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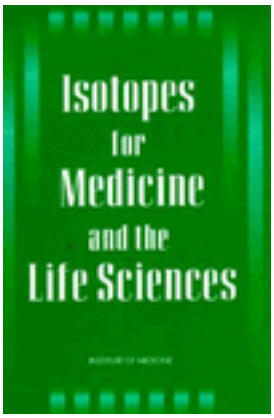

Isotopes for Medicine and the Life Sciences

S. James Adelstein and Frederick J. Manning, Editors;
Committee on Biomedical Isotopes, Institute of Medicine

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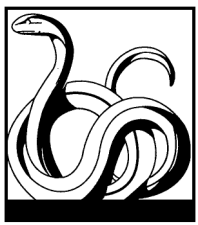
Committee on Biomedical Isotopes
Division of Health Sciences Policy
INSTITUTE OF MEDICINE

S. James Adelstein and Frederick J. Manning, *Editors*



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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

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Preface

Few members of the general public are fully aware of the extent to which the atomic age affects their everyday lives. For many, bombs and power plants are their only associations with the term. The uses and benefits of radioactive isotopes in medicine, agriculture, industry, and science are widespread, however, allowing us to perform many tasks more accurately, more simply, less expensively, and more quickly than would otherwise be possible. In many cases, biological tracers for example, there is no alternative. A recent report assessing the role of isotopes in 80 industries and 475 occupations estimated that in 1991, in the United States alone, radioactive materials were responsible for 3.7 million jobs, $257 billion in total sales, and $45 billion in tax revenues to local, state, and federal governments (See Chapter 1).

This report focuses on isotopes in medicine and the life sciences, areas where their uses are particularly widespread and important in diagnosis, therapy, and research. More than 36,000 diagnostic procedures that employ radioisotopes are performed daily in the United States. Close to 100 million laboratory tests that use radioactive isotopes to measure some constituent of a biological sample are performed each year. In addition, some form of radioactivity is used to treat 150,000 to 200,000 patients each year.

The U.S. Department of Energy (DOE) and its predecessors, the Atomic Energy Commission and the Energy Research and Development Agency, have been instrumental in establishing and supporting these peaceful applications of atomic energy and have succeeded in a "technology transfer" of enormous magnitude. This very success, combined with the end of the Cold War and the general pressure to cut government spending, has created what many see as a crisis in the domestic supply of isotopes. Always a secondary mission at the many DOE

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laboratories, isotope production has suffered as support for the laboratories' primary missions of research in nuclear and particle physics, nuclear weapons, and nuclear power has declined. The concerns of U.S. clinicians and researchers about the continuing availability of enriched stable isotopes and radionuclides have increased sharply since 1989, and the nuclear medicine community in particular has been highly vocal in pointing out that the needs of the various users in the United States will not be met adequately in a future market controlled by one or two foreign sources. It has been strongly urged with regard to those radionuclides needed for future research, that DOE fund a new accelerator facility with isotopes as its primary mission, a National Biomedical Tracer Facility.

In response to this urging and with the realization that changing national and scientific priorities would reduce the funding for the accelerator-based facilities at Los Alamos National Laboratory (Los Alamos Meson Physics Facility) and Brookhaven National Laboratory (Brookhaven Linac Isotope Producer), DOE turned to the Institute of Medicine to undertake an intensive examination of isotope production and availability, including the education and training of those who will be required to sustain the flow of radioactive and stable materials from their sources to laboratories and bedsides. This document is the report of the committee formed to examine these matters and provide recommendations for action.

The committee is comprised of 11 members, who were selected for their expertise in one of the technologies crucial to the production or use of isotopes covered by this report. Nevertheless the committee included members representative of a broad spectrum of viewpoints, including basic and applied researchers in the physical and life sciences, scientific administrators from both academic and government institutions, medical practitioners, and clinical investigators. In the course of the study, the full committee met four times in 2-day meetings, and subcommittees made 1-day site visits to isotope production facilities at Brookhaven National Laboratory on Long Island, Los Alamos National Laboratory in New Mexico, Canada's Tri-University Meson Facility, and the University of Missouri Research Reactor Center. Other important sources of information for the committee were the DOE Isotope Production and Distribution Program, specifically its director at the beginning of the study, Don Erb; representatives of a major isotope purchaser, the radiopharmaceutical industry, who addressed the committee at its second meeting; the half-dozen scientists who educated the committee on the state of the art of isotope separation at that meeting; and the reports of several previous committees, at the National Academy of Sciences and elsewhere, who wrestled with related charges in recent years.

As committee chair, I am acutely aware of the contributions that Institute of Medicine staff have made to the success of the study. Special thanks and acknowledgments are owed Project Assistants Susan Morgan and Margo Cullen. Susan made our meetings and travel as comfortable and convenient as possible and provided outstanding secretarial support both at the meetings and in produc

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ing our numerous preliminary drafts. We owe Margo our profound thanks for her painstaking production of our final product. A. Everette James and Joe Cassells, Senior Program Officers, who initially conceived the project and oversaw its birth, provided sage advice from start to finish. I am particularly grateful to Study Director Rick Manning for his skilled and professional support in shepherding the committee through its difficult task. Finally, I want to acknowledge the individual and collective contributions of the committee members. They represent an admirable example of busy but unselfish professionals volunteering their limited time tending to the scientific "commons" on which we all depend. It was a special opportunity to have worked with this outstanding group.

S. James Adelstein, *Chair*
Committee on Biomedical Isotopes

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Executive Summary

Both radioisotopes and enriched stable isotopes are essential to a wide variety of applications in medicine, where they are used in the diagnosis and treatment of illnesses. This report focuses primarily on these medical uses and those in the allied life sciences, but isotopes also find wide parallel uses in research in chemistry, physics, and geosciences, with additional needs existing in the commercial sector.

The U.S. Department of Energy (DOE) and its predecessors, the Atomic Energy Commission and the Energy Research and Development Agency, have supported the development and application of isotopes in a stellar example of technology transfer that began before the term was popularized. These technologies have been transferred to the private sector and have allowed the development of both the radiopharmaceutical and nuclear medicine instrumentation industries. One of every three hospitalized patients in the United States undergoes a nuclear medicine procedure, with a total value estimated at $7 billion to $10 billion per year. More than 36,000 diagnostic medical procedures that employ radioactive isotopes are performed daily in the United States, and close to 100 million laboratory tests that use radioactive isotopes are performed each year. Radionuclides are also used to deliver radiation therapy to a growing number of patients each year (approximately 180,000 in 1990).

In recent years the very success of nuclear medicine and the increased use of stable and radioactive isotopes in a number of fields have combined with the end of the Cold War to bring DOE to an important crossroad. Since its inception isotope production at the various multimission DOE laboratories has been a secondary mission that has been started and stopped to meet the needs of the laboratories' primary missions of basic and applied research in nuclear and par

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ticle physics, nuclear weapons, and nuclear power production. Support for all three of these areas has declined precipitously in the past decade, even as the demand for isotopes has increased, and aggressive competition from Canada and the Republics of the former Soviet Union in the sale of stable isotopes and radioisotopes threatens to cut DOE out of the market altogether. The concerns of U.S. clinicians and researchers about the continuing availability of enriched stable isotopes and radionuclides have increased sharply since 1989. The nuclear medicine community in particular has been highly vocal in its concern that the needs of the various users in the United States will not be adequately met in a future market controlled by one or two foreign sources and have suggested that DOE fund a new accelerator facility with production of isotopes as its primary mission, a National Biomedical Tracer Facility (NBTF).

In response to this urging and with the realization that changing national and scientific priorities would reduce the funding for the accelerator-based facilities at Los Alamos National Laboratory (Los Alamos Meson Physics Facility [LAMPF]) and Brookhaven National Laboratory (Brookhaven Linac Isotope Production Facility [BLIP]), DOE turned to the Institute of Medicine to undertake an intensive examination of isotope production and availability, including the education and training of those who will be required to sustain the flow of radioactive and stable materials from their sources to laboratories and bedsides. This document is the report of the committee formed to examine these matters and provide recommendations for action.

From its earliest discussions it became clear to the committee that any consideration of a national isotope policy would have to deal with several distinct, but interrelated, parts: the continued supply of enriched stable isotopes, the production of radioactive isotopes by neutron bombardment of targets in nuclear reactors, and the production of radionuclides for nuclear medicine practice and research by charged-particle bombardment in accelerators. The report addresses these three classes of isotope production in turn, attempting in each case to sort out the issues of production of commercially viable products from research and development on future products. It also addresses related matters: research appropriate for a medical isotope facility, requirements for education and training in relation to isotope production facilities, and the possibilities for collaboration between industry and the national laboratories as a means of meeting future requirements and opportunities.

ENRICHED STABLE ISOTOPES

Enriched stable isotopes are critical starting materials in the production of many widely used radioisotopes. They are also important research and diagnostic tools in themselves and offer a number of unique applications to medicine, nutrition, and the life sciences. A dependable supply of enriched stable isotopes con

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trolled by the United States is crucial for research, therapy, diagnosis, and other applications.

An adequate supply of enriched stable isotopes currently exists for the production of most biomedically significant radionuclides, but DOE inventory of enriched stable isotopes is being depleted through sales without replacement. The pool of isotopes formerly available only on a lease basis for nondestructive uses no longer exists. A large portion of the heavy stable isotopes currently being used are supplied by Russian sources. The exact extent of these inventories is unknown, but Russian supplies of most enriched stable isotopes are estimated to greatly exceed U.S. supplies.

Since the electromagnetic isotope separators, the calutrons, at Oak Ridge National Laboratory are currently in the standby mode, U.S. production of the majority of enriched stable isotopes is at a standstill. Future separations are planned only to replace high retail volume isotopes or as distinct contracts are negotiated. Some research communities—for example, those in the biological, physical, and earth sciences—frequently require only small quantities, but a great variety, of enriched stable isotopes. These research isotopes are seldom commercially viable and as a result, are not readily available from either domestic or foreign sources. A national policy of providing a subsidy for enriched stable isotopes used in small quantities for research purposes should be adopted (Recommendation 4, Chapter 2). In the near term this means that the electromagnetic separation capabilities of the Oak Ridge National Laboratory calutrons should be maintained in standby mode until a more cost-effective source of enriched stable isotopes can be developed or external sources fail to meet demand. If a more cost-effective technology does not emerge within 5 years, subsidized operation of the calutrons should be resumed (Recommendation 1, Chapter 2).

New technologies that may provide more cost-effective separation methods within 3 to 5 years are being developed. The development of new separation technologies or improvements in existing ones, must be encouraged and supported, and the most promising of these must be evaluated for their commercial viability. This should include efforts for the efficient, cost-effective production of large amounts of enriched stable isotopes—including kilogram quantities of light isotopes (Recommendation 2, Chapter 2).

The expanded application of enriched stable isotopes into new research areas should be encouraged (Recommendation 3, Chapter 2). The use of enriched stable light isotopes—for example, carbon-13, oxygen-18, and the stable calcium isotopes—will likely increase if they can be produced more cheaply and in large quantities. Research opportunities and applications will be promoted by offering greater amounts of isotopes at reduced costs. A number of enriched stable light isotopes that are crucial for research and other applications are not available or are priced beyond the means of researchers.

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REACTOR-PRODUCED RADIONUCLIDES

The supply of technetium-99m, the workhorse of nuclear medical practice, depends on the production of its parent, molybdenum-99. In the short term the supply of reactor-produced radionuclides for commercial use, including molybdenum-99, is sufficient. Radiopharmaceutical companies state that the present domestic and foreign suppliers are reliable and that they have or soon will sign long-term supply contracts with existing producers. In view of the demonstrated reliability of the current sources of commercially valuable isotopes and their steps to secure adequate backup, the committee recommends that the Omega West reactor at Los Alamos National Laboratory or reactors at other facilities NOT be reopened as a dedicated source of molybdenum-99 and other reactor-produced isotopes (Recommendation 1, Chapter 3). A federally supported U.S. reactor for the production of research radioisotopes is definitely justified. At present, the University of Missouri Research Reactor (MURR) is playing a major role as the supplier of radionuclides for research facilities and radiopharmaceutical manufacturers. Federal support at present is limited to the provision of reactor fuel and peer-reviewed research grants. In order to assure the continued supply of radionuclides (other than molybdenum-99) for medical and research facilities, the committee recommends core support for reactor-based isotope production. The University of Missouri Research Reactor appears to be the best currently available facility that can meet this need (Recommendation 2, Chapter 3).

In the long term, if short-lived reactor-produced radionuclides become important for cancer therapy and other medical uses, the present number and condition of production reactors in North America will be inadequate. Because reactors have finite lifetimes and because future demands may exceed current capabilities, the committee recommends that DOE ensure that plans for the Advanced Neutron Source reflect the importance of isotope production, and in particular of molybdenum-99, by providing funding at an appropriate amount to insure availability (Recommendation 3, Chapter 3).

ACCELERATOR-PRODUCED RADIONUCLIDES

Certain radionuclides (gallium-67, indium-111, iodine-123, thallium-201) are produced by cyclotrons with an energy of about 30 million electron volts (MeV). In the short term, there does not appear to be any problem with the availability of the radionuclides produced on such commercially located accelerators.

There is, however, a clear need for a higher energy machine to provide researchers with radionuclides for new applications. Brookhaven National Laboratory (BLIP) and Los Alamos National Laboratory (LAMPF), as the primary domestic sources of these radionuclides, have been unreliable because of scheduling problems and costs. There is also concern about each of these facilities

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because of their ages and the missions for which they were constructed have changed. The future outlook for LAMPF is not clear, and the expertise that has been assembled there over the years will be lost when the accelerator facility is shut down. The linear accelerator (linac) that BLIP uses is expected to be available in the future since it is one of the injectors that the Relativistic Heavy Ion Collider will employ when it is completed, although for only a few weeks per year. It could probably be available for radioisotope production during the remainder of the year, assuming that operating funds are also available. The present processing facilities at BLIP are inadequate, outdated, and poorly maintained, in part because of their age.

In the short term an upgraded BLIP facility, including an extended running time, and the cyclotrons of Canada's Tri-University Meson Facility (TRIUMF) in Vancouver, British Columbia, can meet many of the radiotracer needs of the research community. However, both facilities have a mandate to operate as basic physics accelerators and cannot meet the full demand for research radionuclides. DOE should create a dedicated, reliable source for research radionuclides that has stable core support for the production of radioisotopes that are not available from commercial suppliers (Recommendation 1, Chapter 4). An NBTF that can incorporate the production facilities with the necessary infrastructure for research and training in isotope production and related activities is essential for the United States to maintain continued leadership in biomedical research using radiotracers.

The choice between cyclotron and linac is beyond the scope and expertise of this committee report, but an accelerator with an energy of 80 MeV would be sufficient for preparation all of the radionuclides envisioned for current and future use. A high-beam current would be required to ensure the production of large quantities of a few commercially viable isotopes and also allow multiple-target irradiations that will produce small quantities of experimental radionuclides.

Until such a facility is established, the needs of the isotope user community should be met by an upgraded BLIP supplemented by additional operating funds to allow for an extended operating period and a processing and distribution section that is similar to that at the University of Missouri Research Reactor (Recommendation 2, Chapter 4). Implementation of this recommendation should alter the current basic research environment and attitude at the BLIP facility and put isotope production and distribution on equal footing with in-house medical research.

The cooperative arrangement between government and industry at Canada's Tri-University Meson Facility (TRIUMF) has lead to successful technology transfer to the private sector (Nordion International, Inc). DOE should explore the utility of such models for coupling commercial production and research in the United States (Recommendation 3, Chapter 4). This idea is discussed further in Chapter 5.

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A national advisory board should be established to assist in the operation of and the setting of priorities for the radioisotope production facilities at both the upgraded BLIP and NBTF (Recommendation 4, Chapter 4). This idea is elaborated upon in Chapter 6.

PUBLIC-PRIVATE PARTNERSHIP MODELS FOR NBTF

The current DOE operations for isotope production (stable and radioactive) are not commercially self-sufficient because the leaders of these operations cannot:

a. negotiate prices freely with customers,
b. commit to long-term supply and pricing,
c. compete with the private sector, or
d. control their costs (e.g., they cannot avoid new DOE regulations with respect to waste management and remediation).

The revolving fund provision of the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101), by reducing DOE flexibility still further, has hindered rather than helped the establishment of a reliable and affordable domestic isotope supply.

The TRIUMF-Nordion model in Canada is an example of a public-private partnership that has addressed this problem in a way which is beneficial to both the scientific and the commercial partners.

In the United States, a healthy set of partnerships exists between national laboratories and universities, primarily involving research. Successful partnerships between national laboratories and industries in research and development have also been established (the cooperative research and development agreement mechanism).

NBTF is not likely to be financially self-sufficient if sales from isotopes and related services are the sole sources of funding, but NBTF could be operated by a partnership of for-profit and not-for-profit organizations. Solicitations for a successful bidder from the private sector could be based partially on the proposed return of part of the profits as royalties to be used for the support of research and education programs. In this partnership scenario,

a. DOE would pay for the cost of construction of NBTF, which would be a dedicated facility (Recommendation 2, Chapter 5);
b. DOE would subsidize the production of research isotopes as well as fund the operation of the research and education programs, in whole or in part, via the not-for-profit institution;
c. the private-sector partner would be responsible for the production, packaging, marketing, pricing, and sales of radioactive isotopes (Recommendation 5, Chapter 5);

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d. there would be an agreement distributing beam time of NBTF between production of commercial products and production of the radioisotopes necessary for approved research programs; and
e. there would be a management board that oversees and approves the distribution of the beam time and the return of royalties from the private-sector partner to the not-for-profit partner.

DOE should encourage such a partnership between one or more for-profit institutions and at least one not-for-profit institution (university, national laboratory, or some combination) to operate NBTF (Recommendation 3, Chapter 5). The Canadian model of TRIUMF-Nordion is one that could be emulated in the United States.

The commercial aspects of NBTF cannot be fully understood at this time. As discussed in this report, some radioisotopes produced by NBTF would be attractive to the commercial market. Others will become attractive in the future as new nuclear medicine techniques evolve. However, it is clear to the committee that the commercial potentials of these particular radioisotopes are limited for the foreseeable future, and are certainly not large enough to allow NBTF to be supported by commercial profits.

The requirement that NBTF be financially self-sufficient should be removed. Production of promising but as yet unprofitable isotopes as well as the in-house programs of research and education should be supported primarily by DOE funds and competitive research grant funds of users, with some contribution from royalties from the private-sector partner (Recommendation 4, Chapter 5).

NBTF should be operated as a user facility in the mold of current physical science operations at national laboratories (Recommendation 1, Chapter 5). Indeed, proposals for NBTF from national laboratories should be reviewed along with those from universities and the private-sector partner (Recommendation 6, Chapter 5). The national laboratories offer a tremendous technical infrastructure that would benefit the construction and operation of the NBTF. An evolving interest and expertise in new models of cooperation with the private sector could make this potential a reality.

A NATIONAL ISOTOPE POLICY

On the basis of its congressional mandate, its historic role, and its technical resources and expertise, DOE has important roles to play in all aspects of isotope production, research, and education. Although the full cost recovery provision of the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101) has hindered rather than helped DOE to promote isotope research and application, the concept of centralized management is not without merit. The important research, development, and educational activities associated with isotope production and distribution are, however, still spread throughout DOE.

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A National Isotope Program, reporting directly to the director of the Office of Energy Research of DOE, should be created to consolidate the administration of all isotope-related activities: production and distribution, research and development, and education and training (Recommendation 1, Chapter 6).

A national advisory committee should be formed to assist the director of the National Isotope Program in prioritizing critical needs in technology development and in choosing among applicants wishing to use the reactor and accelerator isotope production facilities or obtain their products. This National Isotope Program Advisory Committee should also provide advice on the development and execution of the several educational programs associated with isotope production and use (Recommendation 2, Chapter 6).

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1

Introduction

Both radioisotopes and enriched stable isotopes are essential to a wide variety of applications in medicine, where they are used in the diagnosis and treatment of illnesses. In addition, extensive application of isotopes in biomedical research finds wide parallel uses in research in chemistry, physics, biology, and geosciences, with additional needs existing in the commercial sector. Isotopes provide tools to do certain jobs better, easier, quicker, more simply, or more cheaply than any other method. In some cases the job could not be done at all without the use of isotopes. They are ideal tools for making measurements: a single atom can be detected using radioactive isotopes, whereas chemical methods often require a million or more atoms for detection. Because radiation detection can be done at a distance, measurement and analyses of processes, biological, chemical, or mechanical can be done "on-line" without disturbing the process itself. Although this report focuses primarily on medicine and the life sciences, Table 1-1 illustrates the breadth of isotope applications and conveys the importance of the topics addressed for nearly every field of modern science. Nonmedical applications of radioisotopes have also become an integral part of the daily life of every American and countless people around the world (Table 1-2). Among such prevalent uses and applications of radioisotopes are, in smoke detectors; to detect flaws in steel sections used for bridge and jet airliner construction; to check the integrities of welds on pipes (such as the Alaska pipeline), tanks, and structures such as jet engines; in equipment used to gauge thickness of paper and plastic; to control the density of mixtures as diverse as ice cream or concrete; to assess the degree of filling of cans and bottles in manufacturing lines; to sterilize contact lens cleaning solution, diapers, cosmetics, powders, ointments, medical instruments, and bandages; to scan luggage to detect explosives or weapons; and to detect lead in paint.

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TABLE 1-1 Examples of Common Isotope Applications

Field	Selected Applications
Food and agriculture	• Improve nutritional status and health of plants and animals • Maximize optimal crop production • Reduce food-borne diseases and increase food preservation
Biochemistry, biology, biotechnology, chemistry, physics, physiology	• Molecular studies • Metabolic and biological tracers
Cosmology	• Exploration and understanding of the universe
Earth sciences: geochemistry, geology, geophysics, hydrology, and marine, sciences	• Exploration and preservation of natural resources • Study of water resources and maintaining a safe and abundant water supply
Ecological and environmental research	• Environmental chemistry and measurements • Environmental pollution studies: occurrence, cause, and remedy
Health care	• Diagnostic nuclear medicine such as cardiological diagnosis • PET research and applications • Radionuclide treatment of disease such as cancer • Radiopharmaceuticals • Drug research (uptake, binding, metabolism, clearance)
Industrial manufacturing and research	• Materials sciences • Radioisotope thickness gauges for steel plate or paper production • Computer chip production
Nutrition	• Disease prevention and health promotion research (cancer, heart disease, obesity, osteoporosis, etc.) • Energy metabolism in humans and animals • Tracer techniques to determine nutrition requirements
Toxicology	• Risk assessment • Soil and water exposure studies

SOURCE: International Atomic Energy Agency, 1990.

Historically, the U.S. Department of Energy (DOE) and its predecessors, the Atomic Energy Commission and the Energy Research and Development Agency, have supported the development and application of isotopes. This area of science has been a stellar example of *technology transfer*, even before such a term was used. The molybdenum/technetium generator, the mainstay of modern nuclear

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medicine; the Anger scintillation camera, which is the imaging device used in the majority of the U.S. hospitals; thallium-201, the first practical agent used to determine the viability of heart muscle; positron emission tomography (PET); and the radiopharmaceutical 2-deoxy-2-[^{18}F]fluoro-D-glucose, the agent most widely used in combination with PET scanners, were all developed with support from DOE or its predecessors.

TABLE 1-2 International Research Programs That Use Isotopes

Program	Number of Participating Countries
Crop production in salt-affected soils	9
Improving pasture management	16
Nitrogen fixation studies	17
Radiation-induced mutation studies	28
Improving animal production	43
Insect sterilization techniques	17
Pesticide studies	18
Food irradiation	20
Radioimmunoassay reliability studies	4
Radioimmunoassay studies for thyroid-related hormones	12
Studies of respiratory diseases with radio-aerosols	10
Immunodiagnosis of tuberculosis	3
Immunodiagnostic techniques for human schistosomiasis	10
Nuclear techniques for malaria research and control	9
Diagnostic reagents for communicable diseases	5
Determination of absorbed drug dose	5
Sterilization of medical supplies and equipment	18
Radiation treatment of sewage	7
Radiation fermentation studies	12
Environmental pollution studies	26
Study of pollutant transport in the environment	11
Human intake of important trace elements	13
Assessment of toxic elements in foodstuffs	10
Human nutrition research	5
Exploration of natural resources	10
Soil and water studies	7
Polymer radiation treatment for medical and industrial uses	6
Radiation applications in medicine and biotechnology	4
Analysis of agro-industrial products and foods	10
Exploration of geothermal resources	9
Analysis of neutron emission spectra	8
Fast neutron data calculations for structural materials	14
Nuclear data for neutron therapy	6
Waste estimates in fusion reactor technology	5
Data for radiotherapy	7
Gamma-ray calibration of generators	7

SOURCE: International Atomic Energy Agency, 1990.

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These technologies have been transferred to the private sector and have allowed the development of both the radiopharmaceutical and nuclear medicine instrumentation industries. It has been estimated that sales of isotopes and related commodities generate $257 billion in revenues annually and are responsible directly or indirectly for 3.7 million jobs (Management Information Services, Inc., 1994). One of every three hospitalized patients in the United States undergoes a nuclear medicine procedure, with a total value estimated at $7 billion to $10 billion per year. Radioisotopes are administered to patients for diagnostic purposes by inhalation, ingestion, or intravenous or intraarterial injection. The short-lived radionuclides typically employed emit photons that are then used to image body organs, tumors, or other pathologies, or to study normal and abnormal functions. In some cases a radioisotope is administered, biological samples such as blood, urine, or breath are later collected, and the radioactivity in those samples is used to quantify some aspect of the patient's physiological functioning. In still other cases a radioisotope is added to a biological sample itself and is used to quantify specific constituents of that sample. More than 36,000 diagnostic medical procedures that use radioisotopes are performed daily in the United States, and close to 100 million laboratory tests that use radioisotopes are performed each year (Holmes, 1991; Society for Nuclear Medicine, 1986). Radionuclides are also used to deliver radiation therapy to a growing number of patients each year. In 1990 the Nuclear Regulatory Commission staff estimated that approximately 100,000 patients received such therapy from an external cobalt-60 source, that an additional 50,000 patients had a sealed container of a radioisotope inserted into tissue or a body cavity in close proximity to a cancer, and that 30,000 patients had received an unsealed radiopharmaceutical for a similar purpose (e.g., radioiodine treatment of Graves' disease) (Nussbaumer et al., 1993). All of these imaging studies, therapeutic procedures, and laboratory tests use radioisotopes to diagnose or treat a wide variety of diseases, including those responsible for the majority of deaths in the United States, such as heart disease, cancer, and stroke, as well as such conditions as complications of AIDS. The medical use of radioisotopes offers a less invasive alternative to traditional means of diagnosis and treatment and can result in more effective patient management, substantial benefits to the patient, and significant savings to the health care system (Blaufax, 1993; Patton, 1993; Specker et al., 1987). For example, radionuclide studies can identify metabolic and perfusion abnormalities that may occur prior to the development of anatomic abnormalities that would be detected by computed tomographic imaging or magnetic resonance imaging. Tumor imaging studies with radionuclides can result in the avoidance of unnecessary and expensive biopsies or surgery, whereas nuclear cardiology studies can result in the avoidance of unnecessary cardiac catheterization procedures.

In recent years as the very success of nuclear medicine and the increased use of stable and radioactive isotopes have combined with the end of the Cold War to bring DOE to an important crossroad. Since its inception, isotope production at

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the various multipurpose DOE laboratories has been a "parasitic" activity. This unfortunate choice of terms is meant to indicate that isotope production has traditionally been a secondary mission that has been started and stopped to meet the needs of the laboratories' primary missions of basic and applied research in nuclear and particle physics, nuclear weapons, and nuclear power production. Support for all three of these areas has declined precipitously in the past decade, even as demand for isotopes has increased. The concerns of U.S. clinicians and researchers about the continuing availability of enriched materials and radionuclides have increased sharply since 1989, when DOE departing from its previous policy of providing partial financial support, began operating its isotope program on a legislatively mandated full cost recovery basis (the Energy and Water Development Appropriations Act of 1990 [Public Law 101-101]). DOE Prices have jumped particularly for low-demand products still in the early stages of research and development, and aggressive competition from Canada in radioisotopes and from the former Soviet Union in stable isotopes and radioisotopes threatens to cut DOE out of the market altogether. The nuclear medicine community in particular has been highly vocal in its concern that the needs of the various users in the United States will not be adequately met in a future market controlled by one or two foreign sources.

Many of the needs and uses of isotopes were discussed in a 1982 report from the National Research Council, *Separated Isotopes: Vital Toolsfor Science and Medicine* (National Research Council, 1982). The need for a dedicated source of accelerator-produced radioactive isotopes for biomedical research and clinical practice, a National Biomedical Tracer Facility (NBTF), was argued in the *Proceedings of the DOEWorkshop on the Role of a High-current Accelerator in the Futureof Nucler Medicine*, held at Los Alamos National Laboratory, August 16-17, 1988 (Moody and Peterson, 1989), and the *National BiomedicalTracer Facility Planning and Feasibility Study*, prepared in 1991 by the National Biomedical Tracer Facility Task Force for DOE (Holmes, 1991). Further support for an NBTF was presented in the 1992 report from a workshop held at Purdue University (Kliewer and Green, 1992). Those reports emphasized that the United States could not maintain its leading role in the research and development of new tools in medicine without a dedicated source or sources of isotopes for its research scientists.

On February 20–21, 1992, the Institute of Medicine, in collaboration with the Board on Chemical Sciences and Technology, convened a workshop at the National Academy of Sciences entitled, *Availability of IsotopicallyEnriched Materials*. The workshop brought together isotope users (in fields ranging from nuclear medicine, nutrition, and pharmacology to nuclear chemistry, nuclear physics, chemistry, geoscience, and environmental science) and isotope producers from both the private sector and government facilities. Workshops discussions crystallized the widespread sense of urgency about the availability of adequate future supplies of isotopes in the United States. Participants heard anecdotal

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reports of U.S. users seeking potential suppliers of isotopes in Canada, Europe, and Russia. Other reports indicated that the isotopes needed for key radiopharmaceuticals were sometimes unavailable for diagnostic studies and therapeutic procedures, and that scientists had been forced to abandon promising lines of research because the necessary isotopes were no longer available. The workshop participants urged the National Research Council to carry out a full study of isotope needs and availability.

In response to this urging by the workshop participants and with the realization that changing national and scientific priorities would reduce the funding for the accelerator-based facilities at Los Alamos National Laboratory (Los Alamos Meson Physics Facility) and Brookhaven National Laboratory (Brookhaven Linac Isotope Producer), DOE turned to the Institute of Medicine for assistance in verifying the need for and scope of NBTF. Thus, the Health Sciences Policy Board of the Institute of Medicine recommended that a committee be convened to undertake an intensive examination of isotope production and availability, including the education and training of those who will be required to sustain the flow of radioactive and stable materials from their sources to laboratories and bedsides.

CHARGE TO THE COMMITTEE

This document is the report of the committee formed to examine these matters and to provide recommendations for action to DOE. The committee was asked:

- To assess current methods and systems for producing and distributing isotopically enriched material and to consider possible alternatives for ensuring adequate supplies of isotopes for a broad range of clinical and biomedical research applications.
- To examine the relative merits of current and developing technologies for isotope production and the need for new technologies over the long term.
- To assess the relative needs for involvement of the Department of Energy and private sector in isotope production and distribution. As part of this assessment, the committee was also asked to conduct an in-depth review of national needs for the high-energy accelerator-produced radionuclides to be produced at an NBTF in relation to other requirements in the nuclear medicine and biomedical isotope sectors.
- To evaluate the comprehensive research and educational components that have been proposed for NBTF in relation in total personnel needs in the these areas.

In its deliberations, the committee was asked to address the following specific questions: What are the current needs for both radioactive and enriched stable isotopes in the United States? What needs can be anticipated for the future on the basis of recent and expected technological improvements? What is the

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current U.S. capability for radioisotope production and stable isotope separation in both the public and the private sectors? Is the current supply of the radioisotopes adequate for research, diagnostic applications, and patient care in the United States? Is the supply of the enriched stable isotopes in the United States likely to remain reliable? Should existing DOE facilities be maintained or should new facilities to be constructed for the isolation and production of both radioactive and enriched stable isotopes? What strategies can be developed for meeting U.S. needs for isotopic materials? How can the capabilities of the public and private sectors best be utilized?

PLAN OF THE REPORT

From its earliest discussions it became clear to the committee that any consideration of a national isotope policy would have to deal with several distinct, but interrelated, parts. First was the continued supply of enriched stable isotopes. Useful in their own right for studies in both the physical and life sciences, enriched stable isotopes are also needed as targets for both reactor-produced and accelerator-produced radionuclides. The technology for producing or, more accurately, separating stable isotopes has been a spinoff of nuclear weapons manufacture and, until recently, a monopoly of DOE, both in maintaining current facilities (World War II vintage "calutrons," which use massive electromagnets to separate isotopes according to their masses) and the developing new separation techniques. With the end of the Cold War, the inventory and capabilities of the former Soviet Union have now been added to those of the United States, but the size of the combined pool is unknown, and the supply from the former Soviet Union may be unreliable. Decisions need to be made on the disposition of the aging calutrons at the Oak Ridge National Laboratory that are now on standby status and how much to invest in newer technologies promising simpler and more cost-effective separations.

Important decisions also face DOE in regard to the continued production of radioactive isotopes by neutron bombardment of targets in nuclear reactors. For nuclear medicine, the greatest present need is for molybdenum-99, which is used in the production of generators of technetium-99m, the most commonly used radionuclide in clinical medicine (more than 80 percent of all in vivo nuclear medicine procedures employ technetium-99m). Nearly all of the U.S. supply is currently produced by a Canadian facility. Questions have been raised about the reliability of the supply and whether there should be a producer in the United States both to ensure the supply and to provide a profit base for the unprofitable production of other isotopes to be used in research. In addition, the most basic isotopes used in modern biomedical research laboratories (hydrogen-3, carbon-14, phosphorus-32/33, sulfur-35, iodine 125) are produced in reactors. Lastly, some isotopes used for cancer and thyroid treatments (strontium-89, yttrium-90, iodine-131) are also produced in this manner. Support for U.S.-based reactors is

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uncertain, leaving neutron-dependent isotope production facing large incremental costs as other reactor users cut back their use of reactors. DOE will have to make major decisions about the need, desirability, and manner of its involvement in the production of these isotopes.

