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Evaluation of Medical Isotope Production with the Accelerator production of Tritium (APT) Facility

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DISCLAIMER

EVALUATION OF MEDICAL ISOTOPE PRODUCTION WITH THE ACCELERATOR PRODUCTION OF TRITIUM (APT) FACILITY

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ABSTRACT

The accelerator production of tritium (APT) facility, with its high beam current and high beam energy, would be an ideal supplier of radioisotopes for medical research, imaging, and therapy. By-product radioisotopes will be produced in the APT window and target cooling systems and in the tungsten target through spallation, neutron, and proton interactions. High intensity proton fluxes are potentially available at three different energies for the production of proton-rich radioisotopes. Isotope production targets can be inserted into the blanket for production of neutron-rich isotopes.

Currently, the major production sources of radioisotopes are either aging or abroad, or both. The use of radionuclides in nuclear medicine is growing and changing, both in terms of the number of nuclear medicine procedures being performed and in the rapidly expanding range of procedures and radioisotopes used. A large and varied demand is forecast, and the APT would be an ideal facility to satisfy that demand.

I. INTRODUCTION

The value of radioisotopes to both the medical and industrial fields is immense. In the U.S., one out of every three hospital patients undergoes a procedure involving the use of radioisotopes: over 12 million nuclear medicine procedures are carried out annually at a cost of $7 to $10 billion per year (Adelstein and Manning, 1995). Radionuclides have many applications in nuclear medicine including diagnostics, cancer treatment, radiopharmaceuticals, and drug research. In addition to medical uses, nonmedical applications of radioisotopes are an integral part of our society.

Currently, the major production sources of radioisotopes are either aging or abroad, or both. They cannot be depended upon for future radioisotope supplies. Some of these facilities are major suppliers of research nuclides, and their shutdown will effect the future position of the U.S. in the nuclear medicine field. Even at facilities in current operation, many isotopes are not produced at all or only in a discontinuous fashion because they are not economically viable.

The U.S. Institute of Medicine and the U.S. Department of Energy (DOE), in response to congressional, industrial, and research concerns, have investigated over the past several years the expanding demand for radioisotopes. Their reports concluded that the present production facilities are aging and that increased demands for existing radioisotopes and for new, promising radioisotopes would require new production facilities. The Committee on Biomedical Isotopes concluded that a stand-alone facility is not economically justified as a source of radioisotopes, whether such a facility were a reactor or an accelerator (Adelstein and Manning, 1995). However, isotopes produced at a facility in operation primarily for other purposes would incur only incremental cost and be more cost effective.

Representatives from the Medical University of South Carolina, the University of South Carolina, Los Alamos National Laboratory, and Westinghouse Savannah River Company proposed that the highly versatile linear proton accelerator for the APT planned for the Savannah River Site near Aiken, SC, may be suitable for the production of radioisotopes for nuclear medicine. The Medical University of South Carolina was asked to take the lead in evaluating the capabilities of the APT facility for medical isotope production, including medical isotope usage and needs, current markets, and market forecasts. The study was to evaluate all of the assets of the APT program for the production of medically useful isotopes, with the production of industrial isotopes as a secondary consideration.

A prime attraction of the APT facility for radioisotope production is that the accelerator would be a source of large quantities of both neutrons and very high energy protons, and thus could supply large quantities of radioisotopes previously produced only in accelerators or only in reactors. Several isotopes produced at higher energies are considered potentially useful for medical and other applications and there is a renewed interest in their availability. Production costs for medical radioisotopes are a critical factor. The DOE would be funding the design and construction of the APT facility for tritium production, but the entire capacity of the APT might not be required after the initial production stages. The APT represents an ideal facility to produce medical isotopes in significant quantities.

II. CURRENT MEDICAL APPLICATIONS FOR RADIOISOTOPES

There are three major medical uses of radioisotopes: diagnostic imaging, therapy with both sealed (radiation therapy) and unsealed (nuclear medicine) sources, and medical supply sterilization. Research programs in imaging and therapy also require supplies of radioisotopes, some of which are not available. Radioisotopes currently in use are produced by nuclear reactors and relatively low energy accelerators.

The most widely used radionuclide in clinical nuclear medicine today is Tc-99m, the decay daughter of Mo-99. Supplied to hospitals and clinics as a generator system, Mo-99 decays with a 66 hour half-life to Tc-99m, and is extracted regularly for use as a diagnostic tool. The traditional production approach is to fission U-235 in a reactor and chemically separate the Mo-99 fission product. This isotope also could be produced by neutron capture on separated Mo-98 targets or a novel proton induced reaction. All of these production possibilities are provided by the APT design.

The radioisotopes utilized most frequently for diagnostic imaging and therapy today are listed in Table 1, along with their primary pharmaceutical applications, the type of production facility, and an estimate of the percentage of daily use.

Table 1. Frequently used radioisotopes.

