'Low-Priority' Biomedical Studies Hindered

DOE Convenes Workshop to Explore Improved Availability of Research Isotopes

"We're precariously balanced here, where we can do some things but we can't determine our own destiny. . . .We at Los Alamos have been providing isotopes by every hook, crook and method we can figure out, and we're not being supported at the level required to do even what we're doing now."

Recently Phyllis E. Johnson, PhD, a research chemist with the Human Nutrition Research Center for the United States Department of Agriculture, Grand Forks, North Dakota, needed a small quantity of magnesium-28 for an experiment on the mineral's metabolism in humans. But when she called Brookhaven National Laboratory, Upton, New York, to check on the order, she discovered that the Brookhaven LINAC Isotope Production Facility (BLIP) could not provide the material. The reason? The leakage of a target pump had caused the Brookhaven facility—the only source of magnesium-28 in the United States—to shut down. Dr. Johnson nearly suffered a delay that would have invalidated 15 months of preparatory work, including the recruitment of a suitable group of experimental subjects. "We were afraid our volunteers would have gone home because it came just before we would have discharged them," Dr. Johnson said.

The big US accelerators aren't dedicated to providing a reliable supply of isotopes for biomedical research, as regular users know only too well. Instead many of these isotopes are produced, as Thomas P. Haynie, MD, chair of the nuclear medicine department at the University of Texas MD Anderson Cancer Center in Houston put it, as crumbs from the table set for high-energy physics experiments. This may have been tolerable when the use of stable and radioactive isotopes in biomedical investigation was new, but today these researchers, weary of trying to accommodate unreliable supplies, are beginning to demand their own place at the table. Not only are established lines of experimental work hampered by current production limitations, but perhaps more seriously, researchers say, whole new lines of inquiry are being cast aside as impractical because of the unpredictability of supplies of unusual isotopes. This is ironic as the medical uses of radiation are often cited as a justification for funding expensive research into particle physics.

'Only Game In Town'

In an attempt to find a solution to the problem, in August the US Department of Energy (DOE) convened a workshop in Los Alamos, New Mexico, on the role of a high-current accelerator in the future of nuclear medicine. While the title of the workshop suggested that a new accelerator dedicated to nuclear medicine research is the answer, the 50 workshop participants explored a number of other solutions and agreed upon both long-term and short-term proposals. In the view of those at the workshop, the biggest problem with the way research isotopes are produced in the United States now is that there is not a continuous, reliable supply of many of them. "The Department of Energy is the only game in town for the production of radionuclides, and yet it has fallen short in failing to produce radionuclides for research," said John G. McAfee, MD, director of the division of radiological science at the State University of New York at Syracuse. As chair of the Subcommittee on Nuclear Medicine Research, Health and Environmental Research Advisory Committee (HERAC) to the Office of Health and Environmental Research at DOE, he presented the workshop with the latest draft of the advisory group's report. Among other recommendations, the HERAC report urges the development of a facility containing a charged particle accelerator for the continuous production of radionuclides.

The problem was illustrated by Michael J. Welch, professor of radiochemistry at Washington University in St. Louis, who with Mark A. Green, PhD, assistant professor of nuclear pharmacy at Purdue University's School of Pharmacy in West Lafayette, Indiana, is working on an experiment with copper-67 radiopharmaceuticals that was to be performed a few days after the workshop. "We asked that it be processed quickly and offered to pay so that it

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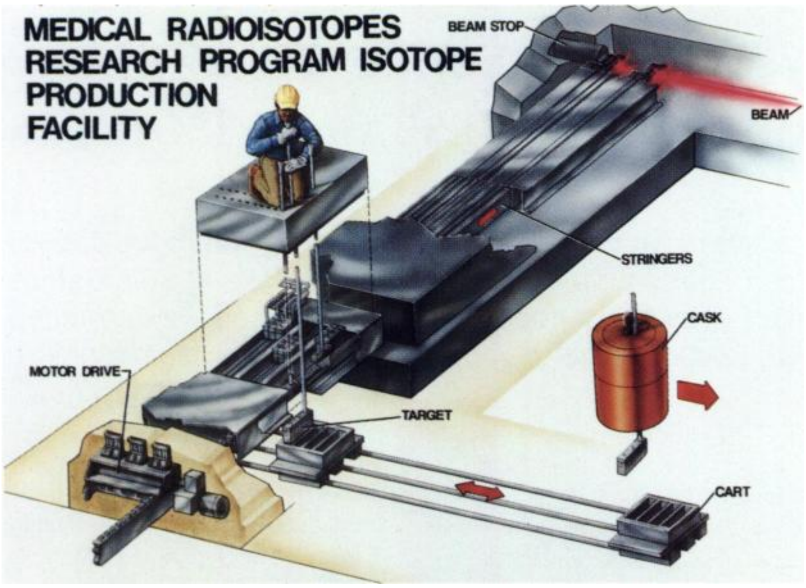

