DOE Nuclear Medicine Program

Energy Agency Examines Radioisotope Needs in Preparation for the Future

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The Department of Energy (DOE) is exploring various avenues to supply the nuclear medicine community with the radionuclides it needs for research, diagnosis, and treatment. Although most routine isotopes can be generated in smaller cyclotrons or in reactors, the DOE production reactors have experienced problems over the past few years. More critically, researchers and clinicians are still subject to precarious reliance on the two large DOE-operated accelerators for supplies of accelerator-produced isotopes including magnesium-28 (^{28}Mg), copper-67 (^{67}Cu), germanium-68 (^{68}Ge), bromine-77 (^{77}Br), strontium-82 (^{82}Sr), ruthenium-97 (^{97}Ru), xenon-127 (^{127}Xe), and others used in myriad techniques from cardiac imaging to monoclonal antibody imaging and therapy.

Membership of HERAC Subcommittee on Nuclear Medicine

John G. McAfee, MD, chairman
William C. Eckelman, PhD
Michael L. Goris, MD
Richard A. Holmes, MD
Samuel E. Halpern, MD
David E. Kuhl, MD
Gerd Muehllehner, PhD
Richard C. Reba, MD
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Richard P. Spenser, MD
Suresh C. Srivastava, PhD
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Sheldon Wolff, PhD

'No Continuous Supply'

"In the United States, we have no continuous supply of radionuclides for research. This is a real handicap," says John G. McAfee, MD, professor of radiology, director of the division of radiological sciences, State University of New York Health Sciences Center, Syracuse. Dr. McAfee chaired an advisory subcommittee of the DOE's Office of Energy Research (OER) that drafted a report in 1988 on the Department's Nuclear Medicine Program (*1*), citing the need for a facility containing a cyclotron or other suitable charged particle accelerator dedicated to the continuous production of radionuclides for research (see *Newsline* Commentaries November 1988, p. 1758, and April 1989, p. 438).

Dr. McAfee notes that the accelerators at Brookhaven National Laboratory (BNL), the Brookhaven Linac Isotope Production Facility (BLIP), and at Los Alamos National Laboratory, the Isotope Production Facility (IPF), exclusively have supplied many radionuclides used in biomedical research in the United States. The accelerators at these facilities operate only during experiments under the control of high energy physics, however, making radionuclide production a subsidiary activity with long periods of interruption.

According to William C. Eckelman, PhD, vice president for research, The Squibb Institute for Medical Research, a member of the Nuclear Medicine Subcommittee, and chairman of Brookhaven's BLIP Users Committee, BLIP "can supply isotopes only four to five months out of the year, making it hard to plan clinical experiments." He further notes that the design of some physics experiments "may preclude our using the machine for isotope production." The same conditions apply at the Los Alamos IPF, which operates over a period of six months during the year, with two-week breaks after every six weeks. There is no funding to operate these facilities between physics projects.

Dedicated Facility Needed

Under these constraints, notes Dr. McAfee, biomedical research has to

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take a back seat to high energy physics research. However, the Subcommittee points out in their report that "a continuous reliable supply of research radionuclides is available in western European countries and Canada," and adds that "this is a worthy goal for the US also, but can be reached only by establishing a facility committed to radionuclide production."

The draft report of the Nuclear Medicine Subcommittee of the OER's Health and Environmental Research Advisory Committee (HERAC), was followed by a DOE-sponsored workshop in August 1988, during which participants expanded on that theme but, more specifically, recommended that the DOE develop a dedicated facility with a "70meV, 500μA variable energy proton accelerator as soon as possible;" evaluate the usefulness of a new or upgraded high-current, high-energy machine; provide for more isotope production personnel; and charge fully for purchases of routine radionuclides rather than subsidizing such sales (see *Newsline*, October 1988, p. 1611).

In a position paper prepared for the workshop—"The Role of a High-Current Accelerator in the Future of Nuclear Medicine" (*2*)—David C. Moody, III, PhD, of the nuclear and radiochemistry group at Los Alamos, indicated that "The current situation. . . for accelerator production of radioisotopes in general—is critical. With limited resources, short operating cycles, and prospects of even further limitations on accelerator operations in the future, we must act now to ensure a steady supply of research radioisotopes for nuclear medicine. . . . If we do not reach a solution to the dilemma, US production of these isotopes could cease in the near future."

Central Isotope Office

The urgency conveyed during the workshop and in the Subcommittee report has yet to be translated into action. But, according to a Congressional mandate, DOE established a central Isotope Production and Distribution Office in Germantown, Maryland in May 1989 (see *Newsline*, December 1989, p. 1934).

Gene Peterson, PhD, deputy group leader of the nuclear and radiochemistry group at Los Alamos, calls the reorganization of the DOE's isotope production and distribution activities, "a step forward in the process of ensuring the future supply of radioisotopes."