Medical Isotope (Pharmaceutical)	Produced In	Est. % of Daily Practice
Tc-99m (heart, bone, kidney, lung, brain, etc.)	Reactor	64%
Tl-201 (heart, tumors, etc.)	Accelerator	18%
I-131 (thyroid, adrenals, MOAB)	Reactor	8%
Xe-133 (lung)	Reactor	5%
In-111 (infection, tumor, MOAB)	Accelerator	3%
Ga-67 (infection, tumor)	Accelerator	1.5%
Other	Reactor	0.5%

With every nuclear event, these isotopes emit a single photon which is captured by a gamma camera to produce images of various organs. This imaging modality complements the anatomical images provided by most radiologic imaging procedures to offer physiologic information for both diagnosis of diseases and monitoring therapy. As an example, Tc-99m is bound to methylenediphosphonate (MDP) to produce a radiopharmaceutical which localizes in sites of newly produced bone. When these sites are placed under a gamma camera, they produce the familiar bone scan. In a similar manner, technetium-bound radioisotopes image the heart, brain, lungs, kidneys and many other organs. Radio-thallium, an analog of potassium, is used to assess the viability of heart muscles and to estimate the aggressiveness of central nervous system tumors. I-131 and In-111 are routinely bound to monoclonal antibodies (MOAB) and peptides (hormones) which seek and bind to tumors, myocardial infarctions, thrombi, and other humoral and cellular antigens.

In a small but growing number of nuclear medicine departments, positron emitting radioisotopes are produced daily for a limited scope of clinical applications. The increasing role for these isotopes in detecting and monitoring tumors, along with proven efficacy in determining the viability of heart muscle and detecting seizure foci, as well as accurately diagnosing dementia, have led to the recent rapid growth of this imaging sub-specialty. The high

cost of positron emission tomography (PET) scanners (i.e. cameras) and the limited availability of positron emitting isotopes in the past have curtailed the use of these potentially very beneficial radioisotopes. Recently, major radiopharmaceutical manufacturers have begun developing a number of regional distribution sites in the U.S. which will facilitate delivery of these very short-lived isotopes to most metropolitan areas. This, combined with newly developed coincidence detector capabilities for gamma cameras which will allow them to image positrons, means that positron emitting isotopes have the potential to become much greater contributors to clinical nuclear medicine.

While single-photon emitting radioisotopes are ubiquitously available and cost-effective, some are significantly limited in their availability thus impeding the practice of nuclear medicine. I-131 is both a gamma and beta emitter; consequently its use results in a significant radiation dose to patients. I-123 is a much more favorable gamma emitter but its expense and availability severely restrain its use in clinical practice. Likewise, In-111 has very favorable chemistry for binding to a number of compounds, including monoclonal antibodies, but it is very expensive. Xe-133 is used to image gas exchange in the lungs, but its energy and proton flux result in crude images. Kr-81m or Xe-127 would be much better radiopharmaceuticals if they could be produced cost-effectively and made available to the nation as a whole.

While technetium is an ideal gamma emitter for imaging, has a low radiation dose, and is widely available in reasonable costs, it is limited by its chemistry. Radiopharmacists have difficulty binding technetium to biologically active metabolites, without altering their biodistribution. New generator systems which could produce an isotope comparable to technetium but with more favorable chemistry would be extremely beneficial.

Nuclear medicine clinics offer radioisotope therapy using unsealed sources of P-32, I-131 and Sr-89. Injection of P-32 into the abdominal cavity is used to treat women with ovarian and uterine carcinoma; injection into the orbit is used for treatment of ocular melanoma. I-131 is used almost daily for ablating hyperfunctioning thyroid glands and treating thyroid cancer. During the past few years, Sr-89 has been routinely administered to patients with extensive malignancies to help ameliorate the pain of bone metastases.

The radioisotopes previously discussed, as well as others, are typically produced in a reactor or an accelerator. The most commonly produced radioisotopes are listed below (Tables 2 and 3) as well as key supply-limited radiopharmaceuticals (Table 4).

Table 2.
Common Reactor-Produced Medical Radioisotopes

Mo-99/Tc-99m
I-131
Xe-133
Co-60
P-32
Sr-89

Table 3.
Common Accelerator-Produced Medical Radioisotopes

6-30 MeV	>50 MeV
F-18 (PET)	Sr-82/Rb-82
Tl-201	Xe-127
In-111	
I-123	
Ga-67	
Rb-81/Kr-81m	
Y-87	

Table 4.
Key Supply-Limited Radiopharmaceuticals

Sr-82 (Rb-82 Generator)	$28,000/mo
In-111 (MOAB, Peptides)	$480/dose
I-123	>$300/dose, if available
Rb-81 (Kr-81m gas)	Not Available

III. NEW APPLICATIONS AND PROMISING RADIONUCLIDES

The use of radionuclides in nuclear medicine is currently growing and changing, both in terms of the number of nuclear medicine procedures being performed and in the rapidly expanding range of procedures and radioisotopes used. Site-directed radiopharmaceuticals are targeting particular body locations for more rapid and accurate diagnosis with subsequent improvements in patient therapy. Biologically active compounds that can act as carrier molecules designed to recognize specific organs or diseases are being investigated. Carrier molecules, such as monoclonal antibodies and peptides, may be labeled with a single-photon emitting or a positron emitting radioisotope and used in diagnostic or therapeutic applications. Radioisotopes with special combinations of photon energy, specific activity, half-life, and chemical properties are being sought and tested. The treatment of cancer or other diseases in a localized manner without affecting nearby tissues or organs is an important area of nuclear medicine that is commanding much research attention. This holds the promise of nonsurgical therapeutic procedures with radionuclides leading to

fewer side effects and potentially both a longer and better quality of life.

