Recent Developments and New Approaches at the Cyclotron for the Preparation of Short-Lived Nuclides for Radiopharmaceuticals

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ABSTRACT

The halogens have more potential as cyclotron produced nuclides of choice for radiopharmaceutical applications than any other family in the periodic table. One of the limiting steps in applying short-lived nuclides to radiopharmaceuticals is the time interval required to obtain the nuclide in the appropriate form(s) for administration. Factors that facilitate the overall operations are a careful choice of cyclotron production conditions, the use of dynamic "on-line" separations and purifications, and kit procedures for the final steps in the radiopharmaceutical preparation. In this paper the desirability and choice of the short-lived halogens, nuclide decay characteristics, cyclotron production methods and yields, preparation of halogenating reagents and applications of the short-lived nuclides to radiopharmaceuticals is reviewed.

Systems design for automation at the cyclotron for the production of anhydrous, carrier-free nuclides, $^{18}$F, $^{34m}$Cl, $^{77}$Kr($^{77}$Br), $^{79}$Kr, $^{123(5)}$Xe($^{123(5)}$I) and the respective labeling reagents, particularly with the short-lived generator systems: $^{18}$Ne 1.5 sec, $^{18}$F, $^{77}$Kr 1.2 hr, $^{77}$Br, and $^{123}$Xe 2.1 hr, $^{123}$I and $^{125}$Xe 16.8 hr, $^{125}$I is stressed. The principles of carrier-free excitation labeling with the rare gas halogen generators are summarized. The scanning electron microscope was used for evaluation of the target performance for $^{125}$Xe.

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The rapid "on-line" methods being developed for the halogens and the rare gases are applicable to other nuclides, and will facilitate the practical application of short-lived nuclides in new radiopharmaceuticals. The limitations of a compact medical cyclotron for the production of many nuclides appropriate for radiopharmaceuticals are noted.

INTRODUCTION

The halogens (particularly fluorine-18, chlorine-34m, bromine-77, iodine-123 and -125 and astatine-211) have more potential as cyclotron produced nuclides of choice for radiopharmaceuticals than any other family in the Periodic Table. The groundwork for the clinical utilization of radioiodine was, interestingly enough, not only a cornerstone in the field of nuclear medicine, but was also the classical experiment in defining a new area of chemistry (Hot Atom Chemistry). In 1934 Szilard and Chalmers (1,2) demonstrated the principle of bond rupture following the nuclear transformation making $^{128}$I in neutron irradiated ethyl iodide, and described a separation method for the radioiodine from the ethyl iodide. Subsequently hot atom experiments were performed (3) with one purpose being the development of radioactive indicators for investigation of biological processes (e.g. anesthesia). The medical application of these observations was applied in 1938 when Hamilton (4) and Hertz et al. (5) adopted the Szilard-Chalmers preparation and separation method in the first physiological studies of the halogens. Both groups recognized the importance of the cyclotron for production of the radiohalogens for biomedical applications. Hamilton (4) compared nuclides of sodium, potassium, chlorine, bromine and iodine in humans. Hertz et al. (6) introduced the use of multiply-labeled iodine
$^{126}$I, $^{130}$I and $^{131}$I in thyroid physiology studies. Bale (7) reviewed the possibilities of the cyclotron for medical application of the radiohalogens and the radionuclides of selenium, arsenic and iron. Indeed we find the state-of-the-art 34 years later to be one that has an increasing reliance on the cyclotron for production of "ideal" nuclides for medical applications. The first example of the interdisciplinary interactions of a hot atom chemist and a physician (Szilard and Chalmers) has been amplified to new dimensions in nuclear medicine today (8).
HALOGEN NUCLIDES

The halogens having the physical characteristics best suited to either diagnostic or therapeutic radiopharmaceuticals are listed in Table I. Pertinent references to accelerator production methods for biomedical applications in addition to the physical properties of each nuclide and the decay product are given. The advantages of using short-lived nuclides has been previously discussed in this symposium. They include: a reduced radiation exposure to the patient; the possibility of serial studies for dynamic imaging; availability from a cyclotron. The use of two or more halogen nuclides having different decay characteristics provides the opportunity for simultaneous detection of differences (either functional, time dependent or isotopic) in metabolic processes and disease states. The selection of a given halogen and the appropriate nuclide from Table I will depend also on the time required to prepare and deliver a particular radiopharmaceutical and on the clinical application.

With the instrumentation presently used, a nuclide decaying with a high abundance of photons in the 110-300 keV range, with an optimum being in the 130-180 keV region, are preferred. With improvements in instrumentation, the imaging of positron annihilation radiation and photons in the 450-550 keV range will be more practical. The nuclides decaying predominately by beta or alpha emission will be suited to therapeutic rather than diagnostic applications.

FLUORINE. Fluorine-18 decays by positron emission with a 110 min half-life. The nuclide is still preferred for bone scanning by some clinicians but its utility as a label in organic compounds is the subject
of increasing efforts. One of the limitations in the application of the nuclide has been its production in an aqueous media or as an irradiated salt. Synthetic chemists have been generally limited to using the fluoride chemical form, and in all published examples carrier fluoride was added thereby lowering the specific activity and increasing the possibility of drug effects.

