COMMENTARY

Celebrating 50 Years of Nuclear Medicine Research

Over the course of Brookhaven's 50-year history, a wealth of knowledge has been gained in the scientific disciplines. Rooted within that firm foundation of basic research, numerous programs have proved to have direct benefit to mankind—to make a difference in people's everyday lives.

When the Atomic Energy Commission (AEC) was created after World War II, one of its missions was to develop peaceful uses for nuclear science, including medical applications. With nuclear technology came the widespread availability of certain radioisotopes generated in nuclear reactors and particle accelerators. These radioisotopes, unstable isotopes of various elements, paved the way for nuclear medicine. From its earliest years under the AEC, Brookhaven National Laboratory (BNL) has had strong nuclear medicine research programs because of its unique combination of facilities and personnel. BNL's reactors and accelerators can produce a wide variety of new radioisotopes, while specialists in chemistry and pharmaceutical design can incorporate them into useful radiopharmaceuticals. Animal studies provide preliminary evaluations of an experimental radioisotope, and, later on, through collaborative programs with area hospitals, clinical evaluations are performed in the diagnosis and study of disease in humans.

Setting the Course in Nuclear Medicine

Initially, Brookhaven scientists made radioisotopes in the Brookhaven Graphite Research Reactor. During its first full year of operation, back in 1951, that reactor supplied nearly 300 different radioisotopes to 26 different research organizations.

In 1972, Brookhaven began using a new facility that, for the first time, made possible the large-scale production of a variety of radionuclides having important biomedical and industrial applications. The Brookhaven Linac Isotope Producer (BLIP) uses excess protons from the linear accelerator that serves as the injector to the Alternating Gradient Synchrotron, the Laboratory's largest particle accelerator.

Technetium-99m and ^{201}Tl were both developed at Brookhaven and later transferred to industry. The quest for new and improved radiolabeled compounds with desirable biological properties continues today. To shore up the domestic supply of medically important radioisotopes produced in accelerators, BLIP was upgraded last year using $6 million in federal funds. Renamed the Brookhaven Isotope Research Center, the facility was designed to meet up to 100% of the U.S. demand for selected accelerator-produced radionuclides. The following radionuclides are currently under production at the Isotope Research Center for commercial distribution: ^{7}Be, ^{28}Mg, ^{52}Mn, ^{52}Fe, ^{65}Zn, ^{67}Cu, ^{68}Ge, ^{82}Sr, ^{83}Rb, ^{95m}Tc, ^{96}Tc.

Development of Technetium-99m

The year was 1958. Scientists knew that certain radionuclides could be used to make internal images of the body. However, the search continued for just that one radionuclide that would expose the patient to as little radiation as possible while having the right energy photon for detection by external imaging equipment.

Brookhaven researchers performing a nuclear medicine study on a patient.

Brookhaven's researchers found their "ideal" radionuclide by accident, as an impurity in another experiment. At the time, Brookhaven had developed and marketed a generator that made 2.3-hour ^{132}I from the decay of 3.2-day ^{132}Te. This was a simple device that involved fixing the ^{132}Te on a small column of powdered aluminum oxide and washing out the ^{132}I by passing a dilute acid solution through the column.

On one occasion, while making the iodine, a trace impurity was found. It turned out to be ^{99m}Tc. A little work revealed that

(Continued on page 44N)

1973	1977	1991	1992	1996
The Brookhaven Linac Isotope Producer (BLIP) opens and initiates new isotope research and development. BLIP begins distributing medical isotopes.	The first brain images were obtained with a positron emission tomography (PET) camera using fluorine-18-flurodeoxyglucose (FDG) that was developed at Brookhaven.	A kit for labeling red blood cells with ^{99m}Tc is approved for commerical distribution.	The first clinical trial begins using ^{117m}Sn-DPTA for the treatment of bone cancer pain.	The Center for Imaging and Neurosciences opens.

but the reactor will be closed at least until the end of this year and probably until the public concerns over the tritium plume are put to rest. "Secretary Peña will make a decision on the reactor by December after consulting with the scientific and local community," said Krebs. "If we decide to propose restarting the reactor, there's no question that we will have to do expensive upgrades first." She said the cost for the upgrades has not yet been determined, nor has the source for the funding.

As of presstime, the DOE's Office of Energy Research had just released an action plan addressing the Oversight Report on Brookhaven. The plan included the appointment of a DOE associate director of environment, safety and health who would report to Krebs. The plan also recommended broadening the DOE's role as landlord of Brookhaven to ensure that decisions regarding the safety of the Lab are "thoughtful, timely, and part of the everyday work performed."

