PART 2

Research Radionuclide Availability in North America

Inadequate North American supplies of research radionuclides limit research opportunities for radiochemists and other nuclear medicine investigators in the U.S. and Canada.

This is Part 2 of a report on the workshop organized by the SNM Committee on Isotope Availability held in June 1996. Part I appeared in the July 1997 issue of the *JNM*.

PARTICLE ACCELERATORS/ CYCLOTRONS

Several large-scale linear accelerators and cyclotrons in the United States and Canada currently produce and distribute research radionuclides (Table 1). Ruth et al. (*1*) published a review of accelerator-produced radionuclides, used or proposed for biomedical research, and a general overview of production techniques. Table 1 also lists the PET cyclotron at the University of Wisconsin, which produces a diverse array of potentially useful research radionuclides.

DOE Facilities

The DOE produces radionuclides for research and commercial applications with high-energy, high-current accelerators at two National Laboratories:

- Brookhaven Linac [linear accelerator]—a 200-MeV proton accelerator with a time-averaged beam current of ≤145 μA, connected to the recently upgraded Brookhaven Linac Isotope Producer (BLIP).
- Los Alamos Neutron Science Center (LANSCE, formerly the Los Alamos Meson Physics Facility, or LAMPF)—an 800-MeV linac that provides a nominal 1-mA beam current, connected to the Los Alamos Isotope Production Facility (IPF).

Brookhaven's linac operates primarily for high-energy physics research; LANSCE receives funding primarily to serve the U.S. government's nuclear defense program. Radionuclide production for medical research is a secondary function at both facilities, conducted only in a parasitic mode when the linacs are online, scheduled according to their primary functions. These operating schedules, coupled with intrinsically high costs of facility operation, prevent these accelerators from serving as reliable, year-round sources of medical radionuclides.

Despite their limitations, Brookhaven and Los Alamos do serve the nuclear medicine research community as somewhat sporadic suppliers of otherwise unavailable radionuclides. BLIP, for example, operates for 16 to 20 weeks/year, irradiating 8 to 12 targets simultaneously. Requests for funding to operate BLIP at ≤145 μA for 46 weeks per year have been denied for fiscal year 1997. BLIP currently produces 14 radionuclides, with most production efforts focused on ^{68}Ge, ^{82}Sr and ^{67}Cu.

The LAMPF-IPF has nine independent target stations. Radionuclide processing takes place at two Los Alamos facilities, one with 16 hot cells designed to handle 100,000 Ci (3.7 million GBq) of radionuclides with 1-MeV gamma emissions, and another with 13 hot cells designed to handle 10,000 Ci (370,000 GBq) of radionuclides with 1-MeV gamma emissions. LAMPF is online for 16 weeks/year, and produces about 30 radionuclides, including 100% of the world's supply of ^{194}Au (used in arthritis research) and ^{73}As (used to research medical toxicity), and 80% of the world's supply of ^{67}Cu (used to label monoclonal antibodies for both imaging and therapy).

TRIUMF

The TRI-University Meson Facility (TRIUMF), operated by a consortium of universities, runs four accelerators that bombard targets with 13- to 520-MeV proton beams, with beam currents up to 500 μA. Thomas J. Ruth, PhD, Director, UBC/TRIUMF PET Program, University of British Columbia, Vancouver, BC, Canada, explained that each cyclotron accelerates negative hydrogen ions, making it possible to extract multiple beams of varying current for simultaneous irradiations of multiple targets.

In TRIUMF's main cyclotron, the 50- to 120-MeV beam at 100 μA is dedicated to radionuclide production. The 500-MeV proton beam of another cyclotron (available for about 26 weeks/year) passes through a multitarget station before the beam dump, allowing for additional radionuclide production in a mode parasitic to TRIUMF's high-energy physics programs.

