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a statement describing the impact of...

The

MEDICAL APPLICATIONS DEVELOPMENT PROGRAM

in the

HL Division

of the

Department of Applied Science

of

BROOKHAVEN NATIONAL LABORATORY

describing work funded by AEC-DAT
budget categories 08-01-02 and 08-01-04

January 1973

a statement describing the impact of...

The
MEDICAL APPLICATIONS DEVELOPMENT PROGRAM
in the
HL Division
of the
Department of Applied Science
of
BROOKHAVEN NATIONAL LABORATORY

Contents

SUMMARY

The Medical Applications Development program of the HLD/BNL*, both presently existing and proposed, comprises work that forms the basis that is required to permit new improvements to be made in nuclear medicine, whether the improvements are made at Brookhaven or elsewhere.

The BLIP** is the only facility operating at present that can supply the new materials that will be needed for further advances in nuclear medicine. Even when the LAMPF's isotope production facility is constructed and becomes operational, it could not do certain things, which will continue to be possible only in the BLIP (or eventually in other accelerator facilities that will have been especially designed for inexpensive isotope production, incorporating the best features of the BLIP).

There are many nuclear medicine groups at various universities and there are two regional Centers of Radiologic Image Research (the latter located at Boston and Chicago and funded by the National Institute of General Medical Sciences) all of which are totally dependent on the BLIP for supplying the kinds of radionuclides that will be needed to:

1. reduce radiation dose to the individual patient and the cumulative dose to the population,
2. improve the quality, reliability, and information content of scintigraphic images, and thus
3. improve the quality and extent of health care available in the United States.

There are several other programs that also are partially dependent on receiving BLIP products.

The demand for large quantities of high purity iodine-123 exists now. There is great certainty in the fact that other "new" radionuclides will also be required in large quantities and high purities. There is equally great certainty that they will be capable of being produced economically in the BLIP. Moreover, it is crystal clear how this technology will be transferred to private industry as nuclear medicine improvements proliferate and demands for these radionuclides and radiopharmaceuticals sharply increase.

*HL Division of Brookhaven National Laboratory's Department of Applied Science (DAS)

**Brookhaven Linac Isotope Producer (an HLD-operated facility attached to BNL's 200-MeV proton injector for the AGS)

THE MEDICAL APPLICATIONS DEVELOPMENT PROGRAM

of the

HL Division*

of

BROOKHAVEN NATIONAL LABORATORY

HISTORICAL

The Medical Applications Development program at Brookhaven National Laboratory has been in continuous operation since 1950. Its public impact began in 1954 when its first product, an iodine-132 generator was introduced. The beneficial effects on mankind began almost immediately thereafter. For example, one of the early uses of this first generator occurred in the case of a little girl who had what doctors thought was a sublingual tumor, which they were about to remove surgically; examination via administration of a large amount of iodine-132 revealed that the mass was a congenitally misplaced thyroid, thus drastically altering the proposed surgical procedure. This case, which was typical of hundreds of thousands of subsequent medical applications of Brookhaven-developed radionuclides, was possible because iodine-132 (in this instance) had properties that were superior to any other of the then available radioisotopes (in particular iodine-131), and these properties permitted the relatively primitive detection equipment available at that time to do things that other radionuclides did not allow.

The iodine-132 generator was the first of a series of generators which permit a variety of short-lived radioisotopes to be shipped around the world, stored in the user's laboratory, and used at his convenience. Compact, safe, inexpensive, and simple to operate, they contain a long-lived "parent" radioisotope which, when it undergoes radioactive decay, is continually generating

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*This document describes a program which is supported by AEC-DAT funds (budget categories 08-01-02 and 08-01-04) and carried on in the HL Division (HLD) of Brookhaven National Laboratory's Department of Applied Science; unless specifically stated otherwise, the work described refers to that underway in the HLD. It also mentions collaborative work outside the HLD (e.g. in the BNL Medical Research Center) that is intimately linked to the AEC-DAT funded work although funded by others; an effort has been made not to confuse or obscure the distinction. This document does <u>not</u> cover any AEC-DAT work that is directed by other divisions at BNL; for example, it does not cover the Atmospheric Diagnostics program, even though this program utilizes other personnel of the HL Division.

fresh quantities of the desired "daughter" product (iodine-132 in the above case). A simple saline solution, when poured through the generator, sequesters only the desired product, and the resulting solution is ready for immediate use. Once removed from the generator, the product decays with its own characteristic half-life, providing the user with all of the many advantages of using short- rather than long-lived radionuclides.

Soon after the introduction of the successful iodine-132 generator, others were developed by the BNL HL Division. They included generators for

technetium-99m,	strontium-87m,	yttrium-90,	aluminum-28,
gallium-68,	cesium-131,	and	scandium-44.

One of these, the technetium-99m generator, was literally revolutionary on three counts. It was the technical breakthrough that permitted refinement and large-scale development of scintigraphy by improving its utility by three to four orders of magnitude. This, in turn, was the principal development that allowed nuclear medicine to develop into the widespread recognized profession that it is today. It was also the principal development that enabled the instrument manufacturing industry to expand its products and services tremendously by offering new lines of isotope cameras. Finally, it was the development that, more than any other factor, permitted profitable radioisotope production and distribution by the private sector. Nuclear medical procedures that had provided only marginal results before became common diagnostic tools, and procedures which previously had been restricted to terminal cases or to those involving dire necessity could now be used for mass screening of large populations. Moreover, the reliability of the information that the diagnostic procedure provided to the physician increased markedly. The magnitude of the impact of the technetium-99m development can be suggested by noting that it has been estimated that in the year 1971 over 2,000,000 doses of technetium-99m were administered to patients in the United States alone.*

During the period 1954 through 1967, Brookhaven made its unique radioisotope products available to the public by manufacturing and distributing them directly to users around the world. These products included

magnesium-28,	iodine-133,	fluorine-18,	argon-38,
tellurium-132,	molybdenum-99,	copper-67,	potassium-43,
xenon-128,	iron-52,	iodine-123,	dysprosium-157,
bismuth-204,	and yttrium-90/fused clay beads,		

in addition to the generators noted above.

Brookhaven's purpose in distributing these products was to provide the public with unique useful materials for which demands were developing and which could be supplied in no other way. However, by 1966 the demand for technetium-99m had grown so great that private industry petitioned the AEC to withdraw from supplying it. Brookhaven willingly complied, and six private companies took over the production and supply of this radioisotope. At the same time Brookhaven turned over to Oak Ridge National Laboratory the task of supplying all of its other radioisotopes, with the exception of magnesium-28 -- a radionuclide for which Brookhaven continues to be the world's sole supplier and of which the Laboratory has made shipments every month since 1955.

Although Brookhaven's products found occasional use in areas other than medicine, the overwhelming proportion of the applications were medical. From

*See Addendum #1: The Impact of Technetium-99m on Health Care

HISTORICAL...

the inception of the Laboratory's radioisotope program in 1950, there was collaboration with members of the BNL Medical Department. In 1963 this collaboration began to intensify, especially between two principals: Dr. Harold Atkins of the Medical Department and Powell Richards of the Department of Applied Science. Thus it was that in 1966, following the meteoric rise in the demand for technetium-99m and its takeover by private industry, the Brookhaven radioisotopes program was re-oriented specifically toward the development of medical applications of radionuclides.

This program fluorished, expanding and drawing continually greater attention and praise from the nuclear medicine profession, as one successful product or procedure followed another in fairly rapid succession. Some idea of the rapid recent growth of this program is gained by noting that prior to 1962 the expenditures in manpower and money were so small that the work did not appear as a line item in the budget of the Department of Applied Science. Up to that time the program's support had come from what was then the Division of Biology and Medicine and, for a short time, from the Research Division. In 1962 the Division of Isotopes Development began to support the program, and for the first six years the funding did not exceed $60,000/year. In FY 1969 the funding level jumped to $90,000/year, and by FY 1972 it was $280,000/year. The combined aggregate for the entire decade FY 1962-1971 was $873,000. This cost of developing and providing products and services which, by now, have been proven to be so highly beneficial to mankind pales into insignificance when compared to the cost of snow removal in New York City for the same period.

