[F-18] 2-DEOXY-2-FLUORO-D-GLUCOSE: NEW APPROACHES INVOLVING NUCLEOPHILIC AND ELECTROPHILIC FLUORINATION.

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Recent efforts to improve the radiochemical yields for the synthesis of F-18 labeled 2-deoxy-2-fluoro-D-glucose ([F-18] 2-FDG) have focused on both the nucleophilic displacement by [F-18] fluoride ion (1) and the use of the mild electrophilic fluorinating agent [F-18] acetyl hypofluorite (2). Because the use of [F-18] F^- can potentially lead to radiochemical yields approaching 100%, and at the no carrier-added level, we have pursued nucleophilic displacement on 1,2-anhydro-3,4:5,6-di-O-isopropylidene-1-C-nitro-D-mannitol [I] with fluoride ion as an alternative method (3,4). Results of fluorination of [I] to yield [F-18] 2-FDG have met with only limited success in our laboratories. Radiochemical yields of [F-18] 2-FDG on the order of 5% along with significant decomposition of [I] under reaction conditions were observed. Assurance of nucleophilic displacement to yield the desired glucose isomer was provided by determination of the x-ray crystal structure of [I]. The results of reactions of [I] with various halides, solvent media, and under different experimental conditions will be discussed.

Because of the recent measurement of the reaction rate between fluorine and water (5), we explored the possibility of conducting a fluorine addition on D-glucal [II] in aqueous media. The reaction proceeds via regio- and preferential stereoselective addition across the double bond with relatively little decomposition of F_2. 2-FDG was prepared by bubbling 0.2% fluorine in neon into an aqueous solution containing an equimolar amount of [II] at room temperature. Hydrolysis of the resultant fluorinated product mixture with 1 N HCl (120°C, 15 m) followed by chromatographic purification using an ion-retardation resin-alumina column gave 2-FDG in about 60% yield. The final product was identified by TLC, ^{19}F NMR [94.1 MHz, deuterium oxide, hexafluorobenzene (external standard) δ + 32.81 ppm (α-anomer, 48.5%) and + 32.51 ppm (β-anomer, 51.5%)],[a] and by its conversion to the corresponding 6-phosphate with yeast hexokinase as shown by HPLC (6). Successful extension of the method to the synthesis of [F-18] 2-FDG has resulted in radiochemical yields of 25-30% with a processing time of 30 min after EOB.

[a]A small peak at + 37.8 ppm may not be attributed to the α-anomer of 2-deoxy-2-fluoro-D-mannose since no signal for the corresponding β-anomer (+56.3 ppm) was observed.

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OPTIMIZATION OF n.c.a. ^{18}F-FLUORINATION OF ALIPHATIC CARBOXYLIC ACIDS VIA NUCLEOPHILIC SUBSTITUTION

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Labelling with fluorine-18 often exhibits a lack of efficient yields and high specific activities even in aliphatic exchange reactions. ω-[^{18}F]-Fluoroheptadecanoic acid (1) and [^{18}F]-fluoracetate (2) are of interest as radiopharmaceuticals, and they have been used in this study for the optimization of n.c.a. radiofluorination via S_N-reactions in an acetamide melt.

In a previous study reasonable yields were only obtained in the presence of fluoride carrier (1,3). This could be avoided by adding the non-nucleophilic and basic potassium carbonate to the reaction melt (Fig. 1). Although the fluorine-for-bromine exchange in bromo-acetylethylester was facilitated by K_2CO_3, the wall activity losses increased up to 80 %. Thus, both parameters had to be optimized, and the effect of temperature, time, and substrate concentration were systematically investigated. To minimize the losses of fluorine by adsorption to the vessel wall various materials were examined. Almost no sorption losses were found with glassy carbon as wall material and the overall n.c.a. radiochemical yield could be increased up to 60 %.

For the nucleophilic fluorine exchange with ω-bromoheptadecanoic acid methylester in glassy carbon vessels a maximum yield of 70 ± 2% was found at 150 °C after 15 min reaction time and with 120 mg of the substrate (Fig. 2). High exchange rates with n.c.a. fluoride have also been obtained with phase transfer catalysts in fatty acids (4). With respect to the less complicated synthesis and purification step the acetamide method seems superior and also generally applicable to other aliphatic molecules of interest.

The quality control of the final product was carried out by HPLC separation of the product from the ω-hydroxy- and ω-methoxy hepta-decanoic acid which are formed during ester hydrolysis. The dilution of ^{18}F in the K_2CO_3-acetamide solution with inactive fluoride was shown to be smaller than 10 using a fluoride specific glass electrode. The carrier content after exchange in the fluoroacetylethylester was determined by means of GC-TC detection, and was shown to be smaller than the detection limit of 3×10^{-9} mole. This corresponds to a specific activity of 1.5×10^5 Ci/mmole in the final product.

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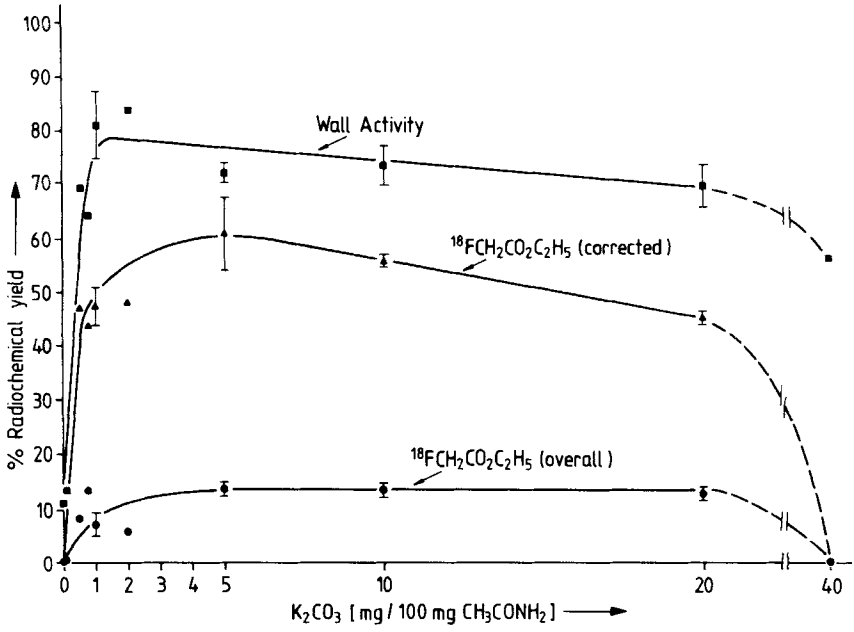

Fig. 1. Effect of K_2CO_3 concentration on $^{18}FCH_2CO_2C_2H_5$ yield (180 °C, 30 min; ▲based on activity in melt; ●based on starting activity)

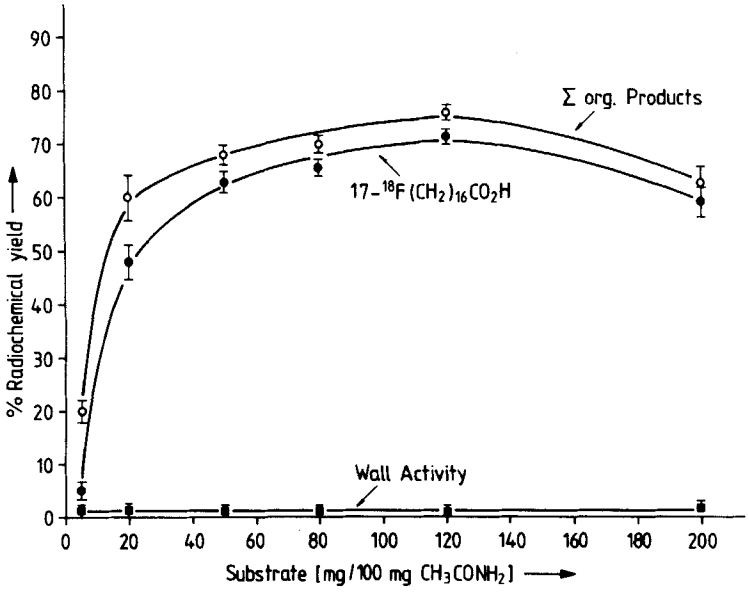

Fig. 2. Effect of substrate concentration on $^{18}F(CH_2)_{16}CO_2H$ yield (150 °C, 15 min)

SYNTHESIS OF NO-CARRIER ADDED ^{11}C-LABELLED CHOLINE*

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The concentration of acetylcholine (ACh) in the human brain, in contrast to that of other neurotransmitters, is maintained within narrow limits. However, the turnover of ACh is several times greater than that of other known neurotransmitters (1). A significant reduction in the activity of choline acetyltransferase, an enzyme converting choline into ACh, has been observed in the brain of dementia patients (2). Continuing our work on the development of new syntheses for radiopharmaceuticals used to study neurological disorders with positron emission tomography, we have devised a synthesis of ^{11}C-labelled choline. Although this material was recently used for PET scanning in monkeys (3), the synthesis was not described.

Our procedure uses ^{11}C-labelled methyl iodide prepared by adapting an established synthesis (4,5). No-carrier-added methyl iodide was reacted with 2-amino-(N,N-dimethyl)-ethanol in isopropanol, acetone or metanol and a presence of tributyl amine, K_2CO_3 or $KHCO_3$ as a base. The reaction was done in a closed reaction vial by heating it for 20-30 minutes in a sand bath kept at a temperature between 60 and 100°C. At the end the solvent was evaporated and the residue dissolved in methanol or acetone. Final purification was done by high-performance liquid chromatography using amino column and CH_3OH-Ether (7:3) as an elution solvent. The elution volume as determined by HPLC was identical to the authentic sample of choline. The R_f-value of 0.48 on Al_2O_3 with CH_3COOH -acetone-methanol - benzine (1:1:4:10) as developing a solvent was also identical to that of an authentic sample.

Radiochemical purity of the final product was over 98% with a radiochemical yield, not corrected for radioactive decay, of about 10%-15% relative to the amount of $^{11}CH_3I$ present in the reaction mixture. The specific activity was measured by HPLC and was found to be ~40 Ci/mmol expressed at the end of the synthesis. The solvent, the base, and the bath temperature all affected the yield of ^{11}C-choline.

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^{11}C-METHYL IODIDE IN N-ALKYLATION REACTIONS OF ^{11}C-LABELLED RADIOPHARMACEUTICALS

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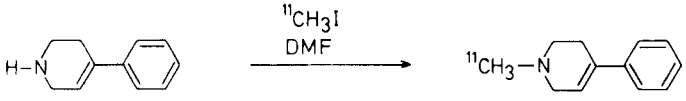
A number of ^{11}C-labelled radiopharmaceuticals have earlier been prepared in our laboratory (1,2) using ^{11}C-methyl iodide in N-alkylation reactions performed in dimethylformamide (DMF) as solvent. In this paper some new compounds prepared by this method are reported, exemplified with the synthesis of N-[^{11}C]methyl-4-phenyl-tetrahydropyridine (MPTP) (I)(3)according to Scheme 1.



I

Scheme 1

In Scheme 2 some of the compounds, apomorphine (II), clozapin (III), mepivakain (IV), hydromorfon (V), zimelidine (VI), prepared by this method are shown. The radiochemical yields are in the order of 50-80 % with respect to the ^{11}C-methyl iodide produced with reaction times between 2-10 min. The radiochemical purity is usually better than 98 % with respect to ^{11}C-methyl iodide after LC-purification. The total preparation time, including LC-purification, is 30-45 min.

^{11}C-Methyl iodide is also very useful in N-amide alkylations as in the synthesis of N-[^{11}C]methylspiperone (4). This synthetic route has also been used in the preparation of a potential muscarin ligand, N-[^{11}C]methyldexetimide (VIII) (5), as shown in Scheme 3, and in the synthesis of a potential serotonin ligand, N-[^{11}C]methylketanserin ((VII), Scheme 2). The LC-purification is simplified in this ion pair alkylation (6, 7) if a long alkyl halide like heptyl iodide is added to the reaction flask after the reaction with ^{11}C-methyl iodide is completed, thus decreasing the amount of the precursor. The reaction times are in the order of 2-7 min. and the radiochemical purity is usually better than 98 %.

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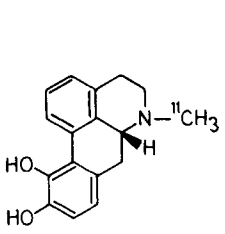

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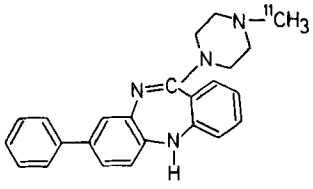

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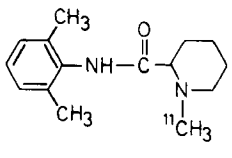

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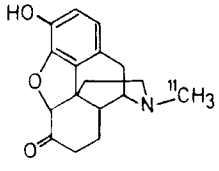

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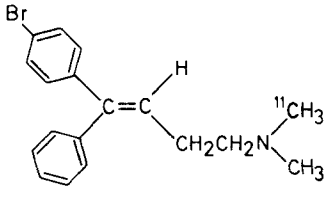

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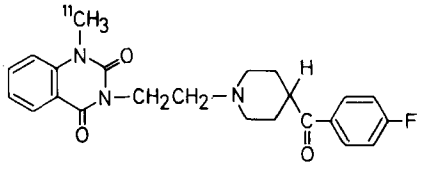
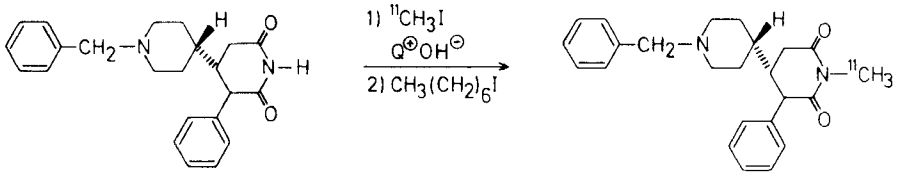


VII

Scheme 2



VIII

Scheme 3

STRUCTURE LOCALIZATION RELATIONSHIP OF DIFFERENT CHAIN LENGTH 1-[C-11]-LABELED BETAMETHYL FATTY ACIDS

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Recently we proposed the use of [1-^{11}C] betamethyl heptadecanoic acid [1-^{11}C]BMHA a branched chain fatty acid as a potential myocardial metabolic tracer for positron emission tomography.

In this study a series of fatty acids of betamethyl varying chain length was prepared. The compounds synthesized were [1-^{11}C] betamethyl undecanoic acid [1-^{11}C]BMUA, [1-^{11}C] betamethyl palmitic acid ([1-^{11}C]BMPA), [1-^{11}CBMHA, [1-^{11}C] betamethyl octadecanoic acid ([1-^{11}C])BMOA), and [1-^{11}C]BMIA). The synthesis for this series is outlined in Scheme 1.

For each compound, biodistribution in rats was performed at various times following intravenous administration. The percentage of radioactivity released as $^{11}CO_2$ was determined by trapping $^{11}CO_2$ in KOH solution.

The biodistribution study demonstrates that [1-^{11}C]BMHA stands out as the compound with highest myocardial uptake and highest ratios of target (heart) to nontarget (blood, lungs and liver), where [1-^{11}C] BMUA showed lowest heart uptake at all times. The fact that for all the [C-11] betamethyl fatty acids studies some of the activity is released as $^{11}CO_2$ suggests that α and or ω-oxidation is taking place to some extent.

Imaging studies in dogs with [1-^{11}C]BMPA showed similar behavior. The syntheses and biodistribution results will be reported. Supported by RØ1HL29462-2.

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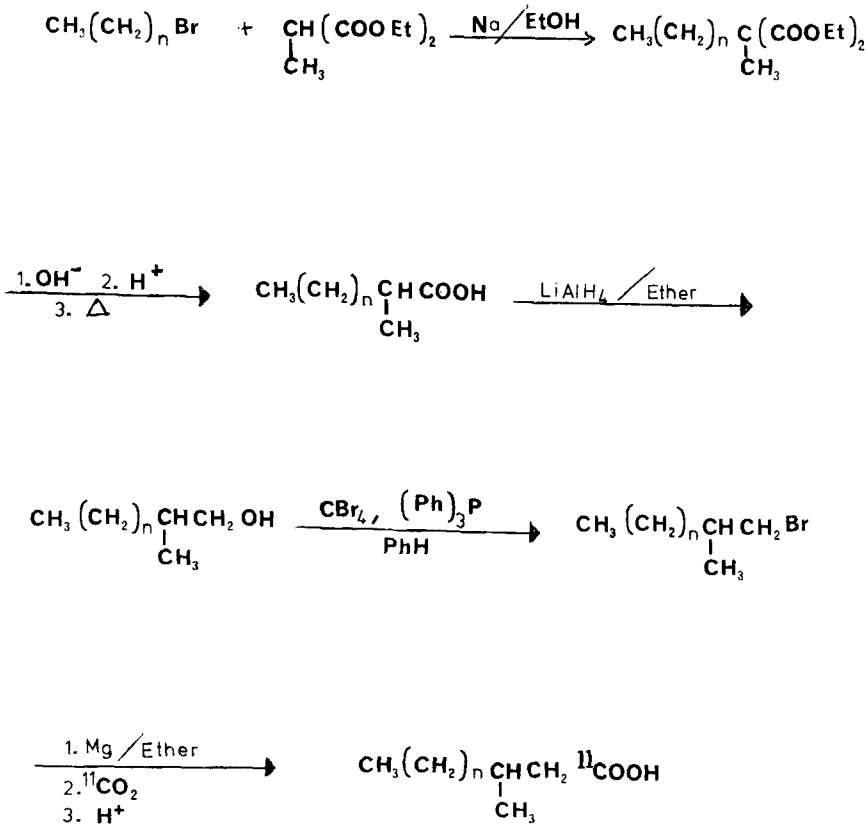
SCHEME 1



n = 7, 12, 13, 14, 17

Chemical Route for the Preparation of [1-^{11}C]Betamethyl Fatty Acid Analogs

THE SYNTHESIS OF ^{11}C-LABELLED ENKEPHALINES

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In this paper the synthesis of some enkephalines and some of their metabolites are reported. Earlier we have shown that ammonia is a good solvent for the alkylation of sulfide anions using ^{11}C-methyl iodide (1-3). This is exemplified here by the synthesis of ^{11}C-Met--enkephaline shown in Scheme 1. The protected peptide was dissolved in ammonia and deprotected with sodium to give a proper peptide precursor shortly before the preparation of ^{11}C-methyl iodide. After trapping of the labelled alkyl halide, the solvent was removed and the residue dissolved in a buffer. LC-purification gave the peptides in radiochemical yields of the order of 50-65 % (decay corrected) with a total reaction time of 30-40 min. including the preparation of the ^{11}C-methyl iodide. The peptides shown in Scheme 2 were all prepared by the same method. The syntheses are also useful in the preparation of unlabelled peptides.

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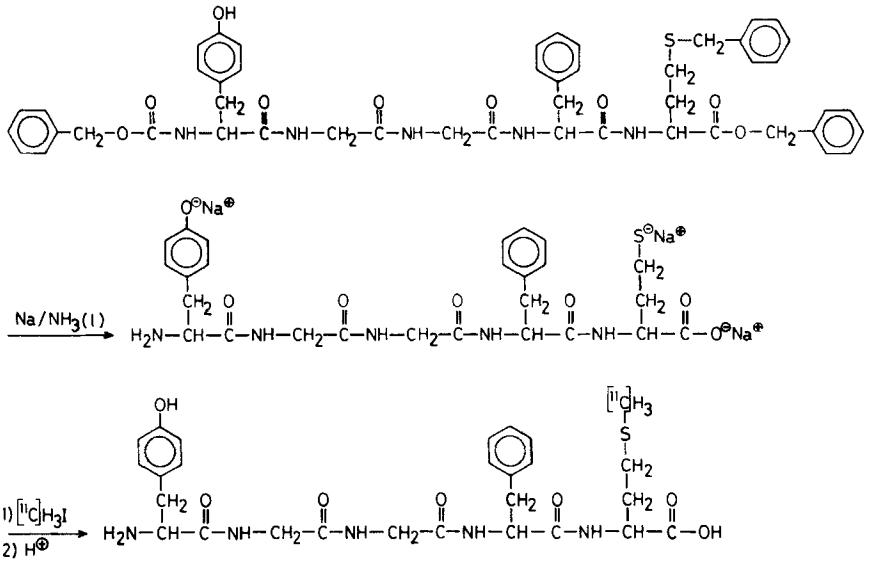
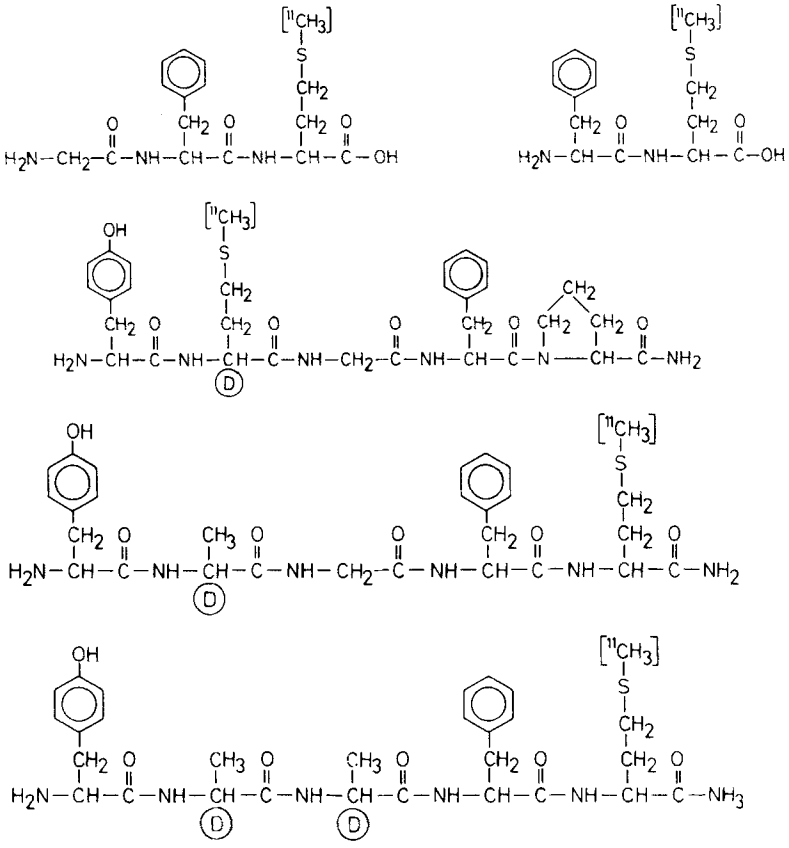


Scheme 1



Scheme 2

NEW LABELLED PRECURSORS - ^{11}C-ALKYL IODIDES AND ^{11}C-PHOSPHOROUS YLIDES

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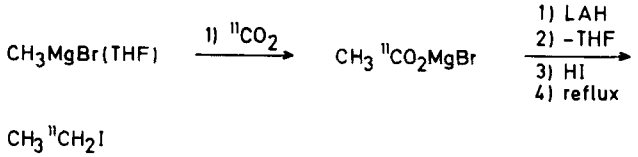
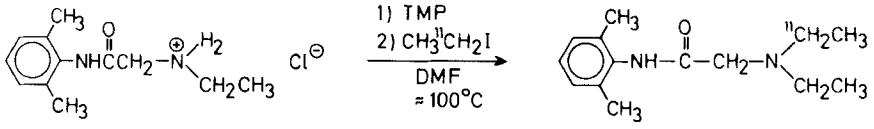
The potential of ^{11}C-methyl iodide in the synthesis of various radiopharmaceuticals is well established. In this paper the syntheses of other useful ^{11}C-alkyl iodides (1) such as [1-^{11}C]ethyl, [1-^{11}C]propyl, [1-^{11}C]butyl and [1-^{11}C]isobutyl iodide are reported. These syntheses are carried out as exemplified in the preparation of [1-^{11}C]-ethyl iodide shown in Scheme 1. The ^{11}C-carbon dioxide was trapped in the appropriate Grignard solution and after a few minutes of reaction, the labelled carboxylic acid salt was reduced with lithium aluminum hydride (LAH). After removal of the solvent, the LAH-complex was hydrolysed and the solution transferred to boiling 54 % hydroiodic acid. The labelled product - the alkyl iodide - was then transferred to the reaction flask by the carrier gas and trapped. The reaction times counted from the release of ^{11}C-carbon dioxide was of the order of 6-20 min. The radiochemical yields varied between 40-95 % due to the purity of the Grignard reagent - old reagents contained other bases than the Grignard reagent thus giving larger amounts of ^{11}C-methyl iodide.



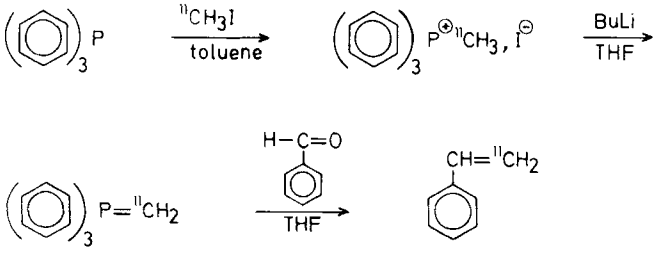
Scheme 1

The use of [1-^{11}C]ethyl iodide in synthesis is exemplified by the preparation of N-[1-^{11}C-ethyl]lidocain (2), a well-known analgetics, as shown in Scheme 2.



Scheme 2

Alkyl halides are also very useful in preparing other potential synthetic precursors as in the synthesis of phosphorous ylides. ^{11}C-Methyl iodide, prepared as described elsewhere (3), was trapped in a solution of triphenylphosphine in toluene and then the phosphorous ylide was generated by addition of butyl lithium. Using this ylide, ^{11}C-styrene was labelled as shown in Scheme 3 in 60 % radiochemical yield within 20 min. (4).



Scheme 3

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PREPARATION OF A POTENTIAL MARKER FOR GLIAL CELLS — (N-methyl-^{11}C)RO5-4864

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Many benzodiazepines, and diazepam is a well known example, bind with high affinity to pharmacologically active receptors in the mammalian brain. Recent studies (1) provide evidence that these receptors belong not to a single homogeneous population, but to multiple populations, each associated with particular cells or tissues. Thus, though the benzodiazepine, RO5-4864 (7-chloro-1,3-dihydro-1-methyl-5-(p-chlorophenyl)-2H-1,4-benzodiazepin-2-one) (1), differs from diazepam (2) only by possessing a p-chloro-substituent, it has been shown that RO5-4864 displaces diazepam from receptors on non-neuronal tissue only. This observation and other evidence (2) indicated that carbon-11 labelled RO5-4864 would act as a marker for glial cells and would therefore have value for the study of regional cerebral gliosis by means of positron emission tomography. Accordingly we have devised a method for preparing carbon-11 labelled RO5-4864 in a form suitable for clinical use. This method involves the N-methylation of nor-RO5-4864 (3) with (^{11}C)iodomethane, and is analogous to the preparations of (N-methyl-^{11}C)diazepam and (N-methyl-^{11}C)flunitrazepam reported by Maziere et al. (3).

The precursor, nor-RO5-4864, was prepared from 5,4'-dichloro-2-aminobenzophenone (19 mmol) (4) and glycine ethyl ester hydrochloride (28 mmol) by a modification of the reported method (5). The structure of the product (m.p. 249 — 250 °C; lit. (5) m.p. 247 — 248 °C) was confirmed by ^{1}H nmr spectroscopy, ir spectroscopy and tlc.

For the radiosynthesis, (^{11}C)iodomethane (prepared as reported by Turton et al. (6)),is collected in cold (0 °C) acetone (0.5 mL) and added to a magnetically stirred solution of nor-RO5-4864 (1 mg) in acetone (0.5 mL) and aqueous sodium hydroxide solution (10 M; 10 µL). This solution is sealed within a reaction vessel (vol. ca 5 mL) and heated at 100 °C for 4 min. Then the reaction mixture is cooled to room temperature, diluted with pentane (10 mL) and loaded onto a silica gel cartridge (Sep-pak; Waters Associates), which is subsequently eluted with diethyl ether (5.0 mL). The ethereal eluate is reduced to ca 0.5 mL by evaporation at 50 °C and injected onto a silica gel column (30 cm X 0.7 cm i.d.; "Porasil", Waters Associates) eluted with diethyl ether at 4 mL/min. (N-methyl-^{11}C)RO5-4864 (4) (retention time, 7.6 min) elutes ahead of nor-RO5-4864 (retention time, 10 min).

(N-methyl-^{11}C)RO5-4864, prepared in this manner, has been shown to be radiochemically and chemically pure by analytical hplc and tlc, using authentic RO5-4864 as reference material. Furthermore, it has been shown that the conditions of the labelling reaction, when applied on a macroscale, afford RO5-4864 in good yield from non-radioactive iodomethane.

(N-methyl-^{11}C)RO5-4864 is formulated for intravenous injection by rotary evaporation to dryness, addition of ethanol (0.1 mL) and human serum albumin solution (10% w/v; 5 mL), and finally millipore filtration (0.22 µm pore size, Millex GS, Millipore Corporation).

The procedure requires 40 min from the end of radionuclide production and provides (N-methyl-^{11}C)RO5-4864 for injection in 27% radiochemical yield (from (^{11}C)carbon dioxide, corrected for decay). Analytical hplc using detectors for both radioactivity and mass (by absorbance at 240 nm) indicates that the specific activity of (N-methyl-^{11}C)RO5-4864 prepared by the above procedure is 1.9 — 3.7 GBq/µmol (50 — 100 mCi/µmol) prior to formulation.

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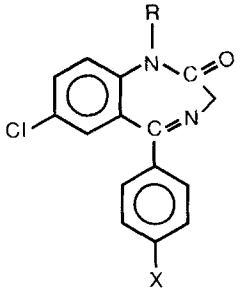

(1) X = Cl, R = Me
(2) X = H, R = Me
(3) X = Cl, R = H
(4) X = Cl, R = $^{11}CH_3$

A MODIFIED PROCEDURE FOR THE PREPARATION OF THE RADIOPHARMACEUTICAL, 3-O-(^{11}C)METHYL-D-GLUCOSE

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3-O-(^{11}C)Methyl-D-glucose (4) is an analogue of glucose that is used with positron emission tomography to study glucose transport in heart and brain (1,2). The method (1) reported for the preparation of this radiopharmaceutical involves the conversion of 1,2:5,6-diisopropylidene-D-glucose (1) into the corresponding oxyanion (2) by prolonged reaction (1 – 3 days) with potassium in diethyl ether, reaction of the oxyanion with (^{11}C)iodomethane and acid hydrolysis of the product. 3-O-(^{11}C)Methyl-D-glucose is then isolated by preparative hplc using acetonitrile – water (4:1 v/v) as eluent. We have modified this procedure to ease the preparation of the required oxyanion (2) and to simplify the work-up, purification and formulation of the radiopharmaceutical.