Isotope Production Facility at Los Alamos National Laboratory. Each of nine target stations, called stringers, can be loaded with a target and placed into or withdrawn from the proton beam without affecting the others.

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could be shipped on Monday," Dr. Welch said. "This is a funded research project where we were willing to pay extra money. We were told 'No, there's not manpower to do this.' So here's an isotope where there's a use, here's a funded project with a feasibility study, and we can't get the isotope. I'm sure there are lots of people around who can tell stories like that." David C. Moody, PhD, a deputy group leader of the Isotope and Nuclear Chemistry division of Los Alamos National Laboratory, wrote in his position paper that both nuclear reactor- and accelerator-produced radioisotopes contribute to the supply for research and clinical use, but that the combination of sources is not sufficient to meet existing demand, much less the demand anticipated for the future. "We're precariously balanced here, where we can do some things but we can't determine our own destiny," he told the workshop. "We [at Los Alamos] have been providing isotopes by every hook, crook and method we can figure out, and we're not being supported at the level required to do even what we're doing now."

Reactor Production of Isotopes

He noted that reactor production of radioisotopes is plagued by problems, such as the recent disruptions in operations at Oak Ridge National Laboratory's High Flux Isotope Reactor (HFIR)—which is expected to restart sometime this fall—and the Oak Ridge Research Reactor, which was permanently shut down in July 1987. The Research Reactor was closed because its scientific mission was completed. Oak Ridge ceased operations at the HFIR in November 1986, when it was discovered that the pressure vessel was being embrittled at a rapid rate by exposure to neutrons. While other DOE reactors have supplemented the supply, Dr. Moody said that production has been severely hindered by the necessity to irradiate targets at other DOE reactors with lower neutron fluxes. (In the case of some isotopes, however, this hasn't happened. For example, Oak Ridge pioneered the production of gadolinium-153 for clinical use, but during the recent temporary shutdown of its reactors others within the DOE system supplemented production, leading to few disruptions in the supply of gadolinium-153, Dr. Moody said.)

Some isotopes can be produced by either reactors or accelerators. Xenon-127 had been produced at Brookhaven since 1973 and at Los Alamos since 1980, but as of September it is no longer being produced at Los Alamos. Production was halted, Dr. Moody explained, because "it takes a tremendous commitment of hardware resources to do the isotope"—at Los Alamos, one hot cell out of only 13 was totally dedicated to xenon-127 production. He said that with the availability of xenon-126 and the literature support for producing xenon-127 from xenon-126 in nuclear reactors, it seemed time to terminate production at Los Alamos.

While the transition to reactor production of xenon-127 is expected to be quite smooth, certain radioisotopes can be produced only in accelerators, and big ones at that, as high energies are required in somes cases to produce a given sample in large enough quantities, or with a given specific activity, or at all. In the case of xenon-127, demand was already close to BLIP and LAMPF's capacity before LAMPF halted production in September, and whether xenon-127's clinical acceptance grows may depend upon successful reactor production of the radioisotope. Dr. Moody believes that the popularity of xenon-127 has been limited by its lack of continuous availability.

There are only two large DOE-operated irradiation facilities in the United States: the BLIP and the Isotope Production Facility at the Los Alamos Meson Physics Facility
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(LAMPF). A few DOE cyclotrons and industry or university accelerators could be used to produce small quantities of selected isotopes, but their production capacity would be limited because of low beam intensities and the difficulties imposed by multiple target irradiations, according to Dr. Moody.

