Core strength. Belgium's BR2 reactor can produce one-quarter of the world's Mo-99, a key medical isotope.

NUCLEAR MEDICINE

Scrambling to Close The Isotope Gap

New technologies are needed urgently to assure the continued supply of radioactive materials essential for diagnosing and treating millions of patients around the world

A year and a half ago, nuclear medicine physicians were hit with a double whammy. On 9 May 2009, the High Flux Reactor in Petten, the Netherlands, was shut down to fix corroded pipes. Ten days later, a heavy-water leak forced a shutdown at the National Research Universal reactor in Chalk River, Canada.

The twin problems created a temporary shortage of technetium-99, a radioisotope used in more than 30 million procedures a year worldwide for imaging everything from blood flow through the heart to bone cancer. Physicians were forced to use less Tc-99 for many procedures, ration what scant supplies remained, and find less desirable substitutes.

The reactors came back on line by fits and starts and were both running again by late 2010. But the return to normalcy—the two reactors produce 60% of the world's radioactive molybdenum-99, which decays into Tc-99—may not last long. With both the Chalk River and Petten reactors decades beyond their intended life expectancy, "the current global Mo-99 supply infrastructure is fragile and aging," says Parrish Staples, who directs the office of European and African Threat Reduction for the National Nuclear Security Administration's (NNSA's) Global Threat Reduction Initiative in Washington, D.C.

The situation isn't just a problem for doctors and patients. Governments around the world are working to phase out civilian uses of the technology to produce nearly all Mo-99 today because of concerns that the highly radioactive material used in the process could be diverted to make nuclear weapons. And finding replacement technologies to produce the Mo-99, and companies willing to take the financial risk of generating it, is proving challenging. As a result, "the clock is ticking for the crisis to reoccur," says Staples.

Less is more

In one sense, the crisis is a sign of how important nuclear medicine has become in diagnosing and treating diseases. The discipline debuted after the first reactors were built in the 1940s and 1950s and grew slowly before taking off sharply in the past 2 decades. The number of nuclear medicine procedures has tripled since 1996, to well over 30 million a year today. A dozen different radioactive isotopes are now in standard use, and another dozen are in advanced development. By far the biggest players are Tc-99 and fluorine-18, used in positron emission tomography (PET) for brain scans.

The widespread use of Tc-99 has put enormous pressure on a handful of reactors. Just five reactors—Chalk River, Petten, and facilities in Belgium, France, and South Africa—produce more than 99% of the world's Mo-99. Demand is measured in units called 6-day curies, referring to the isotope's half-life. Today, medical imagers use roughly 12,000 6-day curies of Mo-99 worldwide annually, a number increasing between 1.5% and 2.5% a year, according to Steve McQuarrie, a medical physicist at the University of Alberta in Edmonton, Canada, who spoke at a meeting of the American Nuclear Society (ANS) on the topic in November 2010. The United States, which accounts for roughly half of that demand, has for years imported all of its medical Mo-99 and other medical isotopes.

When operating at full tilt, the current reactors can keep up with this demand. But in addition to being hobbled by their age and need for frequent maintenance, most make their Mo-99 using weapons-grade uranium. This uranium is enriched in uranium-235, 6% of which decays into Mo-99 during fission. Last April, the United States and 46 other countries signed an agreement to phase out this highly enriched uranium (HEU) for civilian uses to reduce proliferation concerns.

Now engineers at the facilities are scram-

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Podcast interview with author Robert F. Service.

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bling to determine how to continue to make Mo-99 and other key medical isotopes with low enriched uranium (LEU) and other alternatives that don't require fission. On the HEU-to-LEU conversion, there has already been good news. Earlier this year, NNSA announced that it had awarded $25 million to the Nuclear Energy Corp. of South Africa (Necsa) to help it retool its Safari-1 reactor to produce Mo-99 using LEU targets.

Reactors normally make Mo-99 by firing neutrons at plates coated with uranium, part of which turns into Mo-99. Technicians then dissolve the plates in acid and chemically separate out the molybdenum. The process is fraught with pitfalls. Both Mo-99 and Tc-99 decay too quickly to be stockpiled, so new targets must be delivered continuously. The amount of U-235 in the targets—as much as 90% at HEU facilities—raises concern that some of it could be diverted for weapons. To make matters worse, the chemical processing needed to recover the Mo-99 generates high-level radioactive waste, which poses proliferation risks of its own.