The third piece of the isotope problem involves radionuclides made for nuclear medical practice by charge-particle bombardment. Thallium-201, iodine-123, gallium-67, and indium-111 are made with commercial accelerators with maximum energies of 30–40 million electron volts (MeV). The production of many new and promising radionuclides for medical diagnosis and therapy requires particle accelerators of higher energy. These include strontium-82 (the parent of rubidium-82, the only pharmaceutical used in PET scanners to date granted status as a new drug under a new drug application by the U.S. Food and Drug Administration), copper-67, and xenon-122. The latter two are being investigated for use in both diagnosis and therapy and can be produced only with such a machine. It is the production of these and other radionuclides that has been the focus of the NBTF initiative. Such a facility could provide a locus for other activities as well, including the training of scientists needed for radionuclide production and radiopharmaceutical formulation and as a center for isotope research and development.

The report addresses these three classes of isotope production in turn, attempting in each case to sort out the issues of production of commercially viable products from those of research and development on future products. It also addresses related matters: research missions appropriate for a medical isotope facility, requirements for education and training in relation to isotope production facilities, and the possibilities for collaboration between industry and the national laboratories as a means of meeting future requirements and opportunities. Appendix A examines an increasingly important practical issue related to isotope production and delivery, waste management, and Appendix B provides some of the legal background relevant to the problems addressed and the solutions offered. The acronyms and abbreviations used in the report and a table of the elements are provided in Appendixes C and D, respectively. A glossary is also provided in Appendix E.

REFERENCES

Blaufax, M.D.1993. Cost-Effectiveness in Nuclear Medicine Procedures in Renovascular Hypertension. Seminars in Nuclear Medicine19:116–121.

Holmes, R.A.1991. National Biomedical Tracer Facility Planning and Feasibility Study. New York, N.Y.: Society of Nuclear Medicine.

International Atomic Energy Agency. 1990. Isotopes in Everyday Life. Report IAEA/PI/A6E. Vienna, Austria.

Kliewer, K.L., and M.A. Green, eds. 1992. Proceedings of the Purdue National Biomedical Tracer Facility Workshop. West Lafayette, Ind.: Purdue University.

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Isotopes for Medicine and the Life Sciences
http://www.nap.edu/catalog/4818.html

Management Information Services, Inc.1994. The Untold Story: Economic and Employment Benefits of the Use of Radioactive Materials. Report prepared for Organizations United for Responsible Low-Level Radioactive Waste Solutions. Washington, D.C.

Moody, D.C., and E. J. Peterson, eds. 1989. Proceedings of the DOE Workshop on the Role of a High-Current Acceleration in the Future of Nuclear Medicine. Report LA-11579-C. LosAlamos, N.M.: Los Alamos National Laboratory.

National Research Council. 1982. Separated Isotopes: Vital Tools for Science and Medicine. Washington, D.C.: National Academy Press.

Nussbaumer, D., C. Wiblin, and L. Welch. 1993. Health and Safety Impacts from Discrete Sources of Naturally-Occurring and Accelerator-Produced Radioactive Materials (NARM). NUREG/CR-5962. Washington, D.C.: U.S. Nuclear Regulatory Commission.

Patton, D. D.1993. Cost-Effectiveness in Nuclear Medicine. Seminars in Nuclear Medicine23:9–30.

Society for Nuclear Medicine. 1986. Survey of Nuclear Medicine Physicians, Scientists, and Facilities—1986. Journal of Nuclear Medicine30:1–10.

Specker, B. L., E. L. Saenger, C. R. Buncher, and R.A. McDevitt. 1987. Pulmonary Embolism and Lung Scanning: Cost-Effectiveness and Benefit: Risk. Journal of Nuclear Medicine28:1521–1530.

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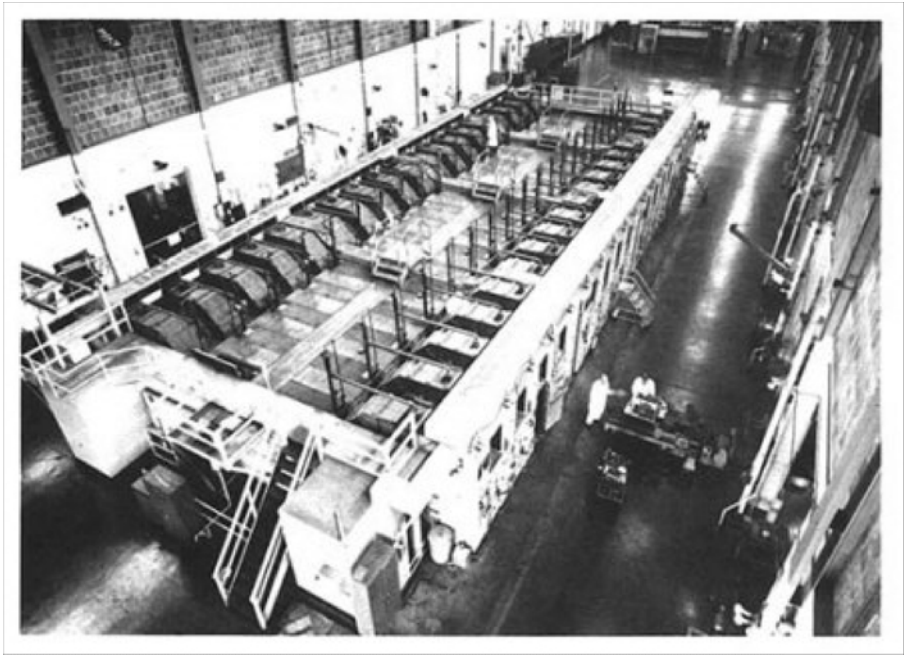

An overhead view of the electromagnetic isotope separators (calutrons)at Oak Ridge National Laboratory. The calutrons are used to divide a wide rangeof elements into their constituent isotopes, providing scientists and radioisotope manufacturerswith concentrated (enriched) samples of specific stable isotopes. SOURCE: Oak RidgeNational Laboratory.

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2

Enriched Stable Isotopes

HISTORICAL PERSPECTIVE

The discovery of stable "isotopes" began with J. J. Thomson's identification of neon-22 in 1912 (Bievre et al., 1984). More than 90 naturally occurring elements have been identified on the earth; they exist as nearly 270 stable isotopes—that is, forms of the elements that do not decay or emit radiation—and hundreds of radioactive isotopes. The various isotopes of a given element differ from one another only in the number of neutrons in their atomic nucleus (the number of protons in the nucleus differentiates the elements from one another), and even highly purified samples of an element are generally a mixture of several isotopes. Pure silver, for example, is composed of nearly equal amounts of silver-107 and silver-109. Iron is mostly iron-56 (92 percent), but it contains small amounts of three other isotopes as well, and tin is a mixture of 10 stable isotopes, the most abundant of which makes up only 33 percent of the total. *Enriched* refers to material that consists largely or exclusively of a single isotope and is usually obtained by one of the separation techniques described later in this chapter.

The use of enriched stable isotopes and their applications as they are presently known emerged from early work with metabolites labeled with deuterium (Schoenheimer and Rittenberg, 1935). Their extra mass made them traceable (usually by mass spectrometry of, for example, blood or urine) as they proceeded through various biochemical pathways. Similar labeling of nearly any compound is theoretically possible by synthesizing it with large quantities of an isotope that is relatively rare in nature. In the last two decades the use of enriched stable isotopes has offered substantial advantages to scientists and clinicians involved in the rapid growth of research on human body composition, energy balance, protein turnover, and fuel utilization (Whitehead and Prentice, 1991). Today,

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increased awareness of the role played by the elements in human health and as etiologic factors in diseases (osteoporosis, heart disease, cancer, diabetes, kidney disease) (National Research Council, 1989; U.S. Department of Health and Human Services, 1988) as well as diagnostic and therapeutic adjuncts (obesity, inborn errors of metabolism, heart disease) has created an explosion in the need for stable isotopes at a time when the production capacity is questionable. Although stable isotopes occur naturally, their utility can be greatly enhanced when they are isolated and enriched through processes such as electromagnetic separation, cryogenic distillation, thermal diffusion, or other physical and chemical processes. These enriched stable isotopes are used as target materials in the preparation of radioisotopes with particle accelerators and nuclear reactors and as biological tracers in biomedical research and clinical applications. In addition, they serve as probes for basic physics and chemistry studies. Table 1-1 in the previous chapter lists some of the many fields that use stable or radioactive isotopes. Selected biomedical research topics and potential clinical uses of stable isotopes are given in Table 2-1.

Despite the pioneering role of the United States in this field, the country is rapidly becoming more dependent on sources in the former Soviet Union for many necessary isotopes. Serious debate is needed regarding the desirability of this dependence and the attendant possibility of the pernicious effects on U.S. science and technology of an isotope monopoly controlled by a single financially distressed foreign source.

CURRENT APPLICATIONS IN MEDICINE AND PHYSICAL AND LIFE SCIENCES

In many areas of research, the need for enriched stable isotopes is as vital as the need for pure chemicals (Friedlander and Wagner, 1982). Stable isotopes used primarily for research are usually purchased intermittently in relatively small amounts, from fractions of a gram to a few grams at a time. However, biomedical research often requires kilogram quantities (e.g., oxygen-18). The general approach to biomedical studies that use stable isotopes involves the same tracer methods used for radioactive isotopes. But since there is no radiation to detect, specialized analytical methods for detection of the specific stable isotopes are used. For example, after ingestion or injection of an isotope of zinc, the absorption of zinc by the human body can be determined by measuring the trace amounts that appear in the blood and urine over a period of days or weeks after ingestion or injection. The dilution of the stable isotope tracer gives information on the distribution of zinc in the body, and the rate of excretion gives information regarding how well a particular mineral is absorbed. The simultaneous use of two isotopes in two different foodstuffs can be used to determine how absorption of calcium, for example, might vary as a function of mode of intake.

The major advantages of using enriched stable isotopes for biomedical re

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search lie in their ease of use on large patient populations in studies of nutrition, in children and adults in clinical studies of metabolic abnormalities of the digestive system, and in investigations of osteoporosis. The availability of several stable isotopes of the same element allows simultaneous investigation of nutrients within various body compartments.

Some of the most important contemporary uses of enriched stable isotopes involve investigations of the human metabolism of calcium, zinc, magnesium, and other cations needed by humans. The minimum dietary requirements of metals needed in trace amounts (e.g., selenium, molybdenum, copper, and rubidium) require enriched stable isotopes for their determination. A major application is the study of calcium absorption from ingested foodstuffs and its subsequent turnover in bone in relation to osteoporosis. By using simultaneous oral and intravenous administration of two or more stable isotopes (e.g., calcium-42 and calcium-44), the absorption of various calcium supplements and food sources can be investigated. This is an area of great potential for metabolic research, particularly in the area of osteoporosis.

Key tools for research on human metabolism relative to obesity, starvation, diabetes, and atherosclerosis are mass spectrometric or magnetic resonance measurement of carbon-13 (^{13}C) levels in human subjects who have received substrates labeled with ^{13}C, and mass spectrometry of the temporal course of excretion after ingestion of water labeled with both oxygen-18 and deuterium. Stable isotopes have been used to determine the metabolic and biochemical bases for familial hyperlipidemia and the kinetic parameters in apolipoprotein B metabolism. In these applications advances are needed to reduce the cost of these ^{13}C compounds and the oxygen-18-labeled water that has been difficult to obtain in the past 3 years (oxygen-18 for double-labeled water studies currently costs about $1,000 per patient).

The dearth of inexpensive methods for incorporation of the isotope into chemical compounds is also limiting their application. For example, ^{13}C is usually shipped as the carbonate or as gaseous carbon dioxide. Calcium isotopes are available as the calcium carbonate. The costs of specialized tools for the study of metabolism in humans, for example, of [1-^{13}C]glucose or calcium-42 or calcium-44 are so great that many investigations of major importance to health care are impeded or not possible. For example, the study of human glycogen synthesis by nuclear magnetic resonance (NMR) requires about 70 g of 1-^{13}C-labeled glucose. The 1994 catalog cost is $10,000. A study of the pentose shunt with [2-^{13}C]glucose requires about 40 g at $400/g and a total cost of $16,000 on the basis of 1994 catalog prices. A very important study of glutamine metabolism that would use nitrogen-15 and NMR would cost $30,000. The major element responsible for these costs is the incorporation of the stable isotopes into biologically important compounds, generally 10 times the cost of the production or separation of the stable isotope. The potential use of stable isotopes in diagnostic tests will clearly be limited without drastic reductions in these costs, no matter how useful

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TABLE 2-1 Selected Enriched Stable Isotopes Used in Biomedical Research

Stable Isotope	Uses
Boron-10	• Extrinsic food label to determine boron metabolism
Calcium-42, -44, -46, -48	• Calcium metabolism, bioavailability, and absorption parameters during physical stress, bed rest, and space flight • Osteoporosis research and bone turnover studies • Role of nutritional calcium in pregnancy, growth and development, and lactation • Bone changes associated with diseases such as diabetes and cystic fibrosis
Carbon-13	• Fundamental reaction research in organic chemistry • Molecular structure studies • Fundamental metabolic pathway research, including inborn errors of metabolism • Noninvasive breath tests for metabolic research and diagnosis • Biological substrate oxidation and turnover • Elucidation of metabolic pathways in inborn errors of metabolism • Amino acid kinetics • Fatty acid metabolism • Air pollution and global climatic change effects on plant composition
Chlorine-35, -37	• Environmental pollutant toxicity studies
Chromium-53, -54	• Noninvasive studies of chromium metabolism and human requirements • Adult onset diabetes mechanisms
Copper-63, -65	• Noninvasive studies of copper metabolism and requirements • Studies of congenital disorders and body kinetics in gastrointestinal diseases • Investigation of role in maintaining integrity of tissue such as myocardium
Helium-3	• In vivo magnetic resonance studies
Hydrogen-2	• Vitamin research • Chemical reaction mechanisms
Iron-54, -57, -58	• Metabolism, energy expenditure studies • Conditions for effective iron absorption and excretion • Research to develop successful interventions for anemia • Metabolic tracer studies to identify genetic iron control mechanisms

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Stable Isotope	Uses
Krypton-78, -80, -82, -84, -86	• Diagnosis of pulmonary disease
Lead-204, -206, -207	• Isotope dilution to measure lead levels in blood
Lithium-6	• Sodium and renal physiology • Membrane transport • Psychiatric diseases
Magnesium-25, -26	• Noninvasive studies of human nutrition requirements, metabolism, and absorption • Kinetic studies of heart disease and vascular problems
Molybdenum-94, -96, -97, -100	• Extrinsic labeling of food for determination of human nutrition requirements
Nickel-58, -60, -61, -64	• Noninvasive measurement of human consumption and absorption
Nitrogen-15	• Large-scale uptake studies in plants • Whole body protein turnover, synthesis, and catabolism • Amino acid pool size and turnover • Metabolism of tissue and individual proteins
Oxygen-17	• Studies in structural biology • Cataract research
Oxygen-18	• Noninvasive, accurate, and prolonged measurement of energy expenditures during everyday human activity • Lean body mass measurements • Obesity research • Comparative zoology studies of energy metabolism
Rubidium-85, -87	• Potassium metabolism tracer • Mental illness research
Selenium-74, -76, -77, -78, -80, -82	• Bioavailability as an essential nutrient
Sulfur-33, -34	• Human genome research and molecular studies • Nucleotide sequencing studies
Vanadium-51	• Diabetes, bioavailability, and metabolism • Brain metabolism studies
Xenon-129	• Magnetic resonance imaging
Zinc-64, -67, -68, -70	• Noninvasive determination of human zinc requirements • Metabolic diseases, liver disease, and alcoholism • Nutritional requirements and utilization studies

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the results. These facts argue for a national initiative on efficient synthesis that could be facilitated through an overall national program on biomedical isotopes.

Although the introduction of stable isotope tracers revolutionized the understanding of biological processes, the field relies heavily on sophisticated chemical techniques and analytical instrumentation not routinely available. Expensive measurement methods are also limiting applications. The instruments used to detect stable isotopes include mass spectrometers, accelerator mass spectrometers, and gas chromatographs, all with wide ranges of sophistication. The use of certain radionuclides for in vivo studies is likely to be increased with the widespread introduction of accelerator mass spectrometry (AMS) for their detection. AMS has been shown to be several orders of magnitude more sensitive than counting of radioactivity for the detection of certain long-lived radionuclides (Elmore et al., 1990; Felton et al., 1990). Of particular interest for tracer studies is the application of carbon-14 and calcium-41. It has been calculated that for experiments with carbon-14 in which the carbon-14 is detected by AMS, the radiation dose to human subjects can be as little as 0.003 millisieverts (mSv). This is only a small fraction of the amount of natural radiation received by humans in a year.

The needs for detection systems for stable isotope applications are as great as the needs for reductions in the costs of incorporating stable isotopes into biomedical compounds. At present any substantial research study can require a dedicated analyst-technician and the acquisition of specialized instrumentation costing more than $100,000. Some solution for this bottleneck in stable isotope applications needs to be developed. The committee found this lack of detection instrumentation one of the most important impediments to the use of stable isotopes.

A reliable supply of enriched stable isotopes is also essential for radioactive isotope production. These materials are used as targets in reactors and accelerators to produce radioisotopes for basic and clinical research (see Table 2-2 and Chapters 3 and 4), and they are the feedstock for the commercial production of radiopharmaceuticals that are used routinely in the clinic and clinical laboratory for diagnosis and therapy. Small quantities of a wide variety of stable isotopes are essential for maintaining the National Institute of Standards and Technology's widely used Standard Reference Materials.

The application of stable isotopes in science and industry continues to be varied and widespread, but the production and sales of these tools are not large or lucrative businesses. The worldwide market for stable isotopes is estimated to be only in the range of $8 million to $10 million, more than half of which is accounted for by only four products: thallium-203, which accounts for one-quarter of all sales, and strontium-88, helium-3, and zinc-68, each of which makes up 10–12 percent of the total market. Overall, nearly 40 percent of the world's enriched stable isotope sales are small purchases for research purposes. Medicine, primarily radiopharmaceutical companies, accounts for about half of all purchases, and industrial users account for the remaining 10 percent.

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TABLE 2-2 Selected Enriched Stable Isotopes and Derived Radioisotopes

Stable Isotope Target	Radioisotope Product[a]
Cadmium-112	Indium-111
Carbon-13	Nitrogen-13
Chromium-50	Chromium-51[b]
Germanium-76	Arsenic-77[b]
Lutetium-176	Lutetium-177[b]
Nickel-58	Cobalt-57
Nitrogen-15	Oxygen-15
Oxygen-18	Fluorine-18
Palladium-102	Palladium-103[b]
Platinum-198	Gold-199[b]
Rhenium-185	Rhenium-186[b]
Samarium-152	Samarium-153[b]
Strontium-88	Strontium-89[b]
Thallium-203	Thallium-201
Xenon-124	Iodine-123
Zinc-68	Gallium-67, Copper-67

[a] For specific examples of radioisotope applications, refers to Chapters 3 and 4.
[b] Produced in a reactor; the others are produced in an accelerator.

ISOTOPE SEPARATION IN THE UNITED STATES

Since the late 1940s the dominant source of most of the enriched stable isotopes produced in the United States has been the calutrons (from California University cyclotron) at the Oak Ridge National Laboratory (ORNL). These large separators were originally developed to separate the isotopes of uranium in World War II. The technology that they employ, which has been relatively unchanged for the last 50 years, is based on the electromagnetic separation of elemental material into its constituent isotopes. The element, or a compound containing the element, is first converted to an ionized gas. A stream of these ions is then bent by a powerful magnetic field. The degree of curvature produced is dependent on the mass of the ion, so the ions with lighter isotopes are bent more than the heavier ones. Metal collector plates situated appropriately then intercept the separated beams of individual isotopes. Approximately 60 of these machines remain at ORNL today, 50 of which have been adapted for the enrichment of 225 stable isotopes of 58 elements (Collins, 1993). The calutrons represent a unique but aged resource for the production of enriched stable isotopes, and no other facility that could duplicate this capability exists in the United States. Operation of the calutrons requires a staff of 35, however (Collins, 1993), and it would cost about $5 million annually to produce a large spectrum of isotopes (Arthur Andersen & Co., 1993). Despite their age, the calutrons have been operated successfully in recent years through the skill and knowledge of longtime opera

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tors. For reasons more fully discussed below, the calutrons are currently not being operated but are in a standby mode (at an annual cost of $2 million). Future operation of the calutrons appears to depend on the ability of the U.S. Department of Energy's (DOE's) Isotope Production and Distribution Program (IPDP) to obtain contracts with the private sector for substantial isotope purchases. The research community cannot afford the costs required to reactivate the calutrons to produce the generally small quantities of enriched stable isotopes required for their programs. Moreover, because many calutron operators have already or will soon be retiring, it seems unlikely that a new operations crew would be capable of restoring the calutrons to full operating efficiency without considerable expense and other difficulties.

In addition to the calutrons, equipment for the plasma separation technique is in place at ORNL, but additional funding would be required before this enhancement of the ORNL isotope separation capabilities could be realized. Plasma separation could be used for the direct production of enriched stable isotopes or to enrich material as feedstock for the calutrons. The plasma separation process is only about half as efficient as the process performed by the calutrons in terms of product purity, but it is 300 times faster. The two processes could thus be used in series to enrich naturally rare isotopes more efficiently.

Large amounts of enriched stable isotopes of the light elements such as carbon, nitrogen, and oxygen are particularly important for biomedical research (e.g., oxygen-18 as a source material for the fluorine-18 used in position emission tomography). The primary source of such isotopes in the United States today resides in the commercial sector. Examples include Isotec in Ohio and the Cambridge Isotope Laboratories in Massachusetts. Cryogenic distillation columns are employed by these companies to separate the light isotopes. At present, there appears to be an adequate supply of such light isotopes; however, researchers have complained about short supplies in the recent past that have forced them to foreign sources (e.g., Israel) and about costs that continue to limit their widespread use. DOE also has capability in this area: cryogenic columns are in place, but in a standby mode, at Los Alamos National Laboratory (LANL). Finally, additional capability for stable isotope separation exists at DOE's Mound Facility in Ohio, which uses thermal diffusion to provide DOE laboratories with isotopes of the halogens and the noble gases.

FUTURE SUPPLIES

Although a substantial capability for the production of enriched stable isotopes exists in the United States—both in the private sector and within the infrastructure of DOE—many of the operations located within DOE must be considered to be in jeopardy. Two recent and unrelated events have resulted in the inability or unwillingness of both private-and public-sector groups to pay DOE's going rate for isotopes and are driving these groups to non-U.S. suppliers. These

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events, the passage of the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101) and the emergence of the Republics of the former Soviet Union as a major force in the isotope market, are detailed in the following paragraphs.

From its beginnings in the Manhattan Project, the U.S. government's enriched stable isotope program operated with modest federal subsidy (approximately $2 million annually in the late 1980s) in support of research deemed to be of programmatic interest to DOE. In 1989, IPDP was established within the Office of Nuclear Energy of DOE to oversee all federal isotope production. Public Law 101-101 incorporated this reorganization into law and, in addition, decreed that, henceforth, isotope production and distribution were to be self-supporting (i.e., fees for isotopes and related services were to provide for full cost recovery, including administrative expenses and the depreciation of equipment). IPDP has not become self-sustaining, and its problems have been the subject of congressional subcommittee hearings, a U.S. General Accounting Office report (1992), and a management study by the consulting firm of Arthur Andersen & Co., 1993). Those studies point to high operating costs, which are largely beyond the control of IPDP; unrealistic capitalization for equipment; and, even less susceptible to remedy, the aggressive entry into the isotope market of the Republics of the former Soviet Union as matters of concern.

The Cold War arms race spawned the expanded development and use of electromagnetic separators and gas centrifuges in the Soviet Union as well as the United States. The functional state of this former Soviet equipment is not known, but many of these facilities have not hesitated in making the leap into a market economy. Although anecdotal information about Russian inventories is abundant, the extent of these supplies is unknown, but it is estimated to be many times that of U.S. inventories (Arthur Andersen & Co., 1993) and priorities for future production in Russia appear to be dominated by the quest for hard currency. Aggressive Russian marketing cut DOE's share of the world stable isotope market from roughly 90 percent in 1990 to less than 60 percent in 1992 (Arthur Andersen & Co., 1993). DOE sales of thallium-203, the stable isotope with the largest world demand, fell from $2.5 million in 1990 to less than $350,000 in 1992. This decline is expected to continue, because Russian suppliers are still setting their prices as a percentage of the IPDP price, and this decline could become precipitous if the Russia or other former Soviet republics set up an efficient distribution system. The committee was informed by a U.S.-based representative of one Russian laboratory as recently as March 1994 that the laboratory was too poor to publish a catalog but that prices would be "about half of those in the Oak Ridge catalog." It seems likely that prices would rise sharply in the absence of at least potential competition from Oak Ridge, but most if not all of the major radiopharmaceutical companies have turned to the former Soviet Union, some with long-term contracts. Industry representatives (Brown, 1993; Seidel, 1993) reported to the committee that, at least for fairly large repeat orders, they

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were generally satisfied with the speed and reliability of delivery as well as the quality of isotopes from their Russian sources. Not surprisingly, the result has been that DOE has suspended its production of enriched stable isotopes.

Enriched stable isotopes may still be purchased from IPDP, which has a substantial inventory of some isotopes still on hand. Although prices have risen sharply, IPDP is the only alternative for researchers without a Russian connection or for scientists needing only small quantities of a variety of isotopes at irregular intervals (for which Russian sources have been unreliable or nonexistent).

In addition, stable isotopes may be leased for nondestructive, nonconsumptive, scientific investigation. Prior to the establishment of IPDP, materials from a circumscribed "loan pool" known as the Research Materials Collection, were reserved for loan to researchers for nondestructive uses; however, this policy has been abandoned, and all materials controlled by IPDP are available for purchase, resulting in a steady depletion of this invaluable collection.

The ORNL calutrons have been in standby mode since August 1991. The committee sees no point in recommending the resumption of production without the promise of substantial sales, something that is unlikely to occur as long as DOE prices must cover the full costs of calutron operations and the Russians continue to deliver isotopes to the major buyers at cut-rate prices. The calutrons are now more than 50 years old. Newer, more efficient technologies could supplant them and provide a buffer against an uncertain Eastern European supply. For this reason, the committee heard reports from a number of DOE-funded scientists exploring alternative separation processes.

NEW AND ALTERNATIVE SEPARATION TECHNOLOGIES

As noted above, the calutrons have been the sources of more than half of the enriched stable isotopes, but they are based on 50-year-old technology and old equipment. Over the last decade or so, considerable effort has been invested by the U.S. government, sometimes in collaboration with industry, in new technologies for producing enriched stable isotopes for a variety of purposes. Some of these new technologies hold the promise of producing research-grade isotopes at reduced costs, in large quantities (grams or even kilograms), and at high levels of enrichment. Although many of these technologies are still in the research and development stage—even, in some cases, in a conceptual stage—they should be studied and developed as potential contributors to the future supply of enriched stable isotopes that will be needed by the research community in the United States and elsewhere. During the November 1993 meeting of the committee, several of these new technologies were described in the public portion of the meeting, although none are yet in a position to replace current methods, and it is difficult to assess how much additional development will be required. These advances are briefly described below. It is important to recognize, however, that these examples by no means represent all of the technologies being studied.

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Three of the new techniques described at the November 1993 meeting—the vacuum arc centrifuge (VAC), the solitron, and atomic vapor laser isotope separation (AVLIS) (Krishnan, 1993; Schwager, 1993; Stern, 1993)—require the use of strong electric and magnetic fields to facilitate the process leading to stable isotope separation. In VAC, separation is achieved via the interaction between an ion beam (composed of the isotopes to be separated) with a suitable magnetic field, with the separation factor between any two isotopes depending on the difference in their masses and the rotation frequency of the plasma. This technique is under development by scientists at the Science Research Laboratory under a grant from DOE. They envision it as a low-cost (ca. $1 million to build and $500,000 a year to operate), modular enrichment tool that could supply a large range of stable isotopes (carbon-13 to heavy elements such as thallium-203) in gram to kilogram quantities (Krishnan, 1993).

The solitron is a device under development at the Lawrence Livermore National Laboratory (LLNL). The goal is to provide an inexpensive (same range as the VAC) and compact (portable) device that can be used to produce a variety of stable isotopes for research applications. Isotope separation is achieved through the selectivity provided by a solitary, traveling electric-field wave imposed on an ion beam. Prototype work is being carried out to demonstrate its feasibility and to understand the scaling properties to a larger device. Like the VAC, products produced in the solitron could readily be switched by changing the ion source. Eventually, the LLNL group hopes to achieve an eight-beam solitron that could separate isotopes at a substantial cost reduction over existing techniques (Schwager, 1993).

The final technique discussed here, AVLIS, was developed at LLNL to provide a uranium enrichment capability for the United States. This goal has been accomplished through a large-scale demonstration project, and any future deployment of this technology for uranium production is now under the control of the newly established U.S. Enrichment Corporation. Both the technology and the $500 million prototype facility at LLNL now have the potential of being applied to production of very large quantities of other isotopes for applied and basic research (e.g., kilogram levels for lanthanides and actinides have been achieved). A wide range of elements can potentially be separated by AVLIS. The process may be capable of providing enriched stable isotopes for more than half of the elements of the periodic table, although annual operating costs for the LLNL plant might be as high as $20 million to $30 million (Stern, 1993). AVLIS achieves isotope separation by the use of intense laser beams tuned to selectively ionize specific isotopes. A two-laser system that dissociates formaldehyde in an isotopically selective manner was also described as a potential high volume system for enrichment of large quantities of carbon-13 and oxygen-18, light isotopes of particular importance to biomedical research. Such large quantities would open up new areas of research with biomedical applications.

Other researchers (Stevenson et al., 1993) have recently reported on the

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observation of isotopic substitution in electron self-exchange equilibrium in chemical reactions. It has been conjectured that this may form the basis for a highly efficient, new technology for separating selected isotopes.

A chemical exchange technique involving gas-liquid, liquid-liquid, and solid-liquid systems is in the research and development stage at DOE's Mound Facility in Ohio and may hold special importance for the separation of calcium isotopes (Eppley, 1993). Other work there involves a thermal diffusion approach that can be applied to both gases (e.g., xenon-124 and xenon-126) and liquids. This process is closer to the production stage and may be especially applicable to isotopes with lower masses.

This brief discussion has drawn attention to new technologies that are being developed and that can be applied to the stable isotope supply question. For a new technology to achieve wide acceptance it will have to provide cost savings over present-day methods. Whether any of these new technologies will become commercially viable is uncertain. But it is absolutely clear that the United States must have a steady supply of enriched stable isotopes for both its applied and basic research programs in the biomedical and physical sciences. The support of promising technologies for stable isotope production is a critical national need, and it is appropriate that the federal government take the lead in this activity.

CONCLUSIONS

1. Enriched stable isotopes are important research and diagnostic tools, and they offer a number of unique applications.
2. Enriched stable isotopes are critical starting materials in the production of many widely used radioisotopes.
3. An adequate supply of enriched stable isotopes currently exists for the production of most biomedically significant radionuclides, but DOE inventory of enriched stable isotopes is being depleted through sales without replacement. The pool of isotopes formerly available only on a lease basis for nondestructive uses no longer exists. Moreover, a number of enriched stable isotopes that are crucial for research and other applications are not available or are priced beyond the means of researchers.
4. Some research communities—for example, biological, physical, and earth sciences—frequently require only small quantities, but a great variety of enriched stable isotopes. These research isotopes are seldom viable as commercial products.
5. Since the electromagnetic isotope separators, the calutrons, at ORNL are currently in the standby mode, U.S. production of the majority of enriched stable isotopes is at a standstill. Future separations are planned only to replace high retail volume isotopes or as specific contracts are negotiated.
6. The use of enriched stable light isotopes—for example, carbon-13, oxygen-18, and the stable calcium isotopes—will likely increase, if they can be

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produced more cheaply and in large quantities. Research opportunities and applications will be promoted by offering greater amounts of isotopes at reduced costs.

7. The extent of inventories in the Republics of the former Soviet Union is unknown, but they are estimated to greatly exceed the U.S. supplies for most enriched stable isotopes.
8. New technologies that may provide more cost-effective separation methods within 3 to 5 years are being developed.

RECOMMENDATIONS

1. A dependable supply of enriched stable isotopes controlled by the United States is crucial for research, therapy, diagnosis, and other applications. In the near term this means that the electromagnetic separation capabilities of the Oak Ridge National Laboratory calutrons should be maintained in standby mode until a more cost-effective source of enriched stable isotopes can be developed, or external sources fail to meet demand. If more cost effective technology does not emerge within 5 years, subsidized operation of the calutrons should be resumed.
2. The development of new separation technologies or improvements in existing ones, must be encouraged and supported, and the most promising of these must be evaluated for their commercial viability. This should include efforts for the efficient, cost-effective production of large amounts of enriched stable isotopes—including kilogram quantities of light isotopes.
3. The expanded application of enriched stable isotopes into new research areas should be encouraged.
4. A national policy of providing a subsidy for enriched stable isotopes used in small quantities for research purposes should be adopted.

REFERENCES

Arthur Andersen & Co.1993. U.S. Department of Energy Isotope Production and Distribution Program Management Study. Washington, D.C.

Bievre, P. D., M. Gallet, N. E. Holden, and I. L. Barnes. 1984. Isotopic Abundances and Atomic Weights of the Elements. Journal of Physical Chemistry Reference Data13(3):809–891.

Brown, R. W.1993. Untitled presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Collins, E. D.1993. Capabilities for Isotope Enrichment at Oak Ridge National Laboratory—Calutrons, Plasma Separation Process, Gas Centrifuges. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Elmore, D., M. H. Bhattacharyya, N. Sacco-Gibson, D. P. Peterson. 1990. Calcium-41 as a Long Term Biological Tracer for Bone Absorption. Nuclear Instrumentation Methods in Physics Research. B52:531–535.

Eppley, R. E., 1993. EG&G Mound Applied Technologies: Chemical Exchange and Thermal Diffusion Processes. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

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http://www.nap.edu/catalog/4818.html

Felton, J. S., K. W. Turteltaub, J. S. Vogel, R. Balhorn, B. L. Glendhill, J. R. Southan, M. W. Daffee, R. C. Finkel, D. E. Nelson, I. D. Proctor, J. C. Davis. 1990. Accelerator Mass Spectrometry in the Biomedical Sciences: Applications in Low Exposure and Environmental Dosimetry. Nuclear Instrumentation Methods in Physics Research. B52:517–523.

Friedlander, G. and H. N. Wagner. 1982. Separated Isotopes: Vital Tools for Science and Medicine. Washington, D.C.: National Academy Press.

Krishnan, K.1993. The Vacuum Arc Centrifuge. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C.November 19, 1993.

National Research Council. 1989. Diet and Health: Implications for Reducing Chronic Disease Risk. Committee on Diet and Health, Food and Nutrition Board . Washington, D.C.: National Academy Press.

Schoenheimer R. S. and E. J. Rittenberg. 1935. Deuterium as an Indicator of Intermediary Metabolism. II. Methods. Journal of Biological Chemistry111:163–192.