The DOE also issued a request for prospective managers to file contract bids and stated that the Department would only consider a bid from a nonprofit organization such as a university. A new manager for Brookhaven is expected to be in place by November 1.

—Deborah Kotz

---

50 Years of Nuclear Medicine

(Continued from page 21N)

the ^{99}Mo/^{99m}Tc parent/daughter pair followed similar chemistry to ^{132}Te/^{132}I pair and that the aluminum oxide generator could be used with only minor modification as a source of ^{99m}Tc. Therefore, the ^{99m}Tc, with its 6-hour half-life, could still be shipped to user institutions around the world with adequate time for use.

Even with production and distribution of the radionuclide made possible by the generator, the usefulness of ^{99m}Tc was not recognized early on. In fact, in 1958, the AEC decided against preparing a patent application on the ^{99m}Tc separation process on the grounds that they could foresee no use for it.

Technetium-99m was used briefly by Brookhaven in 1960 to study thyroid physiology. Then in 1961, Argonne Cancer Research Hospital ordered the first ^{99m}Tc generator for tracer studies in the body. Word about ^{99m}Tc spread rapidly, and institutions in this country and abroad began sending in orders for generators. Finally, the demand grew so great that in 1966, Brookhaven turned generator production and distribution over to commercial suppliers.

Today, more than 85% of the 13 million nuclear medicine procedures performed annually in the U.S. involve ^{99m}Tc. Several characteristics make ^{99m}Tc ideal for clinical work. For example, it emits a single 140-keV gamma ray with no accompanying beta particle, which minimizes radiation exposure to the body. In addition, its gamma energy is well-suited for use with scintillation cameras. Another advantage is that ^{99m}Tc has a short half-life, six hours, which results in a low radiation dose to the patient. However, the short half-life makes radiopharmaceutical transporting and patient scheduling more difficult.

During the 1970s, Brookhaven introduced the first of several easy-to-use kits for labeling various compounds with ^{99m}Tc. An improved version, developed in the 1980s, simplifies the labeling operation and improves the incorporation of ^{99m}Tc into cells. A kit for labeling red blood cells was approved for commercial distribution in 1991. In 1994 alone, the kit formulation was used in more than 200,000 patients to diagnose internal bleeding and cardiovascular problems.

Current Research on Bone Cancer Pain

Since the late 1980s, Brookhaven researchers, in collaboration with the University Medical Center at Stony Brook in New York and the Veterans Affairs Medical Center in Tucson, AZ, have been conducting ^{117m}Sn-DTPA studies on bone cancer patients and have found that it offers substantial pain relief without the severe sedation of conventional drugs.

In clinical trials, about 80% of the 40 bone cancer patients treated with a single dose of ^{117m}Sn-DTPA experienced substantial relief from their pain. Some patients were completely free of pain for as long as one year. When given to patients intravenously, ^{117m}Sn-DTPA has no sedative effect and localizes preferentially in bone rather than in normal soft tissue or bone marrow. Moreover, ^{117m}Sn emits electrons that have a very short range in tissue, so bone tumors receive up to 50 times more dose than radiation-sensitive bone marrow. Thus, ^{117m}Sn-DTPA does not suppress the bone marrow's production of white blood cells or platelets, thereby retaining the body's ability to fight infection and clot blood and eliminating another major side effect of other radiopharmaceuticals used for bone pain palliation.

Since the results from the clinical trial were promising, Diatride Inc., located in Londonderry, NH, has decided to sponsor large-scale clinical trials set to begin this year involving major medical centers worldwide. In these randomized double-blind trials, patients will be given either a single therapeutic dose of ^{117m}Sn-DTPA or one of the other radiopharmaceutical products already on the market to relieve bone cancer pain. A separate trial conducted jointly by Brookhaven and Stony Brook will use higher doses of the tin compound to see if increasing the doses leads to a better response rate.

As Brookhaven scientists look back on the past 50 years, they can see how far they have advanced the field of nuclear medicine. However, they can also look ahead to see what they have yet to accomplish. Over the next 50 years, they hope to continue the commitment to nuclear medicine that has enabled the medical specialty to become indispensable to the practice of medicine.

—Excerpted from articles written by the staff in the Public Affairs Office at Brookhaven National Laboratory in Upton, New York.