Over 100 patient trials have been carried out by 5 hospitals in the UK and diagnoses of kidney, liver, heart and thyroid conditions have been undertaken. Further work on these and also on adrenal and lung scanning is planned.

No. 68

STATUS REPORT ON THE PRODUCTION OF ^{123}I AT IKO

L. Lindner, A. Schimmel, J. A. Bijl, and F. M. Kaspersen

Institute for Nuclear Physics Research (IKO), Chemistry Department, Oosterringdijk 18, Amsterdam, The Netherlands

^{123}I is produced at IKO via $^{127}I(p,5n)^{123}Xe \xrightarrow{\beta^+,EC} {}^{123}I$ with the internal proton beam of the synchro-cyclotron. The basic conception is a dynamic-loop/generator system described previously[1] in which the target material is a circulating fluid from which ^{123}Xe is stripped continuously. At first experience was gained using an aqueous solution of LiI + I_2 as the target fluid. The main difficulty appeared to be the corrosive nature of this solution. In a different approach the possibility of di-iodomethane earlier[1] proposed as target material, was further pursued. The use of this organic liquid required a number of alterations in the original lay-out of the system, whereas at the same time a number of improvements was built in. These modifications including safety devices are reviewed. One problem associated with CH_2I_2 is deterioration due to radiation. This tends to increase the viscosity probably due to the formation of polymers. At the same time the formation of low-boiling organic radiation-degradation products is a potential source of interference in the further use of ^{123}I, if not removed from the ^{123}Xe from which the ^{123}I is generated. Measures to overcome these difficulties are discussed.

It is concluded that the main difficulty is a materials problem with respect to the construction of the target flow-cell, rather than the flow-system itself.

References

(1) L. Lindner, G. A. Brinkman, T. G. H. A. Suèr, A. Schimmel, J. Th. Veenboer, F. H. S. Karten, J. Visser, C. J. Leurs, "Accelerator production of ^{18}F, $^{123}Xe(^{123}I)$, ^{211}At and ^{38}S", Conf. "Radiopharmaceuticals and labelled compounds", Copenhagen, IAEA -SM-171/63.

No. 69

USE OF ONSITE NUCLEAR ACCELERATORS FOR THE PRODUCTION OF ISOTOPES USEFUL IN NUCLEAR MEDICINE

R. Kishore and H. Bakhru

Veterans Administration Hospital, Albany, New York 12208
and State University of New York, Albany, New York 12206

This study was undertaken to evaluate the usefulness of (α,xn) reaction for the production of isotopes which have been demonstrated to be useful[1,2] in diagnostic nuclear medicine. On a number of campuses of academic institutions research accelerators (linear accelerators as well as cyclotrons) are available which can provide medium energy, high intensity alpha particle beams which could profitably be used for the production of isotopes useful in nuclear medicine by piggybacking when the full beam is not being utilized for other research purposes. For the experiments described here alpha-particle beams of 40-MeV energy and average beam intensities of 2 μamp were used. Stacks of thin metal foils (44 mg/cm^2 of enriched ^{165}Ho and 76 mg/cm^2 of natural molybdenum) wrapped in aluminum foil were bombarded with alpha particle beams for 8 to 16 hours. In actual production experiments higher beam intensities and longer times could be used. After suitable period of decay the individual foils were assayed with the help of high resolution Ge(Li) detector. The pulse-height spectra obtained were analyzed for the various gamma-rays produced. Most intense gamma-ray peaks for ^{167}Tm(208-keV), ^{168}Tm(448-keV), ^{97}Ru(215-keV) and ^{103}Ru(497-keV) were used for the evaluation of the amounts of the respective isotopes produced in different foils. The percentage abundance of these gamma rays[3] and the counting efficiency of the detector were used to calculate the production of ^{167}Tm (half-life 9.3 d) and ^{97}Ru (half-life 2.89 d). The amounts of long-lived contaminants ^{168}Tm (half-life 93.1 d) and ^{103}Ru (half-life 39.6 d) which are also produced in these reactions were also estimated. The counting efficiency of the detector was obtained independently by counting known standard gamma-ray sources provided by the International Atomic Energy Agency.

The ratio of the amounts of ^{167}Tm and ^{168}Tm produced at the end of the bombardment was obtained from the peak areas for the 208- and 248-keV peaks and by the use of proper decay constants. In a typical experiment, ratios as high as 590 were obtained which are much higher than those reported by Yano and Chu[4]. In case of ^{97}Ru the ratio of ^{97}Ru/^{103}Ru produced was more than 1400.

From this data it is clear that large amounts of rather pure ^{167}Tm and ^{97}Ru could easily be produced by the use of onsite research accelerators if careful attention is given to the foil thickness and beam energies.

References

(1) R. Chandra et al., "^{167}Tm: A New Bone Scanning Agent", Radiology 100 (1971) 687.
(2) E. Lebowitz et al., "Development of ^{97}Ru and ^{67}Cu for Medical Use", J. Nucl. Med. 15 (1974) 511.
(3) C. M. Lederer, J. M. Hollander and I. Perlman, Table of Isotopes, Sixth Edition, John Wiley and Sons, Inc., New York, 1968.
(4) Y. Yano and P. Chu, "Cyclotron Produced ^{167}Tm for Bone and Tumor Scanning", LBL-2818 (Preprint), 1974.

No. 70

ASPECTS OF THE RADIOPHARMACEUTICAL APPLICATION OF A 103 cm ISOCRONOUS CYCLOTRON

M. Brenner and P. Virtanen

Åbo Akademi, 20500 Turku 50, Finland

A. Kiuru and E. Riihimäki

University Centralhospital of Helsinki, 00290 Helsinki 29, Finland

During one and a half year of operation of the 103 cm isocronous cyclotron at Åbo Akademi, methods for producing ^{123}I, ^{77}Br, ^{81m}Kr, ^{43}K, ^{52}Fe, $^{15}O_2$, $C^{15}O$ and $C^{15}O_2$ have been successfully tried. ^{123}I has been tested in phantoms and rats at several centralhospitals in Finland and the gases $^{15}O_2$ and $C^{15}O_2$ have been administered to rats and dogs in some preliminary tests.

Taking into account the capacity of the cyclotron and the local demand, the production of ^{123}I, ^{123}I-Hippuran and a suitable Thallium radioisotope seem to be urgent in the near future. Using the 28 MeV ^{3}He-beam the yield of 73 h ^{201}Tl from a HgO-target is very small while appreciable amounts of 26 h ^{200}Tl can be produced. The use of the latter isotope for myocardial diagnosis will be investigated.

As to future clinical applications the use of radioactive products of ^{15}O, ^{11}C and ^{13}N seem encouraging.

For clinical practice an isotope or labelled compound which indicates the internal inflammation, e.g. gastric ulcer, would have a promising future. The chances to use some compound for this purpose is discussed.

No. 71

APPLICATION OF THE HEIDELBERGER COMPACT CYCLOTRON IN NUCLEAR MEDICINE

W. Maier-Borst and F. Helus

German Cancer Research Centre, 6900 Heidelberg,
Im Neunheimer Feld 280, Germany

The compact cyclotron of the German Cancer Research Center in Heidelberg is a fixed energy isochronous cyclotron, designed for medical and biological applications. The Heidelberg compact cyclotron has gone into routine operation in 1975 after three years of construction and test phase. Internal and external beams of 22 MeV protons, 10.7 MeV deuterons, 22 MeV alpha and 28 MeV ^{3}He particles are available. Usable intensities of extracted beam up to now were 70 µA for deuterons, 20 µA for protons, 15 µA for the helium particles. The main applications are radionuclide production (40%) and neutron production for radiation therapy (40%). Guest groups are concerned with microdosimetric and radiobiological studies (20%). Main emphasis of the current research programs is the development of special targets for irradiating solid, liquid and gaseous materials. ^{18}F is produced in high yield three times a week. The target is semiautomatic and by bombarding of neon gas with 20 µA of deuterons in 45 minutes yields 150 mCi. ^{123}I is produced by bombarding of enriched $^{124}TeO_2$ and radioiodine is separated by sublimation technique. The practical yield of 10 mCi for a bombardment are obtained. The ^{124}I impurity at the end of bombardment is 0.8%. Radionuclides produced on a regular schedule are ^{111}In, ^{67}Ga, ^{197m}Hg, ^{81}Rb and ^{77}Br. The introduction of other short-lived radionuclides like ^{13}N, ^{11}C and ^{15}O into nuclear medicine diagnostic is being investigated. The radiochemistry group works on developing special separation techniques under the aspects of rapidity and simplicity. Sublimation separation methods are given preference because of the easier recovery of the expensive enriched target material.

No. 72

A PRACTICAL PROGRAM FOR THE PRODUCTION OF MEDICAL RADIONUCLIDES WITH A 200-MeV PROTON LINAC

L. G. Stang

60 Rutherford Drive, Brookhaven National Laboratory,
Upton, New York 11973

The purpose of the Brookhaven Linac Isotope Producer (BLIP) is to utilize the excess capacity of a 200-MeV proton linear accelerator to produce, primarily by spallation reactions, significant quantities of radioisotopes for medical applications. The products of this operation are each unique in some respect such as large quantity, high purity, low cost, special form, etc. This facility began irradiating targets at low currents in November 1972. Since then, the operating activity in terms of microampere-hours received by useful targets has steadily increased. Although the facility cannot yet be regarded as ideal, improvements continue to be made, and it is expected that design specifications will not only be achieved but ultimately exceeded. Meanwhile, the BLIP has already proved to be a practical worthwhile means of economically producing medically useful products which would not otherwise be available.

Part of the information to be presented will be in the form of a written outline to be distributed to the attendees. It will cover the objectives and goals of the BLIP program the concepts involved, illustrated descriptions of the facility as originally built, the original target design, and a recently adopted reusable target holder, and an outline of past operating performance. The verbal presentation will be limited to a mention of the few changes that have been made in the BLIP, an enumeration of the problems encountered in using a complex linear accelerator for isotope production and in transporting a high current proton beam and the modifications that have been made to overcome these problems, a comment on the performance expected in the near future, and finally a discussion of some recent considerations involving target design. The latter will include heat removal problems, particularly as they affect safe operation, and efforts to minimize cost.