Schwager, L. A.1993. The Solitron. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Seidel, C.1993. Untitled presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Stern, R. C.1993. Atomic Vapor Laser Isotope Separation. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Stevenson, C. D., T. D. Halvorsen, D. E. Kage, R. C. Reiter, and D. J. McElheny. 1993. Free Energies of Electron Transfer from Ketyls to Isotopically Substituted Ketones. Journal of Organic Chemistry58(17):4634–4638.

U.S. General Accounting Office. 1992. DOE's Self-Supporting Isotope Program Is Experiencing Problems. GAO/RCED-92-122FS. Washington, D.C.

Whitehead, R. G., and A. Prentice, eds. 1991. New Techniques in Nutrition Research. San Diego, Calif.: Academic Press.

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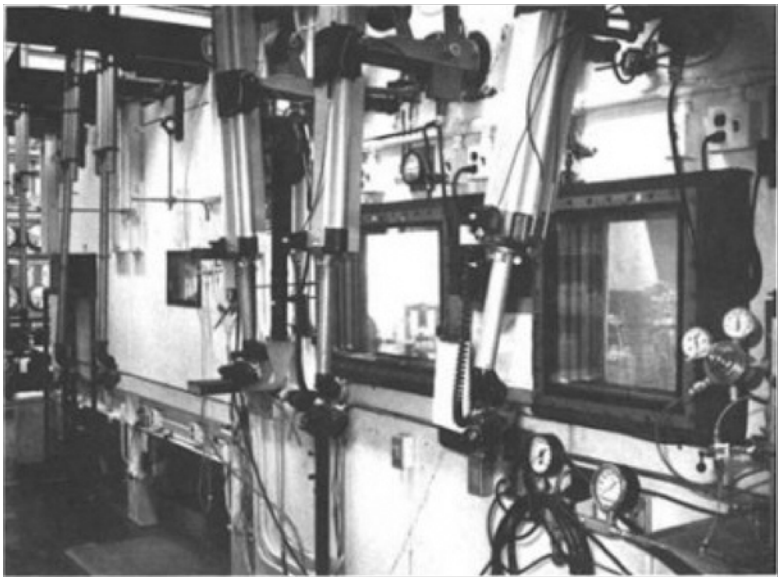

A view of the typical high-radiation-level hot cells at BrookhavenNational Laboratory.These hot cells are utilized for the remote handling and processingof large quantitiesof radioactive isotopes produced at the Brookhaven Linac IsotopeProducer or theHigh-Flux Beam Reactor at Brookhaven National Laboratory.SOURCE: Brookhaven National Laboratory.

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3

Reactor-Produced Radionuclides

HISTORICAL PERSPECTIVE

More than 50 years after the discovery of nuclear fission by Otto Hahn and Fritz Strassmann in 1938 and more than 50 years after the demonstration of a self-sustaining nuclear chain reaction by Fermi and coworkers in 1942, the use of reactor products permeates nearly every field of science. The book by Kamen (1957) documents this progress. A more complete treatment is provided by Stannard (1988). Historically, isotopes were provided to researchers by the Atomic Energy Commission and the Energy Research and Development Agency and are now provided by the U.S. Department of Energy (DOE). Oak Ridge National Laboratory (ORNL) played a pioneering role in the development of the first full-scale operating reactor prototype and the initial production of radioisotopes for applications in medical and biological research (Mirzadeh et al., 1992). Although the tracer principle was established by de Hevesy in the early 1900s (de Hevesy, 1913), the widespread uses of radioactivity began with the production of radionuclides at the reactor at ORNL. Sodium-24 was one of the first radionuclides used to measure the permeability of canine red blood cells in vivo. Although carbon-11-labeled compounds were created shortly after the development of the cyclotron by bombarding boron-10 with deuterons, the boron-10(d,n) reaction, the production of longer-lived carbon-14 by the nitrogen-14(n,p) reaction in the nuclear reactor at ORNL was instrumental in establishing its widespread use throughout the field of biology. The tracer approach was also quickly applied to clinical situations. Among the important "firsts" were the determination of the speed of peripheral circulation using radium by Blumgart and Yens (1927) and the study of thyroid metabolism using radioactive iodine by Hamilton nd Soley (1939). Uptake, retention, and excretion of radiolabeled phosphorus (phospho

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rus-32) and radiolabeled iodine (iodine-131) provided valuable information about the selectivity of proposed therapeutic regimens. Radioisotopes of iron and chromium were also valuable in applications in hematology. Red blood cell survival, iron physiology, and blood volume were some of the important contributions. In the early 1940s, phosphorus-32 and then sulfur-35 and iodine-131, were used to label antigens and antibodies. In the process of studying the behavior of iodine-131-labeled insulin, Berson and Yalow (1959) developed the sensitive assay system for blood components known as radioimmunoassay, the importance of which was recognized with a Nobel Prize in 1977.

This body of work laid the groundwork for modern biomedical and clinical research, in particular with reference to the tracer principle, which became an invaluable tool (Bizzell, 1966; Mirzadeh et al., 1992). The use of radioisotopes is unique in that it provides a method for measuring biochemical processes in vivo, especially in cases in which the process is easily saturated, since radiation makes it possible to detect and localize quantities as small as only a few thousand radiolabeled molecules. The development of generator technology in the 1960s marked another advance in nuclear medicine research and in clinical nuclear medicine. The Brookhaven National Laboratory (BNL) used fission-product molybdenum-99 to produce the first molybdenum-99/technetium-99m (^{99}Mo/^{99m}Tc) generator, revolutionizing the field of nuclear medicine (Tucker et al., 1958). ^{99m}Tc, the isotope used in more than 80 percent of the diagnostic nuclear imaging studies performed today, is the short-lived "daughter" resulting from the decay of ^{99}Mo. Simple devices now enable hospitals to extract ^{99m}Tc from the ^{99}Mo/^{99m}Tc generators as needed, and instant kits provide prepackaged chemicals to simplify its incorporation into organic molecules.

Other reactor-produced radioisotopes continue to play a major role in research, and recent advances in many fields (such as molecular biology, including the Human Genome Project) could not have been accomplished without the use of ^{32}P. In addition, many of the isotopes useful for therapeutic applications, such as strontium-89 for the palliation of metastatic bone pain, are produced in reactors. Two other reactor-produced radioisotopes, samarium-153 and rhenium-186, may also be of use in the treatment of bone cancer and are currently under clinical study. There is therefore a need to maintain a continuous supply of these isotopes both for the benefit of patients and to provide investigators with the tools needed to develop and improve such technologies.

CURRENT APPLICATIONS IN MEDICINE AND PHYSICAL AND LIFE SCIENCES

The peaceful use of radioisotopes has made great progress since 1911, when George de Hevesy demonstrated that various substances could be radiolabeled and subsequently "traced" by spiking his meals with some naturally occurring radioactivity to prove that his landlady was using leftovers instead of fresh food

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(Carmain, 1993). In addition to their use in the clinical practice of nuclear medicine and radiology and in the research conducted in those medical fields, radioisotopes have found applications in a wide variety of scientific fields such as nutrition, genetics, molecular biology, pharmacology, drug development, nuclear physics, environmental chemistry, geology, and industrial manufacturing.

Table 3-1 shows the extraordinarily widespread uses and applications of reactor-produced radioisotopes in the biomedical field.

The most important clinical radionuclide currently is ^{99m}Tc. Disintegration of this short-lived radionuclide product, which is itself the product of the decay of ^{99m}Mo, results in the emission of photons with sufficient energy to be passed through considerable amounts of tissue and to be detected by a sensitive camera. To the extent that the ^{99m}Tc can be confined to a specific organ or tissue (a tumor, for example), these photons produce an image of that organ or tissue. Much radiopharmaceutical research focuses on ways of concentrating ^{99m}Tc (and other radionuclides) in biological targets of interests, generally by tying it to a substance or molecule that is differentially taken up by that tissue. The 6-hour half-life of ^{99m}Tc minimizes the amount of radiation to which the patient is exposed, but puts a premium on scheduling and rapid action once the radiopharmaceutical is produced. The ^{99m}Mo/^{99m}Tc generator discussed above has vastly simplified this process by allowing hospitals to prepare their own radiopharmaceuticals on-site and when needed. Developed at Brookhaven National Laboratory in the early 1950s as part of the program to separate fission products, the ^{99}/^{99m}Tc generator has now become the major source of radionuclides for nuclear medicine (Table 3-2). Other reactor-produced diagnostic radionuclides in common use are iodine-125, iodine-131, and xenon-133.

A potentially very large growth area involves therapeutic radionuclides. Perhaps as many as one-half to three-quarters of all cancer patients receive radiation at some point in their treatment. Cobalt-60 has been a very common source of gamma rays for external-beam treatment, with cesium-137 occasionally substituted for head and neck irradiation. Brachytherapy is often used for very well localized cancers. This originally involved implanting encapsulated "seeds" of radium or radon in or near the tumor, but now iodine-125, iridium-192, or gold-198 used more frequently. A third method has been the object of increasing research; it employs isotopes that naturally accumulate in a specific tissue or that can be attached to a molecule with such specificity. Iodine-131, one of the first isotopes produced with nuclear reactors, has been used for several decades to diagnose and treat thyroid diseases because of its affinity for thyroid tissue. Efforts to expand the therapeutic approach beyond the thyroid have primarily focused on reactor-produced isotopes, although an appreciable number are also produced in accelerators. The major categories of promising therapeutic applications are as follows:

1. Bone agents to reduce bone pain (strontium-89, rhenium-186, rhenium-188, samarium-153, and tin-117).

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TABLE 3-1 Selected Reactor-Produced Radionuclides with Biomedical Applications

Radionuclides	Uses
Arsenic-77	• In cancer therapy
Bromine-82	• In metabolic studies and studies of estrogen receptor content
Calcium-47	• In studies of cell function and bone formation of mammals and to produce Scandium-47
Californium-252	• In brachytherapy for treatment of cervical cancer and potentially for treatment of gliomas
Carbon-14	• For medical research to trace metabolism of new drugs and other organic carbon-containing molecules
Cerium-141	• For research and development on lung densities
Cesium-137	• To treat cancer; to measure correct patient dosages of radiopharmaceuticals
Chromium-51	• To assess red blood cell survival studies
Cobalt-58	• To diagnose pernicious anemia
Cobalt-60	• To treat cancer and sterilize surgical instruments
Copper-64	• As a clinical diagnostic agent for cancer and metabolic disorders
Copper-67	• In cancer therapy and to label antibodies for cancer therapy
Dysprosium-165	• To treat rheumatoid arthritis
Dysprosium-166	• Decays to holmium-166 which is used in cancer therapy
Einsteinium-253	• To radiolabel antibodies for cancer therapy
Erbium-169	• To treat rheumatoid arthritis
Fermium-255	• To radiolabel antibodies for cancer therapy
Gadolinium-159	• In cancer therapy
Gold-199	• In cancer therapy and to treat rheumatoid arthritis
Holmium-166	• In cancer therapy and to treat rheumatoid arthritis
Iodine-125	• As a potential cancer therapeutic agent and for basic biomedical research
Iodine-129	• To check radioactivity counters in in vitro diagnostic testing
Iodine-131	• To diagnose and treat thyroid disorders including cancer and for basic biomedical research
Iridium-191	• To assess cardiac function especially in the pediatric population
Iridium-192	• In cancer therapy
Lutetium-177m	• In cancer therapy and to label antibodies for cancer therapy
Molybdenum-99	• To produce technetium-99m, the most commonly used radioisotope in clinical nuclear medicine
Osmium-191	• Decays to iridium-191m, which is used for cardiac studies
Osmium-194	• Decays to iridium-194, which is used in cancer therapy
Palladium-103	• In the treatment of prostate cancer
Phosphorus-32	• In cancer treatment, cell metabolism and kinetics, molecular biology, genetics research, biochemistry, microbiology, enzymology, and as a starter to make many basic chemicals and research products
Phosphorus-33	• In cancer treatment, molecular biology and genetic research, and biochemical and enzymological studies
Platinum-195m	• In pharmacokinetic studies of antitumor agents

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Radionuclides	Uses
Rhenium-186	• As a bone cancer therapeutic agent and to radiolabel various molecules as cancer therapeutic agents; also used to treat rheumatoid arthritis
Rhenium-188	• For treatment of medullary thyroid carcinoma and alleviation of pain in bone metastases
Samarium-145	• For treatment of ocular cancer
Samarium-153	• To radiolabel various molecules as cancer therapeutic agents and to alleviate bone cancer pain
Scandium-47	• In the therapy of cancer
Selenium-75	• In protein studies in life science research
Silver-111	• In cancer therapy
Strontium-85	• To study bone formation and metabolism
Strontium-89	• To alleviate metastatic bone pain
Strontium-90	• Decays to yttrium-90, which is used in cancer therapy
Sulfur-35	• In studies of cell metabolism and kinetics, molecular biology, genetics research, biochemistry, microbiology, enzymology, and as a starter to make many basic chemicals and research products
Technetium-99m	• The most widely used radiopharmaceutical in nuclear medicine imaging
Tellurium-123m	• For research and development on lung densities and calibrating; also used in cardiology
Tin-117m	• For palliative treatment of bone cancer pain
Tritium (hydrogen-3)	• To make tritiated water, which is used as a starter for thousands of different research products and basic chemicals, and for life science and drug metabolism studies to ensure the safety of potential new drugs
Tungsten-188	• Decays to rhenium-188 for treatment of cancer and rheumatoid arthritis
Xenon-133	• In nuclear medicine for lung ventilation and perfusion studies
Yttrium-90	• To radiolabel various molecules as cancer therapeutic agents

SOURCES: Carmain, 1993; personal communication from T. Rosseel, Oak Ridge National Laboratory, February 11, 1994.

2. Halogen-labeled estrogens for hormone-dependent cancers (bromine-82 and iodine-131).
3. Halogen-labeled nucleosides for cancer treatment (iodine-125, iodine-131).
4. Colloids for synovectomy (dysprosium-165, holmium-166, yttrium-90, and palladium-109).
5. Monoclonal antibodies and tissue-specific peptides for cancer treatment (iodine-125, iodine-131, yttrium-90, copper-64).

An example of drug development from the first of these categories is that of strontium-89 chloride (recently approved by the U.S. Food and Drug Administra

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TABLE 3-2 Technetium-Based Radiopharmaceuticals

Generic Name	Product Name	Use	Manufacturer
Technetium generator	Ultra-TechneKow FM	Supply of ^{99m}Tc	Mallinckrodt
	Technetium generator	Supply of ^{99m}Tc	Medi-Physics
	TechneLite	Supply of ^{99m}Tc	DuPont-Merck
Aggregated albumin	Macrotec	Lung imaging	Squibb
	TechneScan MAA	Lung imaging	Mallinckrodt
	Pulmolite	Lung imaging	DuPont-Merck
	Aggregated albumin	Lung imaging	CIS-US
	MPI MAA	Lung imaging	Merck Sharp & Dohme
Albumin colloid	Microlite	Imaging of RE system	Dupont-Merck
Serum albumin	HSA Kit	Blood pool imaging	Medi-Physics
Disofenin	Hepatolite	Hepatobiliary imaging	Dupont-Merck
Exametazime	Ceretec	Cerebral perfusion	Amersham
Lidofenin	TechneScan HIDA	Hepatobiliary imaging	Merck Sharp & Dohme
Mebrofenin	Choletec	Hepatobiliary imaging	Squibb
Medronate	Osteolite	Bone imaging	DuPont-Merck
	AN-MDP	Bone imaging	CIS-US
	TechneScan MDP	Bone imaging	Merck Sharp & Dohme
	MDP-Squibb	Bone imaging	Squibb
	Medronate	Bone imaging	Medi-Physics
	TechneScan MDP	Bone imaging	CIS-US
Mertiatide	TechneScan MAG3	Renal imaging	Mallinckrodt
Oxidronate	OsteoSan HDP	Bone imaging	Mallinckrodt
Penetate sodium	DTPA	Kidney and brain imaging	Medi-Physics
	AN-DTPA	Kidney and brain imaging	CIS-US
	Techneplex	Kidney and brain imaging	CIS-US
Pyro- and tri-metaphosphates	TechneScan PYP	Bone imaging	Mallinckrodt
	Phosphotec	Bone imaging	Squibb
	Pyrolite	Bone imaging	DuPont-Merck
	AN-Pyrotec	Bone imaging	CIS-US
Red blood cell kit	Ultratag RBC	Blood pool imaging	Mallinckrodt
	RB-SCAN	Blood pool imaging	Cadema
Sestamibi	Cardiolite	Myocardial imaging	DuPont-Merck
Gluceptate	Glucoscan	Kidney and brain imaging	DuPont-Merck
	TechneScan Gluceptate	Kidney and brain imaging	Merck Sharp & Dohme
Succimer	DMSA	Renal studies	Medi-Physics
Sulfur colloid	Sulfur Colloid	Gastrointestinal and organ studies	Medi-Physics
	Tesuloid	Gastrointestinal and organ studies	Squibb
	AN-Sulfur Colloid	Gastrointestinal and organ studies	CIS-US
Teboroxime	CardioTec	Myocardial imaging	Squibb

SOURCE: R. Brown, Mallinckrodt, Inc., personal communication, April 6, 1994.

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tion) for the palliation of bone pain in patients with metastatic bone cancer. Strontium, rhenium, and tin are all preferentially taken up by bone, most readily at sites of active osteogenesis. Primary bone tumors and areas of metastatic involvement can thus accumulate significantly greater concentrations of radioactive strontium (or rhenium or tin) than surrounding normal bone. In addition, strontium-89 is retained in metastatic bone lesions much longer than it is in normal bone. At present, strontium-89 chloride is approved for use only as an adjunct to external-beam radiotherapy, but in such cases a single injection of strontium-89 has been shown to provide significant pain relief for 6 months (Lewington et al., 1991).

Radiohalogen-labeled estrogens are being tested for their ability to selectively deliver radiation to tumor sites in the breast and female reproductive organs (DeSombre et al., 1992; McLaughlin et al., 1989). Scientists at Mallinckrodt Medical Inc., have attached samarium-153 and holmium-166 to hydroxyapatite particles as potential synovectomy agents for the treatment of rheumatoid arthritis (University of Missouri Research Reactor Center, 1994). Radiohalogen-labeled pyrimidine nucleosides have the potential to deliver short-range (Auger) electrons to restricted sites in tumors (Adelstein,1993).

At a meeting on isotope availability at the Los Alamos National Laboratory, Zalutsky (1992) pointed out that the developments in biotechnology have enhanced the possibility of radioimmunotherapy, that is, raising monoclonal antibodies against specific cell surface antigens on a variety of human cell types, especially tumor cells, and using them to deliver radionuclides to those cells and only those cells. A variation on this strategy involves the use of antibody fragments and even smaller "molecular recognition units" like somatostatin and endothelin. Antibody and peptide carriers that can be used to detect and treat cancer are being developed (Hinkle, 1993; Serafini, 1993, Sugarbaker, 1993). Two are currently available for diagnostic purposes, and commercial companies are examining the use of dozens of new proprietary peptides as antitumor agents (Brice, 1994).

Because nuclides that emit radiation with different relative levels of biological effectiveness and ranges of action are available, an advantage of radioimmunotheraphy is the potential for choosing a radionuclide with physical characteristics that are compatible with a particular tumor type. Reviews discussing the potential utility of a variety of nuclides for antibody-mediated radiotherapy have been provided by Jungermann et al. (1984), Humm (1986), Cobb and Humm (1986), and Zalutsky (1992), but the majority of clinical radioimmunotherapeutic trials to date have used iodine-131 as the radionuclide. Although iodine-131 will probably be an adequate label for some therapeutic applications (particularly if improved labeling methods are used), in many circumstances, other nuclides might offer significant advantages (e.g., yttrium-90). Factors for consideration in selecting a nuclide for therapy include tumor size, proximity of the tumor to radiation-sensitive normal tissue, and the radiosensitivity of the tumor itself. The

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ideal nuclide for treating a 0.5- to 1.0-kg advanced-stage liver tumor is likely to be different from the one selected to treat micrometastases of only a few hundred cells. In addition, the degree of heterogeneity in tumor dose deposition that results from regional variations in tumor blood flow, permeability, and antigen expression will dictate the relative efficacy of using radiation. Much work remains to be done in developing radioimmunotherapeutic strategies, and this type of therapy will probably be most useful, at least initially, as an adjunct to less specific forms of treatment such as surgery, chemotherapy, and external-beam radiotherapy. Numerous observers nevertheless see this approach as the door to a whole new era of nuclear medicine (Brice, 1994; Fischman et al., 1993; Schenter, 1993).

SUPPLIES AND SUPPLIERS

Molybdenum-99

Current Sources

In recent years there has been considerable concern about the availability of ^{99}Mo in the United States (e.g., Holmes, 1993; Moody and Peterson, 1992). The sole North American source of this important biomedical isotope is at present a single reactor in Canada. Because ^{99m}Tc from the ^{99}Mo/^{99m}Tc generator is used in more than 80 percent of nuclear medicine procedures, a guarantee of the continuous availability of ^{99}Mo, which has a 66-hour half-life, is essential. A brief strike at the Canadian processing and shipping plant in 1991 focused attention on the potential problems of a single source of ^{99}Mo, but recently the ^{99}Mo supply situation has stabilized and is slowly becoming broader based.

The dominant worldwide supplier of ^{99}Mo is Nordion International Inc. of Canada, which purchases this radioisotope mainly from a single government reactor (the NRU reactor) at Chalk River, 2 hours away from Nordion's processing facilities in Kanata, Ontario, Canada. A second reactor for ^{99}Mo production by Nordion, the Maple-X reactors, was under construction but is currently on hold pending resolution of a dispute over costs with the Canadian Atomic Energy of Canada Ltd. (AECL), a Crown (Canadian government) Corporation that operates all research reactors in Canada. Nordion International, Inc. was formed more than 20 years ago as the Radiochemical Company, a division of AECL. As the Radiochemical Company, it processed and sold reactor isotopes produced by the Research Company of the AECL. In 1991, MDS Health Group Ltd., a private company and Canada's largest diversified health care company, bought the Radiochemical Company for $165 million and renamed it Nordion International, Inc., upon privatization. According to MDS and Nordion, the key to their purchase was a 23-year guaranteed supply contract with AECL, which was then making isotopes with two reactors, the NRU and NRX reactors, and was about to

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begin construction of a third, the Maple-X reactor, whose primary purpose would be isotope production. The NRU reactor was down for repairs for nearly all of 1991, but Nordion was able to meet customer demand from the NRX reactor. The NRX reactor itself was shut down for repairs in January 1992, and in March 1993 the AECL announced that it would not reopen, leaving Nordion without a backup reactor until completion of the Maple-X reactor. In November 1993 AECL announced that despite the $40 million that it had sunk into costs for design, licensing, and a building, projected costs for the Maple-X reactor had grown too high to allow completion. Apparently, neither AECL nor MDS anticipated that the $165 million paid by the latter for Nordion would not go to AECL, but instead would simply disappear into the federal government's consolidated revenue fund.

MDS has filed a lawsuit claiming breach of contract and has asked the court to order AECL to complete construction or pay MDS $300 million in compensation. In a separate action, Nordion and AECL have entered into a prearranged arbitration process as set out in a 1988 agreement. At issue in that process is AECL claim that unforeseen events had forced the closure of the NRX reactor and raised production costs to the extent that AECL is entitled to renegotiate the supply contract.

Arbitration hearings were to begin sometime in the Spring of 1994, but they have been delayed until completion of a report on possible solutions commissioned by the Canadian government's Office of Energy. In any event, Nordion began searching for alternate backup arrangements a year earlier when it became clear that the NRX reactor would not be reactivated. After unsuccessful negotiations with a number of North American reactors, Nordion has struck an agreement with the Institute National des Radioéléments (IRE) in Fleurus, Belgium. IRE can use any of four European reactors for the irradiation of targets: BR-2 in Belgium, SILOE and OSIRIS in France, and HFR in Petten, The Netherlands. All processing takes place at Fleurus, the site of Nordion's European operations. IRE was expected to be capable of producing 50 percent of the world's ^{99}Mo requirements by mid-1994. Table 3-3provides information about a number of other reactors around the world capable of producing substantial amounts of ^{99}Mo. In most cases a decision to produce ^{99}Mo for sale would require considerable time and money for processing and distribution arrangements. Staff at one of these sites, the University of Missouri Research Reactor (MURR), informed the committee of a much simpler plan that would maintain a supply of ^{99}Mo in case of difficulties with the Chalk River reactor. When Nordion was just beginning its search for backup capabilities, MURR proposed that unprocessed sections of spent reactor fuel be shipped to Nordion for extraction of ^{99}Mo. Such sections would contain several thousand curies of ^{99}Mo, just like the fuel elements normally extracted from the AECL NRU reactor. Details of the cost and feasibility of the plan have not been worked out, but it seems reasonable to investigate whether this can be a cost-effective near-term solution to concerns about reliance on a single reactor for ^{99}Mo.

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TABLE 3-3 Reactors with Significant Isotope Production Capability

Country	Location	Reactor	Power (MW)	Isotopes Currently Produced
United States	Hanford, Washington	FFTF	400	None; reactor in standby mode
	Idaho	ATR	250	^{60}Co, ^{63}Ni, ^{192}Ir, ^{153}Gd
	Oak Ridge National Laboratory	HFIR	100	^{252}Cf and other transuranics, ^{85}Kr, ^{64}Cu, ^{67}Cu, ^{117m}Sn, ^{195m}Pt, others
	Brookhaven National Laboratory	HFBR	60	^{47}Sc, ^{55}Fe, $^{64/67}$Cu, ^{119}Sn, ^{153}Sm, ^{186}Re, $^{198/199}$Au, others
	University of Missouri	MURR	10	^{32}P, ^{192}Ir, ^{35}S, ^{198}Au, ^{186}Re, ^{51}Cr, ^{103}Pd, many others
	Los Alamos National Laboratory	OWR	8	None; possible production of ^{99}Mo
	Georgia Tech	GTRR	5	^{90}Y, ^{24}Na, ^{18}F, ^{140}La
	Massachusetts Institute of Technology	MITR-II	5	^{165}Dy, ^{166}Ho, ^{198}Au
	New Mexico	Sandia	2	None; possible production of ^{99}Mo
	Oregon State	OSTR	1	Variety
Belgium	Mol	BR-2	100	^{99}Mo, ^{133}Xe, ^{131}I, ^{192}Ir, others
Sweden	Nykoping	Studsvik	50	^{32}P, ^{60}Co, ^{192}Ir, ^{89}Sr, ^{90}Y, others; principal supplier for Amersham
The Netherlands	Petten	HFR	45	^{99}Mo, ^{133}Xe, ^{131}I, ^{192}Ir, others
Canada	Chalk River	NRU	40	^{99}Mo, ^{60}Co, ^{14}C, ^{32}P, ^{89}Sr, ^{90}Y, ^{125}I, ^{131}I, ^{137}Cs, ^{133}Xe, ^{192}Ir
France	Saclay	OSIRIS	70	^{99}Mo, ^{133}Xe, ^{131}I, ^{192}Ir, others
	Grenoble	SILOE	35	^{99}Mo, ^{133}Xe, ^{131}I, ^{192}Ir, others
Poland	Warsaw	Maria	30	Possible fission products

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Country	Location	Reactor	Power (MW)	Isotopes Currently Produced
Australia	Sydney	HIFAR	10	^{99}Mo, ^{64}Cu, ^{67}Cu, ^{153}Sm, ^{166}Dy, ^{186}Re, ^{188}Re, ^{198}Au
Russia	Chelyabinsk	Mayak	Unknown	^{137}Cs, ^{60}Co, ^{14}C, ^{3}H, ^{88}Kr
	Obninsk	IPPE	Unknown	$^{131/132/133}I$, $^{32/33}P$, ^{133}Xe, ^{99}Mo, ^{140}Ba, ^{95}Zr, ^{95}Nb, ^{137}Cs, ^{147}Pm
	Dimitrovgrad	SM3	Unknown	^{33}P, ^{60}Co, ^{192}Ir, ^{153}Gd, ^{252}Cf
	Unknown	SM2	100	^{192}Ir, ^{60}Co
	Moscow	Unknown	Unknown	$^{99}Mo/^{99m}Tc$, ^{98}Mo
South Africa	Pelindaba	Safari	20	^{99}Mo

Future Sources

One of Nordion's biggest customers, Mallinckrodt Medical Inc., has recently secured its own backup supply of ^{99}Mo by building additional facilities at the reactor site at Petten, The Netherlands, Mallinckrodt's current plan is to produce enough ^{99}Mo to meet its own needs in both Europe and North America but not to go into competition with Nordion for the world market. Their action will substantially reduce that market nevertheless.

DOE, partly in response to the concerns expressed by the U.S. nuclear medicine community, is seriously considering resuming the production of ^{99}Mo using one of two small reactors until recently devoted to defense missions. The Atomic Energy Commission produced ^{99}Mo at the Brookhaven and Oak Ridge National Laboratories until mid-1966, when it stopped production in deference to U.S. commercial production and sales by Union Carbide in Tuxedo, NY, and later, at the General Electric Test Reactor in Pleasanton, Calif. The latter closed in 1977, and Union Carbide's successor, Cintichem, shut down the Tuxedo reactor in 1990. The Isotope Production and Distribution Program (IPDP), with the aid of some quarter of a million dollars from the radiopharmaceutical industry, immediately began a feasibility study that ultimately pointed to the underutilized Omega West reactor at Los Alamos National Laboratory as a potentially viable source of ^{99}Mo and other reactor isotopes (Public Law 101-101, the Energy and Water Development Appropriations Act of 1990, required isotope production and distribution to be self-supporting as of fiscal year 1990). DOE bought the relevant technology from Cintichem and invested $3.5 million dollars for process devel

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opment at Los Alamos National Laboratory, only to have the reactor shut down by a leaking coolant pipe. In addition, the current reactor operator, DOE's Defense Programs division announced plans to halt all use of the reactor, leaving IPDP with all operating costs. In the interim, the major buyers have signed long-term contracts with Nordion or other suppliers, reducing prospects for substantial DOE sales. Additional defects have been discovered since the reactor shut down, the repair of which could cost more than $10 million. Largely because of these recent events, the small (2-megawatt [MW] annular core research reactor at Sandia National Laboratory has been receiving serious consideration as a producer of ^{99}Mo. Start-up costs and perhaps operating costs would be lower, although production capacity would likely be reduced as well.

Although the long-term supply of ^{99}Mo will probably depend in large measure on the outcome of the Maple-X reactor dispute, the committee is convinced that the short-term situation is no longer precarious. Furthermore, the committee is not convinced that DOE can penetrate the market sufficiently at this point to make ^{99}Mo a significant source of net revenue. The committee therefore recommends against government support of a dedicated domestic reactor for ^{99}Mo production.

The Advanced Neutron Source (ANS), a new 330-megawatt (MW) research reactor currently proposed for construction at Oak Ridge National Laboratory, is a potential source for the cost-effective production of ^{99}Mo sometime after 2003. The primary research, education, and training missions of this $2 billion to $3 billion reactor center do not include isotope production at the moment, but focus on condensed-matter research and materials analysis. Its very high rate of neutron production will allow for the high-quantity, high-quality production of any radioisotopes that can be produced by a reactor, and DOE has identified it as a potential future source of isotopes, "to the extent permitted by its primary mission" (White, 1993). Commercial production of ^{99}Mo or any other short-lived isotope is a major commitment, however, and it is the perception of many of DOE's present isotope customers that IPDP's second-class status at the present facilities is a major hurdle to efficient operation of both IPDP and its customers. If ANS is to be the nation's primary source of reactor isotopes, DOE must ensure the availability of appropriate ports and retrieval vehicles in the design of this reactor and equitable treatment of isotope customers in the plans for its administration. A recent report by Mirzadeh et al. (1944) on the projected capabilities of ANS is very encouraging. It makes it very clear that as the the successor to the High Flux Isotope Reactor, ANS is envisioned as a powerful resource for the production of radioisotopes for a wide variety of scientific and industrial applications.

Research and Development on Alternative Sources

Unlike many reactor-produced radionuclides, which are created by the capture of neutrons from the reactor core by a target nucleus, ^{99}Mo is a fission product, one of the pieces into which highly enriched uranium-235 breaks when it is bom

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barded by the reactor's neutrons. The yield of ^{99}Mo is less than 10 percent, with the remainder largely being long-lived radioactive waste. Public concern over radioactive waste provides significant economic and political incentives for the development of alternate methods for the production of this isotope.

The committee was informed of concepts developed by two different groups in the United States for accelerator-based methods for the production of ^{99}Mo. In one of these, the "Molytron" concept (Schmidt, 1993), the primary beam is high energy protons (60 to 150 million electron volts [MeV], whereas the other, advocated by Morgan (1993) of the North Texas Research Institute, proposes using neutrons generated via accelerator-based methods at low energy.

A different approach is being attempted by researchers at the University of Missouri who have used patented gel technology to develop a ^{99}Mo/ ^{99m}Tc generator that produces low-specific-activity ^{99}Mo by neutron activation of 98 instead of the high-specific-activity ^{99}Mo fission product (University of Missouri Research Reactor Center, 1994).

These technologies are far from proven at this point and are competing with a very successful and strongly established commercial operation. The committee recommends that DOE *not* solicit or evaluate proposals for the development of such methods, but rather leave that work to the private sector.

Other Commercial Radionuclides

Table 3-4 shows the estimated 1992 revenues to reactor operators or their packaging and distributing partners from their best selling products. As mentioned above, there are no real leaders beyond ^{99}Mo and cobalt-60, which is used for external-beam radiation therapy. Unlisted but close behind the other isotopes in table 3-4 would be strontium-89 (which could jump up the list now that it has received approval from the U.S. Food and Drug Administration as an analgesic for bone cancer). Nordion, because its focus is on high -volume, high-revenue isotopes, dominates the market for these radionuclides as well. As in the case of ^{99}Mo, DOE reactors were once prime sources of these isotopes, but DOE with drew from production in deference to domestic commercial suppliers who have since gone out of business. At present DOE controls a large share of the market only for californium-252, iridium-192, and tritium (hydrogen-3). All three of these are long-lived and are or will likely be targets of serious competition from Russia and other former Soviet republics. If short-lived reactor-produced radionuclides become important for cancer therapy, however, and Canada's Maple-X reactor is not completed, the number and condition of North American reactors will be inadequate unless the ANS serves as a major producer.