The basis of our modified procedure is the formation of the oxyanion (2) by the rapid reaction of compound (1) (ca 30 mg) with sodium hydride (ca 30 mg) in tetrahydrofuran (1 mL) at 100 °C. For the radiosynthesis the oxyanion solution and (^{11}C)iodomethane (prepared as reported by Turton et al.(3)) are mixed and then heated in a sealed vessel at 100°C for 10 min. The reaction mixture is worked up by addition of pentane (10 mL), elution of the resultant suspension through a disposable silica gel cartridge (Sep-pak; Waters Associates) and evaporation of the eluate to dryness. The residue (3) is then hydrolysed with a mixture of hydrochloric acid 1.2 M (0.4 mL) and ethanol (0.2 mL) at 100 °C for 5 min. Then the hydrolysate is neutralised by passage through a column of ion retardation resin (AG 11A8, Bio-Rad Laboratories; bed volume, 1.2 mL). The radioactive product is eluted with water (0.8 mL) and then injected onto an Aminex HPX - 87P column (30 cm x 7.8 mm; Bio-Rad Laboratories) eluted with water at 0.8 mL/min. 3-O-(^{11}C)Methyl-D-glucose elutes with a retention time of 8 min, and is ready for injection after adjustment to isotonicity and millipore filtration (pore-size, 0.22 μm; Millex FS, Millipore Corporation).

3-O-(^{11}C)Methyl-D-glucose, prepared by this procedure, has been shown to be radiochemically pure by hplc on a 'Lichrosorb-NH_2' column (25 cm x 4 mm i.d.; Merck) eluted at 2 mL/min with acetonitrile-water (9:1 v/v) and by tlc on cellulose developed with pyridine/butanol/water (1:1:1 v/v).

From the end of radionuclide production the preparation takes ca 40 min and produces 3-O-(^{11}C)methyl-D-glucose for injection in 49% radiochemical yield (from (^{11}C)iodomethane, corrected for decay), a value somewhat greater than that (35%) of the original method (1). Work is in progress to optimise the procedure and to improve the radiochemical yield.

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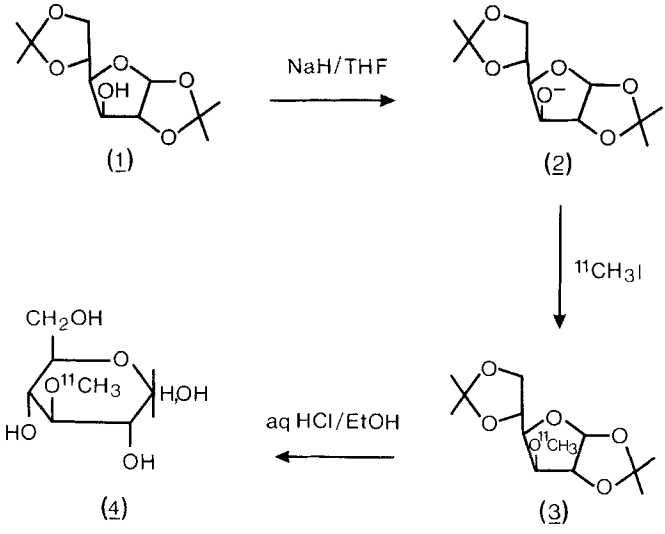
NaH/THF
$^{11}CH_3I$
aq HCl/EtOH
(1)
(2)
(3)
(4)

(^{11}C)-1-GLUCOSE AND MANNOSE AS SPECIFIC TUMOR MARKERS

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Shiue and Wolf (1) have reported the preparation of ^{11}C-1-glucose and ^{11}C-1-mannose mixture by the Kiliani-Fischer cyanohydrin synthesis method, but it is not easy to separate the two isomers for the preparative purpose. According to our observation that both ^{14}C-1-glucose and ^{14}C-1-mannose exhibited a characteristic behavior in tumors after their intravenous injection to tumor-bearing rats (2) (Fig. 1), we intended to visualize tumors in vivo by using the mixture of ^{11}C-1-glucose and ^{11}C-1-mannose.

An automatic apparatus was set up which covered the complete sequence of ^{11}C-cyanide preparation and its selective trapping, addition of arabinose to water-dissolved cyanide and maintenance of neutral pH during the formation of nitriles, acidification of nitriles to pH 4, transport of them to an autoclave to which a high-pressure H_2 and palladium catalyst could be introduced for reduction, and finally takeout of the product. The solution of the product was mixed with dry powder of Dowex 50 (H^+ form) and Dowex 1 (OH^- form), and then shaken and filtered through a Millipore filter. Starting from 100 mCi of ^{11}C-cyanide, about 9 mCi of ^{11}C-glucose-mannose mixture was thus obtained in 30 minutes. The filtrate (~7 ml, transparent, colorless, pH 7) was cyanide-free and contained the above two sugars in the ratio of about 1:3 as tested in a HPLC.

The basis for our expectation of specific visualization of tumors with these compounds was the cumulative uptake of radio-carbon in tumors owing to the metabolic trapping of the label in the tumor-specific large lactate pool. An extensive accumulation of radioactivity in lactate of tumors was proved in our experiment after the intravenous injection of ^{14}C-1-glucose and ^{14}C-1-mannose separately in rats. (Another example of the cumulative uptake of ^{14}C was observed only in the brain and the mechanism of it was ascribed to the metabolic trapping of ^{14}C in the tumor-specific glucogenic-amino-acids pool by chemical analysis.)

A large-field scintillation camera fitted with a 5-cm thick parallel-hole collimator was set to discriminate the 511-keV photon. The camera was interfaced to a digital computer, and scintigrams were digitized in a 64 X 64 matrix. Ten rabbits, average weight of 2.7 kg, with VX2 carcinoma, intramuscularly transplanted in the proximal part of the foreleg and grown up to 10–20 cm^3, were anesthesized with Nembutal and placed under the camera in the supine position. The ^{11}C-labeled glucose and mannose mixture (5–7 mCi) was injected to each of them from the ear vein, and immediately a total of 150,000 counts were collected (~15

seconds) and the image was stored. Ten minutes afterwards another image was taken with the same number of total counts. Images were processed in the computer by subtracting the first image from the second one, pixel by pixel, while the negative numbers were made nul. It was evident that the tumor and the brain were specifically visualized in the subtracted image (Fig. 2). It was possible also to reconstruct the tumor image after eliminating the brain area at first by operating the ROI setting and re-balancing the total counts of the first and second images in the computer before the subtraction. This procedure was sometimes necessary when the tumor was very small in size and faded out due to the interference of the brain counts. A similar situation arose infrequently when the urinary bladder accumulated radioactivity as ^{11}C-bicarbonate in urine.

Our injection solution was not toxic at all in animals. This radiopharmaceutical will exhibit its usefulness most when it is placed in a positron-CT setting. We are now planning a clinical application.

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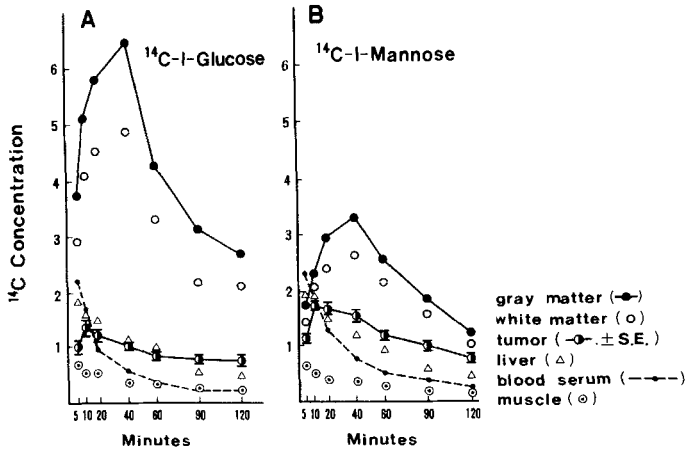

Fig. 1. Distribution of ^{14}C in tumor-bearing rats (Walker 256 carcinosarcoma) after i.v. injection of ^{14}C-1-glucose (A) or mannose (B) (2).

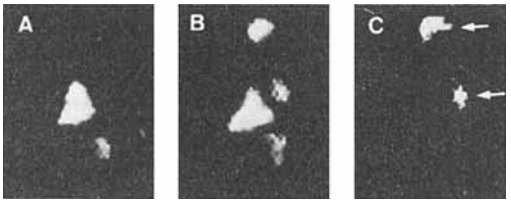

Fig. 2. Digitized scintigrams obtained from a rabbit with VX2 tumor on the right upper foreleg. Scintigrams shown are those obtained immediately after i.v. injection of ^{11}C-1-glucose-mannose (A), 10 minutes thereafter (B) and with subtraction technique (C). Brain and tumor are indicated by the upper and lower arrows respectively.

SYNTHESES OF ^{18}F-DEOXY-ALDOHEXOSES AND THEIR COMPARATIVE STUDY

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^{18}F-2-Deoxy-2-fluoro-D-glucose (^{18}F-FDG) is well known as the excellent radiopharmaceutical, which has been widely used for the study of glucose metabolism (1). ^{18}F-2-Deoxy-2-fluoro-D-mannose (^{18}F-FDM) is also the useful cancer diagnosis agent (2). For the research of new positron emitting radiopharmaceuticals, a series of ^{18}F-deoxy-aldohexoses have been synthesized and the comparative study of their biodistributions has been performed.

^{18}F-2-Deoxy-2-fluoro-D-galactose (^{18}F-FDGal) (II), ^{18}F-2-deoxy-2-fluoro-D-altrose (^{18}F-FDA) (V) and ^{18}F-2-deoxy-2-fluoro-L-glucose (L-^{18}F-FDG) (VIII) were synthesized by the reaction of corresponding tri-O-acetyl aldohexals with ^{18}F-F_2 (Fig. 2). These compounds were synthesized by the similar method to ^{18}F-FDG synthesis (Fig. 1) (3,4). In the reaction of tri-O-acetylgalactal (I) with ^{18}F-F_2, ^{18}F-2-deoxy-2-fluoro-D-talose (III), which was an isomer of ^{18}F-FDGal, was little formed and ^{18}F-2-deoxy-2-fluoro-D-allose (VI) was not obtained in the ^{18}F-FDA synthesis. The radiochemical purities of ^{18}F-FDGal, ^{18}F-FDA and L-^{18}F-FDG were >95 %, >99 % and >98 %, respectively. The total time required for the syntheses of these radiopharmaceuticals was within 120 min from the end of bombardment (EOB). Their radiospecific activities (mCi/mg) at EOB were found as follows; ^{18}F-FDG : 18-25, ^{18}F-FDM : 18-25, ^{18}F-FDGal : 11-14, ^{18}F-FDA : 15-19, L-^{18}F-FDG : 11-12.

The biodistributions of ^{18}F-FDGal, ^{18}F-FDA and L-^{18}F-FDG were studied. ^{18}F-FDA was rapidly cleared away from all organs. L-^{18}F-FDG was also rapidly excreted from the kidney and moderately from all the other tissues. ^{18}F-FDGal was highly accumulated in the liver. Its liver uptake showed a peak at about 30 min followed by a retention over the next 120 min. The blood clearance was very rapid and after 60 min, the blood time-activity curve was flat. The uptake levels of other organs were extremely lower than that of the liver (Fig. 3). It has been suggested that the metabolism of ^{18}F-FDGal can be stopped at the phosphorylation step like that of ^{18}F-FDG because of the absence of OH group at the 2-position.

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Fig. 1 Synthetic Method of ^{18}F-Deoxy-aldohexoses

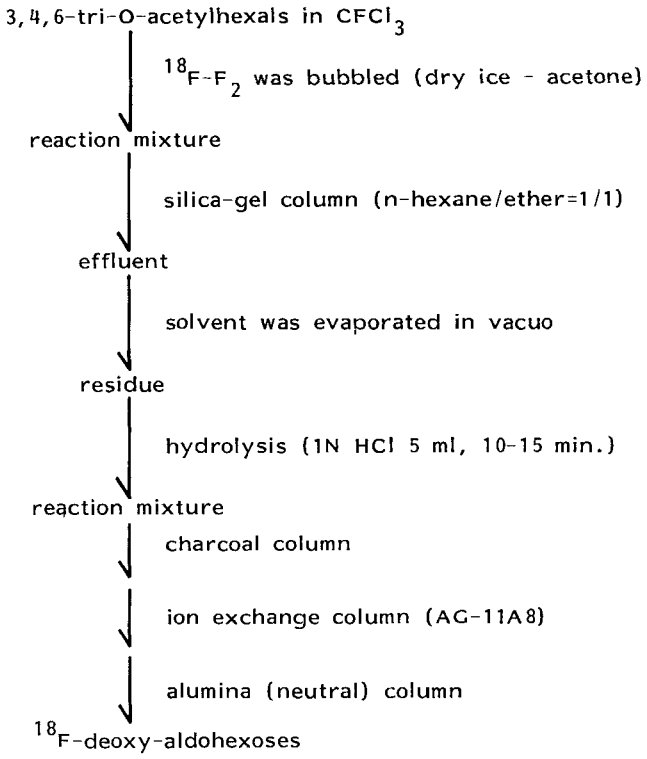


Fig. 2 Syntheses of ^{18}F-FDGal, ^{18}F-FDA and L-^{18}F-FDG

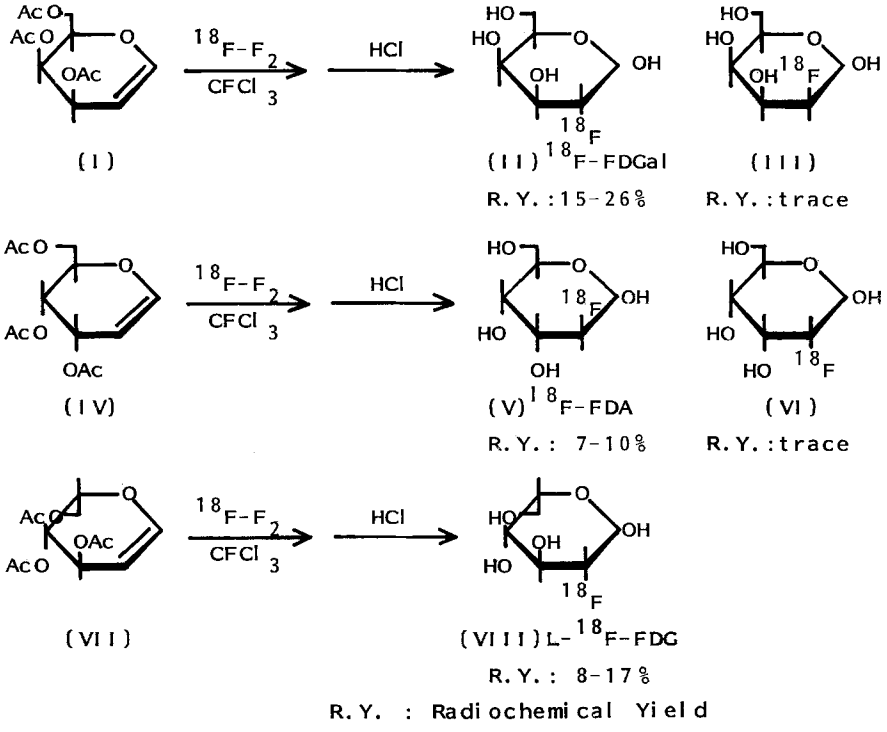
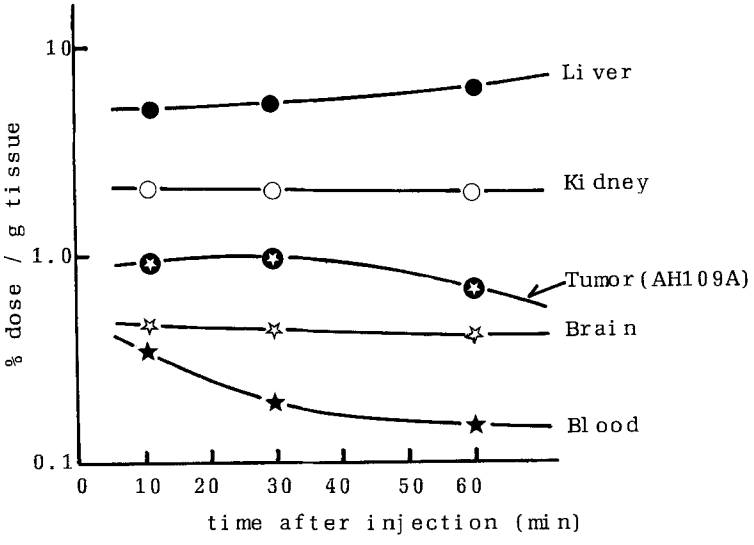


Fig. 3 Time-activity Curves of ^{18}F-FDGal in AH109A Bearing Rats



SYNTHETIC ROUTES FOR LABELING OF 2-DEOXY-2-FLUORO-D-HEXOSES WITH FLUORINE-18

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The increasing importance of the glucose analogs in nuclear medicine has made it attractive to investigate new synthetic routes to 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG)(1). The improved procedures based on ^{18}F-fluoride ion include the nucleophilic displacements by fluoride of methyl 4,6-O-benzylidene-3-O-methyl-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranoside (1b,d) and methyl 4,6-O-benzylidene-β-D-mannopyranoside 2,3-cyclic sulfate (1f,g). In both cases, we sometimes encountered with the lack of reproducibility in the stage of removing the protecting groups from the fluorinated intermediate compounds in non-radioactive runs. Because of the advantages in radiopharmaceutical synthesis based on ^{18}F-fluoride ion, we have developed an alternative approach to FDG, starting from methyl 4,6-O-benzylidene-3-O-benzyl-2-O-(trifluoromethanesulfonyl)-β-D-manno-pyranoside (I) which was chosen as a triflate having a more removable protecting group for C_3-hydroxy.

Treatment of the triflate (I) with CsF in DMF at 145°C for 30 min and Et_4NF in acetonitrile at 50°C for 15 min gave the 2-deoxy-2-fluoro-D-glucopyranoside (II) in 42 and 57% yield, respectively. Subsequent hydrolysis of (II) with 50% CH_3SO_3H afforded FDG in 70% yield. The advantage in the use of the triflate (I) as a precursor lies in the ease of deblocking. This method seems to be suitable for an alternative radiopharmaceutical synthesis of ^{18}F-FDG.

2-Deoxy-2-fluoro-D-mannose (FDM) has been used extensively for studies of glycoprotein biosynthesis and function (2), and, more recently, its ^{18}F-labeled analog has been reported to be a useful radiopharmaceutical for cancer diagnosis in humans by positron emission tomography (3). Exisiting synthetic route to FDM including either electrophilic addition of F_2 or CF_3OF to 3,4,6-tri-O-acetyl-D-glucal has no practical utility for useful amount of FDM or ^{18}F-labeled analog because FDM is produced as a side product in these reactions (4). We have also developed the synthetic routes suitable for labeling of FDM with ^{18}F by the facile displacements of the C_2-triflate function of methyl β-D-glucopyranosides, in which the hydroxy functions were protected by methyl (III), benzyl (IV), or acetyl group (V) at C_3 with 4,6-O-benzylidene moiety.

Fluorinations of the triflates (III) and (IV) with tetra-n-alkylammonium fluorides proceeded smoothly, requiring relative short heating for completion, as expected, to give exclusively the fluorinated intermediates (VI) and (VII) in the yields listed in Table. Similarly, the triflate (V) afforded also totally a high yield of the fluorinated mannopyranosides (VIII) and (IX), as the deacetylated (IX) as a side product was considered to be one of the useful intermediates leading to FDM.

Hydrolysis of (VII) with 30 or 50% CH_3SO_3H under reflux at 20 min gave exclusively the required FDM in the isolated yield of 85%. Hydrolysis of a mixture of (VIII) and (IX) with 5N HCl under reflux at 20 min also gave FDM in 82% yield. On the other hand, attempts to convert (VI) in a single reaction-step into FDM with acidic reagents such as 50% CH_3SO_3H, $B(OCOCF_3)_3$-CF_3COOH, Nafion-H, and BBr_3 were unsuccessful, resulting in resistance of the removal of the glycosidic methyl group and/or the 3-O-methyl group, or in defluorination of the product. The synthetic sequences (IV) → (VII) → FDM and (V) → (VIII) + (IX) → FDM could be easily adaptable for the preparation of the ^{18}F-labeled FDM.

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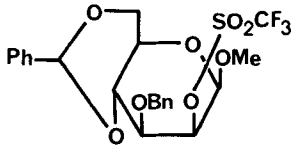
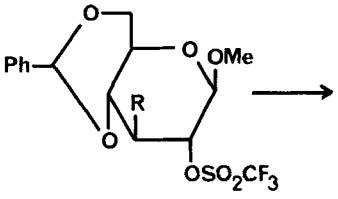
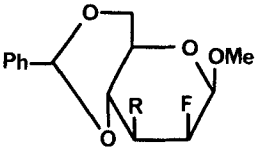


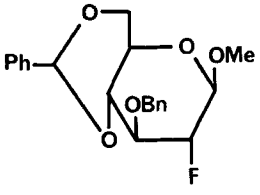
(I)



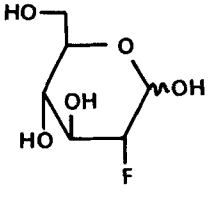
(III) R = OMe
(IV) R = OBn
(V) R = OAc



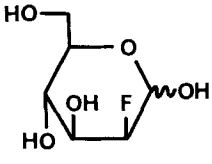
(VI) R = OMe
(VII) R = OBn
(VIII) R = OAc
(IX) R = OH



(II)



F D G



F D M

Table Fluorination of methyl 4,6-O-benzylidene-2-O-trifluoromethanesulfonyl-β-D-pyranoside derivatives

Triflate	Fluorinating agent	Solvent	Time	React.temp.	Product (isolated yield %)
I	CsF	DMF	30 min	145°C	II (42)
	Et_4NF	CH_3CN	15 min	50°C	II (57)
III	Bu_4NF	CH_3CN	40 min	81°C	VI (81)
IV	Bu_4NF	CH_3CN	30 min	81°C	VII (77)
	Me_4NF	CH_3CN	80 min	81°C	VII (68)
	Et_4NF	CH_3CN	40 min	81°C	VII (73)
V	Me_4NF	CH_3CN	30 min	81°C	VIII (51), IX (30)

THE USE OF SEP-PAK's* FOR A SIMPLIFIED SYNTHESIS OF 2-DEOXY-2(^{18}F) FLUORO-D-GLUCOSE.

M.J. Adam, T.J. Ruth, S. Jivan and B.D. Pate. The UBC/TRIUMF Program on Positron Emission Tomography, TRIUMF and the University of British Columbia, Vancouver, B.C. V6T 2A3, Canada.

2-Deoxy-2(^{18}F) fluoro-D-glucose has been prepared by a rapid, simple method based on acetyl hypofluorite (1,2) and reverse-phase C-18 SEP-PAK* chromatographic technology. The acetylated fluoro-sugar produced from the reaction of tri-acetyl glucal (TAG) and ^{18}F-acetyl hypofluorite in acetic acid was effectively extracted from the neutralized reaction mixture by C-18 SEP-PAK cartridges. The product was washed off the cartridges with diethyl ether and then hydrolyzed by HCl. After hydrolysis the product was purified by passage through ion retardation resin, an alumina SEP-PAK and another C-18 SEP-PAK. The radiochemical purity was 98% and the radiochemical yield was 28% EOB with a synthesis time of 35 minutes. Between 20 and 32 mCi of final product (end of synthesis, EOS) are produced depending on irradiation conditions (15-20 μA-h). A schematic of the remotely operated system is shown in figure 1. Table I illustrates the reproducibility of the system.

* Waters Associates (Milford, Mass.)

(1) Adam M.J., J. Chem. Soc. Chem. Commun., 730 (1982).
(2) Shiue C.Y., Salvadori P.A., Wolf A.P., et al. J. Nucl. Med., 23, 899 (1982).

TABLE I

Radioactivity Balance of Ten Patient Runs

ITEM	% Activity **
Charcoal-Sodalime	8.2 ± 1.6
Aqueous +	52.9 ± 1.9
C-18 SEP-PAK ++	36.0 ± 1.8
TOTAL	97.1 ***

** Corrected to EOS
\+ Trap G in Figure 1
++ Sum of items H, J to N in figure 1
*** The remaining ~3% activity in items A and B of figure 1

THE USE OF SEP-PAK's* FOR A SIMPLIFIED SYNTHESIS OF 2-DEOXY-2(^{18}F) FLUORO-D-GLUCOSE.

M.J. Adam, et al

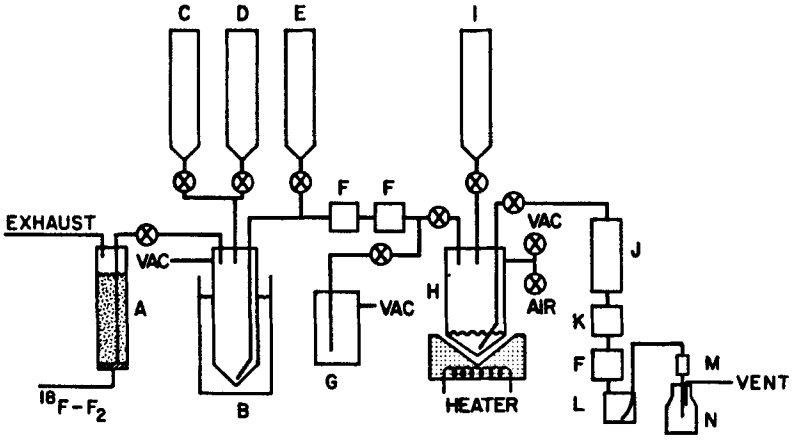


Fig. 1: System for remotely operated synthesis of ^{18}F-2FDG: A = acetyl hypofluorite vessel; B = TAG-hypofluorite reaction vessel and cooling water bath; C = ammonium hydroxide reservoir; D = water reservoir; E = ether reservior; F = C-18 SEP PAK cartridges; G = aqueous waste trap; H = hydrolysis vessel and heater; I = sterile, pyrogen free water reservoir; J = AG11-A8 ion retardation resin; K = alumina SEP PAK cartridge; L = NaCl vial; M = 0.2 μm Millifil filter; N = multi-injection vial.

NEW DEVELOPMENTS IN THE SYNTHESIS OF NO-CARRIER-ADDED (NCA) ^{18}F-LABELED ARYL FLUORIDES USING THE NUCLEOPHILIC AROMATIC SUBSTITUTION REACTION

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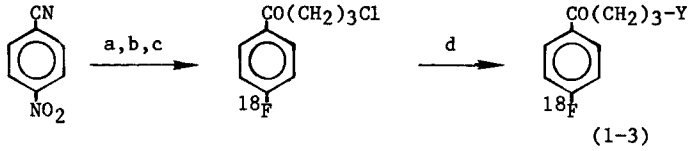
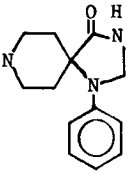
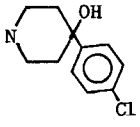
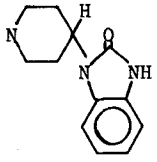
The nucleophilic aromatic substitution reaction has recently been applied to the synthesis of NCA ^{18}F-labeled aryl fluorides (1-4) resulting for the first time in the availability of practical quantities of some important radiotracers such as ^{18}F-labeled spiroperidol. In this reaction, a leaving group on an activated aromatic ring is displaced by ^{18}F-fluoride. The reaction is attractive because ^{18}F$^-$ is available in high yields, economically from recently developed small volume $H_2{}^{18}O$ targets, specific activities are very high and radiochemical yields are not limited. Furthermore, substitution is rapid and yields are high with simple substrates. Thus far, the most widely exploited leaving group is the nitro group and the most general application of this reaction has been to the synthesis of ^{18}F-labeled spiroperidol (1) for study of the dopamine receptor (5). Since this report, this general synthesis has been used to prepare practical yields of



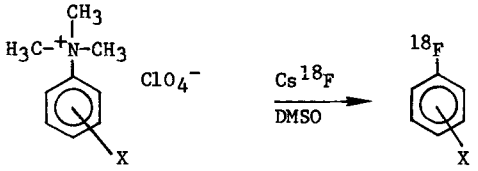
(1-3) (Eq. 1)

a. $Cs^{18}F$; b. ▷Li; c. HCl; d. YH,KI

(1) Y =  , (2) Y =  , (3) Y = 

two other ^{18}F-butyrophenone neuroleptics, [^{18}F]haloperidol (2) and [^{18}F]benperidol (3) (Eq. 1).

Although the nitro group displacement has shown considerable promise, its use requires moderately high temperatures, a limitation in applications where the substrate is thermally labile under the reaction conditions. In order to expand the scope of this reaction, we have investigated the reactivity of other nucleofugic groups with a view to identifying those which undergo the displacement reaction under milder conditions and yield reaction mixtures which were more amenable to rapid purification. We report here that aryltrimethylammonium perchlorates (6) activated by electron-withdrawing groups (p-NO_2, p-CN, p-$COCH_3$, and m-NO_2) undergo displacement by ^{18}F$^-$ (Eq. 2) and that this group surpasses NO_2 in ease of displacement.



(Eq. 2)

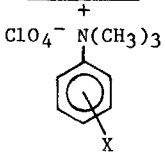
X = p-NO_2, p-CN, p-$COCH_3$, m-NO_2

Reactions of substituted aryltrimethylammonium perchlorates with NCA cesium [^{18}F]fluoride (7) in DMSO gave the corresponding ^{18}F-labeled aryl fluorides in 5-90% yield depending on the reaction temperature and the nature and the position of the activating group in the aromatic ring (Eq. 2, Table 1). For example, at 80° for 20 min, the relative extent of F-to-$^{+}$NMe$_3$ displacement fell in the order: p-NO_2 (70%) > p-CN (25%) > p-$COCH_3$ (10%) > p-CHO ($\ll$ 5%) $\simeq$ m-NO_2 ($\ll$ 5%). The nucleofugality of $^{+}$NMe$_3$ has also been shown to be higher than that of NO_2 as shown in Table 2. The yields of ^{18}F-labeled aryl fluorides also depend on the molar ratio of substrate to cesium carbonate (Table 3). This observation may be due to reaction of the substrate with cesium carbonate to form the free base. This effect was investigated with the p-cyano as the activating group.

In summary, the trimethylammonium group is more reactive than the nitro group in nucleophilic aromatic substitution reactions. Furthermore, because it is a salt, its removal from the aryl fluoride product is facilitated. Based on these initial studies, the application of this strategy to the synthesis of complex ^{18}F-labeled radiotracers is predicted to extend the utility of this reaction.

This research was carried out at Brookhaven National Laboratory under contract with the Department of Energy, Office of Health and Environmental Research and National Institutes of Health Grant No. 15380.

Table 1
Radiochemical Yield of F-18 Aryl Fluorides from the Displacement of a Trimethylammonium Group by ^{18}F-Fluoride[a]

Substrate  X	Temp (°C)	Product	Yield (%)
p-NO_2	40	4-[^{18}F]$C_6H_4NO_2$	10
	60		18
	70		30
	80		71
	120		91
	140		86
p-CN	80	4-[^{18}F]C_6H_4CN	24
	120		91
	140		76
p-$COCH_3$	80	4-[^{18}F]$C_6H_4COCH_3$	15
	140		35
m-NO_2	80	3-[^{18}F]$C_6H_4NO_2$	5
	140		51

[a] Reactions were run in DMSO, reaction time: 20 min. Substrate concentration: 10^{-4} mol ℓ^{-1}.