In 1969 it was realized that Brookhaven had under construction a truly unique accelerator (the 200-MeV proton Linac injector for the Alternating Gradient Synchrotron or AGS). This Linac was capable of not only supplying protons for the AGS but of simultaneously producing usefully large and commercially significant quantities of enough "new" radionuclides to triple the number and variety that could be made available for practical widespread use. This tremendous increase in variety would enable the medical profession to select more nearly ideal radiopharmaceuticals and procedures, thus providing benefits such as more informative and more reliable diagnoses, less radiation dose to the patient, and in many cases the ability to perform procedures that had heretofore been impossible.

HIGHLIGHTS OF THIS PROGRAM

1954 I-132 generator
1955 Mg-28 production technology (reactor)
1956 F-18 production technology (reactor)
1957 Tc-99m generator
1960 Cu-67 technology
1960 I-124 technology
1961 Ga-68 generator
1961 Tc-99m introduced to nuclear medicine
1961 K-43 technology
1963 Sr-87m generator
1963 Tc-99m-sulfur colloid
1964 Fe-52 technology (cyclotron)
1965 I-123 technology (cyclotron)
1967 Tc-99m-HSA, high specific activity
1968 Tc-99m-DTPA
1969 BLIP conceived
1970 BLIP construction begun
1970 Dy-157 technology
1970 Fe-52, millicurie preparation (cyclotron)
1970 I-123, high purity technology (cyclotron)
1971 Bi-204 technology
1971 Tc-99m "instant" compounds introduced
1971 Tc-99m-red blood cells
1972 BLIP completed, tested
1972 Tl-201 high purity technology
1973 BLIP on continuous automatic operation

THE SITUATION TODAY

GENERAL

The HL Division's Medical Applications Development program is highly successful. More than that, however, it is completely unique in many different ways, including the expertise of its personnel and the capabilities of its facilities. In both cases, i.e. of manpower and equipment, the uniqueness applies to individual people and specific devices as well as to the aggregate collection of men and machines.

THE UNIQUENESS OF PERSONNEL

One of the most widely known and universally respected leaders in the nuclear medicine profession is Powell Richards, Associate Head of the HL Division and directly in charge of the Division's Medical Applications Development program, to which he devotes full time. A member of the Board of Trustees of the Society of Nuclear Medicine, he is a frequent participant in the planning and execution of the teaching sessions that are provided at the SNM's national and sectional meetings; he also has organized and conducted various special purpose symposia and working meetings such as the Sunday conference at the Boston SNM Meeting (June 1972) which he assembled for the purpose of assessing for the AEC (at its request) the direction in which future isotope development should proceed. The author of 90 papers in the area of nuclear medicine, of which 50 were co-authored with medical doctors, Richards has given some seven invited papers covering both specific details and broad general aspects of nuclear medicine to scientific meetings in the United States, Japan, Italy, and Denmark. His on-the-spot personal assistance was also instrumental in enabling Turkey, Greece, and Puerto Rico to establish their own nuclear medicine programs. Richards' most recent honor was receiving the American Nuclear Society's Radiation Industry Award in November 1972 for his pioneering work in the development and introduction of technetium-99m into nuclear medicine.

Another widely known leader in the field of radioisotopes development is Louis Stang, Head of the HL Division. Stang's diversified achievements include founding the American Nuclear Society's journal Nuclear Applications (now Nuclear Technology) and serving as its Editor for its first five years. Although Stang spends only 50% of his time on radioisotopes development, he is a recognized expert in this field, having served as an official advisor, consultant, and delegate to IAEA meetings in Vienna (twice), Manilla, and Bombay, having been an official U. S. State Department-supplied consultant to the governments of Yugoslavia and Israel, and having presented invited lectures to the Indian Atomic Energy Establishment (four) and to the Mexican Society of Nuclear Medicine at their expense.

The group, considered as a whole, is also unique in many ways. It is diversified and includes a nuclear chemist, a radiochemist, a radiopharmacist, an inorganic chemist, two chemical engineers (one specializing in practice and the other in theory, the latter being licensed as a Professional Engineer by the State of New York), and several analytical chemists. The group is experienced; in fact, if one computes the combined aggregate of all of the relevant experience of the personnel who are working directly on this Medical Applications Development program in the HL Division, being careful to exclude formal training or general experience that is of only indirect benefit to the present program, the experience amounts to 165 years. The group operates in a highly interdisciplinary manner; of the 115 papers published in archival journals or presented at scientific and professional meetings, 55 were co-authored with members of the Brookhaven Medical Department or with researchers outside of the Laboratory.

The collaboration with people outside the HL Division, just alluded to, needs elaboration since it is one of the major strengths of the group and a factor that makes Brookhaven truly unique. In particular, the Brookhaven Medical Department has a nuclear medicine group under the leadership of Radiologist Dr. Harold Atkins (who, like Richards, is also a member of the Board of Trustees of the Society of Nuclear Medicine). This group, and especially Dr. Atkins, has worked extemely closely with HL Division personnel, especially Powell Richards, for the past decade. Their daily contacts with each other constitute an interdisciplinary collaboration the closeness of which will not be found duplicated at any other institution whether university, national laboratory, or private industry. HL Division personnel supply radioisotopes and radiopharmaceuticals which they have synthesized; the Medical personnel investigate the possible uses of these products, first on animals and then on patients when applicable; and personnel from both departments provide the ideas needed to maintain a vigorous on-going progression of one successful product or procedure after another. As an example, during the calendar year 1972, the HL Division provided the Medical Department with 419 radiopharmaceutical preparations for testing, evaluation, and subsequent routine usage; during this same period five different new "products" were conceived and brought to various stages of testing and evaluation. More recently, this collaboration has been broadened to include members of the BNL Chemistry Department, thus providing within a single organization a nuclear medicine program of truly exceptional strength.

The uniqueness and competence of the group are further attested to by the fact that Belgium, Colombia, Egypt, France, Germany, Greece, India, Israel, Italy, Japan, and South Africa have sent nationals to spend, in most cases, one to two years each working with this group, observing and learning procedures and techniques which were then taken back and applied to radioisotope development and production in the respective countries; the fact that, in all but two of these cases, the expenses of these people were paid by their respective governments is a measure of the value that foreign countries attach to the opportunity to have their people train with this group. Some of these countries have already sent more than one individual, and South Africa is scheduled to send a second person to work for a year beginning April 1, 1973.

THE UNIQUENESS OF FACILITIES

The uniqueness of the expertise of the personnel individuall, and collectively, is equalled only by the uniqueness of the facilities, also considered both individually and collectively. One of the most unique facilities in the world is the brand new BLIP (Brookhaven Linac Isotope Producer) which is operated by the HL Division as an integral part of its Medical Applications Development program and which began routine operation (in its "continually-on" mode) in January 1973. This facility, attached to the 200-MeV proton injector of the AGS, is the first facility in the world to harness a high-current high-energy accelerator to the task of preparing significant quantities of radionuclides. The exciting part of this achievement lies in the fact that the current, energy, and continually-on mode of operation combine the large-quantity capabilities hitherto found only in nuclear reactors with the versatility and flexibility hitherto found only in small-capacity cyclotrons to provide the isotope producer with easy and ready access to three times as many "new" radionuclides as have been hitherto available in commercially significant quantities. To illustrate specifically, the BLIP provides the means of developing and distributing (ultimately through private processors) multi-curie quantities of radionuclides, such as iodine-123, xenon-127, and iron -52, for which there is already a strong demand but which simply cannot be made at present in quantities large enough to make practical their adoption into nuclear medicine procedures; it also provides the only satisfactory means of similarly developing and supplying other radionuclides, such as ruthenium-97, technetium-97m, and thallium-201, for which a large future demand is guaranteed by the favorable properties of these radionuclides; finally, it provides the only means of supplying other radionuclides, such as chromium-44 or vanadium-44 about which nothing is known but whose properties can be predicted to be of practical interest.