There is an apparent need for anhydrous and carrier-free fluorinating reagents for the synthesis of $^{18}$F-radiopharmaceuticals. To alleviate the preparation of $^{18}$F in aqueous solution, and in anhydrous chemical forms, Nozaki (9) used a gaseous oxygen stream bombarded with $^4$He or $^3$He as a source of anhydrous $H^{18}F$ diluted with HF carrier. We used the deuteron reaction on neon $^{20}$Ne(d,a)$^{18}$F and obtained $F_2^{18}$F by scavenging the $^{18}$F with 5-7.5% fluorine scavenger present in a nickel irradiation vessel during the irradiation (10). The rapid synthesis (40 minutes from EOB to delivery) of pyrimidines such as 5-$^{18}$F-fluorouracil and 5-$^{18}$F-fluorocytosine was demonstrated with this reagent (11). The preparation of other carrier-free synthetic intermediates such as $H^{18}F$, $NO^{18}F$ and $Cl^{18}F$ has been effected by the addition of a small concentration of hydrogen or chlorine to the neon in the irradiation vessel (12). Other $^{18}$F synthetic intermediates such as $^{18}F_2^{18}F$, $Pb(OOCCH_3)_{4}^{18}F_2$, $^{18}F_2$, $Pb(OOCCH_3)_{4}^{18}F$ and other hard, moderate or soft fluorinating reagents can be prepared from $F_2^{18}F$, $H^{18}F$ or $NO^{18}F$ (12). For a review on handling fluorine [$^{18}$F] for synthetic purposes see references 8, 12 and 13.

**Production Parameters.** The only absolute cross section measurements for the $^{20}$Ne(d,a)$^{18}$F nuclear reaction were reported at $E_D = 14.7$ MeV as $23.4 \pm 4.7$ mb (14a) and $E_D = 2.73$ MeV as $77.8 \pm 6$ mb (14b). Nozaki (14c) has defined preliminary measurements of the shape of the
excitation function with a peak at \( \sim 6 \) MeV of \( \sim 165 \) mb. Tilbury (15) has recently reported quantitative, although preliminary, data. Tilbury measured nine energies and observed the cross section to be \( 333 \pm 40 \) mb at 6.49 MeV and still rising. A refinement of the measurements and an extension of the cross section measurements to higher energies is planned. Regardless of absolute cross sections and fine structure, the thick target yield for the \( ^{20}\text{Ne}(d,\alpha)^{18}\text{F} \) reaction gives a higher production yield than the other cyclotron production methods to which it has been compared. See Table II.

**Targetry.** The choice of cyclotron targetry for production of anhydrous carrier-free fluorine-18 has been a subject of continued investigations. In the simplest applications, i.e. for the recovery of \( ^{18}\text{F}^- \) in aqueous solution, the Argonne group (16) used a pyrex liner, and the approach has been modified by others (17). The problem of recovery of anhydrous carrier-free \( ^{18}\text{F} \) is more complex, due to the high reactivity of atomic fluorine. The problem to be overcome is obtaining a suitable material with which the \( ^{18}\text{F} \) neither reacts nor which strongly absorbs the element. The desorption of \( ^{18}\text{F} \) from several metals (aluminum, copper, zinc, stainless steel and titanium) and various other materials even under vacuum pumping has been examined (18,19). Nozaki (9), Nagai (20) and Lebowitz (21) tested either rectangular or cylindrical metal targets of silver, gold-plated bronze, stainless steel and copper, all with limited success. Clark et al. (22) have used a silver liner coated with silver fluoride, from which aqueous \( \text{AgF}^-^{18}\text{F} \) and \( \text{AgF}_2^{18}\text{F} \) were subsequently washed.
There is a concerted effort underway at Brookhaven to develop a quantitative recovery system for carrier-free anhydrous $^{18}\text{F}$ and $^{18}\text{F}^{-}$ intermediates from the neon target. We (10,12) selected the highest purity of nickel or Inconel 600 as a choice of the target material. The Inconel is an antimagnetic alloy of nickel and suitable for targets placed in the magnetic field of the cyclotron. The basis of the selection was the report of Boggs et al. (23). There is however some confusion on the point of the absence of exchange between $\text{H}^{^{18}}\text{F}$ and $\text{NiF}_2$ on the walls of a nickel reactor. Nickel, Inconel and monel have general applicability in fluorine systems at elevated temperatures (24). The resistance of a metal to attack by fluorine depends on the formation of a coherent, anhydrous metal fluoride film (25). The target passivation procedure is discussed elsewhere (12). The nickel target design has been subsequently adopted in the laboratories of Drs. Walter Wolf and Roy Tilbury.

**Dynamic Target.** The design for the dynamic recovery of $^{18}\text{F}$ and $^{18}\text{Ne}$ ($T_\text{1/2} = 1.5$ sec) from the neon target during deuteron or helium-3 bombardment is depicted in Fig. 1. The details of automated, remote operation will be published elsewhere (26). The appropriate gases are introduced into the target by means of teflon and/or Inconel tubing. The target gas for refined measurements is Air Products Research Grade Neon of >99.998% purity. For practical applications spark chamber grade Neon (90%)-Helium(10%) is used after it is dried by passage through a gas line purifier. Any gas introduced into the target is dried as much as possible, beforehand. The gas manifold vacuum line and accessories have been described (12). Teflon or Kcl-F surfaces
are utilized where $^{18}$F flow is indicated. In particular the flowmeter controlling the rate of removal of gas from the target during or subsequent to the irradiation was specially fabricated. The device was supplied by Matheson and provides digital readout and remote control of the flowrate from 0-100 SCCM. The pressure-vacuum pumping system for recirculating the neon through the Inconnel target is of the oilless diaphragm type. A filter system (reaction vessel) prior to the inlet of the pump serves to collect the $^{18}$F from the dynamic target. A recirculating gas approach for collection of $^{18}$F on diazonium salts (27) has also been utilized. The target can also be irradiated in the static mode and subsequently removed through an alternate line as shown in Fig 1.

The "on-line" dynamic recovery of fluorine-18 from the target depends on several variables such as the choice of the scavenger and its concentration, the temperature (eg. beam intensity) and the manner in which one attempts to remove the $^{18}$F from the target. The details will be presented elsewhere (26). We have obtained >0.5 Ci of $^{18}$F by use of the neon-target and deuterons degraded from 16.5±0 MeV. The Hammersmith group (28) reported a 56.8% radiochemical recovery yield of 0.32 Ci after 20 μA/H bombardments at 30 μA at a pressure of 7 Kgf/cm$^2$.

