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DONNER LABORATORY

Y. Yano, P. Chu, W. P. Hemphill, R. M. Larimer, and H. J. Harrington

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Production of Radioisotopes for Use in Nuclear Medicine*

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Introduction

The radioisotopes production program, which has been conducted at the Donner Laboratory since the early 1960's, has been used to investigate the production and chemical separation of radionuclides for use in nuclear medicine. These radionuclides were produced for use in diagnostic imaging (scintigraphic) procedures which were done in conjunction with the Donner Laboratory gamma camera, positron camera, whole-body scanner and tomographic scanner, all of which were developed by H.O. Anger [1-3].

For scintigraphic procedures radioisotopes that provide a high yield of useful photons (100-400 keV) while delivering a low radiation dose to the patient are desirable. The radioisotopes of interest usually have half lives ranging from a few hours to a few days. The ideal half life of a radioisotope would meet the criteria of Wagner [4], namely the effective half life of the radioisotope would be 0.693 times the time at which the study is completed. The preferable mode of decay for the radioisotope is by isomeric transition or electron capture rather than by $\beta^-$ emission. In the case of decay by $\beta^+$ emission the 511 keV annihilation photons are useful for coincident detection systems [2]. In addition it is advantageous to have relatively "carrier-free" preparations for uptake in specific tissues or organs of the body.

The localization of the radioisotope in specific biological sites and the possibility of labelling useful chemical compounds are further considerations in the selection of a particular radioisotope for use in nuclear medicine. Many of these radioisotopes are produced by irradiation with cyclotron accelerated particles. Among a number of comprehensive review papers on the cyclotron
production of medical radioisotopes are those by Clark, Mathews, et al [5], by Glass and Sylvester [6] and by Glass [7]. In the latter paper Glass indicates the recent increase in the number of cyclotrons used for medical purposes from four in 1967 to a projected fourteen in 1974. In addition there are five cyclotrons used for the commercial production of radioisotopes for use in nuclear medicine.

**LBL 88-inch cyclotron**

It can be seen from Table I that nearly all of our radioisotopes were produced by irradiation at the Lawrence Berkeley Laboratory 88-inch sector-focused cyclotron which is primarily a research machine for nuclear physics experiments. The production of radioisotopes for nuclear medicine was usually limited to one or two eight-hour shifts per week.

The 88-inch cyclotron accelerates helium-4 to 130 MeV, protons to 60 MeV, deuterons to 65 MeV and helium-3 and heavy ions to over 100 MeV. Most of the production runs were done with irradiations using an average beam current of 15 to 20 µA for 4 to 6 hours. The cyclotron targets were mounted as foil, pressed or packed powder, electroplated or as gas targets. The solid targets were mounted on water cooled backing plates and covered with aluminum foil of 0.001 to 0.005 inch thickness. In some cases the target material was enclosed in platinum foil.

**Chemistry, Hot Laboratory**

Chemical processing of the irradiated targets was done in two inch thick lead-shielded caves. Remote handling was done by tong operations and by semi-automated separation procedures. Figure 1 shows the "hot" laboratory with the shielded caves and
glove boxes. The "hot-lab" was completed about four years ago and it has been used exclusively for the preparation of radioisotopes for nuclear medicine.

The radionuclidic and chemical purity of the product solution are of primary consideration for these radioisotopes which are intended for human use. Either Ge-Li or NaI(Tl) detectors were used for gamma-ray spectrometry on all production runs. The final product solution was sterilized by autoclaving or by Millipore-membrane filtration. Most of the radionuclides were administered directly for patient or animal studies while a limited number were used as parent isotopes of short-lived daughter radionuclides which were milked from a generator system.

In addition to the cyclotron produced radioisotopes, a few isotopes such as $^{117m}$Sn and $^{191}$Os were produced by neutron irradiation in a nuclear reactor. The $^{191}$Os with a half life of 15 days has been used as a generator for the 4.9 sec half life daughter $^{191m}$Ir for blood perfusion studies [8].

Radioisotopes

Table I lists the radionuclides which have been produced, the nuclear reactions, the irradiating particles and their energies, the radionuclidic yields in $\mu$Ci/$\mu$Ah and the uses of the radioisotopes.

