# PRODUCTION OF CARRIER-FREE $^{123}I$ USING THE $^{127}I(p,5n)^{123}Xe$ REACTION

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Iodine is notable among the elements which are part of man's composition in that it has more different radioisotopes than any other element natural to man. These radioisotopes of iodine have different physical characteristics and no one radioisotope is optimal for all biomedical applications. Iodine-123 has physical characteristics which are optimal for most in vivo medical procedures, particularly those which are completed within 24 hr. Iodine-123 decays solely by electron capture; the photon-to-electron ratio is high, indicating a low level of undesirable particulate radiation. Iodine-123 emits 159-keV gamma rays in 84% of the disintegrations, thus providing a high yield of photons suitable for use with imaging systems. The 13.1-hr half-life of $^{123}I$ is long enough to allow for target processing, chemical manipulation, purification, extensive quality control, delivery to the patient, and subsequent development of clinical information. In all respects then, $^{123}I$ is a more ideal gamma radionuclide than any other radioisotope of iodine for in vivo diagnostic procedures (*1*).

In 1962 Myers, et al (*2*) described the merits of $^{123}I$ and several methods for production. They indicated that contaminants of other radioisotopes of iodine were present but did not indicate the amount of these contaminants. Sodd, et al (*3*) and other investigators (*4–8*) have provided an extensive list of nuclear reactions leading to the production of $^{123}I$. Their list does not include the production method to be described in this publication (Table 1). Most of the previously described methods for the production of $^{123}I$ result in contamination with $^{124}I$ which reduces the spatial resolution of imaging procedures and increases the radiation dose to the patient (*9*). We wish to describe a new method for the production of $^{123}I$ which eliminates virtually all radioactive contaminants (Table 2).

## MATERIALS AND METHODS

**Research irradiations.** The $^{123}Xe$ production cross-section information was collected using a small iodine target. A tantalum plate with a recess 1.2 mm deep and 6.5 mm in diam was used as the target holder for resublimed high-purity natural iodine. To prevent

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**TABLE 1. COMPARISON OF VARIOUS REPORTED METHODS OF PRODUCTION OF $^{123}I$**

| Reaction | Activity (mCi/μA/hr) | $^{122}I$ | $^{124}I$ | $^{125}I$ | $^{126}I$ | $^{130}I$ | $^{131}I$ | Ref. |
|---|---|---|---|---|---|---|---|---|
| $^{121}Sb(\alpha,2n)^{123}I$ | 0.23 | ni* | 0.62 | 0.015 | 0.0019 | ni | ni | 3 |
| $^{123}Te(d,n)^{123}I$ | 0.13 | ni | 0.19 | 0.12 | 0.066 | 0.96 | 0.07 | 3 |
| $^{123}Te(\alpha,3n)^{123}Xe$ / $^{123}Te(\alpha,nd)^{123}I$ | 0.25 | ni | 1.5 | 0.03 | 0.009 | ni | ni | 3 |
| $^{123}Te(^3He,2n)^{123}Xe$ / $^{123}Te(^3He,d)^{123}I$ | 0.007 | ni | ni | ni | ni | ni | ni | 3 |
| $^{123}Te(^3He,3n)^{123}Xe$ / $^{123}Te(^3He,nd)^{123}I$ | 0.0014 | ni | ni | ni | ni | ni | ni | 3 |
| $^{122}Te(\alpha,3n)^{123}Xe$ | 0.3 | ni | ni | <0.2 | ni | ni | ni | 7 |
| $^{127}I(p,5n)^{123}Xe$ | 3.0 | — | — | 0.1 | — | — | — | Present work |

* Not indicated in publication.

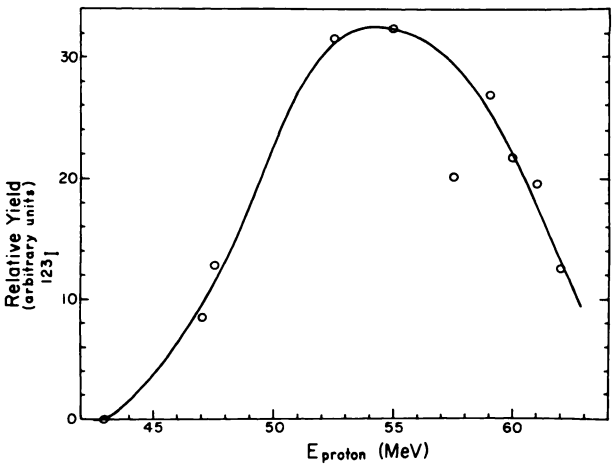


**FIG. 1.** Relative yield of $^{123}I$ as function of incident proton energy. $^{127}I_2$ targets used were about 2.5 MeV thick. Yield is given in arbitrary units. Some uncertainty results because of possible loss of xenon from iodide crystal lattice if target is overheated by incident beam of protons.