The Safari-1 reactor used targets enriched only to about 45% U-235. Switching to LEU enabled it to run on 20%. In July, Necsa delivered the first commercial-sized Mo-99 shipment to the United States for a series of quality tests. And last month, after receiving the U.S. Food and Drug Administration's approval, a Necsa subsidiary made its first commercial shipment of LEU-produced Mo-99 to Lantheus Medical in North Billerica, Massachusetts.

Safari-1's success is good news, but Staples cautions that the solution isn't a panacea. To compensate for lower concentrations of U-235, which produces less molybdenum, targetmakers are using more uranium overall, are making targets denser, and are trying different metal alloys in the targets. But such changes also change the chemical-separation process needed to recover the Mo-99. "Each [reactor] is more or less a unique facility," Staples says. "It's difficult to just transition the solution in South Africa to other reactors, because they use different separation chemistries."

Beyond fission?

Retooled Mo-99 facilities aren't the only ones battling for a piece of the business. Another strategy would revive a decades-old reactor technology called aqueous homogeneous reactors (AHRs). Whereas most nuclear plants today run on solid uranium fuel rods, AHRs are fueled by a uranium salt in an acidic solution. Last year, NNSA gave $9 million to Babcock and Wilcox (B&W) Technical Services Group in Charlotte, North Carolina, to work on ways of using AHRs with LEU to generate the neutrons needed to produce Mo-99.

Frank Hahne, B&W's director of business development, says the company's current design is about the size of a 55-gallon (200-liter) drum. One advantage, Hahne says, is that Mo-99 produced in solution can easily be extracted with "wet" chemical techniques, whereas typical solid targets must be dissolved in acid first. Hahne says the company has completed its conceptual design and licensing through the Nuclear Regulatory Commission and plans to start construction in 2012, with production of Mo-99 in 2014.

Another option does away with fission altogether. Researchers place targets enriched with Mo-98—another naturally occurring isotope—in a nuclear reactor that produces a high flux of neutrons. When Mo-98 atoms in the target absorb neutrons, they are converted to Mo-99, which can then be separated out.

Last year, NNSA awarded $2 million to GE Hitachi Nuclear Energy in Wilmington, North Carolina, to speed up efforts to commercialize Mo-99 production through neutron capture. At the ANS meeting, Jennifer Varnedoe, an engineer with GE Hitachi, said scaling up the approach could provide half of the Mo-99 used in the United States.

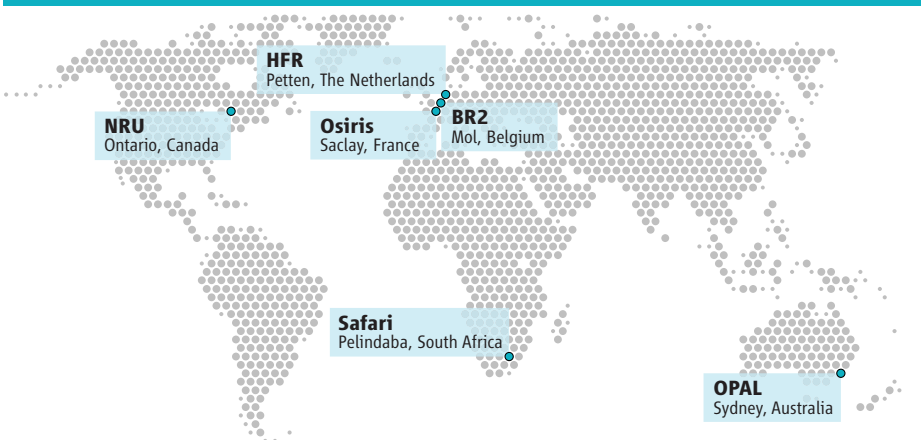
Producing Mo-99 by absorbing neutrons eliminates the need for U-235. The separation process also generates far less radioactive waste than traditional methods do. It does require extremely powerful neutron sources, however, such as the High Flux Isotope Reactor at Oak Ridge National Laboratory in Tennessee. Those sources are already in heavy demand for neutron scattering work and other scientific techniques. So GE Hitachi is also exploring the possibility of carrying out its neutron capture work at commercial nuclear power reactors.

