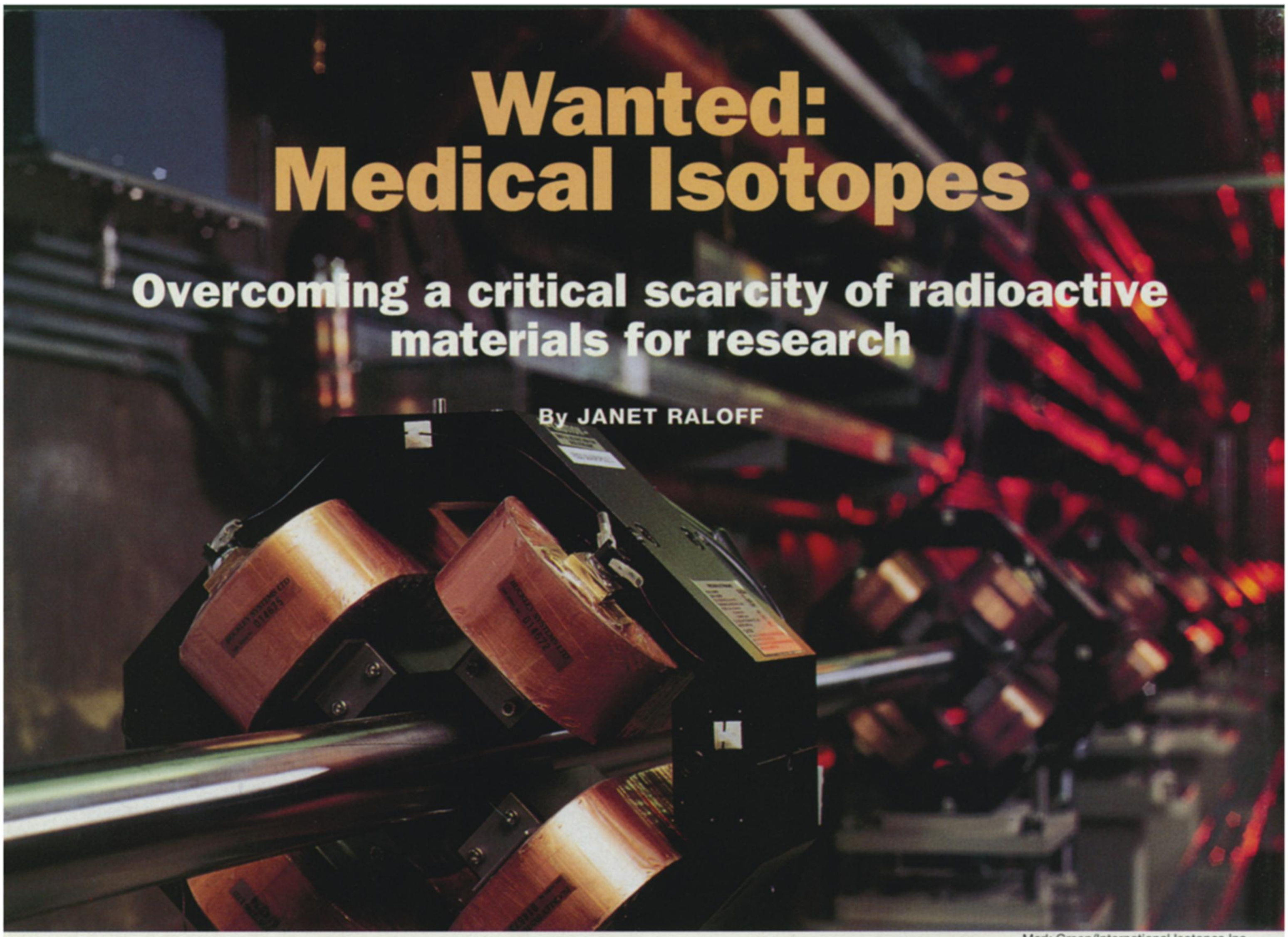
Wanted: Medical Isotopes

Overcoming a critical scarcity of radioactive materials for research

By JANET RALOFF



Mark Green/International Isotopes Inc.