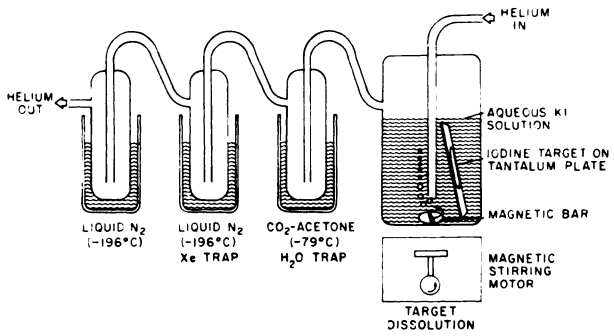


**FIG. 2.** System for isolation of xenon isotopes from $^{127}I_2$ target following proton irradiation.

loss of volatile products during irradiation a 0.25-mm-thick tantalum cover foil was used. The assembled chemical target block was cooled by circulating water on the back and helium across the front of the target. A series of irradiations were made at proton energies increasing from 42.5 to 62 MeV in 2.5-MeV steps to establish the optimum proton energy for producing $^{123}Xe$ (Fig. 1).

**Production irradiations.** Having established the relative cross sections as a function of proton energy for the $^{127}I(p,5n)^{123}Xe$ and $^{127}I(p,3n)^{125}Xe$ reactions, a system was designed for the production and recovery of large quantities of carrier-free $^{123}I$ for subsequent chemical and biomedical studies. The area of iodine target was increased to 4.5 $cm^2$, the thickness to 1.6 mm, and the beam intensity to 6 $\mu A$ of 57.5-MeV protons. To minimize the production of $^{125}Xe$, it was decided to irradiate the target for 3 hr, which would produce 63% saturation of $^{123}Xe$.

**Methods of separation and recovery.** A cyclic or batch processing method similar to that of Sodd, et al (7) was used to separate the xenon from the target. At the end of the irradiation, the target block was remotely removed from the cyclotron and transferred to the radiochemical laboratory. The iodine target was dissolved in an aqueous solution of potassium iodide. Helium was circulated in a closed system through the dissolved sample and subsequently through dry-ice-acetone and liquid-nitrogen traps (Fig. 2). Water vapor and iodine released from the dissolution flask were removed by the dry-ice-acetone-cooled trap and the xenon gas was collected in the liquid nitrogen-cooled trap. Cooling was maintained for about 6 hr to allow the $^{123}Xe$ to decay to $^{123}I$.

**Methods of identification and assay.** Serial gamma-ray spectroscopy was used to identify the kinds and amounts of radionuclides present by virtue of their characteristic photopeak energies and half-lives. A 30 cc Ge(Li) detector coupled to a 4,096-channel analyzer was used for the gamma-ray spectroscopy of the irradiated target and the final product. The resulting spectra were processed using a PDP 15/40 computer to integrate the area under the respective gamma-ray photopeaks. Yields were determined by comparison with an IAEA $^{22}Na$ calibrated standard source counted in a standard geometry. Figure 3 shows the gamma-ray spectrum of the final $^{123}I$ product.

To further establish product purity and suitability for clinical use, paper and cellulose acetate electrophoresis of $^{123}I$ dissolved in distilled water was performed. Paper electrophoresis for 75 min at 170 volts in 0.05 ionic strength barbitol buffer (Beckman buffer B-1, pH 8.6) and cellulose acetate electrophoresis for 15 min at 340 volts in the same buffer system were followed by a determination of the distribution of the radioactivity by radiochromatographic scanning.

The product $^{123}I$ was tested for sterility according to the *U. S. Pharmacopeia* using thioglycollate medium incubated at 32°C for 7 days and Sabouraud medium incubated at 25°C for 10 days.

## RESULTS

Yields measured as a function of proton energy showed that the optimum energy for $^{123}Xe$ production is about 54 MeV for a thin target (Fig. 1). The $^{123}I$ activity recovered from the liquid-nitrogen-cooled trap 6 hr after the termination of a production irradiation was 24 mCi. This figure is based on the following experimental conditions: $^{127}I$ target thickness of 1.0 gm/$cm^2$ (7 MeV thick) with an irradiation time of 1.0 hr at 6 $\mu A$ at 57.5 MeV and target area of 4.5 $cm^2$.