Fluorine-18 and Iron-52

The positron emitting radioisotopes iron-52 ($T_{1/2}$ 8.2h) and fluorine-18 ($T_{1/2}$ 110 min) were produced for bone marrow and bone imaging respectively. Fluorine-18 was produced by irradiating a $\text{H}_2\text{O}$ target with 50 MeV helium-4 ions. Over 100 mCi of $^{18}$F were
produced with a one hour irradiation. The $^{18}$F-$\text{H}_2\text{O}$ solution required no chemical separation and gave a radionuclidically pure product with only insignificant traces of $^7$Be. The preparation of $^{18}$F from a $\text{H}_2\text{O}$ target has been described in the literature [9,10]. Two to three hours after intravenous administration of 250-500 $\mu$Ci of $^{18}$F, positron camera or whole-body scanner scintiphotos were obtained which delineated uptake in normal bone with increased uptake in sites of metastatic lesions or injury [11,12].

Iron-52 has been produced from 1962 until the present time. Four to five hundred patients have been studied for sites of erythropoietic marrow in different disease states [13-15]. The production of $^{52}$Fe has been reported in the literature [16,17]. At the present time we are using chromium targets electroplated on copper backing plates as shown in Figure 2-A. The chromium was plated to a thickness of about 0.025 in. and a diameter of 0.65 in. It is shown mounted on a water-cooled target holder in Figure 2-B. The chromium target was irradiated with 65 MeV helium-4 or 45 MeV helium-3 ions for 3-4 hr with a 15-20 $\mu$A beam current. The Cr target was processed in a lead-shielded cave and separated as shown in Figure 3. The entire chemical separation procedure was done by remote handling with a semi-automated solvent extraction procedure using 7.5 M HCl acid solution and isopropyl ether [13]. The averaged results of ten production runs for $^{52}$Fe using 65 MeV $^4_2\text{He}$ gave a yield of 17.4 $\mu$Ci/$\mu$Ah at the end of irradiation and a specific activity of 22 $\mu$Ci/$\mu$g Fe at the time of administration to the patient which was about 6 hr after the end of the bombardment. When thick Cr targets were irradiated with 65 MeV $^4_2\text{He}$ both the
50Cr (4He,2n) 52Fe and the 52Cr (4He,4n) 52Fe nuclear reactions were contributing to the production of 52Fe.

With the increasing number of small cyclotrons capable of accelerating 3He ions, 52Fe can be made more readily available for medical applications. Nuclear reactions for producing 52Fe by 3He are 50Cr (3He,n) 52Fe, Q-value - 5.7 MeV, and 52Cr (3He,3n) 52Fe, Q-value about - 17 MeV. Irradiation of the plated chromium target with 45 MeV 3He particles produced 28.0 µCi 52Fe/µAh. This was a 60% increase in the yield of 52Fe when compared to 17.4 µCi/µAh with 4He particles.

Cesium-129 and Rubidium-81

Two radioisotopes have been produced for imaging patterns of myocardial blood flow. The first radioisotope of the alkali metals to be investigated was 129Cs which was produced by irradiating a NaI target with 30 MeV 4He particles [18]. The yield of 129Cs ranged from 300-600 µCi/µAh. The only contaminating radioisotope was 22Na with a concentration of less than 3 x 10^-4 parts of the 129Cs at the time of administration. The results of some myocardial studies are shown in Figure 4.

Rubidium-81 was the second radioisotope investigated for myocardial imaging because of the higher extraction efficiency of the myocardium for rubidium as compared to cesium. Rubidium-81 was produced by irradiating NaBr with 29 MeV 4He particles to give the 79Br (4He,2n) 81Rb nuclear reaction. Unfortunately it was difficult to obtain 81Rb relatively free of 82mRb, which emits an abundance of gamma rays with energies greater than 400 keV. By using a relatively thin, about .005 in, NaBr target and irradiating
with 29 MeV $^4$He particles the amount of $^{82m}$Rb could be minimized to about 20% of the $^{81}$Rb activity.

Radioisotope Generators

Rubidium-81 has also been used to generate the 13 sec half life $^{81m}$Kr for imaging lung perfusion and ventilation [19,20]. The radionuclidic purity of the $^{81}$Rb was not of primary concern here since the radioisotopes of rubidium were retained on sulfonic acid cation exchange resin and only the 13 sec $^{81m}$Kr daughter was milked from the generator system shown in Figure 5. For perfusion studies the $^{81m}$Kr was infused intravenously in a water elution which was made isotonic with a saline dilution. The 190 keV photons which are ideal for scintigraphy were used with the gamma camera to image the flow of activity through the right side of the heart and to the lungs. For ventilation studies the $^{81m}$Kr was milked from the dry resin column with 50 cc of air which was inhaled directly by the patient to image the ventilated areas of the lungs. A typical perfusion-ventilation study for a normal subject is shown in Figure 6.