This linear accelerator, recently salvaged from the ill-fated Superconducting Super Collider project, now makes radioisotopes for medicine and research.

Martin Brechbiel had promising results indicating that a radioactive isotope called bismuth-212 could destroy cancers in laboratory animals. Yet his work at the National Cancer Institute in Bethesda, Md., stopped short in April 1998 when his radioisotope supply suddenly dried up.

Alan R. Fritzberg at NeoRx Corp. in Seattle had also been successfully using bismuth-212 to treat cancers in animal experiments. His work, too, was stopped.

The Department of Energy's Argonne (Ill.) National Laboratory had ceased making the generators that hold radium-224, which decays into lead-212. This isotope eventually decays into the therapeutically active bismuth.

After a 17-month hiatus, DOE arranged for the University of Chicago to send a single generator for Brechbiel's experiments. He will need more. Fritzberg received an extension of his research grant but is still waiting to receive a generator.

Each year, U.S. physicians employ radioisotopes in an estimated 13 million nuclear-medicine procedures and another 100 million laboratory tests. Most of these activities rely on only a few nuclides, principally iodine-131 and technetium-99m.

During the past 5 years, the goals of nuclear medicine have been expanding. Instead of just diagnosing diseases, the field has begun to target the treatment of disorders. This shift has spurred exploration of dozens of uncommon isotopes.

Some can be directed—via antibodies or other small proteins—to particular organs or types of cancer cells (SN: 7/19/97, p. 40). Others, like the bismuth-212 used by Brechbiel and Fritzberg, deliver radiation that enables physicians to knock out diseased tissue while avoiding collateral damage either to nearby healthy cells or to the hospital staff.

The majority of these potentially therapeutic isotopes, unfortunately, can't be ordered from a catalog. Some are created in nuclear reactors. Particle accelerators must generate others. A few of the isotopes, including the radium-224 used to produce bismuth-212, decay from wastes created by production of uranium and plutonium for nuclear weapons.

U.S. scientists, mostly in laboratories created by the Atomic Energy Commission (now DOE), pioneered much of the work on extracting these materials, but 90 percent of the medical isotopes used in the United States today come from foreign vendors, primarily in Canada. Indeed, research on therapeutic isotopes has burgeoned at a time when federal labs have been retiring the facilities needed to make them. Demand for these costly materials now greatly surpasses DOE's ability to supply them. For some short-lived isotopes, no source remains.

As chair of a DOE advisory panel exploring the isotope-availability problem, Richard C. Reba of the University of Chicago has just finished a tour of major U.S. radioisotope-production facilities. Though Reba told SCIENCE NEWS that the isotope-availability picture "continues to look grim, at least for the next 2 or 3 years," he sees signs of improvement. Indeed, a host of new programs has been evolving over the past few years—including several outside DOE—to improve research access to unconventional isotopes.

Unreliable supplies of special radioisotopes have undermined a variety of medical research programs. Like Brechbiel and Fritzberg, Gerald and Sally DeNardo at the University of California, Davis School of Medicine were investigating a potential cancer treatment. They attached copper-67 to antibodies to ferry it to malignant cells. Their protocol, which required each patient to receive a copper-67 treatment monthly for 4 months, showed promise against non-Hodgkin's lymphomas resistant to conventional therapies.

The only sources of the isotope in the United States were particle accelerators at DOE labs, where copper-67 was occasionally made by piggybacking its production onto some other activity—typically a physics or nuclear-weapons experiment.