No. 73

RECENT DEVELOPMENTS WITH CYCLOTRON-PRODUCED RADIONUCLIDES AT SIN - USE OF MULTIPLE AND ON LINE TARGETS IN A HIGH ENERGY PROTON BEAM

E. Loepfe, I. Huszàr, and F. Hegedues

Federal Institute of Reactor Research EIR,
CH-5303 Würenlingen, Switzerland

The injector cyclotron of the SIN (Swiss Institute of Nuclear Research) is one of the most powerful facilities in Europe in view of the production of short-lived isotopes for medical use. J-123 is of primary interest and routinely produced by the (p,5n)-reaction with a 72 MeV proton beam at 30 μA, in a weekly amount of about 1 Ci a.c. The irradiation facility, the target design (static system of pressed NaJ) and the apparatus for chemical separation are presented. A two step extraction technique for the Xe-123 allows to raise the effective yield at about 14 mCi/μAh a.c. The nuclidic purity of the produced J-123 is excellent, 0.2% a.c. of J-125 being the only detected contaminant.

The high entering proton energy allows the simultaneous production of several isotopes in static multiple targets. Combined excitation functions, target designs and first experimental results of the following systems are reviewed: J-123/Xe-125/In-111m, J-123/Br-77/In-111m and J-123/Tl-201/In-111m.

With the intent to produce J-123 daily and in a higher amount, an on line system has also been developed. The target material consists of melted sodium iodide, the Xe-123 is continuously stripped off by an internal helium stream. The working temperature of about 700°C is maintained by the conversion heat of the proton beam and controlled by an external helium gas flow cooling. An additional electron beam heating allows one to reach the working temperature rapidly in the starting phase and to maintain it at low current values.

The on line target system is irradiated in the so-called injector waste beam. That means that the target is pushed into the edge of the elliptical 72 proton beam such that 10 to 15% of the current strikes the target. By this technique J-123 can be produced continuously and independently of the experimental program of the SIN facility, at a range of about 700 mCi a.c. per day.

Two rapid labelling methods specially adapted to the short-lived J-123 are presented: the labelling of o-iodo-hippuric acid by isotopic exchange in a melt (at 182°C) and a modified chloramine-T-method for the labelling of antipyrine and bromosulfophthaleine (BSP).

A further work group deals with the possibilities of isotope production by spallations reactions in the 590 MeV beam dump of the π-meson producing ring machine. Projects and first experimental results are briefly reviewed.

No. 74

LINEAR ELECTRON ACCELERATORS FOR PRODUCTION OF RADIONUCLIDES

L. Lindner, G. A. Brinkman, and J. Visser

Institute for Nuclear Physics Research (IKO), Chemistry Department, Oosterringdijk 18, Amsterdam, The Netherlands

A powerful electron-linac ('MEA' = Medium Energy Accelerator) is under construction at a site adjacent to the existing one of IKO. The characteristics of interest of this machine are: E(max) = 500 MeV; beam power = 250 kW max, and a duty factor of several percent. There is a low energy station ($\leq$ 140 MeV) with a facility for physics and one for chemistry. There are three high-energy facilities for e^--scattering, chemistry and π,μ-physics respectively.

The high intensity, high energy Bremsstrahlung to be produced either in special conversion targets or in (or near) beam dumps, represent a potential source for the production of many radionuclides of interest, both short-lived and long-lived ones. Next to photons, fast neutrons can be produced in high abundance. Information on production capacities of linear e^--accelerators is given for two energy ranges:

1) E < 100 MeV. The data presented are based upon both literature values and our own experience with a 85 MeV linac ('EVA', now shut down).
2) E = 200–500 MeV. Predictions are given, largely based upon semi-empirical estimates of others for cross-sections of photo-spallation processes.

Specific factors which exert influence on the yield (type of conversion target; angular distribution of photons, etc.) are reviewed.

Special attention is given to 'parasitic' (rather 'symbiotic') production of radionuclides simultaneously with physics experiments.

No. 75

RADIOCHEMICAL ISOLATION STUDIES OF SPALLOGENIC BROMINE AND ZIRCONIUM FROM MOLYBDENUM

P. M. Grant, R. E. Whipple, A. E. Ogard, and H. A. O'Brien, Jr.

Nuclear Chemistry Group, Los Alamos Scientific Laboratory, Los Alamos, New Mexico 87545

Incident nucleons in excess of 100 MeV cause a complex series of nuclear events within a target, including knock-on cascade, evaporation, fragmentation, and fission processes, in addition to secondary nuclear reactions between the emitted particles and other target nuclei. Although these high-energy reactions have been studied for the past 30 years with great interest by nuclear chemists and physicists as a means of understanding nuclear reaction mechanisms and nuclear properties, they have not, until recently, been of primary concern to those interested in radioactive tracers. With the advent of high-intensity, medium-energy proton linacs and synchrocyclotrons, it is now recognized that the means are at hand to synthesize essentially any nuclide of interest, particularly those on the neutron-deficient side of the stability line, in significant amounts. However, it is important to recognize that the complexity of nuclear processes induced by energetic projectiles results in the formation, to a greater or lesser extent, of every element from Z + 2 or 3 above the target to Z = 1, leading to formidable radiochemical recovery problems for each target selected for irradiation.

For the past five years we have been engaged in a program to utilize the unprecedentedly powerful beam of 800-MeV protons produced at LAMPF for the production of radioisotopes of demonstrated or potential value in medicine or biomedical research. Molybdenum metal targets have been studied for some time, resulting in the publication of radiochemical procedures for the recovery of 25-d ^{82}Sr[1] and 107-d ^{88}Y[2]. Further research has led to the incorporation of modifications into the processing procedure to allow the recoveries of the bromine and zirconium fractions, where the isotopes of interest are 56-h ^{77}Br and 83.4-d ^{88}Zr.

The HDEHP solvent from the ^{88}Y procedure[2] contains only Y, Zr, Nb, and Mo, and stripping with 8 M HCl accomplishes a quantitative removal of yttrium. Subsequent contact of the organic phase with 30% H_2O_2 eliminates molybdenum. The remaining Zr and Nb are converted to fluoride complexes by treatment with dilute HF and effectively stripped into the aqueous phase. The final separation of Zr and Nb is achieved by an extraction of the Nb into diisobutylcarbinol (DIBC). The advantages of incorporating ^{88}Zr into a ^{88}Y-Be photoneutron source will be discussed.

^{77}Br is of interest in radiopharmaceutical research both as an organic halogenating agent and as the 56-h parent of 17.5 s ^{77m}Se. The major portion of Br remains in the aqueous molybdate solution following removal of Sr, Y, Zr, and other elemental fractions. The radiobromine exists as Br^-, but can be oxidized to Br^o with MnO_4^- and extracted into CCl_4. Stripping is accomplished with an aqueous solution of SO_2. A substantial percentage of the bromine activity remains following removal of excess SO_2 by gentle heating.

The significance of this research is the demonstration that a single target material irradiated with 800-MeV protons can yield several elemental fractions containing ample amounts of radioisotopes of research interest. Hence the future utilization of spallation reactions in high-intensity accelerators should result in a wider range of research nuclides and greater economy both in beam time and manpower requirements.

References

(1) P. M. Grant, M. Kahn, and H. A. O'Brien, Jr., J. Inorg. Nucl. Chem. 37 (1975) 413-417.
(2) V. R. Casella, P. M. Grant, and H. A. O'Brien, Jr., Radiochim. Acta 22 (1975) 31-34.

No. 76

^{77}Br-^{77m}Se GENERATOR*

R. M. Lambrecht, E. Norton, A. P. Wolf,

Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973

and S. Treves

Harvard Medical School, Boston, Massachusetts 02115

Selenium-77m has physical characteristics that appear ideal for radionuclide angiocardiography. ^{77m}Se ($T_{½}$ = 18.1 sec) decays by isomeric transition with the emission of 162 keV photons in 50% abundance. A disadvantage with presently available radionuclides is their relatively long physical half-life which precluded the obtention of more than one projection at each time, and to study the effects of exercise and pharmaceuticals on the hemodynamics. Once the study if complete, the patient continues to receive radiation unnecessarily. The actual production of a $^{77}Br \rightarrow ^{77m}Se$ generator system that provides rapid, quantitative elutions of ^{77m}Se suitable for intravenous administration depends on the optimization of four steps.

1) Production of ^{77}Br.
2) The preparation of the ^{77}Br in the appropriate chemical form for the separation of ^{77m}Se without breakthrough (contamination) of ^{77}Br.
3) The loading of the ^{77}Br on the generator support (solid or liquid).
4) Milking the generator.

To date we have found a promising separation of Selenium from Bromine on the strongly basic anion exchange resin, Dowex-1 in chloride form. With dilute hydrochloric acid (0.05 N HCl), ^{82}Br as bromide ion is strongly adsorbed by the resin, while > 90% of tracer quantities of ^{75}Se (IV) can be eluted in a small volume. ^{75}Se (VI) cannot be eluted. In preliminary work ^{82}Br and ^{75}Se were used as tracers and were not carrier-free. With the system < 0.001% of ^{82}Br breakthrough occurred in the eluent with the ^{75}Se (IV). Studies with ^{77}Br as bromide have indicated that the ^{77}Br breakthrough varies if the ^{77}Br is applied to the column in the carrier-free vs. carrier bromide added state. Elution times of 2-8 sec and elution volume of 1-2 ml are typical.

However, the radiochemical yields of ^{77m}Se have varied considerably from 5-80% since the system has not been optimized for all parameters particularly related to loading the generator. Carrier-free yields of ^{77m}Se of 15% are typical. Addition of carrier Se(IV) does not improve the ^{77m}Se yields.

Due to the ultrashort half-life of ^{77m}Se (18.1 sec), it is not possible to determine the chemical form of the ^{77m}Se. (Indeed, it may not all be Se(IV), but also Se(VI), Se^{o} and $Se^{=}$ chemical forms may be present.) The chemical state of the ^{77}Br (e.g., bromide, bromate or bromite) may affect the fraction of ^{77}Se form in a given chemical state.

The parent ^{77}Br ($T_{½}$ = 56 h) of which ~2.5% decays to ^{77m}Se can be produced on a cyclotron by several direct routes: $^{77,78}Se(p,xn)$ and $^{76,77}Se(d,xn)$ (x=1,2), and by the indirect $^{77}Kr \xrightarrow[\beta^+]{1.2\ h} {}^{77}Br$ routes via Br(p,xn) (x=3,5) or (^3He,x) and

---

*This research performed under contract with the U. S. Energy Research and Development Administration and partially supported by the Massachusetts Heart Association Grant No. 1180.

(α,xn) reactions on isotopically enriched Se isotopes. The d, ^{3}He and ^{4}He reactions result in impractical production rates; whereas the ^{77}Se(p,n)^{77}Br (E_p = 13.5→0 MeV) ^{77}Br and ^{79}Br(p,3n)^{77}Kr → ^{77}Br (E_p = 32-25 MeV) reactions result in ^{77}Br production of 0.5 and 0.8 mCi/μAH respectively. The ^{75}As(α,2n)^{77}Br reaction and Hammersmith methods have proved disappointing with ^{77}Br yields being limited to ∿ 20 mCi per run.