Research Radionuclides

A comparison of Tables 3-1 and 3-4 makes it obvious that however ably Nordion is serving the needs of commercial radioisotope users, medical and

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industrial, it is clearly not the driving force in the exploration of new and better uses of radionuclides. In the United States, DOE's national laboratories and DOE-fueled university reactors play a critical role in providing reactor-produced radioisotopes for medical research as well as clinical use, including a number of unique isotopes for medical uses. They produce not only low-demand radioactive and enriched stable isotope products but also a number of associated services to domestic and international customers for medical, research, and industrial applications. However, isotope programs have always depended on the "parasitic" use of reactors, whose primary use was not related to isotope production, and the declining budgets have severely affected the operating times of these reactors, resulting in a curtailed supply of isotopes. Furthermore, the revolving fund provided by the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101) along with the mandate to become financially self-sufficient through sales is already deeply in the red, despite the fact that costs of reactor isotopes have increased beyond the reach of many researchers. This has led to a severe reduction in the development of new radiopharmaceuticals at the very time when research is moving at a rapid pace in complementary areas like molecular biology and cancer diagnosis and treatment (Holmes, 1993).

TABLE 3-4 Leading Commercial Reactor-Produced Radioisotopes

Isotope	Half-Life	Estimated 1992 Wholesale Demand (thousands of $)
Molybendum-99	66 h	25,000–33,000
Cobalt-60	5.3 yr	33,000–44,000
Iridium-192	74 days	4,000–5,000
Carbon-14	5,730 yr	2,600–3,000
Xenon-133	5.2 days	2,100—2,600
Hydrogen 3 (tritium)	12 yr	1,600–2,400
Iodine-131	8.0 days	1,600–2,000
Californium-252	2.6 yr	1,500–2,400
Cesium-137	29 yr	1,500—2,000
Iodine-125	60 days	1,200–1,400
Phosphorus-32	14 days	600–1,000
Sulfur-35	87 days	350–500
Yttrium-90	64 h	250–300

SOURCES: Arthur Andersen & Co. (1993), except for phosphorus-32 and sulfur-35 (A. Ketring, University of Missouri, personal communication, May 17, 1994) and carbon-14 (C. Marchetti, DuPont-NEN, personal communication, May 18, 1994).

Although there are a number of large research reactors at universities in the United States, the primary U.S. source of research radionuclides is MURR. In 1993, 56 of 157 MURR publications were on biomedical or life science projects (University of Missouri Research Reactor Center, 1994). Only MURR is cur

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rently producing a substantial number of radionuclides for use in research in radiopharmaceuticals. Isotopes, irradiation, and related services are supplied to approximately 300 clients in 45 industries, 7 state and federal laboratories, and 31 other universities. The shipments of radionuclides over the past year from MURR as well as the medical and nonmedical applications of these isotopes are listed in Table 3-5. Clients are typically charged only the incremental costs for production of the radioisotopes, with the major proportion of the center's $8 million annual operating costs coming from the state of Missouri, research grants, and non-radioisotope-related services (e.g., topaz irradiation to provide its characteristic color). Income from the last of these sources, much like that from DOE sales of enriched stable isotopes, has recently become threatened by the predatory pricing policy of Russian reactor facilities.

Since 1970, DOE's Office of Energy Research has provided the fuel required to operate some 37 (originally 76) university research and training reactors and, since 1987, has been supporting the conversion of designated university reactors from using highly enriched uranium fuel to using low-enrichment uranium fuel (as part of international nuclear weapons nonproliferation activity). However, DOE has not provided support for the operational costs and facility renovation at university reactors in the past (Riggs, 1993), and recent DOE budget constraints do not allow DOE to provide this support.

It is instructive to review the support of reactors in Western Europe. The National Research Council report (1988) on university research reactors indicated that base support in Western Europe for the operation of individual programs is higher than that in the United States. The base support for two major university research reactor-type reactors (Berlin and Munich in Germany) was $2.5 million each in 1985. Federal support for university reactors in the United States, that is, providing fuel, came to only about $2 million for all 40 university research reactors active in 1987. In addition, significant funding for major upgrades and new equipment has been available to the European reactor centers ($50 million for renovations in Berlin and more than $100 million for a new reactor in Munich).

The National Research Council report (1988) went on to recommend that $20 million be made available annually, for at least 3 years, to support university research reactors for facility upgrades (recognizing that as some are upgraded, others might have to be closed) and operational costs (recognizing that simply matching university contributions would generate a federal share of $37 million). Special appropriations of $1 million a year in fiscal years 1990 to 1993 for some specific instrumentation is all that has resulted from that report. The present committee believes that the observations of the 1988 report are still valid and that the $10 million to $20 million being considered for support of the Omega West or the Sandia National Laboratory reactors would be better spent on radionuclide production at university research reactors, especially the larger ones, and specifically the University of Missouri Research Reactor Center.

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TABLE 3-5 Isotopes Produced at University of Missouri Research Reactor

Radioisotope	Primary Uses	Quantity (Ci) Shipped from July 1992 to July 1993
Sodium-24	Hypertension research and tracer for power reactors	12
Silicon-31	Materials research	172
Phosphorus-32	Therapy for bone cancer (in use)[a,b]	7,964
Sulfur-35[b]	Radiolabeled biological compounds (DNA)	5,064
Calcium-45	Biochemistry research tracer	16
Scandium-46	Biochemistry research tracer and liquid flow tracer	4.3
Calcium-47	Biochemistry research tracer	0.002
Chromium-51	Diagnosis of blood cell volume (in use); biochemistry research tracer	697
Iron-55	Biochemistry research tracer	115
Cobalt-58	Positron source for materials science research	5.8
Iron-59	Biochemistry research tracer	5.7
Cobalt-60	Therapy for cancer (in use); sterilization source and calibration source	0.2
Nickel-63	Detectors for smoke, explosives, analytical instruments	76
Copper-64	Diagnosis of and therapy for cancer (clinical trials)[c]; biochemistry tracer, materials research	2.0
Zinc-65	Biochemistry research tracer	0.05
Copper-67	Biochemistry research tracer	0.01
Selenium-75	Biochemistry research tracer	16
Strontium-85	Biomedical tracer	1.3
Rubidium-86	Biochemistry research tracer	8.2
Zirconium-95	Calibration source	1.0
Palladium-103	Therapy for prostate cancer (in use)	1.99
Ruthenium-103	Instrument calibration source	1.3
Rhodium-105	Therapy for cancer (proposed)[d]	0.2
Palladium-109	Therapy for (proposed), cancer	0.1
Silver-110m	Chemical tracer, gamma calibration source	1.8
Tin-113	Decays to indium-113m	6.6
Cadmium-115	Therapy for arthritis (proposed)	0.03
Tin-119m	Chemical tracer, gamma calibration source	0.03
Tellurium-123m	Mossbauer source; lung, heart research	0.04
Antimony-124	Oil well tracer	5.4
Tellurium-125m	Mossbauer source	0.007
Tellurium-129m	Mossbauer source	0.001
Barium-133	Calibration source for detectors, gamma cameras	0.2
Samarium-145	Therapy for cancer (proposed)	0.1
Samarium-153	Therapy for bone cancer (clinical trials) materials research	51
Gadolinium-153	Diagnosis of osteoporosis (in use)	4.9
Europium-154	Calibration standard	0.02
Terbium-160	Gamma source	0.4
Dysprosium-165	Therapy for arthritis (clinical trials)	2.3

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Radioisotope	Primary Uses	Quantity (Ci) Shipped from July 1992 to July 1993
Dysprosium-166	Therapy for cancer (proposed)	0.005
Holmium-166	Therapy for leukemia, cancer, arthritis (clinical trials)	79
Ytterbium-169	Radiography source	344
Thulium-170	Therapy for leukemia (proposed)	54
Ytterbium-175	Therapy for cancer (proposed)	49
Lutetium-177	Therapy for cancer (clinical trials)	54
Tantalum-182	Gamma ray source for materials research	0.04
Rhenium-186	Therapy for bone cancer (clinical trials)	1,476
Rhenium-188	Therapy for thyroid, bone cancers (clinical trials)	2.5
Osmium-191	Decays to iridium-191m; diagnosis	30
Iridium-192	Therapy for cancer (in use); materials testing; oil well tracer; commercial materials testing	5,922
Platinum-195m	Diagnosis and therapy for cancer (clinical trials)	0.6
Gold-198	Therapy for cancer (in use)	2,845
Gold-199	Therapy for cancer (proposed)	2.2
Mercury-203	Calibration source	1.3
Thallium-204	Beta calibration source	6.1

[a] In use indicates that it is currently approved for human use and marketed in the United States.
[b] Phosphorus-32 and sulfur-35 are the most widely used radioisotopes for biochemical and biomedical research. Programs in genetic engineering, the human genome, cell metabolism, etc., all depend on the availability of these radioisotopes.
[c] Clinical trials indicates that the isotope is being tested in U.S. Food and Drug Administration approved human clinical trials.
[d] Proposed indicates that the isotopes is under scientific investigation but not yet in clinical trials.

Market Analyses

Proponents of the Fast Flux Test Facility, a 400-MW DOE reactor at the Hanford site in the state of Washington scheduled for decommissioning, have predicted an explosive growth in demand for new approaches to radiotherapy, that is, 1.6 million new cancer cases each year in the United States. The business plan produced for the facility by the Freeman School of Business at Tulane University and the Levy Rosenblum Institute in September 1993 projects a global wholesale market (raw isotopes, not radiopharmaceutical end products) of close to a $1 billion by 2002, a 10-fold increase primarily because of therapeutic radiopharmaceuticals. Other observers have been far less optimistic. Landis et al. (1993), although still projecting substantial growth, caution that the Tulane plan assumes U.S. Food and Drug Administration approval of a large number of radiopharmaceuticals that are now in the research or clinical testing stage. The

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timing of these approvals and the cost-effectiveness of the techniques employing the radiopharmaceuticals will determine the extent of actual use of the radioisotopes, making the Tulane assumptions speculative at best.

Arthur Andersen & Co. (1993), in a management study for DOE, is more conservative, pointing out that the isotope market is characterized by high barriers to entry, producers who are government owned or rely on government-owned facilities, and demand driven by less than a handful of major commercial customers. In its market analysis and advice to DOE, it assumed modest annual growth (5 to 10 percent) in the overall radioisotope market, with no large change in the market profile (i.e., cobalt-60 at 40 percent and ^{99}Mo at 34 percent will continue to dominate sales). In fact, their data, substantiated in testimony to the committee by Evans (1993), show that at present no other single radioisotope accounts for more than 5 percent of the market. The rest of the reactor-produced radionuclides, although many in number, are used mainly by researchers, who constitute only 2 percent of the radioisotope market in dollars.

CONCLUSIONS

1. In the short term the supply of reactor-produced radionuclides for commercial use, including ^{99}Mo, is sufficient. Radiopharmaceutical companies state that the present domestic and foreign suppliers are reliable and have or will soon sign long-term supply contracts with existing producers.
2. In the long term if short-lived reactor-produced radionuclides become important for cancer therapy, the present number and condition of production reactors in North America will be inadequate.
3. A federally supported U.S. reactor for the production of research radioisotopes is definitely justified. At present, MURR is playing a major role as the supplier of radionuclides for research facilities and radiopharmaceutical manufacturers. Federal support at present is limited to the provision of reactor fuel and peer-reviewed research grants.

RECOMMENDATIONS

1. In view of the demonstrated reliability of the current sources of commercially valuable isotopes and their steps to secure adequate backup, the committee recommends that the Omega West reactor at Los Alamos National Laboratory or reactors at other facilities NOT be reopened as a dedicated source of molybdenum-99 and other reactor-produced isotopes.
2. To ensure the continued supply of radionuclides (other than molybdenum-99) for medical and research facilities, the committee recommends core support for reactor-based isotope production. The University of Missouri Research Reactor appears to be the best currently available facility that can meet this need.

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3. Because reactors have finite lifetimes and because future demands may exceed current capabilities, the committee recommends that DOE ensure that plans for the Advanced Neutron Source reactor reflect the importance of isotope production, and in particular, molybdenum-99, by providing funding at an appropriate amount to ensure availability.

REFERENCES

Adelstein, S. J.1993. The Auger Process: A Therapeutic Promise?American Journal of Roentgenology160:707–713.

Arthur Andersen & Co.1993. U.S. Department of Energy Isotope Production and Distribution Program Management Study. Washington, D.C.

Berson, S. A., and R. S. Yalow. 1959. Quantitative Aspects of the Reaction Between Insulin and Insulin Binding Antibody. Journal of Clinical Investigation38:1996.

Bizzell, O. M.1966. Early History of Radioisotopes from Reactors, Isotope and Radiation Technology4:25–29.

Blumgart, H. L. and Yens, O. C.1927. Studies on Velocity of Blood Flow: The Method Utilized. Journal of Clinical Investigations4:1–13.

Brice, J.1994. Dual-Head SPECT Lifts Nuclear Medicine Market. Diagnostic Imaging16(1):29–33.

Cobb, L. M., and J. L. Humm. 1986. Radioimmunotherapy of Malignancy Using Antibody Targeted Radionuclides, British Journal of Cancer54:863–870.

Carmain, E.1993. The New Alchemy. Nuclear Energy2nd Quarter:2–13.

de Hevesy, G.1913. Use of Radioelements as Tracers in Chemistry and Physics. Chemistry News108:166.

DeSombre, E. R., B. Shafii, R. N. Hanson, P. C. Kuivanen, and A. Hughes. 1992. Estrogen Receptor-Directed Radiotoxicity with Auger Electrons: Specificity and Mean Lethal Dose. Cancer Research62:5752–5758.

Evans, D. J.1993. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Fischman, A. J., J. W. Babich, and H. W. Strauss. 1993. A Ticket to Ride: Peptide Radiopharmaceuticals. Journal of Nuclear Medicine34:2253–2263.

Hamilton, J. G. and M. H. Soley. 1939. Studies in Iodine Metabolism by the Use of New Radioactive Isotope of Iodine. American Journal of Physiology127:557–572.

Hinkle, G. H.1993. An Overview of Advances in the Radioimmunodetection of Melanoma. New Perspectives in Cancer Diagnosis and Management1(3):774–780.

Holmes, R. A.1993. U.S. Dependence on Foreign Isotopes. Statement to the Subcommittee on Energy, Committee on Science, Space and Technology, U.S. House of Representatives, Washington, D.C., October 14, 1993.

Humm, J. L.1986. Dosimetric Aspects of Radiolabeled Antibodies for Tumor Therapy . Journal of Nuclear Medicine27:1490–1497.

Jungermann, J. A., K. H. P. Yu and C. L. Zanelli. 1984. Radiation Absorbed Dose Estimates at the Cellular Level for Some Electron-Emitting Radionuclides for Radioimmunotherapy. International Journal of Applied Radiation and Isotopes. 35:883.

Kamen, M. D., ed. 1957. Applications to Clinical Research. P. 246. In Isotopic Tracers in Biology, 3rd edition. New York: Academic Press.

Landis, J. W., F. P. Baronowski, and E. H. Klevans. 1993. Future Use of the United States Department of Energy's Fast Flux Test Facility. Final Report of the Independent Review Team for Secretary of Energy. Photostatic copy dated September 20, 1993.

Lewington, V. J., A. J. McEwan, D. M. Ackery, R. J. Bayly, D. H. Keeling, P. M. Macleod, A. T. Porter, and M. A. Zivanovic. 1991. A Prospective Randomized Double-Blind Crossover Study

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to Examine the Efficacy of Strontium-89 in Pain Palliation in Patients with Advanced Prostate Cancer Metastatic to Bone. European Journal of Cancer27:954–958.

McLaughlin, W. H., R. A. Milius, K. M. Pillai, J. P. Edasery, R. D. Blumenthal, and W. D. Bloomer. 1989. Cytotoxicity of Receptor-Mediated 16 -[^{125}I]Iodo-Estradiol in Cultured MCF-7 Human Breast Cancer Cells. Journal of the National Cancer Institute81:437–440.

Mirzadeh, S., C. W. Alexander, T. McManamy and F. F. Knapp, Jr.1994. Projected Medical Isotope Production Capabilities of the Advanced Neutron Source (ANS). Oak Ridge National Laboratory Publication No. 12010/S. Oak Ridge, Tenn.: Oak Ridge National Laboratory.

Mirzadeh, S., R. E. Schenter, A. P. Callahan and F. F. Knapp, Jr.1992. Production Capabilities in U.S. Nuclear Reactors for Medical Radioisotopes. Oak Ridge National Laboratory Publication No. TM-12010. Oak Ridge, Tenn.: Oak Ridge National Laboratory.

Moody, D. E., and E. J. Peterson, eds. 1992. Proceedings of the DOE Workshop on the Role of a High-Current Accelerator in the Future of Nuclear Medicine. Report No. LA-11579C. Los Alamos, N.M.: Los Alamos National Laboratory.

Morgan, I. L.1993. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 20, 1993.

National Research Council. 1988. University Research Reactors in the United States—Their Role and Value. Washington, D.C.: National Academy Press.

Riggs, J. R.1993. Statement to the Subcommittee on Energy, Committee on Science, Space and Technology, U.S. House of Representatives, Washington, D.C., October 14, 1993.

Schenter, R. E.1993. Statement to the Subcommittee on Energy, Committee on Science, Space and Technology, U.S. House of Representatives, Washington, D.C., October 14, 1993.

Schmidt, G. W.1993. Letter to Hillary R. Clinton, July 20, 1993. Copy provided to Donald Erb at the U.S. Department of Energy and in turn provided to the Committee on Biomedical Isotopes, September 11, 1993.

Serafini, A. N.1993. Radioimmunoscintigraphy in Melanoma. New Perspectives in Cancer Diagnosis and Management1(3):83–85.

Stannard, J. N.1988. Radioactivity and Health: A History. DOE Report No. RL01830-T59. Richland, Wash.: Pacific Northwest Laboratory.

Sugarbaker, E. V.1993. Recent Clinical Applications of RAID in Malignant Melanoma. New Perspectives in Cancer Diagnosis and Management1(3):91–93.

Tucker, D., M. W. Greene, A. J. Weiss, and A. Murrenhoff. 1958. Methods of Preparation of Some Carrier-Free Radioisotopes Involving Sorption on Alumina. Report No. BNL-3746. Upton, N.Y.: Brookhaven National Laboratory.

University of Missouri Research Reactor Center. 1994. Annual Report for 1993. Columbia: University of Missouri.

White, W.1993. Statement to the Subcommittee on Environment, Energy, and Natural Resources, Committee on Government Operations, Washington, D.C., December 6, 1993.

Zalutsky, M. R., and A. S. Narula. 1988. Radiohalogenation of a Monoclonal Antibody Using an N-Succinimidyl 3-(tri-*n*-butylstannyl) Benzoate Intermediate. Cancer Research48:1446–1450.

Zalutsky, M. R.1992. Monoclonal Antibodies: Imaging and Therapy. In D. E. Moody, and E. J. Peterson, eds. Proceedings of the DOE Workshop on the Role of a High-Current Accelerator in the Future of Nuclear Medicine. Report No. LA-11579C. Los Alamos, N.M.: Los Alamos National Laboratory.

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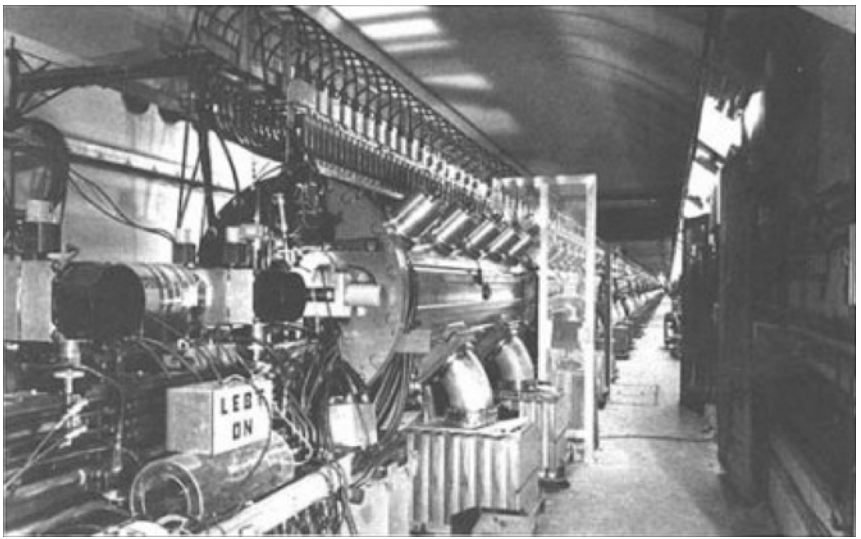

A view looking down into the nine accelerating stations of theproton LINAC atBrookhaven National Laboratory. The LINAC is almost 600-feet longand accelerates theprotons to an energy of 200 MeV. The protons are used for isotopeproduction in theBrookhaven Linac Isotope Producer. SOURCE: Brookhaven National Laboratory.

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4

Accelerator-Produced Radionuclides and a National BiomedicalTracer Facility

HISTORICAL PERSPECTIVE

A decade before the first nuclear reactor, the invention of the cyclotron by Ernest Lawrence in 1931 made it possible to produce radioactive isotopes of a number of biologically important elements. In this machine and its close relative, the linear accelerator, powerful radiofrequency electric fields are employed to accelerate charged particles (such as protons, deuterons, or alpha particles) through an evacuated path into some target material. In the cyclotron this path is an ever-widening spiral, whereas in the linear accelerator, as the name implies, it is a long straight tube. When a suitably accelerated particle collides with the nucleus of a target atom a reaction occurs and a radioactive product is formed. Milestones in the use of these artificially produced radiotracers included experiments by Hamilton and Stone (1937), who used radioactive sodium clinically; Hertz et al., (1938), who used radioactive iodine in the study of thyroid physiology; and the investigations of Lawrence et al., (1940), who studied leukemia with radioactive phosphorus.

In 1941, the first medical cyclotron was installed at Washington University in St. Louis, where radioactive isotopes of phosphorus, iron, arsenic, and sulfur were produced. With the exploitation of the fission process during World War II, most radioisotopes of medical interest began to be produced in nuclear reactors, (see Chapter 3). After the War, the widespread use of radioactive materials in medicine led to the establishment of the new field of what was then called atomic medicine, which was later called nuclear medicine.

Although the first artificially produced radionuclides came from Lawrence's cyclotrons, it was another 30 years before accelerator-produced radionuclides began to play a major role in the production of medically important radio

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pharmaceuticals. Many radionuclides produced in accelerators cannot be produced by neutron reactions. When they can be, the principal advantage of accelerator-produced radioisotopes is the higher specific activity (more disintegrations per mass of desired element) that can often be achieved than is the case with reactor products. Another not insignificant advantage is that a smaller amount of radioactive waste is generated from charged-particle reactions, especially at low (£30 million electron volts [MeV]) bombarding energies.

Both commercial radionuclide producers and research institutions have added accelerators to their armamentaria. The machines have mostly been compact cyclotrons (Martin, 1979) for industrial use (more than 17 in North America alone) or medical use (Wolf, 1984; Wolf and Jones, 1983). The commercial suppliers of radionuclides each possess two or more cyclotrons for their production needs. The mix of radionuclides produced with these cyclotrons is market driven. As a result a number of radionuclides that are used extensively by the biomedical research community are not available from commercial suppliers because of management decisions associated with profitability. In addition, major North American accelerator installations such as the Brookhaven Linac Isotope Producer (BLIP) facility at Brookhaven National Laboratory (Mausner et al., 1986) and the Los Alamos Meson Physics Facility (LAMPF) at the Los Alamos National Laboratory (Grant et al., 1982) in the United States and the Tri-University Meson Facility (TRIUMF) in Canada (Pate, 1979) have significant radionuclide production programs serving both commercial and research clients.

This chapter reviews the use of selected radionuclides and their availabilities from various sources and how this availability would be affected by an accelerator-based National Biomedical Tracer Facility (NBTF) of the sort suggested by previous advisory groups (Holmes), 1991; Kliewer and Green, 1992; McAfee, 1989; Moody and Peterson, 1989).

CURRENT APPLICATIONS IN MEDICINE AND PHYSICAL AND LIFE SCIENCES

As Table 4-1 illustrates, accelerator-produced radioisotopes, like the reactor-produced radioisotopes reviewed in the previous chapter, are both abundant and versatile. As with the reactor products, their uses fall into the general categories of tracer studies, of which imaging is a special and very important case, and radiotherapy. The general principles involved in the use of radioisotopes in the life sciences as well as some of the history and recent research directions were also provided in the previous chapter, so this section will be limited to a few recent successes.

Perhaps the most widely used accelerator isotope in the medical field is thallium-201 (^{201}Tl). ^{201}Tl imaging of heart muscle is employed during exercise to detect and differentiate between diminished blood flow and tissue death from the loss of blood flow in patients with coronary artery disease. Overall, ^{201}Tl is

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used in about 13 percent of all nuclear medicine procedures, making it second only to technetium-99m in volume of use. A potassium analog, ^{201}Tl is readily extracted in proportion to regional blood flow within heart muscle, and at equilibrium, its distribution provides an assessment of the amount and location of viable heart muscle. Single-photon emission computed tomography (SPECT) provides

TABLE 4-1 Selected Accelerator-Produced Radionuclides and Their Uses

Radioisotope	Uses
Beryllium-7	Berylliosis studies
Magnesium-28	Magnesium tracer
Scandium-47	Radioimmunotherapy
Vanadium-48	Nutrition and environmental studies
Iron-52	Iron tracer, positron emitter
Iron-55	X-ray fluorescence source
Cobalt-57	Calibration of imaging instruments
Copper-61	Positron emitter for studies requiring longer time periods
Copper-64	Positron emitter for studies requiring longer time periods; radioimmunotherapy
Copper-67	Radioimmunotherapy
Zinc-62	Parent in the generator system for producing the positron-emitting ^{62}Cu
Germanium-68	Parent in the generator system for producing the positron-emitting ^{68}Ga; required in calibrating PET tomographs, potential antibody label
Arsenic-74	A positron-emitting chemical analog of phosphorus
Bromine-77	Radioimmunotherapy
Bromine-80m	Radioimmunotherapy
Strontium-82	Parent in generator system for producing the positron-emitting ^{82}Rb, a potassium analog
Yttrium-88	Radioimmunotherapy
Zirconium-89	Radioimmunotherapy, positron emitter
Ruthenium-97	Hepatobiliary function; tumor and inflammation localization
Cadmium-109	To analyze metal alloys for checking stock, scrap sorting
Indium-111	Radioimmunotherapy
Iodine-123	SPECT brain-imaging agent
Iodine-124	Radioimmunotherapy; positron emitter
Xenon-122	Parent in generator system for producing the positron-emitting ^{122}I
Xenon-127	Used in lung ventilation studies
Barium-128	Parent in generator system for producing the positron-emitting ^{128}Cs, a potassium analog
Cerium-139	Gamma-ray calibration source
Tantalum-179	X-ray fluorescence source (substitute for the alpha-emitter ^{241}Au which is used in cardiac studies)
Tungsten-178	Parent in generator system for producing ^{178}Ta, short-lived scanning agent
Mercury-195m	Parent in the generator system for producing ^{195m}Au which is used in cardiac blood pool studies
Thallium-201	Cardiac imaging agent
Bismuth-205	Bismuth biological distribution
Bismuth-206	Bismuth biological distribution

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images of a series of sections through the heart, and these images provide an overall sensitivity of up to 90 percent for the detection of coronary artery disease (Berman et al., 1993). In addition to ^{201}Tl for heart studies, significant quantities of iodine-123 and gallium-67 are used for thyroid imaging and for the localization of tumors and infections, respectively.

Accelerator-produced isotopes are also well-represented among the newest efforts at disease-specific imaging via monoclonal antibodies and peptides. The Food and Drug Administration (FDA has already approved an indium-111-labeled monoclonal antibody for radioimmunoscintigraphy of colorectal and ovarian carcinomas (Cytogen's Oncoscint) and is thought to be close to approving the first peptide-based radiopharmaceutical, a Sandoz/Mallinckrodt indium-111-labeled somatostatin agent (Octreoscan) for imaging small cell carcinoma of the lung and neuroendocrine tumors.

Accelerator-produced isotopes are also the basis of positron emission tomography (PET). Most of the important radionuclides in PET have such short half-lives that they must be generated on-site, that is, within a few seconds or minutes of administration. Nearly all of the 60 to 70 PET centers in the United States have their own cyclotrons, with which they produce carbon-(^{11}C), nitrogen-(^{13}N), oxygen-(^{15}O), and fluorine-(^{18}F), for incorporation into metabolically important molecules. A computer uses the radiation emitted to create images reflecting different functions of the body and specific organs. Some of these molecules are very simple, like $^{11}CO_2$ and $H_2{}^{15}O$, which are used for blood flow studies. More complex compounds, for example, ^{18}F-labeled fluorodeoxyglucose, allow for the visualization and quantification of regional glucose metabolism. Other labeled ligands can be used to measure amino acid utilization and receptor binding of neurotransmitters in living human patients. Still largely a research tool, PET already promises to have important clinical applications to heart disease, cancer detection, and cerebral dysfunctions caused by ischemic, degenerative, convulsive, and psychiatric disorders, as well as the detection of metastatic tumors.

SUPPLIES AND SUPPLIERS

The issue of accelerator-produced radioisotope availability has been subdivided into three categories, recognizing that there are essentially three sources: commercial radioisotope and radiopharmaceutical companies, site-specific cyclotrons that produce short-lived PET radionuclides for immediate use, and several large government accelerator facilities where isotope production for both industry and research is "piggybacked" onto other missions.

Commercially Available Radioisotopes

Currently, three major companies in the United States operate cyclotrons for the commercial production and distribution of radionuclides with half-lives in the

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range of a few hours to a few days. The committee heard statements from representatives of all three: Roy Brown of Mallinckrodt Medical, Inc., Carl Seidel of DuPond Merck Pharmaceutical Co., and John Kuranz of Medi-Physics.

These radiopharmaceutical companies each operate at least three cyclotrons, each typically with 30-MeV protons or less. Medi-Physics also operates a 70-MeV cyclotron in Arlington Heights, Ill. Relatively few isotopes are routinely produced by these companies, the main ones being gallium-67 (half-life, 78 hours), indium-111 (half-life, 68 hours), iodine-123 (half-life, 13 hours), and thallium-201 (half-life, 73 hours). To ensure continuous supplies of these radioisotopes to their customers in case of production difficulties, backup agreements between these companies are in place to maintain the supply in case of breakdown or other events that force a halt to accelerator operations. These companies readily made it clear that their product lines are profit driven and that they introduce new products only when market studies predict an attractive return. Their research and development efforts are largely devoted to new carrier molecules for well-studied radionuclides, and they are all in favor of an NBTF, which would help to develop and open new markets. They also see an important educational role for NBTF in training scientists and technicians in the use and handling of radioisotopes and radiolabeled compounds, but they do not expect that an NBTF would compete with them in the commercial market.

These commercially important isotopes are also available through the Canadian company Nordion (see below under the section TRIUMF). Overall, the reliability of supplies of these short-lived, accelerator-produced (profitable) radionuclides does not seem to be in question. Table 4-2 gives the estimated quantities of commercial radioisotopes used in the years 1982 and 1990, as well as estimates of 1992 revenues to the producers of the isotopes (not the end products).

TABLE 4-2 Main Commercial Radionuclides Used in 1982, 1990 and 1992

		Estimated Life Science Retail Use (~Ci/year, time of end use)		
Nuclide	Half-Life	1982[a]	1990[b]	Wholesale Market in 1992 ($ millions)
Thallium-201	73 h	500	6,000	>30[c]
Iodine-123	13.2 h	75	3,100	1–5[c]
Indium-111	68 h	150	185	1–5[c]
Gallium-67	78.3 h	800	820	1.5[d]
Strontium-82	25 days	NA[e]	12[d]	1.2[d]
Xenon-127	36.4 days	100	100	81

[a] SOURCE: Ruth et al., 1989.
[b] SOURCE: J. Porter, Nordion International, Inc., personal communication, February 1994.
[c] SOURCE: Evans, 1993.
[d] SOURCE: Holmes, 1991.
[e] NA, not available.

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Short-Lived Radioisotopes for PET

Because of the very short half-lives of ^{18}F, ^{11}C, ^{13}N, and ^{15}O (110, 20, 10, and 2 minutes, respectively), an NBTF would be unlikely to have a direct effect on the use of these radionuclides. They will generally continue to be prepared with small, on-site accelerators. An important concern related to these radionuclides is the availability of enriched stable target material, especially stable ^{15}N and ^{18}O. This question has been discussed in the section on stable isotopes. (Chapter 2). There is some chance that the ^{18}F, with a half-life of 110 minutes, could be shipped from an NBTF in a major city to facilities in the vicinity (Syncor, Inc., and Mallinckrodt Medical, Inc., have recently established four regional radiopharmacies that produced their own ^{18}F-labeled 2-fluoro-2-deoxyglucose and ship it to nearby hospitals), but the major application of NBTF to these short-lived radionuclides would probably be in the development of high-beam-current targets for the low-energy accelerators that are being proposed. This will be discussed in Chapter 5.

PET could expand beyond the large medical center and become a truly routine clinical tool if some additional sources of positron-emitting radionuclides could be found. One possibility is the supply of medium half-life radionuclides from an NBTF. Candidate radionuclides that have been discussed in the literature (Anderson et al., 1992; Welch and Kilbourn, 1988) include zirconium-89 (half-life, 78.4 hours), bromine-76 (half-life, 16.1 hours), iodine-124 (half-life, 4.2 days), and copper-64 (half-life, 12.7 hrs). Another possibility for an additional source of positron-emitting radionuclide is a "generator" system, similar to the molybdenum-99/technetium-99m generator described in the previous chapter. Such a generator consists of a parent radionuclide absorbed on a column from which a shorter-lived, positron-emitting decay product is eluted by passing a suitable solvent through the column. Table 4-3 lists some candidate parent-daugh

TABLE 4-3 Candidate Parent-Daughter Systems for Positron Emission Tomography

Parent Isotope	Parent Half-Life	Daughter Isotope	Daughter Half-Life	Daughter Positron Yield (%)
Germanium-68	271 days	Gallium-68	68.1 min	90
Strontium-82	25.4 days	Rubidium-82	75 sec	96
Zinc-62	9.2 h	Copper-62	9.73 min	98
Iron-52	8.27 h	Manganese-52m	21.1 min	98
Xenon-122	20.1 h	Iodine-122	3.6 min	77
Tellurium-118	6.0 days	Antimony-118	3.6 min	83
Barium-128	2.43 days	Cesium-128	3.6 min	61
Selenium-72	8.4 days	Arsenic-72	26 h	77
Titanium-44	47 yr	Scandium-44	3.9 h	95

SOURCE: Welch, 1992.

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ter systems for PET. It is difficult to predict at this point which of these will prove to be most useful in the future, but given a reliable year-round supply of the parent nuclides, generators could certainly relieve some potential PET users of the substantial burden imposed by an in-house accelerator (Budinger, 1988). However, none of the generator systems will produce isotopes of carbon, nitrogen, and oxygen for incorporation into physiologically active molecules. Thus, the principal advantage of generator-produced positron emitters lies in the ability of PET technology to provide quantitative mapping of certain functions.