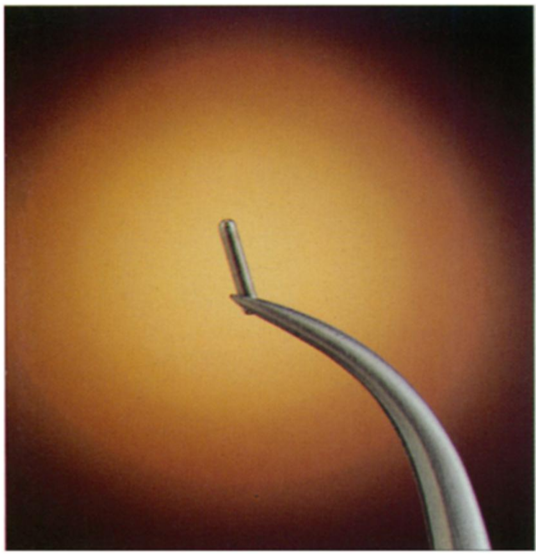
"Because of restricted budgets, [the labs] were unable to operate the accelerators year round, so it became a logistics nightmare to get the patients lined up at the same time the accelerators could make copper-67," says Owen Lowe, associate director of isotope programs at DOE.

DOE's inability to produce the isotope reliably led the Davis scientists to abandon their study, Lowe says.

Researchers using two other radioisotopes, platinum-193 and xenon-127, similarly gave up on their projects when supplies of these became erratic or unavailable, says Reba.

Some potential therapies don't even make it off the drawing board. Time and again, researchers request an isotope for drug-development or -treatment studies only to learn it's not available, says Carol S. Marcus, a consulting scientist and former director of the nuclear-medicine outpatient clinic at Harbor-UCLA Medical Center in Torrance, Calif.

Last year, DOE convened an expert panel to forecast what future U.S. demand for unconventional medical isotopes might be if research were to proceed unimpeded. It found that use of these, including unconventional therapeutic isotopes, could grow 7 to 14 percent per year. In 20 years, the fledgling therapeutic nuclear-medicine industry could be valued at as much as $1.1 billion annually, it found.



Mark Green/International Isotopes Inc.

This metal seed containing radioactive iodine received FDA approval earlier this year as an implant for treating prostate cancer. A novel start-up venture, International Isotopes Inc., produces both the isotope and the seed.

These projections warrant beefing up production of unconventional isotopes, the panel argued. DOE has responded with plans to retool a few of its facilities to provide such isotopes for research.

Over the past decade, the United States' decreasing ability to supply radioisotopes and its growing reliance on foreign producers (SN: 8/1/92, p. 68) trace to two conflicting mandates. First, Congress has directed DOE to make its isotope-production activities nearly self-supporting. Second, by law, the department may not compete with private enterprise. So, when a company begins marketing an isotope, DOE must step out of the picture.

What has developed is a classic catch-22 situation, Lowe told SCIENCE NEWS. When any isotope shows promise of having a market large enough to pay back its production costs, some private company begins making it. Not only is DOE left producing only the hard-to-attain, costly isotopes, but it has to generate most of them with aging, make-do facilities.

The agency hopes to improve the situation with several new programs. Chief among them is an $8-million beam spur that it's adding to an existing accelerator known as the Los Alamos (N.M.) Neutron Science Center.

To produce radioisotopes at this accelerator, the beam must reach the end of a half-mile-long track. When the facility is in operation, however, upstream experiments often siphon off the entire beam. Furthermore, the accelerator doesn't run year-round.

DOE is now putting its isotope-production hardware near the head of the beam. This change should extend the accelerator's production of a wide range of isotopes to roughly 40 weeks a year. The department expects the new beam spur to be on-line by spring 2001.

DOE is also launching an Advanced Nuclear Medicine Initiative. This $2.5-million program will subsidize the production of isotopes for research, placing special emphasis on alpha-particle-emitting nuclides, such as those used by Brechbiel and Fritzberg. Their highly energetic radiation is promising for cancer treatments because it doesn't travel far, just the length of a few cells or so. Throughout its short trip, however, each alpha particle releases a wallop of energy, giving the kiss of death to any cells it crosses.

Several mothballed DOE reactors may also see new service making unconventional isotopes. One is the Annular Core Research Reactor at Sandia National Laboratories in Albuquerque, which DOE has now decided to use to produce a broad range of isotopes for research. It had been slated to produce only molybdenum-99, an isotope widely used in diagnostic medicine and available only from Canada.