$^{18}$Ne → $^{18}$F. We have used the dynamic target system in conjunction with the $^{18}$Ne $^{1.5}$ sec $^{18}$F generator. In this operation the flowrate and hence the residence time of the $^{18}$Ne in the target and the reaction vessel must be optimized because of the limitations of the 1.5 sec half life of $^{18}$Ne. This project is under development. (See the section on Excitation Labeling.)
CHLORINE. The nuclides $^{34m}_{35}$Cl ($T_{1/2} = 32$ min, $\gamma = 140$ keV, 45%) and $^{39}$Cl ($T_{1/2} = 57$ min) are suitable for radiopharmaceuticals. The differences in principle photon energies and half-life make the nuclides attractive for double label experiments. (See Table I.) $^{34m}$Cl can be produced in high yields though not carrier free with either the $^{35}$Cl(p,pn)$^{34m}$Cl or $^{35}$Cl($^3$He,$^4$He)$^{34m}$Cl nuclear reactions. The $^{31}$P($^4$He,n)$^{34m}$Cl reaction using naturally occurring phosphorus can be a source of carrier-free $^{34m}$Cl.

We tested the $^{35}$Cl(p,pn)$^{34m}$Cl reaction on Cl$_2$ gas (2.67 atm) with 32 MeV protons. The production yield obtained was 9.6 mCi/$\mu$Ah for short irradiations. The Cl$_2$(g) was contained in a quartz irradiation vessel (2.54 x 35 cm), and we did not encounter difficulties with vacuum transfer of the $^{34m}$Cl-Cl$_2$. The activity can be used directly for synthesis, or other chlorinating reagents can be obtained from the Cl$_2$-$^{34m}$Cl, eg. chlorine-dipyridine nitrate complex, AlCl$_3$, CuCl$_2$ and TiCl$_4$.

Though we haven’t yet demonstrated the utility of $^{34m}$Cl there are several interesting areas that can be explored, particularly for labeled steroids and carbohydrates. For example, Mills (29) has demonstrated that steroid derivatives of cholesteryl acetate can be prepared in 59% yield by the one step (30 min) reaction of the $\Delta^5$-compound with chlorine-(or bromine)-nitrate-pyrimidine complexes. Non-radioactive aluminum chloride has been used in the preparation of $\beta$-chloroglycosides (30). Mesyl chloride (the synthesis time from Cl$_2$ may be limiting) has been shown to be a good reagent for the replacement of the primary alcoholic group in methyl $\alpha$-D-glucopyranoside to give 6-chloro-6-deoxyhexopyranoside in 97% yield (31).
BROMINE AND KRYPTON. There are four nuclides of bromine listed in Table I that have characteristics suitable for radiopharmaceuticals and which are expected to be produced in high purity and reasonable yield. Of these only $^{77}$Br has been in routine clinical use, namely for electrolyte studies, and more recently as a protein label. The Hammersmith group has measured the excitation function (32) developed targetry (33) and a wet separation method (34) and have used the $^{75}$As($^4$He,$2n$)$^{77}$Br reaction with $E_3 = 28-14$ MeV to obtain yields of 160 μCi/μAh. The radionuclidic purity is >99.9%. The $^{75}$As($^3$He,$n$)$^{77}$Br reaction could also be used.

$^{77}$Kr$\rightarrow$$^{77}$Br. We have been developing bromine-77 by the production of the $^{77}$Kr which decays with a 1.2 hr half-life to $^{77m+8}$Br. One of our purposes being the development of the $^{77}$Kr $\rightarrow$ $^{77}$Br + $^{77m}$Br $\rightarrow$ $^{77}$Br generator for excitation labeling with carrier-free bromine. (See section on excitation labeling.) Several methods are being tested. The most promising method is the use of a sodium bromide salt target and the $^{79}$Br($p,3n$)$^{77}$Kr reaction with $E_3 = 32-25$ MeV. The incident energy is kept below 32.5 MeV to avoid the $^{79}$Br($p,4n$)$^{76}$Kr reaction which would lead to a radionuclidic impurity of $^{76}$Br($T_{1/2} = 16.1$ hr).

The target (similar to Fig 2) is placed in the internal deflected beam of the cyclotron. Dried helium gas purges through the crystalline salt target at 50 ml min$^{-1}$ throughout the proton irradiation. The helium carrier takes out the volatile $^{77}$Kr escaping from the crystalline target. The gas stream is passed through a silver furnace operated at 350°C to remove volatile radiobromine (e.g. $^{81}$Br($p,\alpha n$)$^{80m}$Br) that might be formed and which might escape from the target. The silver furnace will also remove any volatile
Br from the target. A similar concept was used (35) for the rigorous repurification of xenon-123 and xenon-125 in the production of high purity iodine-123 and iodine-125. Using an incident beam of 32.5 MeV protons and a target of crystalline (initially) analytical reagent sodium bromide (depth = 155 mil) we obtained $^{77}$Kr production yields of 1.88 mCi/μA h with a 4±1 μA beam. The target performance as a function of beam intensity, total dose, etc. are topics of a continuing investigation.

Alternate methods of producing $^{77}$Kr being tested are given in Table II. The disadvantages of the selenium target include the toxicity of selenium, its low melting point (217°C), and the cost of enriched selenium isotopes.