Radionuclides Currently Produced at DOE Facilities

For most of the previous postwar decades the U.S. Department of Energy (DOE) facilities at Brookhaven National Laboratory (BLIP) and Los Alamos National Laboratory (LAMPF) have served as the primary sources for most of the accelerator-produced radionuclides used in research in the United States. A brief description of these facilities will be given, along with a description of the TRIUMF facility in Vancouver, British Columbia, Canada, since its radioisotope production capabilities could, and do, supplement the DOE-sponsored effort. Table 4-4 provides a summary of the characteristics of the accelerator at each of these sites.

BLIP

Although BLIP is the acronym for the Brookhaven Linac Isotope Producer, it refers to the infrastructure including the linear accelerator (linac) source for the alternating-gradient synchrotron (AGS), the BLIP building (where the targets are irradiated), and the building where the hot cells are located for processing the targets (Building 801). Building 801 is located about 2 km from the BLIP building, so targets must be transferred in shielded vessels from the point of irradiation to the location of processing. The linac produces 40-microamp (40μA) beams of 200-MeV protons. The target area is immersed in water, and a series of up to 10 targets is irradiated simultaneously, the downstream targets being exposed to beams of lower energy and intensity because of upstream target absorption and attenuation. The processing cells are more than over 40 years old.

The Radionuclide and Radiopharmaceutical Program at Brookhaven National Laboratory is supported by the Isotope Production and Distribution Program, within the Office of Nuclear Energy of DOE, and the Office of Health and Environmental Research (OHER), within the Office of Energy Research of DOE. The program at Brookhaven National Laboratory is a longstanding research program, and the isotope production efforts are supposed to be self-supporting through outside sales. For a variety of reasons, including the perception by the staff that isotope sales is a secondary mission, isotope production has not broken even financially.

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TABLE 4-4 High-Energy Accelerator Facilities for North American Radioisotope Production

Accelerator	Type	Particle	Energy (MeV)	Current (μA)	Comments
TRIUMF					
Beamline 1A	Cyclotron	H-	520	150	Twelve spallation targets
Beamline 2C	Cyclotron	H-	50—120	10—100	Four targets
TISOL	Cyclotron	H-	200—520	1—10	On-line isotope separator
BLIP	Linac	H+, H-	200	40	Ten targets; 20 weeks/year
BLIP upgraded	Linac	H+, H-	200	150	46 weeks/year?
LAMPF	Linac	H+, H-	800	1,000	Expensive; 1996 closing proposed

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BLIP operating time and costs are strongly dependent on the use of AGS by the high-energy-physics researchers at Brookhaven National Laboratory. When AGS is in use, it uses pulses of protons from the linac. The latter operates at 5 Hertz (Hz), and AGS uses, on average, only 4 pulses in 13. The remaining pulses are diverted to BLIP, which is charged at a rate of $12,000 per week (all cost estimates were provided by BLIP staff during a site visit by committee members in November 1993). AGS occasionally uses heavy ions from another source rather than protons from the linac. BLIP then gets all 5 pulses per second,, but operating costs to BLIP escalate to $35,000 per week. In a third scenario, the AGS is not operating at all. Linac operation in this case costs BLIP $55,000 per week. The magnitude and unpredictable variation in these costs, largely salaries and power consumption, have made both year-round operation and predictable isotope pricing impossible. In recent years BLIP has been in operation an average of only 16 weeks per year. Isotope production in fiscal year 1993 is summarized in Table 4-5.

LAMPF

At present, six products represent the major production efforts at the LAMPF (copper-67, germanium-68, strontium-82, aluminum-26, arsenic-73, and cadmium-109). However, another dozen or so radioisotopes are available either in stock or as by-products from routine production. These radioisotopes are extracted from targets irradiated in the LAMPF beam dump area. The maximum energy of the 0.6-mile (1-km) long accelerator is 800 MeV, and its beam current

TABLE 4-5 Radionuclides Distributed by BLIP and LAMPF in Fiscal Year 1993

	BLIP		LAMPF	
Radionuclide	Quantity (mCi)	Income (thousands of $)	Quantity (mCi)	Income (thousands of $)
Beryllium-7	12	3	4	0.9
Sodium-22	—	—	1,645	82
Aluminum-26	—	—	0.0006	18
Silicon-32	—	—	0.03	39
Copper-67	382	25	—	—
Germanium-68	398	100	1,428	336
Rubidium-83	—	—	19	4
Strontium-82	3,753	376	4,611	415
Technetium-96	30	4	—	—
Ruthenium-97	100	6	—	—
Cadmium-109	—	—	3,500	175
Xenon-127	65	2	—	—

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is rated at 1 milliamp (mA). These operating parameters enable thick targets to be irradiated for long periods of time. Like at Brookhaven National Laboratory, operation is dictated by physics research, and although this has occasionally allowed operation for 6 months in a year, it has been operating for only 16 weeks in recent years. Only careful scheduling in conjunction with BLIP has enabled DOE to provide short-lived radionuclides for as many as 30 weeks a year.

The accelerator target area at LAMPF is located about a 10-minute drive from the processing area. To transfer the irradiated targets to the processing unit, the irradiated targets must be placed in a heavily shielded container and this container must be loaded onto a flatbed truck for transport to the laboratories with the hot cells. Because Los Alamos National Laboratory is distributed over a wide geographic area connected by public roadway and the shielded container does not meet current U.S. Department of Transportation standards for public transit, this shipment demands extensive coordination and requires about 24 hours from the time of removal of the targets to their arrival at the processing unit.

The LAMPF facility is scheduled to be shut down in fiscal year 1995 (the President's budget request). Political action may keep LAMPF open for an additional year or so, but the long-term prospects for LAMPF are in doubt, despite some proposed options (e.g., upgrade and continuation of the Neutron Scattering Center by the Defense Programs division of DOE) that could keep its isotope production capability in place. At $60 million per year for its operation this accelerator is clearly too big to be devoted solely to isotope production. Table 4-5 provides a summary of isotope production in fiscal year 1993.

TRIUMF

TRIUMF is a Canadian national laboratory located on the campus of the University of British Columbia and operated by four local universities (the University of British Columbia, University of Alberta, University of Victoria, and Simon Fraser University). As a national laboratory it is supported by the National Research Council of Canada, which provides more than $30 million a year in core support. TRIUMF not only operates the world's largest cyclotron and conducts an extensive program of research in nuclear and particle physics but also has a strong program in technology transfer associated with its Applied Science Program. Biomedical isotopes and the small cyclotrons that produce them are the key components of the transfer program, along with superfast microchips, devices for detecting hidden plastic explosives and removing undesirable components from smokestack emissions, PET software, and pion and proton cancer therapy. Royalties from the sale of these products by commercial partners provide TRIUMF with an additional $1 million per year.

Nordion International Inc., whose exclusive contract for packaging and distributing reactor isotopes from the Chalk River reactor was discussed in the previous chapter, also has a 30-year technical support agreement with TRIUMF,

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making Nordion the sole commercial source of isotopes produced on the 520-MeV cyclotron, and in turn making TRIUMF the sole supplier of accelerator isotopes to Nordion. Nordion also owns and operates two compact cyclotrons, CP-42 (42MeV) and a TR-30 (30 MeV), on-site in the Chemistry Annex. The structure was built by Nordion and is shared with TRIUMF staff. These cyclotrons are used to make thallium-201, iodine-123, indium-111, gallium-67, cobalt-57, and germanium-68. Nordion also uses the main TRIUMF cyclotron to make longer-lived isotopes during the two 13-week periods during which it operates each year. This machine can simultaneously bombard 12 solid targets with 520-MeV protons and has been used in the past to make copper-67, cadmium-109, xenon-127, and germanium-68. It is currently being used to make strontium-82 from natural molybdenum by spallation. This cyclotron also has a variable-energy extractor on one of its many beam lines that can irradiate multiple targets at 65 to 120 MeV. Nordion currently uses a solid target station on that line to make strontium-82 from natural rubidium. A fourth cyclotron, TR-13 (13 MeV), designed by TRIUMF and recently completed by another of TRIUMF's industrial partners, EBCO, will be dedicated to isotope production, primarily for PET research at TRIUMF.

The TRIUMF long range plan requests some $700,000 for a new, highly automated Radiochemistry/Isotope/Pharmaceutical Laboratory for the separation of radiochemicals from targets, the preparation of new radiochemicals that mimic chemicals used in metabolism, and experiments, including animal tissue preparations, that indicate the suitability of these chemicals and associated pharmaceuticals. The justification offered for this laboratory is a desire to continue the isotope research that has been so successfully brought to market by Nordion. Further evidence of this desire was the report of a TRIUMF staff member that he had just returned from a 5-week trip to Moscow. He visited a newly completed accelerator facility (160 MeV; 100μA now, 500 μA later) and arranged a full-blown collaboration that will make strontium-82 and some other long-life isotopes in Russia.

The committee is of the opinion that the relation between TRIUMF and Nordion is beneficial to both partners and to the user community and that the arrangement is one that might serve as a model for a public-private partnership in the United States. This is explored further in Chapter 5.

Future Production

Proposed NBTF

NBTF proposed previously (Holmes, 1991; Kliewer and Green, 1992; Moody and Peterson, 1989) would serve the United States as a national resource dedicated to the production of radionuclides using a particle accelerator. This $40 million-plus facility (five potential sites recently awarded Project Definition Phase

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grants have been charged with making more precise estimates of these costs by February, 1995) would supply isotopes that are not supplied on a routine basis by industry but that are required in medical practice and life science research. It would also serve as a core to facilitate the conduct of research and training directed to the production of many radionuclides from which future products will arise, such as the development of high-beam-current targets and the development of targets for research isotopes produced by NBTF. Initially envisioned as a DOE facility, the provisions of the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101) requiring isotope production and distribution to be a self-sustaining enterprise (i.e., no annual appropriation) and DOE policy dictating noncompetition with private domestic sources would now seem to dictate private-sector involvement and a clear separation of research and training from production and sales. A single accelerator facility probably could accomplish this only with a high-current machine to ensure the adequate production of both the few nuclides currently in high demand and the many nuclides from which tomorrow's products will emerge. The accelerator specifications in previous evaluations have called for proton beams with energy capacities of up to 100 MeV and beam currents from 500 to 1,000 μA.

In trying to assess the requirements for a NBTF, it was thus instructive to examine a subset of radioisotopes that have been suggested for preparation at a NBTF (Holmes, 1991), and an estimate of the time required to prepare them on the basis of various predictions of the demand for these radioisotopes in the next few years. It is important to note that, in choosing the reaction and production rates, it has been assumed that, for those reactions requiring enriched targets, these isotopes are available in reasonable quantities. When alternatives were available, the reaction requiring the lowest possible energy was chosen since the low-energy reactions, in principle, produce less waste material and have the potential for higher specific activity because of the lower production rates of neighboring stable or long-lived isotopes of the desired product. These results are presented in Table 4-6.

As can be seen from Table 4-7, the production capacity of a 500-μA machine easily meets the projected demands for the selected radionuclides. The only challenge will be one of scheduling and processing. A radionuclide such as strontium-82 would have to be produced on a monthly schedule because of its short half-life, whereas tantalum-179 could be produced once every year or 18 months. However, because of its low production rate, it also may have to be produced over an extended period by using a spare beam or in the parasitic mode by using the tungsten target as a support for some other target. All of these issues point to the need for research in the target production and processing areas.

Upgraded BLIP

During fiscal year 1994, $9 million ($6 million from DOE's Office of Health

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TABLE 4-6 Radionuclides Proposed for NBTF with Possible Reactions and Theoretical 24-Hour Yields for a 500-μA Beam

Radionuclide	Reaction	Energy (MeV)	Enriched Target (% natural abundance of target)	Yield[a] (mCi/μA-h)	Production (mCi/day at 0.5 mA)
^{7}Be	^{7}Li(p,n)	20	No	0.166	1,990
^{28}Mg	^{31}P(p,4p)	70	No	0.012[b]	144
^{48}V	^{48}Ti(p,n)	11	No	0.19[c]	2,280
^{52}Fe	^{55}Mn(p,4n)	65	No	0.3[d]	3,600
^{55}Fe	^{55}Mn(p,n)	20	No	0.014	160
^{61}Cu	^{61}Ni(p,n)	12	Yes (1)	15.5[e]	186,000
	^{64}Zn(p,α)	22	Yes (48)	6	72,000
^{64}Cu	^{64}Ni(p,n)	12	Yes (1)	6.4[e]	77,000
	^{65}Cu(p,pn)	30	Maybe (31)	5.5[f]	66,000
^{67}Cu	^{68}Zn(p,2p)	40	Yes (19)	0.02	240
^{62}Zn	^{63}Cu(p,2n)	22	No	2.3	27,000
^{68}Ge	^{69}Ga(p,2n)	30	Yes (60)	0.03	360
	^{nat}Ga(p,xn)	45	No	0.009	100
	^{nat}Ge(p,pxn)	70	No	0.05	600
^{73}As	^{74}Ge(p,2n)	11	Yes (36)	0.02[c]	200
^{74}As	^{74}Ge(p,n)	15	Yes (36)	0.17	2,000
^{77}Br	^{nat}Se(p,xn)	20	No	1.2	14,000
	^{79}Br(p,3n), ^{77}Kr	50	No	0.36	4,300
^{82}Sr	^{nat}Rb(p,xn)	70	No	0.18	2,200
^{88}Y	^{88}Sr(p,n)	11	No	0.026[c]	310
^{89}Zr	^{89}Y(p,n)	15	No	1.0	12,000
^{95m}Tc	^{96}Mo(p,2n)	25	Yes (17)	0.01[g]	100
^{96}Tc	^{96}Mo(p,n)	20	Yes (17)	0.64[g]	7,700
^{97}Ru	^{103}Rh(p,α3n)	60	No	0.74	8,900
^{124}I	^{124}Te(p,n)	26	Yes (5)	0.093	1,100
^{122}Xe	^{127}I(p,6n)	70	No	3.7	44,000
^{127}Xe	^{127}I(p,n)	20	No	0.07	800
	^{133}Cs(p,2p5n)	100	No	0.11	1,300
^{128}Ba	^{133}Cs(p,6n)	80	No	3.1	37,000
^{139}Ce	^{139}La(p,n)	11	No	0.0017[c]	20
^{179}Ta	^{180}Hf(p,2n)	22	Yes (35)	0.005	60
^{178}W/^{178}Ta	^{181}Ta(p,4n)	38	No	0.045	540
^{195m}Hg/^{195m}Au	^{197}Au(p,3n)	30	No	4	48,000
^{205}Bi	^{207}Pb(p,3n)	22	Yes (22)	0.3[h]	3,500
^{206}Bi	^{207}Pb(p,2n)	22	Yes (22)	0.7	8,000
	^{nat}Pb(p,xn)	42	No	1.7	20,000

[a]Yields taken from Ruth et al. (1989) except as noted.
[b]Lunqvist and Malmborg (1979).
[c]Nickles (1991).
[d]Steyn et al. (1990).
[e]Szelecsenyi et al. (1993).
[f]Boothe (1991).
[g]Hogan (1976).
[h]Fischer et al. (1993).

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and Environmental Physics (OHER) and $3 million from High Energy Physics) was allocated to upgrade the BLIP linac and other BLIP facilities. The $3 million upgrade goals for the linac are to increase its beam current its present 40 μA to something approaching the design specifications of 150 μA, to provide energy variability from 66 to 200 MeV in 21-MeV steps, and to add to the production capabilities that three isotopes are currently only available from LAMPF. The $6 million upgrade to the BLIP facilities covers the construction costs involved in the upgrade and expansion of Building 801 hot cells, a structural addition to the BLIP target irradiation building, and modifications of the linac to enhance reliability at high currents. No additional operating costs have been provided to date, but they have been requested for the years following the completion of upgrade construction to increase operations to 46 weeks per year. Table 4-8 compares one prediction of the capability of such an upgraded facility, running for 40 or more weeks annually, with the proposed capability of an NBTF accelerator (Holmes, 1991) and with the current capability of the TRIUMF facility.

TABLE 4-7 Time Required for Production of Selected Radionuclides at NBTF with a 500-μA Accelerator

Radionuclide	Half-Life	Projected Demand[a] (mCi/yr)	Energy Required (MeV)	Time on NBTF per Table 4-6 (alternate demand time estimate)
Arsenic-73	80.3 days	100	11	1 day
Beryllium-7	53.3 days	15	20	12 min
Copper-67	61.9 h	8,700 (24,000)[b]	40	40 days (100 days)
Germanium-68	271 days	2,700 (12,000)[b]	30	9 days (35 days)
Magnesium-28	21 h	2	70	30 min
Strontium-82	25.6 days	30,000 (60,000)[b]	70	15 days (30 days)
Tantalum-179	1.8 yr	10,000	22	170 days
Technetium-96	4.3 days	100	20	A few hours
Xenon-122	20.1 h	100,000 (200,000)[c]	70	2.5 days (5 days)
Xenon-127	36.4 days	330 (3,000)[b]	20	1 day (4 days)
Yttrium-88	106 days	100	20	8 h

[a]Projected demand taken from Cole (1992), except as noted.

[b]Values in parentheses are the projected demands taken from Holmes (1991).

[c]The value in parentheses is the projected demand based on 20 PET centers requiring one shipment (two shipments) per week (T. Budinger, Lawrence Berkeley Laboratory, University of California, Berkeley, personal communication, 1994).

It is apparent from Table 4-8 that an upgraded BLIP, the proposed NBTF, and TRIUMF all would have sufficient energies and currents to meet the projected demands by the research community in the near future. However, there have been a number of serious impediments to the attempts of present DOE facilities to serve as satisfactory sources for the radionuclides used in the bio

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TABLE 4-8 Hypothetical Production of Radioisotopes at Three Facilities

Isotope	Production (mCi) at BLIP[a] (Normal)	BLIP[a] (Upgrade)	Time Required	Production (mCi) at TRIUMF[b]	Time Required	Production (mCi) at NBTF[c]	Time Required
Strontium-82	4,000	18,900	40 days	12,000	30 days	30,000	15 days
Germanium-68	1,100	2,700	50 days	2,700	50 days	2,700	9 days
Copper-67	1,550	7,000	100 days	7,000	180 days	8,700	40 days
Xenon-127	250	330	4 days	330	4 days	330	1 day
Cobalt-55	75	75	1 day	75	1 day	75	1 min
Technetium-96	45	90	3 days	90	3 days	100	Few h
Beryllium-7	10	15	1 day	15	1 h	15	1 min
Magnesium-28	1	2	1 day	2	1 day	2	30 min
Yttrium-88	0	100	3 days	100	3 days	100	8 h
Cadmium-109	0	5,000	60 days	5,000	60 days	5,000	20 days
Sodium-22	0	1,500	1 yr	1,500	1 yr	1,500	150 days
Arsenic-73	0	60	5 days	60	5 days	60	1 day

[a] SOURCE: Cole, 1993.
[b] Estimates calculated from present operating parameters.
[c] Assumes 500-μA current. NBTF could produce many other isotopes as well.

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sciences, none of which will automatically disappear with the completion of the BLIP upgrade now under way. Most serious are the limited operating schedules of the accelerators at Brookhaven and Los Alamos National Laboratories; the age and design of the linacs (meant for physics research, they are more expensive to operate than a new machine designed for isotope production, and target insertion and removal are so inconvenient that making very short lived radionuclides is impractical); the requirement that the production facilities be self-supporting (Public Law 101-101), in concert with DOE policy forbidding competition with the commercial sector; the perception of isotope sales and distribution as second-class activities for a major research laboratory; the relative isolation of these two laboratories from major shipping centers. The committee also believes that no DOE accelerator facility could both pay for itself the sales of isotopes not available from a domestic commercial supplier and satisfactorily meet the requirements of U.S. research scientists. Thus, although the national laboratories have a number of attractive features, including a potentially substantial one in waste management (see Appendix A), the very nature of the mission of DOE accelerators and the resulting lack of flexibility would make it impossible to meet the various mixtures and frequencies of radioisotopes deliveries that the research community desires. Recognition of these problems has led the committee to accept the necessity for a facility whose primary mission is the production and distribution of small amounts of a wide range of radionuclides to research scientists and the medical community: NBTF.

In the original NBTF document (Holmes, 1991) a basic parameter list indicating a proton beam current of 750 μA and an energy maximum of 100 MeV were suggested as appropriate design goals to meet the objectives of NBTF. Although a number of accelerating structures can be used to realize these parameters, attention in the future will probably focus on cyclotrons and linacs, with which there is considerable experience and expertise in both the private and the public sectors. Detailed considerations of the appropriate choice of accelerator technology will not be discussed here. These discussions will develop as NBTF moves from a conceptual design phase through to a final design that will be thoroughly reviewed. At present, upper energies of 70 to 100 MeV appear to be needed for NBTF. The costs for both cyclotrons and linacs vary approximately linearly with energy above about 50 MeV. Other considerations, such as overall operating costs, shielding requirements, and ability to access accelerator and target areas, must be answered before a final choice of accelerator technology is determined. No single solution appears to be favored at this time, but the requirements appear to be well within the reach of present technology.

In-House Research and Education at the NBTF

The committee believes that the field will best be served if the primary focus of research at the upgraded BLIP, the proposed NBTF, and the University of

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Missouri Research Reactor remains production rather than development of further applications, which is being done quite well on a decentralized basis via the peer-reviewed grant process.

The development of target and targets cooling systems capable of withstanding the high temperatures induced by high-current particle beams are essential research and development activities at any radionuclide production facility. Support for this work should be an essential element in the core funding (i.e., noncompetitive) of NBTF. Research into the target choice for any radionuclide might begin with cross-section measurements on feasible target materials. Encapsulation in the accelerator beam, cooling methods, the desired physical phase radiation effects, the optimal thickness, and the optimal density must be determined and tested. Also vitally important are the methods available for the recovery and purification of the desired product(s). The post-irradiation physical and chemical states of both the target and the radionuclides produced must be known for cost-effective and efficient separation to ensure not only pure, high-specific-activity radionuclides but also maximum reuse of often expensive enriched target material.

Some well-known radionuclide production targets could be improved substantially by focused engineering research. In some cases, this type of research has required the reallocation of funds from scientific applications programs, and generally, this type of engineering and chemistry development is not seen as a high-priority investment, even though it could significantly reduce the cost of radiopharmaceuticals. An example is the development of a target for the production of xenon-122, which is the precursor of iodine-122 (a positron emitter with a 3.5 minute half-life). There is a high degree of potential that a xenon-122/iodine-122 generator system (Lagunas-Solar et al., 1986) can be used for economical studies of brain and heart blood flow because this system obviates the need for a local cyclotron to produce ^{15}O-labeled water or 13N-labeled ammonia for similar studies. The target must be developed and married to a particular beam line at an appropriate accelerator facility (e.g., TRIUMF; Crocker Laboratory, Davis, California; BLIP; Medi-Physics, Arlington Heights, III).

The development of targets has always been based on contemporary needs such as the production of fluorine-18 or carbon-11 monoxide and carbon-11 dioxide. No effective mechanism exists for the development of new targets on the basis of an interest in a radionuclide but without knowledge of obvious and widespread applications once it is developed. Without having the radionuclide, the investigator cannot show clinical or research applications, but without some demonstration of successful applications, an investigator cannot obtain funds to develop the target to make the radionuclide in the first place. Thus, new ideas for radionuclides and radionuclide generators do not get tested.

Target technology involves mechanical, materials, and systems engineering, including automation for safe loading and unloading. Target reliability under high currents (e.g., 500 μA) and varying beam optics is an essential area that

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requires a significant investment in engineering time. Target development for a particular accelerator can cost hundreds of thousands of dollars, particularly if more than one chemical compound is synthesized. This category of targeted research is an area of focus highly appropriate for a national facility such as NBTF. Certain work involving the efficiency and/or safety of the facility's accelerator should also be included in core support, as should very early labeling work establishing feasibility. Further labeling work and other application-oriented research should be funded only by peer-reviewed grants, though it should be possible to assign projects to the facility that have been identified by DOE as important but neglected.

As with any high-quality research institution, NBTF scientists would be encouraged to apply for peer-reviewed research grants from government agencies as well as industry. Affiliation with and proximity to a major research university could also expand potential NBTF research by providing access to animal and tissue testing resources as well as patients and individuals with clinical research expertise.

Education in the nuclear sciences plays an essential role in all aspects of the infrastructure involved in the production, separation, development, use and application of isotopes, including the safe operation and maintenance of accelerator and reactor facilities. Without this activity, none of the major discoveries involving the use of isotopes and none of the daily uses and applications of isotopes mentioned in earlier chapters would be possible.

There is, however, a sense from people working in various fields of nuclear science that there is a critical shortage of undergraduate and graduate students and a great dependence on foreign-trained scientists to fill existing needs (Holmes, 1993; Choppin and Welch, 1988; Yates, 1993).

DOE has substantial legislative authority to support university research and related education. The Department of Energy Science Education Enhancement Act of 1990, Section 3161 et seq., amends the basic Department of Energy Organization Act of 1977 to include support for education as one of the major missions of the department and to authorize the development of research and educational partnerships between DOE laboratories and educational institutions at all levels.

Although the National Science Foundation (NSF) has traditionally been the federal government's primary source of support for science education, NSF has usually deferred to DOE as far as nuclear science is concerned, arguing that it is DOE that has the expertise necessary to best direct such programs. A persistent difficulty with this arrangement has been that support for nuclear science education, because it covers a very broad spectrum, has been spread widely throughout various departments within DOE, none of which feels responsible for the entire program and all of which give it a relatively low priority. Between 1989 and 1993, congressionally mandated support was provided through the University and Science Education Program, which provided funds for nuclear education-

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related engineering, graduate, undergraduate, and precollege programs is nuclear technology as well as merit-reviewed nuclear science and engineering research projects (Riggs, 1993). Without a similar congressional mandate in fiscal year 1994, funding for educational activities has declined sharply, resulting in stipend reductions for current students and a reduction in the number of new students admitted. Five programs are being considered for significant cuts in faculty (Kunze, 1994). These programs are at major research universities and train about 30 percent of radiation-based science and technology students.

Similarly, among the important statistics compiled in the National Research Council (1988) report on requirements for nuclear chemists was a 60 percent decrease in radiochemistry faculty and 57 percent decline in nuclear and radiochemistry courses offered in Ph.D.-granting departments between 1978 and 1987, despite a clear and growing need for scientists thoroughly trained in radiochemistry. Figure 4-1 shows the steady decline in the number of doctoral degrees granted in nuclear chemistry over the last two decades (Oak Ridge Institute for Science and Education, 1993).

Within nuclear medicine the primary areas of need are in radiochemistry (analysis and synthesis), training in the use of instrumentation, the design of new radionuclide generators, optimization of radionuclide production at accelerators, and development of new applications. The committee envisions the NBTF playing a large role in training in all of these areas, albeit only with the cooperation with one or more universities.

As the Society for Nuclear Medicine report (Holmes, 1991) suggests, the educational program would be similar to those at the NSF Center of Excellence. Whether sited at a university or not, NBTF must have a close association with a university and a scientific staff with university appointments. NBTF could then be an invaluable location for graduate students as well as postdoctoral fellows and visiting scientists to learn state-of-the-art radiochemical research and production techniques. An association with established research programs in nuclear medicine, radiopharmacy, or radiochemistry at an affiliated university would in turn provide NBTF with continuing sources of extramural collaborations, inexpensive labor, and intellectual stimulation. Pre- and postdoctoral fellowships, faculty scholarships, and incentives for new faculty positions should thus be part of DOE's core support for NBTF, supplemented by industry and government (DOE and others) grants to both university and NBTF staff.

CONCLUSIONS

1. In the short term there does not appear to be any problem with the availability of commercial radionuclides produced on accelerators with energies of about 30 to 40 MeV.
2. There is, however, a clear need for a higher-energy machine to provide researcher with radionuclides for new applications. Brookhaven National Labo

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ratory (BLIP) and Los Alamos National Laboratory (LAMPF), as the primary domestic sources of these radionuclides, have been unreliable because of scheduling and costs. There is also concern about each of these facilities because of their ages and the changing missions for which they were constructed. The future outlook for LAMPF is not clear, and the expertise that has been assemble there over the year will be lost when the accelerator facility is shut down. The linac

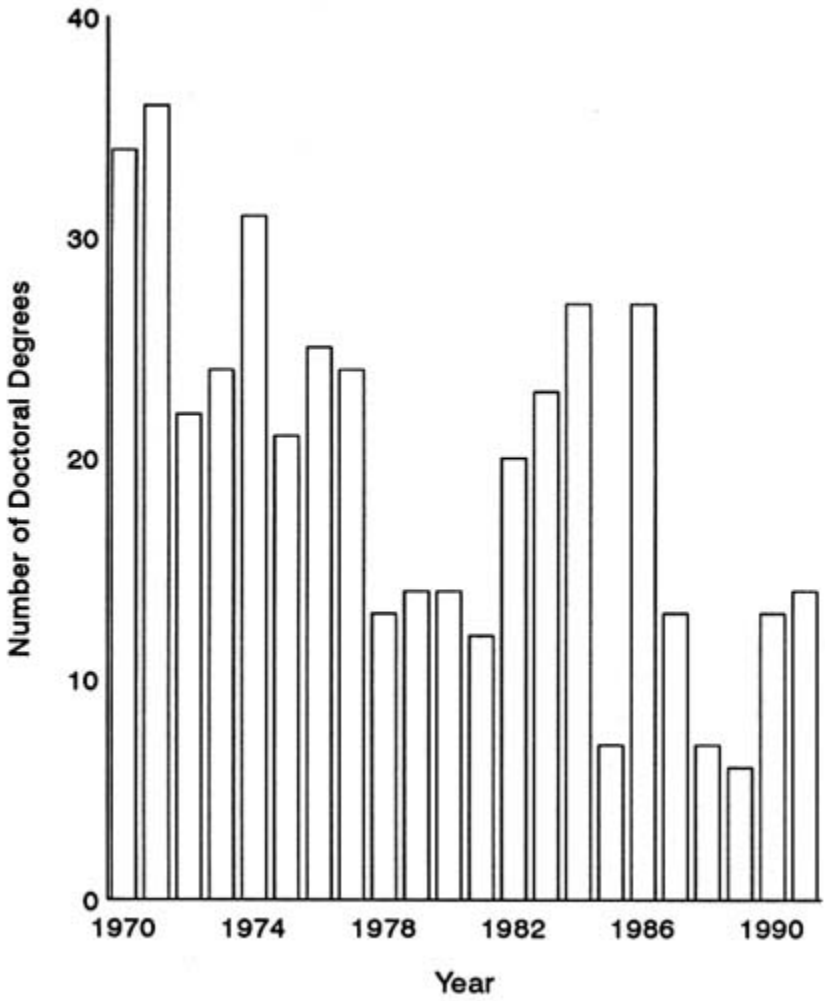

FIGURE 4-1 Doctoral degrees in nuclear chemistry awarded by U.S. universities, 1970–1991. SOURCE: Adapted from Oak Ridge Institute of Science and Education, 1993.

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that BLIP uses will continue to operate in the future since it is one of the injectors that the Relativistic Heavy Ion Collider will use when it starts operating in 1999. It is unclear how available it will be for radioisotope production, assuming that operating funds are also available. The present processing facilities at BLIP are inadequate, outdated, and poorly maintained, in part, because of their ages.

3. In the short term an upgraded BLIP facility, including an extended operating time, and the TRIUMF facility can meet many of the radiotracer needs of the research community. However, both facilities have a mandate to operate as basic physics accelerators and cannot meet the full demand for research radionuclides in their present modes of operation.
4. Base on the production reactions presented in Table 4-7, all of the radionuclides envisioned for current and future use can be prepared on an accelerator with an energy of 80 MeV.
5. The choice between cyclotron and linac is beyond the scope and expertise of this committee report, but a high beam current (750 μA or more) is required to ensure production of large quantities of a few commercially viable isotopes and allow multiple target irradiations that will produce small quantities of experimental radionuclides.

RECOMMENDATIONS

1. DOE should create a dedicated, reliable source for research radionuclides that has stable core support for the production of radioisotopes that are not available from the commercial suppliers. An NBTF that can incorporate the production facilities with the necessary infrastructure for research and training in isotope production and related activities is essential for the United States to maintain continued leadership in biomedical research using radiotracers.
2. Until such a facility is established, the needs of the isotope user community should be met by an upgraded BLIP supplemented by additional operating funds to allow for an extended operating period and a processing and distribution section that is similar to that at the University of Missouri Research Reactor. Implementation of this recommendation should alter the current basic research environment and attitude at the BLIP facility and put isotope production and distribution on equal footing with in-house medical research.
3. The cooperative arrangement between government and industry at Canada's TRIUMF facility has lead to successful technology transfer to the private sector and should be emulated in the United States. DOE should explore the utility of such models for coupling commercial production and research (see Chapter 5).
4. A national advisory committee should be established to assist in monitoring the operation of and in setting priorities for the operation of both the upgraded BLIP and NBTF (see Chapter 6).

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REFERENCES

Anderson, C. J., J. M. Connett, S. W. Schwarz, P. A. Rocque, L. W. Guo, G. W. Philpott, K. R. Zinn, C. F. Meares, and M. J. Welch. 1992. Copper-64-Labeled Antibodies for PET Imaging. Journal of Nuclear Medicine33:1685–1691.

Berman, D. S., H. Kiat, K. F. Van Train, G. Germano, J. Friedman, and J. Maddadi. 1993. Exercise Imaging Studies for the Diagnosis of Coronary Artery Disease. American Journal of Cardiology69:3–8.

Boothe, T. E.1991. Utilization of a Hospital Based Cyclotron for Commercial Radionuclide Production. Nuclear Instruments and MethodsB56–B57:1266–1269.

Budinger, T. F.1988. Single Photon Emission Computed Tomography. In: A. Gottschalk. P. B. Hoffer and E. J. Potchen (eds), Diagnostic Nuclear Medicine (2nd edition), Vol. 1, 111–127. Baltimore: Williams & Wilkins.

Choppin, G. R., and M. J. Welch (eds) 1988. Training Requirements for Chemists in Nuclear Medicine, Nuclear Industry, and Related Areas: Report of a Workshop. Washington, D.C.: National Academy Press.

Cole, D.1992. BLIP Isotope Production Study. Office of Health and Environmental Research, U.S. Department of Energy. December, 1992. Photocopy.

Evans, D. J.1993. Presentation to the Biomedical Isotopes Committee, Institute of Medicine, National Academy of Sciences, Washington, D.C., November 19, 1993.

Fischer, R., J. Wendel, B. Dresow, V. Bechtold, and H. C. Heinrigh. 1993. ^{205}Bi/^{206}Bi Cyclotron Production from Pb-Isotopes for Absorption Studies in Humans. Applied Radiation Isotopes44:1467–1472.