The results obtained to date lead us to believe that a feasibility study with the ^{77}Br-^{77m}Se generator can be accomplished. Excitation functions, targetry and radiochemical results will be discussed.

No. 77

THE PREPARATION OF PURE ^{81}Rb-^{81m}Kr FOR DYNAMIC BLOOD FLOW STUDIES BY THE $^{85}Rb(p,5n)^{81}Sr$ AND $^{85}Rb(\alpha,p7n)^{81}Sr$ REACTIONS

G. van Herk, W. Vaalburg, A. M. J. Paans, and M. G. Woldring

Central Isotope Laboratory, Academic Hospital,
University of Groningen, Groningen, The Netherlands

Contaminant free ^{81}Rb was prepared by the $^{85}Rb(p,5n)^{81}Sr \rightarrow {}^{81}Rb$ and $^{85}Rb(\alpha,p7n)^{81}Sr \rightarrow {}^{81}Rb$ reactions. Natural rubidiumchloride targets with a thickness of 1.0 g/cm^2 were irradiated respectively with 65 MeV protons and 135 MeV α-particles. The produced ^{81}Sr decays with a half-life of 25 min to ^{81}Rb, which further decays with a half-life of 4.6 h to ^{81m}Kr. The half-life of ^{81m}Kr is 13 sec.

The excitation function for the $^{85}Rb(p,5n)^{81}Sr$ reaction has been determined experimentally by bombarding RbCl targets at proton energies varied between 45 and 65 MeV. The cross section at 65 MeV is 44 mbarn. The theoretical excitation function has been determined using a statistical model predicting the "evaporation" of the compound nucleus. At 65 MeV the calculated cross section is 48 mbarn. The shape of the experimental excitation function agrees with the shape of the theoretical excitation function, although the quantitative values appeared to be slightly lower than the theoretical values. For the $^{85}Rb(\alpha,p7n)^{81}Sr$ reaction the total theoretical cross section is 26 mbarn for an integrated α-beam energy from 180 to 100 MeV. This is not much less than the total cross section for the (p,5n) reaction. With the available 135 MeV α-beam we obtained a ^{81}Rb yield of 0.15 mCi/μA.h, 1.5 hours after purification of the produced ^{81}Sr.

Various methods to recover ^{81}Rb from the irradiated RbCl targets were investigated. All methods are based on a two-step process. The first step is the separation of ^{81}Sr from the target material and from the rubidium isotopes formed by direct reactions. This step is performed immediately after the end of bombardment. The second step is the recovery of daughter ^{81}Rb grown in ^{81}Sr. The optimum time of the second step is 96 min after the first separation.

The two-step recovery of ^{81}Rb must meet a number of requirements.

- -- The removal of the rubidium in the first separation has to be as complete as possible. Any remaining rubidium would contribute to undesired contamination in the final product.
- -- The first separation must nevertheless be finished as soon as possible after the end of the irradiation because of the short half-life of ^{81}Sr.
- -- Rubidium-81 must be recovered from the second separation in a small volume, in view of the subsequent intravenous injection in patients.
- -- The final product must meet radiopharmaceutical quality requirements.

A number of column separation methods were compared with a precipitation method suggested by the group of the University of California at Davis. This method is based on the difference in solubility of $SrCO_3$ and Rb_2CO_3. The average experimental yield of ^{81}Rb is found to be 0.83 $\pm$ 0.22 mCi/μA.h. The assay is performed at 1.5 h after the end of the first separation, using 3 irradiations of 20 minutes each followed by immediate separation of 10 min duration. Decay curve analysis of Ge(Li) spectra show that the radioactive contaminant in the separated ^{81}Rb were less than 0.1% of the total activity.

Rubidium-81 has several useful medical applications. This potassium analogue has been used for scintigraphic imaging of the myocardium. Krypton-81m has been applied to determine pulmonary function. The ^{81}Rb-^{81m}Kr ratio can be used for dynamic blood flow studies.[1] After intravenous injection ^{81}Rb concentrates in muscle tissue and also in the kidney. Krypton-81, is continuously generated within the tissue and instantaneously removed by the blood flow. Consequently the ratio of ^{81}Rb to ^{81m}Kr activity in tissue is proportional to organ blood flow. Animal experiments are in progress, proving the sensitivity of the ^{81}Rb-^{81m}Kr ratio to changes in kidney blood flow.

Reference

(1) R. Jones and C. M. E. Matthews, Nature 230 (1971) 119.

No. 78

THE PREPARATION AND TESTING OF KRYPTON-81m GENERATORS FOR USE IN VENTILATION AND PERFUSION STUDIES IN MAN

J. C. Clark

MRC Cyclotron Unit, Hammersmith Hospital,
Ducane Road, London W12 OHS, England

Krypton-81m (half-life 13 sec) emits 190 KeV photons in 65% of its disintegrations and is the daughter of Rubidium-81 (half-life 4.58 h). It may be recovered in the gas phase or in solution by use of a suitable generator system for use in ventilation and perfusion studies respectively. Several production routes are available for the accelerator production of ^{81}Rb using both solid and gaseous targets. The various practicable nuclear reactions and target systems will be discussed. At the MRC Cyclotron Unit we have adopted the $^{79}Br(\alpha,2n)^{81}Rb$ reaction using the external 30 MeV alpha particle beam to irradiate sodium bromide targets. Targets are prepared by melting 1.5 g of NaBr under 5% H_2/N_2 onto a grooved recess in a copper plate using an eddy current heater. Irradiations are carried out at up to 50 μA for up to 1.5 hours when a production rate of ^{81}Rb of 2 $mCi/\mu Ahr^{-1}$ is achieved. Rubidium-81 is recovered from the sodium bromide target solution using a (22 x 6 mm) zirconium phosphate ion exchange column. Better than 98% of the ^{81}Rb is recovered when the (50 mgm ml^{-1}) sodium bromide solution is pumped onto the column (at 8 ml min^{-1}). An exhaustive wash (with $\sim$ 100 ml) of water removes the excess sodium bromide. This provides an opportunity for the estimation of the steady state eluted ^{81m}Kr activity for the column which is used directly as the active element in both gas and solution generators. With the generator loading system currently in use up to six generators can be loaded from each target. When the generator is operated continuously in the gas phase mode it is essential to carry out elutions with air saturated (at $\sim$ 20°C) with water vapour. For operation in the solution mode, water or isotonic dextrose is recommended. Practical designs and operational characteristics of both gas and solution generators will be discussed in detail including the test procedures adopted for solution generators for use in human infusion studies.

No. 73

A STUDY OF THE MECHANISM OF METAL ION METABOLISM BY TUMORS

A. M. Friedman, G. V. S. Rayudu,* J. C. Sullivan,
M. R. Zalutsky, S. L. Ruby, and E. W. Fordam*

Argonne National Laboratory, Argonne, Illinois 60439
and *Rush University Medical Center, Chicago, Illinois 60612

Many metallic compounds have been observed to concentrate in tumors. However, if these compounds are to be useful as tumor scanning agents, they should accumulate in the tumor as a consequence of a unique metabolic property of the tumor. Currently, little information is available concerning the metabolism of these metallic substances by tumors.

In this work, we have investigated the behavior of a series of trivalent, quadravalent, and pentavalent ionic compounds in mice bearing sarcoma-180 tumors. Each compound was injected into the lateral tail vein of the mice, the mice were sacrificed and the tissues of interest were removed for tissue distribution determination. All the compounds studied concentrate in sarcoma-180 tumors. We next studied the tissue distribution of one of these compounds, ^{181}Hf(IV) citrate as a function of its specific activity. We found that by increasing the specific activity, we could greatly increase the percent uptake per gram tumor of ^{181}Hf(IV) citrate.

We have previously proposed that the initial complexing agent is probably not the ligand which is attached to the metal ion when it concentrates in the tumor. To investigate this phenomenon, the Mossbauer spectra of one of these compounds, Sm(III) citrate, was studied in order to better understand the metabolic pathway for its tumor localization. Our results indicate that a hydrated complex, $Sm(H_2O)_6^{3+}$, was initially formed in vivo. Our experiments also suggest that the $Sm(H_2O)_6^{3+}$ complex is ionically bound to serum proteins when it is metabolised by the tumor.

To verify this result, several ^{99m}Tc-labeled and radioiodinated serum proteins were prepared and their tissue distributions in sarcoma-180 mice were studied. As shown below, most of these proteins exhibited uptakes similar to those of the multivalent ionic compounds. However, most of the radioiodinated proteins showed higher uptakes per gram muscle. Of particular interest is the difference between the % uptake per gram muscle for ^{99m}Tc-HSA and ^{131}I-HSA. Since the iodine-protein bond is much less ionic than the technetium-protein bond, this result suggests that ionically bound tracers are cleared more readily from normal soft tissue than covalently bound tracers.

We conclude that the tumor localization of a multivalent cation is generally independent of its counter ion since by the time the cation is metabolised by the tumor, it is ionically bound to a serum protein. Also, the excellent tumor-to-muscle ratios obtained with these highly charged ions are probably due to the ability of normal soft tissue to desorb these highly charged ions. We also conclude that the number of cationic binding sites on the tumor is small since increasing the specific activity of these compounds improve their tumor localization.

No. 80

CORRELATION OF PROTEIN BINDING AND THE LOCALIZATION OF ^{99m}Tc-LABELED PYROPHOSPHATE AND OTHER AGENTS IN INFARCTED MYOCARDIUM

Mrinal K. Dewanjee and Paul C. Kahn

Tufts Medical School and New England Medical Center, Department of Radiology, 171 Harrison Avenue, Boston, Massachusetts 02111

Although ^{99m}Tc-pyrophosphate (Tc-PP) has been used routinely for imaging infarcted myocardium in the acute phase, its mechanism of localization is poorly understood. We have performed double labeling, gel filtration, dialysis and separation of serum and muscle protein in normal and infarcted myocardium in rabbits obtained by coronary artery ligation. Rabbits were injected intravenously with Tc-PP, ^{99m}Tc-glucoheptonate (Tc-GH), ^{99m}Tc-dimercaptosuccinate (Tc-DMSA), Tc-DTPA, ^{131}I-HSA and ^{32}P-pyrophosphate. Tc-PP, a strong serum protein binder gives a ratio of 50:1 for IM/NM (infarcted vs normal myocardium) in contrast to the ratio of 2:1 for Tc-DTPA. On the other hand, the intermediate serum protein binder Tc-GH shows ratio of (10–15):1. Gel filtration of ^{32}P-pyrophosphate shows that Tc-chelation of pyrophosphate enhances protein binding. It is also found that Tc-PP is always in equilibrium with Tc-PP-protein complex. This Tc-PP binds with the denatured soluble protein of cytoplasm of the infarcted myocardium. The separation of serum and muscle protein by the modified method of Katz indicates that myosin of infarcted myocardium contains only (2-4)% of Tc-PP activity in contrast to (50-60)% in the cytoplasmic protein. The double labeling with ^{131}I-HSA and ^{99m}Tc-microsphere shows that although the corpuscular flow is tremendously reduced in the infarcted area, (IM/NM) ratio of (2:1) for ^{131}I-HSA was obtained indicating an equilibrium of plasma flow. These studies indicate that the intensity of plasma protein binding is an important characteristic for the localization of Tc-PP and other Tc-chelates in infarcted myocardium.