The TR-13 (13-MeV) cyclotron is dedicated to production of radionuclides for the University of British Columbia-TRIUMF PET program. Its simultaneous beam capability, however, allows TRIUMF to produce radiotracers for other purposes, such as ^{48}V for biodistribution studies.

Once a high-intensity spallation facility connected to a new separator is brought online in 1999, Ruth predicts that TRIUMF would be able to produce large quantities (0.1 to 1.0 Ci [3.7 to 37 GBq]) of neutron-rich therapeutic radionuclides with very high specific activities.

University of Wisconsin–Madison

The 11-MeV cyclotron at the University of Wisconsin–Madison Medical School has been used extensively to investigate the production of "nonstandard" research radionuclides; it has produced 100 radionuclides (Table 2) of more than 30 elements from 105 proton-induced reactions (*2*).

The cyclotron irradiates four small-area, thick targets of highly enriched stable nuclides with a 50-μA beam; all target yields are extrapolated to end-of-saturated bombardment measured to 20% uncertainty.

R. Jerome Nickles, Cyclotron Director, University of Wisconsin-Madison, School of Medicine, emphasized that the 11-MeV cyclotrons operated by many PET centers can provide numerous radionuclides other than "the big four"—^{11}C, ^{13}N, ^{15}O and ^{18}F—commonly used in PET. Concerns that gamma emissions from the less commonly used positron emitters will erode the quality of PET images are "premature," according to Nickles. He also suggested that facilities producing ^{67}Ga have the potential to isolate high-specific-activity ^{67}Cu and ^{64}Cu from ^{67}Ga waste (*3*).

Potential Use of University Cyclotrons

Copper Radionuclides

Michael J. Welch, PhD, Coordinator of Radiological Sciences, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, described how commercially available low- to medium-energy (11-MeV to 27-MeV) hospital cyclotrons can produce three radionuclides of copper for distribution—^{67}Cu, ^{64}Cu and the ^{62}Zn parent for ^{62}Cu generators— as well as ^{60}Cu and ^{61}Cu for internal use.

Jamriska et al. (*4*) have investigated the production of ^{67}Cu by irradiating ^{70}Zn with low-energy protons to trigger the ^{70}Zn(p,α)^{67}Cu nuclear reaction. Using targets of compressed zinc oxide and of stacked electroplated zinc foils, they have pro-

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Table 1

NORTH AMERICAN ACCELERATORS/CYCLOTRONS AVAILABLE FOR PRODUCING RESEARCH RADIONUCLIDES

Accelerator/Cyclotron, Location	Particle	Energy (MeV)	Current (μA)	Comments
Linac, Brookhaven National Laboratory, Long Island (connected to upgraded BLIP)	H^-	200	up to 145	Primarily used for high-energy physics research; produces biomedical radionuclides in parasitic mode (^{7}Be, ^{28}Mg, ^{52}Fe, ^{55}Co, ^{65}Zn, ^{67}Cu, ^{68}Ge/^{68}Ga, ^{81}Rb/^{81m}Kr, ^{82}Sr/^{82}Rb, ^{83}Rb, ^{95m}Tc, ^{96}Tc, ^{97}Ru, ^{203}Pb). Operates 16 to 20 weeks/year.
LANSCE, Los Alamos National Laboratory, New Mexico (connected to IPF)	H^+ H^-	800	1000	Primarily used for national defense; produces some biomedical radionuclides (^{26}Al, ^{73}As, ^{194}Au, ^{7}Be, ^{67}Cu, ^{153}Gd, ^{68}Ge, ^{22}Na, ^{92}Nb, ^{83}Rb, ^{72}Se, ^{32}Si, ^{82}Sr, ^{44}Ti, ^{88}Y, ^{65}Zn, ^{88}Zr); operates 16 weeks/year.
Main cyclotron, TRIUMF, Vancouver, B.C., Canada (Beamline 1A)	H^-	500	150	Dedicated to meson production; spallation target station for parasitic production of radionuclides; operates 26 weeks/year.
Main cyclotron, TRIUMF (Beamline 2C)	H^-	50–120	10–100	Dedicated to radionuclide production; 4 target stations.
Main cyclotron, TRIUMF (TISOL)	H^-	200–500	1–100	Dedicated to nuclear physics; online isotope separator.
CP-42, Nordion/TRIUMF	H^-	15–42	1–200	Owned by Nordion, used mainly for commercial radionuclide production; 9-beam line switching magnet; available to TRIUMF 10 hours/week for research radionuclides.
TR-30, Nordion/TRIUMF	H^-	15–30	1000 (2 @ 500)	Owned by Nordion, used mainly for commercial radionuclide production; dual-beam operation; available to TRIUMF 10 hours/week for research radionuclides.
TR-13, TRIUMF	H^-	13	200 (2 @ 100)	Dedicated to University of British Columbia PET program.
PET cyclotron, University of Wisconsin, Madison	H^-	11	100	Capable of producing 100 radionuclides of 32 elements; bombards thick enriched targets.