Diagnostic nuclear medicine has seen many changes since the earliest techniques involving P-32 and I-131. Scintillation detectors, rectilinear scanners, and scintillation cameras all ushered in new phases in diagnostic history. The radiopharmaceutical phase, in particular the introduction of the Mo-99/Tc-99m generator, was the real catalyst for the growth of nuclear medicine (Early, 1995). Radioisotopes for use with PET or single-photon emission computed tomography (SPECT) are being thoroughly investigated. For the last decade there has been considerable research and investigation of F-18 tagged to deoxyglucose (FDG), free fatty acids, hormones, and neurotransmitters. For single-photon emitters, the most promising broad-based nuclides for SPECT are Ru-97, In-111, I-123, and Pb-203, because of their unique chemical properties. For PET, Co-55, Cu-62, Ga-68, and I-124 are untested but potentially valuable isotopes (Srivastava, 1996).

Currently, there is a strong focus on the development of new radiopharmaceuticals for radioimmunotherapy (RIT) directed against malignancies in most organs of the body. Important new therapeutic applications of radioisotopes are being tested in clinical trials for relief of bone-cancer pain, cancer treatment using monoclonal antibodies, blood-flow studies, brain tumor treatment, and other applications (Farabee, 1997).

Brachytherapy (short range or close proximity radioimmunotherapy) is receiving a lot of attention for its highly focused therapeutic effects. A few radioisotopes currently used as brachytherapy implant "seeds" placed in or near tumors include Pd-103, I-125, Ir-192, and Au-198 (Adelstein and Manning, 1995). The ability to treat cancer in a localized manner without affecting nearby tissues or organs is an important area of nuclear medicine that will continue to receive much clinical attention.

The analgesic treatment of bone metastases in cancer patients with radioisotopes is an area that is currently expanding rapidly. Bone metastases from lung, prostate, breast, and a variety of other cancers are one of the most painful and debilitating side effects of cancer. When tumors metastasize from their primary site into bone, the subsequent damage causes unrelenting pain as it presses on adjacent nerves. Radionuclide therapy has been shown to relieve this pain and improve quality of life for many patients. Presently, there is considerable interest in using P-32, Sr-89, Sn-117m, Re-186 and Sm-153 as potential radioactive agents for the treatment of this intractable bone pain (Silberstein, 1993). When these radioisotopes are used, "pain relief often occurs in approximately 2-4 weeks and lasts several weeks to months with responses seen in 60-80% of patients, depending on the extent of disease and stage the patient is treated" (Serafini, 1994). Although the majority of isotope use is currently analgesic and not therapeutic, these radionuclides are still being researched for their therapeutic potential. These isotopes could be produced at the APT facility by placing their targets in the appropriate location of the neutron flux surrounding the tungsten target. All of these radioisotopes would be used more extensively if they were more readily available.

Cardiovascular disease is the most common cause of death in the U.S. In this disease, plaque builds up on the inside of blood vessels and impedes blood flow. In the heart this leads to angina, occlusion of the vessels, and death. In the other vessels of the body it leads to a variety of problems, including strokes, hypertension, and the loss of limbs. Early treatment of vascular disease has been facilitated by balloon angioplasty, where a thin catheter is inserted into the diseased vessel and a balloon passed over it. This balloon, when inflated, expands to the size of the vessel and squashes or disrupts the plaque. Unfortunately, in a large percentage of these cases the vessel re-occludes within a matter of months (restenosis) and the procedure must be repeated or the patient must have a surgical bypass. A number of techniques involve inserting tubes, called stents, to fill the vessel and keep it from closing. While this reduces the rate of restenosis, the rate is still high due to the growth of new tissue into the stent. Recently, very exciting research has shown that running a radioactive source through the stent or coating the stent with a beta emitting radioisotope slows the growth of occluding tissue, greatly reducing the rate of restenosis and the need for open heart, bypass surgery with its attendant risks (Nickles, 1997).

An area of interest for potentially useful radioisotopes is the development of new generators that parallel the characteristics of the Mo-99/Tc-99m generator system. In a typical generator system, the short-lived daughter nuclide is regularly eluted from the longer-lived parent. The regular availability of the short half-life progeny overcomes the problems of repetitive production, time, and distance from the supplier; it also minimizes the absorbed radiation dose to the patient (Ice, 1995). Although Tc-99m has excellent physical properties, its chemistry can interfere with the desired therapy. There is a possibility that another generator system could provide better chemical reactivity and binding.

The following (Table 5) is a list of selected radioactive nuclide generator systems located through a search of both the literature and existing data bases. Selection of potential generators was based on several factors, including whether the parent has a half-life appropriate to eluting a reasonably concentrated daughter radionuclide and whether the daughter emission has a high enough flux (i.e. a short half-life) and an energy level that can be detected for imaging. The chemistry of these isotopes is also of great interest, for they need to be capable of binding to a carrier molecule that is of interest to the medical community (Ice, 1995).