Grant, P. M., D. A. Miller, J. S. Gilmore, and H. A. O'Brien, Jr.1982. Medium-Energy Spallation Cross Sections. I. RbBr Irradiation with 800-MeV Protons. International Journal of Applied Radiation Isotopes33:415–417.

Hamilton, J. G., and R. S. Stone. 1937. Excretion of Radio-Sodium Following Intravenous Administration to Man. Proceedings of the Society of Experimental Biology and Medicine35:595–598.

Hertz, S., A. Roberts, and R. D. Evans. 1938Radioactive Iodine as an Indicator in the Study of Thyroid Physiology. Proceedings of the Society of Experimental Biology and Medicine38:617–619.

Hogan, J. J.1976. Isomer Ratios of The Isotopes Produced in 10-65 MeV Bombardments of ^{96}Mo. Journal of Inorganic and Nuclear Chemistry35:705–712.

Holmes, R. A.1991. National Biomedical Tracer Facility Planning and Feasibility Study. New York, N.Y.: Society of Nuclear Medicine.

Holmes, R. A.1993. U.S. Dependence on Foreign Isotopes. Statement to the Subcommittee on Energy, Committee on Science, Space and Technology, U.S. House of Representatives, Washington, D. C., October 14, 1993.

Kliewer, K. L., and M. A. Green, eds. 1992. Proceedings of the Purdue National Biomedical Tracer Facility Workshop. Purdue University, West Lafayette, Ind., April 28–30, 1992.

Kunze, J. F.1994. Letter to House Energy Subcommittee dated May 22, 1994.

Lagunas-Solar, M. C., O. F. Carvacho, L. J. Harris, C. A. Mathis. 1986. Cyclotron Production of ^{122}Xe(20.1 h)Å^{122}I(b+77%; EC 23%;3.6 min) for Positron Emission Tomography. Current Methods and Potential Developments. Applications of Radiation and Isotopes37:835–842.

Lawrence, J. H., L. W. Tuttle, K.C. Scott and C.L. Conner. 1940. Studies on Neoplasms with Aid of Radioactive Phosphorus. I. Total Phosphoros Metabolism of Normal and Leukemic Mice. Journal of Clinical Investigation19:267.

Lunqvist, J., and P. Malmborg. 1979. Production of Carrier-Free ^{28}Mg and ^{24}Na by 50–180 MeV Protons on Si, P, S, Cl, Ar and K: Excitation Functions and Chemical Separation. Applied Radiation Isotopes44:575–580.

McAfee, J. G.1989. Nuclear Medicine. Report for the U.S. Department of Energy Office of Energy Research on the Department's Nuclear Medicine Research Program by the Health

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http://www.nap.edu/catalog/4818.html

and Environmental Research Advisory Committee (HERAC). Washington, D.C.: U.S. Department of Energy.

Martin, J. A.1979. Cyclotrons—1978. Proceedings of the Eighth International Conference on Cyclotrons and Their Applications. Institute of Electrical and Electronics Engineers Transactions of Nuclear ScienceNS26:2443–2651.

Mausner, L. F., S. Mirzadeh, and S. C. Srivastava. 1986. BLIP II: A New Spallation Radionuclide Research and Production Facility. Journal of Labelled Compounds and Radiopharmaceutical Chemistry23:1386–1388.

Moody, D. C. and E. J. Peterson, eds. 1989. Proceedings of the DOE Workshop on the Role of a High-Current Accelerator in the Future of Nuclear Medicine, Report No. LA-11579-C. Los Alamos, N. M.: Los Alamos National Laboratory.

Nickles, R. J.1991. Production of a Broad Range of Radionuclides with an 11 MeV Proton Cyclotron. Journal of Labelled Compounds and Radiopharmaceutical Chemistry30:120–121.

Oak Ridge Institute of Science and Education. 1993. Status of Graduate Programs in Radiochemistry and Nuclear Chemistry, 1992. Oak Ridge, Tenn.: Oak Ridge Institute for Science and Education.

Pate, B. D.1979. Medical Radioisotope Production at TRIUMF. In Proceedings of the 27th Conference on Remote Systems Technology. Washington, D.C. : American Nuclear SocietyPp. 283–284.

Riggs, J. R.1993. Statement to the Subcommittee on Energy, Committee on Science, Space and Technology, U.S. House of Representatives, Washington, D.C., October 14, 1993.

Ruth, T. J., B. D. Pate, R. Robertson, and J. K. Porter. 1989. Radionuclide Production for the Biosciences. Nuclear Medicine and Biology16:323–336.

Steyn, G. F., S. J. Mills, F. M. Nortier, R. S. Simpson, and B. R. Meyer. 1990. Production of ^{52}Fe Via the Proton-Induced Reactions on Manganese and Nickel. Applied Radiation Isotopes41:315–325.

Szelecsenyi, F., G. Blessing, and S. M. Qaim. 1993. Excitation Functions of Proton Induced Nuclear Reactions on Enriched ^{61}Ni and ^{64}Ni: Possibility of Production of No-Carrier-Added ^{61}Cu and ^{64}Cu at a Small Cyclotron. Applied Radiation Isotopes44:575–580.

Welch, M. J.1992. Positron Emission Tomography. In D. E. Moody, and E. J. Peterson, eds. Proceedings of the DOE Workshop on the Role of a High-Current Accelerator in the Future of Nuclear Medicine. Report No. LA-11579-C. Los Alamos, N.M.: Los Alamos National Laboratory.

Welch, M. J., and M. R. Kilbourn. 1988. Potential of Monoclonal Antibodies with Positron Emitters. In S. C. Srivastava, ed., Radiolabeled Monoclonal Antibodies for Imaging and Therapy. New York, N.Y.: Plenum Press.

Wolf, A. P.1984. Cyclotrons, Radionuclides, Precursors, and Demands for Routine Versus Research Compounds. Annals of Neurology15(Suppl.):S19-S24.

Wolf, A. P., and W. B. Jones. 1983. Cyclotrons for Biomedical Radioisotope Production. Radiochimic Acta34:1–7.

Yates, S. W.1993. Future Challengers in Nuclear Science Education. Journal of Radioanalytical and Nuclear Chemistry171:15–21.

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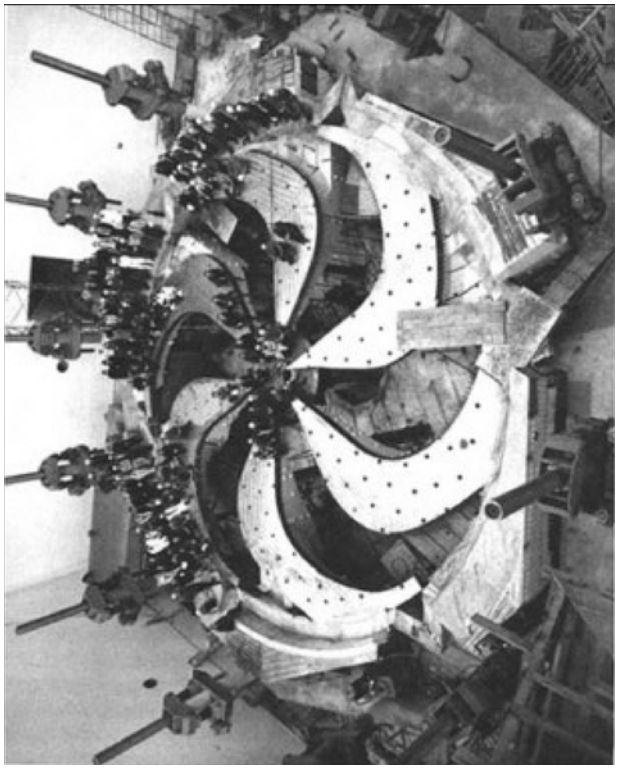

TRIUMF 500-MeV clyclotron lower magnet pole face during construction.SOURCE: Tri-University Meson Facility.

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5

Public-Private Partnership Models for NBTF

The previous chapters have documented the need for a dedicated national accelerator facility, primarily for the production of isotopes for research in the life and physical sciences. There will also be commercial components of this facility, because some radioisotopes produced by a National Biomedical Tracer Facility (NBTF) will become important in the private sector. Indeed, the Committee was specifically asked to address the possibility of some sort of public-private partnership in its deliberations on the best use of the capabilities of each sector. The variety of benefits from the envisioned NBTF coupled with the technical complexity of the facility argue for the formation of a partnership among industry, national laboratories, and universities to operate it. The purpose of this chapter is to review existing examples of such partnerships and to provide a preliminary description of a possible model for operating NBTF. We expect that other models of this general form will be provided by the five grantees now preparing detailed NBTF Project Definition Phase proposals for DOE, and do not wish to imply that the version presented here is the only acceptable one.

The recent failures of the Isotope Production and Distribution Program (IPDP) of the U.S. Department of Energy (DOE), in contrast to the previous long-term successes of U.S. isotopes research programs, are discussed here. The passage of the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101) required the change of that isotope production and distribution be done on a full cost recovery basis, which contributed to the decline of isotope sales and profitability. The difficulty for a DOE operation to function in a standard business mode has led to the suggested involvement of the private sector in a future facility that would include the sale of isotope products and related services. The very successful partnership between the private company, Nordion

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International, Inc., and the Canadian Tri-University Meson Facility, (TRIUMF), impressed the committee, and the committee suggests the establishment of such a partnership in the United States.

There are a variety of existing partnerships involving industries, national laboratories, and universities. The establishment of the national laboratories after World War II led eventually to intimate partnerships, first with universities and, more recently, with private companies. The use of national laboratory facilities by faculty, staff, and students at universities has been very strong in the last 30 years, and these facilities have been established on a peer-reviewed basis with no use charges. Industries also have access to these facilities on a cost-reimbursement basis. In addition, there has been an emphasis on the transfer of technology from the national laboratories to the private sector. Since 1989 a new emphasis has been on cooperative research and development agreements (CRADA), by which the cost of cooperative research at a national laboratory is shared by the facility and the private partner. CRADAs not only bring new sources of joint endeavors and funds to national laboratories but also shift the emphasis from new technology being "pushed" to the private sector to technological advances being "pulled" from the laboratories to industry according to proprietary needs.

The legal basis for the isotope program and related issues are reviewed (and discussed more extensively) in Appendix B. It is clear that public laws have led to the difficulties that DOE experiences in competing with industry for the sale of materials, and it is important to consider their background and full implications.

The desired benefits of NBTF, combined with the legal and operational constraints on DOE, led to the suggestion that an industry-national laboratory-university partnership is important for the operation of NBTF. A university partner is important for leading the educational functions; the technological infrastructure of a national laboratory would greatly benefit the construction and operation of such a highly technical facility; and the industrial partner would take the lead on the marketing, shipping, and sales of those radioisotopes that are commercially attractive. Such a model is discussed below.

THE DOE ISOTOPE PRODUCTION AND DISTRIBUTION PROGRAM

The production, supply, and sale of isotopes have been longstanding activities of DOE and its predecessors, the Atomic Energy Commission and the Energy Research and Development Administration. Even though the production of and the research conducted with a wide variety of isotopes were strictly adjuncts of nuclear physics research, defense, and nuclear power development programs, these isotopes programs are among the best examples of technology transfer from government research to commercial application. The very existence of certain entire industries, the $2 billion a year field of nuclear medicine among them, is

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attributable to basic research with and the continued production of isotopes at DOE's national laboratories. Some isotopes and related services are still provided only by DOE by virtue of both its unique facilities and its tradition and interest in promoting the research and development of new isotopes and applications not yet to the stage where they appear lucrative to commercial producers.

Prior to 1989 responsibility for the management of isotope production and distribution was spread across the Office of Energy Research and several other organizations at DOE headquarters, and actual operations were carried out at a half dozen or more DOE facilities widely scattered throughout the United States. None of the entities supporting work on isotopes was responsible for the entire program, so many problems of supply, cost, delivery, or prioritization went unsolved or were at least not solved to the satisfaction of many of the customers created by the early and widespread success of the work. In 1989, DOE established a single central office within the Office of Nuclear Energy with responsibility for managing the entire isotope enterprise except that for uranium: IPDP. In its 1990 budget request, DOE requested, and U.S. Congress concurred, the establishment of a revolving fund for isotope production and distribution in lieu of annual appropriations to the array of programs and facilities previously funding such work. Public Law 101-101 provided a little more than $16 million as initial capitalization for the fund, and both Congress and DOE envisioned that revenues from sales would subsequently balance expenditures from the fund for production and distribution costs. This statutory requirement for self-sufficiency was apparently based in large measure on the prior year's $15 million in isotope sales, but it was not until after passage of the act that DOE was required to report on the details of such matters as the condition of production facilities and plans for their replacement, expected requirements in the areas of environmental and waste treatment expenses, and detailed financial plans for achieving full cost recovery of isotope production and distribution.

Despite optimistic projections, the IPDP's operating expenditures have consistently exceeded sales revenues (Arthur Andersen & Co., 1993; KPMG Peat Marwick, 1992). In addition, IPDP has spent $11 million on process development for new products (e.g., molybdenum-99, the reactor product that accounts for 30 to 40 percent of the world radioisotope market). As a result, the revolving fund has been depleted and IPDP had to borrow $8.5 million from the U.S. Treasury in fiscal year 1992 and $5 million in fiscal year 1993. The IPDP program director's analysis of the reasons for the program's inability to recover its costs include undercapitalization (the aforementioned lack of detailed financial plans), preexisting DOE policies preventing competition with domestic industry, little control over production costs and schedules because of reliance on manufacturing facilities with missions unrelated to isotope production, competition from foreign suppliers with government subsidies, government bureaucracy, and poor business management practices. A U.S. General Accounting Office (1992) study also identified foreign competition and high operating costs as key factors in the

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inability of IPDP to sustain itself. IPDP subsequently contracted with Arthur Andersen & Co. for a comprehensive business management study and asked for recommendations for making the program efficient and sustainable.

The Arthur Andersen & Co. report (1993) identified four crucial conditions for IPDP success: (1) reliable access to production facilities, (2) reasonable and predictable operating costs at these facilities, (3) reduction in unprofitable capacity, and (4) separate funding for research-oriented isotopes. The report makes the important observation that it is the longstanding research mission of DOE's national laboratories and the deeply ingrained culture that that mission has engendered that has made it impossible to achieve these conditions. The Arthur Andersen & Co. report also provided an extensive series of recommendations for making the IPDP operation more businesslike. The committee believes that although the cultural conflict identified by the Arthur Andersen & Co. report is on target, the solution is not to attempt to transform the national laboratories into efficient businesses but to allow these research and development laboratories to focus on what they do best and leave the conduct of efficient business to efficient businesses.

Isotope production itself has grown up as an adjunct of the admonition of the Atomic Energy Act of 1954 for the Atomic Energy Commission to "insure the continued conduct of research and development … and assist in the ever-expanding fund of theoretical and practical knowledge in fields relating to nuclear processes and the theory, production and use of atomic energy, including specifically, medical, biological, agricultural, health, industrial, and commercial uses." The Energy and Water Development Appropriations Act of 1990 (Public Law 101-101), which established the revolving fund and required full cost recovery by IPDP, does not explicitly change the mission of IPDP and makes no distinction between the production and the distribution of isotopes to the research community and supplying high-volume, commercial-use isotopes to the private sector. To date IPDP has tried to remain faithful to the research mission and culture in which it arose, despite the clear implication of Public Law 101-101 that the production of high-cost, noncommercial isotopes would have to be curtailed or eliminated and facilities operating at less than full capacity would have to be dropped from the program. There is thus a real conflict within IPDP between the practical policies for the production and distribution of isotopes for the research community (in which full cost recovery can hardly work) and the sale of isotopes to commercial users in the private sector (in which such a policy is appropriate). (See Appendix B for a fuller discussion of these and other relevant statutes.)

Although there may be some ambiguity of mission within the IPDP itself, Public Law 101-101 nowhere specifically addresses the implications for the national laboratories on which IPDP depends for isotope production. IPDP still uses production facilities whose main mission is not isotope production but research in physics, nuclear power, radiation effects, and a myriad of other topics. The laboratories are designed, staffed, and operated as research institutions rather than

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efficient manufacturing plants. The costs of operating these facilities are apportioned to the programs that use the facility (reactor, accelerator, etc.) on a pro rata basis, and priority for use of the facility is based on the laboratory director's assessment of scientific and research needs. As a result, IPDP cannot readily reduce its costs, and it may find them rising uncontrollably because of changes in other programs that share the facility. Business success by IPDP, that is, selling more isotopes, may actually result in a profit-erasing rise in fixed overhead, since more production will require more hours of reactor or accelerator use. As a result, the IPDP finds itself unable to negotiate long-term supplies and prices with customers, which are the keys to any successful business. Without more control over operating costs and use of the manufacturing facilities, internal changes in the operation of IPDP will be insufficient to allow for the consistent recovery of the full costs of isotope production. Recognition of these problems is not unique to this committee. In fact, it was precisely this problem of the lack of control of costs and facility use that underlay the proposal by the Society for Nuclear Medicine for a stand-alone, DOE-supported accelerator facility dedicated to the production and distribution of medical isotopes. NBTF. *This committee is in agreementwith the underlying assumption of that proposal that the existingDOE national laboratory system cannot be, and perhaps should notbe, turned on its head to support a successful product of its research,that is, nuclear medicine*. The committee had reservations, however, about simply endorsing a new federally owned and operated facility and explored the possibility of a public-private partnership of the type that the committee observed in Canada.

CANADA'S TRIUMF

The relationship between TRIUMF, Canada's national laboratory for meson research, and Nordion International Inc., a private for-profit company that produces and markets radioisotopes, appears to be a successful marriage, mutually beneficial, and perhaps an admirable model for a U.S. NBTF. Representatives of the committee visited the TRIUMF campus in Vancouver, British Columbia, Canada to investigate this partnership.

The TRIUMF-KAON Ventures Office (recently renamed the TRIUMF Technology Transfer Office) was set up in 1990 to formalize and optimize technology transfer and to generate income for TRIUMF beyond federal funding restricted to research and development and cyclotron operation. These objectives are accomplished by: (1) consulting to industry, (2) using industry-funded rotation of staff to and from industry, (3) providing license agreements to the industries to produce and sell products developed at TRIUMF, (4) creating joint ventures, and (5) creating start-up companies with former TRIUMF staff. The Technology Transfer Office itself was initially funded by a grant from the province of British Columbia, but it is expected to become at least revenue neutral via royalties and salary recovery for TRIUMF staff on loan or consulting to industry. In fiscal year

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1992–1993, TRIUMF received nearly $800,000 in royalties from approximately $20 million in industry sales and about $900,000 in salary recovery.

Located on the campus of the University of British Columbia, TRIUMF operates its 520 million electron volt (MeV) cyclotron with a staff of 370 (supplemented by up to 200 visiting scientists and technicians during experiments, 40 Nordion employees, and perhaps a few employees of other industry-commercial partners). Annual operating costs of about $37 million Canadian dollars are borne by the Canadian National Research Council ($31 million) grants from various funding agencies, mostly federal ($5 million), and royalties from the commercialization of technologies ($1 million).

NORDION AND ISOTOPES

Nordion International has an exclusive 30-year (1989 to 2019) technical support agreement with TRIUMF, making it the sole commercializer of isotopes from TRIUMF and making TRIUMF in turn the exclusive supplier of accelerator isotopes to Nordion. Nordion owns and operates two cyclotrons, a CP-42 (42-MeV) cyclotron and a TR-30 (30-MeV) cyclotron, on the site in the Chemistry Annex, a structure built by Nordion and shared with TRIUMF staff, which also receives CP-42 beam time as part of the technical agreement. During the committee visit, staff from TRIUMF as well as Nordion all insisted that Nordion pays all operational costs for such services, including power, and in addition pays royalties to TRIUMF on all products sold. The committee was unable to obtain a summary statement of those charges for services rendered, although royalties were reported to be $700,000 in 1993 and were expected to reach $900,000 in 1994. In return, TRIUMF contributes world-class expertise in the operation and maintenance of cyclotrons. TRIUMF apparently charges Nordion a somewhat more than nominal salary and benefits when they make official use of this expertise (interactions at the watercooler and coffeepot are still free). Most likely, Nordion is charged in a manner comparable to that recommended by the Arthur Andersen & Co. Report for the federal U.S. IPDP, that is, incremental overhead.

The Nordion site manager gave the committee's representatives a brief history of the Nordion-TRIUMF relationship, which began in 1978 while what was to become Nordion International, Inc. (Radiochemical Company) was still part of Atomic Energy of Canada Limited (AECL), processing and selling reactor isotopes produced by the Research Company of AECL at the Chalk River (NDU) reactor. The CP-42 cyclotron was installed in 1982 and commercial-scale production began. Not until 1987 did the business turn to profit, at which point the Radiochemical Company, renamed Nordion, was sold to MDS for $165 million, the present 30-year agreement was signed, a radiopharmaceutical program was begun, and a second cyclotron was commissioned. Although Nordion has access to TRIUMF's 520-MeV cyclotron, the majority of Nordion's production is accomplished with the smaller cyclotrons (see Chapter 4).

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The TRIUMF long range plan requests some $700,000 for a new, highly automated Radiochemistry/Isotope/Pharmaceutical Laboratory for the separation of radiochemicals from targets, the preparation of new radiochemicals that mimic chemicals used in metabolism, and experiments, including animal tissue preparations, that will indicate the suitabilities of these chemicals and associated radiopharmaceuticals. The justification offered is a desire to continue the isotope research that has been so successfully brought to market by Nordion.

A strongly held belief of both partners in this relationship is that the symbiosis that emerges is a result of the complementary relationship between government-supported high-technology scientists pursuing basic research (not limited to isotopes or medicine) and profit-oriented, market-driven people in the private sector. A purely private NBTF would very likely sacrifice this mixture, as would a purely nonprofit facility, government or private.

UNIVERSITIES AND NATIONAL LABORATORIES IN RESEARCH

DOE's national laboratories have had extensive collaborations with universities and university research groups. Several of these laboratories are actually run by a university or an association of universities under contract to the DOE—for example, Argonne National Laboratory (University of Chicago), Brookhaven National Laboratory (Associated Universities, Inc.), and Lawrence Berkeley, Lawrence Livermore, and Los Alamos National Laboratories (University of California).

One of the functions of the DOE national laboratories is the operation of large, generally one-of-a-kind user facilities such as those employed for research in high-energy and nuclear physics and in condensed-matter and materials research. This is a model that has not been used as frequently in radioisotope production and biomedical research as in the physical sciences. Such facilities are open to researchers from the United States and abroad, typically through a peer-reviewed mechanism that selects the most outstanding research programs. The research teams that use these facilities are often composed of individuals or groups from within the DOE laboratory in collaboration with researchers from one or more universities. Other collaborations may involve a single university group or a collection of university groups, with no in-house research team. In this case, the university groups depend on the laboratory to operate the facility for them. In some cases, a complex national user facility is not required, but rather the appropriate laboratory space (e.g., chemistry labs and hot cells) needed to carry out the research efforts (most of this activity would be in collaboration with an in-house person of a research group). Finally, in many instances, individuals have joint appointments with the university and the national laboratory, which can facilitate the research process.

A rich history of close collaboration between universities and the DOE national laboratories exists. With regard to a future biomedical isotope facility, such

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as NBTF, such cooperation will be required wherever it is located. To facilitate a successful marriage between the university community and the laboratory hosting NBTF, cooperative arrangements and agreements would have to be put in place at the earliest possible time, even before a final site is selected. This will help to ensure that such a facility will be designed and operated to the standards and goals of the national user community.

DOE LABORATORY AND UNIVERSITY PARTNERSHIPS WITH COMMERCIAL VENTURES

Radiation Therapy at Brookhaven

Several existing and planned joint ventures involving federal laboratories provide further encouragement for emulating the TRIUMF-Nordon partnership for a U.S. NBTF. Brookhaven National Laboratory (BNL), for example, has been involved in a for-profit radiation treatment facility operated jointly with the State University of New York at Stony Brook (SUNY-SB). This is a simple contract for services SUNY-SB and the DOE contractor that operates BNL, Associated Universities, Inc. (AUI). In this case, AUI-BNL provides the building and support staff whereas SUNY-SB staff operate the commercially purchased machine and provide the cancer patients who are treated there. Although AUI's only monetary stake in this partnership is reimbursement for expenses, the arrangement also provides patients for clinical research and, in addition, a professional attraction for AUI, BNL, and SUNY-SB scientists.

Along the same lines, plans for a slightly more ambitious venture are also under way at BNL. The plans center around a currently unused beam line from the linear accelerator. According to BNL officials, capital for a proton therapy treatment center on the BNL campus is being sought from a consortium of medical centers, including SUNY-SB and the private sector. The laboratory envisions a contract for services similar to the existing one with SUNY-SB, but encompassing refurbishment of the BNL-owned facility as well as actual operations.

Continuous Electron Beam Accelerator Facility (CEBAF)

Somewhat more complicated and closer to the Canadian model could be an evolving network of partners associated with the Continuous Electron Beam Accelerator Facility (CEBAF), which is nearing completion in Newport News, Va. Scheduled to begin its nuclear physics experimentation in late 1994, this DOE-owned, contractor-operated facility has been managed to date by the 41-member Southeastern Universities Research Association. Two additional partners have emerged during the course of planning and construction: the city of Newport News, which has donated a guest house valued in the range of $700,000, and the Commonwealth of Virginia, which has contributed an estimated 5 per

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cent of construction costs in the form of in-kind assistance and promised $1 million a year for 5 years for professional personnel in the form of faculty appointments at elite universities. Eight commonwealth professorships have been established.

Like TRIUMF, CEBAF has made technology transfer an integral part of its mission. An Industrial Advisory Board (IAB) composed of representatives of local and national industries was formed in 1991, long before the anticipated start of operations, to identify technology transfer opportunities and to provide advice from an industrial perspective. IAB, for example, identified the potential utility of some of CEBAF's X-ray sources to industrial firms specializing in the nondestructive testing of materials like oil pipelines and aircraft wings, and after announcing its intentions in the *Federal Register*, CEBAF has transferred the technology to a local company. IAB also noted the potential of CEBAF's superconducting radiofrequency cavities as a driver for a high-power, free-electron,monochromatic, tunable laser useful to industry in applications ranging from making antistatic coatings for carpets and bonding plastic auto parts to developing synthetic skin and blood vessels. As a consequences, a Laser Processing Consortium has formed. The consortium includes DuPont, IBM, 3M, AT&T, Newport News Shipbuilding, a regional technology development center, CEBAF, and several universities. Funds are being sought to use three spare radiofrequency cavities as the key components of a 1-kilowatt free-electron laser for industrial users. This exciting technology transfer opportunity does, however, illustrate a problem common to public-private partnerships involving highly technical processes: the need for a large capital investment. Funds in the vicinity of $30 million are needed for the construction of this industrially oriented spin-off facility at CEBAF. The private sector is not willing to make such a large capital investment until it can use such a facility to test the applications from the stand-point of their technical and financial feasibilities. If the federal government were to make this investment, industry would test these issues and later construct a scaled-up free-electron laser facility at much higher power.

The director of CEBAF does not envision this joint venture as anything more than an efficient means of making optimal use of CEBAF research and development capabilities, but the possibility of significant royalty streams is obvious.

Technology Transfer and Cooperative Agreements

DOE supports 9 multipurpose laboratories (so-called national laboratories) and in addition 12 major and 8 to 11 smaller single-purpose laboratories. The total budget for these many laboratories is $6.6 billion per year (Schacht, 1993). These laboratories represent a tremendous technology infrastructure and source of research and development in the United States. The primary mission of these various DOE laboratories is research and development according to the defined priorities of the department. Another mission, perhaps more recent in emphasis,

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is technology transfer of the products of past research and development work. This involves the transfer of existing technologies from the laboratories to the private sector. The term commonly used for this process is technology push, in which innovations developed as a result of mission-oriented research and development are pushed to the private sector if there is an eventual need in the market-place. Historically, the emphasis has been on technology push, since the laboratories have, in general, been forbidden from competing with the private sector and can offer help and assistance only when it is not available elsewhere. The laboratories' emphasis is still on the research and development mission, and so different forms of technology transfer must support but not interfere with this basic mission.

Since the late 1980s, a new emphasis concerning technology transfer has arisen within the federal government (Schacht, 1993). Reflecting the change in emphasis, the DOE fiscal year 1993 budget statement emphasized the "strategic" use of the national laboratories through the transfer of technology to the private sector. Through this statement, technology transfer is to be a priority mission of every DOE research and development program. This was further refined in the fiscal year 1994 budget statement from DOE, because it emphasized the full integration of the technology transfer mission to all aspects of DOE research and development. These emphases reflect an attempt to change the technology transfer direction within DOE laboratories from the classical technology push to a perhaps more modern technology pull. DOE is struggling with the ways in which the research and development programs of the laboratories might be positioned through contacts with the private sector, to pull a desired technology from DOE work into a need of industry. Such an emphasis on technology pull is, however, fraught with difficulties, because it seems to require at least some adjustments in the stated missions of DOE laboratories. If the needs of particular private-sector enterprises are considered in the program of research and development work in DOE laboratories, then questions arise as to which industries have priority, whether the selection of one company over another would lead to market distortions, and whether the goals of the federal government and the private sector can really coincide in such intimate detail. Another concern is whether public sector needs would be neglected if too much emphasis at DOE facilities is put upon the technology desires of the private sector. These questions lead to the issue of redefining the mission of the federal laboratories to include assistance to industries as a basic goal. These issues are being debated within the federal government.

Despite this continuing debate over the technology transfer mission, large changes in the mechanisms of the cooperations have occurred in the past 5 years. CRADAs were established through the Federal Technology Transfer Act of 1986, (Public Law 99-502; see Appendix B) as a mechanism for government and industry to be able to work together. The authorization to establish CRADAs at government-owned contractor-operated facilities was established by the fiscal year 1990 Defense Authorization Act, (Public Law 101-189). CRADA is a vehicle for

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cooperative work between an industry and a government laboratory, with a sharing of the costs. The laboratory may accept funds and services from the private-sector partner and may provide personnel and services (but not funds) to that partner. BNL, for example, currently has a CRADA with a private-sector partner and the goal is the development of small radiolabeled peptides for thrombus and inflammation detection. At the moment, the private-sector partner provides candidate compounds and BNL's Medical Department does the laboratory and imaging studies necessary to establish potential utility. The terms of the agreement call for the private-sector partner to provide additional personnel (or funds for such personnel) and instrumentation in the event that a promising compound emerges.

A similar CRADA between the Lawrence Berkeley Laboratory and a private partner (SOMATIX) will evaluate new methods of gene therapy by positron emission tomography (PET) monitoring.

Intellectual property issues are settled at the inception of CRADA. For example, inventions made by an employee of the participating laboratory may, by agreement, be granted to the participating private-sector entity. CRADAs are also sometimes used to formalize collaborations between national laboratories and private research industries for research and development funded by the Small Business Innovative Research program. In such cases, called *funds-in CRADAs*, it is not necessary for either party to provide direct financial support, since the projects can be totally funded through the Small Business Innovative Research program. An example of such a CRADA is one between Argonne National Laboratory and AccSys Technology, Inc., of Pleasanton, Calif., for accelerator development. A goal of this particular program is to develop linear accelerator structures on the basis of superconducting radiofrequency techniques that would lead to more cost-effective, compact machines that produce isotopes for PET. Since the development is also relevant to future DOE programs, it is mutually beneficial.

The establishment of CRADAs came slowly after the legislation was passed, because the DOE took too long and wrote far too many regulations for the establishment of CRADAs (Arthur Andersen & Co., 1993). Common complaints were that the establishment of a CRADA was far too difficult and took far too long for industries to be very interested in this possibility. This criticism has led to an attempt to streamline the CRADA mechanism by DOE, to shorten the time of approval, to give more authority for CRADA establishment to the laboratory director, and to designate more DOE funds to be available in support of CRADAs. By June of 1993 nearly 400 CRADAs between DOE facilities and partners from the private sector had been signed, and the average length of the approval time was 32 weeks (Schacht, 1993). The establishment of new CRADAs accelerated in 1994. For example, Oak Ridge National Laboratory, has now entered into 130 approved CRADAs representing research and development totaling $200 million. The incentive for the laboratories to enter into CRADAs is demonstrated by

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the availability of DOE funds to support the laboratory portion of the cooperative work. In a time of shrinking budgets for basic research, the availability of funds for "strategic" research via the CRADA mechanism is quite important.

POSSIBLE MODEL FOR NBTF

The earlier sections of this report have documented in detail the needs for an NBTF. The report has also discussed the difficulties that DOE has in the marketing and sale of isotopes currently produced at its national laboratories. The current DOE operation for isotope production (stable and radioactive) is not commercially self-sufficient because DOE cannot compete with the private sector, negotiate prices freely with customers, commit to long-term supply and pricing, and even control its costs. It is clear that the commercial aspects of NBTF (i.e., the marketing, distribution, and sale of radioactive isotopes) must be handled by a private company. However, it is also clear to the committee that the research and educational aspects of NBTF must be operated by a not-for-profit institution, that is, a university, a national laboratory, or some combination. This judgment comes from a concern that a private company could not dedicate its personnel and facilities sufficiently to nurture these research and educational activities, since its top mission is to realize a profit. This dichotomy leads the committee to the conclusion that a public-private partnership is essential for the operation of NBTF.

As discussed in previous sections, it is not clear that current DOE regulations, the definition of its missions, and the interpretation of public laws actually allow for the establishment of a public-private partnership for education, research, and the production and sale of materials. The committee is drawn to the Canadian model, in which the private sector company, Nordion has its own facilities (cyclotrons and associated equipment) on-site at the TRIUMF facility (a national laboratory) in Vancouver. Nordion uses both its own cyclotrons and also the large 520-MeV TRIUMF cyclotron for the production of radioisotopes to be sold to their customers. Nordion not only pays the Canadian federal government for the use of space, support, and federal equipment but also returns a royalty to the national laboratory on the basis of isotope sales. This relationship is mutually beneficial, and the interchange of personnel between the two entities is amazingly seamless.

The committee proposes such a public-private partnership for the operation of NBTF. Among the factors in judging a successful bid, DOE would consider the nature of the partnership with a certain national laboratory or university, the market expertise of the company in the production and sale of radioisotopes, and the proposed return of royalties from the profits on the sales to NBTF. In this partnership scenario, DOE would assume the cost of construction of NBTF, and would not seek reimbursement for this from the private-sector partner. At least as it is now envisioned, the main emphasis of NBTF is to produce isotopes not available from other sources for research, which makes it impossible to ask for

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construction funds from the private sector. NBTF would be a facility dedicated primarily to the production of a wide variety of isotopes unavailable from commercial sources, with the anticipated sale of produced radioisotopes whenever a market opportunity occurs. DOE would fund (in whole or in part) the operation of research isotope production and the educational program as part of its public research and development mission. It is clear that these research and teaching elements are crucial to the future health of the field of nuclear medicine, both in the education of new leaders and i the evolution of new techniques and radioisotopes. This funding for teaching and research on isotopes would flow from DOE through the not-for-profit partner of the collaboration. It is anticipated that royalties from the sales of materials by the private-sector partner would contribute to the operation of DOE programs.