Table 2
Relative Yields of F-18 Aryl Fluorides from NO_2 VS $(CH_3)_3N^+$ as Leaving Groups at 80° and 140°

Substrate		Temperature (°C)	Product	Yield (%)
				
X	Y			
CN	NO_2	80	4-[^{18}F]C_6H_4CN	7
		140		40
	+			
CN	$N(CH_3)_3$	80	4-[^{18}F]C_6H_4CN	24
		140		61
NO_2	NO_2	80	4-[^{18}F]$C_6H_4NO_2$	50
		140		62
	+			
NO_2	$N(CH_3)_3$	80	4-[^{18}F]$C_6H_4NO_2$	55
		140		78

[a] Typical substrate concentrations: 3.6×10^{-3} M. [Substrate]/[Cs_2CO_3] ~ 2.

Table 3
The Influence of Cs_2CO_3 Concentration on Yield of p-Fluorobenzonitrile from p-Cyanophenyltrimethylammonium Perchlorate[a]

[Substrate]/[Cs_2CO_3]	Radiochemical Yield (%)
3.3	64
1.3	62
0.6	43
0.13	24

[a] All reactions were carried out at 140° with substrate concentration of 3.5×10^{-3} M.

(1) Cacace F., Speranza M., Wolf A.P., et al., J. Label. Compds. Radiopharm., 18, 1721 (1981).
(2) Cacace F., Speranza M., Wolf A.P., et al., J. Fluorine Chem., 21, 145 (1982).
(3) Attina M., Cacace F. and Wolf A.P., J. Chem. Soc. Chem. Comm., 108 (1983).
(4) Attina M., Cacace F. and Wolf A.P., J. Label. Cmpds. Radiopharm., 20, 501 (1983).
(5) Wolf A.P., Watanabe M., Shiue C.-Y., et al., J. Nucl. Med., 24, P52 (1983).
(6) Kevill D.N. and Shen B.W., J. Am. Chem. Soc., 103, 4515 (1981).
(7) NCA cesium ^{18}F-fluoride was prepared from ^{18}F-fluoride obtained via the $^{18}O(p,n)^{18}F$ reaction on a small volume $H_2{}^{18}O$ target (Wieland B. and Wolf A.P., J. Nucl. Med., 24, P122 (1983) by adding the $^{18}F^-$ to Cs_2CO_3 and evaporating the solution to dryness.

THE CHEMICAL PROPERTIES OF [^{18}F]-ACETYLHYPOFLUORITE IN ACETIC ACID SOLUTION

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In 1981 Rozen et. al. (1) reported the synthesis of CH_3COOF from F_2 and NaX (X=F, OAc, $OCOCF_3$) in a 9:1 freon-acetic acid mixture at -78°C in yields of 15-35% (2). Better yields were obtained by Fowler et. al. (3), who performed the synthesis of [^{18}F]-CH_3COOF at roomtemperature in CH_3COOH containing NH_4OAc (80% chemical yield). However, it appeared that the yield of [^{18}F]-CH_3COOF depended onthe amount of salt present during the synthesis, while the oxidising power of the fluorinating solution remained the same. Besides this, hypofluorites are postulated to contain a positively polarized fluorine atom, which has recently been questioned by Christe (4).

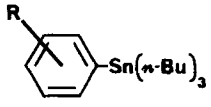
In order to get insight in the stability of CH_3COOF and in the mechanism of our newly developed [^{18}F]-fluorodemercuration method we have studied the organic products resulting from the reaction of the oxidising/fluorinating solution - obtained by flushing [^{18}F]-F_2 through a CH_3COOH/NH_4OAc solution - with cyclohexene (C_6H_{10}) as a model compound.
On reversed phase HPLC analysis six ^{18}F-compounds were observed in a total radiochemical yield of 25-30%. These compounds were identified by GCMS being two isomeric ^{18}F-cyclohexenes(~5%), two isomeric ^{18}F-CH_3-cyclohexanes(~10%) and the expected cis/trans ^{18}F-acetoxycyclohexanes(~15%). GCMS analysis also revealed the presence of an unlabelled compound(15-20%) identified as 2-acetoxycyclohexene. The same experiments performed with cyclohexane(C_6H_{12}) and benzene (C_6H_6) yielded, among others, acetoxycyclohexane and acetoxybenzene respectively. These results strongly suggest that the reaction of CH_3COOF -at least for non-activated compounds - for a great deal follows a radical reaction channel.

(1) S. Rozen, O. Lerman and M. Kol, J. Chem. Soc. Chem. Comm., 1981, 443.
(2) O. Lerman and S. Rozen, J. Org. Chem., 48, 724 (1983).
(3) J.S. Fowler, C-Y. Shiue, A.P. Wolf, P.A. Salvadori and R.R. McGregor, J. Lab. Comp. Radiopharm., 19, 1634 (1982).
(4) K.O. Christe, J. Fluor. Chem., 22, 519 (1983).

FLUORINATION OF AROMATIC COMPOUNDS BY CLEAVAGE OF ARYL-TIN BOND WITH (F-18)F_2 AND CH_3COOF.

M.J. Adam, B.F. Abeysekera, T.J. Ruth, S. Jivan and B. D. Pate. UBC/TRIUMF Program on Positron Emission Tomography, TRIUMF and the University of British Columbia, Vancouver, B.C. V6T 2A3, Canada.

Direct fluorination of aromatic nuclei is difficult since the reaction is usually accompanied by unselective, partial, or total replacement of hydrogen. By attaching the tri-n-butyltin moiety to one position of the ring one can achieve an enhanced reactivity and site selectivity toward electrophilic halogenation (1,2,3). The intent of this study was to demonstrate the utility of the fluorodestannylation reaction for fluorine labelling of aromatic compounds and to compare F_2 and acetyl hypofluorite as the fluorinating agents. Thus, eight stannylated aromatic compounds (1-8) were synthesized



1, R = 3,4-OMe 5, R = o - Me
2, R = p - OMe 6, R = H
3, R = p - Me 7, R = p - Cl
4, R = m - Me 8, R = p - F

via lithium halogen exchange of the bromo precursor and subsequent transmetallation using tri-n-butyltin chloride. The stannylated substrates were treated with F-18 F_2 at -78° C and CH_3COOF (4) at room temperature. Both reagents gave good yields of labelled aryl fluorides. Overall, acetyl hypofluorite gave more consistent yields (70%), while F_2 gave more variable yields (54-95%).

This method is currently being extended to label more complex systems such as L-dopa with F-18 for brain studies with positron emission tomography.

(1) Adam M.J., Pate B.D., Ruth T.J., Berry J.M., and Hall L.D., J. Chem. Soc., Chem. Commun., 733 (1981).
(2) Adam M.J., Ruth T.J., Pate B.D., and Hall L.D., J. Chem. Soc., Chem. Commun., 625 (1982).
(3) Seitz D.E., Tonnesen G.L., Hellman S., Hanson R.N., and Adelstein S.J., J. Organomet. Chem., 186, C33 (1980).
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TABLE I

Cleavage of compounds 1-8 with ^{18}F-F_2 or $CH_3COO^{18}F$

Product from	F_2	r.c. yields % CH_3COOF
1	56	68
2	72	78
3	82	72
4	58	71
5	54	57
6	72	72
7	>95	68
8	>95	73

REGIOSELECTIVE SYNTHESES OF [F-18]ARYL FLUORIDES VIA EASILY ACCESSIBLE [F-18] N-FLUORO-N-ALKYLSULFONAMIDES.

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UCLA School of Medicine, Division of Biophysics, Los Angeles, California 90024

Aromatic radiofluorination has recently received much attention due to the increasing interest on the synthesis of F-18 labeled ligands for neurotransmitter localization in animals and man using positron emission tomography (PET). However, and except for a few examples, most of this attention has been focused on nucleophilic displacements with [F-18] fluoride ion on a variety of leaving groups attached to the aromatic rings (1-4). Some of these reactions have been studied mechanistically (4-6) and extended to the synthesis of F-18 labeled spiperone, a positron emitting labeled dopamine antagonist (6-8).

Recent work by W. Barnette (9) on the use of N-fluoro-N-alkylsulfonamides for the selective fluorination of carbanions prompted us to undertake a careful study on the potential of this reaction for radiofluorination. This preliminary work reports on the generation of [F-18] N-fluoro-N-alkylsulfonamides and their utilization as reagents for aromatic radiofluorination. When $[F\text{-}18]F_2$ diluted in neon (0.2%, v/v), obtained from the Ne-20 (d,alpha) nuclear reaction, was allowed to react with N-alkylsulfonamides, [F-18]N-fluoro-N-alkylsulfonamides were produced in good yields. [F-18] fluorobenzene (1) was obtained in 60% radiochemical yield by treatment of [F-18]N-fluoro-N-endo-norbornyl(p-tolyl)sulfonamide (2) with phenylmagnesium bromide. In an identical manner, phenyllithium was rapidly converted to 1 with similar yields as shown by HPLC analysis (Ultrasil octyl column, 25 cm; solvent: methanol, 75%, water, 25%; flow rate, 1 ml/min; retention time, fluorobenzene, 5.7 min, N-fluorosulfonamide (2), 10.8 min). [F-18]N-fluorosulfonamide 2 was used in these reactions to reduce the possibility of HF β-elimination from the reagent in the strongly basic media.

The observed reactivity of the radiolabeled N-fluoro-N-alkysulfonamides and the regioselectivity of the reaction are attractive features of these electrophilic aromatic substitution reactions. The scope and limitations of this novel radiofluorination procedure have yet to be evaluated, but the reaction shows great potential for the synthesis of [F-18]arylfluorides of moderate specific activity (1-10 Ci/mmol). Such a method can lead to new ways to synthesize a variety of radiotracers (e.g., enzyme inhibitors, substrate analogs, and neurotransmitter ligands) for application in PET.

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(3) Attina M., Cacace F. and Wolf A.P.: J. Chem. Soc. Chem. Commun., 108, (1983).
(4) ibid: J. Label. Compds. Radiopharm., 20, 501, (1983).
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(7) Welch M.J., Kilbourn M.R., Mathias C.J., Mintun M.A. and Raichle M.E.: Life Sci., 33, 1687 (1983).
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(9) Barnette W.: E.I. duPont de Nemours and Co., private communication.

A FAST, HIGH YIELD SYNTHESIS OF ^{18}F-FLUOROMETHANE FROM $^{18}F-F_2$

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Ostmerheimer Strasse 200, D-5000 Köln 91

Fluoromethane seems to be a very promising tracer for measuring cerebral blood flow by positron emission tomography(2).
The method, first introduced by Gatley(1) and Holden(2), has several major advantages:
The label F-18 has ideal physical properties for high resolution measurements in the brain.
Fluoromethane is not metabolized and leaves the body via respiration in a short time(2). A carrier-free product is not needed.
The high Ostwald solubility allows a high fraction of the administered dose to enter the circulation and thus helps to improve image quality.
Blood sampling and monitoring of the expired air together allow a correct determination of the input function,whichprovides the basis for quantitative measurements.

Therefore, an on-line method to produce high amounts of F-18-fluoromethane for CBF-measurements with the positron camera (PC 384,Scanditronix) of the MPI was developed.
F-18 labelled F_2 is produced by deuteron irradiation of a neon gas target containing 0.25% F_2-carrier at the Jülich compact cyclotron CV 28. After the irradiation, the active F_2 is bubbled slowly through a suspension of 100mg Ag_2O and 20mg tetraethylammonium hydroxide in dry acetonitril. In this way, the molecular fluorine is directly converted into anhydrous F^- without an additional drying step.All the reactive fluorine is collected under these conditions. Methyl iodide in dry acetonitrile is added, the closed vessel is heated to 120°C for 5 min and cooled again by a stream of air.Typically 90% of the starting activity can be transferred to a 50ml gas-tight syringe by passing air through the solution.Acetonitrile and residual methyl iodide are removed by filtering the gas stream over activated charcoal.
A schematic view of the setup is shown in the figure below.

No radioactive impurities could be detected by gas chromatography on a porapak S column. Total synthesis time fom EOB is about 25 min.
The process is remotely controlled and can be easily automated.

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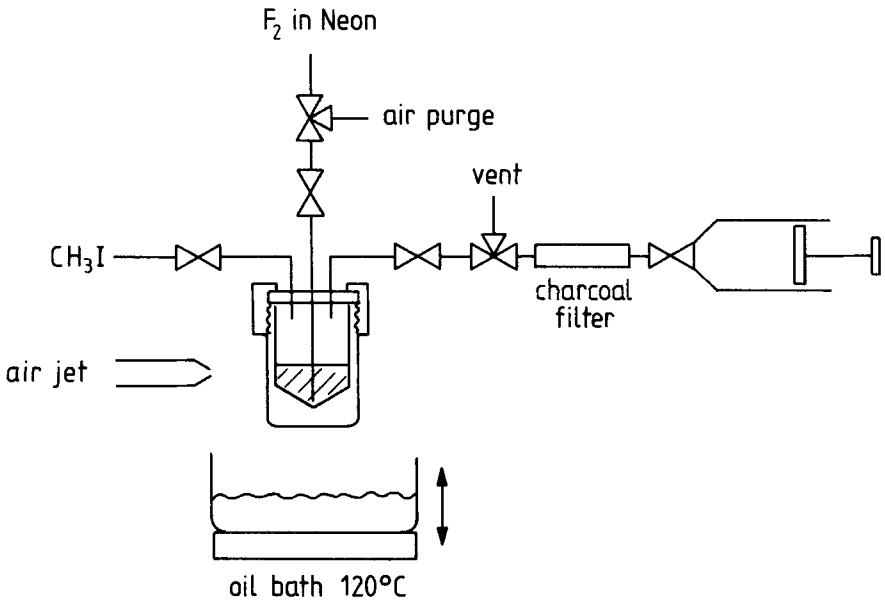

Schematic drawing of the apparatus for production of F-18 CH_3F

AUTOMATED SYNTHESIS OF ^{18}F-5-FLUORO-2'-DEOXYURIDINE

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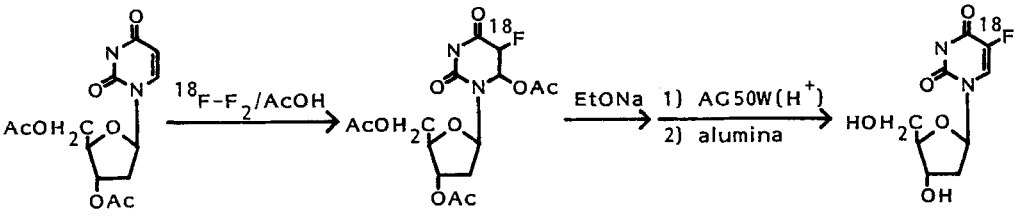
Cyclotron and Radioisotope Center, Tohoku University Sendai, 980, Japan

As 5-fluorouracil(FUra) and its derivatives used in tumor chemotherapy are related in nucleic acid metabolism, the tumor uptakes of ^{18}F-labeled compounds have been investigated(1-2), and ^{18}F-FUra was applied to human study(3). We have also studied the tumor uptakes of ^{18}F-FUra, ^{18}F-5-fluoro-2'-deoxyuridine(^{18}F-FdUrd) and ^{18}F-5-fluorouridine(^{18}F-FUrd) and confirmed that these would be usefull for the tumor detection in human, especially tumors in the brain and lung, by positron emission tomography and that the ^{18}F-FdUrd would be more suitable among three pyrimidines(4). For routine production of the ^{18}F-FdUrd we have developed the automated synthesis system.



^{18}F-FdUrd was synthesized by the method of Shiue et al.(5) with some modifications. The system developed for the computer controlled automated synthesis of ^{18}F-2-deoxy-2-fluoroglucose (6) is applied to the production of ^{18}F-FdUrd and consists of the synthesis unit, the ^{18}F-F production unit, the leak test unit and the controller unit. The system for the production is shown schematically in Fig 1.
The controller unit consists of a microcomputer, a graphic printer, a color CRT, interfaces and a radioactivity monitor.
The synthesis unit is compact(a size of 30x40x30cm) and is installed in a shielded box. Synthetic process consists of three steps: (1) addition of ^{18}F-F_2 to 3', 5-di-O-acetyl-2'-deoxyuridine(diAcdUrd), (2) hydrolysis of the ^{18}F-adduct and (3) chromatographic purification. ^{18}F-F_2 is produced by deutron irradiation(an incident energy of 15.7 MeV) of a Ne target containing 0.1% F_2 at 25 kg/cm^2 with the ^{20}Ne(d, α)^{18}F reaction. After the irradiation, the ^{18}F-F_2 is bubbled into 4 ml gracial acetic acid containing 15-20 mg diAcdUrd in a vessel A with a flow rate of 500 ml/min at room temperature. The reaction mixture is transferred into the vessel B. Acetic acid is then injected into the vessel A for washing and transferred into the vessel B. In the second part of the unit the apparatus that rotates the bottom of the vessel B horizontally is designed to evaporate solvents rapidly but not vigorously at 75°-80°C under reduced pressure or to dissolve residue completely. The solvent of ^{18}F-adduct is evaporated. The residue is dissolved in 4 ml C_2H_5OH containing 0.05 g C_2H_5ONa and hydrolyzed at 75°-80°C for 5 min to give ^{18}F-FdUrd. After the evaporation, the residue is dissolved in 2 ml water and transferred to the serial combined of AG 50Wx8(H^+ form, 1.6x5cm) and neutral alumina(1.6x11cm). The solution is then passed through the columns. The vessel B and the columns are washed with 2 ml water followed by elution with water. On AG50W the solution is neutralized and on alumina the ^{18}F-FdUrd is purified. Finally the fraction of 25-45 ml is collected as the ^{18}F-FdUrd (Fig.2). The transfer of all fluids is controlled by applying He pressure with solenoid and pinch valves. Each synthetic procedure described above

is controlled by a computer with a timer, optical liquid level sensors or a radioactivity monitor.
The radiochemical purity was determined by radio-high performance liquid chromatography on μBondapak C18(Waters) with a solvent system of CH_3OH and water(10:90) with a flow rate of 2 ml/min. The apyrogenicity was confirmed by Limulus Amebocyte Lysate Test (Mallinckrodt).

The synthesis of ^{18}F-FdUrd was carried out within 60 min after the 60 min-deutron irradiation with 12 μA. At the end of synthesis 20-35 mCi of ^{18}F-FdUrd was obtained as a sterile and apyrogenic solution(eluate in the (b) region in Fig 2) with radiochemical purity of over 99% and with radiochemical yield of 15-25%.
^{18}F-FdUrd was purified on an alumina column with water instead of a silica gel column with organic solvent. The use of the combined columns for neutralization and purification makes the automated procedures easier.
Analysis of the eluates in (a) and (b) regions in Fig 2 shows that most radioactive impurities are eluted earlier than the ^{18}F-FdUrd.
^{18}F-FdUrd was separated from 2'-deoxyuridine and the eluate in the (b) resion gave higher radiochemical purity(over 99%)
This system was applied to the production of ^{18}F-FUra by using the same program and could give uracil-free ^{18}F-FUra with radiochemical yield of 43% and with radiochemical purity of over 99%.
In conclution this automated synthesis system is suitable for the production of the ^{18}F-FdUrd in routine clinical study and will be applied to other ^{18}F-FUra derivatives.

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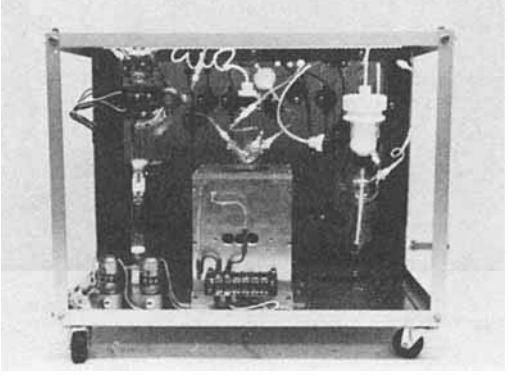

Synthesis Unit

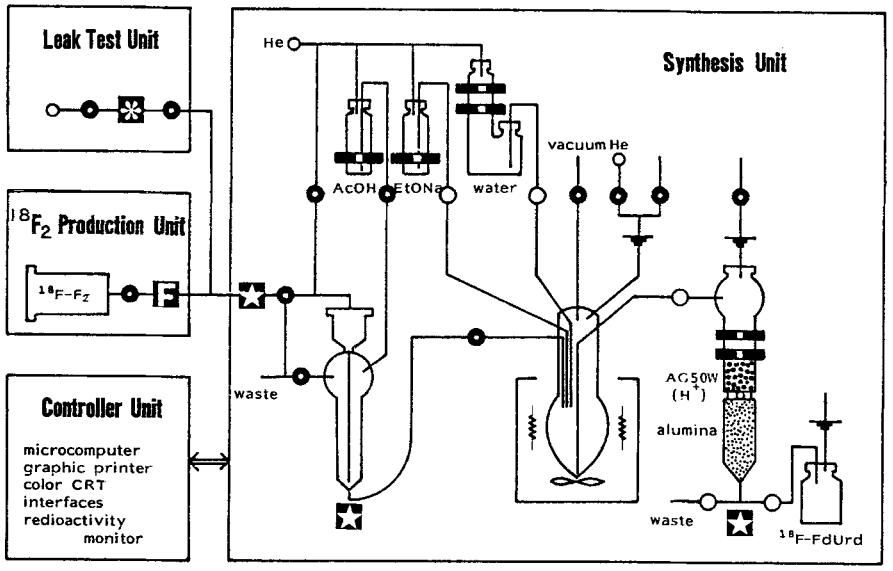

Fig.1 Flow chart of ^{18}F-5-fluoro-2'-deoxyuridine productionsystem. ●:solenoid valve, ○:pinch valve, ▬:optical liquid level sensor, ▶:membrane filter, ⊠:radioactivity detector, Ⓕ:flow controller, ⊛:pressure sensor.

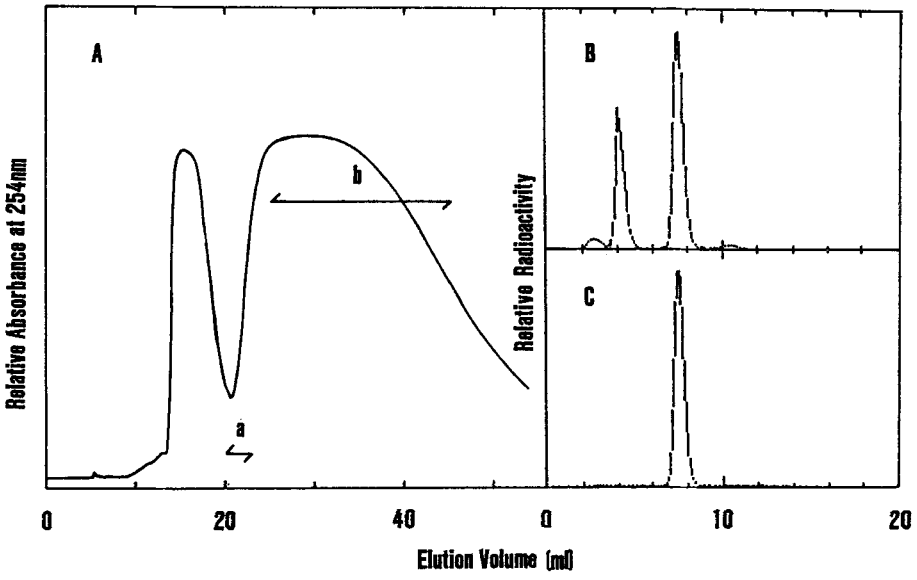

Fig.2 Purification of ^{18}F-5-fluoro-2'-deoxyuridine on AG50W(H^+) and neutral alumina columns. (A) shows the chromatogram. The eluates in (a) and (b) in (A) analyzed by radio-HPLC(μBondapak C18, 10% MeOH, 2 ml/min) are shown in (B) and (C), respectively. Arrow shows the elution volumn of authentic 5-fluoro-2'-deoxyuridine.

SYNTHESIS OF FLUORINE-18 LABELED 1-(2-NITRO-1-IMIDAZOYL)-3-FLUORO-2-PROPANOL, A HYPOXIC CELL RADIOSENSITIZER

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Hypoxic radiosensitizers, such as misonidazole (I), are in clinical use in radiation therapy. There have been recent suggestions that such compounds may selectively accumulate in hypoxic tissue (or tumors); carbon-14 labeled misonidazole has been used in the autoradiographic visualization of hypoxic regions of tumors (1). The labeling of such compounds with a positron-emitting radionuclide might allow their study in vivo using positron emission tomography (PET).

We have prepared a fluorine-18 labeled nitroimidazole, 1-(2-nitro-1-imidazoyl)-3-fluoro-2-propanol (II), which is chemically very similar to the clinically used misonidazole, with a similar lipophilicity and one-electron reduction potential (Table 1).

The preparation of this compound is shown in Figure 1. 1-(2,3-epoxypropyl)-2-nitroimidazole (III) was prepared according to literature methods (2). Fluorine-18 was prepared by the proton irradiation of oxygen-18 enriched water, and the F-18 fluoride converted to carrier-added F-18 tetra-n-butylammonium fluoride by exchange. The reaction of the F-18 TBAF (20 micromoles) with 2 mg of epoxide III in dimethylsulfoxide or dimethylacetamide gave a mixture of products. Separation by HPLC yielded the desired F-18 1-(2-nitro-1-imidazoyl)-3-fluoro-2-propanol (17%) and a second product tentatively identified as the isomeric 2-fluoro-3-propanol (3%). The opening of the epoxide ring to give predominantly the 2-hydroxy-3-fluoro isomer is that which would be expected under nuetral or basic conditions, where the attack of the nucleophile (fluoride ion) is controlled by steric effects. The production of the 2-fluoro-3-hydroxy isomer would be favored in the ring opening with HF.

The biological properties of this compound are under study.

References
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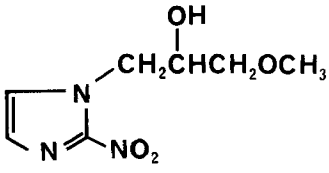
Table 1.

	Compound	Partition coefficient	$E_{\frac{1}{2}}$ (mV)
I	Ro-07-0582	0.43	-389
II	Ro-07-0741	0.44	-383

Acknowledgement. This work was supported by National Institutes of Health grant HL-13851.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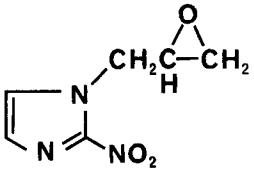
N
N
NO2

I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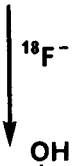
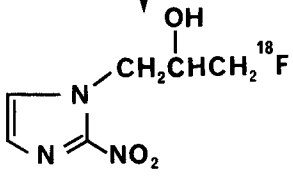
CH2
H
N
N
NO2

III


18F-


OH
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18F
N
N
NO2

II

SYNTHESIS AND DISTRIBUTION OF N-[2-(HYDROXYETHOXY)METHYL]-5-[^{3}H]-METHYLURACIL IN TUMOR BEARING MICE.

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Some acyclic pyrimidine (e.g. 5-fluoro-1-[(2-hydroxyethoxy)methyl]uracil) (1) and purine (e.g. 9-(2-hydroxyethoxymethyl)guanine) (2) nucleosides have been shown to be biologically active. This suggests that the cyclic carbohydrate moiety is not an essential structural requirement for biological activity. It was therefore of interest to synthesize tritium-labelled N-[2-(hydroxyethoxy)methyl]-5-[^{3}H]-methyluracil (3) for evaluation as a tumor diagnostic agent. Compound 3 was synthesized by a modified method of Robins and Hatfield (4) (Scheme I). 5-[^{3}H]-Methyluracil (1) (190 MBq/mmol) was converted to a 2,4-bis-trimethylsilyl intermediate which was coupled with (2-acetoxyethoxy)-methyl bromide to yield 2. Treatment of 2 with sodium methoxide in methanol afforded N-[2-(hydroxyethoxy)methyl]-5-[^{3}H]-methyluracil in 25.4% radiochemical yield from 1. The radiochemical purity of 3 was 98% as determined by radio thin layer chromatography (RTLC). The specific activity of 3, determined by high pressure liquid chromatography (HPLC) and liquid scintillation counting, was 188 MBq/mmol.

The tissue distribution of 3 was examined in male BDF$_1$ mice bearing Lewis Lung carcinomas (Table 1). The kidney contained the highest radioactivity level suggesting a major urinary route of excretion. This was confirmed by analysis of blood radioactivity. The major blood component (96%) was found to have a biological half-life of less than 1 min. The tumor and organs of high mitotic index such as stomach and GIT had low to medium tissue:blood ratios for the first 15 min. The ratios were high after 240 min, indicating incorporation of injected radioactivity.

The title compound is unsuitable for use as a diagnostic agent because of rapid elimination from the body.

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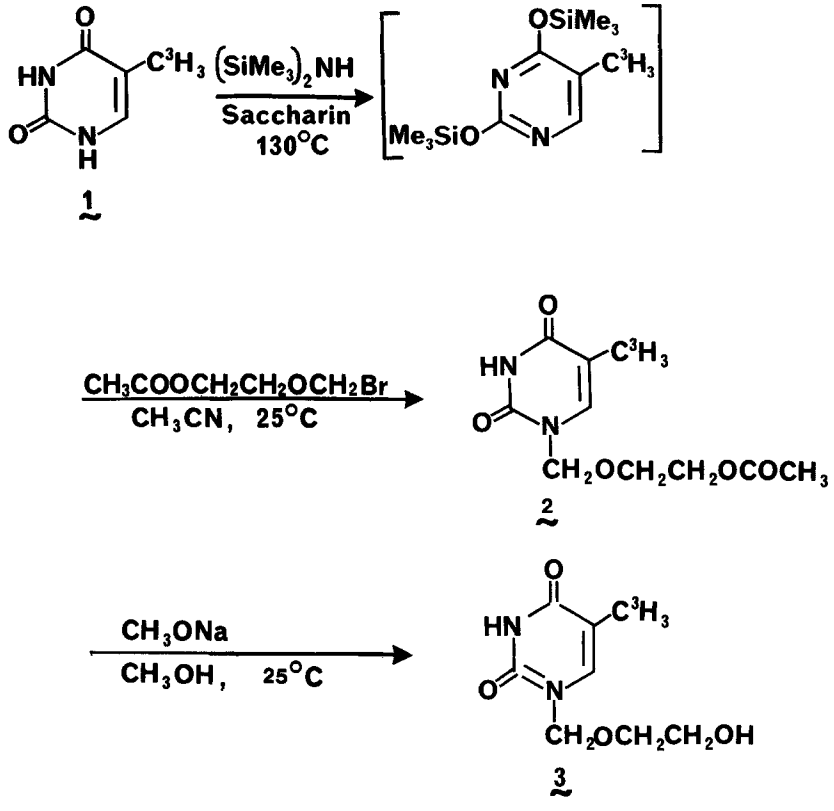

1 2 3

Scheme I: Synthesis of N-[2-(hydroxyethoxy)methyl]-5-[^{3}H]-methyluracil.