IV. FUTURE MARKET DEMAND

Mo-99 and Co-60, typically reactor-produced nuclides, dominate the radioisotope market (Table 6) and are expected to continue to increase in demand in future years. There are or will be several production sources for Mo-99 (MDS Nordion of Canada, Sandia National Laboratory, HFR at Petten in the Netherlands, the IRE in Belgium, and the AEC of South Africa) but all of these are based on aging facilities that cannot be depended upon for Mo-99 production beyond the next ten years. MDS Nordion plans to build two new reactors, but the problem of a sole supplier and no domestic supplier for the U.S. is not alleviated. With a projected annual growth rate of 5-10% and a lack of dependable suppliers in the future, a market potential for the production of Mo-99 is evident. It is estimated that MDS Nordion, the dominant supplier of Mo-99 and Co-60, makes about $50 million a year in Mo-99 sales and about $35 million a year in Co-60 sales (Andersen, 1994). Although Co-60 has many applications in the industrial field, it is predicted to have a significant increase for medical use in future years, primarily for equipment sterilization. The future market value of Co-60, with an estimated annual growth rate (10-20%) which is even greater than that of Mo-99, is very promising (Andersen, 1994).

Table 6. Worldwide Radioisotope Market Share By Major Products (Andersen, 1994).

Total Market
1992: $75 million to $100 million
1994: $92 million to $112 million

Market Share

Product	1992	1994
Mo-99	34%	42%
Co-60	40%	31%
Others	26%	27%

Several other radionuclides have established medical markets that should continue to grow through increased usage and new applications. In-111, which is already widely used diagnostically, is the only isotope for which Norton Haberman of the DOE anticipates a substantial increase in demand (Haberman, 1997). In-111 is therapeutically promising due to the emission of Auger electrons. These electrons, with energies in the eV range, have a short but lethal penetration range in tissues. Much research involving In-111 for imaging and radioimmunotherapy is in progress and likely to result in an increased market value. Tl-201, the major commercial, accelerator-produced radionuclide that is second only to Tc-99m in volume of medical use, also has a promising future. Its wholesale market value in 1992 was over $30 million. Although Tc-99m might be replacing it in some diagnostic applications, there are many new therapeutic applications that should increase its demand.

I-123 and Xe-127 are both underutilized in the U.S. Although I-123 continues to be an important radioisotope for nuclear medicine research (at a high price and low availability), Xe-127 is not readily used in the U.S. due to the lack of a supplier. They both represent potential sources of revenue for a new facility. The APT facility could produce both isotopes; I-123 and Xe-127 would most likely see an increase in market demand if they were available in the U.S.

Sr-82 and Ir-192 represent radioisotopes with a current significant medical market demand and an increasing market potential for the future. Sr-82, in particular, was estimated to have an annual growth rate of 50-100% due to the expected health insurance reimbursements for procedures using this isotope (Andersen, 1994). Rb-82, produced from the Sr-82/Rb-82 generator, could see a huge increase in demand if it becomes useful for SPECT. There are not many producers of Sr-82 because of the high energy protons required for production. Sr-82 could produce significant revenue for the APT facility, since few other facilities are able to produce it. Ir-192 is also widely used because of its many medical and industrial applications. It has been predicted that its worldwide demand will increase due to untapped international markets (Andersen, 1994), and that many new medical applications, such as brachytherapy implant seeds and vascular radiotherapy, are going to increase the market demand of Ir-192.

Therapeutic radiopharmaceuticals represent the fastest growing segment of the medical isotope market. Many people predict that this part of the

market will surpass that of the diagnostic segment when FDA approval of the new radioactive drugs is obtained (Andersen, 1994). Many of the nuclides being studied for their therapeutic qualities have the potential to see a substantial increase in demand because of the 1.6 million new cancer cases diagnosed each year in the U.S. (Adelstein and Manning, 1995). As an example, bone-pain palliation therapy may be indicated in about 350,000 cancer patients per year in the U.S. According to Suresh Srivastava, "if one assumes a 50% use in this group of patients for treatment using radiopharmaceuticals, the total radioactivity required (average two administrations per year per patient) may range from 1.4 x 10^3 Ci for Sr-89 (4 mCi per administration), to 5.25 x 10^3 Ci for Sn-117m (15 mCi per administration), and to about 2.5 x 10^4 Ci for Sm-153 (at 1 mCi/kg per administration)" (Srivastava, 1996). The required volumes of these radioisotopes clearly indicates a future market potential.

The following table (Table 7) was included in the Arthur Andersen report to the DOE. Through surveys, interviews, and research, annual growth rate estimates were developed that represent a consensus view of the future direction of the radioisotope market. The 1994 demand figures represent the approximate midpoint of their estimated range of the worldwide market for the isotopes listed (Andersen, 1994).

Table 7. World Demand (Andersen, 1994).