**Krypton-79.** The $^{79}$Br(p,n)$^{79}$Kr and the $^{81}$Br(p,3n)$^{79}$Br nuclear reactions also occur in the energy region chosen for $^{77}$Kr production. Kishore and Collé (36) have determined the excitation function for $^{79}$Kr and found the cross-section to be 725±52 mb at 10.98 MeV and 204 mb at 24.82 MeV. However, the $^{79}$Kr ($T_{1/2} = 35.0$ hr) can be readily separated from the $^{77}$Br subsequent to $^{77}$Br decay ($T_{1/2} = 1.2$ hr). Wagner (37) has listed $^{79}$Kr as (one of 13 nuclides) being suited for biomedical studies such as perfusion measurements. The $^{79}$Kr nuclide has a reasonable abundance of detectable photons and the (EC/β⁺) decay does not populate the 4.5 sec isomeric state of $^{79}$Br, thereby eliminating the need for corrections if $^{79}$Kr were used in dynamic imaging. We are now in a position to evaluate $^{79}$Kr. However for the direct cyclotron production of $^{79}$Kr the proton energy should be lowered to below the threshold for the $^{79}$Br(p,3n)$^{77}$Kr reaction. The continuous gas-flow target and $^{79}$Br(p,n)$^{79}$Kr production method can be adopted to a compact medical cyclotron.
IODINE AND XENON. Iodine-123 ($T_1/2 = 13.3$ hr, $\gamma = 158$ keV, 83%) has been prepared at Brookhaven in high purity via the $^{122}$Te($^4$He,$3n$)$^{123}$Xe $\text{EC/}B^+ \rightarrow ^{123}$I generator (38), in a radionuclidic purity of $>99.8\%$ where the only radiohalogen is $^{125}$I. Sodd (39) (see 38,56 also) has reviewed $^{123}$I production and its history. The high purity nuclide developed into routine use at BNL has been under intensive investigation and a number of publications dealing with new $^{123}$I-iodination reagents (12,35,40,41,42), synthetic methods (8,12,35,42,43), and preclinical and clinical trials of a number of $^{123}$I-radiopharmaceuticals synthesized with high purity iodine-123 via $^{123}$Xe have appeared.

Sodium $^{123}$I-iodide prepared by a kit (41) has been evaluated by both oral and intravenous administration and has been compared (44) to $^{99m}$TcO$_4$ and $^{131}$I either dynamically for the first 30 minutes or at 2, 6 and/or 24 hours. A Brookhaven study (45) has shown that there are not statistically significant differences between the 24-hr uptakes of $^{123}$I (IV) and $^{131}$I (oral). However, interesting differences in the 30-min uptakes of $^{123}$I (IV) and $^{99m}$TcO$_4$ (IV) have been observed (46).

New $^{123}$I-radiopharmaceuticals which have been prepared include 4,3-DMQ-$^{123}$I an iodinated quinoline compound that looks promising [in the Syrian hamster model] for the detection of eye melanoma (47). Scans
were obtained with the gamma camera at 3 hrs with hamster melanomas (48). Phantom studies defined the minimal detectable tumor as a cylinder of 2 mm diameter and 5 mm depth. Clinical trials are now proceeding. Indocyanine green-$^{123}$I, a water soluble tricarbocyanine dye, has been iodinated by the excitation labeling method for testing as an agent for dynamic studies of liver function, cardiac output and liver blood pool flow measurements (49). An interesting clinical study with hippuran labeled with impure $^{123}$I was reported by Short et al. (50). Goris (51) has recently suggested that $^{123}$I-labeled bromosulphthalein may be useful as a liver and biliary scanning agent, although radioiodine impurities interfered with imaging.

Once substantial quantities of high purity $^{123}$I are generally available and economical, it seems reasonable to conclude that $^{131}$I will be replaced for most non-therapeutic applications of radioiodine requiring studies of 24 hours or less duration.

Xenon-$^{123}$. The alternate methods of producing $^{123}$Xe to obtain high purity $^{123}$I that are starting to come into use in addition to the $^{122}$Te($^4$He,3n)$^{123}$Xe reaction are listed in Table III. The $^{123}$Xe-$^{123}$I generator opens doors to carrier-free labeling methods not previously available. The $^{122}$Te($^4$He,3n)$^{123}$Xe reaction was shown to be feasible (38) for producing $^{123}$Xe
biomedical applications (37). Subsequently Loberg, Phelps and Welch (55) have pointed out that if the lower yield production method $^{122}\text{Te}(^3\text{He},2n)^{123}\text{Xe}$ is employed, the incident $^3\text{He}$ energy must be controlled to eliminate excessive levels of $^{122}\text{Xe}$ ($T_{1/2} = 20\text{ hr}$; daughter $^{122}\text{I}$ $T_{1/2} = 3.5\text{ min}$).

$^{125}\text{Xe} ightarrow ^{125}\text{I}$. Historically Myers (56, see 38,39 also) was the first to note the ideal characteristics of $^{123}\text{I}$, and in an important review (57) he pointed out that $^{125}\text{I}$ had tremendous growth potential in nuclear medicine. Generally $^{125}\text{I}$ has been produced from reactor irradiation of natural xenon. The limitation of the reactor method is that the $^{125}\text{Xe}$ is not carrier free, and the targetry and recovery procedures are cumbersome.

We developed a convenient cyclotron production method for obtaining carrier-free $^{125}\text{Xe}$ via the $^{127}\text{I}(p,3n)^{125}\text{Xe}$ reaction. Our first purpose has been to provide the $^{125}\text{Xe} ightarrow ^{125}\text{I}$ generator for excitation labeling with $^{125}\text{I}$. The generator may be particularly useful for labeling sensitive biomolecules (54) such as used in radioimmunassay.

**Targertry.** A gas flow target for placement in the internal deflected beam of the BNL 60" cyclotron has been developed. Our optimum $^{125}\text{Xe}$ yield is via the $^{127}\text{I}(p,3n)^{125}\text{Xe}$ reaction with $E_p = 33-25$. The $^{127}\text{I}(p,n)^{127}\text{Xe}$ cross section (39) is $30.2\pm2.7\text{ mb at } 24.82\text{ MeV and }^{127}\text{Xe}$ ($T_{1/2} = 36\text{ da}$) is present as a low radionuclidic impurity in the $^{125}\text{Xe}$.

