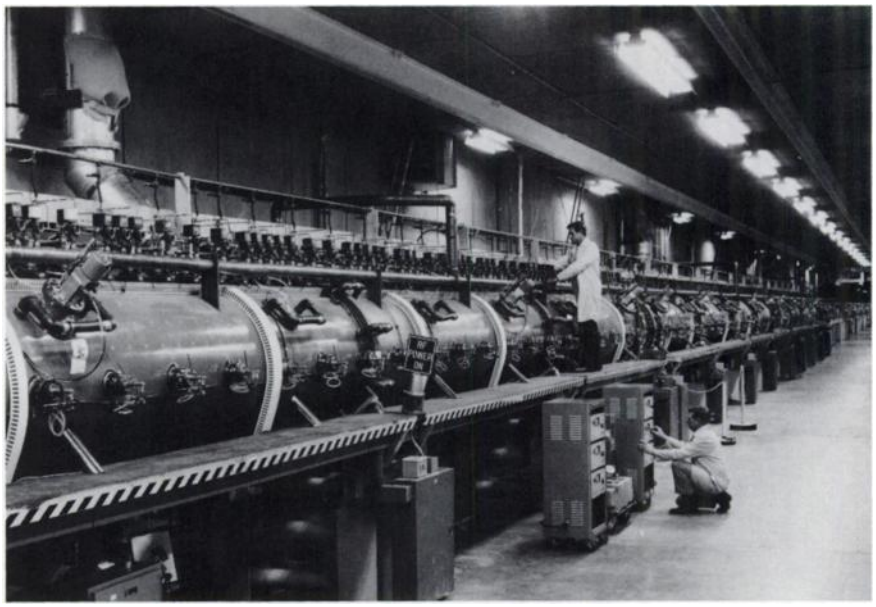
ISOTOPE SUPPLY

EARLY CLOSING OF ACCELERATOR COULD IMPEDE NUCLEAR MEDICINE RESEARCH

THE GIGANTIC PARTICLE accelerator that has supported advanced medical radioisotope research as well as nuclear physics for over 20 years at Los Alamos National Laboratory in New Mexico may close permanently after October 1993. Rather than commit the $55 million needed to run the Los Alamos Meson Physics Facility, or LAMPF, for another year, the U.S. Department of Energy has requested $15 million in fiscal 1994 to prepare plans for dismantling the machine and decontaminating the site.

The unexpectedly early closing of LAMPF means that nuclear medicine researchers and clinicians may face worsening shortages of accelerator-produced isotopes, at least until 1996 when improvements to an existing accelerator will be completed–if all goes as planned.



The half mile accelerator of the Los Alamos Meson Physics Facility in New Mexico.

Medical radioisotope investigators at Los Alamos and nuclear physicists who began long-term experiments, expecting LAMPF to operate through 1995, are stunned by the decision and are mounting a letter-writing campaign to keep the facility open, if only for another two years.

"I would say that the morale at LAMPF facility and medical radioisotope program has been better," says Eugene Peterson, PhD, the director of isotope production at Los Alamos. "People are still hoping that perhaps this will be turned around–but on a practical level, people are planning for changing jobs." The 15 or so scientists involved in radioisotope production at LAMPF would not lose their jobs outright, lab officials say, but they would be transferred to other projects. That's a dismal prospect for scientists like Dick Heaton, PhD, section leader for isotope production. "This is one program that really has an identifiable positive purpose that you can really feel good about," he says, compared to the lab's major programs in weapons research, and now nuclear waste clean-up.

The medical radioisotope program that evolved around LAMPF spawned the rubidium-82 generator for cardiac imaging with PET and other innovations such as labeling techniques for copper-67 monoclonal antibodies for treating cancer patients. Investigators across the continent still depend on LAMPF for ^{67}Cu and other short-lived isotopes, and for centers using positron emission tomography, LAMPF is a major supplier of germanium-68, used as a transmission source for calibrating the multiple detectors in a PET camera, and strontium-82, the parent isotope in rubidium-82 generators.

BLIP Upgrade Likely

Once LAMPF closes, the only remaining source for some dozen radioisotopes will be the Brookhaven Linac Isotope Producer, or BLIP, at Brookhaven National Laboratory in Upton, New York. Although the Energy Department is likely to fund construction to increase production capacity and to run the accelerator nearly all year round, the upgrade will not be completed until 1996. That means investigators already burdened by limited radioisotope supplies now face the prospect of an even more onerous couple of years.