In this model, the private-sector partner would handle and be financially responsible for the production, packaging, marketing,pricing, and sales of radioactive isotopes. The for-profit partner would pay the not-for-profit partner the cost of producing any radionuclide to be sold commercially. Also, the two partners would agree on special pricing (at less than full cost) for radioisotopes produced for research at NBTF or elsewhere. The researchers themselves would of course pay some portion of those costs through their grants, as they do now, with prices most likely negotiated on a case by case basis. It is anticipated that there would be a migration of radioisotopes from the research category to the commercial product category. By this arrangement, most or all constraints that affect DOE efforts in these areas would be absent. Because of the multiple users of NBTF (in-house researchers, extramural researchers, and commercial customers), there would be an agreement between the public- and private-sector partners on the use of the beam time for the production of radioisotopes necessary for approved research programs, for the development of new techniques in approved research projects, and for the production of material for commercial uses. To make such a partnership function on a mutually profitable basis, there would need to be a strong management board that oversees the complete operation, approves the distribution of beam time, understands the financial aspects of the commercial activities, monitors the return of royalties from the private-sector partner to the not-for-profit partner, and sets the board policies for the operation of the facility. Although such a complex partnership would initially be difficult to operate, the committee believes that the model is not only necessary for the goals of NBTF but also important as a model for other federal facilities in different fields of endeavor.

CONCLUSIONS

1. The current DOE operations for isotope production (stable and radioactive) are not commercially self-sufficient because the leaders of these operations cannot:

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a. negotiate prices freely with customers,
b. commit to long-term supply and pricing,
c. compete with the private sector, or
d. control their costs (e.g., avoid new DOE regulations with respect to waste management and remediation).

2. The revolving fund provision of The Energy and Water Development Appropriations Act of 1990 (Public Law 101-101) has hindered rather than helped the establishment of a reliable and affordable domestic isotope supply.
3. The TRIUMF-Nordion model in Canada is a model of a public-private partnership that is mutually beneficial to both partners.
4. In the United States, a healthy set of partnerships exists between national laboratories and universities, primarily involving research. Successful partnerships between national laboratories and industries in research and development have also been estab
5. NBTF is not likely to be financially self-sufficient if sales from isotopes and related services are the sole sources of funding.
6. NBTF could be operated by a partnership of for-profit and not-for-profit organizations. Solicitations for a successful bidder from the private sector could be based partially on the proposed return of part of the profits as royalties. In this partnership

a. DOE would pay for the cost of construction of NBTF which would be a dedicated facility;
b. the private-sector partner would be responsible for the production, packaging, marketing, pricing, and sales of radioactive isotopes;
c. DOE would subsidize the production of research isotopes as well as fund the operation of the production research and education programs, in whole or in part, via the not-for-profit institution;
d. there would be an agreement distributing beam time of NBTF between production of commercial products and production of the radioisotopes necessary for approved research programs; and
e. there would be an management board that oversees and approves the distribution of the beam time and the return of royalties from the private-sector partner to the not-for-profit partner.

RECOMMENDATIONS

1. NBTF should be operated as a user facility in the mold of current operations at national laboratories primarily in the physical sciences.
2. The construction of this dedicated facility should be financed by government funds through DOE.
3. DOE should encourage a partnership between one or more for-profit institutions and at least one not-for-profit institution (university, national laboratory,

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or some combination) to operate NBTF. The Canadian model of TRIUMF-Nordion is one that could be emulated in the United States.

4. The requirement that NBTF be financially self sufficient should be removed.* Production of these promising but as yet unprofitable isotopes as well as the in-house programs of research and education should be supported primarily by DOE funds and competitive grants, with some contribution from royalties from the private partner. However, it is clear to the committee that the commercial potentials of these particular radioisotopes are limited for the foreseeable future and are certainly not large enough to allow NBTF to be supported by commercial profits.
5. The commercial aspects of NBTF cannot be fully understood at this time. As discussed in this report, some radioisotopes produce by NBTF would be attractive to the commercial market. Others will come in the future as new nuclear medicine techniques evolve. The private-sector partner should be charged with making this determination, producing, marketing, and selling isotopes for the commercial market.
6. Proposals for NBTF from national laboratories should be reviewed along with those from universities and the private sector. The national laboratories offer a tremendous technical infrastructure that would benefit the construction and operation of NBTF. An evolving interest and expertise in new models of cooperation with the private sector would make this potential a reality.

REFERENCES

Arthur Andersen & Co.1993. U.S. Department of Energy Isotope Production and Distribution Program Management Study. Washington, D.C.

KPMG Peat Marwick. 1992. Department of Energy Isotope Production and Distribution Program. Independent Auditors' Report on Financial Statements. Washington, D.C.

Schacht, W. H.1993. Department of Energy Laboratories: A New Partnership With Industry?CRS Report to Congress, No. 93-844 SPR. Washington, D.C.: Congressional Research Service, Library of Congress.

U.S. General Accounting Office. 1992. DOE's Self-Supporting Isotope Program Is Experiencing Problems. Washington, D.C.

* The Energy and Water Development Appropriations Act for 1995 (passed after the writing of this chapter) stipulates that the Secretary [DOE] may henceforth set fees for isotopes and related services without regard to the provisions of P.L. 101-101.

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A National Isotope Policy: Proposal for a New Way to Manage theNation's Isotope Resources

This report has emphasized the importance of an adequate and reliable supply of stable and radioactive isotopes for biomedical and other purposes. In particular, it has focused on the 13 million diagnostic nuclear medicine procedures and the 50,000 therapeutic uses of radioisotopes in the United States each year. Current requirements and future opportunities require a stable infrastructure that will secure the chain of production from starting material to finished radio-pharmaceuticals brought to the clinic and laboratory. Such an infrastructure must include sources for enriched stable isotopes as well as reactor-produced and accelerator-produced radionuclides; it must also include related facilities and resources for research, development, and pre- and postdoctoral education and training. The report makes specific recommendations as to how these objectives should be achieved, recognizing that the goals are most likely to be met by a carefully crafted partnership among industry, universities, and the national laboratories.

To recapitulate:

1. Enriched stable isotopes are critical starting materials for the production of many radionuclides; they are also unique research and diagnostic tools in their own right. Major current sources for some of these are in Russia and other former Soviet Republics, but the reliabilities of these sources in the future are unknown. Hence, to secure a continuing and dependable supply of enriched stable isotopes, the United States should maintain the electromagnetic separation facilities (calutrons) at Oak Ridge National Laboratory in a state of readiness until they can be supplanted by new separation technologies or until substantial sales become likely because of rising foreign prices or a breakdown in the distribution of these products from Russia and the other former Soviet Republics.

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Isotopes for Medicine and the Life Sciences
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2. Reactor-produced radionuclides are central to clinical practice ad biomedical research. They currently can be divided naturally into three categories:

a. molybdenum-99 for generators of technetium-99m, the workhorse of diagnostic nuclear medicine;

b. radionuclides used routinely in medicine (phosphorus-32, phosphorus-33, chromium-51, cobalt-58, cobalt-60, yttrium-90, iodine-131, xenon-133, cesium-137, iridium-192, gold-198) and in research laboratories (hydrogen-3, carbon-14, sulfur-35, phosphorus-32, phosphorus-33, iodine-125); and

c. radionuclides for research that promise to be of clinical use in the near future.

It appears that current Canadian supplies of molybdenum-99 backed up by supplies from Western European facilities should be more than adequate to meet U.S. requirements. An additional backup source for this critical radionuclide could be from the reprocessing of spent fuel from the University of Missouri Research Reactor (MURR) and other research and test reactors.

With the closing of many government-run reactors, it is essential that one or more reactors be maintained for isotope production and other uses as well. The research reactor at the University of Missouri is already engaged in this activity and should be supported by federal funds.

Because reactors have finite lifetimes, the committee also recommends that plans for the Advanced Neutron Source at Oak Ridge National Laboratory include a radionuclide production capability.

3. Accelerator-produced radionuclides play an important role in current nuclear medicine practice and promise to play a greater one in the future. As with reactor-produced isotopes, these, too, can be divided into three categories:

a. Short-lived, positron-emitting radionuclides (carbon-11, nitrogen-13, oxygen-15, and fluorine-18) produced by hospital cyclotrons that are the cornerstone of current positron emission tomography (PET) activity. An important concern to PET facilities is the continued and adequate supply of stable nitrogen-15 and oxygen-18 required for the production of oxygen-15 and fluorine-18, respectively.

b. Radionuclides that are routinely used in clinical practice and that can be produced by accelerators operating at 30 million electron volts (MeV) or less (gallium-67, indium-111, iodine-123, and thallium-201). All of the major commercial radiopharmaceutical suppliers own and operate such accelerators, and they back each other up in emergencies.

c. Research radionuclides that can be produced by accelerators operating at greater than 70 MeV with appropriate beam currents. Experience has shown that radionuclides and pharmaceuticals found to be promising in research can be transferred to clinical practice only when a reliable and adequate source can be assured. For this reason the committee strongly recommends the creation of a facility dedicated to the production of ac

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celerator-produced radionuclides. The accelerator could operate at 80 MeV with 750 microams (μA) of beam current. It should be dedicated because experience has proven that isotope production facilities that are piggybacked onto those created primarily for physics research or other activities are generally not available for the year-round isotope production required for medical purposes. A dedicated facility is also not subject to the vagaries of funding that attach to a parasitic relationship and prevent long-term budget planning. In addition to the accelerator, the facility must have a staff and infrastructure capable of providing target handling, isotope separation, and packaging and shipping at high efficiency. Until the new facility is established, the needs of the community should be met temporarily by an upgraded Brookhaven Linac Isotope Producer (BLIP) supplemented by an additional processing and distribution unit and sufficient operating funds for year-round operation.

Research and training needs vital to the national program can be substantially implemented at the new accelerator facility, the National Biomedical Tracer Facility (NBTF), and the designated isotope production reactor (MURR). The research emphasis, perforce, should differ from the basic and disease-oriented research of the universities and academic health centers; rather it should focus on vital areas or critical needs in isotope technology development.

The educational programs of the accelerator and reactor production facilities should also be used to ease the current shortage of nuclear science professionals. In particular, a cadre of scientists trained in accelerator physics, nuclear engineering, and nuclear chemistry and radiopharmaceutical chemistry will be required. Because DOE has the legislative authority as well as a mandate to support education and training in the nuclear and related sciences, only commitment and the appropriate allocation of resources are needed. Forms of support should include pre- and postdoctoral fellowships, incentives for establishing new faculty positions, as well as faculty scholarships that involve collaborations with university departments of chemistry, physics, nuclear engineering, nuclear medicine, and radiopharmaceutical chemistry. The production facilities themselves should be used as training sites.

Rational planning, management, and budgeting can occur only if the various programs of isotope production (stable, reactor-produced, accelerator-produced) and associated activities in research, development, and education are well coordinated. At present, these various activities are spread throughout the DOE organization. The Isotope Production and Distribution Program (IPDP) is imbedded in the Office of Nuclear Energy; the BLIP and Los Alamos Meson Physics Facility receive much of their operations money from the Office of High Energy and Nuclear Physics in the Office of Energy Research of DOE; and the proposed NBTF effort and BLIP upgrade are projected to be funded from the Medical Application and Biophysical Research Division of the Office of Health and Envi

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ronmental Research, also in the Office of Energy Research of DOE. A coherent, rational isotope policy could best be developed and administered if the various elements can be gathered into a single office. Because the committee has suggested that the federal role in isotope production be focused on research and the needs of researchers rather than commerce, that office should be placed among the science and technology programs of DOE. Its head should report directly to the director of the Office of Energy Research, rather than, for example, the director of the Office of Nuclear Energy. Without sufficient autonomy, it is not likely to fulfill its mission or have the ability to form partnerships with private-sector industries and universities. In addition, the broad-based nature of the program suggests that it should be connected to other agencies such as the U.S. Department of Health and Human Services (especially the National Institutes of Health), the National Science Foundation, and the U.S. Department of Commerce. To expedite the coordinated development of new diagnostic and therapeutic agents, DOE representatives should meet with National Institutes of Health review committees concerned with nuclear medicine, such as the Diagnostic Radiology and Radiation Study Sections. In addition, DOE should establish a mechanism by which the National Science Foundation could keep DOE informed of the developments in physics, chemistry, and the life sciences requiring the production of new radioactive and stable isotopes.

A National Isotope Program (NIP) should have responsibility for ensuring adequate radionuclide production by charged particles and neutrons and for the production of stable isotopes. The three production capabilities do not need to be at the same location, but their activities must be well coordinated. Research, education, and training, not only at these sites but at academic and commercial grant sites throughout the nation should be integral parts of the program.

A national committee must be formed to advise the NIP director. It could well have subcommittees for the various aspects of the program. At the reactor and accelerator facilities, this national advisory committee should assist the management in choosing among applicants wishing to use the facilities or obtain their products for research. The matter of which research isotopes should be manufactured will be a central strategic issue at all locations. This NIP Advisory Committee should assist in prioritizing vital areas of critical needs in technology development, performing at the national level a function which is what a number of user organizations now perform at individual laboratories. It should also provide advice on the development and execution of the several educational programs.

CONCLUSIONS

1. On the basis of its congressional mandate, its historic role, and its technical expertise and resources, DOE has important roles to play in all aspects of isotope production, research, and education.
2. Although the full cost recovery provision of Public Law 101-101 has

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hindered rather than helped DOE in promoting isotope research and application, the concept of centralized management is not without merit. The important research, development, and education activities associated with isotope production and distribution are, however, still spread throughout DOE.

RECOMMENDATIONS

1. A National Isotope Program, reporting directly to the director of the Office of Energy Research of DOE, should be created to consolidate the administration of all biomedical isotope-related activities: production and distribution, research and development, and education and training.
2. A national advisory committee should be formed to assist the National Isotope Program Director in prioritizing critical needs in technology development and in choosing among applicants wishing to use the reactor and accelerator isotope production facilities or obtain their products. This National Isotope Program Advisory Committee should also provide advice on the development and execution of the several educational programs associated with isotope production and use.

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APPENDIXES

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APPENDIX A

Waste Management

The Low Level Radioactive Waste Policy Act of 1980 (Public Law 96-573) and its amendment in 1985 (Public Law 99-240, Title I) carry serious implications for any new isotope facility, regardless of its form or location. As succeeding paragraphs will make clear, this legislation puts the onus of disposal of mildly radioactive materials squarely on the states in which they are generated. No new disposal sites have opened since 1980, however, and access to the only two remaining disposal sites in the United States will become severely restricted as of July 1994. One problem for a new facility, thus, is simply ensuring access to a disposal site for the low-level radioactive waste (LLRW) that it generates. A second issue for a facility making and selling radioisotopes and associated equipment, services, or materials arises from the needs of its customers for this same access.

NATURE AND SOURCES OF LOW-LEVEL RADIOACTIVE WASTE (LLRW)

The Low Level Radioactive Waste Policy Act defines LLRW by exclusion in an attempt to distinguish mildly radioactive materials with relatively short half-lives from high level radioactive wastes that must be effectively isolated for many centuries to prevent serious harm to the biosphere. Included in the high level radioactive waste category are spent fuel elements from nuclear reactors, residues from the reprocessing of irradiated uranium to separate out plutonium for weapons production, significant concentrations of radionuclides of transuranic elements (e.g., plutonium), and by-products of reactor operations. LLRW then consists of all other (mildly) radioactive waste, including such things as depleted uranium, activated beam line components; target materials, contami

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nated paper, rags, rubber gloves, and protective clothing; hardware and tools; laboratory glass and plastic; syringes; filters; animal excreta, parts, and carcasses; cleanup materials and irradiated components from nuclear power plants, and even sealed sources that have outlived their utility. An important exclusion from the provisions of the act is radioactive waste generated by the U.S. Department of Energy. The national laboratories are not dependent on the state in which they are located for disposal of radioactive waste. Sixty-five percent of all LLRW is produced and disposed of at the federal level (Coates et al., 1992).

In 1992 waste disposal operators reported receiving over 1,700,000 ft^3 (48,000 m^3)of LLRW, generating a shade over 1 million curies (Ci) of activity (Fuchs and McDonald, 1993). In the United States, such LLRW accounts for about 85 percent of all radioactive waste by volume but only about 1 percent by activity (Hendee, 1993). Table A-1 and Figure A-1 (adapted from Fuchs and McDonald, 1993) break out those totals by the type of generator: academic, which includes university hospitals and research facilities of all types; government; industrial, including pharmaceutical manufacturers; medical, which encompasses hospitals and clinics, nonuniversity research facilities, and private offices; and utility, which primarily includes the 76 active commercial nuclear power reactors. Industrial sources provided over half of the waste by volume, and utilities contributed over 85 percent of the radioactivity. Medical and academic sources generated less than one-half of one percent of the radioactivity and only 4 percent of the total volume.

The U.S. Nuclear Regulatory Commission (U.S. NRC) has subclassified LLRW into classes A, B, and C for the purposes of setting disposal standards (10 CFR 61). On the basis of concentration, half-life, and stability of the waste form, the regulations demand increasing levels of physical security as the radionuclides become longer-lived or more concentrated. Ninety-five percent of all LLRW and nearly all medical LLRW fall in Class A, the lowest level of security. Even at that

TABLE A-1 LLRW Received at Commercial Disposal Sites in the United States in 1992

Generator Category	Volume (ft^3)	Activity (Ci)
Academic	44,322	1,724
Government	158,186	40,780
Industrial	908,452	100,090
Medical	26,251	398
Utility	606,067	857,110
Total	1,743,279	1,000,102

SOURCE: Fuchs and McDonald, 1993.

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level, however, disposal sites must be designed to protect both humans and the environment for 100 years. For example, institutional control of the site for a century is required, including measures to preclude inadvertent disturbance. The site must be a suitable distance from groundwater and surface waters and located in a region where earthquakes and volcanic activity are very low probability

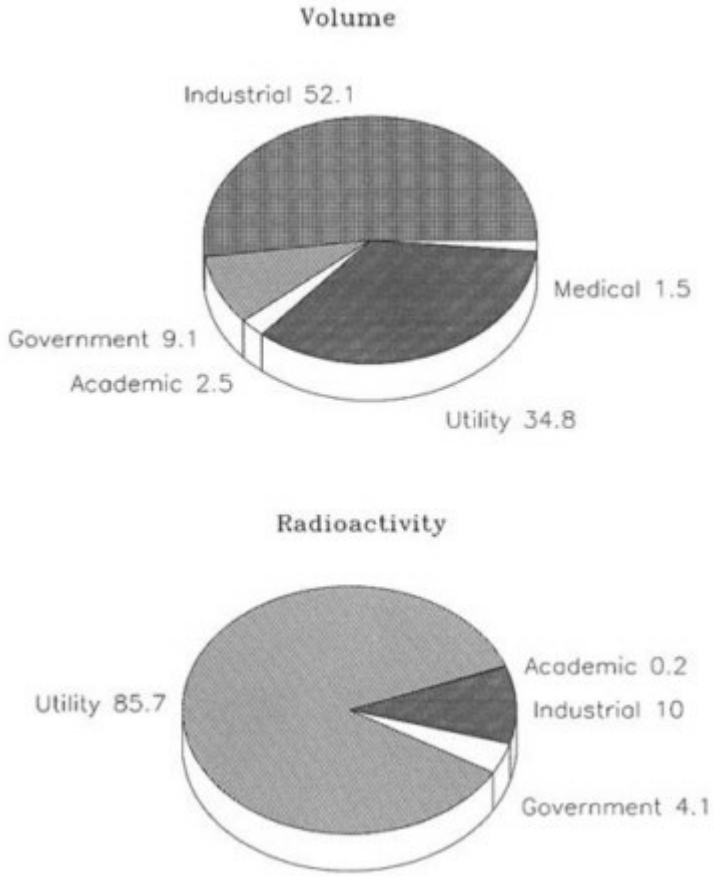

FIGURE A-1 Percentages of volume and radioactivity of low-level radioactive waste by source.

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events. All present U.S. sites employ shallow land burial, the simplest and cheapest method that is allowable under these regulations. Metal containers containing waste are placed in long trenches at least 7.5 m deep and are covered with a clay cap suitably contoured for drainage and erosion control. Future sites are likely to be much more elaborate structures of concrete and steel, because a number of states have already banned the shallow land burial method of disposal.

RISK FROM LLRW

Radiation is very poorly understood by the general public and, as a result, seems to generate fears out of proportion to objective risk. The fact that some radiation injuries become apparent only years after exposure no doubt contributes to this wariness of the public, but radiation standards have been promulgated by various national and international groups for more than 50 years. In the present case, the U.S. NRC has decreed that releases of radiation from any artificial source, including LLRW disposal sites, should not exceed 0.25 milliSieverts (mSv; 25 mrem) per year to the whole body or any organ other than the thyroid, which is given a limit of 0.75 mSv (75 mrem) per year. Eisenbud (1980) estimated that LLRW from isotope use in biology and medicine contributes less than 0.01 mSv (1 mrem) to each person's annual radiation exposure, and the U.S. Environmental Protection Agency estimates that the annual exposures of people living near a disposal facility would be something under 0.1 mSv (10 mrem) (Council on Scientific Affairs, 1989).

Although scientists working with radiation have traditionally taken a very conservative no-threshold view of safety, that is, all radiation is assumed to be injurious, it might be well to put these exposure limits in perspective by considering some of the other sources of radiation to which the general public is exposed. As Table A-2 illustrates the average person in the United States today receives about 3.6 mSv (360 mrem) of radiation annually, of which roughly 3.0 mSv (300 mrem) comes from natural and largely unavoidable sources (National Council on Radiation Protection and Measurements, 1987). Radon gas from radium in the soil is an example of such sources. Cosmic rays are another. Internal radionuclides carried naturally in the body include potassium-40, lead/polonium-210, carbon-14, and radium-228/224. Subsamples of the population can be exposed to much higher doses. Denver residents, who have less atmosphere above them than those who live at sea level, get close to twice the average dose of 0.27 mSv/year (27 mrem/yr) from cosmic rays. Smokers' lungs are thought to absorb as much as 160 to 200 mSv/yr (16,000–20,000 mrems/yr) from polonium in tobacco smoke. Artificial sources of radiation other than from waste may vary greatly as well. Diagnostic radiology is estimated to contribute about 0.5 mSv (50 mrem) to each person's annual exposure, but this obviously could be much greater in those with poor health or many injuries. The LLRW contribution, even for people living near disposal sites and the current exposure standards, are thus

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TABLE A-2 Average Annual Dose Equivalents from Sources of Radiation Exposure in the United States

Source		Dose Equivalent[a] (mSv)	Effective Dose Equivalent		
			mrem	mSv	%
Natural	Radon[b]	24	2,400	2.0	55
	Cosmic	0.27	27	0.27	8
	Terrestrial	0.28	28	0.28	8
	Internal to human body	0.39	39	0.39	11
	Total natural	..	—	3.0	82
Artificial	Medical				
	X-ray diagnosis	0.39	39	0.39	11
	Nuclear medicine	0.14	14	0.14	4
	Consumer products	0.10	10	0.10	3
Other	Occupational	0.009	0.9	<0.01	<0.3
	Nuclear fuel cycle	<0.01	<1.0	<0.01	<0.03
	Fallout	<0.01	<1.0	<0.01	<0.03
	Miscellaneous[c]	<0.01	<1.0	<0.01	<0.03
	Total artificial	—	—	0.63	18
Total natural and artificial		—	--	3.6	100

[a]To soft tissues.

[b]Dose equivalent to bronchi from radon daughter products. The assumed weighting factor for the effective dose equivalent relative to whole-body exposure is 0.08.

[c]U.S. Department of Energy facilities, smelters, transportation, etc.

SOURCE: National Council on Radiation Protection and Measurements (1987).

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extremely low. Public resistance to new disposal sites has nevertheless been formidable and has produced a gridlock that could easily become a crisis for nuclear medicine in the next few years.

DISPOSAL SITES

In the early days of atomic energy shortly after World War II, the Atomic Energy Commission was in charge of all aspects of atomic energy, including waste disposal. This generally meant burial on federal lands or, especially for LLRW, dumping in the oceans or large waterways. The Atomic Energy Act Amendments of 1959 opened the door to state administration of their own radiation safety programs, and by 1971 New York, Kentucky, Illinois, Washington, South Carolina, and Nevada owned LLRW disposal sites and had them operated by commercial contractors. By the late 1970s the first three of these had closed, one because it was full and two because of management problems and increased environmental concerns by state governments (and the public). The three remaining sites took in increased volumes from all over the country, and political opposition to serving as dump sites for the rest of the nation grew quickly. In 1979, the governors of Washington, Nevada, and South Carolina threatened to close the sites unless some more equitable plan for sharing this burden was devised.

The result was the Low Level Radioactive Waste Policy Act of 1980. In it, the U.S. Congress decreed that each state would be responsible, by January 1, 1986, for disposing of the LLRW generated within its borders. It also suggests that the best way to do this would be through regional compacts, or agreements to share a disposal facility. The third key provision was that such compacts would be allowed, after January 1, 1986, to exclude waste generated outside the compact states (without such permission attempts to exclude waste would be prohibited by the commerce clause of the Constitution forbidding the states from impeding the free flow of interstate commerce). In 1985 Congress amended the act because no compacts had been ratified and no new sites had been selected. The amendments extended the deadline until January 1, 1993, but provided a series of planning milestones that states without sites would have to meet to maintain access to existing disposal sites. A very important provision designed to exert additional pressure for site development by state governments was the "take title" provision, which required states that had not arranged for disposal for its in-state LLRW generators by January 1, 1996, to take title to the waste and assume liability for any damages. Even though the "take title" clause of the 1985 amendments was ruled unconstitutional by the U.S. Supreme Court in 1991, effectively shifting the disposal burden from the state governments back to the waste generators themselves, some progress has occurred. All but a few states have joined compacts, four applications for LLRW disposal licenses are under review by the U.S. NRC and seven other states have begun siting studies. On the other hand, no new sites have opened or are likely to open before 1996, the proposed new sites

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are still not fully clear of all legal and political hurdles, the Nevada site has shut down completely, and the Washington site has closed to waste generators outside the Northwest and Rocky Mountain compacts. The South Carolina legislature, after fierce debate, voted to restrict access to its disposal site at Barnwell to Southeast compact states as of July 1994, and on January 1, 1996, that facility will be closed to all wastes. As of that date, LLRW generators in the following states will have access to a disposal site: Alaska, Hawaii, Washington, Oregon, Idaho, Montana, Wyoming, Utah, Nevada, Colorado, and New Mexico. Generators in California, Arizona, the Dakotas, Texas, Vermont, and Maine will probably have to store their wastes on-site for 1 to 2 years; those in the Central and Southeast compacts may have a disposal site before 2000; but the remaining states, mostly in the Midwest and the Northeast, will very likely be without sites at least until the turn of the century. Figure A-2summarizes the current organization of compacts and their access to disposal sites.

IMPLICATIONS FOR ISOTOPE PRODUCTION AND USE

Although numerous critics (e.g., Coates et al., 1992) have called for still further revisions of federal law to speed the process of providing safe, economical, and equitable disposal of LLRW for all U.S. generators, members of the relevant U.S. House and U.S. Senate committees did not revisit the topic in the 103rd Congress (Nuclear Waste News, 1993). Thus, both current and future (e.g., National Biomedical Tracer Facility [NBTF]) LLRW generators will have to deal with this problem of access to disposal sites. To estimate the possible volume and costs of waste disposal by an accelerator facility of the sort proposed for NBTF, data were collected from the Tri-University Meson Facility cyclotron in Vancouver, British Columbia, Canada. This facility typically has two disposal shipments per year. In 1992 the two combined shipments consisted of 11.7 gigabecquerels (GBq) of radioactivity, and weighed 15,940 kg. Each of the two shipments cost about $5,000 (Canadian) for shipping, and about $60,000 (Canadian) for disposal. Isotope production facilities will be affected not merely by their own waste generation but also by problems encountered by their research, medical, and commercial customers. Over the next 5 years at least, regardless of the location or nature of any NBTF, a substantial portion of its potential customers are likely to be faced with on-site LLRW storage as their only option. All users of radioisotopes are limited by the terms of their license to specified quantities of each radionuclide. If forced to store waste on-site, an increasing portion of the allowable amounts of some isotopes could be tied up in wastes. Many of the radionuclides used in clinical medicine have relatively short half-lives and may be stored until they have decayed to background levels (10 half-lives is commonly taken as the rule of thumb in estimating the required storage time) and then disposed of as ordinary trash, albeit still in conformity with regulations governing hazardous chemical or biological waste. Some of the longer-lived

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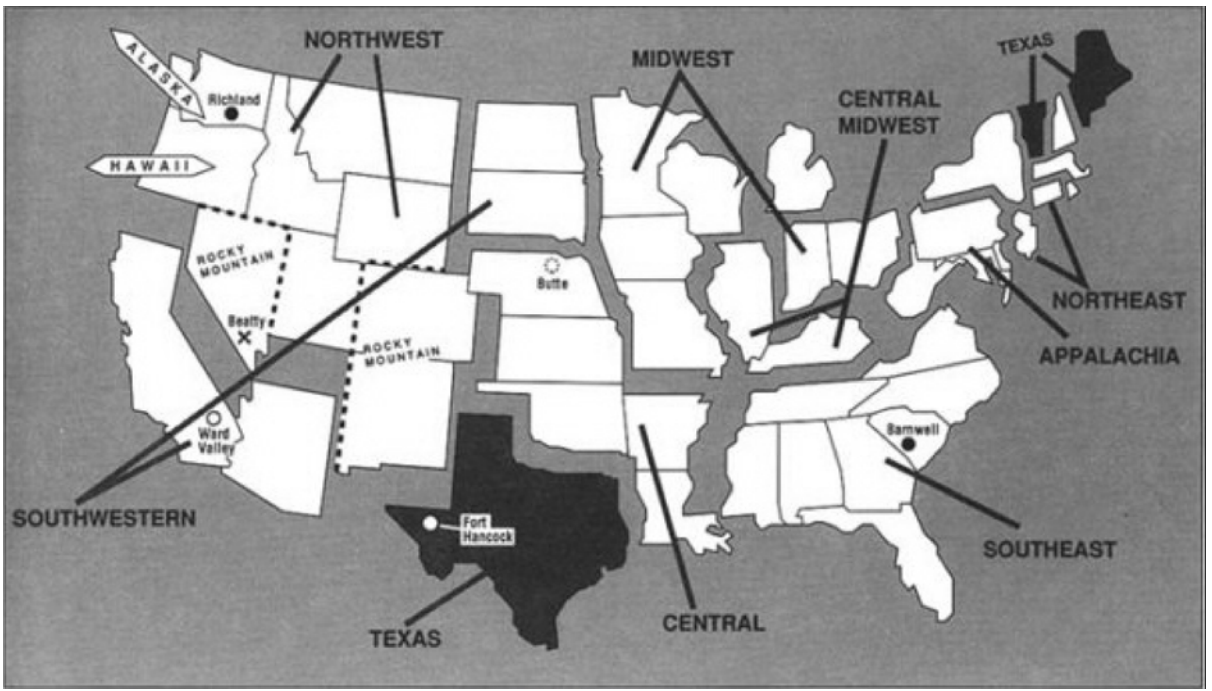

FIGURE A-2 Low-level radioactive waste compacts in the United States. SOURCE: Blake, 1993. Reproduced with permission of the American Nuclear Society.

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isotopes, such as cobalt-60, molybdenum-99/technetium-99m generators, and gadolinium-153 bone densitometry sources, are shipped back to the manufacturer for disposal, but others in wide use have half-lives ranging from months (iron-125, xenon-127, strontium-89, iridium-192) to years (hydrogen-3) or even centuries (carbon-14). Storage requirements will no doubt vary widely. A 1989 paper reports that the Mayo Clinic in Rochester, Minn. generates 6,000 ft^3 (170 m^3) of LLRW annually, and the University of Cincinnati's 1987 waste was 1,755 ft^3 (50 m^3), even though two small hospitals in Illinois found the disposal problem to be negligible (Council on Scientific Affairs, 1989). Much has been done in the way of volume reduction since 1980, despite steadily rising activity levels, as generators correctly anticipated rising prices and dwindling access. Conscientious segregation of nonradioactive and radioactive waste, compaction, evaporation, decontamination, and incineration have reduced the total volume of LLRW sent to commercial dump sites from over 3.5 million ft^3 (99,000 m^3) in 1980, to 1.7 million ft^3 (48,000 m^3) in 1993. It is probably safe to assume that most of the cost-effective volume reduction techniques are already in use for on-site storage as well as for shipment to disposal sites.

New York is one of the states that will be left without access to a disposal site after July 1994, and although the state has begun the process of developing a site of its own, one of its first steps was a survey of its current LLRW generators' on-site storage capacities, their abilities to expand those capacities, and the economic viability of establishing a separate centralized storage site solely for Class A LLRW from medical and academic sources. The recently completed study (New York State Energy Research and Development Authority, 1993) reported that 142 facilities will have to store LLRW on-site for extended periods if New York is denied access to existing disposal sites. These facilities currently expect to produce approximately 50,000 ft^3 (1,400 m^3) of LLRW each year. Forty-eight of these facilities have less than 1 year of storage capacity, and 27 will be able to store LLRW for 6 months or less. This assumes that many of the generators will be able to amend their licenses to accommodate the increases in the amounts of on-site material. Making some further assumptions about the ability of these facilities to expand their storage capacity, the study still finds that 16 facilities will have less than 2 years' capability. Fifteen of those 16 are medical and academic institutions, accounting for about 70 percent of the expected medical and academic LLRW.

The final piece of the New York study attempted to assess the economic viability (i.e., the ability to pay capital and operating costs from revenue) of a hypothetical central storage facility for Class A medical and academic LLRW. It found that generators were extremely sensitive to prices. At the lowest hypothetical storage fee ($25/$ft^3$), such generators reported that they would only send about 25 percent of their anticipated volume, opting instead for on-site storage or treatment or ceasing activities that generate LLRW. This would leave the facility well short of the break-even point, even in the unrealistic capital cost of $10

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million. (North Carolina expects to have spent $80 million by the time that it completes siting and licensing, before ever turning over a spade of soil.)

REFERENCES

Blake, E. M.1993. Twenty Nagging Questions and Not-Necessarily-Satisfying Answers About LLW Management in the United States. Nuclear News (December):42–45.

Coates, D., V. Heid, and M. Munger. 1992. The Disposal of Low-Level Radioactive Waste in America: Gridlock in the States. St. Louis: Center for the Study of American Business.