No. 81

LABELLING OF THE AZO-MUSTARD CB 10-252 WITH Br-82 AND I-123

R. D. Neirinckx

NPRL, CSIR, P. O. Box 395, Pretoria 0001, Republic of South Africa

A series of azo-mustards have been used against hepatocellular carcinoma. The activity of these compounds against liver tumours is due to the reduction of the azo group by azo reductase in the liver cells. The resulting amine is strongly alkylating and poisonous to the tumour cell involved. The alkylating agent has a short chemical half-life and is converted into an alcohol, which is no longer alkylating and as such harmless to the bone-marrow.

By labelling this compound with a radioactive isotope it is hoped that it may be used to localize liver tumours.

The azo-mustard made available to us by the Imp. Cancer Res. Inst. contains a bromine atom in the aliphatic chain, as shown by mass-spectrographic analysis. However, this bromine could not easily be exchanged with fluorine-18, iodine-123 or bromine-82. As the alkylation by the azo-mustard is preceded by the split-off of the bromine atom, it is advisable to label a different site on the aliphatic group in order to secure radioactivity on the alkylating group. This cannot be obtained by synthesizing the azo group from the corresponding amine, since the chemical half-life of that amine is too short. Dehydrobromination of the alkyl-bromide group on the azo mustard, followed by addition of labelled bromine or iodine, however, succeeded in labelling the azo mustard. This was carried out by dissolution of the azo compound in alcohol (or benzene) and boiling this solution with a sodium hydroxide pellet. Aqueous reagents cannot be used since water would immediately add over the double bond. The alcoholic solution is then evaporated to almost dryness and the residue redissolved in benzene. A solution of bromine-82 or iodine-123 in dried benzene is then added. A silica-gel column separation in benzene + 15% ethylacetate separates iodine, iodide and three distinct fractions in the untreated as well as in the labelled azo mustard. The two main fractions (Rf = 0.4 and 0.35), probably corresponding to stereoisomers of the azo-mustard, contain approximately 50% of the activity, while the rest of the activity is mainly in the form of unreacted iodine.

The azo mustard is very poorly soluble in water and is thus not injectable. The benzene solution is evaporated at room temperature and the residue collected in gelatine capsules for oral administration.

No. 82

ON THE PREPARATION OF ^{80}Br- OR ^{82}Br-BIOMOLECULES VIA EXCITATION LABELLING METHODS

Steven H. Wong, Jack F. Mustaklem, and Hans J. Ache

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

The direct decay induced ^{82}Br (or ^{80}Br) labelling by exposing the solid substrate molecules, such as deoxyuridine, L-tyrosine, guanosine, deoxycytodine, phenylalanine and acetic acid, to gaseous $CF_3{}^{82m}Br$ (or $CF_3{}^{80m}Br$) was studied. The radiochemical yields of the brominated products are relatively small and range from 1% in the case of bromo deoxyuridine to 11% for bromoacetic acid. The modification of this technique by adding Cl_2 gas to the reaction mixture improves the yields in several cases drastically (up to 80% for bromo-guanosine and bromo-L-tyrosine). Similar improvement can be achieved by exposing crystalline $KBrO_3$ for some time to $CF_3{}^{80m}Br$) and dissolving subsequently the $KBrO_3$ in an acidic solution of the substrate.

^{80}Br-5-bromodeoxyuridine or ^{80}Br-bromoacetic acid can be achieved if the labelling is carried out by the ^{80}Br-CF_3-$KBrO_3$ gas exposure technique to induce a ^{80}Br for I exchange in the corresponding iodo derivatives.

The effect of several experimental parameters, such as labelling time, substrate concentration, etc. on the efficiency of the ^{80}Br incorporation via the various techniques was investigated.

No. 83

COMMERCIAL DOSE CALIBRATORS: THEIR CALIBRATION AND PERFORMANCE CHARACTERISTICS

Robert L. Ayres

National Bureau of Standards, C-114, RadP, Washington, D. C. 20234

Dose calibrators have become the instrument of choice in medical institutions for the assay of radioactivity in radiopharmaceuticals. Recognizing the importance of these instruments in the nuclear-medicine measurement system, the National Bureau of Standards made an evaluation of a number of available dose calibrators. The objectives of this evaluation program were (1) to determine the needs for calibration standards for this class of instrument and (2) to check the stated calibration values.

Seven different dose calibrators were tested using NBS activity-calibrated sources of 15 to 20 different radionuclides. In addition to checking the calibration values supplied with the instruments, these measurements were used to determine the efficiency as a function of photon energy for each of the individual dose calibrators. Additional measurements were made with special sources to determine: (1) the effect of axial and radial displacement of the source within the well; (2) the variation obtained when using different radiopharmaceutical containers for measurements of the same radionuclide; and (3) the effect of different sample volumes on the measured activity of a source within a single container.

The results of these measurements will be presented and discussed in relation to some typical radionuclides used in diagnostic medicine. The determination of the photon efficiency as a function of photon energy of a typical dose calibrator will be presented as an aid to understanding the operation of these instruments. The use of this efficiency function to estimate the calibration value or setting for a radionuclide, for which neither a calibration setting nor a calibration standard exists, will be described. This is dealt with more fully in the forthcoming NCRP Report, "A Handbook of Radioactivity Measurements Procedures".

No. 84

PREPARATION OF Tc-99m-RADIOPHARMACEUTICALS BY "ELECTROLYTIC LABELING"

P. Angelberger

Institut für Chemie, Forschungszentrum Seibersdorf, Austria

All labeling procedures for Tc-99m-compounds are based on the reduction of TcO_4^- to lower valence states with reducing agents, most common, $SnCl_2$ in aqueous solution. $SnCl_2$, however, contains variable amounts of Sn(IV) and is unstable against air oxidation and hydrolysis in dilute aqueous solutions, while the reduction potential depends on the Sn(IV)/Sn(II) ratio.

Therefore we generate Sn^{2+} ions in the reaction mixture of $^{99m}TcO_4^-$ and compound to be labeled by anodic oxidation of a thin tin wire. A precision constant current controlled by electronic timing is used to pass an accurately known charge through the solution and liberate the amount of Sn^{2+} ions given by Faraday's Law.

For a number of chelating compounds the optimum labeling conditions, mainly pH, chelate/Sn molar ratio and molar concentrations have been elaborated. Data are presented for DTPA, DMSA, Phytate, Human Serum Albumin, Albumin Microspheres, Bleomycin and Methylene diphosphonate.

Advantages of the method are simple and rapid labeling with no need to exclude oxygen, low tin content, excellent radiochemical purity and extended in vitro stability of the labeled compounds.

No. 85

TECHNETIUM-99m LABELLED METHIONINE BY REDUCTION WITH HYDRAZINE

Ioan Galateanu, Cristina Bratu, and Aurica Petride

Institute of Atomic Physics, Department of Radioisotopes and Labelled Compounds, P. O. Box 5206, Bucharest, Romania

At present a number of ^{99m}Tc-radiopharmaceutical preparations require the reduction of pertechnetate anion. In this respect the reduction of Tc(VII) to lower valence states using hydrazine, in alkaline media by means of chromatography and polarography was investigated. For this purpose Technetium-99 in concentration of 10^{-3} M in 0.1 N NaOH and L-methionine solutions at pH = 11 was used. Chromatographically we determined that the reduction of Tc(VII) by hydrazine in alkaline medium at room temperature occurs rapidly with high yield. In presence of L-methionine the reduction of Tc is followed by a complex formation. The optimal reaction time for complexation of reduced Tc with L-methionine is 15-20 minutes. Comparative studies of Tc-L-methionine complex formation using rhenium-methionine complex as refering compound were performed by means of IR, NMR and chromatography methods. The polarographical studies indicated a reduction of Tc(VII) by hydrazine at pH = 11 to lower valence states Tc(V) and Tc(IV) able to be incorporated into pharmaceuticals. This was confirmed also by the shift of the half-wave potential from $E_{\frac{1}{2}} = -0.72$ to more positive values $E_{\frac{1}{2}} = -0.48$ V which is in good concordance with chromatographical results in detecting of Tc-methionine complex and of reduced technetium spots. Concerning the hydrazine amounts required for reduction of Tc(VII) it was determined that ultra-small quantities are sufficient to reduce several millicuries of Tc-99m (e.g. 2 µl of diluted 150 hydrazine for 5 mCi). The reactions involved in the reduction of Tc(VII) are:

$$N_2H_4 + H_2O \longrightarrow N_2H_5^+ + OH^-$$

$$N_2H_5^+ + 4OH^- \longrightarrow N_2 + 4H_2O + 4e^- + H^+$$

In our previous communication (J. Radioanal. Chem. 26 (1975) 5), it was studies the reduction of Tc(VII) by stannous chloride, ascorbic acid in HCl and acetonitrile media and mentioned the great tendency of the reduced technetium species to hydrolize giving metastable species like: $TcO(OH)^+$, $TcO(OH)_2$ and $TcO(OH)_2^+$, $TcO(OH)_3$. The reduction of hydrolized species of Tc(VII) can be supposed as following:

$$Tc(VII) + 2e^- \longrightarrow Tc(V)$$

$$3Tc(V) \longrightarrow Tc(VII) + 2Tc(IV)$$

$$2TcO_2(OH)_3 + 4e^- \longrightarrow TcO(OH)_2^+ + TcO(OH)_3$$
$$\searrow\ 2TcO(OH)_2^+ + 2OH^-$$

During the reduction of Tc(VII) with hydrazine a strong catalytic reaction was observed and we attributed it to the evolution of oxygen from system caused by decomposition of hydrolized species:

a) $TcO_2(OH)_3 + 2e^- \longrightarrow TcO(OH)_3 + O^-$

$OH^- + O^- \longrightarrow HO_2^-$ which in alkaline medium does

dissociate $HO_2^- \longrightarrow H^+ + O_2^-$

b) $Tc(VII) + 3e^- \longrightarrow Tc(IV)$

$TcO_2(OH)_3 + 3e^- \longrightarrow TcO(OH)_2 + OH^- + O^-$

A kit for L-methionine-^{99m}Tc based on technetium reduction with hydrazine was proposed.