Table 1: Tissue:blood ratios ± S.D. of N-[2-(hydroxyethoxy)methyl]-5-[^{3}H]-methyluracil in BDF_1 mice bearing Lewis Lung carcinomas. n = 3.

	Time (min)		
	5	15	240
Stomach	0.75 ±0.33	1.22 ±0.32	12.97 ± 4.21
GIT	1.33 ±0.17	1.55 ±0.18	7.56 ± 2.91
Kidney	2.09 ±0.33	2.72 ±0.59	2.78 ± 0.40
Muscle	0.91 ±0.06	1.19 ±0.22	1.53 ± 0.73
Liver	1.06 ±0.28	1.14 ±0.18	1.90 ± 0.26
Tumor	0.48 ±0.08	1.06 ±0.17	6.25 ± 3.53

SYNTHESIS AND TUMOR UPTAKE STUDIES OF ^{14}C-LABELED α-AMINOISOBUTYRIC ACID ANALOGS.

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^{11}C-Labeled α-aminoisobutyric acid (AIB) has been synthesized by Schmall and Bigler (1) and found to be potentially useful as a tumor-imaging agent. AIB is an unnatural, nonmetabolizable amino acid and, therefore, quite similar to the alicyclic amino acids, 1-aminocyclobutanecarboxylic acid (ACBC) and 1-aminocyclopentanecarboxylic acid (ACPC). We have previously synthesized ^{11}C-labeled ACBC and ACPC and demonstrated their potential for tumor imaging in both preclinical (2,3) and clinical (4) studies. We have also reported (5) a striking structure-activity relationship within the series of alicyclic α-amino acids. Compounds with four- and five-membered ring systems showed good tumor uptakes, whereas those having three- and six-membered ring systems did not. Therefore, we have synthesized a series of ^{14}C-labeled analogs of AIB (Fig. 1) and studied their tissue distributions in tumor-bearing rats with the expectation that one or more analogs would have better tumor localization than the parent amino acid.

The ^{14}C-labeled AIB analogs of varying chain length of R and R' (compounds I, II, III, and IV) were synthesized using our high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis (6). A monofluorinated derivative of AIB (DL-α-monofluoromethylalanine; compound V) was synthesized by a traditional Strecker synthesis, as reported by Christensen and Oxender (7). Because of the long half life of carbon-14, we did not attempt to minimize the time required for the synthetic reactions. Purification was by anion-exchange followed by cation-exchange chromatography (6). The purity of the radiolabeled amino acids was assessed using thin-layer chromatography in conjunction with a spark chamber (Birchover Instruments, Bancroft, U.K.).

Male Buffalo rats bearing transplanted Morris 5123-C hepatomas (50-60 days post-implantation) were used as an animal model to compare the tumor uptakes of ^{14}C-labeled AIB and its analogs. The ^{14}C-labeled amino acids were administered via the tail vein and, 30 minutes later, the rats were sacrificed by exsanguination via the abdominal aorta. Selected tissue samples were taken and assayed by standard liquid scintillation counting techniques.

The results obtained are shown in Table 1. Increasing the chain length of R and/or R' produced a progressive decrease in the tumor uptake. However, DL-α-monofluoromethylalanine (compound V) gave a tumor concentration that was statistically indistinguishable from AIB's. This result is in agreement with our hypothesis that the size of the R and R' groups is the major factor that determines tumor uptake, because the atomic radius of a fluorine atom is only slightly larger than that of a hydrogen atom. Significant differences between the 30-minute tissue concentrations of AIB and DL-α-fluoromethylalanine were observed only for kidney, muscle, and small intestine. The high pancreatic uptake of AIB and its analogs may be an artifact due to use of rodents for the tissue distribution studies, as was observed previously for ACPC (8).

The good tumor uptake of ^{14}C-labeled DL-α-monofluoromethylalanine suggests the potential of the ^{18}F-labeled amino acid for positron tomographic tumor imaging. Previous studies with DL-α-monofluoromethylalanine have demonstrated it to be resistant to metabolism and apparently nontoxic and to show characteristic biological transport (7). Tissue distribution studies at times later than 30 minutes postinjection have not yet been carried out. However, times of up to 4 hours postinjection are clearly practical for fluorine-18 ($T_{1/2}$ = 110 minutes). Such studies as well as development of methods for synthesis and purification of ^{18}F-labeled DL-α-monofluoromethylalanine are currently in progress.

(This report is based on work performed under Contract No. DE-AC05-76OR00033 between the U.S. Department of Energy, Office of Energy Research, and ORAU. Part of this work was done by J.K. Lingen while a Student Research Participant at the Medical and Health Sciences Division of ORAU.)

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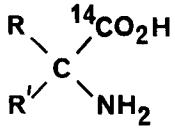

I : R and R' = CH_3 (AIB)
II : R = CH_3CH_2 ; R' = CH_3
III : R and R' = CH_3CH_2
IV : R = $CH_3CH_2CH_2$; R' = CH_3CH_2
V : R = CH_2F ; R' = CH_3
(DL-α-monofluoromethylalanine)

Fig. 1 Structures of ^{14}C-labeled analogs of α-aminoisobutyric acid (AIB)

Table 1

Tissue Distribution of ^{14}C-labeled Analogs of α-Aminoisobutyric Acid (AIB) in Rats Bearing Morris 5123-C Hepatomas at 30 Min Postinjection

	Percent Injected Dose/g*				
Tissue	I	II	III	IV	V
Tumor	3.38 ± 0.53	1.55 ± 0.15	0.80 ± 0.05	0.66 ± 0.04	3.10 ± 0.10
Liver	0.41 ± 0.05	0.26 ± 0.01	0.31 ± 0.03	0.37 ± 0.01	0.49 ± 0.02
Spleen	0.63 ± 0.04	0.42 ± 0.01	0.37 ± 0.02	0.43 ± 0.01	0.50 ± 0.03
Kidney	7.56 ± 1.05	9.83 ± 0.50	4.30 ± 0.31	3.84 ± 0.21	13.73 ± 0.42
Lung	0.59 ± 0.06	0.47 ± 0.02	0.48 ± 0.01	0.45 ± 0.01	0.59 ± 0.04
Muscle	0.12 ± 0.01	0.12 ± 0.00	0.10 ± 0.00	0.15 ± 0.00	0.26 ± 0.01
Brain	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.04 ± 0.00
Pancreas	4.45 ± 0.29	3.63 ± 0.61	3.75 ± 0.31	2.70 ± 0.08	3.62 ± 0.10
Blood	0.21 ± 0.03	0.29 ± 0.02	0.23 ± 0.02	0.28 ± 0.01	0.23 ± 0.04
S. Int.	1.55 ± 0.12	0.30 ± 0.07	0.35 ± 0.02	0.46 ± 0.07	0.97 ± 0.09

*Normalized to total body weight of 250 g.

MECHANISMS OF EXCHANGE BETWEEN RADIOLABELLED CYANIDE AND NITRILES AS A METHOD FOR THE RADIOSYNTHESIS OF POTENTIAL INHIBITORS OF MONOCYTE CHEMOTAXIS

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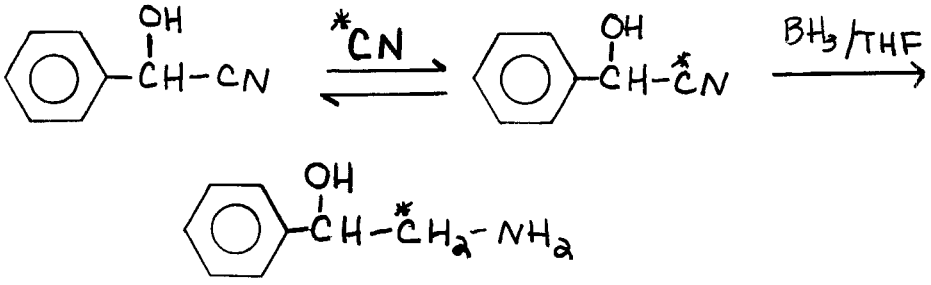
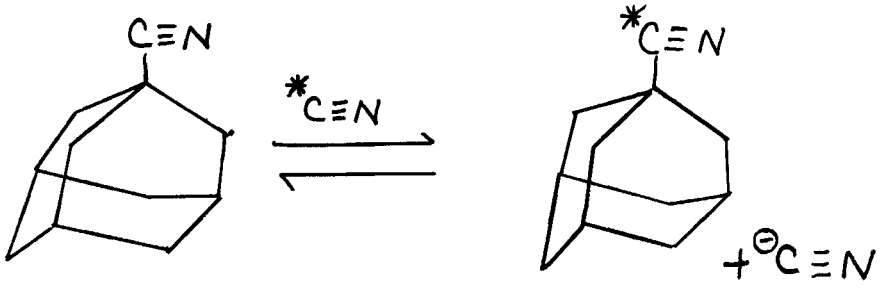
As part of our program for the development and evaluation of potential pharmacological agents in the treatment of smoke-induced pulmonary emphysema, it was necessary to produce radiolabelled inhibitors of monocyte chemotaxis for receptor binding studies. In the course of the development of the synthesis of radiolabelled precursor amines, some interesting observations were noted in the exchange between ^{14}C-labelled sodium cyanide and a number of organic nitriles. Precedent for such reactions have appeared in the literature (1).

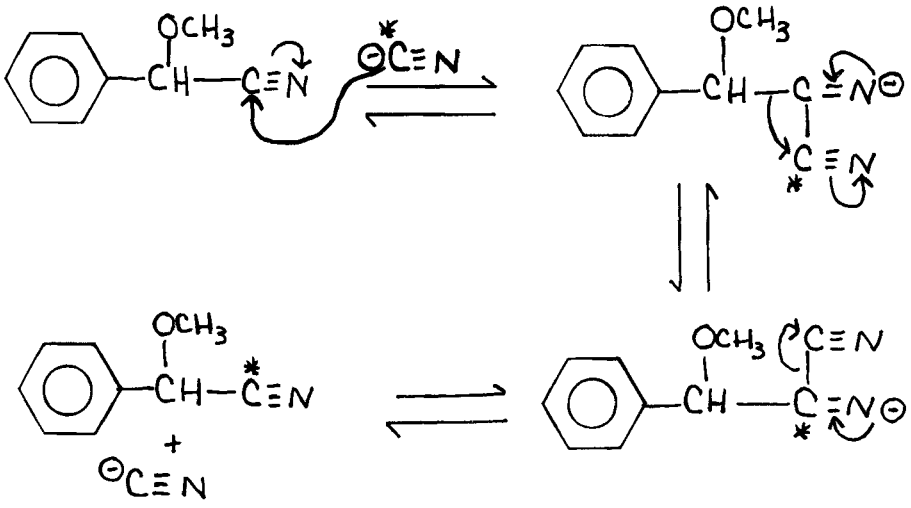
The exchange between mandelonitrile and cyanide was studied by employing $Na^{13}CN$ and ^{13}C-NMR in which a significant increase in the intensity of the nitrile signal was noted in the ^{13}C-NMR spectrum. The exchange was also carried out using $Na^{14}CN$ and the product was reduced to ^{14}C-phenylethanolamine with borane in THF. The purity of the product was confirmed using a radiomonitored HPLC which indicated a 20% radiochemical yield for the exchange reaction (Scheme I).



Various other exchange reactions were performed in order to elucidate the mechanism of exchange. The reaction between $Na^{14}CN$ and adamantanecarbonitrile was performed to demonstrate that such exchange reactions could occur by mechanisms other than a simple SN_2 reaction by using a substrate in which the pivotal carbon atom was not available for a back-sided attack (Scheme II).



Support was obtained for mechanisms involving an equilibrium between mandelonitrile and benzaldehyde-cyanide and an alternative mechanism analogous to a benzilic acid-type rearrangement (2-). The late observation was provided by the exchange between $Nc^{14}CN$ and α-methoxyphenylacetonitrile (Scheme III) in which a benzeldehyde intermediate cannot account for the exchange mechanism.



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PREPARATION OF N-13 LABELED PHENETHYLAMINE

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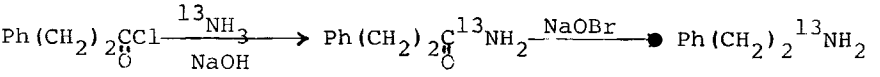
ß-Phenethylamine(PEA) has important functions as a neuromodulator in the central nervous systems with an amphetamine-like action. Systemically administered PEA readily enters the brain and is deaminated by monoamine oxidase(MAO) into phenylacetic acid(PAA) and ammonia. In some kinds of mental diseases, changes in biosynthesis, metabolism, and disposition rates of PEA are presumed, and the PEA hypothesis has been proposed(1).

The synthesis and the preliminary organ distribution study of C-11 labeled PEA has already been reported(2). More detailed informations about in vivo metabolism of PEA are expected to be obtained using C-11 PEA and N-13 PEA in combination. While the synthesis of N-13 amphetamine using N-13 ammonia as a precursor has been reported, the labeling efficiency and the specific activity are very low. We investigate the synthesis of N-13 PEA using Hofmann rearrangement reaction of the N-13 acid amide synthesized from phenylpropionyl chloride and N-13 ammonia as follows.



The first step reaction(synthesis of the N-13 acid amide) was completed within 1 min. The total labeling yield was determined by thin layer chromatography(TLC, silicagel, chloroform/methanol=4/1), and the results are summarized in Table 1. Although both the labeling yield(about 12%) and the specific activity(about 400mCi/mmol) of the labeling amine were much higher than those of N-13 amphetamine, they still need to be improved for the clinical application. The yield was found to be much dependent upon the ratio of the amount of bromine to that of the acid amide. Since the N-13 acid amide could be synthesized in a non carrier added state, we are now investigating the optimal labeling conditions of the following Hofmann rearrangement reaction step.

For the preliminary animal experiments study, N-13 PEA was purified by two step extraction of the reaction mixture(first with ethyl acetate, and the extract was then extracted with 0.1N HCl solution). The solution of N-13 PEA was intravenously administered to the control and the pargyline(100mg/kg) pretreated mice, and the organ distribution study was performed(Table 2).

In the control mice, high accumulation in the brain and the heart soon after the administration, and considerablly long term retention of the activity were observed. These data indicate that N-13 ammonia, derived from N-13 PEA, might be incorporated into glutamine and trapped in these tissues. In the case of C-14 PEA, the accumulation soon after the administration didn't differ from that of N-13 PEA, but no retention of the avtivity was observed, which showed that C-14 PAA, the metabolite of C-14 PEA, was rapidly eliminated from the tissues(Fig.1).

In the pargyline pretreated mice, the brain radioactivity after the administration of both C-14 and N-13 PEA remained for at least 20 min, on the other hand, in the heart, the activity was rapidly decreased. These results suggest that other metabolic pathways of PEA exist in the brain.

In conclusion, N-13 PEA, used in combination with C-11 PEA, may contribute much to clarify the distribution and the metabolism of PEA in live animals including human.

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Table 1 Yield and Specific Activity of ^{13}N-PEA

Run	Yield (%)	Spec. Act. (mCi/m mol)
1	10	360
2	10	320
3	12	450

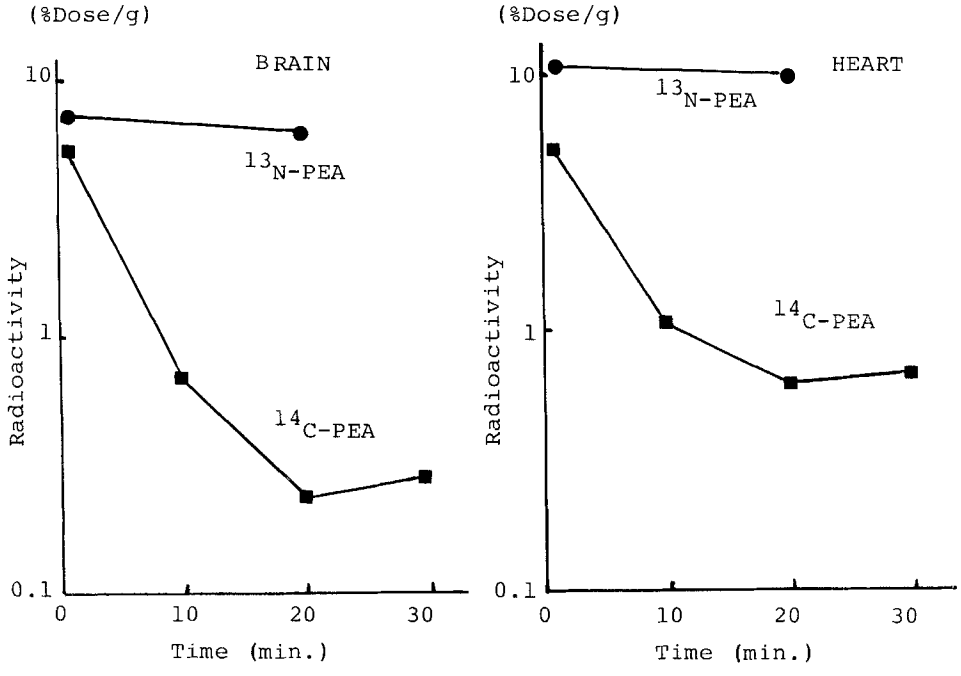
Reaction Conditions

N-13 ammonia 40 mCi/1 ml, carrier ammonia 50μmol, phenylpropionyl chloride 20μl, Br_2 5μl, NaOH 2 mmol. temperature 100°C,time 5 min. (Hofmann Rearrangement)

Table 2 Organ Distribution of ^{13}N-PEA in Mice (male C3H) (% Dose/g)

Organ	1 min.	20 min.
Brain	7.04±1.72	6.10±0.43
Heart	11.30±0.97	10.17±3.51
Lung	13.13±1.80	2.45±0.26
Kidney	7.81±0.20	7.90±1.66
Blood	3.09±0.41	1.61±0.02
Liver	3.43±0.81	4.56±0.86

Fig. 1 Brain and Heart Radioactivity after i.v. of ^{13}N- and ^{14}C-PEA



PREPARATION ON N-13 LABELED ADENOSINE AND NICOTINAMIDE BY AMMONOLYSIS

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For studies of the biological functions and bio-distributions of physiologically active amines and amides it is very interesting to utilize N-13 amine or amide labeled compounds as in vivo tracers. However, there is a few reports concerning N-13 chemical labeling, perhaps because N-13 has a very short half-life(1,2).

We attempted to develop a rapid chemical N-13 labeling by means of ammonolysis using N-13 ammonia as a precursor, since it is a one step, simple reaction and since N-13 ammonia can be obtainable in a large radioactive scale in a short preparation time. The labeling of adenosine and nicotinamide was first tried because of the possibility of labeling and their biological interest.

Ammonolysis is generally carried out in excess liquid ammonia or alcoholic medium. In the labeling procedure, N-13 ammonia should be used in an non-carrier-added or in a very small amount in order to obtain both a high radiochemical yield and a high specific activity. Under such conditions the pH in the labeling medium would be an important factor, because the ratio of a neutral form of N-13 ammonia would affect the labeling yield as expected from the reaction mechanism. Therefore, the labeling conditions such as medium pH, reaction temperature and time were examined in these labeling.

In the case of adenosine, two substrates, 6-chloro and 6-fluoro derivatives, were examined. In carrier-added labeling, the conditions were typically as follows; 200 μl of N-13 aqueous ammonia, 10 μmol of substrate and 5 μmol of carrier ammonia. The initial, calculated pH of such a medium is about 10.8, where ammonia (pKa=9.3) almost exists in a neutral form. With about 18 % of the yield N-13 adenosine was obtained from 6-fluoro derivative in 10 min heating at 80-100°C, and with a little higher yield by alkali addition, though 6-chloro derivative gave much less yield than 6-fluoro. In non-carrier-added, the labeling was performed under alkali added. The yield was expectedly much dependent on the amount of added alkali. About 10 % was obtained at the optimal condition, whose pH was around 12. These data are shown in Table 1.

In the case of nicotinamide, nicotinic acid chloride was used as a substrate. The labeling was much more dependent on the reaction temperature, and the optimum at 4-20°C. The yield also depended on pH condition both in carrier-added and non-carrier-added labeling. The optimal radiochemical yields were respectively about 28 % and 25 %, which were reached only within 5 min. The results are summarized in Table 2.

In these labeling, the radiochemical yield was determined by T.L.C. The rapid separation method by H.P.L.C. is in progress. Both N-13 labeled adenosine and nicotinamide can be prepared with a practical yield with a high specific activity from N-13 aqueous ammonia, and this would be available for other amines and amides.

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Table 1-a The radiochemical yield of N-13 adenosine in carrier-added labeling

alkali (aq. NaOH 20μl)	pH (calculated)	radiochemical yield(%)	
		F-derivative	Cl-derivative
-	10.8	18.2	-
10^{-3}N	10.9	22.5	2.3
10^{-2}N	11.2	21.2	3.5
10^{-1}N	12.0	24.5	5.2

conditions; aq. N-13 ammonia : 200μl, carrier ammonia : 5μmol, substrate : 10μmol, 10 min heating at 100°C.

Table 1-b The radiochemical yield in non-carrier-added labeling

alkali (aq. NaOH 20μl)	pH (calculated)	radiochemical yield(%)
-	-	< 2
10^{-4}N	9	< 2
10^{-3}N	10	2.5
10^{-2}N	11	5.0
10^{-1}N	12	11.0

conditions ; aq. N-13 ammonia : 200μl, substrate(F-deriv.): 10μmol, 10 min heating at 100°C.

Table 2 The radiochemical yield of N-13 nicotinamide

alkali (μmol)	radiochemical yield(%)	
	carrier-added	non-carrier-added
10-50	< 2	< 2
100	14.6	6.4
200	19.5	18.9
500	28.5	25.3
1000	18.9	19.3

conditions; aq. N-13 ammonia : 250μl , substrate : 140μmol, carrier ammonia (in carrier-added) : 10μmol, 1 min reaction at 20°C.

SYNTHESIS OF ^{15}O-LABELED BUTANOL VIA ORGANOBORANE CHEMISTRY: PRELIMINARY REPORT

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A requirement for tracers for measuring cerebral blood flow (CBF) is that they be freely diffusible over a wide range of flows and that this property not vary with regional pathology. ^{15}O-Labeled water is used clinically in combination with PET. Since the brain is not diffusible to water, the use of $H_2{}^{15}O$ leads to an underestimation of CBF in areas of high flow(1-3) and a hypothetical correction factor must be applied. ^{11}C-Butanol and ^{14}C-butanol have been utilized successfully in animal studies(4-7). ^{11}C-Butanol has been proposed as a standard to compare CBF tracers since it has been shown to be freely permeable up to a CBF of $\geq$ 180•mL(100g min)$^{-1}$ and has been validated for CBF measurement with PET(7).

Oxygen-15 labeled butanol would appear to be ideal for use as a CBF agent since the estimated radiation dose is much lower for ^{15}O-labeled butanol than for ^{11}C-labeled butanol. The synthesis of ^{15}O-labeled alcohols presents a formidable challenge due to the time restraint imposed by the 2.04 minute half-life of ^{15}O.

Organoboranes have proven to be useful intermediates for incorporating radioisotopes into organic molecules(8-10). Organoboranes react rapidly (<2 min.) with ^{17}O-O_2 to yield ^{17}O-labeled alcohols in high yields(11). We now wish to report that the reaction of ^{15}O-O_2 with tributylborane yields ^{15}O-butanol.

$$[CH_3CH_2CH_2CH_2]_3B + {}^{15}O_2 \longrightarrow CH_3CH_2CH_2CH_2{}^{15}OH$$

The ^{15}O-O_2 was generated via the $^{16}O(p,pn)^{15}O$ reaction with 33 MeV irradiation of ultrapure O_2 utilizing the BNL 60" cyclotron. Tracer level ^{15}O-O_2 (0.25 mmole) was added to a well stirred solution of tributylborane (2mL of a 1 M solution in THF) via a gas inlet tube. Immediately after addition of the oxygen, the butanol was isolated by chromatographing the reaction mixture (HPLC) utilizing a C-18 reverse phase column and aqueous ethanol as eluent (elution time ~2 min). In the preliminary experiments 50% of the radioactivity in the reaction mixture was associated with the butanol. [The absolute yields, which were not optimized, were <20%]. It is apparent from feasibility studies that the reaction of organoboranes with ^{15}O-O_2 is potentially useful for the syntheses of a variety of ^{15}O-labeled alcohols.

Research supported by Office of Health and Environmental Research, Dept. of Energy

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THE CYCLOTRON: CONCURRENT RADIONUCLIDE PRODUCTION AND RADIOPHARMACEUTICAL QUALITY CONTROL

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Radiopharmaceutical preparations incorporating cyclotron-produced radionuclides such as carbon-11($t_{\frac{1}{2}}$=20.4m), nitrogen-13 ($t_{\frac{1}{2}}$ = 9.97m), or fluorine- 18($t_{\frac{1}{2}}$ = 109.7m), require their formulations be performed at or near the imaging facility. The half-life of the particular radionuclide contained within a given compound permits only a few to be delivered as a ready-for-use patient dose at any distance from the manufacturing plant. "In-house" radiopharmaceutical preparations require the efforts of a multi-disciplinary team combining good synthetic and pharmaceutical technique, attention to excellence in manufacturing practice, and quality control assurances to ensure a consistent, uniform radiopharmaceutical product of proven safety and efficacy be achieved.

Mount Sinai Cyclotron Facility is extremely active in the preparation of a variety of radiopharmaceuticals incorporating radionuclides possessing a gamut of half-lives and decay characteristics(1,2,3,4,5). The increased clinical demand for cyclotron products has mandated the most efficient utilization of the cyclotron operating time and technical staff.

In addition to employment of tandem targetry for simultaneous, on-line preparation of radiopharmaceutical compounds containing various radionuclides (4), currently we are utilizing effectively the neutron fluence originating from the high-power, internal target irradiations (p,xn) for application of neutron activation analyses to our quality control procedures. The neutron fluxes and energies at various vault locations are measured using foil monitors(6). The results have been applied to a determination of the chemical contaminants resulting during the syntheses of carbon-11 labelled valproic acid. The inclusion of this technique has resulted in various subtle chemical procedural alterations to the classical Grignard reaction involving carbon-11 labelled carbon dioxide with 2-n-propylpentylmagnesium bromide in order to provide a uniform radiopharmaceutical product. The radiochemical aspects and quality assurance procedures are presented in detail.

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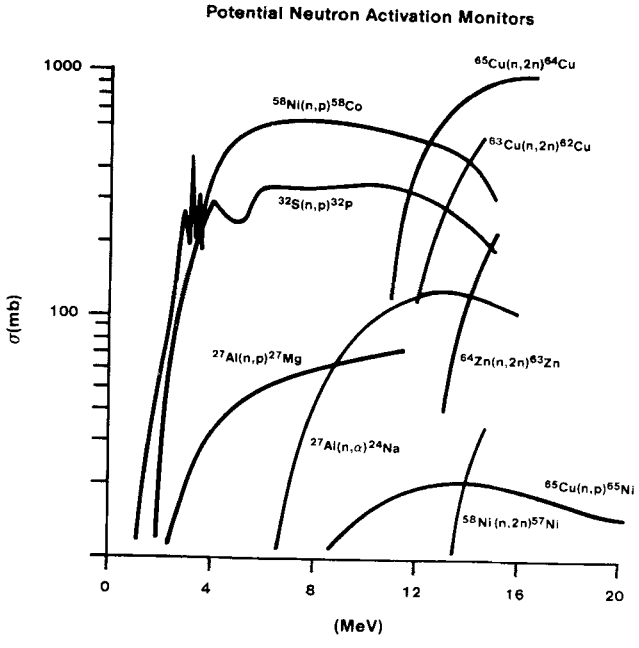
Potential Neutron Activation Monitors
1000
100
σ(mb)
0
4
8
12
16
20
(MeV)
$^{65}Cu(n,2n)^{64}Cu$
$^{58}Ni(n,p)^{58}Co$
$^{63}Cu(n,2n)^{62}Cu$
$^{32}S(n,p)^{32}P$
$^{27}Al(n,p)^{27}Mg$
$^{64}Zn(n,2n)^{63}Zn$
$^{27}Al(n,\alpha)^{24}Na$
$^{65}Cu(n,p)^{65}Ni$
$^{58}Ni(n,2n)^{57}Ni$

MULTI-PURPOSE TARGET UNIT FOR SMALL CYCLOTRONS

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A multi-purpose target unit (MPTU) is being developed to facilitate automated radionuclide production using the JSWBC1710 cyclotron at Brookhaven National Laboratory (BNL). A tandem configuration of targets will deliver rapid sequences of ^{11}C, ^{13}N, ^{15}O, or ^{18}F to the chemistry laboratory or directly to the PETT VI facility via underground tubes. The gas target is evacuated to pass beam through its exit window for single-use liquid target operation. The design is modular to allow rapid replacement of collimator, vacuum window, target windows, targets, or flanges used to supply chilled recirculated helium for window cooling.

The basis for the design is a careful compromise of window thicknesses and target geometries to accommodate 17.4 MeV proton and 10.0 MeV deuteron beams, target gas pressures required for efficient nuclear reaction yields at high beam currents, and small angle multiple scattering in windows and targets. Since limited space prohibits switching magnets to multiple beam lines and imposes restrictions on target changer hardware, an important feature of this design is that the MPTU assembly remains fixed with all radionuclide changes are accomplished by remotely changing charged particles, target gases, and target liquids.

Table 1 shows examples of single and simultaneous target production modes. Two other options not shown are a $^{15}N(p,n)^{15}O$ gas target and a $^{13}C(p,n)^{13}N$ powder target (1). The only commonly used nuclear reaction not possible with the MPTU is $^{20}Ne(d,\alpha)^{18}F$ for $^{18}F\text{-}F_2$ production, which requires a separate dedicated gas target due to its high sensitivity to surface conditions and contaminant gases (2,3).

Several target technologies previously studied at BNL are contributing significantly to the MPTU development. These include target gas density reduction quantification (4,5), the fabrication of high strength conical target bodies electroformed from high purity nickel and compatible with electron beam welding processes (6), the use of small volume targets using enriched $H_2{}^{18}O$ to produce aqueous ^{18}F-fluoride (7), and the selection and testing of beam window materials using an infrared thermal monitor (8).

As a prerequisite to final construction and testing of the MPTU, studies are in progress using conventional single targets to demonstrate the ability to purge and change three different target gases while maintaining radionuclidic and radiochemical purity of the nuclides produced. For example, a single target has been used successfully for $^{11}CO_2$ and $H^{11}CN$ production. The fabrication of three conical nickel gas target bodies for the MPTU is complete (1.3 cm front diameter flaring to 3.8 cm rear diameter by 25.4 cm long), allowing construction of the total assembly to proceed.

This research was carried out at Brookhaven National Laboratory under contract with the U. S. Department of Energy and NIH Grant No. 15638.

