Desperately Seeking Moly

Unreliable supplies of feedstock for widely used medical imaging isotope prompt efforts to develop U.S. sources

By Janet Raloff

Of all the radioactive isotopes used in medical diagnostics, none plays a more pivotal role than technetium-99m. Each weekday, hospitals and clinics around the world use it to perform about 60,000 diagnostic procedures. Used in about 80 percent of nuclear imaging tests, the isotope is one of modern medicine's major tools for detecting, evaluating and treating cancers, heart disease and other serious illnesses. It helps doctors lengthen patients' lives.

Trouble is, Tc-99m itself has a very short life. Radioactive decay depletes it by half every six hours. The feedstock that supplies it—molybdenum-99—also has a rather short half-life (66 hours), so neither isotope can be stockpiled. New Mo-99, or "moly," must be made continually and delivered to imaging centers weekly.

But now the system for supplying the feedstock for nuclear imaging's star isotope is in peril. Just five geriatric nuclear reactors in Canada, Europe and South Africa produce roughly 90 percent of the global Mo-99 feedstock. At an average age of 47, those plants frequently shut down for the kinds of repairs commonly needed in reactors operating well past their prime. This summer such shutdowns led to technetium shortages so severe that U.S. officials now say efforts must begin, at long last, to establish American sources of these critical isotopes.

On again, off again

Problems began on May 15, when reactor operators found a small leak at the biggest Mo-99 producer, Canada's 52-year-old National Research Universal reactor near Chalk River, in Ontario. Inspections would eventually turn up widespread corrosion in the reactor's outer wall.

This University of Missouri reactor core could be harnessed to make moly for the short and eventually the long run.

Atomic Energy of Canada Limited, which runs the facility, recently announced that the reactor would not restart until well after the first of the year.

Routine maintenance brought down the second biggest Mo-99 producer — the Dutch High Flux Reactor in Petten — for roughly a month this summer. With the Canadian reactor offline as well, worldwide supplies of Mo-99 plummeted to about 30 percent of normal. Although the Petten reactor resumed operation in mid-August, its return to service will be short-lived. By March 2010, the 47-year-old reactor must shut down for an estimated six months to undergo delayed repairs of corrosion damage.

The precarious health of Mo-99–production reactors had already spurred the Society of Nuclear Medicine to petition Congress for help in 2008. Led by Robert Atcher of Los Alamos National Laboratory in New Mexico, then president of the society, these scientists and physicians campaigned for development of new, more reliable — and preferably domestic — sources of Mo-99. Even before this summer's technetium crisis emerged, the White House launched a federal interagency panel to look at developing homemade moly — perhaps, on an emergency basis, as early as spring 2010.

Such developments are fueling optimism, Atcher says, because the erratic availability of Tc-99m and its feedstock are "finally on the radar screen." Many U.S. companies, he adds, are now lining up to help bring moly production home.

Few good alternatives

A Society of Nuclear Medicine survey in August of 710 members found that 80 percent felt the impact of the summer's Tc-99m shortage. Only 31 percent of participants reported having enough isotope to perform at least three-quarters of their normal imaging workload; 5 percent were working at no more than 25 percent capacity. Of the respondents, 16 percent expected to "be down to zero percent capacity within a month."

Since the Canadian reactor's Mo-99 production stopped in May, Tc-99m supplies to Vanderbilt University Medical Center in Nashville have been only about two-thirds of what was requested, and sometimes have been as low as 25 percent of normal, says Jeff Clanton, who runs the radiopharmacy there.

What worries him most: the Petten reactor's long outage beginning next spring — especially if the Canadian reactor isn't back in operation. "I expect we'll be down to 10 or 20 percent of our normal supply," he says. That would be a serious shortfall for a hospital system that had been performing 1,000 Tc-99m tests weekly.

Some hospitals report that by scheduling procedures carefully — say early in the week when supplies haven't decayed as much — they have been managing fine with the limited technetium.

"They may be fine," says Chaitanya Divgi, who heads nuclear medicine at the University of Pennsylvania School of Medicine in Philadelphia, "but in many cases the patient will not be fine."