No. 86

INDIUM-113m LIQUID GENERATOR

Valeria-Viorica Lungu and Ioan Galateanu

Institute of Atomic Physics, Department of Radioisotopes and Labelled Compounds, P. O. Box 5206, Bucharest, Romania

Indium-113m liquid generator is based on the extraction of Sn-113 with Tridecylphosphite (TDP) and offers economical advantages especially for medical units from developing countries having small nuclear reactors. In this case targets of natural tin instead of high enriched tin are used, which are less expensive. The neutron irradiation (10^{13} n/cm^2 sec) of natural tin was performed during 12 weeks. Irradiated tin was dissolved in 11 N HCl by heating on water bath adding few drops of 30% H_2O_2. After dissolution of the target the obtained solution was diluted to 1 N HCl using distilled water and transferred into an extraction funnel. TDP was added in a proportion of 2:1 and mixed with aqueous phase 30 minutes by stirring. Finally Sn-113 was 95-98% extracted from 1 N HCl solution into TDP phase. Further, the TDP phase was evaporated in a shielded box by heating on a sand bath until the volume remained 1/8 from the initial one. At this point the concentration of natural tin is increased from 3.8 mg/ml up to 32 mg/ml. Thus it was possible to obtain a In-113m liquid generator having a total volume ranging 10-300 ml of concentrated TDP with a total Sn-113 activity of 50-150 mCi. If targets of low enriched tin (10%) were used an activity up to 1.5 Ci/300 ml of liquid generator can be obtained. The TDP phase can be stored more than 1 year without radiolytic decomposition. The extraction of In-113m was performed using 1 N HCl solution (TDP: 1 N HCl = 0.5) by stirring 5 minutes in the extraction funnel with a 97-99% yield. The separated aqueous phase was neutralized with few drops of conc. NaOH until pH = 1.5-2 and sterilized by passing through a Millipore filter (0.22 μ).

The extraction of tin from 1 N HCl solution into TDP is based on complex formation TDP-Sn which is very stable under radiation even up to 8 Mrad absorbed dose. This dose is 20 fold greater than the absorbed dose attributed to the self-irradiation of a 500 mCi TDP-Sn-In113m generator within the whole period of its utilization. Several methods were used for investigation of the structure of TDP-Sn complex.

The gamma spectra of the obtained eluate In-113m indicated a radionuclidic purity greater than 99.99% and no break of Sn-113 was observed. The traces of antimony radioisotopes formed during the neutron irradiation of natural tin, were removed from TDP phase within the first 5 elutions with 1 N HCl.

No. 87

^{99m}Tc-OPSONIN: RADIOPHARMACEUTICAL FOR ABSCESS AND TUMOR LOCALIZATION

R. Kishore, R. H. Kihm, and S. S. Ciccio

Veterans Administration Hospital, Albany, New York 12208

The phagocytic clearance ability of the R.E. cells in liver and spleen is regulated by the blood level of a glycoprotein called opsonic protein or Opsonin[1]. This α-2 globulin kind of protein serves as the hormonal recognition factor in the discrimination of endogenous from exogenous and effete autologous material. From this knowledge it was argued that the concentration of Opsonin should increase at the site of tissue injury, abscess formation and tumor growth. Tagging of Opsonin with a suitable gamma emitter provides us with a radiopharmaceutical for abscess and tumor detection.

Rat Opsonin[2] was labeled with ^{99m}Tc in a Krebs-Ringer-Phosphate (KRP) buffer solution. The labeling vial contained 5 mg of lyophilised Opsonin in 2 ml KRP. 200 µg of Sn as stannous chloride dihydrate in 50 mM of HCl was added followed by 50 mM of NaOH to maintain the pH of the buffer. The sample was incubated for 10 mins at 0°C. The incubation was continued for another 10 mins after addition of 0.1 to 2 ml of ^{99m}Tc-sodium pertechnetate from a 'Minitic' ^{99}Mo-^{99m}Tc generator. Terminal sterilization of the product was done by filtration through a 0.22 µ 'Milipore' membrane filter. Labeling yields obtained were routinely 90-95%.

Biological distribution of ^{99m}Tc-Opsonin was studied in rats from 2 mins to 24 hrs. The highest organ/blood ratio of the activity was in the kidneys. This ratio is about 28 ± 10 at 4 hrs and remains at the same level for up to 24 hrs. At 24 hrs, kidneys contain ≈ 5% of the injected dose corrected for the radioactive decay. Most of this activity is in the renal cortex.

Septic abscesses were created in the thigh muscle of rats by the intramuscular injection of saline solution of rat feces. Septic abscesses were produced in about 72 hrs. The presence of abscesses was verified surgically as well as by ^{67}Ga-citrate scintiscanning. These abscesses could be clearly visualized on scintiscanning after ^{99m}Tc-Opsonin was administered to these rats by tail vein injection. Further experiments on ^{99m}Tc-Opsonin are in progress.

References and Notes

(1) T. M. Saba and W. A. Scovill, Surgery Annual 7 (1975).
(2) Rat-Opsonin was kindly supplied by Dr. T. M. Saba of Albany Medical College.

No. 88

TECHNETIUM-99m DIHYDROXY FATTY ACIDS: CHEMICAL AND DIAGNOSTIC IMPLICATIONS

James McRae and Bengt Langstrom

Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley, California 94720 and Department of Organic Chemistry, University of Uppsala, Uppsala, Sweden

To explore the potential of binding technetium to molecules with adjacent hydroxyl groups some dihydroxy fatty acids were synthesized. It was assumed that a different biological distribution would result from their lipophilic properties in comparison with small hydrophilic compounds containing at least two vicinal hydroxyl groups which localize within the kidney. The principal ligand was threo 9,10 dihydroxystearic acid, but the 9,10 erythro form was also used. In addition some different acids with at least two adjacent hydroxyl groups were investigated. Labeling was done at pH 12 using stannous chloride or tin electrodes to reduce the technetium. The technetium complex was stable to a pH of 8. Little exchange occurred with sodium gluconate *in vitro*, whereas calcium gluconate resulted in more exchange but was complicated by the calcium ion precipitating the fatty acid. The organ distribution was followed in rats and dogs. Liver activity in the rat reached a maximum of 20 percent of the injected activity around 15 minutes, fell to 15 percent at 2 hours and 5 percent at 24 hours. Intestinal activity confined to the upper small bowel rose rapidly with 45 percent of the activity in the lumen by 30 minutes. The kidneys contained 8 percent at 1 hour. Urinary excretion was approximately 20 percent by three hours. In one experiment the urine was withdrawn from the bladder of one rat and injected into a second rat. The principal location of activity in the second rat was within the kidneys indicating the possibility of *in vivo* ligand exchange or the presence of other compounds in the initial preparation. There was very low activity within the myocardium at all times with 9,10 threo stearic acid but preliminary results with dihydroxy fatty acids still possessing carbon double bonds showed somewhat higher myocardial activity. There was very little absorption after subcutaneous or intramuscular injection and no evidence for intestinal hepatic recirculation. There were differences in distribution with preparations of the threo and erythro forms of dihydroxystearic acid, the latter producing more kidney activity.

The blood $T_{\frac{1}{2}}$ in the dog was 8 minutes, and liver and gall bladder were visualized. No excretion into the intestine was seen in an anesthetized dog but prompt excretion occurred in a conscious dog.

The results confirm the possibility of labeling compounds with vicinal hydroxyl groups and show that changes in the properties of the ligand produce different biological distributions.

No. 89

FACTORS INFLUENCING THE RADIOCHEMICAL ANALYSIS OF TECHNETIUM-99m RADIOPHARMACEUTICALS BY PAPER CHROMATOGRAPHY

Azu Owunwanne, David A. Weber, Robert O'Mara, and George Wilson

University of Rochester, School of Medicine,
Rochester, New York 14642

Earlier studies suggested that ^{99m}Tc pertechnetate ($^{99m}TcO_4^-$) was the main radiochemical impurity present in ^{99m}Tc radiopharmaceutical formulations. Now, it is a well-known fact that there are other ^{99m}Tc radiochemical impurities, the most notable of which is reduced, hydrolyzed technetium, technetium-99m dioxide ($^{99m}TcO_2$). With the exception of $^{99m}TcO_4^-$, a paper chromatographic strip developed in an organic solvent such as methanol, acetone, methyl-ethyl-ketone or butanol, will not separate most ^{99m}Tc radiopharmaceuticals from other radiochemical impurities. Both the impurities and the majority of the ^{99m}Tc radiopharmaceuticals tested do not migrate from the origin. These solvent systems, therefore, are of limited value in the analysis of radiochemical impurities in ^{99m}Tc radiopharmaceuticals.

Among the factors which govern compound migration on paper strips are the extent of the solubility of the compound in the developing solution and the nature of the paper strip itself. These two factors have been investigated for the ^{99m}Tc radiopharmaceuticals. The present account deals with ^{99m}Tc phosphorous compounds: ^{99m}Tc hydroxy-ethylidene diphosphonate, ^{99m}Tc methylene diphosphonate and ^{99m}Tc pyrophosphate.

Chromatograms were obtained on the following papers: Whatman No. 3MM, ashless paper No. 40, carboxymethyl cellulose ion exchange paper No. CM 82 and resin loaded ion exchange paper No. WA-2. Whatman No. 3MM was pretreated by dipping in distilled water; WA-2 paper was soaked in 2.0 M NaCl and then washed in distilled water. Both papers were dried for approximately 1 hour before use. Ashless and CM 82 papers were used without pretreatment. All paper strips were developed in solvents by the ascending method. Organic solutions such as methanol, acetone, methyl-ethyl-ketone or butanol and aqueous solutions such as acetate buffer, phosphate buffer, hydrochloric acid and sodium chloride were tested.