An easily transportable radioisotope generator system for imaging myocardial blood flow is shown in Figure 7. The 25 day parent, $^{82}$Sr, was produced by the $^{37}$Rb (p,4n) $^{38}$Sr nuclear reaction [21,22]. The $^{82}$Sr activity was adsorbed on a weakly acidic cation exchange resin. The 75 sec $^{82}$Rb daughter was milked from the generator with 2-3% NaCl solution and infused intravenously directly into the subject. Rubidium-82 is produced continuously by decay of the $^{82}$Sr parent, thus the $^{82}$Rb can be milked from $^{82}$Sr every 5-10 minutes while the 25 d parent $^{82}$Sr provides a useful generator life of 1-2 months. Rubidium-82 decays 96% by positron emission accompanied by a 0.77
MeV gamma ray (9.0% abundant). The very short half life of $^{82}$Rb offers low radiation exposure and the possibility of quick repeat studies. Because it is a positron emitter, the positron scintillation camera, with its high sensitivity and excellent image-forming characteristics for deep-lying organs can be used. However saturation occurs in this camera at activity levels required for good statistics with the short-lived $^{82}$Rb. The more recently developed Brownell multi-crystal positron-camera provides a fast-response system which functions in a high field of radioactivity [23].

**Dysprosium-157 and thulium-167**

Dysprosium-157 ($T_{1/2}$ 8.1 h) and thulium-167 ($T_{1/2}$ 9.6 d) which are radionuclides of the lanthanide series of the rare earth elements have been investigated for scintigraphic studies of metastatic bone lesions and uptake in soft tissue tumors respectively. Dysprosium-157 was produced by irradiating 300 mg of TbCl$_3$.6H$_2$O with 30 MeV protons [24]. The production yield of $^{157}$Dy was 2.5 mCi/$\mu$Ah or 39.6 mCi/hr. The contaminating radionuclides were $^{159}$Tb ($T_{1/2}$ 5.1 days) $< 10^{-4}$ parts and $^{160}$Tb ($T_{1/2}$ 72.1 days) $< 10^{-5}$ parts of $^{157}$Dy. Although the half life and gamma energy of $^{157}$Dy are well-suited for bone scanning, the slower clearance from blood and soft tissues are limiting factors in the usefulness of $^{157}$Dy for bone imaging. Furthermore the introduction of $^{99m}$Tc labeled bone scanning agents such as polyphosphates, diphosphonates and pyrophosphates has made most other bone agents obsolescent. Dysprosium-157 might be of value for soft-tissue tumor uptake as proposed by Hisada [25] for the radiolanthanides.

Thulium-167, another radiolanthanide, was produced by irra-
diating $^{165}\text{Ho}$ with 30 MeV $^4\text{He}$ to yield 20-30 $\mu\text{Ci}/\mu\text{Ah}$. Thulium-167 was separated from the HoCl$_3$ target material by cation exchange column chromatography by the method of Ketelle and Boyd [26] using Bio-Rad AG 50 x 10, -400 mesh resin and 4.75% ammonium citrate as the solvent. Chandra [27] proposed the use of $^{167}\text{Tm}$ for bone scanning and Hisada [25] considered $^{167}\text{Tm}$ to be useful for tumor localization on the basis of work with $^{170}\text{Tm}$ in tumor bearing rodents. $^{167}\text{Tm}$ might be of use for either tumor or bone scanning in those areas where the availability of radiopharmaceuticals is limited. The 9.6 day half life of $^{167}\text{Tm}$ would provide a useful shelf life of 10-20 days. The radiation dose to the patient would be acceptable because of the absence of $\beta^-$ emission. However internal conversion of the 208 keV photons increases the radiation dose, which would be about 0.455 rad/100 $\mu\text{Ci}$ to bone.