For instance, imaging centers normally use roughly half of their Tc-99m in procedures to monitor blood perfusion into heart tissue following cardiac stress tests. When technetium — the gold standard for such heart studies — is in critically tight supply, as it now is in Divgi's hospital, physicians have been substituting a much older procedure that uses thallium-201.

Thallium is not as energetic as Tc-99m, "so the diagnostic quality of the image is not as good," explains Dean Broga, a medical physicist at the Medical College of Virginia in Richmond. The test's false negative rate is potentially higher, he says, which means some heart problems might be missed.

Divgi points out another potential problem: "An old dog like me has seen plenty of thallium images. But there's a whole slew of cardiologists and nuclear medicine physicians out there who've never seen a thallium image and could have some trouble reading it."

Switching to thallium also substantially increases how long a patient must

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lie still on a hard table as the heart scan proceeds following a stress test. Perhaps 4.5 hours with thallium, instead of two with Tc-99m. The patient's radiation dose will roughly double as well.

The trade-off, Divgi and others explain, is that by shifting cardiac-stress test scans to thallium, Tc-99m can be reserved for applications with no good or affordable alternatives. These include scans to measure irreversible damage to heart function by chemotherapy drugs and probes in the emergency room of potentially serious gallbladder inflammation.

About 16 percent of technetium imaging tests scout for cancer in bone. Here, another procedure, sodium-fluoride positron emission tomography, is as good as Tc-99m — and is recommended by the Food and Drug Administration as a suitable alternative during the current isotope crisis. However, Medicare won't cover it. So few hospitals will consider using this PET scan as a substitute.

At the request of five medical societies, Medicare officials are reevaluating their agency's exclusion of coverage for PET bone scans. But officials say they plan no announcement before March.

In a pinch

The White House, meanwhile, has recognized the growing vulnerability of moly imports to the United States. "We decided it was time to move forward, as quickly as we could, on establishing domestic production," says Jean Cottam in the White House Office of Science & Technology Policy.

Even if expedited, new facilities would take some four to 10 years to build, license and put into operation. Since the United States might not be able to wait that long, the White House office set up an interagency group and charged it with finding bridge tactics.

To make moly today, existing reactors bombard targets — essentially metal plates containing 95 percent–pure uranium-235 — with neutrons. This prompts some uranium to fission, or break apart, into fragments that include the sought-after isotope.

The easiest way to spur domestic isotope production, Cottam says, would be to take existing targets from Chalk River, irradiate them in a similar facility and then send those irradiated targets back to Canada to have their moly extracted. Letting the Chalk River facility extract the isotope would avoid having to get FDA licensing of some new facility, which "can take years," Cottam says.

At least a few reactors in the United States, such as the University of Missouri Research Reactor, known as MURR, and the High Flux Isotope Reactor at Oak Ridge National Laboratory in Tennessee, are good candidates for irradiating Canadian targets, Cottam notes.

But licensing those facilities to irradiate targets and to send them to and from Canada might take six months, she says. Chalk River targets contain bomb-grade uranium, albeit in small quantities. So obtaining clearance to transport the targets in large quantities requires permission from the National Nuclear Security Administration, part of the Department of Energy.

Although some scientists worried that this might be a nonstarter, the agency recently jumped on board. "NNSA supports the White House decision to implement any interim solution for the supply of this important medical isotope, including irradiation of highly enriched uranium targets in appropriate and available facilities," says agency spokesman Damien LaVera.

Long-term solutions

As bad as this year's Mo-99 shortages became, Atcher points out that things could get even worse. The Department of Homeland Security "could close our borders at any given time because of some real or perceived threat," he notes. Also, considering the age of the Chalk River reactor, its frequent outages and a summer-long escalation in the recognition of how serious its corrosion problems are, "many are speculating that this reactor will never restart," he observes. It had been providing about one-third of global Mo-99 supplies.