The BLIP uses the excess proton beam capacity of the linear accelerator that injects into an alternating gradient synchrotron. This LINAC has a maximum energy of 200 million electron volts (MeV) and maximum beam current of 60 microamperes, although a beam current of 40 to 50 microamperes is typical. Because the proton energy degrades as the beam passes through a group of targets, the selection of target position in the array allows some control of the incident energy. This makes it possible to optimize desired reaction products while minimizing unwanted impurities. BLIP's major limitations are its low beam intensity, which limits yields for long-lived isotopes, and its short operating schedule, which is dictated by funding. As a result, BLIP is just barely keeping up with the demand for several major isotopes (see Table 1, page 1613). Research demands, such as those associated with the Strategic Defense Initiative ("Star Wars") defense project, could help or hinder BLIP's production.

More Than 30 Isotopes

LAMPF, the most powerful medium-energy accelerator in the world, is a half-mile-long linear accelerator with 800 MeV and 1.1 milliamperes in capacity. It has nine target stations, each capable of irradiating one to three targets, depending on their size. Dr. Moody noted that the Medical Isotopes Research Program at Los Alamos produces more than 30 different radioisotopes and is the sole US supplier of 15 of these. LAMPF, too, is approaching the limits of its production capacity for certain popular isotopes (see Table 1).

Los Alamos is committed to maintaining a six-month operating schedule for LAMPF as long as possible, Dr. Moody said. As about four months each year are needed for maintenance and upgrades, it would be possible to run LAMPF eight months a year were it not for budgetary constraints. Yet the longevity of this commitment is unclear. Los Alamos has proposed construction of an Advanced Hadron Facility that would use LAMPF as an injector into a booster ring, to explore the next level of understanding of nuclear forces by using higher energies—perhaps as high as 60 GeV. This project, which has yet to be funded, could bring radioisotope production to a halt as early as 1993, Dr. Moody said, as irradiating targets with a beam in the multi-GeV range is impractical because the beam tends to penetrate everything in its path, making targeting and shielding difficult. "We have enough of a problem stopping an 800 MeV beam as it is," he points out. But even without this new project, LAMPF and BLIP operating funds could be affected by two other projects: the Continuous Electron Beam Accelerator Facility (CEBAF), which is under construction in Virginia, and the Relativistic Heavy Ion Collider (RHIC), which is not yet funded but under consideration for Brookhaven National Laboratory. James N. Bradbury, PhD, deputy division leader for medium-energy physics at Los

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TABLE 1. Production of Selected Isotopes

Brookhaven National Laboratory

Isotope	Irradiation Time	Yield	Present Demand
^{82}Sr	4 weeks	600 mCi/month	400 mCi/month
^{68}Ge	18 weeks	133 mCi/month	> 300 mCi/month
^{127}Xe	4 weeks	3 Ci/month	3–4 Ci/month
^{67}Cu*	1 week	200 mCi/month	500 mCi/month

*Includes 200 mCi/month Los Alamos National Laboratory requirement.

Los Alamos National Laboratory

Isotope	Irradiation Time	Yield	Present Demand
^{82}Sr	4 weeks	1–2 Ci/month	400 mCi/month
^{68}Ge	4 weeks	350 mCi/month	> 300 mCi/month
^{127}Xe*	4 weeks	5 Ci/month	3–4 Ci/month
^{67}Cu**	1 week	6 Ci/month	500 mCi/month

*Los Alamos National Laboratory ceased production in September, 1988.
**Includes 200 mCi/month Los Alamos National Laboratory requirement.

Table 1. The demand for some isotopes is already approaching the production capacities at the two largest accelerators in the United States. (Information courtesy of David C. Moody.)

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Alamos, notes that the operating funds for all of these projects come from the same budget, and that some DOE facilities may have to curtail their activities as a consequence. "But as long as LAMPF is operating for nuclear and particle physics research, there is no reason [isotope production] can't occur. It's a parasitic operation—they use the remnants of the beam and aren't charged for beam time," he said. Neither the Brookhaven LINAC nor the LAMPF were built expressly for isotope production, but rather for basic research. Their schedules are designed to accommodate the high-level physics studies that pay for their operation. LAMPF costs $4 million a month to run, with $1 million to pay the electricity bills alone; BLIP costs $125,000 a week. As the total DOE budget for research in the application of nuclear technology to medicine for fiscal year 1988 is about $35 million, and the cost of operating LAMPF for eight months is $25 million to $30 million, it would not be possible for this budget to support LAMPF without help. The fees charged to researchers for the material are no where near the actual cost of producing the isotope, Dr. Moody added.