No. 90

FACTORS INFLUENCING THE RADIOCHEMICAL ANALYSIS OF TECHNETIUM-99m RADIOPHARMACEUTICALS BY PAPER CHROMATOGRAPHY

Azu Owunwanne, David A. Weber, Robert O'Mara, and George Wilson

University of Rochester, School of Medicine,
Rochester, New York 14642

In general, each ^{99m}Tc phosphorous compound stayed at the origin with the organic solutions, while $^{99m}TcO_4^-$ moved with an R_f value of 0.6-0.75. When the paper strips were developed in dilute concentrations of the aqueous solutions, both $^{99m}TcO_4^-$ and ^{99m}Tc phosphorous compounds migrated with or closely behind the solvent front. The use of more concentrated solutions resulted in decreased $^{99m}TcO_4^-$ migration and enhanced its separation from ^{99m}Tc phosphorous compounds. The best separations were obtained with CM 82 developed in 0.5 M NaCl or 1.0 M acetate buffers, and ashless or 3MM paper developed in 2 M NaCl or 1.0 M acetate buffer. In these systems, $^{99m}TcO_2$ remains at the origin while $^{99m}TcO_4^-$ and the remaining ^{99m}Tc phosphorous compounds move with R_f values of 0.56-0.75 and 0.82-1.0 respectively.

These results indicate that the solubility of a compound in a developing solvent system can exert control over the extent of the migration of the compound along the paper strip. Very soluble compounds migrate with or closely behind the solvent front, while less soluble compounds move to intermediate positions and insoluble compounds stay at the origin. Both ^{99m}Tc phosphorous compounds and $^{99m}TcO_2$ are insoluble in the organic solutions and therefore do not move from the origin. In the aqueous solutions, $^{99m}TcO_2$ is not soluble, and it remains at the origin. Both $^{99m}TcO_4^-$ and ^{99m}Tc phosphorous compounds are soluble, and each migrates from the origin.

The extent of the migration of each compound is determined by: the nature of the paper, the concentration and the pH of the developing solvents. By experimentally varying these parameters, a combination was obtained to give distinct, differential R_f values for $^{99m}TcO_2$, $^{99m}TcO_4^-$ and the ^{99m}Tc phosphorous compounds.

No. 91

CHEMICAL CHARACTER EFFECT OF 99m-Tc-PENICILLAMINE COMPLEXES ON THE IN VIVO BEHAVIOR

Akira Yokoyama, Hideo Saji, Kazuko Horiuchi, and Yoshiaki Terauchi

Faculty of Pharmaceutical Sciences, Kyoto University,
Yoshida, Sakyo-ku, Kyoto, Japan 606

In the reaction of labeling 99m-Tc-penicillamine, several complexes were detected as reported elsewhere. After a detailed study of different parameters, a labeling method for each of those complexes was established, and the organ distribution and biliary excretion of complexes were evaluated in mice, rats and rabbits.

Whenever highly hydrolyzed 99m-Tc complex was administered, radioactivity in the kidney, liver and stomach was higher than the observed in Complex I (the unhydrolyzed complex) and Complex II (the low hydrolyzed complex). This difference may be due to the low stability of that complex, which easily suffers displacement toward TcO_4^- and TcO_2.

The administration of Complex I and II in mice and rats showed almost no accumulation in the organs except in the gallbladder and urinary bladder. However, in rabbits, although the behavior of Complex I was similar to the above mentioned, the administration of Complex II showed high accumulation of 99m-Tc in the liver, kidney, blood and an appreciable increment in the stomach.

This interesting phenomenon of Complex I and II observed in different animal species leads us to analyze their in vitro behavior. These studies showed that while Complex I remains stable over a wide dilution range, Complex II changes rapidly to other 99m-Tc species such as highly hydrolyzed complex TcO_4^-, and/or Complex I. The formation ratio of every of these 99m-Tc species depends upon the dilution degree.

These results show that the dilution phenomenon and the chemical character are closely related with its behavior in vivo.

No. 92

NEW Ga-68 LABELED SKELETAL IMAGING AGENTS FOR POSITRON SCINTIGRAPHY

Mrinal K. Dewanjee, R. Beh, and D. J. Hnatowich

Tufts Medical School - New England Medical Center, Massachusetts General Hospital, 171 Harrison Avenue - Fruit Street, Boston, Massachusetts 02111

We have synthesized two new gallium chelates, Ga-68-ethylenediamine tetramethylenephosphonate (Ga-EDTMP) and Ga-68-diethylenetriaminepentamethylenephosphonate (Ga-DTPMP). Addition of carrier gallium is not necessary for skeletal uptake. The radiopharmaceuticals were prepared by adding $GaCl_4^-$ complex to 20-50 mg of EDTMP or DTPMP stock solutions and neutralizing to pH 5.5. The solution was then sterilized by membrane filtration. Paper chromatography indicates that the labeling efficiency is essentially 100%. The organ distribution of Ga-67-EDTMP and Ga-67-DTPMP was performed in 30 Sprague-Dawley rats. The results show that (50-60)% of the injected dose accumulates in bone at 1 hour after injection; and (25-30)% is excreted with the urine. Except for the slower blood clearance of Ga-67-EDTMP, the general trends of organ distribution of both the complexes are similar. At 3 hours after intravenous injection the (bone/blood) and (bone/muscle) and (bone/marrow) ratios are 15,70; 10,47; and 4,8 for Ga-67-EDTMP and Ga-67-DTPMP respectively.

Ga-68-labeled chelates were used for positron scintigraphy in dogs. Dogs were injected intravenously with 8 mCi of Ga-68-EDTMP or Ga-68-DTPMP, imaged and sacrificed at one, two, and three hours post injection. Satisfactory images with positron camera were obtained after 2 hours with both complexes, however superior images were obtained with Ga-68-EDTMP. The (bone/muscle) and (bone/blood) ratio of Ga-EDTMP in dogs increased from 3 to 10 and 2 to 8 respectively from 1 to 3 hours. At the end of three hours, 35% of the injected dose was in bone, 1% in blood and 50% in urine. Gel filtration studies indicate that like Tc-99m and In-113m-labeled polyphosphonates the Ga-labeled chelates also bind with serum protein. Due to slower blood clearance of Ga-68-DTPMP, Ga-68-EDTMP appears more suitable for skeletal imaging by positron scintigraphy.

No. 93

NEW ^{67}Ga- AND ^{113m}In-LABELED POLYMETHYLENE PHOSPHONATES FOR IMAGING INFARCTED MYOCARDIUM

Mrinal K. Dewanjee, D. J. Hnatowich, and Paul C. Kahn

Tufts Medical School and New England Medical Center,
Department of Radiology, 171 Harrison Avenue, Boston, Massachusetts 02111

We have investigated the usefulness of two new ^{67}Ga-chelates, i.e. ^{67}Ga-ethylene diamine tetramethylenephosphonate (^{67}Ga-EDTMP), ^{67}Ga-diethylenetriamine pentamethylene phosphonate (^{67}Ga-DTPMP) and two ^{113m}In-chelates, i.e. ^{113m}In-EDTMP and ^{113m}In-DTPMP for imaging myocardial infarct in rabbits. The agents were prepared by adding $^{113m}In^{3+}$ or $^{67}GaCl_4^-$ ion to (20-50) mg of EDTMP or DTPMP stock solution and neutralizing to pH of 7. Myocardial infarcts were introduced into 15 rabbits by ligation of the left anterior descending coronary artery. The rabbits were then injected with a mixture of ^{113m}In-EDTMP, ^{45}Ca-EDTMP or ^{67}Ga-EDTMP and corresponding DTPMP chelates. The radioactivity mapping of the heart was made by removing the outer and inner layers of pale or hemorrhagic infarct. Beta and gamma radioactivity in the heart and other tissue samples were obtained. There was excellent correlation between the radioactivity distribution of the ^{45}Ca and ^{113m}In-chelates. The predominant concentration was in the bones, bladder, kidney and infarcted myocardium. For ^{113m}In-EDTMP, an average ratio of 30 to 1 between infarcted and normal myocardium (IM/NM) was obtained at 24 hours after ligation. This ratio peaked at 48 after ligation to 50:1. For ^{67}Ga-EDTMP this ratio varied from (7-10):1. The blood clearance of ^{67}Ga-EDTMP was slow. Gel filtration of serum containing ^{113m}In-EDTMP and ^{67}Ga-EDTMP shows that 45% and 86% of the radioactivity are protein bound. We observed that protein binding is an important characteristic for localization in myocardial infarct. The two pair of ^{113m}In-EDTMP and $^{201}Tl^+$ ion or ^{68}Ga-EDTMP and $^{13}NH_4^+$ ion should be useful for multiple imaging of myocardial infarct with the gamma and positron camera respectively.

No. 94

BIOLOGICAL PROPERTIES OF MOLECULES LABELED WITH METAL IONS USING BIFUNCTIONAL CHELATES

D. A. Goodwin, C. F. Meares, C. I. Diamanti, and J. T. Bushberg

Veterans Administration Hospital, Nuclear Medicine Service, 3801 Miranda Avenue, Palo Alto, California 94303

This paper describes the use of a new class of chelating agents for the binding of metal ions to biomolecules as a novel approach to labeling radiopharmaceuticals.

The compounds studied included the conjugates of human serum albumin (HSA), rabbit serum albumin (RSA), bovine fibrinogen (BF) and the anti-tumor antibiotic bleomycin (Bleo.). The chelate conjugates of the molecules studied were first synthesized and purified, and the radioactive metal ions (usually In-111) added later when the product was required for tracer experiments. Chelation of the radioactive metal took only a few minutes.

Rabbit plasma disappearance curves following I.V. In-111 HSA were identical to I-125 HSA disappearance curves and both showed a smooth curvilinear drop to day 6, at which time antibodies to the heterologous protein caused a rapid fall in activity. When In-111 rabbit albumin was used identical curves resulted, with no rapid drop after 6 days but a smooth continued fall in activity for two weeks.

The plasma disappearance of 1.4 mc of Indium-111 chelate-labeled HSA was followed 16 days in a patient studied by whole body scanning. The biological $T_{\frac{1}{2}}$ was 7.4 days, with 85% of the radioactivity still in the albumin by electrophoresis on day 7. An excellent whole body scan in a human was obtained following 1.4 mc of In-111 HSA with the vascular structures visible for 48 hours, and no bone marrow concentration.

The relatively rapid fall in whole body radioactivity in mice after injection of In-111 HSA, as well as the high kidney concentrations suggested that the metabolism of this conjugate involves primarily cleavage of the protein into smaller fragments containing the intact of In-111 chelate, which are rapidly excreted by the kidney. This will prevent undesirable background accumulation following injection of radiopharmaceuticals labeled using this technique.

Unconjugated bovine fibrinogen (BF) which was used for biological studies was 98% clottable *in vitro*. After reaction with three equivalents of azo-ϕ-EDTA it was 89% clottable, after fifteen equivalents 72% clottable, and after forty-five equivalents 50% clottable. Following the injection of In-111 labeled BF and HSA into the tail veins of specially prepared Balb/c tumor mice, the organ distribution and tumor uptake of radioactivity were determined. The tumor uptake of In-111 HSA and In-111 fibrinogen was approximately double (9.5%/gm and 8.0% gm) that of I-131 HSA and In-111 Cl_3 controls, suggesting a potential use of these radiopharmaceuticals in cancer localization in humans.