In addition to this particular highly unique facility, the entire aggregate of other facilities available constitutes, in itself, a unique combination that is found nowhere else. This is true regardless of the functions of other laboratories with which Brookhaven might be compared, but it is especially true if one confines the comparison to laboratories having programs in nuclear medicine. This aggregate includes specialized machines such as the High Flux Beam Research Reactor (capable of delivering an epithermal flux of 1.5×10^{15} neutrons cm^{-2} sec^{-1}), the Medical Research Reactor with its special irradiation ports, the Tandem Van de Graaff generator (capable of delivering 140-MeV bromine ions, 80-MeV oxygen ions, and correspondingly energetic ions with atomic numbers above and below these examples), two smaller Van de Graaff generator which yield 3.5- and 5.5-MeV particles, respectively, an azimuthally varying field 60" cyclotron capable of delivering protons, deuterons, and helium-3 and -4 ions, a 33-GeV proton Alternating Gradient Synchrotron, and a 700-curie plutonium-238-beryllium neutron irradiation facility. It also includes a wider variety of machines of lesser capability such as neutron generators, X-ray generators and X-ray diffraction instruments, electron microscopes, and computers, not to mention a complete line of equipment needed for fabricating almost any kind of equipment from literally any kind of material.

PRIMARY RESEARCH AND DEVELOPMENT PROGRAMS

The remainder of this document is devoted to a more specific description of the present on-going work of this group and a brief glimpse of the projected possibilities for the future. As may be imagined from the foregoing introduction, the present and future programs heavily emphasize nuclear medicine. However, other non-medical programs also benefit, and these will be described too.

NUCLEAR MEDICINE

To place in proper perspective the detailed program descriptions that will follow, it is necessary to make some general comments concerning the role of Brookhaven's Medical Applications Development program and its effect on mankind as a whole and on private industry in particular.

The Role of the Program in the Nuclear Medicine Field

It is important to realize that continued and accelerated growth of the field of nuclear medicine is vital to the improvement of health care in the United States and, indeed, throughout the world.* Nuclear medicine offers imaging and visualization techniques that provide the physician with more information than he would otherwise have had about his patients, thus permitting a more accurate diagnosis. The addition of these imaging techniques to the conventional techniques, in itself, provides the doctor with helpful corroboration. However, health care can be improved still further by improving the quality of the information that these techniques provide. Improving this quality of information is doubly beneficial: First, it increases the reliability of the technique by clarifying the image being observed, thus reducing errors in interpretation. Second, it permits a reduction in radiation dose during diagnosis.

However, improving the quality of information provided by nuclear medicine techniques requires the making available of "new" radionuclides -- radionuclides which have already been discovered and characterized but of which the present availability is totally unsuitable. In most cases higher purity is required than can be obtained at present, and in every case quantities required are very much higher than presently obtainable. These new radionuclides can be made available only through the BLIP (described above under "Uniqueness of Facilities"). This facility is a totally new unique concept which for the first time allows the large-scale exploitation of spallation reactions for the production of radionuclides while permitting the simultaneous large-scale utilization of the more conventional lower-energy "cyclotron" reactions for the same purpose.

It should be noted at this point that the Brookhaven Medical Applications Development program is, for reasons outlined above, not only of crucial importance to the further development of nuclear medicine but that, in addition, it is the ultimate source of new material that is needed by an extremely large number of research groups throughout the United States that are engaged in developing and utilizing new nuclear medical techniques. Groups with whom specific collaborative work is in progress or planned are mentioned below under "Specific Collaborative Programs, Existing" and "The FY 1974 Prospects". The latter section also lists some of the groups from whom specific written requests for assistance have been received but with whom the collaboration might be expected to be no broader than simply supplying the requested assistance. This latter list is incomplete on two counts: (1) The limited time available for preparing this document precluded a

*See Addendum #1: The Impact of Technetium-99m on Health Care

thorough search of the files. (2) As more operating experience is gained with the BLIP and its impact becomes felt, many more inquiries for information and requests for assistance can be expected.

Worth special note are two groups not otherwise mentioned below, viz. the Center of Radiologic Image Research recently established at the University of Chicago and a similar center established a year ago in Boston, both funded by the National Institute of General Medical Sciences. Of eight research projects to be undertaken by the Chicago group, three will clearly be either totally dependent on or very much benefitted by the results to come out of the Brookhaven Medical Applications Development program; these projects are described as "development of new radionuclear imaging agents", "in vivo radionuclide distribution studies", and "clinical evaluation of imaging techniques in nuclear medicine". The work of the Boston center will be equally dependent on or benefitted by the Brookhaven program.

The Effect of this Program on Mankind

The goal of this program is to constantly improve the quality and increase the quantity of health care that the medical profession can provide the public at large. More specific examples of this general goal include

(1) the development of the means that will enable the physician to make a more reliable diagnosis than has been possible heretofore,

(2) the direct improvement of the health of the public by reducing the radiation dosage received by patients undergoing medical examination, and

(3) the accomplishment of the first two goals at a cost that is not burdensome to the public.

Examples of each goal can be cited here. For instance, diagnoses have already been improved in certain categories of patients by providing the physician with more information than he has been able to obtain with previous procedures. Consider one example: It used to be virtually impossible to "visualize" (i.e. to observe in a manner similar to that provided by the familiar X-ray picture) an amorphous non-bony organ such as the liver, and in treating disorders of the liver the doctor had to rely on a variety of indirect tests from which he inferred the condition of the liver. Now, however, by administering a radiopharmaceutical such as the technetium-99m-sulfur colloid and then scintigraphing the patient it is possible to synthesize an image of the liver which shows the physician not only its location, size, and shape but also whether some parts of it are not functioning and/or other parts of it are overworking. Similar techniques with other radiopharmaceuticals now permit other organs, such as the kidneys, heart, and spleen, to be visualized; this technique even permits the doctor to look inside the bones and observe the functioning of the bone marrow or the areas in which a fracture is healing rapidly or not at all.

Diagnoses have been made more reliable not only by increasing the amount of information available to the doctor but also by increasing the reliability and certainty of whatever information is provided. For example, a few years ago a doctor could only infer the existence and location of a brain tumor from the behavior of the patient during a few indirect tests or by procedures which carried considerable risk to the patient and were very costly. Now, however, many such tumors can be visualized -- positively located and identified -- by administering radiopharmaceuticals, such as technetium-99m in its pertechnetate form, with essentially no discomfort or risk to the patient. The test is therefore more readily applicable to a large population (i.e. as a screening procedure). Moreover, the mere fact of providing additional methods of diagnosis means that the result will be more reliable by virtue of the mutual corroboration of each test, even if any single test were in itself not completely reliable.

The reduction of the radiation dose received by the patient has a two-fold benefit. On the one hand, it means a reduction of the overall dose received by the public at large, thus contributing to a reduction in radiation-induced genetic damage which, in turn, means potentially thousands of fewer birth defects annually. On the other hand, it also means that certain individual patients, such as children and pregnant women, can receive the benefits of the newer more accurate diagnoses available via radiopharmaceuticals, although such patients in the past would not have been given the older radioisotopes at all for fear of incurring immediate or near-future radiation damage in that individual. The difference is that the newer radiopharmaceuticals, such as those developed at Brookhaven, utilize radionuclides such as technetium-99m, which, because of their particular nuclear decay properties, contribute a radiation dose to the patient that is frequently a factor of 100 lower than the radiation dose that the patient would have received from the older radioisotopes such as iodine-131.

Improved health care would be useless if it were so costly that few, if any, could affort it. One of the goals of the BNL Medical Applications Development program has been to make its products utilizable to the widest possible extent. To this end, procedures and equipment required by doctors to administer the Brookhaven products have deliberately been kept extremely simple, requiring no additional training on the part of the doctor's nurse or technician. Moreover, the costs of the BNL developed products have always been kept so low as not to add noticeably to the cost of patient care. In this connection, it is worth noting that it should be possible to make an isotope like iron-52 in the BLIP for approximately one dollar per millicurie, whereas prepration today on the cyclotron costs about $100/millicurie; (this high cost today is, of course, a drawback that must be added to the fact that there are not enough cyclotrons to make it possible to add iron-52 to the procedures available to the specialist in nuclear medicine).