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Table 1. Example of Multi-Purpose Target Unit Using Two-Particle Bombardment of Two Target Gases and Two Target Liquids to Produce High Levels of Four Radionuclides in Six Chemical Forms (Simultaneous Modes Possible for $^{11}C/^{18}F$ or $^{11}C/^{13}N$)

	Single Target Operation				Simultaneous Target Operation		
	^{15}O or ^{11}C	or ^{18}F	or ^{13}N		^{11}C plus ^{18}F	or ^{13}N	
Mode	Single (gas)	Single (gas)	Single (liquid)	Single (liquid)	Simultaneous (gas)	Simultaneous (liquid)	Simultaneous (liquid)
Reaction	$^{14}N(d,n)^{15}O$	$^{14}N(p,\alpha)^{11}C$	$^{18}O(p,n)^{18}F$	$^{16}O(p,\alpha)^{13}N$	$^{14}N(p,\alpha)^{11}C$	$^{18}O(p,n)^{18}F$	$^{16}O(p,\alpha)^{13}N$
Energy, MeV	7.55 to 0.00	16.43 to 0.00	15.55 to 4.00	15.55 to 4.00	16.43 to 12.00	10.77 to 0.00	10.77 to 0.00
Target	N_2 or N_2/5% H_2	N_2 or N_2/5% H_2	$H_2{}^{18}O$ (98%)	$H_2{}^{16}O$	N_2 or N_2/5% H_2	$H_2{}^{18}O$ (98%)	$H_2{}^{16}O$
Pressure, Atm.	5	20	1.3	1.3	10	1.3	1.3
Product	$^{15}O_2$ or $H_2{}^{15}O$	$^{11}CO_2$ or $^{11}CH_4$ (for $H^{11}CN$)	Aqueous ^{18}F-fluoride	Aqueous ^{13}N-nitrate	$^{11}CO_2$ or $^{11}CH_4$ (for $H^{11}CN$)	Aqueous ^{18}F-fluoride	Aqueous ^{13}N-nitrate
Beam Time, Min.	10	40	110	30	40	40	40
20 μA Yield[a], mCi	1140[b]	3465[c]	1740[d]	543[e]	1650[c]	575[d]	300[e]

a. Yields do not account for recovery losses. Gas target pressures allow for density reduction factor of 0.33 for deuterons and 0.50 for protons.

b. Calculated from the excitation function of Ruiz and Wolf, Radiochimica Acta 24, 65-67 (1977).

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e. Calculated from the excitation functions of Whitehead and Foster, Can. J. Phys. 36, 4276 (1958) from 6.2 to 15.6 MeV, and of Kim, Milner and McGowan, Nuclear Data A3, 123 (1967) from 15.6 to 17.8 MeV.

A MULTI-PURPOSE TARGET SYSTEM FOR HIGH-CURRENT IRRADIATIONS

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A facility for irradiation of solid, liquid and gaseous materials with extracted beams from our compact cyclotron CV 28 has been developed. The system is suitable for low to medium current irradiations used in research and development work, as well as for high-current irradiations needed in the production of radioisotopes. It consists basically of a frame in which different target holders can be easily fitted, and rotated, if necessary. A sketch of the system is shown in Fig. 1. Some of the characteristics of the system are as follows:

- Heat dissipation through efficient cooling with water containing freezing inhibitor (up to -10 ^{o}C), or with He (up to -15 ^{o}C), or with both of them.
- Homogenization of the beam profile through its direct observation during the irradiation (endoscopic system).
- Beam manipulation through the use of subsystems like beam degrader, chopper, beam stop and endoscopy.
- Possibility of use of rotating target heads (up to 400 rotations/min) in production runs.
- Easy change of target holders and easy removal of the irradiated samples.
- Possibility of exact measurement of the beam current, also in the case of a rotating target.
- Adaptability of the system to remote handling. The actuator and impetus are pneumatically controlled.

By virtue of the efficient cooling and rotation of the target holders it is possible to irradiate even expensive, highly-enriched low melting metals without any appreciable loss. So far a Ne gas target for the production of ^{18}F via the ^{20}Ne(d,α)^{18}F reaction, and a rotating target using 96.48 % enriched ^{76}Se-metal on Al-backing for the production of ^{75}Br via the ^{76}Se(p,2n)^{75}Br reaction have been developed.

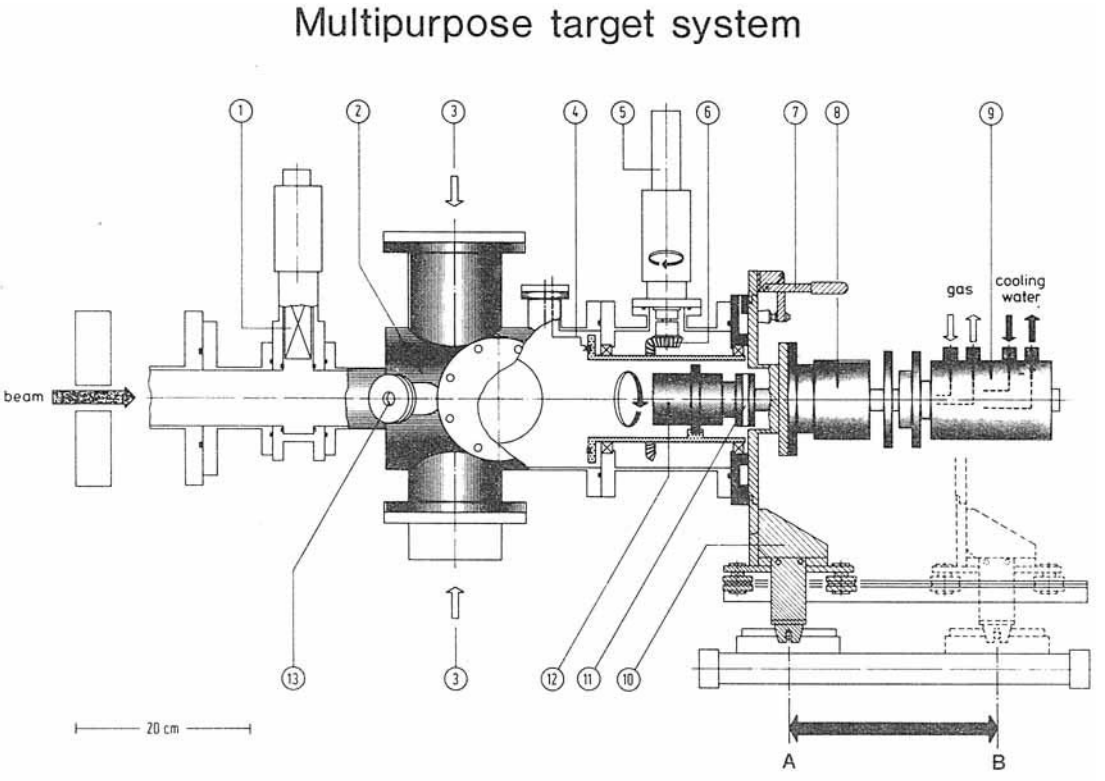

Fig. 1. 1. Vacuum shutter, 2. Cross piece, 3. Connecting flange for subsystems, 4. Sliding contacts, 5. Pneumatic motor, 6. Bevel wheel, 7. Clamping lever, 8. Airtight rotor, 9. Four way rotary transmission, 10. Target coupling and decoupling system (A, irradiation position; B, target removal), 11. Insulator, 12. Target, 13. Connection for endoscope.

PRODUCTION OF CARBON-11 WITH RESPECT TO SPECIFIC RADIOACTIVITY- A TARGET STUDY

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The most convenient nuclear reaction for production of carbon-11 ($T_{1/2}$= 20.4 min) is the $^{14}N(p,\alpha)^{11}C$ reaction in nitrogen gas. The production of ^{11}C having high specific radioactivity requires careful consideration of the production conditions. The abscence of stable carbon isotopes in the target gas and the target system material is of special importance. In order to develop a target system for production of ^{11}C-carbon dioxide of high specific radioactivity a photographic study of proton beam scattering and range in nitrogen gas was performed in an experimental windowed target chamber. The results obtained in this study were then used to construct a production target chamber.

Experimental target chamber. In an earlier study of the influence of intense ion beams on high-pressure gas targets an assymetric density reduction in the beam volume of the target was observed.(1) On the basis of the results a conical target chamber equipped with a glass window was constructed (Fig.1). Direct photography of the light emitted by target gas atoms in the beam was used to study particle ranges in the target. The same technique was used to study particle scattering in the target and the two 12.5 μm stainless steel foils (Goodfellow Metals Ltd.), separating the accelerator vacuum from the target pressure. The beam was photographed in both the vertical and horizontal plane. The visible aperture of the target chamber was 87x25 mm (Fig.1). The length of the target chamber was 187 mm and the volume 55 cm^3 . The particle beam was collimated by apertures of 3-5 mm diameter before entering the target. The target chamber was made of aluminium and equipped with channels for cooling media. Nitrogen N4.8 (Aga Special Gases) was used as target gas. The irradiations were carried out with the Åbo Akademi 103 cm isochronous cyclotron.

Results with experimental target. The range of 11.5 and 10.4 MeV proton beams in the nitrogen-gas target was studied as a function of the target pressure and beam current. An increased proton penetration in the target was seen when the beam current was increased. This was due to density reduction of the target gas in the beam volume. The range of the lowest part of the proton beam agrees within experimental errors with the tabulated particle range.(2)The effect on the beam of two different cooling media, water (5°C) and alcohol (-25°C), was studied. No significant difference in proton penetration could be observed, but a more focused proton beam was seen in the nitrogen gas using chilled alcohol as cooling medium due to more efficient cooling and faster heat transfer from the heated gas in the beam volume of the target. The target pressure during the irradiations was observed with a Kulite XTM-190 pressure transducer. A 5 μA beam current of 10.4 MeV protons on the nitrogen gas target resulted in a 23% pressure increase as compared to an initial target pressure 870 kPa.

Production target chamber. A conical production target chamber (entrance aperture diam. 15 mm, base aperture diam. 34 mm, length 188 mm and volume 93.5 cm^3) was constructed to give a thick nitrogen-gas target for an initial pressure of 900 kPa and a 10.4 MeV proton beam of 5 μA, taking into account beam penetration and scattering. The beam was collimated by an aperture of 6 mm diam. before entering the target. The target chamber was made of aluminium (DIN AlMgSi1). The 12.5 μm stainless steel beam entrance foil (Goodfellow Metals Ltd.) was sealed with a PTFE O-ring. A gold O-ring (thickness 0.5 mm) was used as sealing material between the target body and the back flange. The production target chamber was adapted to the Scanditronix multi-target holder at the Uppsala University Tandem Accelerator Laboratory.

Gas handling, preparation and conditioning of target. A gas handling system (Fig.3) was designed for filling and conditioning the target chamber with the target gas,

nitrogen N60 (l'Air Liquide, France). The gas lines, fittings and valves (Swagelok, Nupro and Whitey) were of stainless steel. All components of the target system were carefully cleaned with chloroform, ethanol, distilled water, diluted nitric acid, absolute ethanol and diethyl ether (p.a.) and dried in a vacuum oven at 140°C. The total target system volume was 97 cm^3 (NTP), including gas lines and trapping system. To avoid leakage of atmospheric carbon dioxide and water into the target system, columns packed with Ascarite® and activated molecular sieve 4A were used. The target system was thoroughly conditioned before irradiation in order to remove traces of carbon dioxide and other impurities.

Specific radioactivity measurements. The specific radioactivity of the ^{11}C-carbon dioxide produced was analysed on a Varian 202B gas chromatograph equipped with a thermal conductivity detector in series with a radioactivity detector. The GC-separation was performed on a glass column (150 cm long, 1/4 in. o.d.) packed with Porapac Q (60-80 mesh, Waters Associates,Inc.).The eluted carbon dioxide was trapped in Ascarite® after passing the TC-detector and the radioactivity detector. The amount of ^{11}C-carbon dioxide was measured with an ionization chamber. Specific radioactivity of ^{11}C-carbon dioxide was measured as a function of beam current on the target at constant radiation dose and as a function of irradiation time for 5μA beam current. The specific acitivities of ^{11}C-carbon dioxide have been in the order of 2 Ci/μmol.

Discussion. Leakage of carbon dioxide into the target system couldn't be eliminated although the system was tight (no pressure decrease was observed at 850 kPa during 10 h). The increase of the carbon dioxide level in the target gas may be caused by diffusion of atmospheric carbon dioxide into the system (the partial pressure of atmospheric carbon dioxide is more than 10^3 times that of the target gas), diffusion of carbon present in the aluminium and by sputtering in the target entrance foil. A windowed target chamber is conveniently used as a beam diagnostic tool in order to determine target pressure for a thick target at a certain beam current and energy. The volume of the windowed target chamber has to be comparable to the volume of theproduction target chamber due to the volume dependent penetration and density reduction effects in the target.

Acknowledgement. A grant from the foundation for Nordic Research Courses is gratefully acknowledged.

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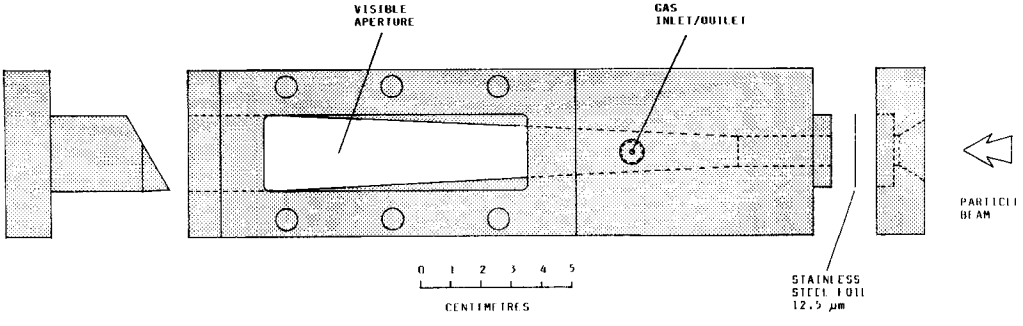

Fig.1. Scale drawing of windowed target chamber for photographic beam study.

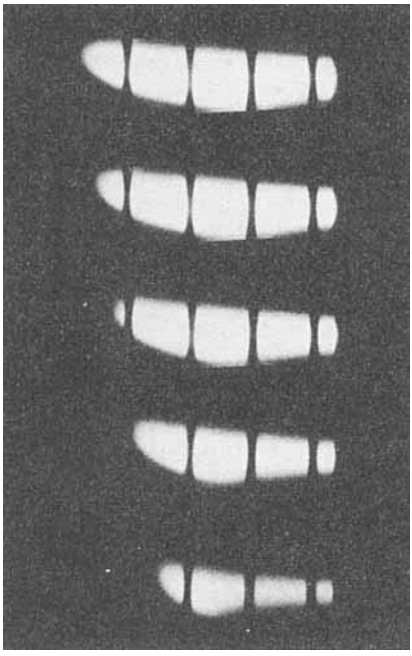

Fig.2. Horizontal views of N_2 at 1.05 MPa initial pressure, bombarded with 11.5 MeV protons of 1-5 μA beam current. Beam entrance from the right.Distance between two vertical lines is 17.5 mm.For location of visible aperture, see Fig. 1.

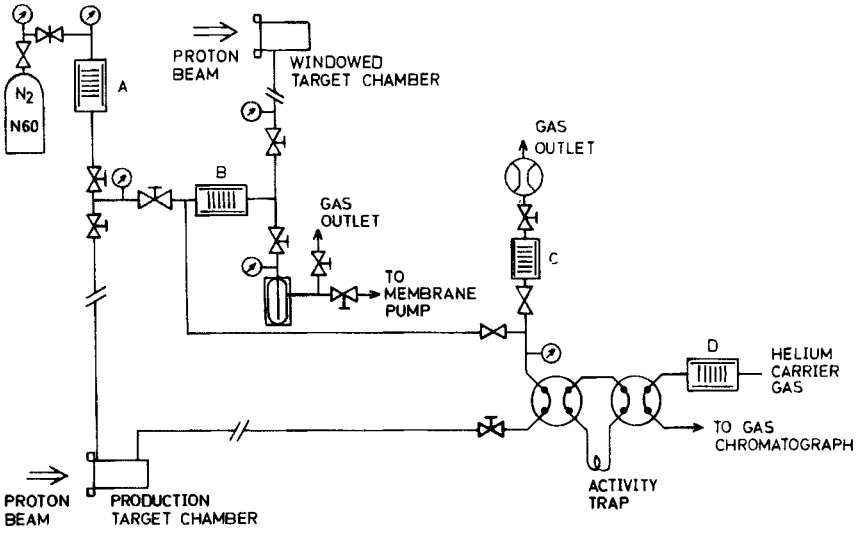

Fig. 3. Manifold for handling of target gas. A,B,C and D are columns packed with Ascarite^R and molecular sieve 4A.

AN ON-LINE SYSTEM FOR LONG-DISTANCE TRANSPORT OF ^{15}O-LABELLED GASES

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Oxygen-15 labelled molecular oxygen and carbon dioxide are produced with the Åbo Akademi 103 cm isochronous cyclotron via the $^{14}N(d,n)^{15}O$ reaction by deuteron bombardment of nitrogen gas containing 1 % of O_2 or CO_2, respectively. Separate target systems are used in order to avoid contamination of the target chambers (made of aluminium, Fig. 1). Two stainless steel foils (thickness 12.5 μm, Goodfellow Metals Ltd), with helium gas streaming in between, separate the cyclotron vacuum from the target pressure and attenuate the extracted 7.4 MeV deuteron beam to 6.15 MeV incident on the target (1). The ^{15}O-labelled molecular oxygen or carbon dioxide is transported from the target chamber to the Departments of Radiotherapy and Clinical Physiology of the Turku University Central Hospital (distances from the target 650 and 970 m, respectively) through a polyethylene tube. The transport over the long distances is possible with the help of a high target pressure driving the gaseous radioactive products through a narrow-bore transport tube.

In order to optimize the ^{15}O-concentration in the tubing outlet of the transport line the target chamber volume has been minimized. This results in a high ^{15}O-concentration in the target and reduces the dwell time of the $O^{15}O$ or $CO^{15}O$ in the target chamber during the on-line production. The deuterons are scattered both in the two entrance foils and in the target gas (2). The particle scattering has been studied by direct photography of the beam in the light emitted by atoms of the target gas. A double-windowed target chamber, previously described (2), was used. The scattering has been taken into account in the construction of the production target chambers (Table 1) for minimization of the dead volume in the chamber.

The transport tubing (13 polyethylene tubes, i.d. 1.2-3.0 mm), together with 16 electric cables for control of magnetic valves and for telephone lines, are placed in a bunch, shielded with a plastic layer, an aluminium foil and, outermost, with a 2 mm thick layer of PVC. Between the cyclotron and the hospital the cable (manufactured by Etola Oy, Finland) is placed 70 cm under the ground level. The target and transport system is schematically shown in Fig. 1. The distance between the target position and the radiochemical laboratory at Åbo Akademi is 20 m. The gas transport is controlled from panels in the radiochemical laboratory and at both receiving ends of the transport system in the hospital. The gas line to be used is selected and opened by the user in the hospital by activation of magnetic valves in the radiochemical laboratory (Fig. 1). The target/sweep gas pressure is raised to a level giving tuned conditions for the gas line in use. With the help of a dual limit switch, flow alarm levels of the balanced thermal mass flowmeters (Brooks flow sensor model 5810, Brooks Instrument Division, Emerson Electric Co.) are selected when the gas flow is stable. An upper limit is set in the radiochemical laboratory and a lower limit at the user site. The gas flow is directed to patient inhalation by activation of a magnetic valve (Fig. 1).

The gas pressure, flow rates and concentrations of ^{15}O-radioactivity in the tubing are monitored at both ends of the gas lines. The transport control system involves automatic shut-down of the transport from the target chamber in case of target window rupture or leakage in the tubing system. This is regulated by the balanced flowmeters. The transport stops automatically in case of power failure or if some of the electric control cables is broken accidentally. The transport can also be stopped, when needed, from both ends of the gas lines.

The transit times and gas flow rates for the two gas lines were measured as functions of the target drive pressure for the 1.2 mm i.d. tube. A short deuteron irradiation resulting in a well defined radioactivity bolus in the gas flow was used for measurements of the transit time as the time difference between arrival of the bolus at the user site and departure of the bolus from the radiochemical laboratory. The measured transit times and gas flow rates were compared to values predicted by laminar gas flow theory (Fig. 2). A computer program, GASLIN (3), was used in the

calculations. In order to look for optimal values for transport parameters ^{15}O-concentration measurements were carried out at the tubing outlets of the two gas lines as a function of the target drive pressure at a laminar flow through the 1.2 mm i.d. tubing (Fig. 2). The ^{15}O-concentrations were measured for two target chambers of different lengths (A and B, Table 1).

For routine transport of $O^{15}O$ and $CO^{15}O$ through the 630 m tubing (i.d. 1.2 mm) a target drive pressure of 550 kPa is used. The measured transit time is 6 min 32 s, the calculated one 6 min 41 s (3). The measured gas-flow rate is 470 ml/min and the calculated flow rate is 390 ml/min. At the 550 kPa target pressure the 6.15 MeV deuteron beam is fully attenuated in the target (chamber A, Table 1). The ^{15}O-concentration measured at the tubing outlet is 460 kBq/ml for a 5 μA beam current on the target. For the 950 m tubing (i.d. 1.2 mm) the measured transit time is 10 min 21 s and the measured gas-flow rate 535 ml/min with a target drive pressure of 750 kPa. The calculated transit time is 10 min 44 s and the calculated gas-flow rate 500 ml/min (3). The ^{15}O-concentration measured at the tubing outlet is 97 kBq/ml for a 5 μA beam current on the target. The routine production and transport parameters are summarized in Table 1.

The optimization of the ^{15}O-concentration in the tubing outlet at the user site is of special importance when short-lived radioactive gases are transported over long distances. The measured gas-flow rates and transit times for the 630 m and 950 m transport tubings are in good agreement with the values predicted by laminar gas-flow theory (Fig. 2). The decrease in the ^{15}O-concentration measured at the tubing outlet of the 650 m line for target chamber A at high target pressures (Fig. 2c) is caused by dilution of the ^{15}O-radioactivity in the larger amount of nitrogen in the thick target. For a 6.15 MeV deuteron beam the nitrogen gas target corresponds to a thick target at pressures of 450 kPa (target chamber A) and 730 kPa (target chamber B), respectively, if one does not take into account density reduction effects (2,4, 5) in the beam volume of the target (1). The transport system is easily operated and reliable in routine use. The system has been used routinely during two years without any interruptions in the delivery of ^{15}O-labelled gases during normal runs with 5-15 μA beam currents on the target.

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Table 1. Oxygen-15 production and transport parameters. The two target chambers are called A and B. Further explanation in the text.

Conical target chamber	A	B
– entrance aperture, diam.	10 mm	10 mm
– base aperture, diam.	20 mm	14 mm
– length	65 mm	40 mm
– volume	11.9 cm^3	4.57 cm^3
Target pressure (absolute)	550 kPa	750 kPa
Gas-flow rate	470 ml/min	535 ml/min
Tubing inner diam.	1.2 mm	1.2 mm
Transport distance from radiochem. lab.	630 m	950 m
Transit time	6 min 32 s	10 min 21 s
Beam current on target	5 μA	5 μA
^{15}O-concentration, tubing outlet	460 kBq/ml	97 kBq/ml
^{15}O-production rate, tubing outlet	216 MBq/min	51.9 MBq/min

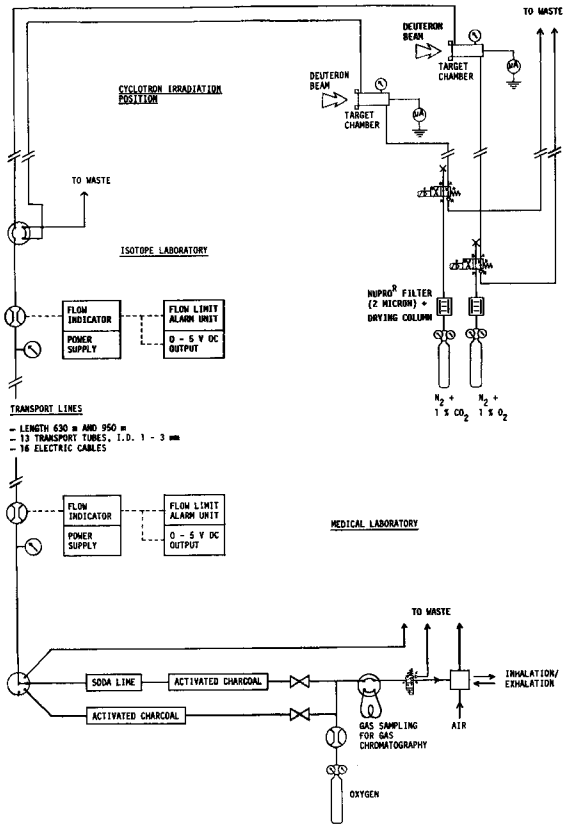

Fig. 1. Gas flow system for transport of ^{15}O-labelled molecular oxygen and carbon dioxide from Åbo Akademi Accelerator Laboratory to Turku University Central Hospital. The dashed lines represent electric lines. The soda lime and activated charcoal columns are at room temperature.

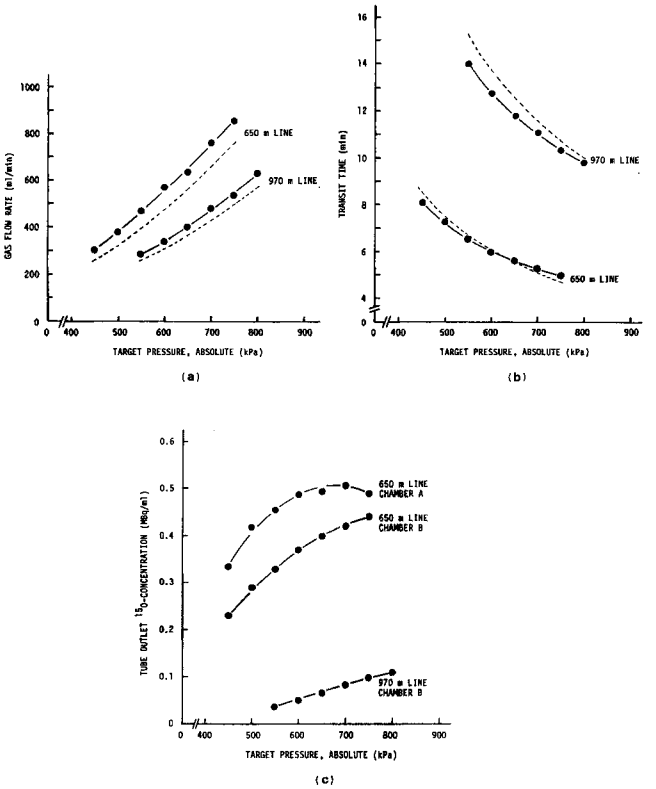

Fig. 2. Gas flow rates (a), transit times (b) and ^{15}O-concentrations (c) as functions of target pressure for the 630 m and 950 m transport tubings(i.d. 1.2 mm). The lines are drawn to guide the eye. The dashed lines represent values calculated by laminar gas flow theory[3].Further explanation in the text.

EXCITATION FUNCTION FOR THE $^{15}N(p,n)^{15}O$ REACTION

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Nuclear reaction cross section data were required in order to evaluate the method best suited to the compact cyclotron production of ^{15}O for biochemical applications. The literature for the $^{15}N(p,n)^{15}O$ reaction shows clear discrepancies (1-7). A detailed excitation function over the range E_p = 3.78-12 MeV was reported by Barnett et al. (1). Their relative cross section curve was normalized to absolute measurements at 5.52, 5.68 and 5.75 MeV. It is difficult to obtain a correct normalization factor since the excitation function has about 18 resonances. Measured (8) thick target yields were found to be a factor of two lower than expected from Barnett's data.

We have now determined the absolute cross sections for the $^{15}N(p,n)^{15}O$ nuclear reaction (90 experiments) between 3.72 and 16.58 MeV with 99.9% isotopically enriched ^{15}N as N_2. The activation method was used in combination with the BNL Tandem Van der Graaff (energy resolution ± 10 keV). The overall experimental uncertainty in the cross section measurements was 7%. The consistencies and discrepancies with the earlier cross section measurements will be discussed.

Our data agree with the shape of Barnett's excitation function (1) and are within 15% of the experimental thick target yields reported for several energies in reference 8. The relative merits of the $^{15}N(p,n)^{15}O$ and the $^{14}N(d,n)^{15}O$ reactions (9) as a source of ^{15}O for tracers to measure cerebral blood flow, oxygen extraction fraction and oxygen metabolism will be compared.

The development of a solid target, e.g. titanium nitride-^{15}N, is in progress.

This research was carried out at Brookhaven National Laboratory under contract with the U. S. Department of Energy and the Office of Health and Environmental Research.

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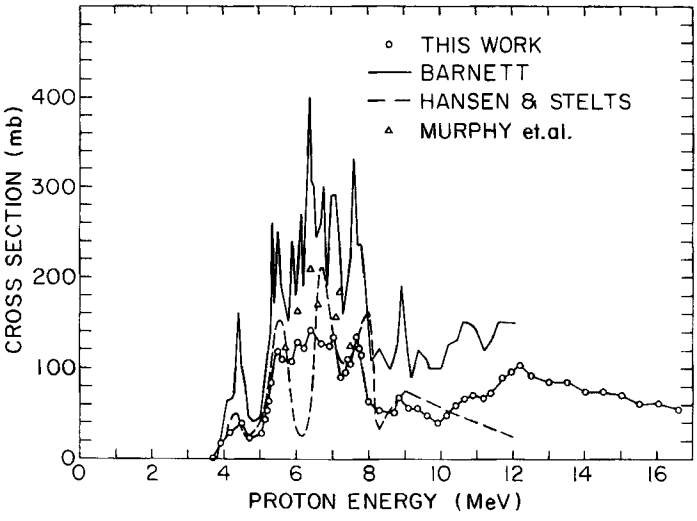
THIS WORK
BARNETT
HANSEN & STELTS
MURPHY et.al.
CROSS SECTION (mb)
PROTON ENERGY (MeV)
0
100
200
300
400
0
2
4
6
8
10
12
14
16

SYNCHRONIZED PRODUCTION AND INSTILLATION OF $H_2{}^{15}O$ FOR THE QUANTITATIVE MEASUREMENT OF BLOOD FLOW AND REGIONAL EXTRAVASCULAR WATER

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Production of radioactive gas occupies essential position in the production line of the recently installed cyclotron (CYPRIS), as valuable diagnostic tool for the investigation of pulmonary, cardiac and brain malfunctions. As a complementary project, the quantitative measurement of regional blood flow and regional extravascular lung water, called for the design of 15-O labeled water production and administration under continuous and constant flow. In our search for simple methodology, suitable for clinical routine facilities, two remote-controlled systems were designed; their applicability for continuous and constant infusion of $H_2{}^{15}O$ were then tested.