"The crisis is upon us and we're not ready," says Suresh Srivastava, a senior scientist at Brookhaven and head of radionuclide and radiopharmaceutical research. Dr. Srivastava says the looming shortages might have been avoided altogether if the DOE had funded the BLIP upgrade when it was originally proposed in 1988. Now he says, "No matter how hard we try, we couldn't have the facility running all year until, at the earliest, fall of 1995. At the

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the study "goes right to the point of the matter–can you do the kind of things I'm trying to do from the bowels of government? I think the answer is no."

In stark contrast, radiopharmaceutical investigator Robert W. Atcher, PhD, of the University of Chicago, says his "worst nightmare" is the prospect of a private company running isotope production. Privatization like Canada is an inappropriate model, he says, "because the Canadians were making money before they went private." Dr. Atcher predicts that an industry/government joint venture would increase production costs. "A better solution would be to put all of isotope production within the Office of Energy Research and have no fantasies at all about this being a money making proposition."

"This at least forces Congress to face the issue of support for research isotopes."

Regardless of which route the Energy Department chooses to follow, the Arthur Andersen study recommends several obvious ways for isotope production to become more efficient. Overhead costs could be reduced substantially if the isotope program weren't forced to pay facilities costs that would be incurred regardless of isotope production activities. Were it not for such costs, the study estimates that the isotope program could have shown a $1 million excess rather than an $8 million deficit.

The study recommended closing unprofitable facilities and consolidating production at fewer sites, dropping out of markets where the government is no longer competitive, centralizing the management of marketing efforts rather than leaving much of it to each laboratory, improving delivery reliability, appointing product managers and holding them responsible for product profitability.

Supporting Research Isotopes

Beyond these basic business tips, the study concurs with what many scientific investigators have been saying for the past two years: The DOE must define the difference between commercial and research isotopes, and then decide which research isotopes are important enough to produce using money from tax payers. Given the existing self-supporting structure of the isotope program, Arthur Andersen states firmly that the DOE should simply stop making unprofitable isotopes, unless separate research funding has been appropriated for continued production. This straightforward statement for separate funding for research isotopes is applauded by nuclear medicine investigators and other scientists who use radioisotopes in their work. "This at least forces Congress to face the issue of support for research isotopes," says the incoming president of the Society of Nuclear Medicine, Richard Reba, MD of the University of Chicago.

"They're telling the DOE to address the same problem we've seen for years, the need for separate funding for research isotopes," says Michael J. Welch, MD of Washington University's Mallinckrodt Institute of Radiology."Indirectly, that's what the Society has been recommending by trying to get the DOE to fund the National Biomedical Tracer Facility separately."

Other researchers, such as Wynn Volkert, PhD, of the University of Missouri, express concern about the mechanism for deciding which isotopes will be produced. Dr. Volkert says, "If the DOE had a budget to support, say, the NBTF, and an oversight committee could decide what were the best isotopes to produce for research, I think that would be fine."

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moment we're projecting January 1996."

While nuclear medicine investigators and clinicians lament the early demise of LAMPF operations, they are not surprised. And even investigators dependent on accelerator-produced radioisotopes for their research are lukewarm about efforts to keep LAMPF open. Many are pushing instead for the establishment of a National Biomedical Tracer Facility that would house a powerful accelerator dedicated to production of radioisotopes and related research and teaching.

"LAMPF hasn't been worth too much in the last couple of years," says Gerald L. Denardo, MD, of the University of California at Davis, who is developing cancer therapies using copper-67 labeled antibodies.

Cancer Treatment Stalled

Even prior to the announcement of LAMPF closing, supply of radioisotopes "has been chaotic at best," says Dr. Denardo. "We've had a very uncertain supply of radionuclides that are vital for clinical research as well as care of patients." Dr. Denardo and collaborator (and spouse) Sally J. Denardo, MD, have struggled through preliminary trials of copper-67 labeled antibodies to treat people afflicted with lymph node cancers.

Despite knowing for many years that ^{67}Cu is one of the best radionuclides for cancer therapy, researchers have been hamstrung by limited availability. "Supply problems have really slowed its development greatly," Dr. Gerald Denardo says. So extremely promising work with ^{67}Cu remains largely unexplored. The Denardos have managed to treat three patients who were dying from leukemia or lymphatic disease despite conventional treatment. Of the two who responded to radioimmunotherapy, one patient remained completely free of disease after more than three years.

Dr. DeNardo says that with LAMPF

closed and BLIP only running three to four months out of the year, "we would have to seriously assess the situation and probably concentrate our major therapy efforts on another radioisotope." Putting it another way, he says, "We could not treat patients who are dying of lymph node and leukemic cancers who have responded to copper-67 radioimmunotherapy."