The Effect of the Program on Private Industry

The Brookhaven program, far from constituting competition with private industry, has not only cooperated wholeheartedly with private industry and continues to do so but it actually has in a very direct material way increased the business that private industry enjoys.* As noted above, Brookhaven withdrew from its radioisotope production business in 1966 in order that six private companies could take over the production and distribution of technetium-99m, when the demand for this BNL-developed product reached the point where the industry could see a sure profit in it. Moreover, the advent of this particular radioisotope so increased the demand for more sophisticated radioisotope cameras that the effect was one of virtually adding an entire new line of products for the instrument manufacturers.

Brookhaven intends to continue in this tradition by offering to irradiate

*See Addendum #1: The Impact of Technetium-99m on Health Care

targets for private companies who can then process and distribute their own spallation-induced radioisotopes. To this end, the Brookhaven group invited 72 companies to send representatives to Brookhaven to learn of the potential of the new BLIP and how they could utilize this national resource, and the BNL team briefed the representatives of the eight companies that have thus far responded to the invitation. Brookhaven has stated repeatedly on every possible occasion that it is interested only in developing "new" radioisotopes, new radiopharmaceuticals, and medical applications utilizing these new products, that it would supply any of these new products that could not be obtained from other sources, but that it is not interested in performing any processing or distributing that private companies agree to undertake, except that it will do the target irradiations that will allow the industry to do its own processing and distribution.

Specific Collaborative Programs, Existing

The following is a brief outline of the various specific collaborative programs presently underway.

BNL Nuclear Medicine Program. The collaborative program of greatest importance, longest standing, and widest scope is Brookhaven's own integrated Nuclear Medicine Program. This program began in the early 1950's as a collaboration between the HL Division and the BNL Medical Research Center; more recently the BNL Chemistry Department has joined this collaboration. For nearly twenty years the HL Division produced and supplied a variety of radionuclides to staff members of the BNL Medical Research Center. Early examples included copper-67 to Dr. Cotzias (1960), iodine-124-labelled proteins to Dr. Lippincott (1960), and over 60 batches of potassium-43 to Dr. Dahl (1962-1964), who was studying potassium metabolism in his hypertension program.

However, the most intensive collaboration has been with Dr. Harold Atkins, beginning in 1963 and continuing to the present. Centered largely around the development of technetium-99m, technetium-99m-labelled compounds, and clinical evaluation of these materials, the program has already produced several important contributions to nuclear medicine. Examples include the development of

(1) techniques for using technetium-99m for thyroid uptake studies,

(2) improved technetium-labelled human serum albumin (HSA),

(3) technetium-tagged diethylenetriaminepentaacetic acid (DTPA),

(4) the labelling of red blood cells (RBC) with technetium-99m, and

(5) the application of such labelled RBC for visualizing the spleen and the vascular system.

Although technetium-99m has been the radionuclide most frequently studied in this program, others are also being studied. For example, the HL Division is studying radionuclides of ruthenium and indium, the Chemistry Department is studying the labelling of compounds with carbon-11, and both groups are studying fluorine-18 and iodine-123, with the Medical Department, of course, being heavily involved in all of these studies.

Iodine-123 deserves special mention because of its rapidly increasing importance and is discussed in more detail below under "Bureau of Radiological Health, Food & Drug Administration". The statistics and descriptive comments in that section apply equally well to Brookhaven's collaborative Nuclear Medicine Program, except that the latter has for the past two years been evaluating iodine-123 for thyroid imaging and investigating several iodine-123 labelled compounds. Because this particular material has been made on the BNL 60" cyclotron, the quantities that have been available for test have been limited. However, the recent startup of the BLIP will provide ample material for evaluation and development.

Altogether literally thousands of radiopharmaceuticals and labelled compounds have been supplied by the HL Division to the BNL Medical Research Center for evaluation and nuclear medicine service. For example, during the 1972 calendar year, 241 radiopharmaceutical preparations were supplied for clinical studies, and an additional 178 labelled compounds were furnished for development and product evaluation studies. Altogether, 32 papers in archival journals and 22 presentations before scientific meetings, resulting from this program, have been jointly authored by Medical Department/Department of Applied Science personnel. Considering all of these numbers and the fact that the program is truly a joint one, it is clear that the contribution of the HL Division is crucial and vital to this part of the Medical Department's program. At the present, the part of the program of the Medical Department directly affected involves three M.D.'s, a physicist, a chemist, and three technicians, and is funded at $570,000/year.

Recently, a program entitled "The Brookhaven Nuclear Medicine Training Program" has been established. Under this program residents who are training at universities and hospitals in the field of nuclear medicine spend time at Brookhaven learning various techniques to supplement the training at their institution. For example, they spend a week in the HL Division learning radionuclide production and radiopharmaceutical preparation techniques (see especially p. 18).

It is interesting to note that a different type of cooperation also exists in which another member of the Medical Department, Dr. Richard Stoner, provides the HL Division with experimental determinations of the distribution in small animals of a variety of materials furnished by the HLD. These studies are helpful in determining the probable utility of a potentially useful material. Examples have included fluorides, strontium, technetium, tin, indium, colloids, and various chelates which the HL Division is using to develop such things as superior bone-seeking agents. The interesting feature of this cooperation is that the work is not of primary interest to Dr Stoner's own program, and the fact that he is willing to provide this service is a measure of his desire to assist another program that he recognizes as being valuable and meritorious.

National Cancer Institute. Breast cancer is the most common cancer in women in the United States. Five to six percent of all women can expect to develop cancer of the breast during their lifetimes. Breast cancer causes approximately 13 deaths per 100,000 population per year. One attempt to deal with this problem is to pmprove early diagnosis with the help of mammography, i.e. X-rav examination of the breasts. The ability to use this technique as a screening procedure in the appropriate segment of the population is limited by the radiation dose to the skin incurred by this examination. Theoretically, a monochromatic source of low-energy radiation should be ideal in that it would increase the quality and, therefore, the reliability of the examination and, at the same time, reduce the radiation dose by a factor of, perhaps, 100.

Technetium-97m, with its 18- to 21-keV X rays and 90-day half-life, could provide the required good contrast and the desired reduction in radiation dose, provided that it is available in high purity (to eliminate other photon-emitting impurities). Implementing a mass screening procedures implies large-scale availability of the radionuclide. Consideration of possible alternative radionuclides and/or preparation procedures leads one to the conclusion that the objectives of a mass mammography program cannot be met except via the route of producing technetium-97m in the BLIP.

Accordingly a collaborative program between the Medical and Applied Science (HL Division) Departments of BNL is being funded (at the level of $69,000 for the first year) by the National Cancer Institute. The purpose of this program is to develop a technetium-97m source suitable for mass mammographic screening.

<u>Bureau of Radiological Health, Food & Drug Administration.</u> Arrangements for a collaborative program between BNL's HL Division and the FDA's Bureau of Radiological Health/Nuclear Medicine Laboratory at Cincinnati (BRH/NML) have reached the contract writing stage. In this arrangement BRH/NML will pay Brookhaven $15,000 via an interagency transfer of funds to enable BNL to expedite the development of large-scale production technology for high-purity iodine-123 and to provide BRH/NML (Dr. Vincent Sodd, principal investigator) with material for a preliminary evaluation of the desirability of this radionuclide for medical applications.

The FDA's interest in expediting this work is part of a broader but intense interest in the medical community in the use of iodine-123 for thyroid studies and as a label for many useful radiopharmaceuticals. This interest stems from the fact that high purity iodine-123 is certain to lower patient radiation doses by factors of about 100, relative to the radioisotopes such as iodine-131 which it will supplant. However, this interest of the medical community is predicated on the premise that iodine-123 will be available

(1) reliably,

(2) in large quantities,

(3) in pure form, and

(4) at a competitive cost.

The BLIP is the only facility capable of meeting all four requirements. (The Los Alamos LAMPF may be capable of providing iodine-123, but because of the higher proton energies that Los Alamos will be using, it is unlikely that the LAMPF could achieve the same iodine-123 radiopurity as can be achieved in the BLIP, and the reduction in patient radiation dose, which is the reason for the medical interest in iodine-123, depends on the iodine-123 being free of impurities such as iodine-124. Moreover, the construction of the LAMPF's isotope production facility is still far from complete, whereas the BLIP is now operating in its normal routine "continuously-on" mode.)