Isotope	1994 ($000's)	Est. Annual Growth Rate
Medicine		
Molybdenum-99	43,000	5-10%
Iodine- 125	2,900	3-4%
Xenon-133	2,300	3-4%
Iodine- 1 3 1	2,000	5-6%
Cesium-137	1,700	5-6%
Cobalt-60 (medical)	1,500	10-20%
Strontium-82	1,400	50-100%
Others	4,200	4-5%
Total Medicine	59,000	5%
Industry		
Cobalt-60 (industrial)	30,000	3-4%
Iridium-192	4,500	5-6%
Californium-252	1,600	5-6%
Tritium	1,000	3-4%
Germanium-68	500	3-4%
Others	1,700	4-5%
Total Industry	39,300	4%
Research		
Tritium	1,100	2-3%
Yttrium-90	500	5-6%
Others	2,100	2-3%
Total Research	3,700	3%
Total Radioisotope Market	102,000	5%

There are many differing opinions as to the future growth of the medical isotope market. The Freeman School of Business at Tulane University and the Levy Rosenblum Institute produced a business plan for the Fast Flux Test Facility in September of 1993. They projected a global wholesale market (raw isotopes, not radiopharmaceutical end products) of close to $1 billion by 2002, which represents a 10-fold increase (primarily because of therapeutic radiopharmaceuticals) (Adelstein and Manning,1995). However, not all observers have been quite so optimistic. Landis, Baronowski, and Klevans also project a substantial growth but they note that such growth could only occur with FDA approval of a large number of radiopharmaceuticals that are now in the research or clinical testing phase (Adelstein and Manning, 1995). With so many of these radiopharmaceuticals possessing such great promise, it seems very likely that many will develop a substantial market growth. Arthur Andersen & Co., in an isotope market report prepared for the DOE, predicted a reasonable annual growth rate of 5% for the total radioisotope market (Andersen, 1994). This projection, however, seems conservative considering that some isotopes, such as Sr-82, are expected to see as much as a 50-100% increase in growth rate.

V. FEASIBILITY OF THE APT FACILITY FOR RADIOISOTOPE PRODUCTION

The APT linear proton accelerator design has a high current (100 mA) at an energy of about 1.7 GeV. The facility is designed to produce ~3 kg of tritium each year. The accelerator will produce a continuous-wave (cw) proton beam and accelerate it in a series of room temperature radiofrequency acceleration structures to 217 MeV. The proton beam is then accelerated to 1.7 GeV in a series of radiofrequency superconducting cavities. The protons strike tungsten and lead targets to produce large quantities of neutrons through a spallation process. The spallation process produces forty to sixty high energy neutrons per incident proton to transmute helium-3 to tritium.

The APT provides several locations for isotope production as a consequence of the tritium production scheme (Figure 1). Some isotopes may be extracted from light water and heavy water cooling systems and from the spent tungsten target rods with no beam path modifications. With varying degrees of minor modification, the opportunity to generate an even richer variety of artificially produced nuclides is presented. Advantage can be taken of the intense proton beam, which varies over a wide energy range, and the rich neutron flux field in the target/blanket area. Intrusions and impacts on tritium production would be small and controllable. Full scale production of isotopes using either a portion of the neutron flux in the target assembly or by taking occasional packets of protons from the main beam would have an impact of much less than 1%.

The Savannah River Site already has most of the built-in infrastructure to handle, process, and distribute radioisotopes and to dispose of radioactive waste. Real estate, expertise, and support systems for isotope extraction and purification are already available on-site; only the dedicated equipment and buildings would need to be added. Even more importantly, APT can produce many isotopes (now produced by fission) through the use of non-fission methods thus greatly reducing the volume and activity of the waste stream and, of course, avoiding the use of fissile material.

VI. ISOTOPE PRODUCTION WITHOUT PERTURBATION

The APT design provides a wide variety of possibilities for the production of medical and industrial isotopes. Proton fluxes are potentially available at three different energies and high intensity. Neutron fluxes at high intensities are also available. Production possibilities are provided by harvesting by-products of the tritium production scheme and by inserting targets in several possible locations in the accelerator or in the target/blanket facility, some of which have little or no impact on the tritium production.

The two cooling water systems are possible locations for the production of radioisotopes as by-products of the tritium production scheme (without affecting the tritium production rate or process). There is, however, a significant concern regarding isotopic yield. The first cooling system is the light water system used to cool the proton beam entrance window. The exposure area is about 13 cm by 144 cm, and the total proton flux is 6.24×10^{17} protons per second. The current design uses pure H_2O as coolant and, consequently, the nuclide population resulting from the proton flux field spans only H-1 to Ne-21. The most interesting isotope here is F-18, but production is too low to warrant competition with cyclotron production. In addition, F-18 has a very short half-life (1.8 h) so it would be of importance only very near the production site.

The second cooling system is the heavy water (D_2O) system used to cool the tungsten (W) spallation targets. Because this system is exposed to both protons and neutrons, because the deuterium nucleus is abundant, and because the nuclide production modeling reflects the pipe wall materials, the nuclide production profile spans H-1 through Ga-70 and Ge-70. This makes many interesting low-mass radionuclides available for harvesting. The quantities of these isotopes are quite small, however, which would probably preclude their processing for actual use. The production of isotopes in these coolant systems assumes the use of pure light and heavy water and does not consider the addition of any chemicals as corrosion inhibitors (for example) or as intentional target nuclides (i.e. "doping" or "spiking"). Either adding a corrosion inhibitor or pH buffering agent, or adding an intentional target nuclide in the cooling fluid would greatly extend the nuclide profiles of each of these cooling systems and could be done in such a manner as to have minimal and controllable impact on tritium production.