We have prepared a stable radiopharmaceutical by attachment of the In-111 chelate of the bifunctional reagents azophenyl EDTA and chloroacetyl EDTA to bleomycin. The biological excretion and tumor and organ distribution was compared to Co-57 bleomycin in Balb/c mice bearing a KHJJ adenocarcinoma. For the azo derivative the tumor uptake was 25% of that observed with Co-57 bleo, and for the chloroacetyl derivative the tumor uptake was somewhat better than Co-57 bleo. The tumor/organ ratios were superior to directly labeled In-111 bleo, due to lower background especially in liver and bone marrow.

The stability and biological integrity of the conjugates demonstrated in these experiments, provides forceful evidence that this technique has significant applications in labeling other biomolecules for use in nuclear medicine.

No. 95

RECENT IMPROVEMENTS IN THE ^{191}Os-^{191m}Ir RADIONUCLIDE GENERATOR

S. Kulprathipanja, D. J. Hnatowich and S. Treves

Massachusetts Institute of Technology and Children's Hospital Medical Center, Boston, Massachusetts 02139

An improved ^{191}Os-^{191m}Ir radionuclide generator has been under development in our laboratory; the daughter activity ^{191m}Ir ($T_{\frac{1}{2}}$ 4.9 sec) is separated rapidly from its parent ^{191}Os ($T_{\frac{1}{2}}$ 15 days) and used in radionuclide angiocardiographic studies. The 129 keV photons atom iridium is optimum for imaging on the gamma camera. Reactor produced ^{191}Os, along with stable ^{190}Os, is converted to the hexachloro-osmate(IV) chemical form and adsorbed on Bio-Rad Ag 1 x 4 anion exchange resin. The resin is loaded into a column which contains Ag 1 x 8 resin and is fitted at the bottom with a second column containing Ag 1 x 4. The second column is replaced whenever osmium breakthrough becomes excessive. The eluant, 8.7% NaCl at pH 2.2, has been chosen as safe for human use and to provide reasonable iridium yields with minimum osmium breakthrough.

The breakthrough of osmium in the hexachloroosmate(IV) chemical form is reduced below detectable levels by these methods. The hydrolysis products of hexachloroosmate(IV), namely the pentachloroaquoosmate(IV) has been detected in the generator eluant along with a previously uncharacterized species, hydroxotetrachloroosmate(IV)-μ-oxohydroxotetrachloroosmate(IV). The rate of formation of these species is relatively rapid particularly in a large radiation field. We have found that these products may be washed from the generator so that in subsequent elutions the osmium breakthrough is 0.001% of total osmium. This rinsing is not required more frequently than every few hours.

To date, generators have been constructed with up to 350 mCi of ^{191}Os to provide 18 mCi of ^{191m}Ir in 1.5 cc of eluant. The eluant has been administered repeatedly to Rhesus monkeys and images obtained on a gamma camera which clearly show the pulmonary artery, aortic arch and abdominal aorta in addition to the chambers of the heart.

No. 96

CARRIER-FREE ISOTOPE PRODUCTION VIA NUCLEAR RECOIL MOMENTUM

I. L. Preiss, D. Bozak, and R. Kishore*

Rensselaer Polytechnic Institute, Cogswell Lab.,
Troy, New York 12181

The utilization of isotope or even isomer separation based on recoil momentum in nuclear processes dates back to the original experiments of Szillard and Chalmers. The basis of such processes is simply the conservation of momentum resulting from the emission of a nucleon or photon from a nucleus. The emitted or incident particle momentum must be equal and opposite to the recoil momentum of the residual nucleus P_R. The resulting kinetic energy $T_R = P_e^2/2m$ is in, most instances, sufficient to rupture chemical bonds. The residual nucleus may have sufficient energy (T_R) to not only rupture the bonds but to recoil completely out of the target matrix itself.

A judicious choice of target isotope and nuclear reaction can be coupled to the recoil mechanism in order to produce a virtually carrier-free radionuclide. That is, most target nuclei are not limited to a single reaction with a given projectile, but advantage can be taken of the relative reaction cross-sections, the half-lives of the products involved and the excitation functions in order to limit or negate the existence of interfering radionuclides.

As a typical example of the application of this general method, we have chosen to examine the production of ^{75}Se from a natural Se target utilizing the (n,2n) reaction at 14.8 MeV.

In this system the interfering products would be those from (n,p) and (n,α) reactions. Neutron capture products, at this energy, have negligible cross-sections. The recoil momentum for the (n,2n) reactions is that supplied by the incident neutron since it is assumed that the two evaporated neutrons have momentum coupling equal and opposite and are emitted isotropically. Similarly, the emission of protons and alphas is also isotropic for all practical purposes. However, the cross-section for the (n,2n) reaction is of the order of 600 mb while that for (n,α) and (n,p) is at least an order of magnitude less. Hence, even though the competing reactions do produce recoil the yield is, at minimum, an order of magnitude less and the reaction products have half-lives that insure they will decay out before use. In this preliminary study enriched isotopes were not employed. Additional enhancement of the ratio of those isotopes of interest can easily be achieved by use of the enriched ^{76}Se target. The technique in no way destroys the target and hence it is reusable on an almost indefinite basis.

The targets are prepared by vacuum evaporating or electro depositing the selenium on a suitable backing. In the initial studies, 3 mil aluminum was employed so as to also act as a neutron flux monitor. Be or similar material that would themselves produce no residual activity can be employed.

The targets, 2 to 5 mg/cm^2 with dimension 3 cm x 3 cm are immersed in an aqueous solution of 0.1 N NaH CO_3, and irradiated with fast (14.8 MeV) neutrons with the backing facing the neutron targets. The recoils are then collected directly in solution. The $NaHCO_3$ serves two purposes. First, it acts as a buffer precluding dissolution of the target and second, and most significant, advantage is taken of the solution mobility of Na^+ vis-à-vis Se^{+2} or Se^{+3} (the charge status expected to recoil). The sodium ion therefore neutralizes the charge buildup on the target surface rather than the Se ion migrating to neutralize the potential.

A total recovery of about 40% was achieved in these initial studies. The relative yield could be enhanced by a more exact choice of target thickness.

*Permanent Address: Veterans Administration Hospital, Albany, New York 12208

No. 97

LABELLING AND ANIMAL DISTRIBUTION STUDIES OF 5-ASTATOURACIL AND 5-ASTATODEOXYURIDINE (^{211}At)

K. Rössler, G.-J. Meyer, and G. Stöcklin

Institut für Chemie der KFA Jülich GmbH,
Institut 1 : Nuklearchemie, 517 Jülich (FRG), Germany

In view of the potential radiobiological and therapeutical consequences of the incorporation of the α-emitter ^{211}At (T = 7.2 h) into DNA, it was attempted to label the pyrimidine bases uracil and deoxyuridine. These nucleic acid precursors might serve as a vehicle for ^{211}At to the nuclei of heavily proliferating cells such as in tumors.

Since classical pathways of carrier-free halogenation are rather disadvantageous due to the only small electrophilicity of such agents as AtO^- or At^+, it seemed more promising to make use of the pronounced complexing character of At. After systematic studies on the reactivity and selectivity of inorganic At-forms and interhalogen compounds AtX and AtX_2^- with benzene derivatives[1,2], the decomposition of diazonium salts in the presence of At^- proved to be a very selective and efficient method of labelling. This could be demonstrated in the successful preparation of the ortho-, meta- and para-isomers of all possible astatohalobenzenes[3].

5-^{211}At-uracil (AtU)[4] and 5-^{211}At-deoxyuridine (AtUdR) were prepared starting from the corresponding 5-amino-derivatives, *via* formation of 5-diazonium salts with At^- and rapid decomposition. Radiochemical yields amounted to more than 30% and about 3%, respectively. AtUdR was also prepared *via* At-for-I exchange of ^{211}AtCl with 5-iododeoxyuridine with similar yields. High pressure liquid radiochromatography was used for identification, purification and quality control. The stability of the compounds under the chromatographic conditions applied could be demonstrated by multiple injection.

The distribution on various organs and the excretion of both At-compounds and of inorganic At^- was studied in normal mice and animals with experimental tumor Sarcoma-180 after intravenous injection. Despite some slight differences in the distribution pattern, all the three forms showed an increased incorporation into liver, spleen and lungs of the tumor bearing animals with respect to the normal controls. The concentration of ^{211}At in the tumor tissue is by a factor of 3 greater than that of the corresponding iodine labelled compounds (15% to 5% of total radioactivity). The data indicate for ^{211}At an enhanced rate of attachment to cells of the reticuloendothelial system (RES) and of Sarcoma-180 possibly *via* an intermediate binding to serum proteins.

References

(1) G.-J. Meyer and K. Rössler, Radiochem. Radioanal. Letters 25 (1976) 377.
(2) G.-J. Meyer, K. Rössler, and G. Stöcklin, AED-CONF-75-404-029 (1975).
(3) G.-J. Meyer, K. Rössler, and G. Stöcklin, Radiochem. Radioanal. Letters 21 (1975) 247.
(4) G.-J. Meyer, K. Rössler, and G. Stöcklin, J. Lab. Comp. Radiopharm. (1976), in press.

No. 98

THE ROLE OF POSITRON EMITTERS IN NUCLEAR MEDICINE WITH SPECIAL REFERENCE TO SCANDIUM-44

Fazle Hosain, Ibrahim B. Syed, and Richard P. Spencer

Department of Nuclear Medicine, University of Connecticut Health Center, Farmington, Connecticut 06032

Recent developments in tomographic devices for studies involving radionuclide imaging, and the possibility of using Carbon-11 and Nitrogen-13 compounds in clinical studies have created a renewed interest in positron-emitting radionuclides. Indeed, a number of positron emitters could be made available with half-lives of few minutes to several days. They could cover a wide range of elements that could be incorporated into a variety of chemical compounds. They could not only provide structural information but also help in understanding functional aspects of pathophysiological conditions.

It would be convenient to have suitable short-lived positron-emitting radionuclides that could be obtained from generator systems. Earlier Ge(68)-Ga(68) had been used, and recently Sr(82)-Rb(82), Zn(62)-Cu(62) and Ti(44)-Sc(44) have been suggested. It is interesting to note that Sc-43 and Sc-44 decay by positron emission and have the same half-life (3.92 h). Scandium-44 can be obtained as a decay product of Sc-44m or Ti-44. It is not practical to use Sc-44m as a parent but the long-lived Ti-44 appears to be most promising as a source for Sc-44. The cost of production of Ti-44 is very high, but large scale production by spallation reaction is feasible.