The importance of iodine-123 can be gauged to some extent by consideration of a 1966 survey of radionuclide use in medicine. That year saw a total of 651,426 studies on patients performed with iodine-131. This usage constituted 84.9% of all function studies and 49.8% of all scanning (imaging) procedures. With the tremendous growth in nuclear medicine in the seven years since then, it is clear that iodine-131 utilization has risen substantially. Substitution of iodine-123 for iodine-131, by reducing the radiation dose to each patient, will therefore be of significance to the entire population. Clearly the earlier that iodine-123 can be put into clinical use in place of iodine-131, the greater will be the cumulative dose reduction to the patient population -- hence the FDA's strong interest in expediting the development of this radionuclide and the radiopharmaceuticals derived from it. With regard to the quantities of iodine-123 needed, it must be emphasized that existing facilities other than the BLIP (i.e. cyclotrons) certainly cannot be expected to begin to make enough to satisfy the demand. This particular collaborative program will provide for clinical evaluation of thyroid function and visualization studies on 500 to 1,000 patients.

It is useful to point out that iodine-123 will provide scintigraphic images containing a much higher quality of information than is available from procedures with other radionuclides. This is an important factor that will increase the reliability of a diagnosis.

Bureau of Radiological Health, Food & Drug Administration...

Although the accelerated program described above is only for one year, it is expected that following its successful completion the collaboration would be expanded to include the development of iodine-123-labelled organ-specific radiopharmaceuticals and possibly the development and evaluation of other radionuclides for the purpose of still further reducing patient radiation dose.

Argonne Cancer Research Hospital. Another collaborative program of long standing (since 1961) is that with staff members of the Argonne Cancer Research Hospital (ACRH), especially with Dr. Paul Harper. It was this colaboration that actually resulted in the introduction of technetium-99m into nuclear medicine. Several other developments by the HL Division of BNL grew out of this collaboration, including improvements in the quality and design of the technetium-99m generator, the preparation of the technetium-99m-sulfur colloid, and improvements in the methyl ethyl ketone (MEK) solvent extraction method for separating technetium-99m from its parent molybdenum-99. During the period between October 1961 and June 1965, Brookhaven supplied 132 technetium-99m generators containing a total of approximately 18,000 millicuries of molybdenum-99 to ACRH.

Although a mutual interest in further technetium-99m developments still exists, the major collaboration underway at present centers around the development and evaluation of thallium-201 as a cardiac imaging agent. As soon as sufficient thallium activity is produced, material will be supplied to ACRH for evaluation. ACRH is also interested in various other BLIP radionuclides as they become available.

Hospital of the University of Pennsylvania. Since early in 1964 a collaborative association has been maintained between HL Division members at BNL and staff members of the Nuclear Medicine group at the University of Pennsylvania, principally Dr. David Kuhl. The original purpose of this collaboration was to assist the University in incorporating the use of technetium-99m into their nuclear medicine program. In particular, Brookhaven assisted in setting up their equipment and procedures for producing the technetium-99m-sulfur colloid and later in establishing their techniques for labelling red blood cells with technetium-99m. During the period between March 1964 and August 1966, when BNL discontinued the distribution of technetium-99m generators, Brookhaven supplied the University with 116 generators containing a total of approximately 20,000 millicuries of molybdenum-99.

More recently the Pennsylvania group's interests have included sending residents to Brookhaven for training in radionuclide production and radiopharmaceutical preparation techniques (see p. 13).

Dr. Kuhl is extremely interested in several of the products that will come from the BLIP (e.g. tantalum-179, iron-52, and xenon-127, in particular), and this collaboration will be expanded to include them as soon as they are available. He has also expressed an interest in gallium-67 and iodine-123.

Harvard Medical School. The objective of this collaboration between BNL HL Division members and those of the Harvard Medical School (in particular Dr. S. James Adelstein) is to exchange information of mutual interest in the areas of radioisotope technology, radiopharmaceuticals, and applications of these materials and this information to nuclear medicine. This exchange occurs via periodic joint meetings between staff members from each institution, the first occurring in Boston in July 1973 and the second at Brookhaven in December 1972. Future such meetings will be held every six months.

Initially the Harvard interests have mainly revolved around technetium chemistry and technetium-labelled radiopharmaceuticals, particularly technetium bone-scanning agents such as the polyphosphates. Later, as BLIP products become available, the Harvard group will participate in studies and evaluation of some of the radionuclides produced. It is expected that this collaboration will result in the submission of joint proposals for funding specific areas of work of mutual interest.

State University of New York at Stony Brook (SUNYSB). The Stony Brook branch of SUNY has four off-site "clinical campuses" located at:

(1) Brookhaven National Laboratory's Medical Department, including the Nuclear Medicine Program under Dr. Harold Atkins,

(2) Long Island Jewish Medical Center under Dr. Lester Levy,

(3) the Northport VA Hospital under Dr. Walton Shreeve, and

(4) the Nassau County Medical Center under Dr. Stanley Goldsmith.

The HL Division is in the process of establishing a collaborative program with the four campuses, collectively. The role of the HL Division would be

(a) to train residents and others in the production of radionuclides and the methods and quality control involved in the preparation of radiopharmaceuticals,

(b) the supplying of radiopharmaceuticals to the clinical campuses for training and educational purposes, and

(c) participation in joint research projects involving medical applications of radionuclides.

Johns Hopkins Medical Institutions. Since 1963 a collaborative association has been maintained between the HL Division and staff members of the Nuclear Medicine group, especially with Dr. Henry Wagner, at the Johns Hopkins Medical Institutions. The principal objective of this program is the development of medical applications of technetium-99m and of technetium-99m-labelled radiopharmaceuticals. During the two-year period between December 1963 and December 1965, Brookhaven supplied them with 93 technetium-99m generators containing approximately 17,000 millicuries of molybdenum activity, and during 1971 Brookhaven supplied them with technetium-99m-DTPA "kits" for their testing and evaluation. (This latter item represented the first of several so-called "instant" procedures that Brookhaven developed, by which the user simply mixed together a specified reagent with a particular radionuclide to produce immediately or "instantly" a material having specific nuclear medical properties; the Brookhaven objective in this instance was to have its own in-house results evaluated and confirmed by a completely independent competent outside group.) The Johns Hopkins group was so pleased with this first kit that they continued to make their own using the Brookhaven technique until private industry made available a satisfactory commercial product.

Brookhaven has also assisted the Johns Hopkins group in the labelling of red blood cells with technetium-99m, and the JH group has recently published a paper describing the use of this method for measuring red blood cell volume. In addition, Brookhaven has supplied the JH group with many magnesium-28 and iodine-132 generator shipments over the years.

Dr. Wagner is much interested in participating in the evaluation of several BLIP products as they become available in the near future.

State University of New York, Upstate Medical Center (SUNYUMC). In 1970 a collaborative program was established between the HL Division and SUNYUMC, principally with Drs. John McAfee and G. Subramanian, for the purpose of developing the production technology for dysprosium-157 and evaluating it as a radiopharmaceutical for the visualization and diagnosis of bone and bone marrow. Eight 10- to 25-millicurie shipments were made, and three publications resulted from this part of the program.

As BLIP products become available, this collaboration will be expanded to include the evaluation of several of them.

University of Iowa Hospitals. The objective of this on-going collaborative program between the HI. Division and the University of Iowa Hospitals, principally Dr. Richard Petersen, is to develop the production technology for bismuth-204 and to evaluate it for the visualization and diagnosis of tumors. The incentive for this program lies in the fact that for many years bismuth has been reported to localize in certain types of tumors, and bismuth-204 would be one of the best bismuth radionuclides to use for this purpose. Seven shipments of bismuth-204 ranging from five to ten millicuries each have been made, and additional shipments will be made in which the bismuth will be in a different chemical form in an effort to improve its distribution in the test subjects. Although bismuth-204 would eventually be made in the BLIP, the above test material was made on the BNL 60" cyclotron, for the use of which the University of Iowa reimbursed BNL.