BLIP = Brookhaven Linac Isotope Producer; LANSCE = Los Alamos Neutron Science Center; IPF = Isotope Production Facility; includes polarized H^-; TRIUMF = TRI-University Meson Facility; TISOL = TRIUMF Isotope Separator On-Line; PET = positron emission tomography.

Table 2
Diverse Radionuclides Potentially Available from an 11-MeV Proton Accelerator*

Radionuclide	Half-Life	Yield	
		mCi	MBq
^{18}F	2 hr	120	4,440
^{43}Sc	3.9 hr	11	407
^{44m}Sc	2.4 d	1.7	62.9
^{48}Sc	43 hr	40	1,480
^{45}Ti	3 hr	47	1,739
^{48}V	16 d	108	3,996
^{51}Cr	28 d	140	5,180
^{52}Mn	5.7 d	15	555
^{54}Mn	312 d	131	4,847
^{56}Co	79 d	77	2,849
^{57}Co	271 d	129	4,773
^{58}Co	71 d	150	5,550
^{61}Cu	3.4 hr	76	2,812
^{64}Cu	13 hr	73	2,701
^{65}Zn	244 d	228	8,436
^{66}Ga	9.4 hr	105	3,885
^{67}Ga	78 hr	51	1,887
^{69}Ge	38 hr	103	3,811
^{72}As	26 hr	102	3,774
^{73}As	80 d	60	2,220
^{74}As	18 d	176	6,512
^{76}As	26 hr	41	1,517
^{76}Br	16 hr	37	1,369
^{77}Br	57 hr	30	1,110
^{82}Br	35 hr	44	1,628
^{83}Rb	83 d	23	851
^{84}Rb	33 d	38	1,406
^{86}Rb	19 d	65	2,405
^{86}Y	15 hr	70	2,590
^{87m}Y	13 hr	83	3,071
^{87}Y	80 hr	157	5,809
^{88}Y	108 d	96	3,552
^{89}Zr	78 hr	100	3,700
^{90}Nb	15 hr	44	1,628
^{92m}Nb	10 d	88	3,256
^{96}Nb	23 hr	66	2,442
^{94}Tc	5 hr	3.2	1184
^{95m}Tc	61 d	21	777
^{96}Tc	4 d	95	3,515
^{99m}Rh	5 hr	40	1,480
^{99}Rh	15 d	18	666
^{100}Rh	20 hr	63	2,331
^{101m}Rh	4 d	50	1,850
^{102m}Rh	206 d	66	2,442
^{107}Cd	6 hr	66	2,442
^{109}Cd	453 d	48	1,776
^{111}In	2.8 d	54	1,998
^{112m}In	21 m	139	5,143
^{113m}In	1.6 hr	143	5,291
^{114m}In	49 d	5.5	2034
^{120}Sb	6 d	2.2	81.4
^{122}Sb	3 d	20	740
^{124}Sb	60 d	46	1,702
^{121m}Te	154 d	16	592
^{121}Te	16 d	21	777
^{123m}Te	120 d	17	629
^{123}I	13 hr	34	1,258
^{124}I	4 d	3.2	1184
^{130}I	12 hr	2	74
^{127}Xe	36 d	8	296
^{139}Ce	137 d	8	296
^{55}Co†	17 hr	1.3	481
^{57}Co†	271 d	5.8	2145

