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NUCLEAR MEDICINE AT BROOKHAVEN NATIONAL LABORATORY*

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NOTICE
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Introduction

Traditionally the United States Atomic Energy Commission (AEC) was the governmental agency concerned with fostering the development of Nuclear Medicine as a discipline. In recent years a problem area has developed with relationship to responsibilities of governmental agencies for clinical research. The Energy Research and Development Administration (ERDA) has inherited Nuclear Medicine from the now defunct AEC. While an extensive review of the research program in Nuclear Medicine in ERDA has been carried out and there is at present continued support, the long term outlook is somewhat uncertain because of the rather more defined mission orientation of ERDA compared to the AEC. Meanwhile, no other governmental agency has assumed responsibility for Nuclear Medicine as a discipline although support has been provided along the line of organ or disease oriented research from the National Institutes of Health.

The National Laboratories, now under ERDA administration, provide exceptional facilities and opportunities for interdisciplinary research. Especially interesting is the possibility for interaction with scientists in non-medical fields such as chemists, accelerator physicists, engineers and mathematicians. At Brookhaven National Laboratory (BNL) a Nuclear Medicine Program exists which attempts to exploit the resources available to it and to pursue a broad program in radiopharmaceutical research. The scope of the program is such as to encompass all the aspects of such research from concepts of a radiopharmaceutical, perception of a need, development of nuclide production techniques, labeling and synthetic methods, animal distribution studies and clinical investigation. Two broad and complementary efforts exist, one in basic research and understanding

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of behavior of radiopharmaceuticals and the other in practical application toward the solution of clinical problems.

Description of Organization and Facilities

Brookhaven National Laboratory is operated for ERDA by Associated Universities, Inc., an organization composed of representatives from 9 eastern universities. The Nuclear Medicine Program is an interdisciplinary Laboratory program involving the Chemistry Department, the Department of Applied Science and the Medical Department with close association with the Instrumentation Division. Basic funding is through ERDA but some support has been obtained through grants and contracts from the National Institutes of Health and the Food and Drug Administration.

The laboratory is not far from the State University of New York at Stony Brook and many staff scientists at BNL hold appointments in the physical sciences at Stony Brook. The Medical Department is a Clinical Campus of the Health Sciences Center at Stony Brook.

A number of special facilities exist at the laboratory which are of importance to the Nuclear Medicine Program. The major accelerator for the high energy physics program is the 33 GeV alternating gradient synchrotron. The injector for this accelerator is a 200 MeV proton linac. Excess beam capacity of the linac is diverted to the Brookhaven Linac Isotope Producer (BLIP) which utilizes the beam for radionuclide production (1). The linac is designed for operation at 180 μamps but thus far has operated in the 50-100 μamp range. Up to ten targets can be irradiated simultaneously to produce large quantities of radionuclides, some of which would otherwise not be available in requisite quantity or purity.

The BNL 60" cyclotron, while nearly a quarter of a century old, has energy and particle characteristics which place it in an advantageous position relative to many "medical" cyclotrons (2). Its peak proton energy is over 30 MeV and it can accelerate deuterons, ^{3}He and ^{4}He particles as well. The machine is devoted almost entirely to the Nuclear Medicine Program and is under the control of the Chemistry Department, rather than being a physics machine.

Special facilities exist for the safe handling of large quantities of radioactivity and there are "clean" areas for radiopharmaceutical preparation.

Three gamma cameras (one with a positron attachment) and a whole body, single crystal rectilinear scanner are available for imaging. A 57 detector whole body counter has extreme sensitivity and ability to correct for variation in body build (3). Animal facilities exist for both large and small animals. The Hospital of the Medical Research Center has a capacity of 44 beds.

Activities

Research activities involving the labeling of organic molecules with short-lived positron emitters such as ^{11}C and ^{8}F are described by Dr. Joanna Fowler in this symposium and therefore will not be discussed in detail here. I will only indicate what have been the particular interests of the Brookhaven group.

Methods for producing carrier free ^{11}C-labeled compounds were developed at BNL a few years ago. We have explored the localization of ^{11}C-dopamine in adrenals (4) and ^{11}C-norepinephrine in the heart (5). A serious problem with these compounds is appropriate instrumentation for imaging their distribution, particularly in man. It seems that this problem is on the way to being solved and several devices may be available in the near future.

Work in ^{11}C-labeled amines is continuing, particularly with regard to the lung. The lung has a certain specificity for some amines and has the capability of detoxifying them, e.g., serotonin. We have been using ^{11}C-octylamine as a means of examining the monoamine oxidase activity of the lung (6). Early results are interesting but the practical application of the method is, as yet, uncertain.

Fluorine-18 has been used as a label for aromatic amino acids (7) and 5-fluorouracil (8). Newer methods for large scale production will probably mean considerably more effort going into ^{18}F-labeled compounds in the future.