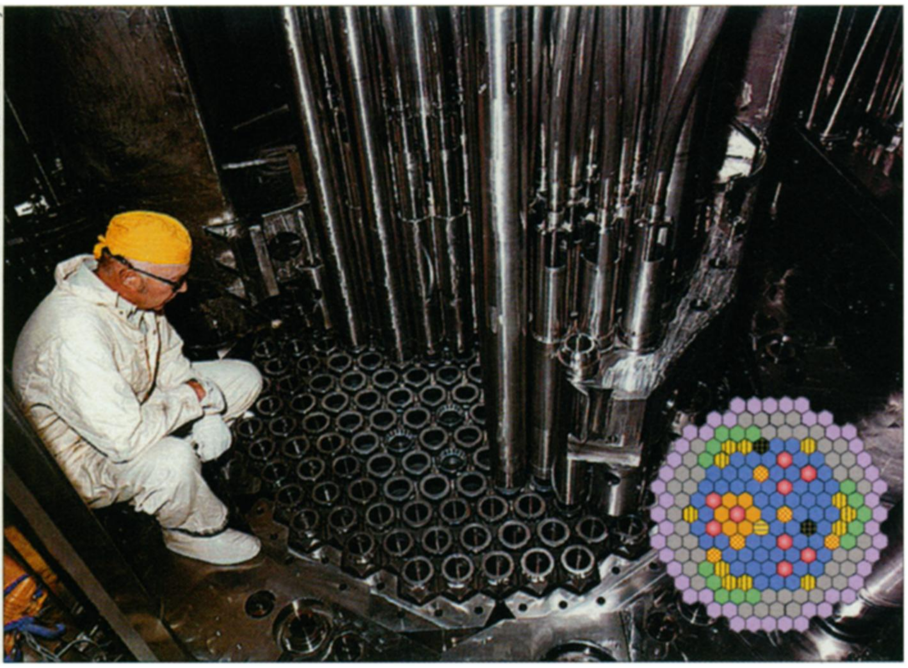
The future of DOE's $1-billion Fast Flux Test Facility near Richland, Wash., remains less certain. During its dozen years of operation, ending in 1992, the facility produced 60 isotopes as a sideline to its reactor-physics research. These included some isotopes for medical uses.

The reactor's design allows it to make certain isotopes, such as gadolinium-153, at higher purity than in any other facility in the Western Hemisphere, observes Robert E. Schenter, a nuclear physicist who worked on isotope production at the facility. Moreover, he notes, this reactor "is also unique in being able to make enough [of any desired isotope] to serve all hospitals," not just a few, occasional users.

Although this reactor has been out of service for 8 years, its unusual liquid-sodium coolant prevents DOE from shutting down the facility without destroying it. So, DOE has been spending $40 million a year to reserve the option for the reactor to be put back in operation someday.

In July, DOE commissioned an environmental review for the reactor as a first step in deciding the facility's future. In a report issued in late August, the reactor's caretakers catalogued ways to make the

Pacific Northwest National Laboratory



Entry platform for fuel rods at the Fast Flux Test Facility during its construction. Now in cold standby, this reactor could find new use making high-quality medical and research isotopes. Inset diagram denotes rods where different isotopes might be made: yellow with black vertical lines, long-lived isotopes; yellow with red honeycomb, short-lived nuclides; green, plutonium for space missions; light blue, cobalt-60; and yellow with horizontal green lines, gaseous isotopes.

reactor pay for itself. High on their list: production of medical isotopes valued at up to $34 million per year.

Outside the government, several novel programs have developed that also promise to make more isotopes available.

At Washington University School of Medicine in St. Louis, for instance, radiochemist Michael J. Welch became fed up with having to schedule his team's studies to coincide with physics experiments at a national lab. So, working with Newton Scientific of Cambridge, Mass., he figured out how to use his university's cyclotron accelerator to generate some of the radionuclides needed. The cyclotron had previously been reserved for conducting positron-emission tomography (PET) scans of hospital patients.