*Adapted from: Nickles RJ. Production of a broad range of radionuclides with an 11MeV proton cyclotron. *J Label Cmpd Radiopharm* 1991;30:120-122. End-of-saturated-bombardment at 1 μA, assuming a thick elemental target with 100% isotopic enrichment. All radionuclides obtained by (p,n) reactions, except where otherwise noted.

†Obtained by (p,α) reactions.

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duced "reasonable" quantities of ^{67}Cu with 16- to 18-MeV proton beams. Extrapolation of their data suggests that a weekend irradiation using an 18-MeV cyclotron can produce >200 mCi (>7.4 MBq) of ^{67}Cu at approximately US$45.00/mCi (US$1.22/MBq).

Currently, high-specific-activity ^{64}Cu can be routinely produced in high-flux nuclear reactors, such as MURR, that irradiate zinc with fast neutrons (*5,6*). The MURR Center is a major supplier of ^{64}Cu, but access to MURR's flux trap for target retrieval is available only once a week, which seriously limits the availability of this short-lived radionuclide ($t_{1/2}$ = 12.7 hours).

As an alternative, McCarthy and coworkers (*7,8*) have described a system for using a small biomedical cyclotron to produce large quantities (up to 0.5 Ci [18.5 GBq] per day) of ^{64}Cu with specific activities up to 20,000 Ci/mmole (740,000 GBq/mmole). The investigators estimate that, with this system, PET cyclotrons could produce up to 2 Ci (74 GBq) of ^{64}Cu per day for less than US$2.00/mCi (US$0.54/MBq).

Using a ^{63}Cu (p,2n) ^{62}Zn reaction on a medium-energy cyclotron, irradiation with protons degraded from 27.5 to 13.5 MeV yields 4.5 mCi (166.5 MBq) of ^{62}Zn/^{62}Cu per μamp/hour (*9*). An automated modular generator can produce ^{62}Cu-labeled radiotracers for myocardial perfusion studies with PET (*10*).

These techniques suggest that the current and future demand for ^{62}Cu, ^{64}Cu and ^{67}Cu can probably be met with low- to medium-energy cyclotrons. By making use of commercial cyclotrons at various radiopharmaceutical manufacturers, along with university cyclotrons at the major PET centers, enough ^{62}Zn/^{62}Cu generators can readily be produced to supply nuclear medicine facilities throughout the United States. In addition, all facilities with 11- to 27-MeV cyclotrons could produce ^{64}Cu, and all facilities with 16- to 27-MeV cyclotrons could produce ^{67}Cu.

The techniques described above for producing large quantities of copper radionuclides clearly illustrates the successful application of low-energy production routes. Similarly, high-yield targets could be developed for producing many of the radionuclides listed in Table 2.

Halogen Radionuclides

Medium-energy cyclotrons (up to 28 MeV) might produce enough therapeutic halogen radionuclides to meet the current research demand. Michael R. Zalutsky, PhD, Director, Radiopharmaceutical Chemistry Laboratory, Duke University Medical Center, Durham, NC, noted that a variety of radionuclides, with various half-lives and emission characteristics, would be useful for investigating how different types of tumors could best be targeted for radionuclide therapy. As a more practical, cost-effective approach, however, he proposed focusing on the best candidate radionuclides of each emission type: alpha-particle, beta-particle, positron and Auger-electron emitters. Assuming that reactor facilities will generally provide beta-particle

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mation to enable an intelligent choice. The patient should make his own determination on treatment." In addition one must have the best possible relationship and lines of communication with primary physicians and specialist physicians (Fig.17).