Neutrino Experiments

Because physics experiments are the first priority, the supply of isotopes for research is vulnerable to disruption. Three years ago BLIP was forced to shut down for four to five weeks because of a high-energy physics study that employed beam intensities too low for isotope production. More recently, evaluations at Los Alamos showed that an experiment to explore the interconversion of one type of neutrino into another, and to put some limits on the mass of a neutrino, might preclude radionuclide production for up to three years (see *Newsline*, Sept. 1987, pp. 1371-1382). Researchers feared that in-flight pion decay in the area of the isotope targets might lead to neutrino-induced background noise. To assess the extent of the noise, isotope production was briefly suspended last December and a solid chunk of copper just large enough to maximize the problem was placed in the path of the beam. In the end, researchers found that even this material didn't contribute noticeably to background noise, and so LAMPF returned to its six-month production schedule. But there is no guarantee that a similar problem might not arise again, and even with LAMPF currently operating six months a year and BLIP operating 18 to 22 weeks a year, and with efforts to stagger operating cycles, the isotope supply remains neither continuous nor secure.

Moreover, both BLIP and LAMPF, like aging family cars, are subject to mechanical breakdowns at inopportune times. A recent upgrade has helped the 16-year-old BLIP, and major hardware changes are underway at LAMPF, which is about the same age, but neither facility can match today's equipment for reliability and economy. Dr. Moody adds that while the new physics accelerators being considered by Congress would remedy this problem, they are being designed to operate at too high an energy (billions of electron volts, or GeVs) to make radioisotope production practical.

The vulnerability of isotope production is nothing new. In his written report, Dr. Moody described a previous instance in which production capacity was imperiled and finally lost. In the 1950s, an 86-inch cyclotron was constructed at Oak Ridge National Laboratory for classified programmatic radioisotope production and physics experiments. Medical radioisotope production began in the 1950s, and increased through the 1960s with the distribution of more than 120 different products, 20 of which were routine. Beam time was rented to the National Aeronautics and Space Administration (NASA) to help support the facility as programmatic needs diminished. But as accelerators in the private sector began to take over production of the most profitable isotopes in the 1970s, Oak Ridge was left with only cobalt-57 and gallium-67 as large-volume irradiations. Physics experiments ended, NASA built its own facility, and, despite the need for the research isotopes produced in the 86-inch cyclotron, it proved too expensive to operate the mammoth facility for the nuclear medicine community alone. The cyclotron was shut down in 1984.

New Directions for Research

Whether nuclear medicine can grow in new directions in the United States depends upon the availability of certain radioisotopes. Dr. Welch noted that the number of positron emission tomography (PET) centers either installed or planned in the United States and Canada is now approaching 40. Others estimate that the number of PET installations in North America could easily double by 1990. The majority of these centers will use radionuclides produced with in-house cyclotrons, Dr. Welch said; other options include using generator-produced activity combined with regional delivery of fluorine-18 compounds plus, perhaps, an oxygen-15 production system.

In his presentation to the workshop, Dr. Welch listed nine parent/daughter generator systems that could have utility in PET, including germanium-68/gallium-68, strontium-82/rubidium-82, xenon-122/iodine-122 and zinc-62/copper-62 generators. While it is difficult to predict which generators are likely to be useful in the fu-

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ture, without the routine availability of zinc-62 and iodine-122 Dr. Welch believes it will be impossible for these generators to have an impact on the future of PET. Nuclear reactions can produce the parent isotopes, but all can also be produced by spallation reactions using high-energy proton beams.