A method for production of pure ^{123}I via the decay of ^{123}Xe was developed with the use of the BNL 60" cyclotron (9). The iodine-123 has been used to study thyroid function and anatomy as well as for labeling a number of compounds (10,11). A unique method of excitation labeling using xenon-123 has been investigated (12). At the present time indocyanine green and analogs of indocyanine-green are being evaluated for hepatobiliary function testing and imaging (13). These show interesting biological properties with extremely rapid hepatic uptake and biliary excretion with no entero-hepatic recirculation. Substitution of different halogens on the indole rings causes some change in the rapidity of excretion.

Following the development of the technetium-99m generator at BNL a number of labeled formulations were devised. Among these are technetium sulfur colloid (14), ^{99m}Tc-DTPA (15) and, more recently, the ^{99m}Tc red blood cell labeling kit (16). The last is a simple method for high efficiency labeling to provide a high quality myocardial function blood pool agent and a spleen imaging agent. In the course of developing the kit there was the uncovering of the carrier effect of ^{99}Tc and the problem of available stannous ion in rela-

tion to the amount of ^{99m}Tc. This may have important implications for the development of new kits and the quality control of presently used kits.

A number of BLIP radionuclides are now in production with several others planned in the near future. The major product is xenon-127, as a replacement for ^{133}Xe. The long physical half-life (36.4d) is convenient with regard to shelf-life while the short biological T-1/2 results in a low radiation dose, even lower than with ^{133}Xe. The favorable photon energies (203, 172 keV) provide more useful photons for imaging. Comparison studies of ^{133}Xe and ^{127}Xe are now in progress and the ^{127}Xe is now being supplied to a number of users.

Iodine-123 is being produced by the xenon-123 precursor method on the BLIP but its production is more susceptible to short term problems of linac operation. Consistency and reliability of ^{123}I production has been somewhat unsatisfactory but this should improve considerably following some impending improvements in the machine. Iron-52 has been supplied to a number of users. It is generally not available in large quantities elsewhere in this country.

A by-product of iodine-123 production is xenon-122 which is being developed into a new ^{122}Xe-^{122}I generator. The half-lives are 20.1 hrs for the parent and 3.6 min for the daughter. This may be a useful product for angiographic studies.

Also under investigation are the production of ^{68}Ge (the parent of ^{68}Ga), ^{55}Fe and ^{97}Ru.

Clinical interests have centered on the lung, heart and tumor localization. The laboratory is in the process of establishing a pulmonary toxicology program to further ERDA's mission of studying the environmental and health aspects of energy production. The ^{11}C labeled amines and xenon-127 will be used in support of this program.

The development of thallium-201 is a part of the effort related to heart disease (17,18). This radionuclide is now in wide-scale use although still on an investigative basis. Other developments related to heart disease are the ^{99m}Tc-red blood cell kit for gated imaging of the heart and the ^{122}Xe-^{122}I generator for rapid dynamic studies.

Tumor imaging has been related primarily to methods for detection of ocular melanoma (19). Two tumor models, one in hamsters and the other in rabbits are maintained for testing new agents.

Collaborative Program

The Laboratory has always served as a resource for investigators from many institutions in order to pursue areas where the special facilities and expertise of Brookhaven are particularly applicable. This situation exists, as well, relative to the Nuclear Medicine Program.

The collaborative and educational efforts take many forms. Some postdoctoral fellows spend varying periods of time learning cyclotron techniques and synthetic methods. Others learn how to handle large quantities of radioactive materials. Investigators may come to Brookhaven to work in the laboratories on specific research projects. Students spend electives or summers participating in the research program. Special materials such as radionuclides or kits under investigation are sent to collaborators at other institutions.

As part of its association with the Health Sciences Center at the State University of New York at Stony Brook the Clinical Campus at Brookhaven is affiliated with a newly approved residency program at the Veterans Administration Hospital in Northport, N.Y.

Summary

The Nuclear Medicine Program at the Brookhaven National Laboratory seeks to develop new materials and methods for the investigation of human physiology and disease processes. Some aspects of this research are related to basic research of how radiopharmaceuticals work. Other aspects are directed toward direct applications as diagnostic agents for everyday use. It is likely that positron emitting nuclides will assume greater importance in the next few years. This can be attributed to the ability to label biologically important molecules with high specific activity without affecting biological activity, using ^{11}C, ^{13}N and ^{15}O. Large quantities of these short-lived nuclides can be administered without excessive radiation dose and newer instrumentation will permit reconstructive axial tomography, providing truly quantitative display of distribution of radioactivity.

Not only is our attention being directed toward using the cyclotron products as discussed by Dr. Fowler, but other possibilities are being investigated. We have mentioned the ^{122}Xe-^{122}I generator as having the potential for looking at rapid dynamic processes. Another generator, the ^{68}Ge-^{68}Ga generator places a positron emitter in the hands of those far removed from cyclotrons. The possibilities for ^{68}Ga radiopharmaceuticals are as numerous as those for ^{99m}Tc diagnostic agents.

The program remains receptive to collaborative work with other institutions that can open up additional areas for the advancement of Nuclear Medicine.

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