Because the isotopes of xenon, including $^{123}Xe$,

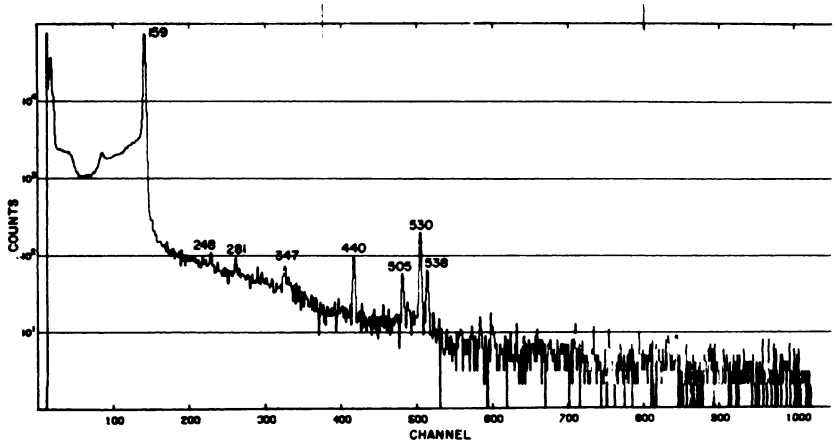


**FIG. 3.** Gamma spectrum of final product. Only $^{123}I$ is observed after separation. Line energies are given in keV.

can be readily separated from the target and final product, the only contaminants in the product are isotopes of iodine from xenon decay (Table 2). Radionuclides of iodine produced directly in the target remain in the dissolution flask. Furthermore, $^{124}Xe$ and $^{126}Xe$ are stable so they do not result in $^{124}I$ and $^{126}I$. Xenon-125 is a contaminant initially (17-hr half-life) which constitutes about 5% of the $^{123}Xe$ (2.1-hr half-life) activity at the end of irradiation with 57.5-MeV protons. If the residual xenon is removed at the optimal time for maximum $^{123}I$ activity (6 hr), only 22% of the $^{125}Xe$ will have decayed to $^{125}I$. This results in $^{125}I$ contamination of 0.1% of the $^{123}I$ activity. Also some $^{122}Xe$ (20-hr half-life) is produced by $^{127}I(p,6n)^{122}Xe$. This isotope is not a problem because the $^{122}Xe$ is removed as described previously, and the $^{122}I$ daughter promptly decays to stable tellurium with a half-life of 3.5 min.

Electrophoresis of the final aqueous $^{123}I$ product indicates that the $^{123}I$ migrates as one substance and in the same manner as the $^{125}I$-iodide standard. The product, which was cultured in Sabouraud and thioglycollate media to establish clinical suitability further, was found to be sterile.

**TABLE 2. POSSIBLE CONTAMINANTS AND METHODS OF REMOVAL**

| Reaction | Isotope | Method of removal |
|---|---|---|
| $^{127}I(p,xn)$ | $^{122}Xe$ | Decays to 3.5 min $^{122}I$ |
| | $^{124}Xe$ | Stable, is blown off |
| | $^{125}Xe$ | Decays to and remains a 0.1% $^{125}I$ contaminant |
| | $^{126}Xe$ | Stable, is blown off |
| | $^{127}Xe$ | Proton energy too high for significant production |
| $^{127}I(p,xnd)$ | $^{122}I$, $^{124}I$, $^{125}I$, $^{126}I$ | All resultant iodine remains in dissolution flask or is collected in $CO_2$-acetone trap |
| $^{127}I(p,xn\alpha)$ | $^{122}Te$, $^{123}Te$, $^{124}Te$ | All resultant tellurium remains in dissolution flask or is collected in $CO_2$-acetone trap |