Clinical PET Concerns

The projected demand for strontium-82, the generator parent most often cited as the one that could bring clinical PET to facilities unable to support an in-house cyclotron, would be especially difficult to meet, according to Dr. Moody. If BLIP and LAMPF could operate on staggered six-month cycles, there might be ample production of the strontium isotope to meet current demand; however, if demand grows but modestly, it could easily outstrip BLIP's capacity to produce strontium-82. Even if upgraded, BLIP could not meet the projected demand in three to five years, Dr. Moody said, and Los Alamos would have to devote three irradiation stations, or one-third of its capacity, just to irradiating molybdenum to make strontium-82. Production could be augmented by supplies from Canada and Europe, but not if the number of PET installations worldwide grows at a rate comparable to that anticipated in the United States. The 100 PET centers that could be operating in the world by 1990 collectively would require approximately 12 Ci/month of the strontium isotope, far more than can be produced by existing equipment, according to Dr. Moody's estimates.

Moreover, Dr. Welch pointed out that even if gallium-68 is not used in radiopharmaceutical production, the germanium-68/gallium-68 system is still required at PET centers, as the gallium is used as an emission source to determine the uniformity of the imaging device, as well as in most cases to obtain a transmission image to quantitate the emission image. Dr. Moody pointed to the tremendous increase in the demand for the radioisotope since fiscal year 1981, a demand that already leads Los Alamos to sell every bit of the germanium-68 it can produce (see chart, page 1616). BLIP's lower beam current severely limits production of such long-lived isotopes as germanium-68, Dr. Moody said.

Monoclonal antibody research, too, has a need for relatively exotic isotopes. Michael R. Zalutsky, PhD, associate professor of radiology and assistant professor of pathology at Duke University Medical Center, Durham, North Carolina, pointed out that the alpha-emitting astatine-211 and bismuth-212 may offer advantages in tumor treatment, such as their high effectiveness: only two to 15 alpha traversals per cell are required to kill cells, according to several independent studies. In general, such alpha emitters may offer advantages over beta emitters for the treatment of micrometastatic disease, tumors of the circulatory system, ovarian cancers, medulloblastomas and in cases where toxicity to highly radiosensitive normal tissue, such as that in the spinal cord, is a potential problem.

Bismuth-212 can be obtained as a product of lead-212 decay from a radium-224 parent, while astatine-211 can be produced in a cyclotron by alpha bombardment of natural bismuth. Unfortunately, Dr. Zalutsky said, few cyclotrons in the United States have alpha beams suitable for this purpose, and none of those that have been used to make astatine-211 have sufficient incident alpha energy to permit the use of 4 pi, water-cooled targets, an approach that has been used in Europe to dramatically increase yields.

TABLE 2. Accelerator-produced Radioisotopes

LAMPF
^{7}Be
^{22}Na
^{26}Al
^{32}Si
^{44}Ti
^{44,46}Sc
^{48}V
^{52}Mn
^{52,59}Fe
^{56}Co
^{67}Cu
^{68}Ge
^{72}Se
^{72,73}As
^{77}Br
^{82}Sr
^{82,83,86}Rb
^{88}Zr
^{88}Y
^{109}Cd
^{105,109m}Ag
^{123,125}I
^{127}Xe
^{139}Ce
^{145}Pm
^{145}Sm
^{146,148}Gd
^{163}Ho
^{172}Hf
^{172,173}Lu
^{207}Bi

BLIP
^{7}Be
^{7}Be (carbon)
^{28}Mg
^{52,59}Fe
^{56}Co
^{67}Cu
^{68}Ge
^{81m}Kr
^{82}Sr
^{82}Rb
^{97}Ru
^{117m}Sn
^{118}Te
^{123}I
^{127}Xe
^{128}Ba
^{203}Pb

Table 2. Some isotopes are produced only at the Brookhaven LINAC Isotope Production Facility (BLIP), while others can be obtained only from the Isotope Production Facility at the Los Alamos Meson Physics Facility (LAMPF). Supplies are supplemented by production in nuclear reactors in some instances. (Information courtesy of David C. Moody.)