Mo-98 neutron capture also requires new equipment to transport the reaction products, which contain lower concentrations of Mo-99 than those created by the traditional fission process. Once produced, Mo-99 is loaded onto an affinity column in a technetium "generator" and sent to hospitals. There, the Tc-99 is eluted from the column as the Mo-99 decays. A lower Mo-99 concentration would require larger columns, says Robert Atcher, a radiopharmacist at Los Alamos National Laboratory in New Mexico who directs the U.S. Department of Energy's (DOE's) virtual National Isotope Development Center. But because the current generators are standardized, the changeover would likely be costly for Tc generator companies as well as for the hundreds of radiopharmacies around the world.

Instead of adding a neutron to Mo-98, scientists can also make Mo-99 by removing a neutron from Mo-100, a stable isotope that makes up about 10% of natural molybdenum. Researchers at the Institute for National Measurement Standards in Ottawa, Canada, are using a room-sized electron linear accelerator to fire energetic electrons through a tungsten target. The interactions produce gamma rays that can knock a neutron out of Mo-100 atoms, transmuting them into Mo-99.

At the ANS meeting, Raphael Galea, a radiation metrology specialist with the institute, reported that he and colleagues had demonstrated all of the steps needed to convert Mo-100 to Mo-99. The researchers calculate that the process could meet all of Canada's demand for Mo-99 and Tc-99 with just two electron accelerators, at costs below what the market charges today. In addition to the Canadian group, in October 2010, NNSA awarded $500,000 each to two Wisconsin companies—NorthStar Medical Radio-

WHERE MOLYBDENUM-99 IS MADE



Fragile and aging. The small number of production sites makes consistent Mo-99 supplies vulnerable.

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A Field Back in Vogue

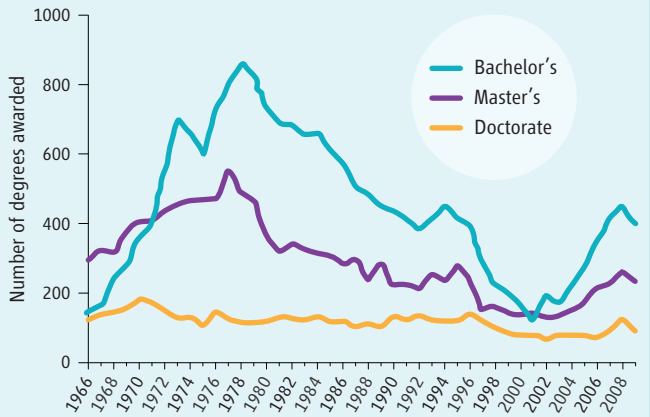
Radioisotopes aren't the only bottleneck confronting nuclear medicine. For years, the United States has struggled to train enough nuclear engineers, radiochemists, and medical physicists to keep the field healthy.

Students shunned nuclear sciences in the wake of the nuclear accidents at Three Mile Island in Pennsylvania in 1979 and Chornobyl in 1986. By the mid-1990s, only 600 nuclear engineering students were enrolled in graduate and undergraduate programs in the United States—down two-thirds from a decade earlier, says John Gutteridge, who runs the education grants program for the Nuclear Regulatory Commission (NRC) in Bethesda, Maryland. Much of that decline probably occurred because fewer nuclear plants were being commissioned and built. Even so, a mid-1990s study by the University of Michigan suggested an annual shortfall of 400 nuclear engineers needed to keep up with attrition and retirement in the field.

Among radiochemists, the output of Ph.D.s dropped from between 30 and 40 per year in the 1970s to as few as three in some years in the early 2000s. "I would say the situation was desperate," Gutteridge says. Now numbers are up again, and Gutteridge and others say recently minted doctorates have been awash in job offers. "Our Ph.D. graduates are snapped up right away," says John Gilligan, a nuclear engineer at North Carolina State University in Raleigh, who also directs the Department of Energy's (DOE's) Nuclear Energy University Programs integration office.