Also, the design model specifies that the tungsten will be clad; the conceptual design report (CDR) contains no estimate for the development of micro-cracks over the operational life of the target rods. Nuclear reactor experience would indicate, however, that at least some of the gaseous or highly soluble spallation products could leach into the heavy water cooling system in small amounts. This would extend the list of available nuclides beyond atomic mass 70. Some of these radioisotopes, such as Hf-172 and Ta-179, are expected to be available in multiple gram quantities. Nuclides near the mass of iron result from irradiation of the piping system; most of these masses will remain in the pipe walls. The LCS/CINDER model used to predict these nuclide profiles assumes the tungsten and heavy water are homogeneously mixed and does not include any nuclides that would be present due to the use of cladding materials. There is some potential for a significant extraction of these nuclides for commercial utilization. Research is currently being done at Los Alamos National Laboratory to process individual radioisotopes out of a mixture of many isotopes. In 10-15 years, techniques may be developed to efficiently process radioisotopes for medical and industrial use.

The blanket region slows neutrons to thermal

energies by collision and scattering. Some further neutron production takes place by spallation, thus producing another spectrum of isotopes analogous to the spallation product spectrum obtained from the tungsten targets. The blanket assembly is cooled by light water which runs through aluminum piping. Some of the isotopes should migrate or recoil through the aluminum piping walls into the cooling water and thus become available for extraction from the coolant.

VII. ISOTOPE PRODUCTION WITH PERTURBATION

The proton energies potentially available for APT fall into three ranges (Table 8), each corresponding with a different physical location for extraction of the protons from the main beam. The injector and pulse shaping RFQ will produce proton currents of ~ 100 mA at an energy of ~6.7 MeV in a cw mode. After a sufficient number of RF cavities the beam will have reached an energy of 20 MeV. This is ample energy to overcome the coulombic barrier between a target nucleus and an incoming proton, thus enabling most proton absorption reactions and (p,n) charge exchange reactions. The absorption reactions in this energy range tend to yield only one particle or a gamma photon as a result of the absorption. Design changes to facilitate this would include a diverting or switching magnet or RF-kicker in the beam path to allow switching occasional packets of protons to a radionuclide production target. Because of the low proton energy, a diverter at this location would be smaller and require less power than a diverter further downstream. This region would produce nuclides similar to those produced by the larger cyclotrons now in use, but potentially at higher production rates, depending on the rate at which packets are switched out of the main beam path. These would tend to be the lighter nuclides of interest. The specific proton energy at which tap-off would be optimum is not well-known yet but is probably 20-40 MeV.

At the end of the CCDTL section, prior to the supercooled section, the beam remains ~100 mA but has been accelerated to an energy of 217 MeV. At this energy some proton absorption reactions still take place, but usually with a consequential emission of a greater number of particles. In this region, the (p,2p), (p,pn), and (p,2n) reactions are more favored. This region would tend to favor production of the heavier nuclides of interest.

The highest energy protons (1.7 GeV) would be the ones entering the target blanket assembly through the beam entrance window. The easiest way to use protons to produce isotopes here would be to add an intentional target nuclide to the cooling water for the beam entrance window. Impact on tritium production here would be a minimum because many of the light spallation products would produce neutrons which could be utilized for tritium production.

Additionally, it might be possible to use scattered protons (<100 MeV) in the target/blanket assembly that remain after the proton beam strikes the tungsten target. These protons would be useless for spallation of tungsten but still energetic enough for proton absorption or charge exchange reactions. Target nuclides that preferably absorb protons over neutrons would be best for this technique. A list of some of the radioisotopes that could be produced by proton induced reactions at one of the three energies or by scattered protons is shown in Table 9.

Without more detailed knowledge of the design of the target/blanket assembly, it is assumed that the easiest and most likely location to situate targets for neutron-induced reactions (Table 10) would be to incorporate tubes in the lead blanket and allow the mechanical insertion, positioning, and extraction of manufactured targets ("rabbits") while the beam is on-line. Chain driven rabbit systems are commonly used in nuclear reactors allowing access for target insertion without shutting down the facility, but in the APT the systems would probably be pneumatically driven. The removal of neutrons will reduce the tritium production by only a small amount. Considering a target volume of 360 cm^3 and a lead blanket volume of 3.57×10^7 cm^3 the impact of one target on tritium production would be much less than 0.1 % (based on a purely volumetric ratio). The target size used in this example is a tube of length 45 cm and diameter 3.2 cm, similar to a Cintichem target for Mo-99 production. (If the target contained fissile material, such as the uranium targets at Sandia National Laboratory, they would produce neutrons and could actually boost the tritium yield).