Without any U.S. capacity to process irradiated targets, Atcher notes, either scenario could result in an almost immediate suspension "of all but about 20 percent of the imaging that we do in nuclear medicine." This explains the premium that the White House and the medical community are placing on domestic moly processing as well as its production.

Any next-generation moly makers in the United States, meanwhile, must adhere to a new federal policy: They can no longer use targets containing more than 20 percent uranium-235 (compared with the current 95 percent). While this alleviates the risk of targets being hijacked by terrorists to make bombs, it could also quintuple the number of targets needed to produce a given amount of Mo-99 and jack up moly extraction costs.

Worldwide Supplies of Moly

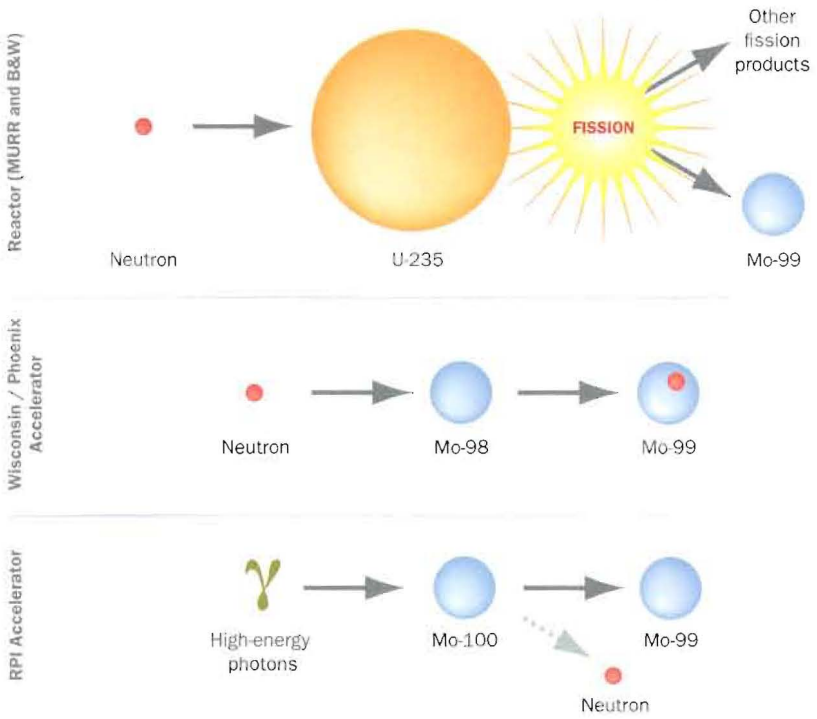
Most molybdenum-99, feedstock for the most-used radioisotope in medical imaging, comes from just five aging reactors. A little is made by newer reactors, such as OPAL. Outages at older reactors have created shortages, prompting calls to make moly in the United States.

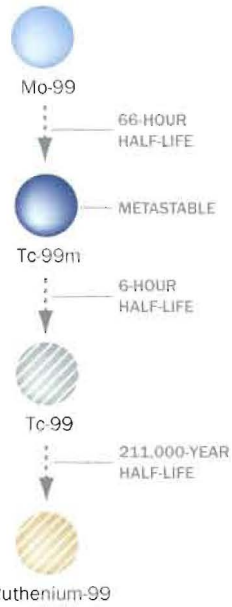
Country	City, Province	Facility Name	Reactor Age (Years)	% World Supply of Moly	Power Output (Megawatts)
Canada	Rolphton, Ontario	NRU Chalk River	52	33%	135
The Netherlands	Petten	HFR	47	33%	45
Belgium	Mol	BR2	47	10%	100
France	Saclay	OSIRIS	42	8%	70
South Africa	Pelindaba	SAFARI	43	3%	20
Australia	Sydney	OPAL	2	N/A	20

TABLE: A. NANDY; SOURCE: SOCIETY OF NUCLEAR MEDICINE

New Routes to U.S. Moly

Currently, the conventional approach to making molybdenum-99 uses neutrons to bombard uranium-235 atoms, which fission, or split, to form Mo-99 and other products (top). An alternative approach being investigated by a Wisconsin team would use an electron-beam accelerator to produce neutrons, which would strike targets containing molybdenum-98 to create Mo-99 (middle). One New York researcher suggests shooting high-energy photons at a target of Mo-100 atoms (bottom). Mo-100 atoms would then shed a neutron, forming Mo-99.