However, Robert W. Atcher, PhD, group leader for nuclear medicine research at Argonne National Laboratory, points out that within the legislation mandating the Isotope Office, Congress called for full cost recovery from DOE's isotope production operations, eliminating the traditional subsidy. He says this results in "pressure to have these facilities pay for themselves" and leads to price increases for radioisotopes. "The price of isotopes," he adds, "in some cases, is going to quadruple. . .and the price is very likely to keep going up" given these circumstances. "This is especially bad for users who have budgeted for isotopes based on unrealistically low cost figures" from the past. Dr. Atcher is also concerned about what will happen to the demand if prices continue to rise.

In an attempt to address these concerns, the Isotope Office is currently working on a status report that will outline for Congress its priorities and

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needs for the future. In addition to the status report, the staff of the Isotope Office has been engaged in discusssions with some of the national laboratory scientists in an effort to formulate an effective proposal for the future.

Leonard Mausner, PhD, scientist in charge of BLIP operations and radionuclide research, has suggested proposals for the short and long term with the DOE. In the short term, Dr. Mausner proposes that with additional funding Brookhaven could extend the BLIP's schedule for radionuclide production. In the long term, he notes that "a dedicated facility is needed. . .the parasitic mode of operation of BLIP and IPF has been economical and efficient, but due to a progressive decline in physics funding resulting in reduced beam availability, this situation won't hold in the future."

However, Dr. Mausner considers a 120meV, 200μA machine more flexible than the 70meV, 500μA machine recommended during the workshop. Both he and Suresh C. Srivastava, PhD, head of the radionuclide and radiopharmaceutical research division, within the medical department of BNL, a member of the HERAC Subcommittee, espouse the concept of a center with such a dedicated accelerator, within which radionuclide research "is the centerpiece." The center they envision would also enable considerable production for commercial interests as well as "provide the badly needed training role to ensure the future supply of competent radiochemists and radiopharmaceutical scientists," according to Dr. Mausner.

Flexibility for the Future

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Dr. Mausner agrees. "The future of nuclear medicine may depend on one or more of these future isotopes," he says, "but you will never know if you don't have a chance to develop them."

Dr. Srivastava predicts that a dedicated, high-energy, high-current facility is "not in the cards" at least for the next several years. James Robertson, MD, PhD, director of the human health and assessments division within the DOE's Office of Health and Environmental Research (OHER), agrees that while a "dedicated machine is something [the DOE] want[s] very much. . .right now [the agency does not] have money for a dedicated cyclotron."

Donald E. Erb, director of the DOE's Isotope Office, sees a dedicated facility as a viable option in two or three years, provided the agency could be assured "up front" that the facility would have enough sales to generate sufficient funds from its users. He says that a physicist within the Isotope Office is examining what the existing facilities can provide, with and without modification, as well as what the necessary characteristics of a new machine would be. He notes that the 70meV, 500μA accelerator recommended at the workshop was "probably in the ball park" of what they would consider. He maintains, "If I can make and sustain an argument that we've got revenue that would be forthcoming, of a magnitude

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Additional Recommendations of the Nuclear Medicine Subcommittee

Beyond the emphasis on the need for an accelerator dedicated to isotope production, the Subcommittee report included the following additional recommendations:

Accelerator Projects

The Subcommittee recommends that several "projects of high priority" be undertaken if a dedicated accelerator can be obtained: "greater exploitation of short-lived radionuclides for diagnosis...trials of various radionuclides theoretically optimal for radiation therapy...exploration of novel gamma-emitting radionuclides for incorporation into diagnostic radiopharmaceuticals, and...further development of generator systems for ultra-short-lived daughter radionuclides."

Focus on SPECT

Noting the limited number of PET centers and the contrasting availability of SPECT technology, the Subcommittee recommends that the DOE continue its support of PET, but at the same time place more emphasis on the development and refinement of SPECT imaging devices. "Such instrumentation would become widely used at the community level, taking advantage of the variety of gamma-emitting radiopharmaceuticals already available," notes the Subcommittee. "In recent years, it has become apparent that many lesions missed on planar camera images are detectable by SPECT. However, industrial development has been limited largely to rotating single scintillation cameras, with inherent low photon detecting sensitivity. Improvements in detector arrays are needed to increase sensitivity."

Overregulation Hinders Radiopharmaceutical Development

The Subcommittee also recommends that "support for new radiopharmaceuticals should be increased because many approaches for their development are coming close to fruition. In diagnosis, these include new [technetium-99m] agents for imaging the heart and brain...After a period of slow progress," notes the Subcommittee, "research in labeled monoclonal antibodies for both diagnosis and therapy is now showing encouraging results. This approach has great potential for targeting radionuclides in vivo to specific cell types and specific tissues, and the technical problems of this complex technique are becoming resolved. Other radiopharmaceuticals recently designed for radiation therapy look promising."