To combat the downward trend, beginning in 1998 DOE launched a dozen different grant programs amounting to about $30 million a year to support different constituencies within nuclear sciences: universities, faculty members, and Ph.D., master's, and bachelor's students. Those programs continued until 2007, when DOE officials in the Bush Administration decided to shift the money elsewhere. In 2008, NRC launched its own program to support education and training in the field at about $20 million a year. And more recently, the Obama Administration and Congress restarted the DOE programs, which now spend $50 million to $80 million a year on student, faculty, and research support.

U.S. NUCLEAR ENGINEERING DEGREES AWARDED



Rebound. More than a decade of support programs have helped bolster the number of students earning degrees in nuclear engineering.

The rebound has been dramatic: Enrollments in undergraduate and graduate nuclear engineering programs have nearly doubled since 2004, to 4752 in 2010. As many as 30 Ph.D.s in radiochemistry are likely to be awarded in 2011, R. Craig Williamson, who directs the South Carolina Universities Research and Education Foundation in Aiken, told at a November 2010 meeting of the American Nuclear Society in Las Vegas, Nevada.

Crisis averted? "By no means," says Rolf Zeisler, a radiochemist with the National Institute of Standards and Technology in Gaithersburg, Maryland. "Right now we are catching up with the demand of the last decade." J. David Robertson, a radiochemist at the University of Missouri, Columbia, cites health physics—a training ground for radiation safety officers—as one area of concern. But he and others agree that, like the production of medical isotopes, the training of students in the field has stepped back from the abyss. **–R.F.S.**

CREDIT: ADAPTED FROM U.S. DOE NUCLEAR ENERGY UNIVERSITY PROGRAMS BASED ON DATA FROM OAK RIDGE INSTITUTE OF SCIENCE AND EDUCATION

isotopes LLC and Morgridge Institute for Research—to pursue variations on the use of accelerators to produce Mo-99.

The biggest remaining downside to converting Mo-100 is scale. Canada uses only one-tenth as much Tc-99 as the United States. Producing enough Mo-99 for the United States would require about 54 linacs, says Yaron Danon, a nuclear physicist at Rensselaer Polytechnic University in Troy, New York, who has been working on a similar Mo-100 transmutation effort. Having a distributed network of Mo-99 producers would prevent a crisis if any one facility had to shut down. But the logistics of building such a large network could be complicated. "So it may make more sense [for Canada] than for the U.S.," Danon says.

Perils of success

Several other Mo-99 production schemes are also under investigation, including one that would use medical cyclotrons that currently make radioisotopes for PET. With so many candidate technologies in the running, says J. David Robertson, a radiochemist at the University of Missouri, Columbia, "I'm pretty confident one or more will pan out."

Once the technical side falls into place, the policy questions move to the forefront, in particular, who will build the new facilities and at what cost? Historically, medical isotopes have been produced at government-sponsored research reactors. Last year, the International Atomic Energy Agency (IAEA) released an economic analysis showing that companies were at a competitive disadvantage because of the millions of dollars in government support for research reactors worldwide. With aging reactors going off line and governments looking for ways to cut costs, however, those subsidies could soon end. Either way, the IAEA study recommended that governments move to charge full price for their Mo-99 production services in order to give companies an incentive to develop technologies capable of providing Mo-99 at a cheaper price. A very different sort of problem could arise if multiple technologies succeed and the world winds up with a glut of Mo-99. That could cause prices to crash, forcing some suppliers out of business.

As a way through some of these issues, the last U.S. Congress passed legislation authorizing DOE to spend $165 million on the development of new Mo-99 production technologies. Then-Senator Kit Bond (R–MO) blocked a similar bill in the Senate out of concern that it could disrupt HEU shipments from the United States to other countries. But Bond has retired, and his departure bolsters the chances that the new Congress will approve alternative Mo-99 production technologies.

With Mo-99 production technology, financing, and policy all up in the air, many nuclear medicine experts are concerned. In July 2010, a coalition of nine professional nuclear medicine organizations suggested that the combination of potential changes threatens to put patients worldwide in harm's way. They concluded: "Forcing a change to a new, and as yet unproven, technology without proper research and development, or regulatory and financial support will most certainly cause harm." **–ROBERT F. SERVICE**

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