Rubidium Shortage Possible

In clinical practice, hospitals and clinics using positron emission tomography might face shortages of rubidium-82 generators due to the LAMPF shutdown. "It will have in impact, but right now it's hard to quantify," says George Thompson, director of radiodiagnostic drug operations at Bristol Myers Squibb Co., Princeton, New Jersey, maker of the strontium-82/rubidium-82 generator (CardioGen-82). "With Los Alamos gone, supply will become even more difficult," Mr. Thompson says.

Besides LAMPF, Squibb already has two suppliers of ^{82}Sr: BLIP and Canada's Nordion International, Inc., in Kanata, Ontario. But neither of these sources yet produce year-round, nor could they make up for the quantity of materials produced by LAMPF while operating. The Los Alamos machine routinely runs at energies unmatched by facilities anywhere else in the world, yielding thousands of millicuries of high-specific activity radioisotopes.

Squibb has approached other potential suppliers, but any new supplier would have to be qualified by the U.S. Food and Drug Administration, a process that could take many months. The upshot: PET centers are bracing for generator shortages in late 1994.

Whether pricing will be affected, Squibb's Mr. Thompson says, "I really can't say that costs won't go up. But PET is something we want to grow, so even if the cost of strontium-82 doubled, we're not in a situation where we could turn around and double the price of generators to our customers–we would destroy the market."

While nuclear medicine investigators can somewhat content themselves with the BLIP upgrade, no fix is in sight for the physicists dependent on LAMPF. The DOE's nuclear sciences advisory committee urged the department to keep LAMPF operational through 1995 to allow completion of key experiments in which physicists have already invested thousands of dollars of grant money and months of time.

The physicists have built elaborate instruments like the Liquid Scintillator Neutrino Detector, essentially a huge tank of oil surrounded by thousands of photomultiplier tubes, designed to capture fleeting traces of neutrino-proton interactions. Such evidence might answer elusive questions about the quark content of the proton. This and other experiments have barely gotten off the ground, and those involved are incensed at the waste of time and effort that will be caused by early closure of LAMPF.

"Typically about eight experiments are running at once, and in two years I'm sure it's a hundred experiments," says Jerry Peterson, PhD, a physicist at the University of Colorado, Boulder, and chairman of board of directors of the LAMPF Users Group. He estimates that 50 PhD scientists will lose their jobs at Los Alamos if LAMPF closes. "The clever ones will be leaving first, so this summer operations could be rocky," warns Dr. Peterson. But he adds that the looming problems are solvable, "if the community unites."

While the plight of the nuclear physicists at Los Alamos might seem reason enough to evoke feelings of sympathy among all scientists, some radiopharmaceutical researchers, such as Robert Atcher, PhD, of the University of Chicago, say they find the call for solidarity somewhat belated from the group that has dominated LAMPF operations. In the summer of 1987, Dr. Atcher points out, physicists conducting a neutrino-detection experiment at LAMPF wanted to install solid shielding to reduce neutron background to acceptable levels and the plan nearly put an end to radioisotope production.

NBTF Takes Priority

Instead of battling to pour millions into a facility that will be closed in two years, groups such as the Society of Nuclear Medicine and the American College of Nuclear Physicians are seizing the moment to step up their campaign for the establishment of a National Biomedical Tracer Facility.

"I would be very supportive of the people at Los Alamos, but we should not lose sight of our main goal, the NBTF," says the incoming president of SNM, Richard C. Reba, MD, of the University of Chicago. "Our goal is to get the BLIP upgrade and eventually the NBTF."

In support of LAMPF, Dr. Peterson of Los Alamos points out that the NBTF will take years to construct. In the meantime, he says, "If the materials are not available, people will use other technologies to supplant what's being done with radioisotopes."

If the NBTF is fully funded in the next two years, the new facility could be ready by 1998, according to some estimates. So far, at the urging of Congress, the Energy Department has only set aside $2 million in the fiscal 1994 budget to conduct the search for a suitable site and design for the NBTF.

In its delayed response to isotope supply problems, the Energy Department seems to have firmly decided that LAMPF is too expensive and that the BLIP upgrade is the best interim solution. Although the upgrade will take about two years, scientists at Brookhaven hope to gradually increase the running time of the accelerator, which last year amounted to just 20 weeks. "In fiscal year 1994, we may be able to run 30 weeks and leave the remainder for construction," says Dr. Srivastava. "In fiscal year 1995, we could push it to 36 weeks, that is possible."

As for LAMPF, its future is now in the hands of Congress.

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