In the first system (A), the production of $H_2{}^{15}O$ was based on the fast exchange reaction between carbon dioxide and carbonic acid: $C^{15}O_2 + H_2O \rightarrow H_2C^{15}O_3 \rightarrow H_2{}^{15}O + CO_2$ (1). As shown in Fig.1-a, a stream of $C^{15}O_2$ gas, produced by irradiating 0.5% CO_2 in N_2 mixture with 7.5 MeV deuteron beam was continuously bubbled through 25 ml of saline solution. The $H_2{}^{15}O$ produced was then circulated by a pump at a rate of 4 ml/min. Bubbling vessel was fed with saline solution, at the same rate as that for infusion. As shown in Fig.1-b, the radioactivity level of the infusate (2.6 mCi/min, 40 uA) reached a constant level, with a diviation of less than 0.3%. Correlation between the gas bubbling rate and the radioactivity showed a maximal yield at a 300 ml/min. Assay of the infusate, using barium hydroxide, demonstrated the presence of more than 94% of the radioactivity as $H_2{}^{15}O$. In the second system (B) studied, the reaction of $^{15}O_2$ with H_2 using palladium as a catalyst was adopted (2). Using a mixture of 2% O_2 in N_2 as the target gas and bombarded with 7.5 MeV deuteron, the $^{15}O_2$ gas produced was combined with H_2 over a heated Pd catalyst (150 °C). The produced $H_2{}^{15}O$ was washed out with saline pumped at a constant flow rate and received in 50 ml saline reservoir flowing continuously and constantly, keeping the saline washing rate and the infusate rate constant (Fig.2-a). The infusate reached a constant radioactivity level of 14 mCi/min, at a flow rate of 1 ml/min (40 uA), with a deviation of less than 1.2% (Fig.2-b). Clinical applicability of both fully automated system for the production of sterile $H_2{}^{15}O$ at a continuous and constant rate is discussed. Namely, system (A), being very simple seems more suitable for any closely located facility but system (B) generating higher radioactivity level is more suited for separated facilities. Also, system (B) seems more favorable for regional brain blood flow studies.

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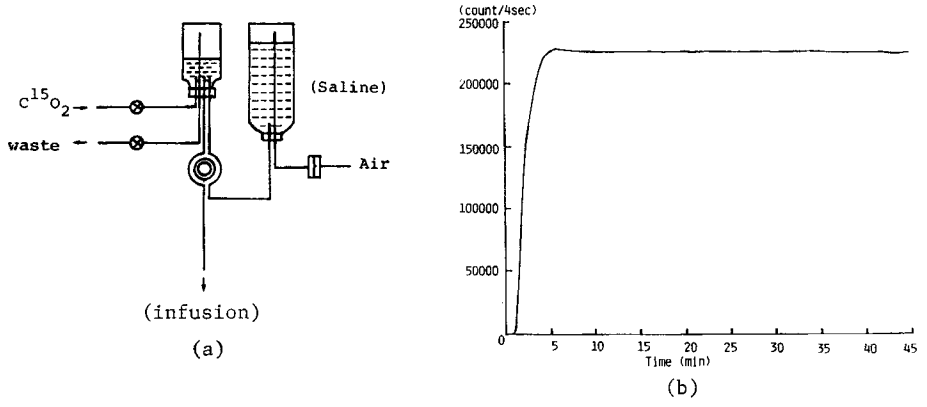

Fig.1. System (A) : (a) Diagram of the system (⊗: Electric solenoid valve, ◎: Pump) (b) Time-activity curve of $H_2{}^{15}O$ production

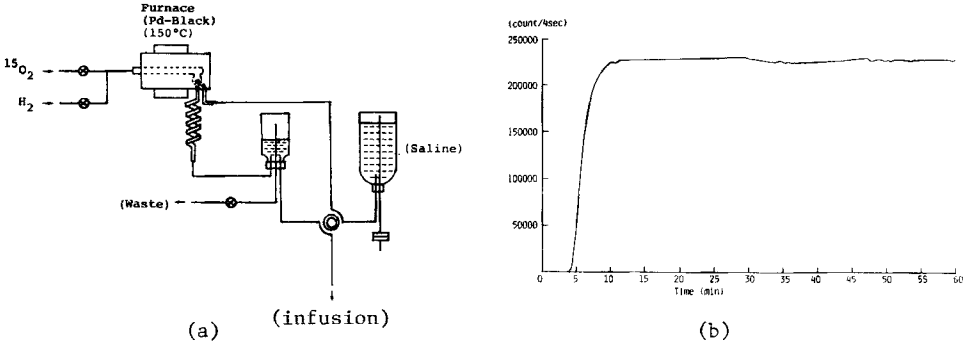

Fig.2. System (B) : (a) Diagram of the system (⊗: Electric Solenoid Valve, ◎: Pump) (b) Time-activity curve of $H_2{}^{15}O$ production

RADIONUCLIDE PRODUCTION ON THE TRIUMF CP42: A GAS TARGET FOR SEQUENTIAL PRODUCTION OF ^{18}F-F_2 AND ^{15}O-O_2

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A gas target that was constructed for the production of ^{18}F-F_2 has also been used for producing large quantities of ^{15}O-O_2 since early fall 1983.

The TRIUMF/AECL CP42 cyclotron built by The Cyclotron Corporation is a proton only machine which accelerates negative ions allowing for efficient beam extraction (200 μA on target). The cyclotron as delivered has three beam ports; two fixed energy ports (26 MeV ± 2 MeV) and a variable energy beam line (11-42 MeV). The Atomic Energy of Canada Ltd. (AECL) has target stations on all of the beam lines. The PET target station is located on the variable energy beam line in series with one of the AECL high power solid target station (1).

With these constraints for the PET targets the nuclear reactions available for ^{18}F and ^{15}O production were reduced to the two most feasible reactions for each product as listed in table I. The two (p,n) reactions give very high yields, however they require the development of either a reliable recovery system for the target gas or a target design that would allow the expenditure of the target gas. In order to make the radionuclides available with minimum delay we opted for the two higher energy reactions.

A nickel target was constructed to produce ^{18}F-F_2 using natural neon gas as target material. The target chamber is 30 cm in length. The entrance foil is Havar 25 μM thick. A He cooling chamber between collimator (10 mmID) and target window allows the target to be operated at 2.5 MPa (25 atm). The 41 MeV protons are reduced to ~40 MeV through the window and cooling gas and the target gas reduces the beam an additional 6 MeV.

When the target is used for ^{15}O production the target is flushed with He and then O_2. The target oxygen pressure is 400 kPa (4 atm) and beam energy on oxygen is ~29 MeV.

When changing from ^{15}O production back to ^{18}F production the target is flushed first with He and then with Ne and is ready for ^{18}F production. As noted in the literature (5) only very high purity gases should be used in the F_2 target.

Typical beam and target parameters are listed in table II.

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TABLE I

Radionuclide	Reaction	Optimal Energy Range	Comments
^{15}O	$^{15}N(p,n)^{15}O$ [2]	8 - 6	Requires enriched target gas
^{15}O	$^{16}O(p,pn)^{15}O$ [3]	30 - 25	Low specific activity
^{18}F	$^{18}O(p,n)^{18}F$ [4]	10 - 4	Requires enriched target gas
^{18}F	$^{20}Ne(p,2pn)^{18}F$*	?	Data not available**

* ^{20}Ne 90.5% of natural neon
** Threshold is 26 MeV

TABLE II

Reaction	Energy (MeV)	Maximum Beam Current(μA)	Typical Yield (mCi @ EOB)
$^{Nat}Ne(p,x)^{18}F$	40	15	150-180 as F_2
$^{16}O(p,pn)^{15}O$	29	10	250 as H_2O

REMOTE, SEQUENTIAL PRODUCTION OF $H_2{}^{15}O$, $^{15}O_2$ AND $^{18}F_2$ FOR 2-^{18}FDG

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The introduction of a multiple target system greatly increases the ease of routinely producing the positron emitting radiopharmaceuticals. The need for short bombardments and quick switchover is dictated by the short half-lives and rapid sequence of measurements usually desired by the user. Typical solutions to multiple target needs involve beam switching through a multiport magnet, target switching with a carousel, stack loader or a movable platform (1). This report describes a series target system for the sequential production of $H_2{}^{15}O$ vapor, $^{15}O_2$ and $^{18}F_2$ for 2-^{18}FDG synthesis. Our institution required the rapid, sequential delivery of these radiopharmaceuticals for studies of cerebral blood flow, and oxygen and glucose metabolism on the same subject.

A series target, as shown in Figure 1, was designed with appropriate valving and controls so that $H_2{}^{15}O$, $^{15}O_2$ and $^{18}F_2$ could be produced in rapid sequence using the deuteron induced reactions $^{14}N(d,n)^{15}O$ and $^{20}Ne(d,\alpha)^{18}F$.

The target system combines two targets, one for ^{15}O and one for ^{18}F. These targets are separated from accelerator vacuum by a 51 μm aluminum foil window and from each other by a 510 μm aluminum foil window with a 25 μm nickel liner. A remotely actuated gate valve separates the accelerator beam line from the target assembly. Vacuum is monitored between the gate valve and first target window. The ^{15}O target-sweep gas is either 5% H_2 in N_2 for ^{15}O water vapour, or 2% O_2 in N_2, for $^{15}O_2$. Valving directs the continuous flow of both gases around the ^{15}O target chamber while it is evacuated for ^{18}F bombardment. For ^{15}O production, one of the target-sweep gases flows through the chamber while the other bypasses it. Continuous gas flow that is only momentarily interrupted during switchover is important in our application. ^{15}O is transported at a drive pressure of 20-40 psig (1.4 - 2.8 kg/cm^2) to a location 1 km distant, for use in the ^{15}O equilibrium studies. A high pressure BNL type neon target is used for ^{18}F production. Gas valves are remotely controlled and vacuum gate valve position, water cooling, gas valve position and beam line vacuum are remotely indicated. This target system, with its gas plumbing, is integrated into the operation of a FN-6 tandem accelerator which is used primarily for nuclear physics research (2).

For the sequential production of $^{18}F_2$, $H_2{}^{15}O$ and $^{15}O_2$, the operation of this target system proceeds as follows. The ^{18}F target is filled with neon and 0.1% F_2 gas at 300 psig (21 kg/cm^2). The ^{18}F bombardment is started after the ^{15}O target is evacuated. During the 60 min ^{18}F bombardment with 5-10 μA of 15 MeV deuterons, flow is established with 5% H_2 in N_2 and 2% O_2 in N_2 but the gases bypass the ^{15}O target chamber. After ^{18}F production is completed, the deuteron beam is briefly stopped (and reduced to 2 μA and 11 MeV), 5% H_2 in N_2 is switched through the ^{15}O target, and $H_2{}^{15}O$ water vapor production commences. During ^{15}O production, the $^{18}F_2$ is transferred to a reaction vessel for the start of the 90 min 2-^{18}FDG synthesis. ^{15}O water vapor production proceeds for 40 min, after which 2% O_2 in N_2 is diverted through the ^{15}O target chamber. $^{15}O_2$ production proceeds for another 40 min, at which point the 2-^{18}FDG synthesis is complete. Each of the switchovers takes 1-2 min.

The conditions of operation and radionuclide yield from this series target system are identical to the separate targets which we previously used (2). No problems have been encountered with window integrity or vacuum or pressure leaks in the system.

Quick switching permits the sequential determination of CBF, $CMRO_2$ and CMRglu in the same subject within 1 1/2 hrs of each other. This series target approach is

inexpensive, uses no extra space in the accelerator vault and permits shielding of the target assembly in a 15.2 cm diameter cavity of a large cylindrical water tank. Personnel radiation dose due to beam line or target handling is avoided with a system of this type. The concept of this series target could be applied to any medical accelerator facility using other gas phase targets.

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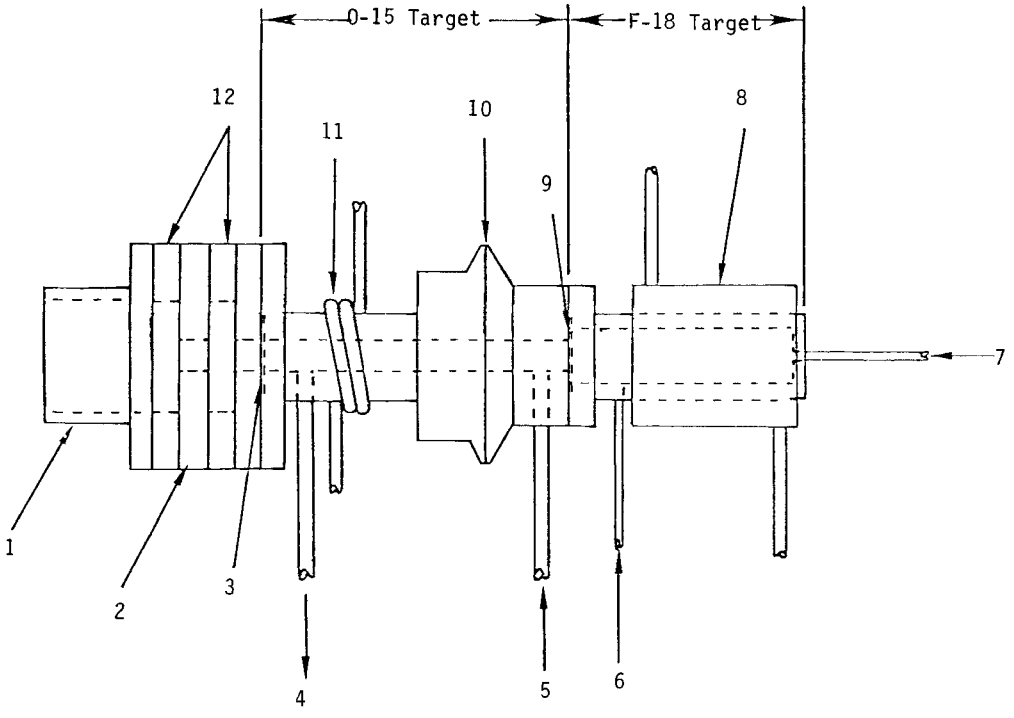

1. Coupling to FN-6 beam line
2. Collimator
3. ^{15}O target front foil
4. ^{15}O target gas outlet
5. ^{15}O target gas inlet
6. ^{18}F target gas inlet
7. ^{18}F target gas outlet
8. Cooling jacket (^{18}F target)
9. Target divider double foil (Al on ^{15}O side; Ni on ^{18}F side)
10. Marmon flange coupling
11. Cooling coils (^{15}O target)
12. Insulators

Fig. 1. The deuteron beam enters from the left, passes through the ^{15}O target foil (#3), into the ^{15}O target chamber, through the ^{18}F target foils (#9) and into the ^{18}F target chamber. ^{15}O production is performed with the ^{15}O chamber at a pressure of 80 psig (5.6 kg/cm^2). For ^{18}F production, the ^{15}O chamber is evacuated and the beam passes through to the ^{18}F chamber, which is filled to 300 psig (21 kg/cm^2). The drawing does not include the O-rings or seals used between flanges.

ACTIVATION OF CARBON PARTICLES WITH Be-7 BY PROTON IRRADIATION

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Carbon has many properties that make it attractive for particle uptake and distribution studies. It is insoluble, relatively non-toxic and is available in high purity with varying particle sizes. The carbon isotopes one might consider as a radiolabel are not suitable for this application. Carbon-11 (created by (p,pn) reactions) has an inconveniently short half-life while C-14 (created by neutron absorption) has no gamma rays which are required for in-vivo detection and is very long-lived. Although there have been many publications concerning neutron activation of coal and other carbon containing substances, it is the impurity elements which yield useable radionuclides. For these reasons we have developed a unique radiotracer, Be-7 labeled carbon particles. It is produced by proton spallation reactions on dry carbon black. Beryllium-7, with a 53 day half-life and 478 keV gamma ray (10% abundant) is the only important long-lived activity produced and is created directly in the carbon lattice structure.

The target material was pure carbon black, with a particle diameter of 27 nanometers. Three grams of powder were poured into an aluminum foil package and sealed into a stainless steel disk capsule. Irradiations were carried out at the Brookhaven Linac Isotope Producer (BLIP) with incident energies of 191 MeV and 58 MeV for periods varying between 4 and 16 days. After bombardment, the targets were cut open and the carbon poured into 100 ml of 1:1 ethanol and water and suspended by stirring. This mixture was then centrifuged and filtered to separate the carbon. The carbon was "washed" twice more with water in this manner and the combined supernate was assayed. These washings served to remove Be-7 only loosely bound on grain surfaces and to remove Na-22 found on the target surface (produced from recoil out of the aluminum wrapping). The remaining Be-7 was very firmly held in the carbon since extensive dialysis removed only negligible further quantities of activity. The fraction of Na-22 activity remaining was about 2×10^{-4}. Finally the carbon was dispersed in a solution of Tween 80 by vigorous stirring. Microscopic examination of the samples was used to find suspension conditions with minimum clumping. Once suspended, there was no settling even after days of standing. The pH of this mixture was 5.2.

The activity concentration of Be-7 in carbon can be easily controlled by variation of the duration of bombardment. Typically, we produced 11 μCi/mg of carbon in 2 weeks bombardment at 50 μA but levels up to ∿100 μCi/mg could be achieved at saturation. The activity concentration of the Tween suspension was typically 300-400 μCi/ml, which has been sufficient for initial applications.

This material was used in a study of the intestinal absorption of non-digestible particulate matter in animal models. The gamma radiation is sufficiently energetic that whole body counting allowed the determination of the kinetics of clearance and the biodistribution of residual particulate material (1). The Be-7 labeled carbon has also been utilized to characterize the distribution of material intratrachially introduced in rodents (2).

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ELECTROLYTIC ISOLATION OF CU-67 FROM PROTON IRRADIATED ZINC OXIDE

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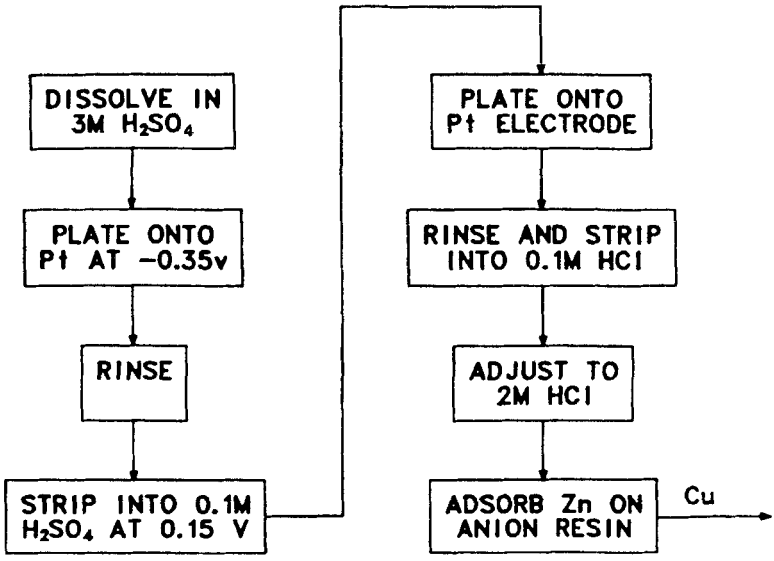
Copper has been identified as an essential trace element in human nutrition for over fifty years, and is associated with a variety of disease states in man. These include conditions such as Menke's syndrome, Wilson's disease and various inflammatory diseases. Copper metabolism is amenable to tracer studies if a suitable high specific activity isotope is available. Copper has eleven unstable isotopes, only three of which have half lives greater than one hour. Of these three, only copper-67 has a sufficiently long half life (61.7 h) and gamma emissions suitable for tracer and imaging studies.

The irradiation of zinc oxide target material in the primary proton beam at the Los Alamos National Laboratory Meson Physics Facility results in the spallation production of copper-67. Approximately 70 grams of target material are irradiated per target for a one- to two-week time period resulting in the production of curie quantities of copper-67 as well as other spallation products (Table 1). Copper is separated from the zinc target material and the other spallation products by plating the copper onto a platinum working electrode. The potential of the working electrode is controlled so that only copper is plated onto it. It is recovered from the electrode by applying a potential that is sufficiently anodic to oxidize copper to copper(II). Any zinc that is mechanically carried along with the copper is removed from the final product by anion exchange. The overall process is detailed in Figure 1.

The copper product is characterized for radionuclidic purity by Ge/Li spectroscopy, and for specific activity and stable contaminants by plasma emission spectroscopy. A typical final product will have a specific activity of 4000 to 5000 Ci/g (theoretical is 76,500 Ci/g), total stable contaminants of 15 micrograms, and no radionuclides present other than copper.

Table 1. Summary of Nuclides Present

Element	No. of Isotopes	Total A_0 Ci
Be	1	2.0
Na	1	0.2
K	1	0.27
Sc	2	1.87
V	1	4.4
Cr	2	6.2
Mn	2	1.0
Fe	2	0.38
Co	5	8.95
Ni	1	1.0
Cu	3	24.8
Zn	4	7.8
Ga	2	2.12



Flow chart for the separation of ^{67}Cu from irradiated ZnO.

COMPARATIVE STUDIES ON THE PRODUCTION OF ^{75}Br

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Among the various radioisotopes of bromine, ^{75}Br [$T_{1/2}$ = 1.6 h; β^+(75.5%); EC(24.5%); $E\beta^+_{max}$ = 1740 keV; E_γ = 286 keV (91.6%)] is the most suitable isotope for positron emission computed tomography (1). It can be produced via several methods, a summary of which has been recently given (2). From the viewpoint of yield and ^{76}Br-impurity level the $^{75}As(^3He,3n)^{75}Br$ and $^{76}Se(p,2n)^{75}Br$ reactions are more suited.

Over the last several years large scale production of ^{75}Br has been carried out in our laboratory via the $^{75}As(^3He,3n)^{75}Br$ reaction using a high-current Cu_3As-alloy as target material (3). Irradiations are done with 36 MeV ^3He-particles using an automatic internal target system at an incident angle of 3.2° and beam currents up to 120 μA. The beam adjustment presented some difficulty which has now been overcome through the use of a thermoelement. The major drawback in this process is the level of ^{76}Br ($T_{1/2}$ = 16 h) impurity. Since thin layers (∿ 7 μm) of the Cu_3As-alloy needed to cover the optimum energy range of the ^3He-particles (36 → 25 MeV) are difficult to prepare, the level of ^{76}Br-impurity in ^{75}Br at EOB, therefore, amounts to between 5 and 8 %.

The $^{76}Se(p,2n)^{75}Br$ reaction was first suggested by the Groningen group (4). We investigated some targetry and chemical separation problems related to this process. Se-containing alloys like Cu_2Se and Al_2Se_3 were unsuitable as target materials. A 140 μm thick layer of 96.48 % enriched metallic ^{76}Se on Al-backing was therefore used. Irradiations were carried out using a rotating target system (5) with 24 MeV protons at an incident angle of 19° (E_p = 24 → 21 MeV). The loss of selenium for beam currents up to 20 μA was < 1%. For the chemical separation of radiobromine a dry distillation method using a quartz apparatus was developed (temp. 290 °C, Ar-carrier flow rate 100 ml/min, distillation time 30 min). The loss of selenium during distillation was 3 to 4%. The separated radiobromine was taken up in a small volume of hot water. The overall radiochemical yield of the process lies presently between 40 and 45%. The level of ^{76}Br-impurity at EOB amounts to about 3%.

Tests on the radiochemical and chemical quality control of the products obtained via both the $(^3He,3n)$ and (p,2n) processes described above gave similar results. The radionuclidic impurity in the (p,2n)-process, however, is smaller. Together with the higher cross section this reaction seems to be preferable when at least 24 MeV protons are available.

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PRODUCTION OF KRYPTON-85m

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Xenon-133 is widely used for lung imaging, although it has relatively poor physical properties (E_γ = 80.9 keV, p = 36 %). Krypton-85m has an optimal γ-energy for gamma cameras (151 keV) with rather high intensity (76 %). These properties make it much more sensitive than Xe-133. Its half-life (4.4 h) is reasonably long for short-range transportations. The only interfering γ-energy is 305 keV (14 % intensity).

Krypton-85m was produced in the TRIGA reactor in gaseous form for the Helsinki University Hospital's Clinic of Lung Function and in solution for the Clinic for Radiation Therapy.

Natural krypton gas was loaded in a 100 ml aluminum high pressure vessel, which was irradiated in the reactor for 2 - 3 hours. After irradiation it was cooled for half an hour.

By slow constant flow the krypton was allowed to go through a NaCl 0.9 % solution.

For the lung function studies krypton was conducted to a mask where it was mixed with air and breathed.

When 1.2 grams of krypton was irradiated 2.5 hours in $8 \cdot 10^{12}$ $n \cdot cm^{-2} \cdot s^{-1}$ neutron flux, the yield was 1.1 MBq (30 mCi) ^{85m}Kr one hour after the end of irradiation. The specific activity of ^{85m}Kr-NaCl 0.9 % solution was 25 - 75 μCi/ml.

The purity of the irradiated natural krypton gas was at least 99.999 %.

The other identified radionuclides are listed in the table.

Table Other existing radionuclides when produced 1.5 GBq (41 mCi).

	$T_{1/2}$	Main γ	and its intensity	Activity 1 hour after irradiation
^{41}Ar	1.83 h	1293 keV	99 %	< 2 MBq
^{79}Kr	34.9 h	511 keV	15 %	15 MBq
^{83m}Kr	1.86 h	9 keV	9 %	10 GBq
^{87}Kr	1.27 h	403 keV	84 %	0.2 GBq
^{85m}Kr	4.4 h	151 keV	76 %	1.5 GBq

The first results are very encouraging and the work with both solution and gas is continued.

FULLY AUTOMATED, MICROPROCESSOR CONTROLLED SYSTEM FOR THE ROUTINE PRODUCTION OF THE NEW TYPE Rb-81 - Kr-81m GENERATORS

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The use of ^{81m}Kr for routine imaging of regional lung function is one of the most important advances in radionuclide application in clinical medicine of recent years. ^{81}Rb (4.57 h) is a typical cyclotron radionuclide and parent of ^{81m}Kr (13.3 sec). ^{81}Rb can be produced either by alpha irradiation of natural or enriched bromine targets (1), or by mostly used proton irradiation of gaseous natural or enriched ^{82}Kr (2,3).

The main problems which will be considered and presented in this work are:

(1) Cyclotron production of useful quantity of ^{81}Rb parent (up to 200 mCi per batch) over the $^{82}Kr(p,2n)^{81}Rb$ reaction.

(2) Design and construction of remotely and by microprocessor controlled target system and construction of the device for loading of one or more generators, as desired, with the ^{81}Rb from the target chamber.

(3) Design and study of the new type of generator and testing it in function. Preparation of program for a microprocessor controll for the whole production run.

The remotelly controlled target system was developed (4), the production rate of ^{81}Rb and co-produced contaminants was measured and is presented. The described system, which has not been reported up to now, has following characteristics:

(1) Diagnosis of the system setup conditions before the production run started.

(2) Full automation of the whole production procedure from the irradiation of the target material to the loading of desired number of generators.

(3) Compact design of the production system and intelligent control using a microcomputer. In addition to the automated control, the computer provides all manual operation.

(4) The particular advantage of this conception lies in the fact, that the personnel exposure during the production procedure is markedly reduced. This system will be applied in our labora-

tory for the routine production of other radionuclides (^{18}F, ^{13}N, ^{11}C and with ^{11}C labeled compounds).

The second part of presented work describes the preparation of the new type of ^{81}Rb-^{81m}Kr generator. Generally, the generators are small column packed with inorganic (5) or organic (6) ion exchange materials, which allows extraction of ^{81m}Kr in either gas phase or in the solution (7,8). Disadvantages in the function of these type of generators are - variable elution efficiency, high operating pressure, large internal volume, difficulties in elution with solvents and they need careful handling on the medical site and skillful personnel in the preparation of generators.

For these reasons has been designed a simple generator which eliminate the described drawbacks. It based on the use of strong acid cation chromatography paper as sorbent for ^{81}Rb instead of ion exchange resin. Four pieces of round papers (25 mm in diameter) are hold between two stainless steel support screens in a leak proof holder, which is situated in shielding container. The capacity of used ion exchange paper (Macherey-Nagel, MN 616-LSA-50) is sufficient for the sorption of produced ^{81}Rb and other co-produced radiorubidium isotopes. Preparation of generators, which in our arrangement withstand pressure of 10 bar is very simple. We have measured the absolute yield and elution efiiciency of ^{81m}Kr in dependence on different conditions and different eluents (gases and solvents).

The advantages of presented generator are: constant elution eficiency (over 80% related to sorbed ^{81}Rb aczivity) in long time experiments; neglected internal volume; low elution pressure; simple and cheap construction and preparation.

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PRODUCTION OF ^{81}Rb FROM Kr - A TARGET STUDY

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As gas target chamber for production of ^{81}Rb via the ^{82}Kr((p,2n) reaction ($E_{threshold}$= 14 MeV) has been constructed. The maximum proton energy for external beam at the Åbo Akademi cyclotron is 18.3 MeV, i.e. in this contest rater low. Furthermore,expensive enriched gas has to be used in order to get useful high yields of Rb(^{nat}Kr contains 11.6% ^{82}Kr) . (1,2) Thus the target chamber volume must be carefully optimized. With this in mind some experiments were made.

Natural Kr-gas was irradiated with 18 MeV protons at a pressure of 6 bar in a windowed target chamber (length 103 mm) previously described. (3) The energy of the proton beam was degraded to 14 MeV in the target (4), thus making use of the effective energy region of the ^{82}Kr(p, 2n) cross section. (5) Photographs were taken in the light emitted by the beam interacting with the target gas, showing the particle scattering in the two 12.5 um thick stainless steel foils and in the target. The findings of this experiment were then used to construct a steel target chamber with a conical shape (length 100 mm, inlet aperture 11.4 mm, base aperture 21.4 mm).

In another experiment a 7 MeV deuteron beam was used to study the heat transfer the gas during irradiation. The same windowed target chamber mentioned earlier was used. (3) The interferograms in Fig. 1 a-d show the strong upward gravitational transport of the gas from the beam region immediately after the beam was switched on, before steady state conditions were reached (the time between successive interferograms is 0.5 s). This upward flow of the heated gas from the beam region indicates a possible uneven distribution of the radioactivity attached to the target chamber inner surface. In order to check this a thin (12.5 um) stainless steel liner was inserted into the production target chamber before filling with ^{nat}Kr to a pressure of 6 bar and irradiating with 18 MeV protons of 1 uA for 5 minutes. After the irradiation the liner was removed, covered with an adhesive foil and cut into ten vertical sections representing a distribution along the beam. Each section was cut into four pieces representing a distribution around the beam. Each piece was measured separately with a Ge(Li)-detector in order to determine the amounts of ^{81}Rb(γ-line at 190 keV) and ^{82m}Rb (γ-line at 776 keV). The results can be seen in Fig. 2, showing the radioactivity distribution along the beam axis (i.e. the sections), and in Fig. 3 a-b, a) showing the distribution of Rb along the beam axis in different directions around the beam and b) showing the same for ^{81}Rb (the solid lines are drawn to guide the eye). The segmental division shown in Fig. 3 was chosen assymetric with respect to the gravitational axis in order to get more detailed information about the upward transport of the radioactivity.