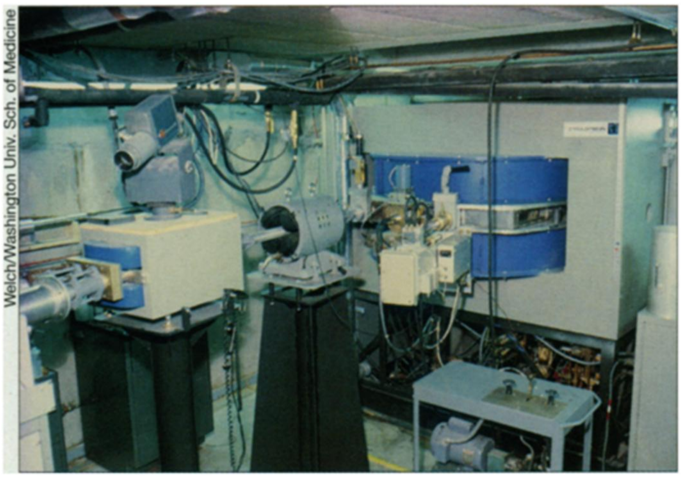
Last month, the National Cancer Institute issued Welch a grant that will subsidize his team's making of copper-64 for itself and other medical researchers around the country. Within a year, Welch hopes to also begin shipping iodine-124, bromine-76, bromine–77, yttrium-86, and gallium-66. None of these research isotopes, he notes, is currently available in the United States.

Because he's working with a tiny accelerator, he would not be able to fill the demand for these nuclides if any of the applications for them became "clinically attractive," Welch notes. He points out, however, that there are about 60 similar PET cyclotrons around the country that could license his techniques to make these isotopes locally.

A bonanza for isotope-hungry scientists may eventually come from the demise of the $11-billion Superconducting Super Collider project in Texas (SN: 10/30/93, p. 276). A linear accelerator that I. Lon Morgan of the University of North Texas in Denton bought from the abandoned project has become the centerpiece of a new company. His International Isotopes Inc., also in Denton, now boasts a staff of more than 100.

Since April 1998, the firm has been marketing cobalt-60, iridium-192, strontium-89, barium-133, and nickel-63. In June, FDA approved the company's first medical product, implantable metal seeds containing iodine-125 for treating prostate-cancer patients.

Welch/Washington Univ. Sch. of Medicine



A hospital cyclotron was retrofitted to produce radioactive copper-64, which is then separated out via an automated process in a shielded cabinet nearby.

Not only has the 4-year-old company acquired a second accelerator, but it has also signed contracts to make reactor-generated isotopes at facilities owned by DOE and several universities. Ultimately, the firm plans to make dozens of isotopes.

Explains company president Carl W. Seidel, "We're trying to provide a reliable supply of raw materials." He expects universities and companies to come to him for radioisotopes as they undertake research. He hopes they will return for drug-purity radioisotopes—and even commercial products that include them—when the companies are ready to market the products that result. Right now, he notes, no other domestic company offers that range of isotopes and services.

Today, nearly one in three people admitted to a U.S. hospital is given tests or treatments that depend on radioisotopes, notes Richard A. Holmes, director of nuclear medicine and oncology at Mallinckrodt Inc. in St. Louis. Over the next 2 decades, he expects the use of nuclear materials in medicine to grow exponentially.

However, Holmes observes, the availability of these future generations of diagnostic materials and therapeutic drugs will depend on a healthy investment in research isotopes today.

While acknowledging that small start-up companies and clever engineering feats can relieve research-isotope shortfalls, he argues that it's the responsibility of the federal government to ensure that these radioactive materials will be available to medicine. He says he'd like to see DOE build reactors and accelerators dedicated to isotope production rather than just make more time available on physicists' tools at the national labs.

Reba is less certain that DOE should be the primary provider of unconventional radioisotopes. His DOE committee will mull over the problem and offer its recommendations in December.

The real obstacle, he and others contend, remains Congress' unwillingness to pay for the production of these materials. Although DOE has accepted the responsibility for seeing that medical researchers have access to novel radioisotopes, the $21 million that Congress now provides annually for this activity doesn't go far. □