INTRODUCTION

Since its beginning the field of nuclear medicine has witnessed numerous significant advances in diagnostic medicine, and has assumed a rightful position as a separate speciality. The rapid ascent of the field can be attributed in large measure to the marvelous collaboration of scientists from broad areas of medicine and the physical sciences. Of a fundamental nature, however, nuclear medicine is dependent on the availability of radioisotopes, and the question of risk vs. benefit is often raised. Quite naturally the major goal is to minimize the risk or radiation dose to the patient while at the same time attempting to maximize the amount of useful information derived from the procedure. Many potentially useful procedures, such as myocardial scans with $^{43}$K and diverse diagnostic studies with $^{123}$I, remain too costly for general usage due, in large measure, to the low yields and high cost of the isotopes from existing methods of production. In addition, a number of potentially useful radioisotopes such as $^{82}$Sr, $^{172}$Hf, and $^{194}$Hg, have until now been unavailable for evaluation as no suitable means existed for preparing sufficient quantities for study.

Over ten years ago a proposal was made to develop and construct, at Los Alamos, a linear accelerator with the capability of accelerating 1 mA of protons to energies up to 800 MeV. Major construction funds were made available in October of 1968; and on June 9, 1972, the first 800-MeV protons appeared at the end of the accelerator. Although the accelerator, since that time, has been operating at considerably less than design intensity, all indications are that the accelerator performance objectives can be achieved without major retrofitting. However, this still remains to be demonstrated.

As detailed calculations of the beam parameters following transition through the several experimental target areas of the accelerator were made available, it became obvious that a significant fraction of the primary proton beam would reach the main beam stop. A new program, now designated the Medical Radioisotope Research Program, was proposed to investigate the utilization of the excess proton beam as a means of preparing radioactive isotopes by spallation processes for applications in the health sciences. I shall discuss the principal objectives of this program, review our accomplishments, and explore future directions.

THE CLINTON P. ANDERSON MESON PHYSICS FACILITY (LAMPF)

At the heart of the Clinton P. Anderson Meson Physics Facility (designated by the acronym LAMPF) is a half-mile long linear accelerator designed to accelerate high-intensity beams of protons to energies well beyond the pion-production threshold. One of the underlying principles governing the design of the accelerator and experimental areas was that the facility possess the capability to accommodate ten or more experiments simultaneously without sacrificing beam quality or duty factor. In order to maximize the number of experiments which can be run simultaneously, the decision was made to accelerate, concurrently, both negative and positive ions.

The accelerator comprises three stages. The first is a pair of almost-conventional Cockcroft-Walton injectors that produce $^1$H and $^2$H ions of energy 750 keV. These ions are made to encounter accelerating fields of opposite sign by appropriate longitudinal separation in the linac. The second stage is a modified drift-tube accelerator that provides 100-MeV $^1$H$^-$ and $^2$H$^-$ ions. The novel feature of this section is the positioning of copper rods opposite each drift tube, having the effect of converting the structure from a $2\pi$ mode to a $\pi/2$ mode. The third stage of the accelerator is the side-coupled waveguide accelerator, an innovation in accelerator technology discovered and developed at Los Alamos. In the $\pi/2$ mode, every other cell contains a node of the electromagnetic wave, providing no acceleration, only unwanted accelerator length. It was

* Work performed under the auspices of the U. S. Atomic Energy Commission
found possible to remove the empty cell from the beam line by providing a side-coupling cavity.

The experimental area of the facility is organized to accommodate many experiments concurrently. This is accomplished by the installation of numerous secondary beam lines, by the separation of the H and D beams in the switchyard to supply major sections of the experimental area, and by reconstituting the beam after each target transversal. Although the primary mission of the facility remains the pursuit of basic research, LAMPF technologies and beams are also being directed toward immediate practical applications, such as radiation damage studies with high intensities of fast neutrons, production of special pion and muon beams for medical studies, and utilization of the by-product beam to produce radioisotopes.

**THE ISOTOPE PRODUCTION FACILITY**

Between 30% to 50% of the initial beam intensity is estimated to reach the main beam stop. Various target materials can be inserted into the by-product beam near the beam stop to produce a broad spectrum of radionuclides, primarily neutron-deficient nuclides, through a complex series of nuclear interactions called spallation reactions. The Isotope Production Facility represents an addition of about 37 sq. m. to the LAMPF main beam stop structure. Functionally, this facility is designed to enable an operator to: 1) remotely attach a target-containing chamber to the end of a stringer (7.9 m. long x 20.3 cm high x 5 cm wide); 2) drive the stringer through a slot in the shielding so that the target is in position to intercept the proton beam; 3) carry out the irradiation with adequate water cooling of the target; and, after an appropriate period, 4) retract the stringer, remove the target chamber, and transfer it to a shielded cask for transport to hot cell facilities located elsewhere in the laboratory for chemical processing. Initially four stringers will be provided, but space is available for future expansion to twelve stringers.

A number of unfortunate delays in the completion of the facility have occurred, but we expect soon to finish installation of sufficient equipment to begin testing one of the stringers for a period of three months. By next July as LAMPF begins high-intensity beam acceleration, we plan to have four operational stringers together with the capability of inserting additional stringers as needed.