Moly Decays to Technetium

Mo-99 is the feedstock for technetium-99m, the isotope used in 80 percent of diagnostic nuclear medicine. Roughly every three days, half of the Mo-99 will decay into Tc-99m (the m stands for metastable). Every six hours, half of that decays into the long-lived Tc-99 (not useful in medicine), which glacially decays into ruthenium.

Making the old new again

The top two homegrown candidates for supplying moly are the 43-year-old MURR, in Columbia, Mo., and a reactor still undergoing development by Babcock & Wilcox Co. of Lynchburg, Va. Both rely on designs that are conceptually old.

MURR is a small, conventional reactor that houses highly enriched uranium-oxide fuel in rods that are inserted into a pool of water. The reactor already creates dozens of different isotopes for use in medicine and research and can fairly easily be adapted to produce Mo-99. The first thing MURR needs are uranium targets. The fission — or splitting — of the reactor's fuel releases neutrons. If those neutrons strike a target containing uranium-235, the resulting fission generates a mix of products, including Mo-99. (This is what happens at Canada's Chalk River facility, for instance.)

MURR also lacks Chalk River's ability to chemically dissolve uranium from those targets, extract the moly and enrich that isotope into a clean, medical-grade product. The University of Missouri is, however, planning to develop such onsite processing capabilities for this isotope.

Once initial federal approval comes through, "it's probably going to take us three years to design and construct the processing facility, and another six months to do the commissioning and testing," says MURR director Ralph Butler. "We're very optimistic that we could supply at least half of the United States' [Mo-99] needs."

Production could begin by 2013, he says — especially if DOE helps fund the processing facility's construction.

The Babcock & Wilcox reactor employs a totally different design — a pool of water seeded with uranium, which serves as both the fuel and molybdenum-producing target. More than 30 of these homogenous aqueous-phase reactors have been operated around the world, notes Bob Cochran, president of B&W's Technical Services Group. His company has patented elements of the design that would make it suitable for Mo-99 production.

Part of this reactor's appeal — what could satisfy critics worried about nuclear safety — is that "this is what we refer to as an inherently safe reactor," Cochran says. It's not pressurized. To shut it down, he says, "just pull the plug" and drain the water into tubing or tubs that alter the geometry of the fuel.

That's also how any moly would be retrieved. The aqueous fuel would be drained from the reactor's core and passed through separation columns, now under design. Following moly retrieval, the uranium-laced water would return to the reactor, where unfissioned atoms would become the fuel again.

This reactor should produce very little waste compared with conventional reactors and can be quite small — probably

A. NANDY

smaller than a 55-gallon drum. Its design, Atcher says, also makes it difficult to extract weapons-grade material, "thus providing a reactor design that can be safely installed around the world."

How soon? "In the best case," Cochran says, "probably the end of 2013. But no later than 2015."

Slower, but accelerated

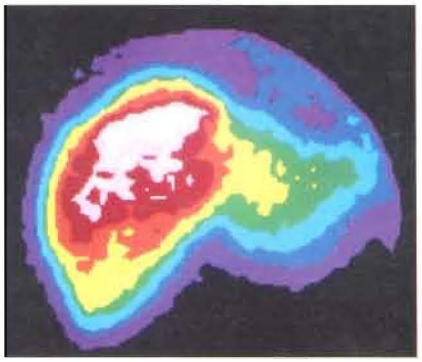
Although it will take them appreciably longer to get isotopes to market, at least three teams are looking to sidestep reactors and make moly using accelerators.