## DISCUSSION

The merits of $^{123}I$ for diagnostic biomedical applications have been appreciated for some time; its advantages of decreased radiation exposure and increased spatial resolution can only be fully realized if other radioactive contaminants are absent or negligible. A variety of production methods have been proposed or developed (Table 1). These production methods may be direct, that is, the $^{123}I$ is produced immediately in the target by the irradiation, or indirect, that is, $^{123}Xe$ is produced in the target and subsequently decays to $^{123}I$. Several investigative groups (*2,4,5,6,10*) have described a variety of direct methods for the production of $^{123}I$. These methods also result in the production of radioactive contaminants including $^{124}I$, $^{125}I$, $^{126}I$, $^{130}I$, and $^{131}I$ (Table 2). The amounts and combinations of these contaminants varies with the production method, but in all cases the radiation dose to a patient is increased and spatial resolution in imaging is suboptimal (*9*). This is particularly true for $^{124}I$ because of its positron and 604-keV gamma emissions. Blue, et al (*4*) and Sodd, et al (*7,8*) described two indirect methods for the production of $^{123}I$ following the decay of $^{123}Xe$ which is produced by the irradiation of $^{122}Te$ or $^{123}Te$. These indirect production methods eliminate all contaminants except $^{125}I$. For imaging, $^{125}I$ contamination does not affect spatial resolution because all its photon emissions are less energetic than the 159-keV gamma ray of $^{123}I$. Iodine-125 does, however, result in increased radiation dose to the patient. In the iodide form, the thyroid irradiation from $^{125}I$ is 40 times greater than from an equal amount of $^{123}I$. All methods previously described require relatively expensive isotopically enriched tar-

gets which usually must be processed before re-irradiation. In addition, the indirect methods previously described do not result in high yields. The method described in this publication has several advantages. It uses inexpensive, readily available iodine as a target. Moreover, it results in relatively large yields of carrier-free $^{123}I$ with only 0.1% $^{125}I$ contamination and no contamination from $^{124}I$. The $^{123}I$ can be readily processed for immediate use in vivo or for subsequent incorporation into biologically active compounds.

The disadvantages one encounters are the following: The proton beam energy required (>50 MeV) is not readily available from most cyclotrons, and the poor thermal conductivity afforded by the crystalline iodine requires careful handling of the beam. Both theoretical calculations and experimental observations indicate that beam intensities at 57.5 MeV exceeding 3 $\mu A/cm^2$ result in "burn out" of the target material. This necessitates establishing a uniform beam density over the entire target area, and restricts the thickness of the target to 1 $gm/cm^2$ (7 MeV thick).

The total yield of $^{123}I$ can be increased by using a longer bombardment time and increased current. If a 3-hr bombardment were used with a beam current of 10 $\mu A$ (beam current density of approximately 2 $\mu A/cm^2$), a yield of 0.9 Ci of $^{123}Xe$ will be obtained at the end of bombardment and 89 mCi of $^{123}I$ would be available at 6.0 hr after irradiation.

## SUMMARY

A cyclotron procedure for the production of high-purity, carrier-free $^{123}I$ suitable for immediate radiopharmaceutical use has been developed. Proton irradiation of natural elemental iodine results in the production of $^{123}Xe$ which subsequently decays to $^{123}I$. The primary reaction for 57-MeV protons is $^{127}I(p,5n)^{123}Xe$; other reactions yield $^{125}Xe$ and the neutron-deficient radioisotopes of iodine. At the end of bombardment, the target iodine is dissolved in aqueous KI, and helium gas is bubbled through the solution, sweeping the xenon through a recirculating system. The xenon gas is collected in a liquid nitrogen-cooled trap. The isolated xenon is contained for 6 hr during which time the $^{123}Xe$ ($T_{1/2}$, 2.1 hr) decays to $^{123}I$. The $^{123}I$ may be recovered by adding a small volume of physiological saline.

An irradiation on the Crocker Nuclear Laboratory isochronous cyclotron of 1 hr, using a 1 $gm/cm^2$ thickness of iodine (7-MeV proton energy loss in the target) and 57.5-MeV protons at 6 $\mu A$, resulted in 24 isolable mCi of $^{123}I$. The only detectable contaminant in the final product was $^{125}I$ which was about 0.1% of the $^{123}I$ activity.

A reasonable extrapolation of our irradiation experience indicates that a yield of 89 mCi can be obtained in practice. This production figure is based on a target thickness of 1 $gm/cm^2$ and an irradiation time of 3 hr at 10 $\mu A$.

The advantages of this method over existing methods are (A) readily available, inexpensive, isotopically pure targets; (B) multimillicurie yields of carrier-free $^{123}I$, and (C) significantly reduced radionuclidic contamination. When used in vivo the radiation dose to the patient is reduced and optimal spatial resolution is possible for imaging procedures. This method, however, requires 50–60-MeV protons which are not universally available.

## ACKNOWLEDGMENTS

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