**THE MEDICAL RADIOISOTOPE RESEARCH PROGRAM**

Basically the principal objectives of the Medical Radioisotope Research Program are to investigate medium-energy, proton-induced spallation processes as a means of providing a new source of radioactive isotopes of demonstrated or potential value in the health sciences, and to support research and application studies using these spallation-produced radioisotopes in biomedicine through a cooperative radioisotope research program. The major areas of program activity are: 1) spallation reaction research; 2) chemistry research; 3) remote processing development; 4) cooperative radioisotope applications research; and 5) target and irradiation facilities development.

Let us now turn our attention to the accomplishments that have been achieved. In preparation for the start-up of the Isotope Production Facility and in accord with the current interest in \(^{82}\)Sr, \(^{123}\)I, and \(^{127}\)Xe, we concentrated our efforts on the measurements of the yields of these nuclides or their precursors from several potential target materials and on the chemical recovery of these isotopes following irradiation.

Strontium-82 has a half-life of 25 days and decays by pure electron capture to the ground state of its 75-second daughter, \(^{82}\)Rb. Rubidium-82 decays by 95% positron emission and 5% electron capture to stable \(^{82}\)Kr, and exhibits prominent gamma rays at 511.0 keV (189% annihilation) and 776.5 keV (13%). It is because such a short-lived alkali metal activity is generated from a long-lived parent that the availability of \(^{82}\)Sr is of interest in biomedical studies. The very short half-life of \(^{82}\)Rb keeps the radiation dose to the patient low, and, with a suitable positron imaging device, this generator system appears to have considerable potential medical applications in cases where repeated, rapid dynamic blood-flow information would be of value, such as in coronary occlusion, cardiac output, arteriography, and tumor vascularity.
The measured cumulative yields of $^{82}$Sr from thin molybdenum, niobium, and zirconium targets irradiated with 590-MeV protons are: Mo, $15 \pm 3$ mb; Nb, $22 \pm 4$ mb; and Zr, $19 \pm 4$ mb.\(^{(3)}\) As the yields from these targets are essentially equivalent, molybdenum was selected for further study on the basis of anticipated simplicity of chemical procedures leading to the isolation of a strontium fraction. We have succeeded in the development of a six-step procedure resulting in a complete, high-yield separation of strontium activities from macro amounts of molybdenum and nine other spallation-produced elements having long-lived isotopes.\(^{(4)}\) It remains to be seen whether or not other spallation-produced elements seen only in targets irradiated with a high-intensity beam will cause interferences.

In order to assume a useful role in nuclear medicine, a generator yielding a rapid and complete strontium-rubidium separation with a resultant rubidium-containing solution that is compatible with biological systems is required. We have developed a system that appears to satisfy these criteria; namely, quantitative rubidium removal in less than 30 sec., strontium-rubidium separation factor in excess of $10^4$, long-term generator stability, and a rubidium-containing solution consisting of 15 ml of 0.2 M $\text{NH}_4\text{Cl}$.\(^{(5)}\)

I am pleased to report to you that on July 31 of this year the first shipment of LAMPF-produced strontium-82 was delivered to the Veterans Administration Hospital in Denver, Colorado, where it will be used in pre-clinical cardiac studies. Although the quantity of the isotope in this shipment was small (<150 \(\mu\text{Ci}\)), it represents a significant step forward in our goal to provide from LAMPF, on a timely basis, isotopes for evaluation in nuclear medicine applications.

The desirable nuclear properties of 13.1-h $^{123}$I for usage in nuclear medicine are well known and do not require repetition here. But why, you may ask, is there interest in xenon-127? This nuclide decays solely by electron capture to stable $^{127}$I with the emission of the following gamma rays: 145 keV (4.2%), 172 keV (22%), 203 keV (65%), and 375 keV (20%). All of the photons, with perhaps the exception of the 375 keV photon, are within the optimum energy range of the Anger camera, and, consequently, the use of $^{127}$Xe should result in imaging studies superior to those obtained by using $^{133}$Xe. Hoffer, et. al.\(^{(6)}\) have reported that by the use of the combined 172-203 keV photon emissions (the combined emissions of these two photons are 87/100 disintegrations) in a single window of a gamma camera with a 1.27-cm thick crystal and medium-energy collimator, the radiation dose per detected photon from $^{127}$Xe is about ten times less than that from $^{133}$Xe. In addition, the longer physical half-life of $^{127}$Xe (36.4 days) is an asset in terms of extended shelf-life. In summary, the advantages of $^{127}$Xe are: higher photon yield per millicurie, better photon energies for imaging with the Anger camera, greater tissue penetration by the photons, lower radiation dose to the patient per useful photon detected, and longer shelf-life.