Figure 2 depicts the KI salt target after a total irradiation dose of $48.5\mu\text{Ah}$ with $33\text{ MeV}$ protons. (The Havar window has been replaced with a clear plastic cover.) The $^{125}\text{Xe}$ is continuously purged from the target.
during the bombardment, in a manner similar to our gas flow target for $^{77}$Kr or $^{79}$Kr production. Any carrier or radiiodine (e.g. $^{127}$I($p$,pn)$^{126}$I) from the target is removed by scrubbing the method previously described (38).

In order to understand and predict how a gas flow target will perform as a function of production variables such as beam density, irradiation dose and dose rate, etc. we have begun to rely on the use of the SEM, scanning electron microscope (38). The SEM is one of the newest and more convenient methods of examining gross crystal structure, particularly gross surface configuration of irradiated and ion-implanted solids. Figs 3-5 depict the type of information obtained. All magnifications are at 1000x. Fig 3 depicts the KI salt crystals placed in the target (salt depth = 155 mil). The visual inspection of the target (Fig 2) is after a proton irradiation to 48.5 μAh. The alkali halides develop color centers (defects) when irradiated. In this example, one is fortunate to be able to compare the visual differences, with the microscopic examination of gross structure, and with the production yields. The SEM samples were taken from the center (Fig 4) and the greenish border (Fig 5) of the target salt shown in Fig 2. Visual inspection of Fig 2 indicates the location and density center of the beam. The SEM indicates the breakdown (including melting) of the KI crystals, i.e. extensive damage in the center of the beam density (Fig 5) and relatively moderate damage (Fig 4 vs Fig 3) at lower total irradiation dose.

The observations can be related to the target performance in the continuous gas flow mode. The average production rate of $^{125}$I after a 7-day decay period for the $^{125}$Xe were measured. For the irradiation with a 5±1 μA beam from 0 to 12.2 μAh total dose the yield was 27.6 μCi/μAh.
The average production rate between 20.5 and 48.5 μAh total dose at the same dose rate on target was 18.7 μCi/μAh. These data combined with the SEM's suggest that the operation of the target in this mode, would indicate replacement of the target material between production runs. Furthermore to maintain an "optimum" production rate, the beam should be scanned uniformly or continuously across the salt during irradiation.

Apparently as the condition in Fig 4 is reached, the 125Xe does not escape into the helium stream as efficiently.

Astatine. Astatine-211 has been suggested as a nuclide well suited for therapeutic applications because the 7.2 hr half-life is suitable for labeling and the 5.86 MeV alpha is efficient for localized tissue destruction. The pertinent references (58-62) to the cyclotron production, chemical separation, labeling and product identification by high pressure liquid chromatography of astatine compounds in nuclear medicine are all very recent contributions.

ADVANTAGES OF GAS FLOW TARGETS

Gas flow targets of the types described are particularly advantageous in radiopharmaceutical operations with short-lived nuclides. The continuous supply of the nuclides to the chemist during the irradiation eliminates the losses due to radioactive decay in the target. On-line repurification is effected. Often steps requiring target processing and recovery can be eliminated. A clearcut advantage of dynamic targets is that anhydrous and carrier-free nuclides (e.g. 18Ne with a 1.5 sec half-life) that would otherwise not be obtainable reagents become accessible. A disadvantage is that continuous flow targets are
apparently susceptible to irradiation conditions, target annealing, 
operating temperature and other variables. The scanning electron micro-
scope is an invaluable aid to the radiochemist concerned with the develop-
ment and use of dynamic and continuous flow targets.

EXCITATION LABELING

Principles. Excitation labeling is so called because the Auger 
electron cascade associated with certain nuclear disintegration processes
(i.e. electron capture, isomeric transition, positron emission, and other 
processes which induce internal conversion) results quite often in a high,
wide-spectrum charge build-up on the nuclide. The subsequent neutralization
occurs within \( \sim 10^{-14} \) sec, a time scale much shorter than the time required
for a hot atom reaction, and results in neutral atoms or ions in the ground
or low-lying excited states that subsequently react. Our example is limited
to the reactivity of \( ^{123}\text{I} \) and \( ^{125}\text{I} \). Loberg (63) estimated the charge state
spectrum of \( ^{123}\text{I} \) when it is initially formed from \( ^{123}\text{Xe} \) decay and concluded
that initially <15% of the \( ^{123}\text{I} \) atoms were born as \( ^{123}\text{I}^- \), and that the average
charge state of \( ^{1+}\text{I} \) was +7 with the maximum extending to +16. Stöcklin and his
coworkers (54) have observed differences in \( ^{123}\text{I} \) and \( ^{125}\text{I} \) leading to organic
products, and have ascribed the findings to the different charge state and
energy spectrums of the two species subsequent to \( ^{123}\text{Xe} \) decay. Our work
(35,42) suggests the involvement of \( \text{I}^+ \) and \( \text{I}^- \) in reactions leading to \( ^{123}\text{I} \)
products. Welch (63) has proposed a model involving molecular ion complexes
to account for the reactivity of \( ^{123}\text{I} \) in simple hydrocarbons.

What is important to understand is that this aspect of labeling by
the chemical effects of a nuclear transformation is unlike recoil labeling
or hot atom labeling where the labeling process is affected primarily by the
kinetic energy of the reacting species. Radiation damage to the substrate is virtually non-existent with excitation labeling. For example the recoil energy spectrum of $^{123}\text{Xe}(\text{EC},\beta^+)^{123}\text{I}$ decay has not been measured, but one would expect the maximum translational energy of the $^{123}\text{I}$ to be 27–38 eV (35). $^{125}\text{Xe}$ decay is 100% via electron capture and would result in a maximum kinetic energy of about 4 eV. The chemical reaction, labeling, occurs as a result of the charge state of the labeling species or the state of electronic excitation that the species possesses subsequent to its neutralization.