It is interesting to note that the distribution of the radioactivity along the target chamber inner surface seems to reflect the cross sections of the reactions producing the isotopes in question. Together with the distribution around the beam, this indicates that the "hot" atoms produced in the nuclear process are rapidly transported to the target chamber wall. To a large extent the Rb-atoms seem to get attached to the chamber walls immediately they come in contact with the metal. It should however be noted that about 15% of the Rb-atoms produced are removed with the Kr-gas when the target chamber is emptied.

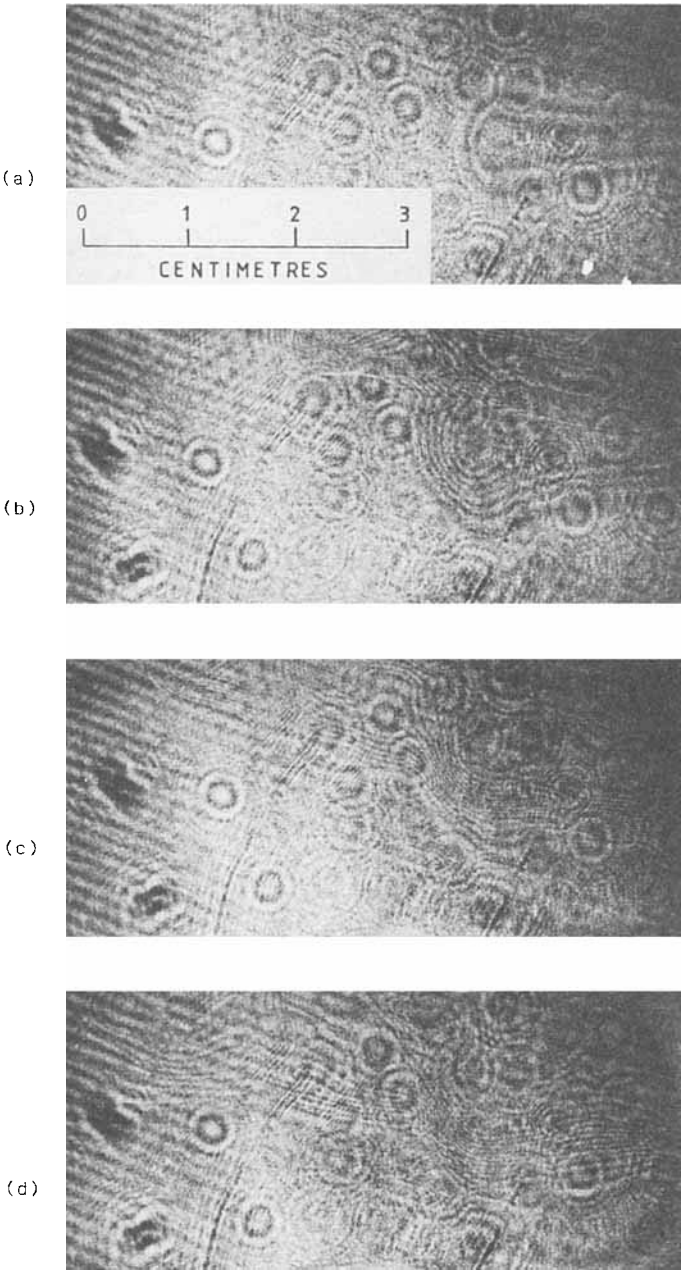

Fig. 1. Successive interferograms (a-d) of a 7 MeV deuteron beam (1 μA) on Kr-gas (P = 500 kPa) showing the heat transfer in the gas. Beam entrance from the right. Further explanation in the text.

In production runs the radioactivity is removed from the target walls with water circulated through the target chamber with a peristaltic pump. The yield of Rb is less than 1 mCi/uAh. Enriched target gas (70% ^{82}Kr) and cryopumping (for recovery and reuse) (2) will be used in the future.

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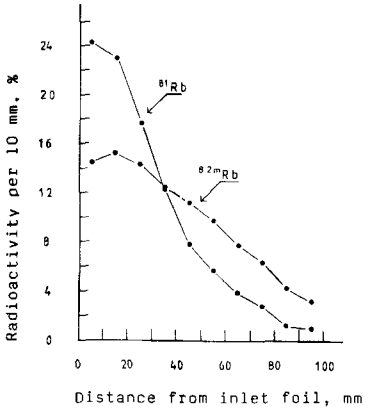

Fig. 2. Distribution of radioactivity on target chamber inner surface along beam axis.

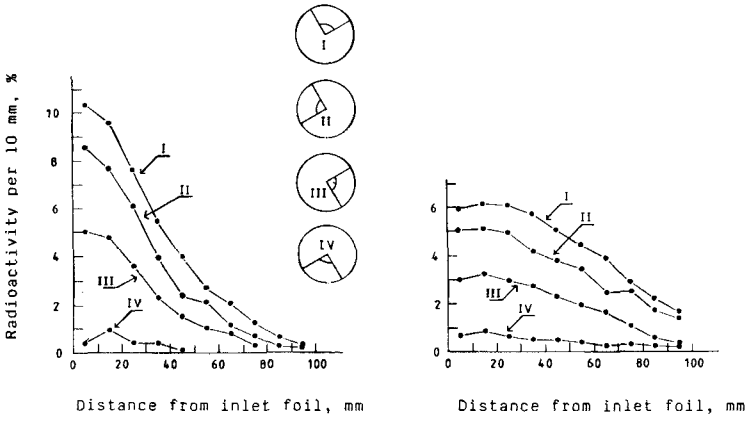

Fig. 3. a) Distribution of ^{81}Rb on target chamber inner surface along the beam axis in different directions (I-IV) around the beam.
b) Distribution of ^{82m}Rb on target chamber inner surface along the beam axis in different directions (I-IV) around the beam.

DENSITY REDUCTION AND TEMPERATURE MAPPING IN A Ne-GAS TARGET

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A method has been developed by which the density reduction and temperature increase in a pressurized gas target bombarded with high energy particles can be quantified by studying the behaviour of the atomic emission lines from the target medium. (1) Such information is of interest when gas targets are constructed for radionuclide production.

The dominating interactions between the beam particles and the target atoms are elastic and inelastic scattering. The energy exchange in these collisions is low and results in a recoil kinetic energy for the target atoms which is less than the average thermal kinetic energy. The atoms excited in these collisions can therefore be expected to reflect the conditions of the gas in the beam region at thermodyna - mic equilibrium.

It is known (2) that the spectral lines emitted from a dense gas are broadened and sometimes displaced in wavelength due to collisions between the excited atoms and the surrounding atoms. These phenomena depend strongly on the gas pressure. The simplest possible model for line broadening is that the collisions with the excited atoms interrupt the de-excitation, resulting in a Lorenzian line-profile of a FWHM given by

$$\Delta\omega = 1/\pi\tau_0, \qquad (1)$$

where τ_0 is the average time between collisions and ω is the frequency of the emission line. As τ_0 decreases with pressure the collision broadening increases with pressure.

Theoretically (See e.g. Refs 3 and 4) the widths of spectral lines are well understood at low densities, the width being proportional to the density. One has

$$\Delta(1/\lambda) = k \cdot \rho, \qquad (2)$$

where the broadening constant k depends on both the initial and the final states of the transition.

Previously Eq. (2) has been assumed to hold strictly only at very low pressures (of the order of a few torr). We have measured the FWHM:s for two Ne-lines, Ne 5852 Å and 6402 Å, as functions of the pressure in the range 20-500 kPa in a Ne-gas target bombarded with a 7 MeV deuteron beam, at a constant beam current of 2 μA. The experimental setup can be seen in Fig. 1. The measured FWHM:s were reduced by the instrumental FWHM and plotted as functions of the pressure (Fig. 2). In spite of the high pressures involved there is a linear relation between the reduced line widths and the pressure. The broadening constant is much larger for the Ne 5852 line than for the Ne 6402 line, the value being consistent with theory as well as extrapo - lations from low density. For the Ne 5852 line the broadening is 0.00323 Å/kPa and 0.00076 Å/kPa for the 6402 line.

It is known that the density in the beam region of the target gas is reduced with increasing beam current (5,6). Measuring the line profile of the Ne 5852 line at constant target pressure exhibits this density reduction as a reduction in the line width. Results from measurements of the width of this line at 1, 2,3 and 4 μA beam current at an absolute pressure of 208 kPa are shown in Fig. 3. It can be seen that the reduction in the line width is 0.0365 Å/μA. It should be noted that this reduction is a function of the pressure in the target, the beam diameter and the position at which the measurement is done (the beam diameter was 5 mm at the entrance).

As the broadening constant itself is temperature independent the results of Fig. 3 can be combined with the equation of state and used to calculate the temperature increase in the beam region at the observed position and pressure

$$dT/dI = - T/P(dL/dP)^{-1} \; dL/dI. \qquad (3)$$

Substitution of the numerical values of the quantities in Eq.(3) (T=283 K, P = 208 kPa) gives dT/dI = 15.4 K/uA, corresponding to the conditions under which the results of Fig.3 were obtained. The numerical value of dT/dI indicates that at 4 uA current the average temperature increase is about 60 degrees (at 200 kPa absolute pressure).

This study has shown that within the pressure range of 20-500 kPa there is a linear relation between the broadening of the spectral lines excited by the ion beam and the pressure (density) for the neon gas target. We have measured the sensitivity of the line broadening to variations in the pressure (dL/dP) which depends on the spectral line selected, i.e. on the initial and final states involved in the transition. As a result of this, we have obtained a method to measure the temperature increase at any position of the beam volume. A map of the temperature distribution in the target gas could thus be obtained.With equipment specially designed for this purpose temperature mapping could be done rapidly and accurately (to an estimated accuracy of 1 degree), in a noninvasive way.

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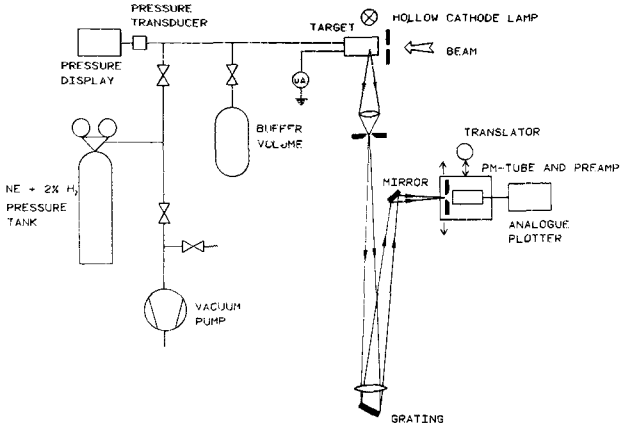

Fig. 1. Schematic diagram of experimental setup.

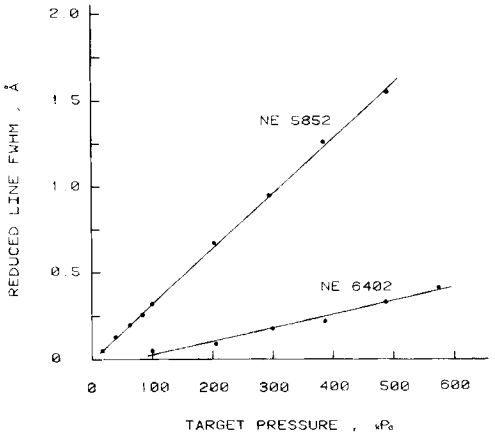

Fig. 2. Reduced line widths as functions of pressure for the Ne lines 5852 Å and 6402 Å.Beam current 2 μA.

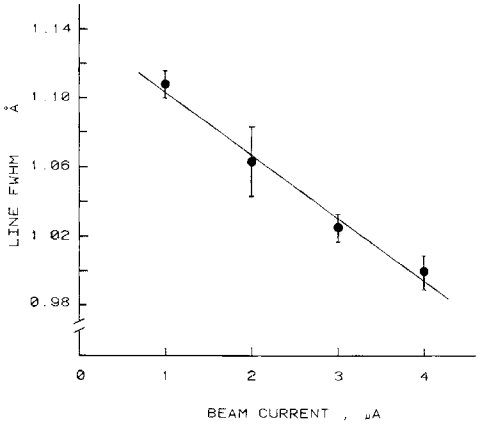

Fig. 3. Line width as function of beam current for the Ne line 5852 Å.Target pressure 208 kPa.

^{109}CD → ^{109m}AG BIOMEDICAL GENERATOR

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The decay characteristics of ^{109m}Ag, 39.6 sec half life and 88-keV gamma, suggests that this isotope is suitable for blood flow experiments where repetitive measurements with low patient exposure are desirable. The availability of curie quantities of ^{109}Cd (1) has focused attention on the feasibility of a ^{109}Cd → ^{109m}Ag generator as a long-term source of ^{109m}Ag for the nuclear medicine community.

^{109}Cd → ^{109m}Ag generators developed in the past have suffered from excessive ^{109}Cd breakthrough (2) or required the use of a stripper column for reduction of the breakthrough (3). We have investigated the use of several inorganic ion exchange materials including $Cd_3(PO_4)_2$, $AlPO_4$,$Al(PO_3)_3$, and tin phosphate as the solid phase in a generator.

Pretreated tin phosphate and an eluent consisting of ascorbic acid, $Na_2S_2O_3$, and phosphate buffer were selected as the generator system on the basis of low ^{109}Cd breakthrough. The ^{109m}Ag yield from this generator increased to a maximum of 75% by the 14th sample (1.5 ml per sample). By sample 143 the ^{109m}Ag yield had decreased to 45%. This decrease occurred during storage of the generator. The 45% yield has remained constant through sample #389. ^{109}Cd breakthrough was 1×10^{-6} at sample #14, 0.3×10^{-6} at sample #143, and 0.3×10^{-6} at sample #389.

Several enhancement techniques such as elevated temperature elutions and column rinses have shown promise of providing a stable generator with higher ^{109m}Ag yield and low ^{109}Cd breakthrough.

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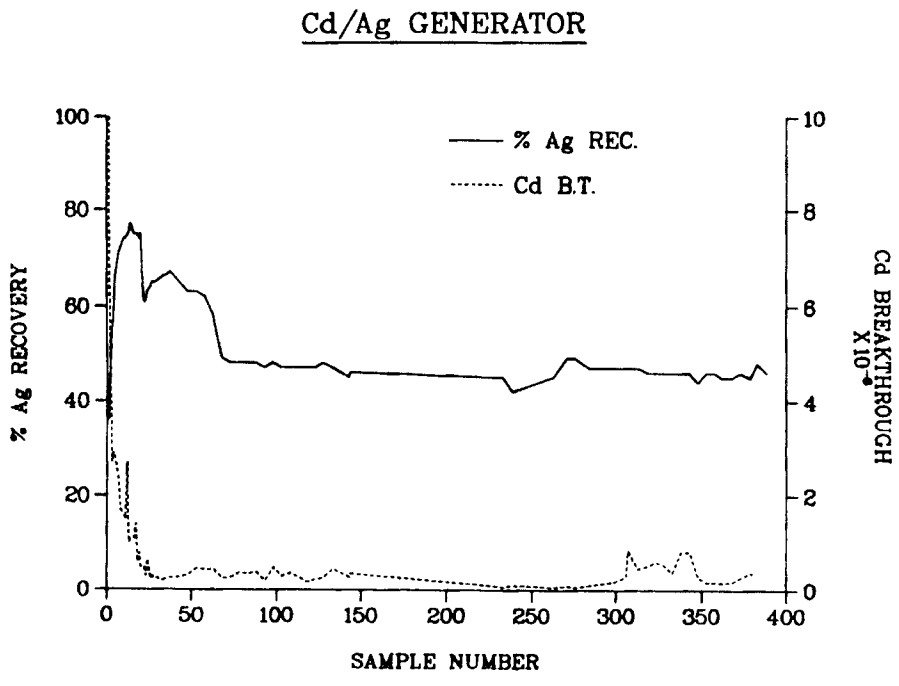
Cd/Ag GENERATOR
% Ag REC.
Cd B.T.
% Ag RECOVERY
Cd BREAKTHROUGH X10⁻⁴
SAMPLE NUMBER
100
80
60
40
20
0
10
8
6
4
2
0
0
50
100
150
200
250
300
350
400

PRODUCTION OF NO-CARRIER-ADDED ^{117m}Sn

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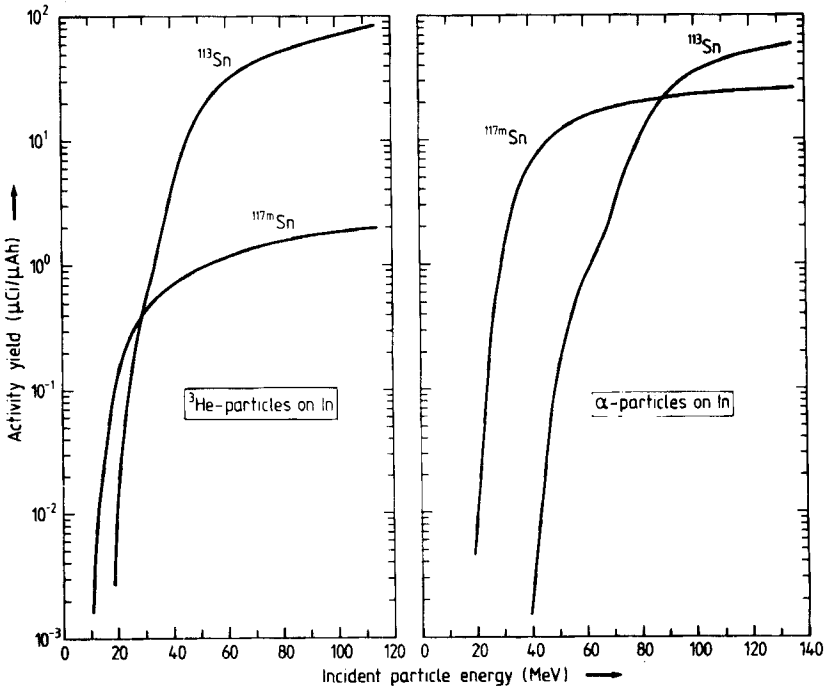
The radioisotope ^{117m}Sn ($T_{1/2}$ = 14.0 d) is practically a pure γ-ray emitter (E_γ = 159 keV; I_γ = 86.4 %) and is therefore of potential interest for single photon emission computed tomography. It is generally produced via the $^{116}Sn(n,\gamma)^{117m}Sn$ reaction in a nuclear reactor. The achievable specific activity is, however, low. We investigated its production in a no-carrier-added form.

Excitation functions were measured by the stacked-foil technique for the formation of ^{117m}Sn and ^{113}Sn in the following four cases:

a) ^3He-particle induced reactions on cadmium
b) α-particle induced reactions on cadmium
c) ^3He-particle induced reactions on indium
d) α-particle induced reactions on indium

The maximum energies used were $E_{^3He}$ = 120 MeV and E_α = 140 MeV. The thick target yields of ^{117m}Sn in ^3He- and α-particle induced reactions on In are shown in the figure. The $^{116}Cd(\alpha,3n)^{117m}Sn$ and $^{115}In(\alpha,pn+d)^{117m}Sn$ reactions were found to be suitable for the production of ^{117m}Sn. Various production parameters relevant to the latter process were investigated. The optimum energy range was found to be E_α = 45 → 20 MeV; the theoretical thick target yield of ^{117m}Sn amounts to 9.2 μCi/μAh and the ^{113}Sn-impurity level to 0.22 %. The target consists of a thin layer of In on a Cu-backing and can withstand 120 MeV α-particle internal beam currents of up to 7 μA. A dry distillation method for the separation of radiotin as $^{117m}SnCl_4$ was developed. The experimental batch yield of ^{117m}Sn amounts to 0.8 mCi (EOB) and the level of ^{113}Sn-impurity to < 0.5 %.



PRODUCTION AND SEPARATION OF TIN-117m FOR BONE RADIOTHERAPY

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It has recently been shown (1,2) that the non-phosphate Sn-117m(4+)DTPA has high affinity to normal bone with little soft tissue deposition. Since the uptake is primarily in cortical bone, the long physical half-life (14 d) and the abundance of short range Auger and conversion electrons make Sn-117m(4+)DTPA an attractive therapeutic agent for bone tumors. Compared to P-32 phosphates (with high energy β's) this tin radiopharmaceutical offers similar bone dose but significantly lower bone marrow and whole body exposures. However, the low specific activity of reactor produced Sn-117m is a limitation in this application.

To this end, a study has been made of the feasibility of producing clinical quantities of no-carrier added Sn-117m by irradiating a natural antimony metal target with protons using $Sb(p,2pxn)^{117m}Sn$ reactions at the Brookhaven Linac Isotope Producer (BLIP). Although antimony is a good target in that adequate yields of both Sn-117m and Te-118, also of interest to our program, can be produced simultaneously, the separation of Sn and Te from a large Sb target is difficult.

Antimony metal can be readily dissolved in hot conc. HCl (∿80°C) saturated with Cl_2. Vigorous mixing will speed the dissolution. No loss of Sn was observed even when the solution was near boiling. We have dissolved 4 g of Sb metal in 6 ml of conc. HCl in less than 2 hours while Cl_2 was passing through the mixture.

Isolation of Sn from Sb can be achieved by anion-exchange chromatography from a dilute HCl solution (1-2 M) in which Sn(IV) is retained by the column (D_v ∿100) and Sb(IV) is eluted (D_v ∿1). The solubility of Sb(IV) in 1.2 M HCl is about 3 mg/ml at room temperature. Above this metal concentration, Sb will precipitate as an oxychloro complex. Therefore, a typical 20-g Sb target would require several liters of solution resulting in an impractical column size. It is shown that in dilute HCl solutions (≥1 M) coprecipitation of tracer amount of Sn with $Sb(OH)_xCl_{5-x},YH_2O$ is only a few percent. Therefore, a strongly acidic chloride solution of Sb can be diluted until a 1-2 M solution of HCl is obtained without appreciable loss of Sn. We have used this procedure to remove more than 80% of the Sb target prior to the anion-exchange step. Tellurium(IV), in tracer concentration, will quantitatively coprecipitate with Sb, but In(III) and Ag(I) will remain with Sn(IV) in solution. Separation of Sn from these elements and the last traces of Sb was achieved by washing the column with 1.2 M HCl. The Sn activities were eluted from the column with 2.8 M $HClO_4$, evaporated to near-dryness with conc. HNO_3 without loss of Sn and finally were taken up in 1.2 M HCl.

In order to select optimal irradiation conditions at the BLIP, the determination of relevant thin target excitation functions from 22-75 MeV on ^{121}Sb and ^{123}Sb are underway. Data from 43-60 MeV are complete and show the $^{121}Sb(p,2p3n)^{117m}Sn$ reaction cross-sections increasing from 2.1 mb to 5.2 mb in this energy range, while the $^{123}Sb(p,2p5n)^{117m}Sn$ reaction cross-sections are essentially constant at 5 mb.

The results from several preliminary thick target bombardments at nonoptimal energies are shown in Table 1. These yields are sufficient to produce at least 500 mCi of Sn-117m (t_b = 14 d, I = 50 μA). Although the yield is somewhat higher at 190 MeV, there is an unacceptable amount (36%) of Sn-113 produced. This was expected and was done purposely to allow use of the 391 keV peak of Sn-113 as an internal tin tracer since the 159 keV gamma ray of Sn-117m coincides in energy with a gamma ray of Te-123m and would then require a time consuming decay curve analysis. At 55 MeV (t_b = 14 d) the fraction of Sn-113 is about 0.02. The measured thick target yield at 55 MeV is 80% of theoretical

(based on our cross sections). The specific activity is wholly dependent on the tin impurity in the antimony target and is calculated to be 30 mCi/μg for each ppm of tin impurity in the target.

We have also investigated methods of improving the specific activity of Sn-117m attainable with reactors, such as the High Flux Irradiation Reactor at Oak Ridge National Laboratory (ORNL). Table 2 summarizes the data on a series of irradiations at different core positions in the BNL High Flux Beam Reactor on natural tin, enriched Sn-116 and enriched Sn-117. The yield increased for both targets when the fast flux increased even though the thermal flux decreased. The effects of Sn-117m burn-up are small. Therefore, these measurements indicate the importance of fast neutron reactions in giving increased yield of Sn-117m due to several strong neutron absorption resonances at neutron energies of 4-125 eV. The highest specific activity is obtained by irradiating Sn-117 at position V-15 in the HFBR rather than irradiating Sn-116, despite a thermal neutron flux only 0.08 times that available at ORNL.

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Table 1. Production of ^{117m}Sn at BLIP

Target	Dose μAh	Weight (g)	T_b	Proton energy (MeV)	Saturation yield (mCi/μA-g)
Sb metal	52.	36.	1h	55–38	0.61
Sb metal	0.42	0.66	5m	191–190	1.1
Sb metal	7924	20.	11d	191–180	0.5*

*Based on two analyses of 4 g and 2.6 g target samples.

Table 2. Reactor Production of ^{117m}Sn

Target	Irradiation location	Primary nuclear reaction	Effective cross section (mb)	Saturation yield (mCi/mg)	(Sn-116) + (Sn-117)
Sn-nat	V-14*	(n,γ),(n,n'γ),(n,2n)	-	0.55	
Sn-nat	V-15**	(n,γ),(n,n'γ),(n,2n)	-	1.27	
Sn-116	V-14	(n,γ)	19.8 ± 1.2	2.3	x0.147
Sn-117	V-14	(n,n'γ)	162 ± 9	2.2	x0.077 } 0.51
Sn-116	V-15	(n,γ)	182 ± 10	5.0	x0.147
Sn-117	V-15	(n,n'γ)	190 ± 10	8.0	x0.077 } 1.35
Sn-116	ORNL†	(n,γ)	-	4.0	

*HFBR in core location; ϕ_t=8.25x10^{14} n/cm^{2}sec, ϕ_f=9.0x10^{13} n/cm^{2}sec
**HFBR in core location; ϕ_t=1.95x10^{14} n/cm^{2}sec, ϕ_f=3.0x10^{14} n/cm^{2}sec
†HFIR in core location; ϕ_t=2.5 x10^{15} n/cm^{2}sec, ϕ_f 2x10^{14} n/cm^{2}sec

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RECENT IMPROVEMENTS IN THE DEVELOPMENT OF A ^{195m}Hg-^{195m}Au GENERATOR SUITABLE FOR BOLUS AND CONTINUOUS INJECTION TECHNIQUES.

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Interest in very short-lived generator-produced radionuclides for angiography studies is now very well established (1). The outstanding suitability of the nuclear pair ^{195m}Hg - ^{195m}Au as a generator has determined different centers to find out the most convenient characteristics and properties of a ^{195m}Au generator compatible for clinical use (2)(3)(4).

Nevertheless, no one so far proposed ^{195m}Au generator fulfils all the following "ideal" requirements which make it routinely usable on a large medical scale :

1. Have a practical elution efficiency of the daughter element as high and constant as possible at "clinical" flow rates in order to give a suitable highdose of ^{195m}Au and minimize the total ^{195m}Hg activity to be produced and loaded on the column, and, subsequently the radiation protection.

2. Allow the elution process either by continuous technique or by repeated single bolus method, with a safe and injectable eluting solution of a maximum volume of 200 ml.

3. Present a ^{195m}Hg breakthrough lower than 10^{-6}/ml and constant during the life time of the generator which should reach a full week.

4. Have a stability with time which equally prevents loss of elution efficency and increase of Hg breakthrough in both modes of elution, ensuring a practical shelf-life of 5 days.

5. Be easy and safe to operate and reasonable in cost in relation with the practical clinical use.

The present work reports on the recent development of this generator to the point where it gives the closest answer to the previous requirements.

The time dependance of elution yield reported in the litterature as the main limiting factor compelled us to make an exhaustive screening on the adsorption of ^{195m}Hg on more than 50 inorganic exchangers and on the desorption properties of ^{195m}Au from these supports in two defined injectable media : 9 ‰ sodium chloride solution and 5 % glucose solution, TRIS buffered at pH 7.7 (25 °C).
Hydrated titanium dioxide (OXTI) prepared under defined thermal conditions showed unexpected results different from those reported in the litterature (5).
The variation of Kd (Hg) as a function of pH shows a plateau of 3000 ml/gr for pH values between 6 and 8.

A column of 4 mm diameter, 8 cm long was loaded with 1.5 g titanium dioxide preequilibrated in a 0.5 M TRIS buffer solution with HNO_3 to pH 7.2. The ^{195m}Hg solution at pH 7.2 was slowly loaded on the prepacked column at a flow rate of 1 ml/h. A typical fixation rate better than 99.5 % is commonly reached.

^{195m}Au was eluted with a solution of 5 % glucose solution buffered to pH 7.7 (25°C). The two conventional modes of elution (batch or continuous) have been both studied and quantitatively characterized.

Under steady state conditions, an elution yield of 30 % is obtained at a flow rate of 12 ml/min. The corresponding ^{195m}Hg breakthrough was found between 2.10^{-5} and 8.10^{-6} per eluted ml.

In bolus-injection technique, elution profiles for 9 ‰ NaCl and 5 % glucose solutions showed that satisfactory elution yield ($\geq$ 10 %) can be obtained with 2 ml of eluant, with corresponding breakthrough of 4.10^{-5} per bolus.

The generator stability with time was strictly determined, in function of the total ^{195m}Hg, ^{195}Hg and ^{195m}Au activities loaded on the column. With an activity of 100 mCi ^{195m}Hg (maximum presently experienced) no significant dependance of the effective shelf-life of the generator on the integrated dose was observed. Further investigations with higher ^{195m}Hg loaded activities are presently being evaluated.

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ASTATINE-211: PRODUCTION, RADIOCHEMISTRY AND NUCLEAR DATA

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The potential of ^{211}At for therapeutic biomedical applications was recognized (1) in 1941 due to the radiotoxicity associated with its alpha particle emission and that of its daughter ^{211}Po ($T_{1/2}$ = 0.56s). ^{211}At has a 7.21 half-life which is sufficient for production, synthetic chemistry, transportation, quality control and biological application for treatment of certain diseases. Radiopharmaceutical efforts have focused on the preparation and in vivo evaluation of labeled antibodies, proteins, drugs and inorganic colloids (2-9). This research concentrated on resolving discrepancies (10-11) in the nuclear decay scheme and the $^{209}Bi(\alpha,2n)^{211}At$ excitation function, while firmly establishing production related parameters and radiochemical procedures for the routine use of ^{211}At as astatide.

The nuclear decay properties (alpha, x-ray and gamma emissions) were evaluated for ^{211}At and its daughter ^{211}Po in order to refine or obtain the prerequisite decay data for subsequent radiopharmaceutical development and therapeutic applications of ^{211}At.

The excitation functions for the $^{209}Bi(\alpha,2n)^{211}At$ and $^{209}Bi(\alpha,3n)^{210}At$ reactions were measured at 17 energies between 21.1 and 29.2 MeV by activation of stacked thin targets. Our cross section data determined by γ-spectrometry were in general agreement with Kelly and Segrè (13); in good agreement with Ramler et al. (11) who utilized α-spectrometry; but significantly different than those reported by Sticker and Hofstetter (12).