Particularly Attractive Isotope

Bromine-77, an emitter of low-energy electrons of subcellular range, is another promising isotope that is rarely available in the United States, Dr. Zalutsky said. It could be produced routinely if the right accelerator were available. He finds this nuclide particularly attractive because of the ease of protein radiobromination and the fact that its radiotoxicity after intra-nuclear localization has been documented. William C. Eckel-

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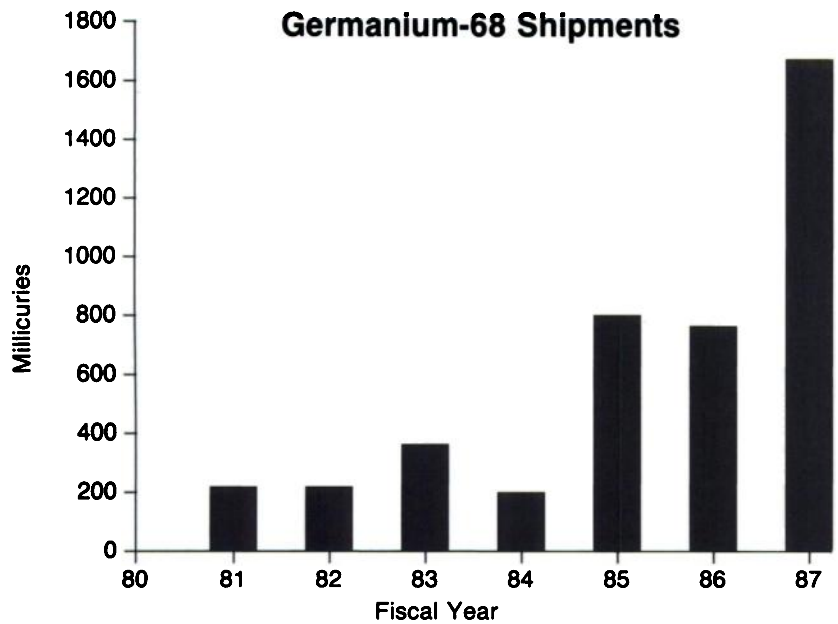

Growth of germanium-68 shipments from Los Alamos, fiscal year 1981 through 1987. (Information courtesy of David C. Moody.)

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man, PhD, vice president of diagnostics research and development at the Squibb Institute for Medical Research, New Brunswick, New Jersey, provided the workshop with the results of a literature review of isotopes used in single photon emission computed tomography (SPECT) and in general nuclear medicine imaging. He found a need for a high-flux dedicated reactor for many of the therapeutic radionuclides and for molybdenum-99/technetium-99m, and a need for a high beam current cyclotron for a few key therapeutic radionuclides and for iodine-123, which becomes contaminated with image-blurring iodine-124 when produced on low-energy machines.

The HERAC report also provided a shopping list of desirable isotopes. But regardless of the area of study or the question to be investigated, workshop participants agreed, infrequent or sporadic supplies of an isotope discourage research efforts using that isotope. The Department of Agriculture's Dr. Johnson recently cancelled animal studies involving copper-67 because she couldn't be sure the isotope would be available when she needed it. Dr. Moody also cited the case of copper-67 in his position paper. Several years ago, the need for a longer-lived copper isotope became critical, as the 12.7-hour half-life of copper-64 limited researchers' abilities for further investigation by tracing copper metabolism in living organisms. In response, Los Alamos scientists developed the spallation production of 62-hour copper-67 from a zinc oxide target and the chemical separation methods required for its purification, which were later replaced by an electrochemical procedure. Since September 1981, copper-67 has been available to the research community, and because of its attractive characteristics—convenient half-life, gamma emissions for imaging and beta decay for therapy—it has been used for labeling monoclonal antibodies. Demand for copper-67 continues to grow, and Los Alamos has been contacted by industrial concerns eager to explore the isotope's potential. But even current clinical trials are severely hampered by LAMPF's six-month operating cycle, Dr. Moody said. BLIP can produce small quantities of the material, but the specific activity averages only 2,000 Ci/gm compared with the 15,000 Ci/gm activity of LAMPF-produced copper-67. For this reason, Dr. Moody said, several companies with a research interest in copper-67 are waiting for the workshop's conclusions and other indications of the prospect for a continuous supply before committing themselves to further research. Meanwhile the demand for copper-67 continues to grow: Dr. Moody estimates that it might easily reach 2 Ci/month in five years, a demand that could be met by LAMPF when it is running, but that could not be met by BLIP alone even after the upgrade proposed by Leonard F. Mausner, PhD, director of BLIP.