The Subcommittee notes that researchers must fulfill increasing regulatory requirements before beginning human trials of radiopharmaceuticals, so "their development will require larger budgets than in the past." Calling this the second major problem after supply hindering nuclear medicine development, Dr. McAfee told *Newsline*, "there is overregulation of the development and use of radionuclides in the US compared to other countries—this creates the huge lag time associated with radiopharmaceutical development." Pointing to figures indicating that during an 11-year period, the United Kingdom approved 140 radiopharmaceuticals, while the US approved 40, he said, "in pharmaceuticals, we're not keeping up with other countries." ■

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sufficient to maintain such a facility, then I could go to the Office of Management and Budget and Congress ...I believe the monies would be forthcoming." Mr. Erb says that such an accelerator dedicated to isotope production is "illustrative of the kinds of new ventures [DOE] ought to be prepared to consider and undertake."

Dr. Srivastava, however, says, it is unlikely that the Agency could obtain prior committment from users for funding. "In addition," he says, "the revenues from a 70meV, 500μA machine may not be sufficient to recover costs and may depend too much on one or two current isotopes." Dr. Atcher notes that because of concerns that commercial vendors might expect that such an arrangement would "buy us some rights," it would be inappropriate. Rather than have industry subsidize the facility, DOE should resume such a role in keeping with the tradition of "government supporting medical research," Dr. Atcher says.

But even if government does fund the project, he says, planning for such a facility could be complicated by the discontinuation of a particular isotope when a commercial version becomes available. Dr. Srivastava points out that a center approach with functions other than production would be a less vulnerable alternative under such circumstances.

The Short-term Picture

Few hold out hope that anything concrete will happen in fiscal 1991, but the agency is still working on its 1991 budget. Sheldon Wolff, PhD, chairman of HERAC, professor of cytogenetics in the radiology department and director of the laboratory of radiobiology and environmental health at the University of California, San

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Francisco, says that the OER is preparing for the budget process and is expected to use the Nuclear Medicine Subcommittee report (final report issued in August 1989) as "ammunition to defend why they're asking for certain things." He says, "in most cases, [HERAC Subcommittee] recommendations have been followed. . . but everything depends on how much money [DOE] gets from Congress and the other priorities of the agency. We hope that the department will be able to carry out as many recommendations as possible within the constraints of the budget."

Dr. Robertson says, "the question is—how much money can we spend, and what are the requirements? The first thing that we'll get is money to do a study to determine the requirements. We know what radionuclides are needed, but what instrument do we need to satisfy the bulk of it?" He says that such a needs assessment study could be provided for in 1991's budget.

Along with the option of a dedicated facility, the agency is examining alternatives that Dr. Robertson says may satisfy most of the needed isotopes, with BLIP and IPF providing the remaining higher energy, accelerator-produced isotopes. Dr. Robertson told *Newsline*, "a smaller machine might be able to handle the bulk of the requirements" and that such a "a lower energy machine would be a lot cheaper."

Serge Lamisse, vice president, Ion Beam Applications of North America, one of a limited number of companies with expertise in building such accelerators, estimates that a 120 meV, 200μA accelerator would cost between \$12 million and \$15 million and a 70 meV, 500μA machine would cost between \$8 million and \$10 million.

Dr. Srivastava noted that upgrading existing DOE facilities, BLIP and IPF, would be another temporary option, "whose capital costs would be considerably less than establishing a dedicated cyclotron."

At any rate, if something is not done, the supply problems could prove to be insidiously damaging to the field of nuclear medicine. Dr. Srivastava notes that "the situation with routine isotopes may be okay because they can be made with commercial cyclotrons or in reactors, but some research isotopes, especially many that are being considered as imaging and therapy labels for monoclonal antibodies, and others, such as ^{68}Ge, ^{82}Sr, and ^{127}Xe, cannot. Those are the isotopes of the future. That's what has pushed the frontiers of our field further and further. If we don't continue to develop them, the field will stagnate."

Referring to sporadic interruptions in the supply of ^{67}Cu, Dr. Eckelman says, "There's always a problem when clinicians, such as oncologists, get interested in a treatment, then you tell them you can't get it for six months."

Scientists within the national laboratories argue that the nuclear medicine community must develop a concerted effort to educate the DOE and Congress on the need for isotopes for research and clinical applications. Dr. Srivastava says, "It's time to do something about it and stop just talking about it." The outcome depends, "in large part, on how strong a case the nuclear medicine community makes," says Dr. Atcher. "If there's a perception that there's a need, start educating now. The more we delay, the costlier it will be."

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References

1. Review of the Office of Health and Environmental Research Program, Nuclear Medicine Subcommittee of the Health and Environmental Research Advisory Committee, Office of Energy Research, United States Department of Energy, August 1989.

2. Moody, DC, Peterson, EJ. Proceedings of the DOE Workshop on The Role of a High-Current Accelerator in the Future of Nuclear Medicine, May 1989.

Nuclear Medicine Within Medical Applications Program

The OER has already acted on one issue discussed by the Subcommittee. Response to concerns of some in the nuclear medicine community, the DOE has renamed the umbrella program under which nuclear medicine as well as other areas are funded. Nuclear Medicine is now a separate section under the general heading Medical Applications. Dr. Wolff says this should dispel any fears about where nuclear medicine dollars are going. "What is called nuclear medicine is what nuclear medicine truly considers nuclear medicine." ■