**Advantages.** The advantages of excitation labeling are:

1. carrier-free labeling is attained without specificity of position. This can be particularly important in physiological molecules that lose biological activity or dehalogenate when introduced into a physiological environment. On a statistical basis not more than one labeling species should enter a given molecule.
2. High molecular weight or complex organic molecules can be conveniently labeled where labeling by conventional synthetic techniques would be difficult, e.g. halogenation of natural products.
3. The labeling procedure is fast and convenient, one need only repurify the compound subsequent to the decay of the parent nuclide.
4. The excitation labeling method can be used to screen classes of molecules for specific biological behavior. A disadvantage of excitation labeling is that in some cases the labeling yields are low. Though the labeling results in carrier-free product, the overall specific activity may be limiting in some instances, even if a high radiochemical yield is obtained (35).
**Generators for Excitation Labeling.** Table III lists the tested and potential generator systems for excitation labeling with the halogens. The cyclotron production methods, suggested cyclotron energies, and production yields are given in addition to the mode of decay and half-life of the generator parent.

Table IV contains a set of comparative results for the excitation labeling of elaidic acid with the $^{18}$Ne $\beta^+(100\%) \rightarrow 18F$, the $^{77}$Kr $\beta^+(80\%) \rightarrow 77\text{Br}$, and the $^{123}$Xe $\beta^+(28\%) \rightarrow 123\text{I}$ generators. The experimental conditions and labeling yields are noted. In brief, the parent nuclide was condensed at $77^0\text{K}$ onto crystalline elaidic acid (Analabs) and allowed to react through 10 half-lives of the generator parent. Subsequently the fatty acid was taken into solution, recrystallized to constant specific activity, and then passed through a Dowex-1 ion exchange column. The radiochemical yield for the $^{18}F$ labeling was $\sim 27\%$ of that obtained with either $^{77}\text{Br}$ or $^{123}\text{I}$. On first inspection one might speculate that the charge state spectrum from the decay by positron emission results in a $^{18}F$ labeling species that is less effective in labeling the substrate. However, $^{77}\text{Kr}$ and $^{123}\text{Xe}$ have nearly opposite branching ratios via positron emission or electron capture, and identical $^{77}\text{Br}$ and $^{123}\text{I}$ labeling yields were obtained. The highly reactive nature of atomic fluorine ($^{18}F$) and the exothermicity of the reaction leading to $^{18}F$ formation, in addition to the experimental technique, may well explain the lower labeling yield observed.

For comparative purposes $^{123}\text{Xe} \rightarrow 123\text{I}$ excitation yields are compared in Table IV. The labeling yield for crystalline elaidic acid was 1.1%, but in oleic acid as a liquid at $22^0\text{C}$, the yield was enhanced to 28.4%.
The two fatty acids are stereoisomers. Additional efforts along these lines are in progress. Oleic acid was chosen as a model compound in view of the recent report (64) that $^{131}\text{I}$-oleic acid showed promise as a myocardial scanning agent. Oleic acid could be labeled in high specific activity with carrier-free $^{123}\text{ICl}$ (formed by excitation labeling of Cl$_2$). A detailed description of the experimental methods for excitation labeling, systematics of yields with target molecule structure, and other variables will be published separately (42).

**COMMENT**

It is unfortunately apparent that the in-house production of excitation-labeling generators will be difficult for some and impossible for others who are restricted to the use of the smaller compact cyclotron that are now marketed as medical cyclotrons. Indeed a continuously variable energy machine with 70 MeV protons and alphas, and 100 and 25 MeV helium-3 and deuterons respectively with an operating beam power rating of the order of 2 Kilowatts seems highly appropriate for installation as a medical cyclotron. The higher energy machines would be advantageous for production of generators of the excitation labeling type for "in-house" use. The generator parents have a half-life too short to be shipped from regional installations, unless the excitation labeling can be done during shipment.

Figure 6 is a general plot of the number of nuclides (466 including acceptable isomers) vs the half-life of the nuclides that were selected on the basis of decay characteristics and thought suited to some aspect of either diagnostic or therapeutic nuclear medicine. The figure
indicates 213 nuclides with a half-life between 30 sec and 1 hr are potentially available by either direct cyclotron production or from cyclotron produced generators. Only 18% of the potentially useful nuclides have a half-life greater than 1 day. A cyclotron of substantial characteristics would be required to produce a large number of the nuclides even, in some instances, for limited testing and evaluation. This factor combined with the increasing demands for large quantities of high purity nuclides (e.g. $^{123}$Xe-$^{123}$I) may reinforce the suggestion (12) that higher energy, high beam intensity medical cyclotrons are more suitable for nuclear medicine applications than was previously thought.
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† Research performed under the auspices of the U.S. Atomic Energy Commission.


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Table I. Cyclotron Produced Halogens having Decay Characteristics Most Suited for Radiopharmaceuticals.