With a personal computer, the nuclear physician can store his or her records of all patients, as well as take advantage of one's colleagues' experiences via databases on the Internet. Molecular nuclear medicine is the knowledge specialty. Informed patients and physicians can bring about not only "smart surgery," but also "smart radiotherapy," and "smart chemotherapy." Nuclear medicine can benefit greatly from the increasing attention being paid to the quality and value of all facets of the health care system.

Many presentations from the U.S. and overseas showed what can be accomplished by experienced, well-trained nuclear medicine physicians who can fathom the complex problems of patients and provide in vivo physiological and biochemical knowledge to help solve the patient's problems.

What do physicians provide, particularly nuclear medicine physicians? They provide knowledge. What do patients want? They want certainty. It is time we stopped fiddling on the roof and move down into the house where the physicians and sick patients live.

—Henry N. Wagner, Jr., MD

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emitters, university cyclotrons may provide adequate quantities of the others.

Astatine-211 ($t_{1/2}$ =7.2 hours) is a promising alpha-particle emitter for certain oncologic applications, such as the treatment of patients with ovarian cancer or brain tumors. Research centers in Finland, Germany, Italy and Switzerland have discussed the possibility of collaborating to produce the European supply of ^{211}At for clinical research (*11*). A similar approach in the U.S. could meet the North American demand for ^{211}At.

Bombarding natural ^{209}Bi targets with 28-MeV alpha-particles can produce ^{211}At via the ^{209}Bi(α,2n)^{211}At reaction. Larson et al. (*12*) recently described an internal target system that provides ^{211}At production yields of 1.1 mCi/μA/hour (40.7 MBq/μA/hour) (*13*). An 8-hour run at 90 μA would yield 527 mCi (19.5 GBq) of ^{211}At. Assuming a 65% distillation efficiency and 8-hour decay in transport, about 160 mCi (5.9 MBq) of ^{211}At could be delivered from that 8-hour run. Zalutsky estimated the production cost at US$21/mCi (US$0.57/MBq); he proposed that a reasonable 100% mark-up to US$42/mCi (US$1.14/MBq) would still make this material available at an acceptable cost.

Iodine-124 ($t_{1/2}$ = 4.2 days), a positron emitter, could be used in PET imaging to provide dosimetry estimates for radiotherapeutic compounds labeled with ^{131}I. Most methods for producing ^{124}I involve irradiation of enriched tellurium targets with deuterons or protons (*13-16*). Yields from thick targets range from 0.5 to 1.8 mCi/μA/hour (18.5 to 66.6 MBq/μA/hour). Certain reactions with ^{124}Te and ^{125}Te—e.g.,the ^{124}Te(p,n) and ^{125}Te(p,2n) reactions yield—sufficient quantities for patient doses at proton energies of <18 MeV.

To date, the largest batches of ^{124}I have been produced using the ^{124}Te(d,2n) reaction; a 6.25-hour irradiation with an 80-μA deuteron beam yielded 270 mCi (9.9 GBq) of ^{124}I (*13*). Therefore, an estimated 300 mCi (11.1 GBq) of ^{124}I could be delivered offsite from one production run with an 8-hour irradiation, 90% recovery of ^{124}I, and 8-hour decay during transport. Based on the US$425/hour cost of running the CS-30 cyclotron at Duke University, the estimated cost of producing ^{124}I would be US$11/mCi (US$0.30/MBq); a reasonable marked-up price would be $22/mCi (US$0.60/MBq).

Bromine-77 ($t_{1/2}$ = 57 hours), which emits Auger electrons, might serve as a useful alternative to ^{125}I for therapeutic radiopharmaceuticals designed to target sites close to cellular DNA. Irradiating natural ^{75}As with 28-MeV alpha-particles can produce ^{77}Br via the ^{75}As(α,2n)^{77}Br reaction. The chemical form of the arsenic target determines the potential yield of ^{77}Br. An arsenic trioxide target, for example, can handle beam currents up to 65 μA; a 1-hour run has yielded 18.9 mCi of ^{77}Br, very close to the theoretical yield of 293 μCi/μA/hour (10.8 mBq/μA/hour) (*17*).