Researchers at Rensselaer Polytechnic Institute in Troy, N.Y., use accelerators that create a beam of high-energy electrons. As these particles slam into a metal target, they create high-energy photons, similar to gamma rays, called bremsstrahlung, or braking radiation, explains nuclear engineer Yaron Danon. The trick is to put a batch of stable, or nonradioactive, molybdenum — Mo-100 — into the path of those bremsstrahlung photons. The energy they deposit when they hit the isotope can knock a neutron from its nucleus. The result: Mo-99.

After extracting this new isotope, the stable moly that is left over would get recycled back for another encounter with the beam. One batch of Mo-100 should last a long time, he says.

This process generates far fewer waste products than fission-based Mo-99 production, Danon says, and yields almost no radioactive waste. The primary radioactive material is the commercial product.

Advanced Medical Isotope Corp. of Kennewick, Wash., hopes to commercialize a somewhat related concept, one developed by researchers at the University of Missouri and which was the subject of a patent filing earlier this year. Robert Schenter, the company's chief science officer, envisions the system as a squat, meter-long vessel containing heavy water (deuterium oxide) and uranium. Shooting a beam of high-energy electrons at a tungsten target produces bremsstrahlung. The bremsstrahlung photons then rip apart deuterium, releasing neutrons. As these neutrons hit uranium, they'll cause it to fission, producing some Mo-99.



A healthy liver as viewed with nuclear imaging. Scans like this one, produced using a radioactive isotope of technetium labeled with a sulfur compound, assist doctors in assessments of organ function and in diagnoses.

To boost the efficiency of this system, Schenter came up with the idea of blanketing the vessel with a material that acts like a neutron mirror; it should reflect any unreacted neutrons back and forth within the vessel, thereby increasing their chance of hitting a uranium atom. A blanket of polyethylene would work well, his calculations indicate, potentially increasing the effective flux of neutrons more than a thousandfold. On August 18, Schenter filed for patent protection on this blanket reflector.

Tests in August confirmed that the accelerator could make neutrons in heavy water, as predicted, but this system did not include uranium. A full prototype is probably a couple of years away, Schenter says.

Meanwhile, for the past six months researchers in Madison, Wis., have been investigating the idea of turning an electron beam loose in an ionized gas, thereby producing neutrons to direct into a pool of heavy water seeded with molybdenum-98. Some of the neutrons would merge with Mo-98 nuclei, creating Mo-99, explains Paul DeLuca Jr., the University of Wisconsin–Madison's provost and a codeveloper of the idea.

So far, there's been no construction or design development. The idea "is purely on paper," DeLuca says, although based on neutron studies performed in his lab. Phoenix Nuclear Labs in Middleton, Wis., hopes to commercialize the concept.

What lies ahead

Right now, the Office of Science & Technology Policy and DOE are trying to figure out "exactly which research groups are the most technically mature and have the highest production capability," Cottam says. "Then we will work with them to assist bringing them online," providing money for nonproprietary research and technical assistance on design issues.

Legislation supporting the development of domestic moly production has also emerged in Congress this summer, suggesting the isotope's precarious supplies are on lawmakers' radar screens.

As encouraging as the developments are, Atcher says, what the medical community needs is action. After all, no blueprint yet exists for ensuring stable supplies of Mo-99, the federal government has yet to give any financial support to domestic companies and a host of regulatory obstacles must still be hurdled.

Meanwhile, Broga noted in August, "I was in a hospital this morning, and I could only schedule two patients [for Tc-99m imaging]. Normally we'd do eight to 10." He suspects a lot of elective procedures — such as for cardiac stress tests — are being postponed. Undoubtedly, he adds, some emergency room scans for pulmonary embolisms, inflamed gallbladders or heart blockages are being shifted to less sensitive screening technologies, "which represents a severe in-hospital risk."

Divgi concurs. "In most instances," he says, "these compromises can make a difference in the quality of patient care." ■

Explore more

- Nuclear and Radiation Studies Board. *Medical isotope production without highly enriched uranium*. National Academies Press, 2009.
- Society of Nuclear Medicine www.snm.org
- H.R. 3276 (American Medical Isotope Production Act of 2009). July 21, 2009. http://bit.ly/7uW2S

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