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>$T_{1/2}$</th>
<th>Principal Photon Detected Energy, KeV</th>
<th>Intensity</th>
<th>Positron Energy, MeV</th>
<th>Decay Product Characteristics</th>
<th>Principal Production Methods</th>
<th>Selected Accelerator References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}\text{F}$</td>
<td>110 min</td>
<td>511</td>
<td>97</td>
<td>0.635</td>
<td>$^{18}\text{O}$ (stable)</td>
<td>$^{20}\text{Ne}(d,a)^{18}\text{F}$</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>145</td>
<td>45</td>
<td>2.48</td>
<td>$^{34}\text{S}$ (stable)</td>
<td>$^{35}\text{Cl}(p,pn)^{34}\text{Cl}$</td>
<td>This work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>246</td>
<td>44</td>
<td>$\beta^-$ 3.45(7%)</td>
<td>$^{39}\text{Ar}$ (269 yr)</td>
<td>$^{40}\text{Ar}(p,ap)^{39}\text{Cl}$</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>511</td>
<td>~50</td>
<td></td>
<td>$^{34}\text{Cl}(p,pn)^{34}\text{Cl}$</td>
<td>$^{31}\text{P}(p,n)^{34}\text{Cl}$</td>
<td>This work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1270</td>
<td>50</td>
<td>$\beta^-$ 2.18(8%)</td>
<td>$^{40}\text{Ar}(\gamma,p)^{39}\text{Cl}$ (Linac)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{74}\text{Br}$</td>
<td>31.8 min</td>
<td>511</td>
<td>42</td>
<td>4.7</td>
<td>$^{74}\text{Se}$ (stable)</td>
<td>$^{75}\text{As}(3\text{He},4n)^{74}\text{Br}$</td>
<td>12</td>
</tr>
<tr>
<td>$^{77}\text{Br}$</td>
<td>57 hr</td>
<td>240</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300</td>
<td>6</td>
<td></td>
<td>+</td>
<td>$^{77}\text{Se}$ (17.5 sec)</td>
<td>$^{75}\text{As}(a,2n)^{77}\text{Br}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>520</td>
<td>24</td>
<td></td>
<td>+</td>
<td>$^{77}\text{Se}$ (stable)</td>
<td>$^{77}\text{Kr}(\beta^+,1.2$ hr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>511</td>
<td>1</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclide</td>
<td>$T_\beta$</td>
<td>Detected Energy</td>
<td>Intensity</td>
<td>Positron Energy</td>
<td>Decay Product Characteristics</td>
<td>Principal Production Methods</td>
<td>Selected Accelerator References</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>----------------</td>
<td>-----------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>$^{78}$Br</td>
<td>6.5 min</td>
<td>511</td>
<td>92</td>
<td>2.55</td>
<td>$^{78}$Se (stable)</td>
<td>$^{78}$Se(d,n)$^{78}$Br</td>
<td>12</td>
</tr>
<tr>
<td>$^{83}$Br</td>
<td>2.4 hr</td>
<td></td>
<td>$\beta^-$ 0.93</td>
<td>+ $^{83m}$Kr (1.86 hr)</td>
<td>$^{83m+}$Se $\beta^-$ 70 sec $^{83}$Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{122}$I</td>
<td>3.5 min</td>
<td>511</td>
<td>3.1</td>
<td></td>
<td>$^{122}$Te (stable)</td>
<td>$^{122}$Xe (EC) 20 hr $^{122}$I</td>
<td>56</td>
</tr>
<tr>
<td>$^{123}$I</td>
<td>13.3 hr</td>
<td>159</td>
<td>83</td>
<td>28</td>
<td></td>
<td>$^{123}$Te (10.13 yr)</td>
<td>$^{123}$Xe (EC, $\beta^+$) 2.1 hr $^{123}$I</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>60 da</td>
<td>35</td>
<td>7</td>
<td></td>
<td>$^{125}$Te (stable)</td>
<td>$^{125}$Xe (EC) 16.8 hr $^{125}$I</td>
<td>This work</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>7.2 hr</td>
<td>$\alpha$ 5.87 MeV</td>
<td>41</td>
<td></td>
<td></td>
<td>$^{211}$Po ($0.52$ sec) + $\alpha$ 7.45 MeV</td>
<td>$^{209}$Bi($\alpha$,2n)$^{211}$At</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$^{207}$Bi (38 yr)</td>
</tr>
</tbody>
</table>
Table II. A Comparison of Fluorine-18 Production Rates Relative to the $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$ Reaction on the Cyclotrons at Various Laboratories.

