats originally developed by the late Dr. Dahl. It is clear that the S strain (which develops permanent hypertension on a high salt diet) and the R strain (which does not) differ already in their baseline blood pressures, and differ in their susceptibility to other

hypertension producing agents, e.g. stress or cadmium. Multifactorial genetic differences are clearly implicated. The incomplete genetic separation of the two strains will require careful quantitative assessment during the coming five years (the estimated time period for the 20-generation inbreeding program.) Dr. Neel has offered to spend additional time at Brookhaven immediately preceding the next meeting of your Visiting Committee to review the program and advise Dr. Haber further.

Your committee would like to see efforts intensified to identify the biochemical pathways by which multiple agents produce hypertension in the S rats. The interesting observation that guanethidine treated and thus functionally sympathectomized S strain rats are exquisitely sensitive to catecholamines but do not develop hypertension when fed a high salt diet is of great fundamental interest and should be followed.

The induction of hypertension by small (and not by large) doses of cadmium strongly suggests deleterious effects of higher doses of cadmium which coincidentally counteract the development of hypertension. Even smaller doses of cadmium should be investigated in the future. The nature and activity of the cadmium binding protein demonstrated by Dr. Iwai's group needs to be pursued vigorously, particularly the fact that hypertension resistant R rats do not have any of this binding protein in the plasma.

In summary, the committee applauds the recent move toward basic investigations and would like to see concentration on

quantitative genetics and biochemical mechanisms rather than continuation of purely phenomenologic observations.

Radiation effects: With the aid of the unique RARAF facility for production of monoenergetic neutrons and charged particle beams, Drs. Rohrig and Bird have developed a novel scheme to test directly the dual radiation action theory of Rossi. Using a mylar window they have produced beams separated by 0.16 to 0.3 $\mu$ m. Apparently the biologic effect at that track separation is less than predicted by Rossi's theory. The work is of great practical as well as theoretical importance, as it may provide more reliable estimates of RBE and OER than are presently available. These estimates are crucial for dose calculations of both neutron and high Z beam radiation therapy, and for the correct assessment of dangers of diagnostic x-ray and of potential neutron hazards.

The project also may allow to assess separately the effect of radiation damage on cell membrane and cell organelles. These investigations thus use unique opportunities offered by BNL in an original manner to solve questions of potentially broad impact to the community.

Pulmonary program: This program has been greatly strengthened by the recruitment of Dr. Drew and your committee urges that everything possible should be done to encourage Dr. Francis Chinard to join the Medical Department. Dr. Chinard would provide needed leadership in the meaningful application of newly developed tracer methodology for pulmonary function studies with (20 hour Xenon),

and complement the excellent experimental studies in pulmonary environmental hazards under Drs. Kuschner and Drew with appropriate human studies.

Dr. Kuschner's studies on characterizing size and geometry rather than chemical composition of inhaled particles as the major hazard in the production of pulmonary fibrosis act are of obvious importance to environmental protection. The thoughtful design of the new facility for experimental evaluation of pulmonary toxicologic hazards as described by Dr. Drew appears to meet every need that can be envisaged at this time. The availability of on-site clinical research facilities will be essential to the development of the pulmonary program.

In summary, the early work and direction of future effort of the pulmonary program, particularly with the addition of Dr. Chinard, will optimally combine the strengths and availability of the faculty of Stony Brook, and the unique physics and medical research facilities of BNL, and promise to meet ERDA's programmatic demands in a truly exemplary manner.

#### Medical Application of Medical Technology

This is a program, heavily backed by ERDA, to use the unusual developmental opportunities in physics and chemistry at BNL for the improvement of diagnostic techniques. Again the availability of a small but adjacent medical research facility is essential.

"Feasibility" alone is not enough. Utility needs to be assessed medically before the methodology is fully developed.

We have already noted the relevance of 20-hour Xenon for the

pulmonary program. The work is generally confirmatory, but the meticulous quantitation of the phenomenon of closing volume completed by Dr. Suskind deserves a wide audience and he should be encouraged to publish his results in a major journal read by clinical investigators. Although the excellent and highly refined technique is not likely to be applied to large numbers of patients, it would be of considerable interest to the pulmonary research community. Production of other shortlived radionuclides has already been highly useful; e.g. shortlived  $^{79}\text{Kr}$  is being used to determine the partition of Krypton in order to estimate the hazard of long lived  $^{85}\text{Kr}$ , an important potential pollutant.

The newly acquired PETT III imaging device for positron emitters should allow useful in vivo quantification of metabolism and clearance of both physiologic and therapeutic compounds.

Of particular interest appear the in vivo neutron activation measurements which are now centered on cadmium. It may be pointed out that mercury may yield to quantitation by the same technique. Mercury is potentially a greater hazard with increased use of coal of which it is a contaminant. The possible mobility of the instrumentation should be explored since the greatest utility of the new methodology may depend upon sampling of exposed populations in their own locale.