A target assembly was designed to optimize the production of ^{211}At with external beam currents of < 10 μA for < 5 h irradiations. The experimental thick target yield under production conditions avoiding co-production of ^{210}At was 4.37 ± 0.06 $mCi \cdot \mu A^{-1}$. A novel one-step distillation and radiochemical recovery apparatus was developed to permit elution of ^{211}At into small, controlled volumes and solvents required for subsequent radiopharmaceutical chemistry. Less than 2% of the ^{211}At remained in the target for a 50m distillation at 650-680°C. If the temperature was elevated, ^{209}Bi became a chemical contaminant in the product eluent. Typically 80% of the ^{211}At was collected on a silica gel column from a dry N_2/O_2 carrier gas flowing at 25 $mL \cdot m^{-1}$. An overall radiochemical yield of 56 ± 13% was obtained for weekly production runs in which 0.45-0.6 mL of 0.5 M NaOH and 0.1 M $NaHSO_3$ was used as the eluent to collect the ^{211}At. The methods are reliable when the glassware and reagents are properly pretreated, dryed and cleaned, and if the cyclotron irradiation conditions are controlled.

$^{210}Po(T_{1/2}$ = 138d,$\alpha)$ arising from the $^{209}Bi(\alpha,t)^{210}Po$ reaction was observed at the ppm level on thick targets irradiated with 27.7-21 MeV alphas. ^{210}Po has not been previously mentioned as a radiocontaminant in ^{211}At preparations except as it arises from the decay of ^{210}At, if the incident alpha energy is greater than the threshold of the $^{209}Bi(\alpha,3n)^{210}At$ reaction.

The $^{211}Rn \rightarrow ^{211}At$ generator has been proposed as a source of ^{211}At (15), possibly for excitation labeling of radiopharmaceuticals. The lower limit of the effective cross-section of the $^{232}Th(p,x)^{211}Rn$ reaction was determined at 28.5 GeV to be 0.72 ± 0.1 mb. The ^{211}Rn ($T_{1/2}$ = 14.7h) was recovered 15 h post-irradiation by dissolution of the foil in conc. HCl, HNO_3 and HF. A He stream carried the ^{211}Rn through a Ag trap for purification to a charcoal collection trap at -196°C.

This research was carried out at Brookhaven National Laboratory under contract with the U. S. Department of Energy and its Office of Health and Environmental Research.

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THE PREPARATION OF THE RADIOPHARMACEUTICAL, (1-^{11}C)ACETATE — IMPROVEMENTS AS A RESULT OF ADAPTING FROM MANUAL TO MICROCOMPUTER CONTROL

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(1-^{11}C)Acetate has proved a valuable radiopharmaceutical for the study of myocardial metabolism in humans (1,2). Within our Unit the required doses of (1-^{11}C)acetate were originally prepared via the carbonation of methylmagnesium bromide with cyclotron-produced (^{11}C)carbon dioxide in a well-established procedure that uses manually-controlled apparatus (1). Though this apparatus performs reliably, it was found that regular use of the apparatus exposes its operator to significant radiation. Thus, the average finger dose is 7 mSv (0.7 rem) for preparations starting with 9 — 13 GBq (250 — 350 mCi) of (^{11}C)carbon dioxide. In order to be able to prepare (1-^{11}C)acetate more regularly and in greater safety from radiation we set out to achieve remote control of the operations involved in the manually-controlled preparation. Apparatus has been built in which an "Apple II" microcomputer controls and times all the operations in the radiosynthesis via an interface (a digital output card) with twelve solenoid valves (to direct fluid flow and hydraulically-powered syringes), one hydraulic oil pump, one heater and one stirrer (all operated at 24 V d.c.). This apparatus produces a sterile and apyrogenic solution of radiochemically pure (1-^{11}C)acetate for intravenous injection, with greatly reduced radiation exposure to the operator. Thus, from preparations starting with 9 — 13 GBq (250 — 300 mCi) of (^{11}C)carbon dioxide, the average finger dose is < 2 mSv (0.2 rem). Moreover (1-^{11}C)acetate is prepared nearly twice as efficiently with the microcomputer-controlled apparatus than with manually-controlled apparatus (Table 1). This increased efficiency is attributed to both an increased chemical yield and a shorter preparation time (Table 1).

The reliably high performance of the microcomputer-controlled apparatus has been found to permit useful flexibility in the design of clinical experiments with (1-^{11}C)acetate and positron emission tomography. For example, the high average yield (5.2 GBq; 141 mCi) permits two doses of (1-^{11}C)acetate, each of about 370 MBq (10 mCi), to be administered up to at least 60 min (i.e. 2 — 3 half-lives of carbon-11) apart. This possibility has proved very valuable in the study of transient myocardial ischaemia, where it is desirable to administer (1-^{11}C)acetate with the patient at rest and 40 — 60 min later with the patient at exercise (2).

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Table 1. Radiochemical yields, preparation times and efficiencies for the preparation of (1-^{11}C)acetate by manual and microcomputer control.

Control of preparation	No. of studies	Radiochemical yield[a] (mean ± SD)%	Preparation time (min)	Efficiency[b] of preparation (mean ± SD)%
Manual	35	48 ± 16	20	24 ± 8
Microcomputer	8	70 ± 11	11.5	47 ± 8

[a] Decay-corrected and based on the activity of $^{11}CO_2$ dispensed

[b] Non-decay-corrected radiochemical yield from $^{11}CO_2$

REMOTE-CONTROLLED SYNTHESIS SYSTEM FOR PRODUCTION OF C-11 HYDROGEN CYANIDE

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Hydrogen cyanide is one of the most useful C_1 compound in organic synthesis. Similarly, C-11 hydrogen cyanide is important C-11 source in the synthesis of C-11 labeled organic compounds. It can produce sugars, deoxysugars, amino acids, amines and other labeled compounds useful in cyclotron nuclear medicine. As in the case of other C-11 precursors, production of C-11 HCN should be performed in a shielded cell to avoid radiation exposure to personnel because large amount of activity will be required for the syntheses of C-11 labeled compounds mentioned above. Here we report remote-controlled system for production of C-11 hydrogen cyanide.

Figure 1 shows a schematic diagram of the C-11 HCN production system. Production of C-11 HCN was conducted by the catalytic reaction of C-11 methane and ammonia on platinum wire. C-11 methane was produced in the target box using N_2-H_2 gas mixture or by the reduction of C-11 carbon dioxide in the reduction unit. Production of C-11 methane by the latter seemed to be advantageous because of relatively low recovery of C-11 methane in the former owing to the accompanied hot atom reactions. Ammonia gas was mixed by the bubbling of labeled gas through liquid ammonia or continuous flow of ammonia gas. Liquefaction of ammonia was conducted in a dry ice-acetone bath and automated with a optical liquid level sensor. The bubbling method provided better yield than the continuous flow method because moisture that hamper formation of C-11 HCN was removed in the liquid ammonia vessel (1). More than 50 % yield of C-11 HCN was obtained by this system.

A block diagram of the control system is illustrated in figure 2. It consists of dual microcomputer system. One computer is for graphic display, which displays on/off state of actuators, flow rate, temperature et al. Command inputs and alteration of synthesis parameters are possible with a light pen or a keyboard. Second computer drives actuators such as solenoid valves and electric furnaces and inputs signals of sensor devices according to the stored program in read only memory (ROM) or command through light pen. Second computer can hold up to five separate programs, so it can drive other synthesis system such as for N-13 ammonia, C-11 methyl iodide or F-18 FDG. The computer for graphic display can communicate with one of three computers and their communication is able to interchange at any time with a intervention of interface box, so two or three synthesis systems can operate concurrently.

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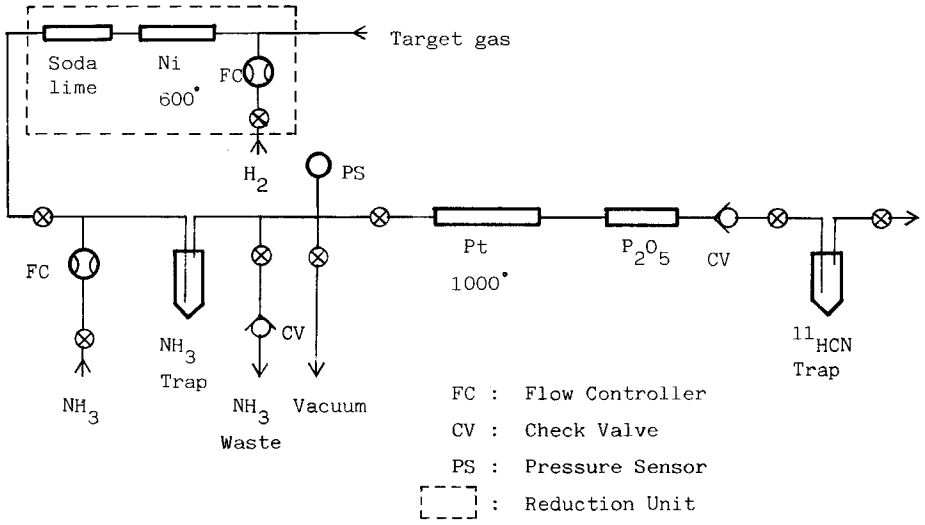

Fig. 1 C-11 HCN Production System

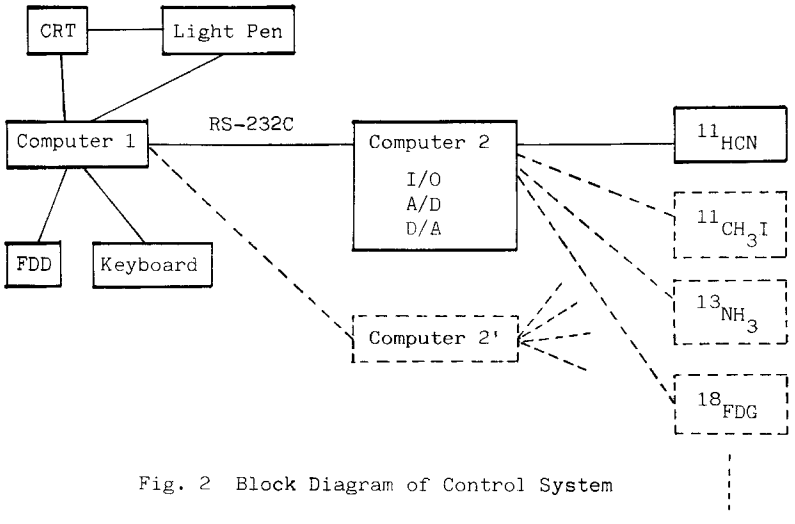

Fig. 2 Block Diagram of Control System

ENRICHMENT OF ^{11}C METHANE BY CAPILLARY GAS CHROMATOGRAPHY

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The need to have high specific activity precursors for the synthesis of ^{11}C radiopharmaceuticals which are toxic or are used for in vivo observation of specific receptors has led us to enrich methane, the simplest precursor, by capillary gas chromatography.

This has been done on 300 m. long soft glass columns (1), previously hydrated by several hours passage of the carrier gas on $Cu\ SO_4\ 5H_2O$ (2).

$^{11}CH_4$ produced by 20 MeV proton irradiation of nitrogen + 5 % hydrogen (^{14}N, $p\alpha$, ^{11}C) is collected on a first Porapak trap (l = 15 cm, Ø = 0.4 cm) cooled at -196°C, then it is transferred to a smaller one (l = 7 cm, Ø = 0.2 cm). The nitrogen which is collected at the same time as methane is swept off by a current of helium.

All these operations, including the injection on the column, are remote controlled by electrovalves (fig. 1).

Chromatography is performed at -207°C-208°C. This temperature is obtained by adiabatic evaporation of liquid nitrogen. The carrier gas is a mixture of helium +2,5 % nitrogen.

Starting with 200 mCi ^{11}C methane, with an inlet pressure of carrier gas of 1.5 bar, 20-30 mCi of purified methane are obtained 50 mn later (fig. 2). The specific activity at this time is 40 Ci/µmole and the number of theoretical plates measured on radioactivity is 20×10^6.

This is the first step for routine production of highly enriched $^{11}CH_4$: chromatography must be now performed with several curies, the retention time must be shortened.

The next problem will be the transformation of methane into a more reactive precursor : ICH_3, CH_3OH, CNH or HCHO. This operation must be quantitative, rapid and without isotopic dilution.

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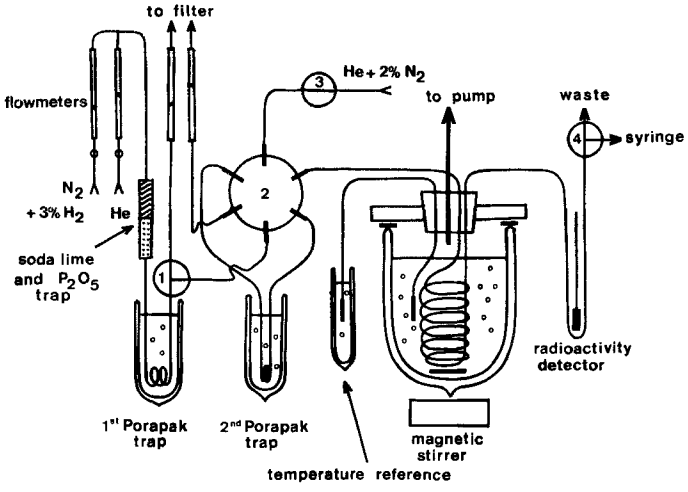

Fig. 1 - Scheme of the apparatus
1 and 4 : 3-port electrovalves
2 : 6-port electrovalve
3 : 2-port electrovalve

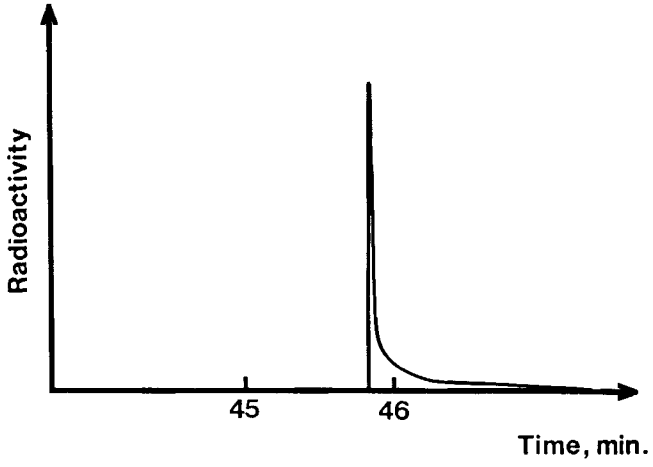

Fig.2- Capillary gas chromatography of $^{11}CH_4$ radioactivity
carrier gas : mixture He + 2.5 % N_2
temperature : -207°
inlet pressure : 1.5 bar

DEPYROGENATION OF RADIOPHARMACEUTICALS WITH THE ULTRAFILTER

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Pyrogen causes a very severe problem in the preparation of short-lived radiopharmaceuticals for an intravenous injection, especially in the biosynthesis with an automated equipment since it is very difficult to sterilize and depyrogenate valves, tubes, enzyme column. etc. assembled in the automated equipment.

It is possible to decrease the concentration of pyrogens by the use of a commercially available ultrafilter(1). A small dead volume in a filter holder, a fast filtration speed and an easy assembling of the filter into a holder must be achieved for the application of the ultrafilter to the preparation of short-lived radiopharmaceuticals for an intravenous injection.

The penetration ratios of E. Coli endotoxin, glutamate dehydrogenase (molecular weight Mw=340000) and bovine serum albumin(Mw=66000) through the ultrafilter(nominal molecular weight limit NMWL=10000) were determined by Limulus amebocyte lysate(Pyrogent) test, measurement of enzyme activity and the Lowry method, respectively. The results are summarized in Table 1.

The cyclotron-produced radiopharmaceuticals, (N-13)-ammonia, L-(N-13)-glutamate and 3-(I-123)-iodotyrosine were prepared without any sterile procedure other than ultrafiltration with an specially designed filtration assembly which was previously sterilized. Pyrogens were not detected in any product solution. A small dead volume(≈0.6 ml) was achieved with the 47 $mm^{\emptyset}$ filter assembly.

The results suggest that the ultrafiltration method can be widely applied to the preparation of other short-lived radiopharmaceuticals (2).

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Table 1. Penetration Ratios of Macromolecules through an Ultrafilter(NMWL=10,000)

	BSA	GDH	ECE
Molecular Weight	6.6×10^4	3.4×10^5	------
Penetration Ratios	$(1.0 \pm 0.1) \times 10^{-4}$	$<3 \times 10^{-6}$	$<6 \times 10^{-7}$ $>2 \times 10^{-7}$

BSA: bovine serum albumin, GDH: glutamate dehydrogenase
ECE: E. Coli endotoxin

PRODUCTION OF RADIONUCLIDES USED FOR INTERCAVITARY CANCER THERAPY

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This work investigated the ability, the advantages and disadvantages of the local production of special radionuclides on the cyclotron and a small research reactor for medical use. The Heidelberg Cancer Research Center has such a facility for the production of radionuclides for medical and biological experimental research work.

The application of unsealed radionuclides typically represented by medical use seems to be increasing in short-lived, mostly positron-emitting radionuclides of organic elements (^{11}C, ^{13}N, ^{15}O etc.), used as labels in physiological studies (positron emission tomography). However, the reactor produced isotopes will also continue to expand paralleled by advancement of its application technology. The authors compare the production of radionuclides on both machines for this scientifical field and describe especially the development in the production and use of reactor radionuclides in the last two decades and the contemporaneous situation.

In fact there seems to be in the last years lower medical interest in simple radioactive formulations with the exception of ^{99m}Tc. ^{99m}Tc as the radionuclide with almost ideal nuclear properties for application in nuclear medical diagnostic, is not suitable for many metabolic studies and not at all for the therapy. Experimental nuclear medicine has moved on to sophisticated diagnostic and therapeutic systems in which radioactive component plays a minor, but a very special role. On the other hand, the search for the radionuclides for the cancer therapy with favourable aspects in nuclear data seems to be increasingly important new field in reactor radionuclide production. The role for unsealed radionuclides in cancer therapy remains largely unrealised; the reason being the scarcity of carrier molecules with which to achieve differential tumour accumulations and the paucity of appropriate radionuclides in the tumour. Classical radiotherapy is gradually replaced by local remote-controlled afterloading procedures in the intracavity treatment of tumours. The first results of the treatment justify

to speak of good perspective for this contact radiation therapy. The possibility of this method is discussed with regards to the physics and chemistry of the used and produced radionuclides.

The therapeutic range of the radionuclides which can be used for cell destruction is dependent on its physical characteristics and on the suitable chemical form for application. Two types of radioactive decay, which satisfy the therapeutic requirements are: electron capture with subsequent Auger cascade and pure weak beta (or alpha) decay. Among the currently available used radionuclides with therapeutic efficacy are - ^{125}I(1); ^{211}At(2); ^{252}Cf(3); ^{90}Y(4) etc.

Based on the requirements for the "ideal" radionuclide for the therapy of tumours: the physical half-life; the average particle energy; the range in the water; the linear energy transfer and the chemical behaviour and biological toxity - we have chosen and studied as the radionuclide of interest, the following isotopes: ^{103}Pd; ^{111}Ag; ^{119m}Sn; ^{159}Dy and ^{181}W. The targetry, irradiation conditions, measurement of the yield figures and testing of the purity of the products are described and production methods have been developed. The reactor production of ^{103}Pd and ^{111}Ag were compared with the production of these radionuclides on the compact cyclotron.

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MULTI-CURIE GENERATOR PRODUCTION OF HIGH-PURITY, NO-CARRIER-ADDED IODINE-123.

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Because of its unquestioned properties, the utilization of I-123 as a radiotracer continues to be the subject of numerous research efforts dealing with the development of I-123 radiopharmaceuticals for diagnostic nuclear medicine applications. Renewed interest in continuing expanding I-123 production capabilities has arisen mostly due to the diagnostic potential of new brain-imaging agents (amines and diamines), myocardial agents (phenyl fatty acids), and the possibility of its use in localizing tumors with new antibody/fragments radiopharmaceuticals (1). At UC Davis, and since the initial development of a molten-NaI target and a continuous-flow system for the production of high radionuclidic purity I-123 (2,3), research has continued in order to improve the production techniques and to maximize yield, purity, and the product's overall radiochemical quality.

As reported in 1982 (4), a new transportable Xe-123->I-123 generator system was developed and tested for multi-Curie production of I-123. Since September of 1982, when production with this system began, improvements in I-123 yields and radiochemical quality have been achieved. However, the use of generators also required that many production techniques be modified. A schematic of the complete production system, as is presently in operation, is shown in figure 1. Multiple back-up options, complete automation, and remote-control capabilities resulted in 100% system reliability in more than 240 production runs (Sept. 82-Dec. 83). In comparison to the fractionated production mode (2,3) used before, the implementation of the generator system resulted in a 24% average increase in the I-123 production rate, to 21 $\pm$ 2 mCi/uAh for 10-12 h runs (88% of theoretical). A design modification for the generator trap allowed higher Xe trapping efficiency, while a reduction in the trap's volume (from 20-22 mL to 6-8 mL) made possible to obtain I-123 with radioactivity concentrations greater than 1.5 Ci/mL (EOP). By keeping every system component free from oxygen and/or organic matter, solutions with > 95% I-123 iodide are routinely obtained. However, the operation of the continuous-flow generator system also resulted in an increased need for complex on-line radionuclidic quality controls, off-line and prompt I-125 radioassay methods, and time-consuming procedures for reusing generators. This was mostly due to measurable variations in the I-125 levels (0.05-0.15% EOP) resulting from target, beam, and flow fluctuations, and residual I-125 in the system. The I-125 level is also affected by the length of bombardment and the parent-daughter decay times. The effect of time-of-bombardment on the I-125 level, for a 2-h ingrowth time (TOP) is shown in figure 2. Many other functions of the type shown in figure 2 are possible by variations of production parameters.

Despite these requirements, the production of (p,5n)-made I-123 based upon these techniques have been shown to be efficient and highly reliable. The expected increased demand of "I-124 free" I-123 radiopharmaceuticals will most likely be met by using similar systems, in conjunction with yet-to-be-developed higher intensity 70-MeV proton accelerators.

(*) Benedict Nuclear Pharmaceuticals Inc., Golden, Colorado 80401 USA.

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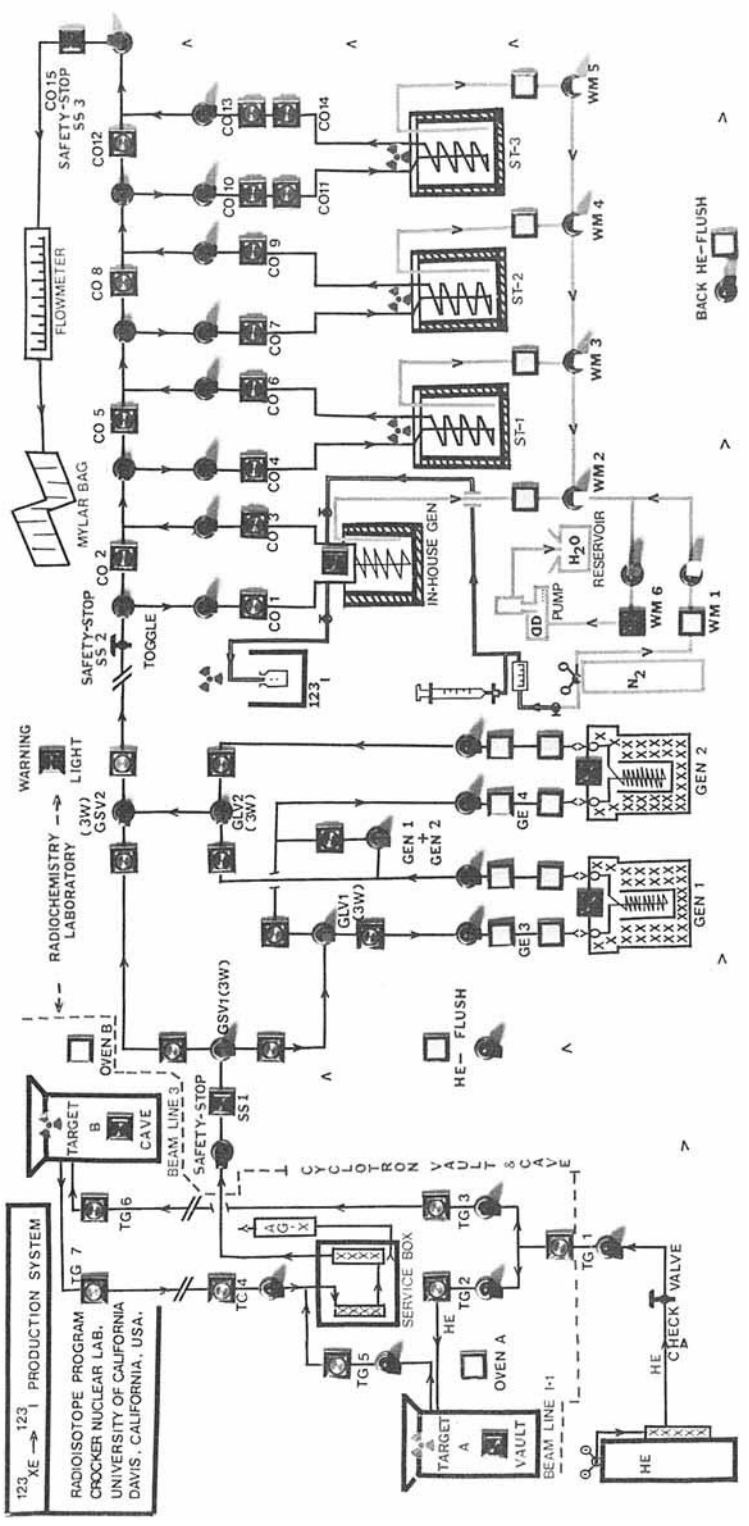
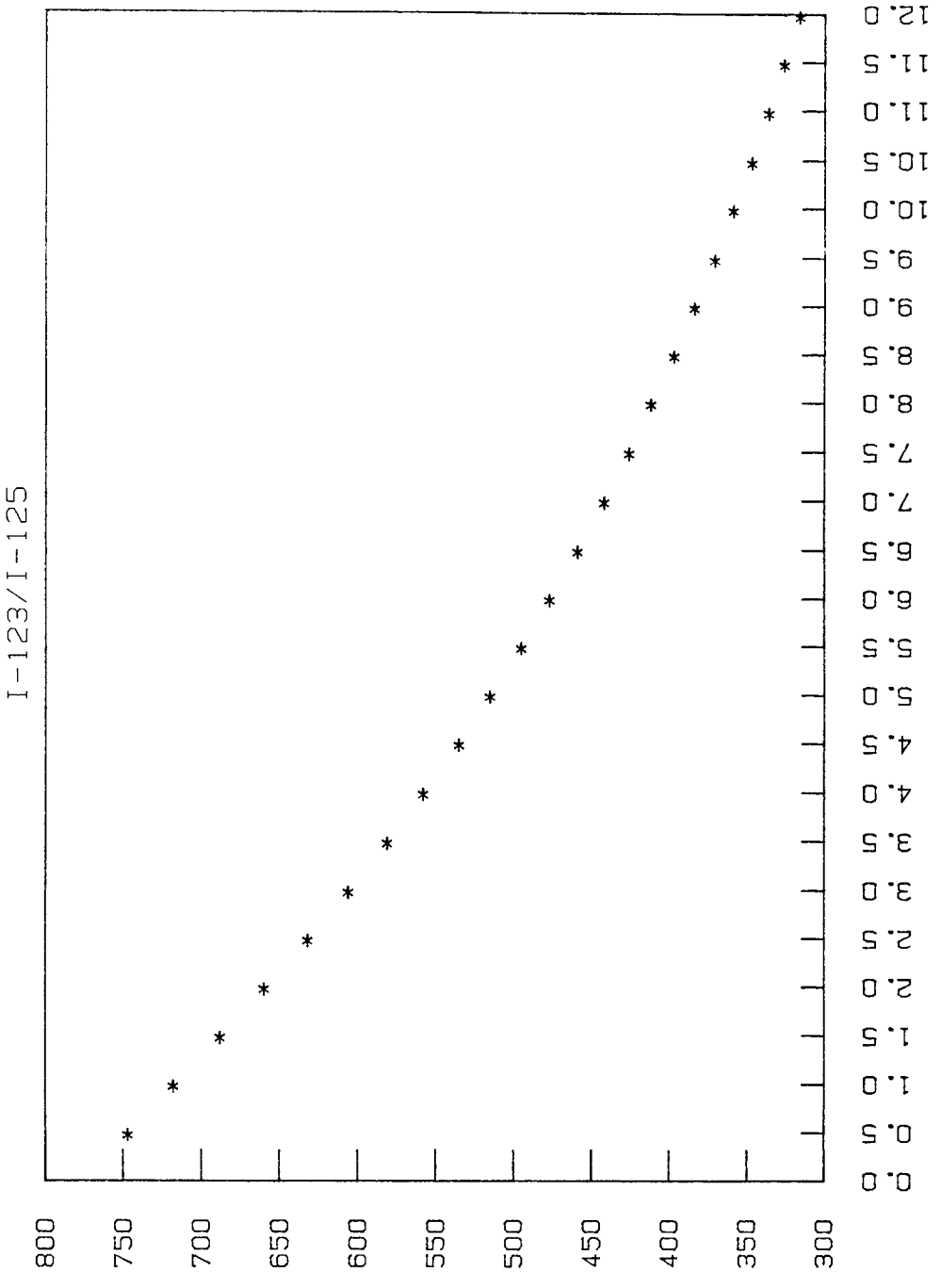

123 XE → 123 I PRODUCTION SYSTEM
RADIOISOTOPE PROGRAM
CROCKER NUCLEAR LAB.
UNIVERSITY OF CALIFORNIA
DAVIS, CALIFORNIA, USA.
TG 7
TG 6
TG 5
TG 4
TG 3
TG 2
TG 1
TARGET B CAVE
BEAM LINE 3
SAFETY-STOP SS1
GSV1(3W)
OVEN B
RADIOCHEMISTRY LABORATORY
WARNING LIGHT
GSV2 (3W)
GLV2 (3W)
GLV1 (3W)
SAFETY-STOP SS2
TOGGLE
MYLAR BAG
FLOWMETER
SAFETY-STOP SS 3
CO 1
CO 2
CO 3
CO 4
CO 5
CO 6
CO 7
CO 8
CO 9
CO 10
CO 11
CO 12
CO 13
CO 14
CO 15
IN-HOUSE GEN
ST-1
ST-2
ST-3
WM 1
WM 2
WM 3
WM 4
WM 5
WM 6
BACK HE-FLUSH
HE- FLUSH
PUMP
RESERVOIR
GEN 1
GEN 2
GEN 1 + GEN 2
GE 3
GE 4
CYCLOTRON VAULT & CAVE
SERVICE BOX
OVEN A
TARGET A VAULT
BEAM LINE 1-1
CHECK VALVE

FIGURE 1


I-123/I-125
800
750
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12.0

FIGURE 2