State University of New York, Downstate Medical Center (SUNYDMC). An especially active collaboration is maintained between the HL Division and SUNYDMC, particularly Drs. Nathan Solomon and Joseph Steigman. In fact, Dr. Steigman, who is a Radiochemist on the SUNYDMC staff, holds an appointment as Guest Scientist on the BNL Scientific Staff and spends one or two days a week at Brookhaven (in the HL Division) working on this program. The mutual interests in this case center around the chemical and clinical evaluation of new technetium-labelled compounds. Joint studies of the chemistry of technetium in common technetium-labelled radiopharmaceuticals are underway. Preliminary studies to evaluate the clinical usefulness of xenon compounds have already begun and should later expand into research and applications development involving the use of xenon-127 in studying lung function; (this is a related effort described more completely below under "The FY 1974 Prospects"). Thus far, one publication has resulted from this joint collaboration.

Albert Einstein College of Medicine. An active collaborative program in radiopharmaceutical development is in progress between the HL Division and the Albert Einstein College of Medicine, principally involving Drs. M. Donald Blaufox and Rau Chervu. Dr. Chervu is a Research Collaborator on the Scientific Staff at BNL, where he spends several days a month in the HL Division investigating problems of mutual interest involving technetium-99m radiopharmaceuticals and indium-111 and tin-117 compounds that are potential bone visualizing agents.

Washington (D.C.) Hospital Center. An active collaborative program is underway between the HL Division and the Washington Hospital Center, particularly with Drs. William Eckelman, who is a former member of the HL Division and now a Research Collaborator at BNL, and Richard Reba. Joint work is in progress in the development and evaluation of technetium-99m-labelled radiopharmaceuticals and in studying the chemistry of technetium relating to labelled biomedical products, such as technetium-99m-labelled red blood cells.

South African Council for Scientific and Industrial Research. Through the initiative of the South African Council for Scientific and Industrial Research, complete arrangements have already been made to have one of its staff members, Dr. Rudi Neirinckx, spend a year in the BL Division working and exchanging ideas on problems of mutual interest in the area of the development of radionuclides, radiopharmaceuticals, and medical applications of these materials. A one-year appointment to commence April 1, 1973 has already been offered to and accepted by Dr. Neirinckx. The SACSIR will pay all of Dr. Neirincks' expenses to and from BNL and will continue to pay his full South African salary during his stay at BNL, and BNL will contribute an equal amount of salary to compensate for the higher cost of living in this country.

The FY 1974 Prospects

All of the existing programs described above will continue into FY 1974, and most of them will continue well beyond. In addition, new programs, some of which are described below, are in various stages of proposal preparation and consideration, such that if sufficient funds were available all of them could begin some time in FY 1974.

National Heart and Lung Institute (NHLI). Several of the programs are applicable to the interests of NHLI. They include the following:

Myocardial Infarction Diagnosis. Heart disease is the leading cause of death in the United States, the rate being 350-400 deaths per 100,000 population. In a significant proportion of these individuals, diagnosis of the existence of coronary artery disease is not apparent early in the course of the condition when myocardial infarction is occurring. A radionuclidic method for diagnosing myocardial infarction would be extremely helpful in saving many lives and preventing disability. Such methods are usually of little discomfort and no risk to the sick patient.

Preliminary work with one radiopharmaceutical, thallium-201, suggests that it would be ideal for this purpose. It should be capable of producing high quality myocardial imaging with low radiation dose. Only small amounts have been available for experimental use due to the difficulty of producing the thallium-201 on the cyclotron. Only the BLIP is capable of producing the quantities of high purity thallium-201 that will be required to evaluate this radionuclide properly and to make its widespread use practical.

A research grant proposal covering the experimental evaluation of thallium-201 has been submitted to the National Institutes of Health. This proposal also considers rubidium-82 as another potential agent for this purpose, but it, too, would have to be produced in the BLIP to be practical.

National Heart and Lung Institute (NHLI)...

Myocardial Blood Flow. A proposal is being made to NHLI by the Nuclear Medicine Division of a leading university to study myocardial blood flow via rubidium-82. The head of that division has invited the HL Division to collaborate in this study and has offered to include in the proposal funds which the HL Divisiin would use to develop a generator for making rubidium-82 available (from its BLIP-produced parent, strontium-82). They have, of course, also expressed an interest in receiving rubidium-82 generators once they become available. Although the discussions are at too early a stage to predict the outcome with certainty, it seems quite likely that the collaborative arrangement requested by this group would be set up. This group also expressed an interest in thallium-201 and xenon-127.

National Heart and Lung Institute (NHLI)...

Lung Perfusion and Ventilation. An important and already widely used diagnostic procedure in nuclear medicine is the study of lung perfusion and ventilation via radionuclides. However, xenon-133, which is what is currently in use for these procedures, is far from ideal because absorption and scattering of its low-energy photons by bone and tissue make external studies difficult. Xenon-127, with its higher energy photons and longer half-life, would be vastly superior to xenon-133 for this application.

The BLIP is the only operating facility that is feasible for making xenon-127 in the quantities and purities that would be required for practical introduction of this radionuclide into nuclear medicine. The HL Division is already developing the production/purification technology for xenon-127. It is proposed to expand this on-going work to include the evaluation of perfusion and ventilation techniques with this radionuclide -- areas which should be of special interest to the NHLI. This latter work would be a joint collaboration between the HL Division, the BNL Medical Research Center, and the State University of New York Downstate Medical Center (see above, page 24).

National Heart and Lung Institute (NHLI)...

Hemodynamics. Another proposal already submitted to NHLI for funding involves collaboration within the Brookhaven Nuclear Medicine program (although the main thrust comes from the HL Division) in a study of hemodynamics from a chemical engineering standpoint. This study aims at an elucidation of thrombogenesis as affected by parameters such as flow rate, turbulence, etc., and the immediate emphasis is on the practical improvement of permanently implanted cannulae and arteriovenus shunts such as are needed for procedures like hemodialysis, extracorporeal irradiation of blood, etc. The experiments would be in vivo. Although various instruments would be used, one of the key factors in this proposal is the use of various blood components that will have been labelled with different suitable radionuclides. While it may be possible to conduct this study with conventional presently available radionuclides, this study will be much improved and the results easier to interpret through the use of the wider variety of radioactive labels for the various components that are becoming available via the BLIP.

National Heart and Lung Institute (NHLI)...

Non-Thrombogenic Surfaces. Another proposal, not yet submitted, which will be of interest to the NHLI is similar in many ways to the Myocardial Infarction Diagnosis proposal (described above, page 28). However, in this case the thrust is aimed at understanding thrombogenesis not as a function of geometry of the blood vessel or the flow factors within it but rather as a function of surface material. Nevertheless, the proposal would utilize similar techniques of tagging the different compounds of the blood with different radioactive labels so that the order in which the different components enter into thrombogenesis and the kinetics with which the various thrombogenetic steps occur can be determined as a function of type of surface material associated with the thrombogenesis. As in the previous proposal, the availability of the new radionuclides that will be available in practical quantities only from the BLIP will make the results easier to interpret and more reliable.

National Institutes of Health Clinical Center (NIHCC). All of the arrangements have been completed for this collaboration between the HL Division and the NIHCC Department of Nuclear Medicine, which is headed by Dr. Gerald Johnston. Mr. Robert Chandler, a Radiopharmacist at NIHCC, has been appointed a Research Collaborator at BNL to serve as the liaison between the two groups. The objective of this program is to make Brookhaven's unique capabilities and facilities for radionuclide production available to the nuclear medicine program of NIH and to enable the NIHCC to participate in the development of preparative, quality control, and analytical techniques for BLIP-derived radiopharmaceuticals that are of particular interest to NIHCC. These include, among others,

technetium-99m compounds, labelled red blood cells, iodine-123, radiocolloids, iron-52, and indium-111.

The Brookhaven role in this effort is to be funded by the NIHCC at an initial support level of one man. Delays in the passage of the HEW appropriations have forced a delay in this funding. However, it is BNL's understanding that NIHCC intends to provide these funds as soon as their budgetary problems permit.