Investigations in this program are aimed at improving imaging and thus allow reduction in x-ray exposure for diagnostic procedures; hence they are of obvious importance. A variety of approaches are under way: use of gadolinium instead of aluminum

filters and a barium fluorochloride screen each would reduce the conventionally necessary x-ray exposure by half.

All of the work reviewed appears imaginative and of high quality.

#### Genetic and Biochemical Sciences

Work on experimental carcinogenesis was considered of high quality and appropriate. It clearly relates to environmental (carcinogenic) hazards. Dr. Bender's program on cytogenetics aims in part at the development of practical screening systems for detection of mutagens and carcinogens. The track segment exposure offered by RARAF will be used to settle questions of fundamental importance for the understanding of the relationship of achromatic lesions to chromatid deletion.

Dr. Tice is using differential staining of sister chromatids in an imaginative manner not only for the study of sister chromatic exchanges, but for studies of cell kinetics. The methodology allows determination of the number of sequential divisions after administration of bromodesoxyuridine by measurement of fluorescence in the interphase nuclei as well as during mitoses. The potential of integrating this methodology with microfluorimetry for much simplified and much more precise kinetic studies than have been possible to date with cumbersome autoradiographic techniques is exciting and should be encouraged.

#### Host Defense Mechanisms

Dr. Cronkite and his group have occupied for many years a position of leadership in the study of kinetics of normal and

abnormal hemopoiesis. Appropriately, the basic hematologic and immunologic research of the group receives substantial support from NIH. The group has also reoriented part of their research toward programs meeting the ERDA mission.

In particular, Dr. Chanana is studying the traffic of cells in the lymphatics of the lung in conjunction with the role which deposition of proteolytic enzymes by macrophages may play in emphysema.

Dr. Reincke and Cummerford are studying the potential marrow toxicity of pollutants by novel and ingenious technique. Marrow is removed from the experimental animals at varying intervals after ingestion or inhalation of radiolabeled pollutants frozen and radiation damage allowed to accumulate. The surviving fraction of stem cells is assessed in colony assays and compared with suitable calibration curves. It indicates the concentration of pollutants in the critical stem cells since the radio label reduces their capacity to form colonies. Prolonged freezing itself does not alter survival of the stem cells in the assay. It is of interest that this technique was developed for basic investigation of stem cell kinetics but found subsequently to be applicable for the study of distribution of pollutants to the stem cells, which are of particular interest because they are the target of leukemogenic compounds and compounds producing fatal aplastic anemia. The pending recruitment of Dr. Marilyn Miller will add considerable strength to this program. Her accomplishments in both basic and clinical research are substantial. Dr. Miller's chief interest in regulation of erythropoiesis by changes in pulmonary and renal

function will add new links to other programs.

Conclusion

The Medical Department has undergone a substantial reorganization which has both improved its management and made it responsive to ERDA's mission. At the same time, the research effort continues to be at a very high level of excellence and is clearly intellectually satisfying to both old and new staff.

Dr. Cronkite deserves high praise for this successful reorganization and for the recent recruitment of young, enthusiastic investigators.

GB:jb

ASSOCIATED UNIVERSITIES, INC.  
 MEDICAL DEPARTMENT  
 1977 VISITING COMMITTEE

Committee Members	Term Expires
Dr. George Brecher (Chairman) Department of Clinical Pathology and Laboratory Medicine University of California 1378 Third Avenue San Francisco, California 94143	1977
Dr. Herman Suit Chief, Department of Radiation Medicine Massachusetts General Hospital Fruit Street Boston, Massachusetts 02114	1977
Dr. Leon Miller Department of Radiation Biology and Biophysics University of Rochester Rochester, New York 14627	1978
Dr. Kenneth Sterling College of Physicians & Surgeons Columbia University New York, New York 10027	1978
*Dr. Gareth Green Chairman & Professor Department of Environmental Health Sciences 1102 School of Hygiene The Johns Hopkins University 615 N. Wolfe Street Baltimore, Maryland 21205	1979
Dr. Louis Tobian Professor of Medicine University of Minnesota Hospital Minneapolis, Minnesota 55455	1979
Dr. David V. Bates Dean, Faculty of Medicine University of British Columbia Vancouver, B.C., Canada V6T 1W5	1980
Dr. James V. Neel Department of Human Genetics University of Michigan Ann Arbor, Michigan 48104	1980

Trustee Representatives:

Dr. Leon Jacobson  
 Director, The Franklin McLean  
 Memorial Research Institute  
 950 East 59th Street  
 Chicago, Illinois 60637

Dr. William H. Sweet  
 Massachusetts General Hospital  
 Fruit Street  
 Boston, Massachusetts 02114

\*Address Change

1124817