Xenon-123 and Neon-18

Xenon-123 and Ne-18, the radioactive inert gases of the eighth group of elements were produced to study the recoil labeling of organic compounds when these gases decay to $^{123}\text{I}$ ($T_{1/2}$ 13 hr) and $^{18}\text{F}$ ($T_{1/2}$ 110 min) respectively. Fifty to fifty-five MeV protons were used to irradiate $^{127}\text{I}$ as NaI to produce $^{123}\text{Xe}$ ($T_{1/2}$ 2.1 h). The $^{123}\text{Xe}$ was continuously removed from the target material during the irradiation and the $^{123}\text{Xe}$ was collected in evacuated liquid nitrogen traps which contained the organic compounds to be labeled (i.e. o-iodohippurate, serum albumin, progesterone or bleomycin). The $^{123}\text{Xe}$ was then allowed to decay for about four hours to yield $^{123}\text{I}$, some of which was bound to the organic compound. The yield of $^{123}\text{I}$ was about 1.5 mCi/$\mu\text{Ah}$, however it was
difficult to recover more than 20% of the $^{123}$Xe from the NaI target either by sweeping with helium gas or into evacuated high vacuum traps. The labeling yields ran from a few percent to 20 percent iodination of the compounds. The work of Fusco et al [28] and of Blue and Sodd [29] indicate that the trapping $^{123}$Xe as a separation procedure will produce high radionuclidic purity and "carrier-free" $^{123}$I.

In the case of producing $^{18}$Ne and allowing labeling to occur during decay to $^{18}$F, the 1.5 sec half life of $^{18}$Ne requires the compound, which is to be labeled, to be in contact with the gases in the target vessel. The glass-lined walls of an aluminum gas target vessel were coated with progesterone and then filled with CO$_2$ gas to a pressure of 2 atm. It was then irradiated with 50 MeV $^4$He. The progesterone was washed from the target vessel and precipitated in water to separate the unbound $^{18}$F. The distribution of $^{18}$F labeled progesterone in rats showed a distribution unlike anionic $^{18}$F. These results indicate that recoil labeling did occur; however the labeling efficiency was <10% of the total $^{18}$F activity which might be indicative of either poor recoil labeling or a higher cross-section for the $^{16}$O ($^4$He,pn) $^{18}$F reaction compared to the $^{16}$O ($^4$He,2n) $^{18}$Ne cross section.

**Conclusions**

A number of radioisotopes have been prepared by cyclotron irradiation for use in nuclear medicine. Some of the radioisotopes such as $^{18}$F and $^{52}$Fe have proven to be very useful in the diagnosis of disease states in human subjects. Other radioisotopes such as the radiolanthanides have been investigated but their usefulness
has yet to be demonstrated. Some of the parent radioisotopes such as $^{82}\text{Sr}$ and $^{81}\text{Rb}$ have made it possible to produce generator systems for very short-lived radionuclides whose applications and benefits in nuclear medicine remain to be explored.

It is very likely that new uses, yet unexplored, will be found for some of the radioisotopes described here. Although the total number of possibly useful radionuclides in nuclear medicine is rather limited, there undoubtedly remain a few radioisotopes still to be investigated for use in nuclear medicine. The construction of many small cyclotrons for medical use will expand the investigation of biologically important chemical compounds labeled with 20 min $^{11}\text{C}$, 10 min $^{13}\text{N}$, or 2.5 min $^{15}\text{O}$.

Large quantities of medically useful radionuclides will also be made available in the near future from high energy proton irradiations at Brookhaven Linac Isotope Producer (BLIP) [30], and at the Los Alamos Meson Production Facility (LAMPF) [31].
References


<table>
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<tr>
<th>Isotope</th>
<th>T1/2</th>
<th>Primary Photon keV</th>
<th>Nuclear Reaction</th>
<th>Energy MeV</th>
<th>Yield μCi/μAh</th>
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Figures

Figure 1. "Hot" laboratory for processing radioisotopes for nuclear medicine. In the foreground is the $^{52}$Fe separation cave shown with control panel for semi-automated extraction.

Figure 2-A. Chromium electroplated on copper backing plate (second from right) and water-cooled target holder, disassembled.

Figure 2-B. Assembled chromium target and water-cooled probe.

Figure 3. Semi-automated $^{52}$Fe solvent extraction in diisopropyl ether from Cr in 8-N HCl.

Figure 4. Myocardial uptake of $^{129}$Cs as shown by scintigraphy in patients with (A) normal, (B) cardiomegaly (C) hypertension and (D) coronary disease.

Figure 5. $^{81m}$Kr generator system for perfusion and ventilation studies of the lungs.

Figure 6. Normal perfusion and ventilation study of the lungs with 13 sec $^{81m}$Kr.

Figure 7. Rubidium-82 generator for delivering millicurie amounts of activity in 2-3% saline solution.
KRYPTON-81m

0-4 sec

4-8

8-12

12-16

16-30 sec

PERFUSION
(Anterior)

VENTILATION
(Anterior)

A.H. 3-11-69

TRANSMISSION

0-4 sec

4-8

8-12

12-16

16-26 sec

Fig. 6
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