National Cancer Institute. A research proposal by members of the BNL Medical Research Center to the National Cancer Institute will, if funded, measure blood, plasma, and red cell volume and blood flow, transit times, and clearance rates in tumors. To be carried out effectively, this proposal depends on receiving from the HL Division

(1) red blood cells tagged with technetium-99m and possibly other labelled blood components,

(2) a gas such as xenon-127 (which requires production in the BLIP) to measure washout rates, and

(3) advice on the techniques for measuring the rates of flow of blood.

The furnishing of these types of service was mentioned briefly above under "BNL Nuclear Medicine Program" and below under "Services Provided".

Other Laboratories. In addition to the laboratories noted in the programs described above, many other laboratories will be receiving BLIP-produced radionuclides for the purpose of evaluating them for nuclear medical purposes and for conducting their own development programs in nuclear medicine. The following table indicates some of the institutions from which the BL Division has received letters expressing strong interest in receiving the radionuclides indicated.

	Xe^{127}	I^{123}	Fe^{52}	K^{43}	Other (See Notes)
Va Hospital, Denver, Richard S. Trow	x	x	x	x	(1)
State University of New York at Buffalo, Monte Blau	x	x	x		
Washington University, St. Louis, R. James Potchen	x	x	x	x	
University of Minnesota, Minneapolis, Lawrence E. Williams	x	x			(2)
The University of Chicago, Paul Hoffer	x	x			
The University of Texas, Dallas, Frederick J. Bonte					(3)
Sloan-Kettering Institute for Cancer Research, New York City, Roy S. Tilbury	x		x	x	(4)

(1) gallium-67, dysprosium-157
(2) technetium-97m
(3) thallium-201
(4) sulfur-38, chromium-48, krypton-79, rubidium-81, tin-113

NON-NUCLEAR MEDICINE PROGRAMS

The HL Division's Medical Applications Development program clearly depends heavily on the operation of the BLIP, and, although the BLIP will be devoted almost exclusively to making radionuclides that will be developed for medical applications, this is not its sole use. At least two other non-medical research and development programs are described here, and the relationship to private industry is described below.

Controlled Thermonuclear Research

The Metallurgy and Materials Science Division in BNL's Department of Applied Science, has a $50,000 program underway to measure radiation damage in materials exposed to very high fluences of fast neutrons. Accordingly, they plan to irradiate test samples to fluences of 2×10^{20} neutrons per square centimeter (14 ± 5 MeV). Placement of these samples near a special target in the BLIP should provide such fluences with a one-year irradiation. The BLIP is the only facility at Brookhaven (and there are virtually none elsewhere, except the LAMPF) that could provide such fluences.

Neutron Source Development

One of the products that is readily made in the BLIP in commercially significant quantities but otherwise unavailable is yttrium-88. This radionuclide emits photons which, when it is mixed with beryllium, will make a neutron source that is far superior to presently used antimony-124-beryllium sources and, for some purposes, even to californium-252 sources. Some interest in obtaining BLIP-produced yttrium-88 has been expressed already by two categories of people. One group is involved in the AEC's Safeguards Program, for which an yttrium-88-beryllium source would appear to have many advantages over other neutron sources for non-destructive interrogation of larger diameter tanks and pipes than are possible at present. Another group is found in the private instrument industry, which is already developing antimony-124-beryllium neutron sources for special in-the-field neutron activation analysis purposes. The HL Division plans to make yttrium-88 for testing and evaluating these applications, but under the present funding and with medical applications development receiving such a high priority, it is unlikely that this will occur prior to FY 1976, unless extra funding is forthcoming or unless private industry requests irradiation of targets for their own studies along these lines (see below under "Services Provided - Private Industry").

SERVICES PROVIDED

The foregoing text described programs in which the HL Division is engaged in varying degrees of collaboration in primary research and development. However, important additional effort is also expended in providing related work for others on a service basis.

NUCLEAR MEDICINE

Two of the sections above ("BNL Nuclear Medicine Program", pp. 12-13, and "The FY 1974 Prospects - National Cancer Institute", p. 34) mentioned briefly that the HL Division supplies certain radiopharmaceuticals, radionuclides, and other forms of assistance on a service basis to these programs. Although this service work is not of primary interest to the HL Division, it is nevertheless a very important benefit derived by other groups. The types of service and conditions under which it is supplied can be illustrated. For example, even after a radiopharmaceutical product or procedure has been fully developed it is often desirable to make further routine use of the product or procedure in the BNL Medical Research Center, as a means of maintaining cognizance of possible problems that may later develop, as a means of monitoring other new developments such as new instruments that become available, and, in some cases, as a means of providing ancillary treatment to a condition of a patient other than the primary condition for which the patient was admitted. Whatever the reason or the need, the HL Division prepares on request a number of radiopharmaceuticals from radionuclides that it has either purchased from private industry or has prepared in a BNL accelerator. For example, in calendar 1972 alone, 241 radiopharmaceutical preparations were supplied on a service request basis to the Medical Research Center in addition to the 178 labelled compounds that were furnished for development and evaluation as part of a collaborative program. When it is remembered that the BLIP did not become operational until the end of this period, it is clear that its advent, together with its many new and unique products, will serve to maintain the demand for this service work.

PRIVATE INDUSTRY

The BLIP and the unique expertise and considerable experience of the HL Division personnel are regarded as a national resource for the direct benefit of the public and of private industry, through which the public will also benefit indirectly. Thus, the BNL program can be summed up as follows:

> When a demand for a radionuclide has built up to the point where private industry desires to take over the production and distribution of the radionuclide, industry will be encouraged to do so and will be assisted in every way possible.

To this end, Brookhaven will irradiate targets in the BLIP for private companies and will ship the raw irradiated targets to them so that they can process them according to their own proprietary recipes and distribute them to their own customers. The charge for this irradiation will not be high enough to generate a profit for Brookhaven nor will it be so low as to work a hardship on companies that have already invested in their own cyclotrons. The only situation under which Brookhaven would undertake to do all of the processing and final distribution to the end user would be one, if it develops, in which a demand for a particular product builds up but private industry for some reason is uninterested in supplying it. Brookhaven's history provides precedent for this policy and eloquent evidence that it will be adhered to:

PRIVATE INDUSTRY...

In 1966, when the demand for technetium-99m had increased to the point where private industry desired to take over its production and distribution, Brookhaven withdrew from this work and turned it over to six private companies. At the same time it turned over to Oak Ridge National Laboratory the production and distribution of all of its other isotopes except one, magnesium-28. To this day, no one has offered to take over the production and distribution of magnesium-28, and it continues to be the one isotope that Brookhaven produces and supplies every month to a half dozen or so different customers each time.

Of interest to note is the fact that as new products are developed and demands for them mount and as industry consequently begins to make increasing use of the BLIP, the operation of the BLIP facility *per se* is expected to become self-supporting through the income from the service irradiation of targets for industry. Moreover, this is expected to occur while making only reasonable charges for these irradiations.

It should be noted also that some very preliminary considerations undertaken recently at Brookhaven suggest the possibility of building a second generation linear accelerator that will incorporate only the features that will have been shown by BLIP operation to be needed or desirable for radioisotope production, omitting all features that are not necessary for this purpose. The cost of such a machine is believed to be low enough that it could be built and operated on a self-supporting basis some five to ten years hence.

INFORMATION SOURCE

Considerable effort has been made to eliminate errors from this draft. If any remain, I accept sole responsibility for them. I will also be pleased to supply additional details as needed.

Louis G. Stang, Jr.

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IN[illegible]F RADIONUCLIDES

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ADDENDUM #1

The Impact of Technetium-99m on Health Care

The following figures and statements, recently compiled by the Society of Nuclear Medicine, show the impact of nuclear medicine in general and of technetium-99m generators in particular on the health care available in the United States:

1. The innumerable contributions of nuclear medicine to the diagnosis and treatment of patients are reflected in the fact that the Joint Commission on Accreditation of Hospitals now requires that nuclear medicine services be made available to patients in hospitals seeking accreditation.

2. Of the 6,622 hospitals reporting to the American Hospital Association, 35% deliver nuclear medicine diagnostic services to patients. There are 5,982 licenses for the medical use of radionuclides in the United States.