Council on Scientific Affairs, American Medical Association. 1989. Low-Level Radioactive Wastes. Journal of the American Medical Association262:669–674.

Eisenbud, M.1980. Radioactive Wastes from Biomedical Institutions. Science207:1299.

Fuchs, R. L., and S. D. McDonald. 1993. 1992 State-by-State Assessment of Low-Level Radioactive Wastes Received at Commercial Disposal Sites. Prepared for the U.S. Department of Energy by EG&G Idaho, Inc.Idaho Falls, Idaho.

Hendee, W. R.1993. Disposal of Low-Level Radioactive Waste. J. American Medical Association269:2403–2406.

National Council on Radiation Protection and Measurements. 1987. Ionizing Radiation Exposure of the Population of the United States. NCRP Report93:15, 40, 53. Bethesda, Md.

New York State Energy Research and Development Authority. 1993. Low-Level Radioactive Waste Storage Study. Albany, N.Y.: New York State Energy Research and Development Authority.

Nuclear Waste News. January 21, 1993. Not with a 10-foot pole. Nuclear Waste News13(3):21.

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APPENDIX B

Legal Considerations

Two major public laws provide the authority to regulate isotope production and distribution in the United States: these are the Atomic Energy Act of 1954 and the Energy and Water Development Appropriations Act of 1990 (Public Law 101-101). These acts were passed for different reasons and attempt to achieve different goals. The 1954 act promotes the production of isotopes (radionuclides) for research, whereas Public Law 101-101 focuses on an entirely different mandate: revenue generation.

Because there are operating issues that relate to this conflict between generating revenue and supplying research entities with isotopes, "Policies and Procedures for Transfer of Commercial Radioisotope Production and Distribution to Private Industry," which was adopted by the U.S. Department of Energy (DOE) in 1965, has guided the department's decision on initiating and ceasing the production and distribution of specific isotopes. The culture, organizational structure, operating decisions, manufacturing capability, and marketing approach of the Isotope Production and Distribution Program (IPDP) to date have been geared toward fulfilling the research isotope availability objectives of the Atomic Energy Act of 1954. The revenue generation objectives of Public Law 101-101 would seem to require a different approach, one that would make IPDP an effective supplier to commercial customers and that would generate revenue above expenses. Although modified somewhat by language accompanying the fiscal year 1995 (FY95) Energy Appropriations Act, the legal implications of this dichotomy will be addressed below.

THE ATOMIC ENERGY ACT OF 1954

The Atomic Energy Act of 1954 provides the statutory and legal authorities under which IPDP can produce its products and provide related services. The

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section of the act that applies depends on the type of isotope, radioactive or stable, and the production method. Legal opinions from DOE note that reactor-produced radioisotopes, as by-product materials, are governed by Sections 81-82, and other radioisotopes and stable isotopes are governed by Section 161 of the Atomic Energy Act:

> The Commission [Atomic Energy Commission (AEC), now DOE] may distribute, sell, loan, or lease such by-product material as it owns to qualified applicants with or without charge: Provided, however, that, for by-product materials to be distributed by the Commission for a charge, the Commission shall establish prices on such an equitable basis as, in the opinion of the Commission, (a) will provide reasonable compensation to the Government for such material, (b) will not discourage the use of such material or the development of sources of supply of such material independent of the Commission, and (c) will encourage research and development. In distributing such materials, the Commission shall give preference to applicants proposing to use such material either in the conduct of research and development or in medical therapy. (Section 81; 42 U.S.C. 2111)

To execute this mandate, the DOE is authorized to

> acquire, purchase, lease and hold real and personal property, including patents, as agent of and on behalf of the United States, … and to sell, lease, grant, and dispose of such real and personal property as provided in this Act. (Section 161g; 42 U.S.C. 2201).

Because financial considerations and the business arrangements were not specifically addressed, the legal ramifications surrounding those issues might become apparent only on implementation, and then only on a case-by-case basis.

PUBLIC LAW 101-101

In 1990 Title III of Public Law 101-101 (the Energy and Water Development Appropriations Act of 1990) established a revolving fund that required IPDP to finance itself through operating revenues, but there was no financial provision for the production of isotopes made exclusively for research. The intended goal was to provide an incentive for cost-effectiveness, bringing the management of isotope production and distribution under the aegis of a single, accountable headquarters so that revenue and expenses could be properly quantified. The designated revolving fund was characterized:

> For necessary expenses of activities related to the production, distribution, and sale of isotopes and related services, $16,243,000, to remain available until expended: Provided, That this amount and, notwithstanding 31 U.S.C. 3302, revenues received from the disposition of isotopes and related services shall be credited to this account to be available for carrying out these purposes without further appropriation: Provided further, That all unexpended balances of previous appropriations made for the purpose of carrying out activities related to the

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> production, distribution, and sale of isotopes and related services may be transferred to this fund and merged with other balances in the fund and be available under the same conditions and for the same period of time: That fees shall be set by the Secretary of Energy in such a manner as to provide full cost recovery, including administrative expenses, depreciation of equipment, accrued leave, and probable losses: That all expenses of this activity shall be paid only from funds available in this fund: Provided further, That at any time the Secretary of Energy determines that moneys in the fund exceed the anticipated requirements of the fund, such excess shall be transferred to the general fund of the Treasury.

Although no further guidelines or instructions were provided, the revolving fund clearly was meant to induce or at least to encourage IPDP to operate as a for-profit business but without any guidance regarding business principles. The law did not take into account the distinction between supplying isotopes to the research community, characteristically at a financial loss, and supplying commercially used isotopes to the private or clinical sector at "full cost recovery." Subsequent interpretations within DOE have led to isotopes being priced at full cost; the recent Conference Report on the FY95 Energy and Water Development Appropriations included language specifically freeing the Secretary of Energy from the provisions of Public Law 101-101 in setting fees for isotopes and related services, however.

Since the outset of the government's isotope production activities, a persistent issue has been when the government should terminate the production of specific isotopes so as not to compete with the private sector. This initially was to occur when private industry demonstrated that it could be a reliable supplier of the isotopes that it agreed to produce. The relevant policies that DOE adopted in 1965 state that the government is to refrain from competing with private sources when the materials are *reasonably* available commercially. What determines "*reasonable*" is not detailed. The *Federal Register* (March 9, 1965, p. 3247—3248) notes:

Withdrawal guidelines.

1. The AEC will voluntarily withdraw from the commercial production and distribution of particular radioisotopes whenever it determines that such radioisotopes are reasonably available from commercial sources.
2. The AEC will withdraw from the commercial production and distribution of particular radioisotopes on petition from a private organization based upon a demonstrable private capability and encompassing the following but recognizing that all these factors need not be completely satisfied:

a. There is effective competition in the production and distribution of the radioisotopes in question; however, a single source of supply under certain conditions may be acceptable (e.g., very limited market). [This will be further considered below in the discussion of antitrust.] Foreign producers will be accepted in determining effective competition provided they are actively marketing the radioisotopes in the U.S.

b. There is assurance that the private producers will not discontinue the

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venture in a manner that would adversely affect the public interest, to the extent resumption of production by AEC would involve a significant delay. [This may become an important issue in legal responsibility.]

c. The proposed private radioisotope prices are reasonable and consistent with encouragement of research and development and use.

Government isotope requirements. It is the Atomic Energy Commission's policy to obtain radioisotopes from commercial sources where it has formally withdrawn from the production and distribution of those radioisotopes. However, the AEC maintains the right to produce an isotope for Government use in those circumstances where the Government is a substantial user, or the use is of special programmatic interest to the AEC, and, where procurement from industry would result in significantly higher cost to the Government.

Filing a petition.

1. An organization requesting that the AEC withdraw from the production and distribution of a particular radioisotope may submit a formal petition to this effect. Such a petition to this effect. Such a petition should contain sufficient evidence to demonstrate adequate technical, financial and managerial resources, as well as seriousness of intent.:
2. The petition should include:

a. Product specifications to show evidence of their comparability to AEC products or adequacy to meet user demands.

b. Estimate of current demand. (The petitioner's production capabilities in conjunction with that of other suppliers should be adequate to meet this demand.)

c. The petitioning organization's production, processing and distribution capability, including identification of the production facilities (e.g., nuclear reactors and/or cyclotrons) available to it and the extent of commitment upon them in relation to market requirements.

d. Price schedule.

e. Delivery schedule.

f. Proposed date of AEC withdrawal.

The AEC may request additional information if the above information is inadequate for AEC to make a ruling.

3. Upon making a finding favorable to the petition, the AEC will publish for public comment:

a. The private organization's petition or a summary thereof, exclusive of company confidential information, and will designate the place where a copy of the petition, exclusive of company confidential information, may be seen. (The petitioner should identify those portions of his petition which contain company confidential information; however, the information published must be sufficient to permit meaningful public comment.)

b. A notice of AEC's intent to withdraw. AEC will make a final decision on the withdrawal petition upon receipt and evaluation of public comment.

4. Upon making an unfavorable decision on a petition, either prior to or subsequent to receipt of public comment, AEC will inform the petitioning organization of the reasons for its decision.

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5. When AEC determines to withdraw voluntarily from the commercial production and distribution of particular radioisotopes, it will similarly publish a notice of such intent for public comment.

[This methodology allows private industry to obviate the production of certain isotopes (presumably the most profitable ones) upon statement of intent with rather modest performance requirements. It also places substantial "burden of proof" responsibilities upon the AEC (DOE).]

AEC radioisotope prices.

1. AEC radioisotope prices will be established to provide reasonable compensation to the Government (which ordinarily will be the higher of AEC full cost recovery or reasonable commercial rates) unless this would significantly interfere with (a) research and development and use or (b) encouragement of private sources of supply. In individual cases, if (a) and (b) cannot be equally accommodated, greater weight will be given to encouragement of research and development and use.
2. The AEC will publish a 30 day prior notice of proposed price changes, including the reason for the proposed changes.
3. The AEC will not change the price of a radioisotope during the period it is reviewing a petition for AEC withdrawal from production and distribution of that isotope.

AEC radioisotope production technology research.

1. AEC will place the conduct of radioisotope production technology research and development it deems necessary to be carried out with groups most qualified to perform such work, whether these be AEC facilities or private organizations.
2. AEC will conduct or support production technology research and development on radioisotopes from which it was withdrawn as it deems necessary, but only to the extent that AEC has satisfied itself that industry is unable, is unwilling or simply is not carrying out such work adequately or where it determines that direct AEC effort is necessary in the interest of the atomic energy program.

These guidelines provide the environment which the partnerships proposed in other parts of this report would enter. The multiple guidelines and instructions clearly have legal implications.

The enriched stable isotopes represent another class of products. Although nonradioactive, the production of these isotopes utilizes technologies that have originated in and, in the United States, that are largely confined to the research and development programs of DOE (or its predecessors, the Energy Research and Development Agency (ERDA) or AEC. Most of the enriched stable products from which DOE was "petitioned out" of commercial sales came at the request of ISOTEC, a company that has been the sole commercial supplier of many of these products. In the view of many isotope customers and others, the ISOTEC monopolistic (or quasimonopolistic) position has not served the marketplace well, lead

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ing to repeated customer requests for DOE reentry into the production of many of these withdrawn enriched stable isotope products. Since mid-1989, ISOTEC has been wholly owned by Nippon Sanso, a Japanese firm. In the case of Cambridge Isotope Laboratories, there appears to be a need to consider the possibility of DOE competing with a U.S.-owned firm through reentry into the production of enriched stable isotopes from which DOE (ERDA/AEC) had previously withdrawn.

The reactor products, on the other hand, could apparently be reentered into the market by DOE with no objection from U.S. suppliers, since none exist. To date, however, no isotope withdrawn from the DOE program has ever been reinstated. The result has been that DOE produces only those commercial isotopes that private industry either cannot produce because of the unique facilities required or will not produce because of their unprofitability. With the enactment of Public Law 101-101 in 1990, which required IPDP to be self-sustaining, IPDP may have gained greater authority to compete with private industry and foreign producers, but this has been of little assistance to the financial viability of the program. DOE has been considering revision of policy to state that IPDP will end production of a specific isotope only when demand no longer exists or the isotope's commercial price is lower than IPDP's full cost of production. The DOE's explanation for this change is that existing policy often created monopolies in the marketplace that could result in shortages of critical isotopes. This of course not only has implications financially but implications legally under antitrust analysis.

THE TECHNOLOGY TRANSFER ACT OF 1986

Also germane to the present considerations of partnership relations and various legal and financial arrangements for isotope production is the Technology Transfer Act of 1986 (Public Law 99-502). The purpose of the act was to amend the Stevenson-Wydler Technology Innovation Act of 1980 to promote technology transfer by authorizing government-operated federal laboratories to enter into cooperative research agreements and by establishing a Federal Laboratory Consortium for Technology Transfer within the National Bureau of Standards. Public Law 99-502 enables each federal agency to permit the director of any of its government-operated federal laboratories to:

(1) enter into cooperative research and development agreements on behalf of the agency with other Federal agencies; units of State or local government; industrial organizations (including corporations, partnerships, and limited partnerships, and industrial development organizations); public and private foundations; nonprofit organizations (including universities); or other persons (including licensees of inventions owned by the Federal agency); and

(2) negotiate licensing agreements under section 207 or under any authorities for Government-owned inventions made at the laboratory and other inventions of Federal employees that may be voluntarily assigned to the Government. (Section 12)

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The act also enables government-operated federal laboratories to exchange personnel, services, and property with collaborating parties; grant patent licenses or assignments, or options thereto, in any inventions made in whole or in part by a federal employee; and retain for the government a nonexclusive, nontransferable, irrevocable, paid-up license to practice the invention or have the invention practiced throughout the world by or on behalf of the government. It also permits the employees or former employees of a laboratory to participate in efforts to commercialize inventions or products that they made while in the service of the government.

A laboratory director, in deciding what cooperative research and development agreements to enter into, shall give special consideration to small business firms and consortia involving small business firms and give preference to business units located in the United States that agree that products embodying inventions made under the cooperative research and development agreement or produced through the use of such inventions will be manufactured substantially in the United States. Public Law 99-502 also details the authority of the head of a government agency (e.g., DOE) to approve, disapprove, or require the modification of any such agreement as well as the records to be kept by each agency entering into such agreements.

Financial rewards for federal laboratories and scientists are also addressed by the Technology Transfer Act. Public Law 99-502 allows each agency to develop and implement a:

> cash awards program to reward its scientific, engineering, and technical personnel for—(1) inventions, innovations, or other outstanding scientific or technological contributions of value to the United States due to commercial application or due to contributions to missions of the Federal agency or the Federal government, or (2) exemplary activities that promote the domestic transfer of science and technology development within the Federal Government and result in utilization of such science and technology by American industry or business, universities, State or local governments, or other non-Federal parties. (Section 13)

The act also delineates the distribution of royalties received by a federal agency from the licensing or assignment of inventions under agreements entered into under its provisions. At least 15 percent of the royalties or other income shall be paid to the inventor or coinventors or the agency may enter into an agreement with the inventor that guarantees a fixed minimum payment to each such inventor each year that the agency receives royalties from that inventor's work. The balance of the royalties or other income shall be transferred by the agency to its government-operated laboratories with the majority share of the royalties or other income going to the laboratory where the invention occurred.

Public Law 99-502 allows an inventor who is or was a government employee and made the invention during employment by the agency to retain title to the invention if the federal agency that has the right of ownership of the invention

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does not intend to file for a patent application or otherwise to promote the commercialization of such an invention. Public Law 99-502 also preserves the rights of the government to a nonexclusive, nontransferable, irrevocable, paid-up license to practice the invention or have the invention practiced throughout the world by or on behalf of the government. The act would provide a suitable mandate for the various partnership initiatives and obviate certain legal and proprietary claims. The rights of all parties are not clearly delineated here, and the legal implications are apparent.

The implications of Public Law 101-101 for the financial viability of the DOE isotope production program have been discussed at length in this report. In summary, the historical posture of DOE and the mandate implied by Public Law 101-101 as well as the concept of "prioritization" have resulted in what has proven to be a financially problematic program of isotope production. Among the most frequently offered measures for solution have been partnerships and arrangements involving federal agencies (DOE), universities, and commercial businesses (private enterprise). In the area of scientific research, a number of successful examples can and have been cited. The Nordion-Tri-University Meson Facility arrangement in Canada appears promising and is outlined in some detail in Chapter 5. For a realistic approach, the committee recommends the exploration of these possibilities, with the caveat that the legal implications, especially those regarding antitrust, be considered before specific agreements are entered into or even recommended as policy. Because of the complex and important issues of antitrust, certain basic principles are outlined in the following discussion.

ANTI-TRUST CONSIDERATIONS

A general consideration of antitrust law usually begins with the Sherman Act of 1890, which has two important sections. Section 1 proscribes contracts, combinations, or conspiracies in restraint of trade. The mandate for Section 1 is broad and at times difficult to define accurately. Section 2 of the Sherman Act is more circumscribed and forbids all activities that may lead to monopolization. Both have implications for the various partnerships proposed in this report. The latter components of antitrust legislation such as the Clayton Act of 1914 forbid certain tie-in arrangements and exclusive-dealing group policies, whereas the Robinson-Pattman Act proscribes predatory pricing and price discrimination. The Federal Trade Commission Act, passed subsequently to the Sherman Act forbids unfair methods of competition. This latter mandate has often been interpreted by the U.S. Federal Trade Commission (FTC), and sometimes by the courts, to include anything prohibited by either the Sherman or the Clayton Act. FTC has expanded the perceived mandate even further to forbid whatever is deemed contrary to the public's best interest.

The general area of antitrust and exclusive contracts has become an increasingly important one for medical practice, especially in the new and more publicly

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visible areas. The discipline has experienced the application of antitrust regulation in resource allocation and distribution (e.g., magnetic resonance imaging and computed tomography imaging equipment), determination of the exclusivity and market capture of delivery contracts, and analysis of the fairness of compensation schemes.

The central concern embodied in antitrust laws is the fear of exercise or abuse of market power (i.e., the power to control price or to exclude competitors). In principle, market power may be exercised by a firm or by a group of firms acting collectively. Analysis of Section 1 of the Sherman Act determines whether an agreement between competitors unreasonably restrains trade. The act provides "that every contract, combination or conspiracy in restraint of trade or commerce among the several States, or with foreign nations … is illegal." This section of the Sherman Act includes two preliminary requirements: (1) at least two firms or economic units must be involved, and (2) there must be some form of agreement or collaboration between the two or more parties such as an exclusive contract to perform the procedures and to be compensated for this service. Proving the existence of market capture becomes necessary only if these threshold requirements are satisfied. Depending on the type of agreement and its anticompetitive effects, the court either will commence a "rule of reason" analysis or will declare the activity "per se" illegal.

The U.S. Department of Justice Merger Guidelines (Antitrust Division, 1984) and Vertical Restraints Guidelines (Antitrust Division, 1985) define a market in essence as a group of products and associated geographic area in which the exercise of market power would be feasible. Formally, a market was defined as a product or group of products and a geographic area in which the product is sold. According to this definition, a hypothetical, profit-maximizing firm such as a private partner in DOE isotope production, not strictly subject to price regulation, would be the only present and future seller of those products in any patient area. This firm could impose a "small but significant and nontransitory" increase in charges above the prevailing ones for similar but not identical demand for products or likely future levels of demand for products or services.

Obviously, marketplace analysis and determination in a complex field such as isotope production would be difficult. The trier of fact in such considerations often may be perplexed by the implications of the technology and the need for services, as well as the products at issue. Tying arrangements in antitrust suits are often alleged when it appears that the choice or selection of one product is tantamount to selecting a second and different product. As an illustration, this was a major issue in the landmark case of *Hyde v. JeffersonParish Hospital*. Such a circumstance of an exclusive contract for one medical group was felt de facto to preclude choice or potential rejection by the consumer (patient) of the tied product. Clearly, violation of antitrust is possible if both products are controlled by the same person, group, or entity. In this case, however, the U.S. Supreme Court was convinced the market was large and that alternatives were available. For a particular isotope, this may well not be the case.

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Although partnerships between academia, industry, and government agencies have served us well in the biomedical research enterprise, there is limited successful experience with purely commercial arrangements. In the United States there is indeed significant concern regarding not only the financial implications but the legal exposure of these types of arrangements as well. It may be that the most appropriate model would be a combination whereby the academic institution would be primarily responsible for the education function in its broadest context, the government agency would be responsible for research (in collaboration with academia) and the facility, and industry would be for marketing, sales, and distribution. An arrangement of this type, although complex and probably unprecedented, might well obviate many of the financial and legal challenges.

REFERENCES

Antitrust Division, U.S. Department of Justice, Merger Guidelines §2, 49 Federal Register 26, 823–827 (June 19, 1984).

Antitrust Division, U.S. Department of Justice, Vertical Restraints Guidelines §6.1, 50 Federal Register 6, 263–272 (February 14, 1985).

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APPENDIX C

Acronyms and Abbreviations

AEC	Atomic Energy Commission
AECL	Atomic Energy of Canada, Ltd.
AGS	alternating gradient synchrotron
AMS	accelerator mass spectrometry
ANL	Argonne National Laboratory
ANS	Advanced Neutron Source
AUI	Associated Universities, Inc.
AVLIS	atomic vapor laser isotope separation
BLIP	Brookhaven Linac Isotope Production Facility
BNL	Brookhaven National Laboratory
CEBAF	Continuous-Electron-Beam Accelerator Facility
CFR	Code of Federal Regulations
Ci	curie
CRADA	cooperative research and development agreement
DOE	U.S. Department of Energy
ERDA	Energy Research and Development Agency
FDA	U.S. Food and Drug Administration
FTC	U.S. Federal Trade Commission
GAO	U.S. General Accounting Office
IPDP	Isotope Production and Distribution Program
IRE	Institute National des Radioéléments

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KeV	thousand electron volts
LAMPF	Los Alamos Meson Physics Facility
LANL	Los Alamos National Laboratory
LBL	Lawrence Berkeley Laboratory
Linac	linear accelerator
LLNL	Lawrence Livermore National Laboratory
LLRW	low-level radioactive waste
MeV	million electron volts
MURR	University of Missouri Research Reactor
MW	megawatts
NBTF	National Biomedical Tracer Facility
NIP	National Isotope Program
NMR	nuclear magnetic resonance
NRC	U.S. Nuclear Regulatory Commission
NSF	National Science Foundation
OHER	U.S. DOE Office of Health and Environmental Research
ORNL	Oak Ridge National Laboratory
PET	positron-emission tomography
RCC	Radiochemical Company (division of AECL)
SPECT	single-photon emission computed tomography
SUNY-SB	State University of New York - Stony Brook
Sv	Sievert
TRIUMF	Tri-University Meson Facility
VAC	vacuum arc centrifuge

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APPENDIX D

Table of Elements

Element	Atomic Symbol	Atomic Number	Weight
Actinium	Ac	89	(227)
Aluminum	Al	13	26.98
Americium	Am	95	(243)
Antimony	Sb	51	121.75
Argon	Ar	18	39.948
Arsenic	As	33	74.92
Astatine	At	85	(210)
Barium	Ba	56	137.34
Berkelium	Bk	97	(249)
Beryllium	Be	4	9.012
Bismuth	Bi	83	208.98
Boron	B	5	10.81
Bromine	Br	35	79.909
Cadmium	Cd	48	112.40
Calcium	Ca	20	40.08
Californium	Cf	98	(251)
Carbon	C	6	12.011
Cerium	Ce	58	140.12
Cesium	Cs	55	132.91
Chlorine	Cl	17	35.453
Chromium	Cr	24	52.00
Cobalt	Co	27	58.93
Copper	Cu	29	63.54

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Element	Atomic Symbol	Atomic Number	Weight
Curium	Cm	96	(247)
Dysprosium	Dy	66	162.50
Einsteinium	Es	99	(254)
Erbium	Er	68	167.26
Europium	Eu	63	151.96
Fermium	Fm	100	(253)
Fluorine	F	9	19.00
Francium	Fr	87	(223)
Gadolinium	Gd	64	157.25
Gallium	Ga	31	69.72
Germanium	Ge	32	72.59
Gold	Au	79	196.97
Hafnium	Hf	72	178.49
Helium	He	2	4.003
Holmium	Ho	67	164.93
Hydrogen	H	1	1.0080
Indium	In	49	114.82
Iodine	I	53	126.90
Iridium	Ir	77	192.2
Iron	Fe	26	55.85
Krypton	Kr	36	83.80
Lanthanum	La	57	138.91
Lawrencium	Lr	103	(257)
Lead	Pb	82	207.19
Lithium	Li	3	6.939
Lutetium	Lu	71	174.97
Magnesium	Mg	12	24.312
Manganese	Mn	25	54.94
Mendelevium	Md	101	(256)
Mercury	Hg	80	200.59
Molybdenum	Mo	42	95.94
Neodymium	Nd	60	144.24
Neon	Ne	10	20.183
Neptunium	Np	93	(237)
Nickel	Ni	28	58.71
Niobium	Nb	41	92.91
Nitrogen	N	7	14.007
Nobelium	No	102	(253)
Osmium	Os	76	190.2
Oxygen	O	8	15.9994
Palladium	Pd	46	106.4

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Element	Atomic Symbol	Atomic Number	Weight
Phosphorus	P	15	30.974
Platinum	Pt	78	195.09
Plutonium	Pu	94	(242)
Polonium	Po	84	(210)
Potassium	K	19	39.102
Praseodymium	Pr	59	140.91
Promethium	Pm	61	(147)
Protactinium	Pa	91	(231)
Radium	Ra	88	(226)
Radon	Rn	86	(222)
Rhenium	Re	75	186.23
Rhodium	Rh	45	102.91
Rubidium	Rb	37	85.47
Ruthenium	Ru	44	101.1
Samarium	Sm	62	150.35
Scandium	Sc	21	44.96
Selenium	Se	34	78.96
Silicon	Si	14	28.09
Silver	Ag	47	107.870
Sodium	Na	11	22.9898
Strontium	Sr	38	87.62
Sulfur	S	16	32.064
Tantalum	Ta	73	180.95
Technetium	Tc	43	(99)
Tellurium	Te	52	127.60
Terbium	Tb	65	158.92
Thallium	Tl	81	204.37
Thorium	Th	90	232.04
Thulium	Tm	69	168.93
Tin	Sn	50	118.69
Titanium	Ti	22	47.90
Tungsten	W	74	183.85
Uranium	U	92	238.03
Vanadium	V	23	50.94
Xenon	Xe	54	131.30
Ytterbium	Yb	70	173.04
Yttrium	Y	39	88.91
Zinc	Zn	30	65.37
Zirconium	Zr	40	91.22

*Values in parentheses indicate the mass number of the most stable isotope.

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APPENDIX E

Glossary

Accelerator A machine designed to accelerate charged particles (typically electrons, protons, deuterons, or ions) to energy levels suitable for bombarding a target and studying the resulting nuclear reactions. Among the types of accelerators are Van de Graff electrostatic accelerators, linear accelerators, cyclotrons, and synchrotrons.

Alpha particle A positively charged particle consisting of two protons and two neutrons, identical to the nucleus of the helium atom, emitted by several radioactive substances.

Alpha radiation Some radioactive elements, particularly those with a high atomic number, decay by emitting a positively charged particle, the alpha particle, which is identical to the nucleus of a helium atom. Alpha radiation has very little penetrating power, but it may present a serious hazard if alpha emitters are inhaled, ingested, or taken in through the skin.

Atom The smallest particle of an element that retains the characteristics of that element. The atom consists of a small positively charged nucleus surrounded by a cloud of negatively charged electrons. An atom is characterized by its mass number (A) and its atomic number (Z).

Atomic number (Z) The number of protons in an atomic nucleus.

Background radiation The radiation produced by naturally occurring radioactive isotopes in the surroundings and biological tissue. Cosmic rays also contribute to the background radiation.

Beta decay Radioactive transformation of a nuclide in which the atomic number increases or decreases by unity with no change in the mass number; the nucleus emits a beta particle during beta decay.

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Beta particle	A synonym for an electron or a positron when it is emitted in the process of beta decay.
Beta radiation	Some radioactive elements emit from the nucleus charged particles of low mass called beta particles. Positive beta particles are positrons, and negative beta particles are identical to the electrons in the atom. Such beta radiation has a penetrating power intermediate between that of alpha and gamma radiation.
Charged particle	A particle whose net charge is not zero; protons and electrons are examples of charged particles; neutrons, by contrast, are uncharged.
Curie (Ci)	A unit of measurement describing the radioactive disintegration rate of a substance; 1 curie = 3.700 × 1010 disintegrations per second.
Cyclotron	A machine capable of accelerating a beam of charged subatomic particles in an outward spiral pathway to high energies and speeds by the application of electromagnetic forces.
Cyclotron vault	The massive concrete structure that completely surrounds the cyclotron, beam tubes, and target stations and that acts as a biological shield against the neutron and gamma radiation emitted by the cyclotron when it is in operation.
Decay product	The substance formed by the radioactive decay of a radioactive nuclide. Some radionuclides decay through a sequence of steps with many successive decay products.
Detector	Any device that can detect the presence of a particle or nuclear fragment produced in a nuclear reaction and measure one or more of its physical properties.
Deuterium	A naturally occurring isotope of hydrogen. A deuteron, the nucleus of the deuterium atom, consists of one proton and one neutron; hence, it is approximately twice as heavy as ordinary hydrogen.
Diagnostic medicine	Identification of disease by means of the patient's symptoms and other objective measurements.
Dose	The amount of energy delivered to a mass of material by ionizing radiation passing through it.
Electron	A particle that has unit negative charge and 1/1,840 the mass of a proton. Atoms consists of a cloud electrons around a nucleus.
Electron volt, (eV)	The amount of energy acquired by any particle with a unit electric charge when it is accelerated through a potential difference of 1 volt; 1 keV = 1 thousand electron volts; and 1 MeV = 1 million electron volts.
Element	A substance that cannot be divided into simpler substances by chemical means, being made up of a collection of atoms that have the same number of protons in their nuclei, and therefore the same atomic number.
Epithermal neutron	A neutron with kinetic energy typically in the range of between 1 keV and 1 MeV.

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Fast neutron	A neutron with kinetic energy typically of 1 MeV.
Fission	The process whereby the nucleus of a heavy element, for example, uranium or plutonium, splits into two nuclei of lighter elements (fission products) accompanied by the release of substantial amounts of energy and particles, usually neutrons.
Fission products	The complex mixture of substances produced in the process of fission. The primary fragments produced in fission are themselves radioactive and decay through succession of radioactive isotopes until a stable form is reached.
Gamma radiation	Most radioactive elements emit from the nucleus electromagnetic radiation called gamma rays. Gamma radiation is penetrating and can cause radiation exposure many tens of meters from external sources. It is also the radiation that is most readily measured by monitoring equipment such as film badges and dosimeters.
Gamma ray	An extremely energetic photon emitted in many nuclear reactions and in the decay of many radioactive nuclides.
Half-life	The time in which the activity of a radioactive species will decline to half of its initial activity value by radioactive decay. The half-life of a radioactive species is a characteristic property of that species and is independent of its amount or physical condition.
Hot cell	An enclosure for the safe handling of radioactive substances; it protects the operator against both internal and external radiation.
Isotopes	Forms of the same element whose nuclei contain different numbers of neutrons and therefore have different mass numbers. Isotopes of an element have nearly identical chemical properties but differ in their nuclear properties. For instance, some isotopes of an element, but not others, may be radioactive. An example is hydrogen, which has three isotopes with relative masses of 1, 2, and 3. The two lighter isotopes, hydrogen (relative mass of 1) and deuterium (relative mass of 2), are stable but the third, tritium (relative mass of 3), is radioactive.
Mass number (A)	The total number of protons and neutrons contained in the nucleus of an atom. The mass number is used to characterize isotopes, for example, uranium-235 is the isotope of uranium that has a mass number of 235. The nuclei of different elements can have the same mass number.
Metabolism	All of the physical and chemical processes by which the living body is maintained and also those by which energy is made available for various forms of work.
Monoclonal antibody	A protein produced in an animal or human by a single family of cells response to stimulation by an antigen and capable of reacting specifically with that antigen.

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Neutron	A nuclear particle having no charge and a mass approximately equal to that of a proton. Neutrons are present in all atoms except those of the lightest isotope of hydrogen. Neutrons are released in large numbers in nuclear explosions and are very penetrating.
Neutron number (N)	The number of neutrons in an atomic nucleus.
Nuclear medicine	A branch of medicine in which radioisotopes are used principally to diagnose or treat disease.
Nuclear physics	The study of the characteristics, behavior, and internal structure of the atomic nucleus.
Nuclear reaction	Any change brought about in the states of one or more nuclei as a collision or spontaneous decay.
Nucleus	The small, dense, positively charged core of the atom, consisting of neutrons and protons held together by strong nuclear forces.
Nuclide	An atomic nucleus characterized by the number of protons, the number of neutrons, and energy content.
Photon	The unit of energy associated with the element with the electromagnetic wave; the unit of the electromagnetic field, which carries energy and momentum.
Positron	A fundamental particle of matter having the same mass and the same magnitude of charge as those of an electron, but with a positive charge.
Positron emission tomography (PET)	Often known by the acronym PET. A technique in nuclear medicine in which the physiological and pathological processes occurring in the tissues of a patient may be visualized and quantified through the application of positron-emitting radioisotopes.
Proton	A positively charged particle found in all atoms. The nucleus of the lightest isotope of hydrogen consists of one proton.
Radiography	The technique of generating radiographs or pictures produced on a sensitized surface or film by a form of radiation, typically X-ray radiography or neutron radiography.
Radioisotope, radionuclide	The name given to a substance in which the number of neutrons in the atom's nucleus have been increased or reduced to bring about nuclear instability, which is manifested by the emission of radiation.
Scattering	When two particles collide, they are said to scatter off each other during the collision.
Spallation	A nuclear reaction in which nuclei, on being bombarded by high-energy particles, liberate a number of other particles (protons, neutrons, and alpha and heavier particles). Also known as fragmentation.
Spectroscopy	The branch of physics concerned with the production, measurement, and interpretation of the electromagnetic spectra arising from either the emission or absorption of radiant energy by various substances.

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Target	The substance bombarded with neutrons or other particles to produce radioisotopes.
Therapeutic medicine	Treatment of disease to secure a cure or a reduction or palliation of symptoms.
Thermal neutron	A neutron with kinetic energy typically in the range of less than 1 kiloelectron volt (keV).
Transmutation	A process in which a nuclide of one chemical element is transformed into a nuclide of a different chemical element. A common transmutation process is neutron capture followed by beta decay.
Tritium	A radioactive isotope of hydrogen (3H or T). The nucleus of the tritium atom consists of one proton and two neutrons; hence, it is approximately three times as heavy as ordinary hydrogen.
X-ray	Highly penetrating radiation emanating from atomic transitions of an element; X-rays are produced, for example, by electron bombardment of a metallic target.

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