To prepare $^{123}$I with a minimum of radiocontaminants via medium-energy proton-induced spallation reactions, the xenon fraction containing its precursor, 2.1-h $^{123}$Xe, must be isolated from the target soon after the end of bombardment, allowed to decay for a suitable period, and then removed from the collection vessel. Lanthanum target materials have been selected for the $^{123}$I and $^{127}$Xe studies on the basis of both high spallation yields of the xenon isotopes and favorable thermal properties of these materials.\(^{(3)}\) Using thin targets of lanthanum-copper eutectic, yields of selected isotopes were measured at various proton energies from 100 to 590 MeV, and the results indicate substantial amounts of both $^{123}$I and $^{127}$Xe can be made at LAMPF. Tests using an induction furnace have demonstrated that, under conditions of dynamic vacuum $(<1 \times 10^{-4} \text{torr})$, essentially all of the xenon activities are rapidly removed from the lanthanum-copper eutectic samples heated to 1400°C in tantalum crucibles. Furthermore, the rate and percentage release of $^{127}$Xe from pure lanthanum are essentially the same as the values observed from the eutectic (i.e., >98% release in 15 min, at 1400°C in a vacuum). This process is being scaled for operation in a hot cell, and requires the installation of a 100-kw motor generator and ancillary equipment to power the needed heavy-duty furnace. Testing of this equipment is expected soon after the start-up of the Isotope Production Facility.
Already over a dozen requests for varying amounts of radioisotopes for evaluation studies have been received from extramural investigators. Each of these requests, submitted in a format developed at our laboratory, will be reviewed by an impartial panel of experts on the basis of feasibility and scientific merit. It is expected that only a limited number of the approved requests will be implemented this year, but the program is expected to gain in significance beginning next July.

On the basis of our cross section and yield measurements, we can project, with reasonable assurance, yields of $^{82}$Sr, $^{123}$I, and $^{127}$Xe from LAMPF. During the next few months the beam intensity will remain at the 10 $\mu$A level and beginning next July, following the major shutdown to provide needed shielding for greater intensity operation, the beam intensity will gradually increase from 100 $\mu$A to 1 mA. In anticipation of this schedule, we have prepared two tables showing expected yields assuming beam intensities of 10 $\mu$A and 500 $\mu$A for varying irradiation and processing periods.

In the near future we are planning to investigate the preparation of $^{43}$K, $^{52}$Fe, $^{67}$Cu, $^{113}$Sn, $^{129}$Cs, $^{174}$Hf, and $^{194}$Hg, including yield measurements, chemical separations, and remote processing. The production capabilities of the facility will be expanded as needs dictate, and efforts devoted to collaborative studies should increase. Let me say that the radioisotopes selected for future development are by no means fixed and we welcome suggestions from all colleagues throughout the world.

In conclusion, I would like at this time to pay special tribute to Dr. Louis Rosen and his marvelous staff at LAMPF for providing us all with this magnificent new facility, which they have labored long and hard to bring into being, and for the excellent cooperation they have given in the development of an adjunct radioisotope facility that is of such import to the future of nuclear medicine worldwide.

### TABLE I

Near-Term Isotope Yields from LAMPF

(October - December, 1974)

(Assume: Target = 3.8 cm thick; $E_p = 600$ MeV; $\phi = 10$ $\mu$A)

<table>
<thead>
<tr>
<th>Target</th>
<th>Isotope</th>
<th>Bomb't Time</th>
<th>Yield (mCi)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>$^{123}$I</td>
<td>2 h</td>
<td>120</td>
<td>2-h proc. + 2-h decay</td>
</tr>
<tr>
<td>La</td>
<td>$^{127}$Xe</td>
<td>48 h</td>
<td>315</td>
<td>Allow 11.4-h decay for $^{125}$I recovery</td>
</tr>
<tr>
<td>La</td>
<td>$^{125}$I</td>
<td>48 h</td>
<td>81</td>
<td>4-h proc. + 110-h decay</td>
</tr>
<tr>
<td>Mo</td>
<td>$^{82}$Sr</td>
<td>48 h</td>
<td>332</td>
<td>Parent of 75-sec. $^{82}$Rb</td>
</tr>
</tbody>
</table>

NOTICE

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TABLE II
Long-Range Isotope Yields from LAMPF
(Assume: Target = 3.8 cm. thick; Ep = 600 MeV; \( \phi = 500 \mu A \))

<table>
<thead>
<tr>
<th>Target</th>
<th>Isotope</th>
<th>Bomb't Time</th>
<th>Yield (Ci)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>13-h ( ^{123}I )</td>
<td>2 h</td>
<td>6.0</td>
<td>2-h proc. + 2-h decay</td>
</tr>
<tr>
<td>La</td>
<td>36-d ( ^{127}Xe )</td>
<td>36 d</td>
<td>228</td>
<td>209 Ci after 110-h decay for ( ^{125}I ) recovery</td>
</tr>
<tr>
<td>La</td>
<td>60-d ( ^{125}I )</td>
<td>34 h</td>
<td>3.8</td>
<td>Optimize for ( ^{125}I )</td>
</tr>
<tr>
<td>Mo</td>
<td>25-d ( ^{82}Sr )</td>
<td>25 d</td>
<td>154</td>
<td>Parent of 75-sec. ( ^{82}Rb )</td>
</tr>
</tbody>
</table>

REFERENCES:
5. P. M. Grant, B. R. Erdal, and H. A. O'Brien, Jr. (Submitted for publication)