The next most feasible location of targets for neutron irradiation would be in or near the decoupler. Again, a "rabbit" system which moves targets into and out of a tube while the APT is on-line is envisioned. The impact on tritium production by introducing a target material for the production of medical isotopes is expected to be very small. For example, consider the production of four times the entire, current U.S. need for Mo-99 by the neutron irradiation of Mo-98. This amounts to about 12 000 Ci, or about 25 mg per week of Mo-99. Using the flux in the lateral decoupler (1.7×10^{13} n/cm^2 s) as

an example, it would take about 184 g of Mo-98 (13 b cross-section) to provide the needed Mo-99 at 1.3 GeV beam operation levels. These calculations are made using thin-film assumptions and ignoring decay during bombardment. Since about 20-30% of the several kilograms of He-3 in the target/blanket assembly is in the decoupler, we can use about 2 kg as an estimate of the He-3 mass (5330 b cross-section) which would mean that a 184 g Mo-98 target in the decoupler would have a 6.7 parts per million (6.7 x

10^{-6}) effect on the tritium production, based on macroscopic cross-section ratios. Since about 36% of total production takes place in the decoupler, the overall impact will be on the order of 2.5 parts per million. Even in the worst case, geometric (nonhomogeneous distribution) effects should be less than one order of magnitude in their contribution. Since all other isotope productions would be lower than this particular case, medical isotope production in the APT by the introduction of targets for neutron bombardment can be seen as being transparent to the production process.

Table 10. Radioisotopes that could be produced by neutron induced reactions.

Radioisotope	Half-life	Production with the APT
P-32	14 d	P-31 + neutron
Sr-82/Rb-82	26 d/1 min	fission product
Sr-89	51 d	fission
		Y-89 (n,p)
Sr-90	29 y	fission
Y-90	64 d	Y-89 + neutron
Mo-99/Tc-99m	66 h/6 h	U-235 fission
		Mo-98 + neutron
Sn-117m	14 d	Sn-116 + neutron
I-131	8 d	Xe-131 (n,p)
Xe-133	5 d	Cs-133 (n,p)
Sm-153	46 d	Sm-152+ neutron
Ir-192	74 d	Ir-191 + neutron
Au-198	2.7 d	Au-197 + neutron

VIII. CONCLUSIONS

With its high beam current and energy, the APT facility would be highly capable of producing radioisotopes in significant quantities thus assuring the U.S. a reliable supply of diagnostic, therapeutic, and research medical nuclides. The APT capabilities for radioisotope production could comfortably meet present market needs and have the capability to adapt to dynamic market demands of the future including the likely rapid expansion of numerous existing markets as well as unforeseen new isotope markets. A critical motivation force of medical radioisotope production with APT is the aging of the existing, rare U.S. production facilities and the increasingly vulnerable U.S. reliance upon non-domestic suppliers. APT radioisotope production would place the U.S. on the leading edge of critical medical advances for decades.

The APT design lends itself to the production of radioisotopes at several proton energies and in the neutron flux. Mo-99, dominate in the radioisotope market, could be produced with either proton or neutron reactions. Other high demand radioisotopes, including P-32, Co-60, I-131, Xe-133, and Tl-201, could also be produced. Perhaps more critically, APT production capabilities could supply numerous isotopes currently in high demand but with low availability due to present inadequate production capabilities. Such isotopes include Rb-81, Sr-82, In-111, I-123, and Xe-127. Other new and promising isotopes critical for improved diagnosis and therapy of numerous progressive, debilitating diseases are set to emerge from on-going research. These include Ga-67, Sr-89, Y-90, Sm-153, and Re-186. The APT facility could also play an important economic and diagnostic role as a regional PET isotope (e.g. F-18) producer. The APT facility design clearly has the potential flexibility to assure the U.S.'s continued prominence in medical diagnostics, therapy, and research for its own citizens' benefit as well as worldwide applications of such medical advancements.

Very preliminary market projections of APT production revenues for medical radioisotopes range from $50 to $400 million/year. Thus, isotope production might make a significant contribution to the APT's estimated operating costs of $150 million/year. Because the Savannah River Site already has most of the built-in infrastructure to handle, process, and ship radioisotopes and to dispose of radioactive waste, additional capital investments would be limited to around $100 million to enable isotope production and distribution in the APT facility. The addition of a $100 million isotope production facility would be a small investment to secure a future supply of radioisotopes. The United States government has the opportunity to simultaneously meet the defense needs for tritium and gain more support for the construction of the APT facility by meeting the health care needs of our society.

As a result of this review of the isotope market and the conclusion that the APT is a viable facility to supply market needs, further studies are recommended to better define a potential isotope program at the APT facility. Workshops with knowledgeable nuclear medicine researchers and clinicians should be held to better review and identify those isotopes with the most potential after the year

2005. A more detailed physics study of the perturbations on tritium production and its impact on plant operations is needed if the APT facility is to be considered for isotope production. In addition, further study is required to determine the viability of producing short-lived isotopes for regional PET centers.

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Table 5. New and promising generator systems.