BLIP Upgrade Proposal

The upgrade Dr. Mausner described was not endorsed by workshop participants, probably because of fears that it would siphon off funding from other existing projects. The proposal would increase isotope availability by expanding BLIP's operations to 46 weeks a year instead of only 18 to 22. Dr. Mausner noted that the Brookhaven facility is different from LAMPF because it isn't a parasitic operation: "We're not the beam stop," he said. Instead, the BLIP uses pulses from the 500-foot linear accelerator that are diverted to it specifically to produce isotopes. The capital costs for an upgrade would total about $3.4 million over three years and include $150,000 for a new ion source to increase beam current, $850,000 for a new preaccelerator and improved beam diagnostic

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instrumentation, \$400,000 for expansion and renovation of the hot lab, and about \$2 million to support simultaneous H-minus and H-plus ion co-acceleration (the lab uses only H-minus now). This latter enhancement would help insure compatibility of isotope production with future physics experiments, Dr. Mausner said. BLIP would also incur \$1.5 million to \$2.35 million in net operating costs each year, with the amount dependent on how much support could be obtained from other projects, such as SDI and a proton beam therapy program. Isotope sales would generate about \$750,000 each year.

After this upgrade, BLIP would be able to meet 100 percent of the current demand for xenon-127, strontium-82, and copper-67, as well as 67 percent of the demand for iodine-123 and perhaps 49 percent of the demand for germanium-68, Dr. Mausner said.

> "To me, nuclear medicine is number one. It's been number one all my professional life and it will likely stay that way. I don't want to take the crumbs off of anybody's table."

Workshop Recommendations

In the end, workshop participants agreed to recommend that the Department of Energy and Congress:

• *Immediately provide additional support for radionuclide production (people and supplies) at both Los Alamos and Brookhaven National Laboratories.* This would ensure, for example, that BLIP would have more than one person available to process radionuclides. This has been a problem for BLIP: in March isotope production was suspended for a week because the radiochemist's mother died.

• *DOE should establish policy allowing future radionuclide production to support technicians from the sale of routine radionuclides.* Instead of being subsidized, users would be charged what it directly costs to produce these isotopes. Dr. Moody explained that the intent is to recognize that there are two classes of isotopes: those "routine" ones that are commonly produced, and those that are produced only in minute quantities for specialized research purposes. Routine isotopes would no longer be available at subsidized "research" prices.

• *The United States should have a 70 MeV, 500 microamperes, variable energy proton accelerating machine. Committees on site and machine selection would be appointed, and BLIP and LAMPF would be used for radionuclide production requiring higher energy.* An accelerator dedicated to producing routine radionuclides would help free resources at Brookhaven and Los Alamos for the isotopes that couldn't be produced on the new machine. In addition, many workshop participants hope that it could help relieve the severe shortage of radiochemists and physicists by providing a training facility for them. As organizations bid for the project, the kind of training opportunities they are prepared to provide could be one of the criteria employed by the selection committee.

• *DOE is to solicit proposals to evaluate the usefulness of a new or upgraded, high-energy, high-current machine for production of research radionuclides.* The size of the accelerator was left unspecified because the workshop lacked consensus as to the most desirable size. But according to Dr. Moody's calculations, a high-current, 150 MeV linear accelerator, with five beams and five to 10 targets per beam, would cost about \$45 million to build, plus another \$25 million for hot cells unless they already existed on the site. Such a machine would require \$2 million a year to operate, including \$500,000 a year for electricity alone.

Whether any of these proposals will be adopted depends upon the decisions of Congress and the Department of Energy, and the willingness of government and industrial concerns to work together. Perhaps most critically, improvement depends on the ability of researchers and practioners to explain how a dependable supply of isotopes could result in the kind of basic research and clinical care that benefits everyone. "To me, nuclear medicine is number one," said Dr. Haynie. "It's been number one all my professional life and it will likely stay that way. I don't want to take the crumbs off of anybody's table. . . . I think what we need is for somebody to light a fire under our pants so that we get upset every now and then about the fact that we're not getting what we need."

Karla Harby