CONCLUSION

The future of nuclear medicine depends on the long-term, uninterrupted availability of research radionuclides on a routine basis at reasonable costs. The radiopharmaceuticals of tomorrow depend on the investigational radiotracers and therapeutic nuclides of today. The vast potential of molecular nuclear medicine may not be realized with current limitations in the supply of research radionuclides.

Ideally, a National Biomedical Tracer Facility (NBTF) in the United States would provide a reliable supply of accelerator-produced radionuclides for biomedical research. A facility dedicated to biomedical radionuclide production would resolve the untenable dependence on unrelated research programs of U.S. national laboratories.

Until an NBTF becomes reality, however, a coordinated effort among national laboratories, universities and industry to pool accelerator resources may provide an interim solution. Although production of some radionuclides, such as ^{67}Cu, may be most efficient with the high-energy accelerators of the national laboratories, many others can be readily produced with low- or medium-energy cyclotrons. Several PET centers, for example, have low-energy (≤15 MeV) cyclotrons that could produce ^{18}F and ^{64}Cu—and many of the other radionuclides listed in Table 2—for investigators outside those institutions. It may also be possible to make use of medium-energy (30 to 40 MeV) cyclotrons at commercial facilities (e.g., Mallinckrodt, DuPont, Amersham/MediPhysics), if radiopharmaceutical manufacturers agreed to participate in this effort.

Several reactors are currently available for complementary production of reactor-based research radionuclides. It is essential that their efforts also be coordinated to ensure a constant, uninterrupted and affordable supply of neutron-rich radionuclides to the biomedical research community.

In addition to supporting the DOE's ongoing efforts to stabilize the supply of research radionuclides, nuclear medicine investigators may need to plan strategies for establishing and funding consortia of university, commercial and federal production facilities. These consortia would then need to devise innovative approaches for distributing radionuclides to meet current and future research demands.

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An IDTF is a new entity independent of a hospital or physicians' office in which diagnostic tests are performed by licensed, certified nonphysician personnel under appropriate physician supervision. This does not apply to clinical labs under CLIA regulations. IDTFs must meet the following requirements: one or more physicians who are responsible for the direct and ongoing oversight of the quality of the testing performed, the proper operation and calibration of the equipment and the qualification of nonphysician personnel; the supervising physician must evidence proficiency in the performance and interpretation of each type of diagnostic procedure performed by the IDTF; maintain documentation to demonstrate sufficient physician attendance during all hours of operation to assure that the required level of supervision is furnished; nonphysician personnel that perform tests must demonstrate basic qualifications to perform the tests in question and have appropriate training and proficiency as evidenced by licensure or certification by the appropriate credentialing body; and all procedures must be ordered in writing by a physician who treats the beneficiary (the referring physician).

Actual Charges

According to current Medicare policy, physician payment is based on the lower of either the actual charge or the Medicare fee schedule amount. For those beneficiaries who have full-service private insurance plans as Medicare secondary insurers, HCFA proposes to broaden the definition of "actual charges" to include the non-Medicare rate contracted with the secondary insurer. Beneficiaries with MediGap coverage are excluded. HCFA is proposing these changes to protect beneficiaries and to permit Medicare to share in the savings.

Under this proposed rule, the physician's administrative costs will increase as the physician will be responsible for submitting accurate charge information. In addition, if the claim is not properly documented, the physician may be subject to "false claim" charges. Physician and staff will require education on this proposed regulation so that they can be in better compliance.

If you have questions concerning proposed Medicare payment policies, please contact Wendy Smith, Associate Director of Health Care Policy at (703) 708-9000, ext. 242 or via e-mail at wsmith@snm.org.