Parent	Parent half-life	Daughter	Daughter half-life	Gamma E	Decay (keV)	APT production
Fe-52	8.3 h	Mn-52m	21.1 min	378	IT	spallation of Fe
Br-77	57.0 h	Se-77m	17.4 s	162	IT	spallation of Br
Y-87	80.3 h	Sr-87m	2.8 h	388	IT	spallation of Y-89 or Zr
Cd-107	6.5 h	Ag-107m	44.3 s	93	IT	spallation of Cd
Ag-111	7.5 d	Cd-111m	49 min	150	IT	spallation of Cd
Sn-113	115 d	In-113m	1.7 h	393	IT	spallation of natural Sn
Cd-115	2.2 d	In-115m	4.5 h	340	IT	neutron capture by Cd-114
Xe-123	1.85 h	I-123	13.1 h	159	EC	fission
Hg-194	1.3 yr	Au-194	1.6 d	328	EC	spallation of natural Hg or natural Pb

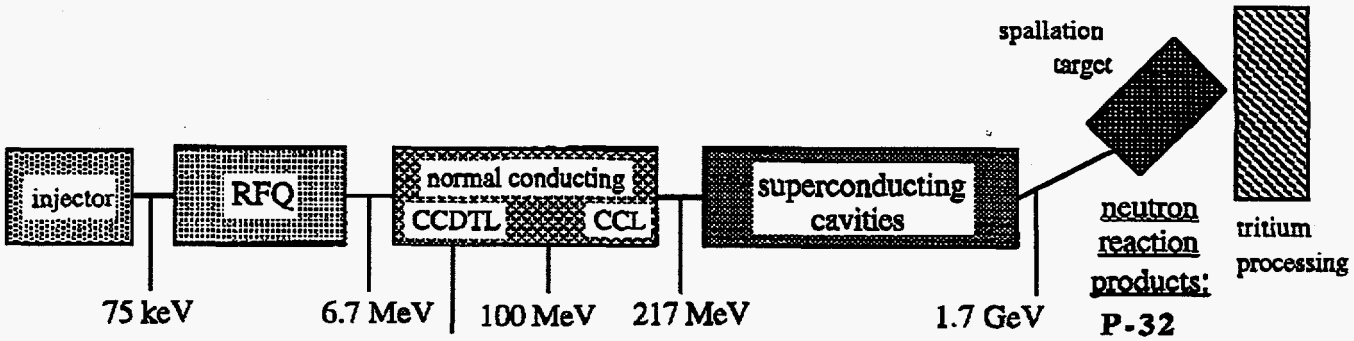
Table 8. Proton energies potentially available from APT for isotope production.

Energy	Typical Reaction Process	Possible Radioisotopes to be Produced
<40 MeV	proton absorption reactions (p,n) charge exchange reactions	F-18, I-123, Tl-201
40-217 MeV	(p,2p), (p,pn), and (p,2n) reactions	Sr-82, Xe-127, Sm-153
1.7 GeV proton	spallation spiking or doping the coolant	In-111, I-131, Ir-192

Table 9. Radioisotopes that could be produced by proton induced reactions.

Radioisotope	Half-life	Production with the APT
Ga-67	3.3 d	Ga-69 (p,p2n) (60%) Zn-67 (p,n) (4%)
Y-87/Sr-87m	80 h/2.8 h	Y-89 (p,p2n) spallation of Zr-90 Sr-87 (p,n) 7% Sr-88 (p,n) 83%
Y-90	64 d	Zr-91 (p,2p)
Mo-99/Tc-99m	66 h/6 h	spallation of Ru Mo-100 (p,pn) Mo-100 (p,2p) Nb-99 [Nb-99 decays with a half-life of 15 seconds to Mo-99] U-238 (p,fission)
Pd-103	17 d	Pd (p,pn) spallation on Ag
In-111	3 d	Cd-111 (p,n) (13%) In-113 (p,p2n) (4%) spallation of Sn
Sn-117m	14 d	spallation of Sn
I-123	13 h	Te-123 (p,n) (1%)
I-125	60 d	I-127 (p,p2n) spallation of Xe or Cs
I-131	8 d	Xe-132 (p,2p) (27%) spallation of Xe or Cs
Xe-133	5 d	spallation of Ba
Sm-153	46 d	Sm-154 (p,pn) (23%)
Ir-192	74 d	Ir-193 (p,pn) (63%)
Tl-201	73 h	Hg-201 (p,n) (13%) Tl-203 (p,p2n) (29%)

Figure 1. Accelerator Production of Tritium Concept with Possible Radioisotopes for Production



≤ 40 MeV proton reaction products:

F-18
V-48
Fe-55
Co-55
Co-57
Cu-61
Cu-64
Zn-62
Ga-67
Ge-68
As-73
As-74
Br-75
Rb-81
Y-87
Y-88
Zr-89
Mo-99
Tc-99m
In-111
I-123
I-124
Ce-139
W-178
Ta-179
Hg-195m
Tl-201
Bi-205
Bi-206

40-217 MeV proton reaction products:

Be-7
Na-22
Mg-28
Fe-52
Cu-67
Br-77
Sr-82
Tc-95m
Tc-96
Ru-97
Xe-122
Xe-127
Ba-128
Sm-153
Pb-203
At-211

1.7 GeV proton reaction products:

Sr-82
Pd-103
In-111
Xe-127
I-131
Ir-192

neutron reaction products:

P-32
Sc-47
Co-60
Sr-89
Y-90
Mo-99
Pd-103
Rh-105
Sn-117m
I-125
I-131
Sm-153
Re-186
Re-188
Ir-192
Au-198
Bi-213

Isotopes listed in bold type are of particular interest and are discussed further in the report.