3. Of the 32,663,000 patient admissions reported to the American Hospital Association for 1972, an estimated 2,900,000 patients (or 9%) received a radiopharmaceutical containing technetium-99m derived from generators.

4. Five of the larger radiopharmaceutical manufacturers and distributors shipped the following total numbers of technetium-99m generators:

60,979 in 1970
70,348 in 1971
79,185 in 1972

(Note: The impact of radiopharmaceuticals containing technetium-99m is even greater than the above figures indicate. This is because some hospitals use technetium-99m obtained directly from a distributor via solvent extraction, rather than via a generator, and the above figures apply only to generators.)

ADDENDUM #3

Industry-Brookhaven Interaction in the Development of the Medical Applications of Radionuclides

The interaction between private industry and Brookhaven is a synergistic one. Both play vitally important roles in the development and the implementation of nuclear medicine. This addendum delineates these roles.

Brookhaven's role is

...to carry out research and development,

...to explore new concepts in radionuclide utilization (e.g. by developing various generator systems such as for technetium-99m),

...to explore new concepts in radioisotope production (e.g. currently via spallation reactions, but formerly via reactor-produced tritons, Szilard-Chalmers reactions, etc.),

...to explore the radioisotope production capabilities of new machines (e.g. the 200-MeV proton Linac),

...to develop the technology needed by industry before new machines can be used for radionuclide production (e.g. safe, suitable, economic target designs and target handling systems that permit continuous automatic bombardment),

...to explore the feasibility of producing new radionuclide systems (e.g. milking iodine-123 from gaseous parent in transit to extent shipping time),

...to develop new radiopharmaceuticals (e.g. technetium-99m-labelled red blood cells),

...to develop new forms of existing radionuclides (e.g. technetium-99m-sulfur colloid),

...to develop new medical applications using radionuclides (e.g. increasing opportunities for scintigraphic applications via improved radiopharmaceuticals),

...to assist in the evaluation of new products for medical applications (e.g. by establishing collaborative programs and furnishing trial amounts of new materials, see p. 12-38),

...to assist in getting approval for new radiopharmaceuticals (e.g. by collecting data generated in its collaborative programs),

...to assist in the creation of a demand for the products that are developed (e.g. by publishing results of clinical trials with them),

...to assist industry to take over BNL-developed products (e.g. by providing industry with detailed information via "operating manuals", presentations at meetings convened for industry representatives, invitations such as those issued by BNL on 2/8/72 to 75 radioisotope companies to send representatives to Brookhaven for individual private briefings and to see the BLIP, to ask questions about it and about Brookhaven's plans, and to comment or offer suggestions on these plans, etc.),

...to assist industry to get into new product lines (e.g. by offering to irradiate industrial targets on a service basis at cost),

...to assist industry to operate in the manner that industry chooses to operate (e.g. by respecting the privacy of proprietary information and recognizing it as a major asset of a company),

...to develop prototypes for more economical higher capacity second generation machines suitable for industry to acquire and operate (e.g. by adopting the BLIP's best features and rejecting its unnecessary ones), and

...to strengthen the radioisotope industry in every way possible (because without a strong viable industry there is no point in doing any radioisotope development, either at Brookhaven or elsewhere).

<u>Industry's role is</u>

...to monitor Brookhaven's program to see what new items are becoming available,

...to maintain close contact with Brookhaven and to advise of special problems or particular needs,

...to adopt BNL-developed items as fast as practical,

...to assist Brookhaven in determining what parameters of second generation machines are important to commercial producers,

...to assist Brookhaven to appreciate and understand economic problems, and

...to assist Brookhaven in determining probable demand or market for contemplated new products.

Brookhaven's role is NOT

...to provide products* that can be obtained satisfactorily from other sources; (Brookhaven is operated by Associated Universities, Inc., under a New York State educational institution charter),

...to compete with private industry*; (witness the turning over to industry of Brookhaven's isotope production business in 1965, once industry was ready to accept it),

...to make improvements in small increments; (the day-to-day improvements in efficiency, purity, profit, etc. are best made by the companies that have to operate the system; Brookhaven's role is to conceive of new systems), or

...to tell private industry what it must do; (the demands that develop for Brookhaven's products will be more persuasive than eloquent arguments).

*This position is supported by the AEC, as exemplified in the following statement from E. E. Fowler, Assistant Director for Isotopes Development, Division of Applied Technology, USAEC, to the Editor of Business Week on 9/1/72:

"We noted with interest the timely article in your August 26 issue on the forthcoming use of the U. S. Atomic Energy Commission's (AEC) high energy accelerators for radioisotope activities ("AEC's New Breed of Particles"). However, some might gain the impression that AEC was planning to compete with private industry in the marketing of radioisotopes. We feel it is important that your readers be made aware that this is not the case.

"The Brookhaven and Los Alamos machines will focus on production technology research and development of new or technically improved radioisotopes to serve otherwise unfulfilled needs. The facilities are not intended to produce and distribute radioisotopes which are adequately and reasonably available from private sources of supply."

Within the framework just delineated above, the following are reasons for maintaining a strong program of Medical Applications Development at Brookhaven:

1. The BLIP is...

...unique,

...a completely new concept in isotope production that incorporates such innovations as..

..the means for utilizing spallation reactions,

..very high current,

..optimum particle energy,

..fully automatic operation,

..continuous around-the-clock operation,

...only now beginning to operate in its fully automatic "continuously-on" mode (following its recent construction completion),

...a national resource that should be fully exploited..

..to provide the target design and handling technology needed for future high current isotope production accelerators,

..to provide the data needed for building second generation machines, and

..to demonstrate that ultimately the operation of second generation machines by industry will be profitable.

(Note: A second generation machine would be radically different from the present BLIP, which utilizes an available Linac that, for isotope production purposes, is unnecessarily flexible and, therefore, unnecessarily costly. However, this flexibility makes it ideal for learning about the special problems involved in making radioisotopes by this technique. It is equally ideal as a tool for generating the data needed for designing a much simpler, less expensive, special purpose isotope production accelerator.)

Shutdown of the BLIP at this time would provide the taxpayer with the lowest possible return on tax dollars invested, at a time when all of the construction costs have been incurred but the benefits have not yet had a chance to be reaped.

2. The development of new products and procedures at Brookhaven is very rapid because...

...of the presence at Brookhaven of a unique, smoothly functioning, very competent, well diversified group which has taken years to assemble,

...of the existence of numerous collaborative programs with many outside institutions involving all relevant disciplines.

3. The primary concern of the Brookhaven group is for the public good, but the public includes the radioisotope industry collectively as well as the medical profession and the patients receiving the treatment. Only by fostering a healthy profitable viable industry can Brookhaven hope to have its products receive the public usage which they merit and which is intended for them.

ADDENDUM #4

The Role of User-Support in the Development of the Medical Applications of Radionuclides

One who is firmly convinced that Brookhaven's Medical Applications Development program is extremely valuable might possibly ask the question:

> "Why not let the users, rather than the federal government, support this program either through the granting of funds as part of their collaboration or through the purchase of the test quantities of new products that they plan to evaluate?"

This addendum answers that question.

Pages 12-38 of this document identified a large number of groups that in various ways utilize or benefit from the Medical Applications Development program at Brookhaven. The purpose of that was to indicate the impact that this program is having on the medical, scientific, and industrial communities and to illustrate the immediate practical applications that are resulting from this work. That part of the document and Addendum #3 (p. 48-51) showed that without such a strong core program at Brookhaven a very large amount of vitally needed work would be impossible.

Even though some of the collaborative programs do indeed provide financial support to the Brookhaven program, it simply is not practical to support the entire program by contributions from the user groups. Such an arrangement would not assure the steady income needed for a stable group, and the fluctuations caused by the phasing in and out of different groups would require setting up some kind of a fund that could be carried over from one year to the next in order to achieve the necessary financial staibility. This kind of funding is not permitted by present AEC policies.

Moreover, it would be neither fair nor practicable to expect the groups that are active collaborators to pay for the entire cost of maintaining the Brookhaven group, whose work benefits not only these active collaborators but the entire nuclear medicine community throughout the United States. The government must continue to underwrite the costs of the Brookhaven group, if the interests of the public are to be served.