<table>
<thead>
<tr>
<th>Nuclear Reactions Compared</th>
<th>Energy Range Compared</th>
<th>Ratio of Production Rates</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{20}\text{Ne}(d,\alpha)^{18}\text{F}$</td>
<td>$^{16}\text{O}(^3\text{He},x)^{18}\text{F}$ ($x=n,p$)</td>
<td>6.8+0 19.7+8.3</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>15 $\rightarrow$ 0 52 $\rightarrow$ 0</td>
<td>~2.7</td>
<td>Palmer et al.$^{28}$ Christman (12)</td>
</tr>
<tr>
<td>$^{20}\text{Ne}(d,\alpha)^{18}\text{F}$</td>
<td>$^{6}\text{O}(^4\text{He},x)^{18}\text{F}$ ($x=np,2n,d$)</td>
<td>15 $\rightarrow$ 0 30 $\rightarrow$ 0</td>
<td>&gt;&gt;1</td>
</tr>
<tr>
<td></td>
<td>15 $\rightarrow$ 0 51 $\rightarrow$ 0</td>
<td>~1.5</td>
<td>Clark et al.$^{28}$ Lindner et al.$^{61}$</td>
</tr>
<tr>
<td>$^{20}\text{Ne}(d,\alpha)^{18}\text{F}$</td>
<td>$^{20}\text{Ne}(3\text{He},x)^{18}\text{Ne}+^{18}\text{F}$ ($x=2p3n,^3\text{He}2n,^4\text{He}$)</td>
<td>16.5+0 58+41</td>
<td>~4</td>
</tr>
<tr>
<td>Nuclear Reaction</td>
<td>$E_{\text{MeV}}$</td>
<td>Activating Transformation</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>$^{20}\text{Ne}(^3\text{He},x)^{18}\text{Ne}$</td>
<td>&gt;58-41</td>
<td>$^{18}\text{Ne} \xrightarrow{1.5 \text{ sec}} ^{18}\text{F}$</td>
<td>Dynamic target required 1.8 mCi/$\mu$AH of $^{18}\text{F}$ with $\text{F}_2$ scavenger present</td>
</tr>
<tr>
<td>($x = 2p3n, ^4\text{He},^3\text{He}2n$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{40}\text{Ar}(p,3p)^{38}\text{S}$</td>
<td>52 (+)</td>
<td>$^{38}\text{S} \xrightarrow{2.83 \text{ hr}} ^{38}\text{Cl}$</td>
<td>With thin gas target, 20 $\mu$Ci/$\mu$AH of $^{38}\text{S}$. Higher yields predicted with solid target and higher energy, alpha reaction too low at 55 MeV</td>
</tr>
<tr>
<td>$^{40}\text{Ar}(^4\text{He},3p)^{38}\text{S}$</td>
<td>&gt;55 (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{79}\text{Br}(p,3n)^{77}\text{Kr}$</td>
<td>32-25</td>
<td>$^{77}\text{Kr} \xrightarrow{1.2 \text{ hr}} ^{77}\text{Br} + ^{77}\text{Br}$</td>
<td>gas flow target suitable</td>
</tr>
<tr>
<td>$^{76(7)}\text{Se}(^4\text{He},xn)^{77}\text{Kr}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{76(7)}\text{Se}(^3\text{He},xn)^{77}\text{Kr}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{122}\text{Te}(^4\text{He},3n)^{123}\text{Xe}$</td>
<td>46-35</td>
<td>$^{123}\text{Xe} \xrightarrow{2.1 \text{ hr}} ^{123}\text{I}$</td>
<td>static target, $^{123}\text{Xe}$ production rate of 4.3 mCi/$\mu$AH, $E_2$=43-35 MeV</td>
</tr>
<tr>
<td>$^{123}\text{Te}(^3\text{He},3n)^{123}\text{Xe}$</td>
<td>39-22</td>
<td></td>
<td>static target $^{123}\text{Xe}$ yield 4.9 mCi/$\mu$AH, peak at $\sim$29 MeV</td>
</tr>
<tr>
<td>$^{127}\text{I}(p,5n)^{123}\text{Xe}$</td>
<td>65-50</td>
<td></td>
<td>static $^{123}\text{Xe}$ target, $E_2$=57.5-50.5 MeV, production rate 3 mCi/$\mu$AH Blip development liquid flow targets</td>
</tr>
<tr>
<td>$^{127}\text{I}(d,6n)^{123}\text{Xe}$</td>
<td>$\sim$ 56-50</td>
<td></td>
<td>gas flow target</td>
</tr>
<tr>
<td>$^{127}\text{I}(p,3n)^{125}\text{Xe}$</td>
<td>32-25</td>
<td>$^{125}\text{Xe} \xrightarrow{16.8 \text{ hr}} ^{125}\text{I}$</td>
<td>gas flow target</td>
</tr>
<tr>
<td>$^{127}\text{I}(d,6n)^{125}\text{Xe}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear Transformation</td>
<td>Experimental Conditions</td>
<td>Radiochemical Yield, %</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------</td>
<td>------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>$^{18}\text{Ne} \beta^+ (100%) \rightarrow ^{18}\text{F}$</td>
<td>Elaidic acid. $^{18}\text{Ne} + ^{18}\text{F}$ in dynamic flow through 10 mg of crystalline compound in a capillary at 77°K.</td>
<td>0.3</td>
<td>This work</td>
</tr>
<tr>
<td>$^{77}\text{Kr} \beta^+ (\sim 80%) \rightarrow ^{77}\text{Br}$</td>
<td>Elaidic acid, crystalline, $^{77}\text{Kr}$ adsorbed onto 5 mg at 77°K</td>
<td>1.1</td>
<td>This work</td>
</tr>
<tr>
<td>$^{123}\text{Xe} \beta^+ (\sim 28%) \rightarrow ^{123}\text{I}$</td>
<td>Elaidic acid, crystalline, $^{123}\text{Xe}$ adsorbed onto 5 mg at 77°K for 24 hrs. Oleic acid, liquid, $^{123}\text{Xe}$ dissolved into 100 mg at 22°C. Human serum albumin, crystalline, $^{123}\text{Xe}$ adsorbed onto 4 mg at 77°K 100 mg at 77°K Tyrosine, crystalline, $^{123}\text{Xe}$ adsorbed onto 3 mg at 77°K</td>
<td>1.1</td>
<td>This work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>35</td>
</tr>
</tbody>
</table>

Experimental error = ±5%. Radiochemical yields based on the total activity in the reaction vessel.
FIGURE CAPTIONS

Figure 1. Design of system for production of anhydrous, carrier-free fluorine-18 and synthetic intermediates.

Legend: $S_1-4$ Skinner Electric Co, solenoid valves
$S_5-7$ Fluorocarbon Co, Delta Solenoid Valves
$FC_1$ Vactronics, VVM-50-Q continuously variable flowcontroller
$FC_2$ Matheson (Brooks) special, digital flow controller and transducer
$FC_3$ flowmeter
$F_9$ R.D. Mathis Co., gas line purifier
$P_1-2$ Vacuum pumps
$P_3$ oilless, diaphragm, pressure-vacuum pump
$C_1$ soda lime scrubber
$C_2$ NaF (HF) scrubber
$T$ CGS Datagraphics, special, Ni plated transducer
$R$ reaction vessels

Figure 2. Photograph of potassium iodide salt target after 48.5 $\mu$Ah proton irradiation. scale = 1 to 1.

Figure 3. SEM of KI before irradiation 1000x.

Figure 4. SEM of KI, center of target at 48.5 $\mu$Ah on target, 1000x.

Figure 5. SEM of KI, greenish edge crystals at 48.5 $\mu$Ah on target, 1000x.

Figure 6. Number of potential medically useful cyclotron produced nuclides vs. half-life of the nuclides.
The diagram shows a histogram indicating the number of nuclides in different half-life categories. The categories are:

- 0.5 min ≥ T/2 < 1.0 hr
- 1.0 hr ≥ T/2 < 1.0 da
- 1.0 da ≥ T/2 < 30 da

The bars represent the number of nuclides in each category, with the following counts:

- 0.5 min ≥ T/2 < 1.0 hr: 213
- 1.0 hr ≥ T/2 < 1.0 da: 168
- 1.0 da ≥ T/2 < 30 da: 85

The y-axis represents the number of nuclides, ranging from 0 to 80.