We have prepared experimental generators with low activities of Ti-44, and characteristics of several Sc-44 radiopharmaceuticals have been studied. Detailed dosimetry of blood-pool, lung, liver, kidney and bone scanning agents with Sc-44 has been calculated, and compared with other similar compounds. Scandium-44 and its chemical nature might prove valuable in nuclear medicine.

No. 99

MICROSCALE SYNTHESIS OF PHOSPHORUS TRICHLORIDE LABELED WITH HIGH-SPECIFIC-ACTIVITY PHOSPHORUS-33*

D. V. Woo and A. F. Rupp

Oak Ridge National Laboratory, P. O. Box X,
Oak Ridge, Tennessee 37830

The chlorides of phosphorus are important intermediate reagents used in the synthesis of various organo-phosphorus compounds of biomedical interest. Previous syntheses of macro quantities of phosphorus trichloride (PCl_3) have been established, but little work has been done to provide millimole amounts of this compound labeled in high specific activity with radio-phosphorus-33 (^{33}P, 25-day half-life, 0.25 MeV pure beta emitter). A micro-scale flow-through process to synthesize high-specific-activity $^{33}PCl_3$ or $^{33}POCl_3$ (> 100 mCi/mmole) has been developed for synthesis of phosphorus compounds with tumor-specific uptake as possible radio-cytotoxic agents. (Phosphorus-32 may be also used interchangeably with or in addition to ^{33}P.)

The synthesis is initiated by addition of carrier-free radiophosphoric acid ($H_3{}^{33}PO_4$) to a known quantity of carrier H_3PO_4 and allowing the mixture to react (metathesize) with PbO in excess of the stoichiometric amount. The metathesis proceeds under ultrasonic agitation with the product, lead phosphate [$Pb_3(PO_4)_2$], being formed. The $Pb_3(PO_4)_2$ is subsequently reduced in a flow-through hydrogen atmosphere at 750°C. Elemental phosphorus distills out as it is liberated from the reduction of $Pb_3(PO_4)_2$ and collects in the cooler distal portions of the reaction tube while the Pb metal reductate remains behind. After the hydrogen is replaced with an argon atmosphere and the reaction tube is allowed to cool, chlorine gas is introduced to convert the phosphorus to PCl_5. The $^{33}PCl_5$ is sublimed through a reactor containing a thin film of red phosphorus on borosilicate glass balls and is reduced to the desired product, $^{33}PCl_3$. The $^{33}PCl_3$ is collected in a freeze trap where it is distilled and then sealed in an ampule.

Characterization of the product is conducted by observing the freezing and boiling point behavior of the PCl_3 during processing. Final chemical purity is established by laser Raman and nuclear magnetic spectral analysis. Radioassay is estimated through measurement of ^{32}P-^{33}P bremsstrahlung from the product ampule in an ion chamber. Purity and yield are > 92% and 70% respectively.

*Research sponsored by U. S. Energy Research and Development Administration under contract with Union Carbide Corporation.

No. 100

SYNTHESIS OF LABELLED 3β-IODOCHOLESTEROLS FOR ADRENAL IMAGING

T. Yu, D. M. Wieland, R. D. Ice, and W. H. Beierwaltes

College of Pharmacy and Division of Nuclear Medicine,
The University of Michigan, Ann Arbor, Michigan 48109

Adrenal imaging with 19-Iodocholesterol-I-131 (NM-145) has provided a non-invasive method of determining adrenal anatomy and function. 6-Iodomethyl-19-norcholesterol-I-131 (NP-59) has demonstrated increased adrenal uptake, better T/NT ratios with resultant enhanced images as compared to NM-145 (J. Nucl. Med 16 (1975) 1038). The chemical instability and a difficult 7 step synthetic sequence from cholesterol precludes the widespread utilization of NP-59 and NM-145 as clinically useful drugs.

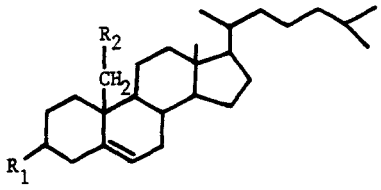
Recent work by Szinai and Owoyale indicates that 3β-Iodocholesterol-I-125 (NP-85) concentrates in the dog adrenal nearly 2½ times greater than 19-Iodocholesterol-I-125 (NM-145). Thus the 3-hydroxy group in cholesterol is not necessary for adrenal localization (Figure 1).

In an effort designed to enhance the adrenal image produced by NP-85, we have increased specific activity, modified the formulation and prepared a series of analogs that would potentially increase the nontarget organ excretion rates. The Iodosteroids synthesized in this study as shown in Figure 2.

Each radioiodinated steroid was prepared directly from the corresponding tosylate by refluxing with sodium iodide-I-125 in ethanol.

The compounds were evaluated at one and five days in dogs. With enhanced formulation NP-85 has the same relative uptake in the adrenal cortex as does NP-59. NP-92 rapidly deiodinated *in vivo* and *in vitro* while NP-91 deiodinated *in vivo*. NP-95 had adrenal localization less than NM-145 but NP-88 and NP-90 localized in the adrenal cortex in concentrations greater than NM-145 but less than NP-59 and NP-85.

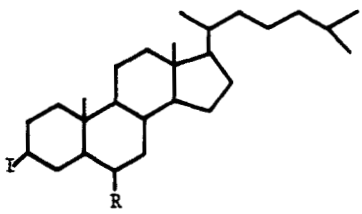
The radioiodinated steroid NP-85, when properly formulated is an inexpensive, easily labeled, stable compound that localized preferentially in the adrenal cortex.



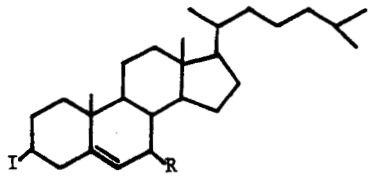
R_1=OH, R_2=I (19-Iodocholesterol)

R_1=I, R_2=H (3β-Iodocholesterol)

Figure 1



R=H (NP-88)
R=O (NP-90)
R=OH (NP-91)
R=OAc (NP-95)



R=H (NP-85)
R=OH (NP-92)

Figure 2

No. 101

IODINE-123 ORTHO-IODOHIPPURATE FOR COMPUTER ASSISTED ASSESSMENT OF INDIVIDUAL KIDNEY FUNCTIONS

F. Zielinski, G. D. Robinson, Jr., A. V. Bocksrucker, M. Easton, and A. W. Lee

Department of Radiological Sciences, University of California, Los Angeles, California 90024

I-123 sodium o-iodohippurate for kidney function studies in man was synthesized because its use would give statistically significant regional and temporal data from the γ-camera. This data can be computer processed to obtain very high quality renograms, kidney images and effective renal plasma flow.

Our research was initiated to develop a rapid, reliable and simple chemical method of synthesizing 99 to 100% radiochemically pure I-123. (The high initial purity is required to eliminate time-consuming purification steps.)

One hundred millicuries of I-123 are isolated after proton irradiation (100 μamp hr, 22 MeV) of the target containing 20 mg aluminum and 180 mg of 96% enriched Te-124. The target is dissolved in 25 ml 7 M sulfuric acid and 2 ml 30% hydrogen peroxide. Carrier iodide (4 μg) and water are added to insure distillation of more than 90% of the I-123 from 3.5 M sulfuric acid into a dilute NaOH trap. An aliquot of the distillate is evaporated to near dryness, the pH adjusted to 3 and radioiodate, if present, is reduced to iodide with 0.05 ml of 0.06 N thiosulfate. I-123 iodide (20-40 mCi in 0.9 ml) is oxidized to a reactive form with 0.1 ml of 0.06 N iodate, then 150 mg sodium o-iodohippurate in 0.5 ml at pH 5.6 is added. The mixture is sealed in a glass ampule and heated at 121°C for 90 min. The product is transferred into sterile, pyrogen-free vials. Rapid chromatographic analysis using Whatman #1 paper and n-butanol:water:glacial acetic acid (4:1:1 v/v) distinguishes between iodide (R_f 0.1) and OIH (R_f 0.8). The entire procedure including analysis of the final dosage form takes 4 hours. The yield in each of the last 50 runs exceeds 99%.

In vitro stability studies at room temperature showed that I-123 OIH synthesized in this manner is radiochemically stable for 10 days.

Clinical data obtained after administration of 1.5 mCi of I-123 OIH to 120 patients confirms that it is suitable for computer assisted measurements of total and individual kidney function.

No. 102

CHEMICAL EFFECTS OF RADIOIODINE DECAY IN RADIOPHARMACEUTICALS

V. W. Jiang and M. J. Welch

Division of Nuclear Medicine, George Washington University Medical Center, Washington, D. C. 20037, Mallinckrodt Institute of Radiology, Division of Radiation Sciences, Washington University School of Medicine, St. Louis, Missouri 63110

With the advent of convenient production methods for ^{123}I many biochemicals, drugs and proteins are being radioiodinated. In addition, many proteins are labeled with ^{125}I for radioimmunoassay. High specific activity is desirable for the radiopharmaceuticals so that nonphysiologic amounts can be administerd. For radioimmunoassay high specific activity is important for sensitive assays. But there is a high probability that one target molecule will contain more than one atom of radioiodine. Rosa et al. indicate that the iodination of human serum albumin at radioiodine levels of 0.5-1.0 atoms per protein molecule produces about 39 to 60% disubstitution. Therefore, model systems such as iodophenol and iodotyrosine were studied in aqueous media to determine the chemical effects produced as a result of the nuclear transformation.

Doubly labeled ^{131}I-^{14}C-3-iodotyrosine was synthesized from ^{14}C-labeled tyrosine and ^{131}I using the chloramine-T method of iodination. The ^{131}I atom which was chemically bound to the ^{131}I-^{14}C-3-iodotyrosine molecule was allowed to decay in aqueous solution containing electron scavengers and various additives. Reference systems of ^{127}I-^{14}C-3-iodotyrosine in which the ^{131}I was added as free iodide were also studied. The reference systems were used to correct the products observed in the ^{131}I-^{14}C-3-iodotyrosine systems for those formed by the hydrolysis of the carbon-iodine bond.

It was found that the primary reaction after the decay of the ^{131}I atom in the ^{131}I-^{14}C-3-iodotyrosine molecule led to the formation of a second hydroxyl group on the aromatic ring of the molecule. Observed decomposition products can be accounted for as the oxidation products of the primary product 3,4-di-hydroxyphenylalanine. However, some products were formed as a result of bond breakage. The energy involved in the reactions was sufficiently high to cause a carbon-carbon bond rupture on the side chain of the molecule following a small percentage of the decay events. The products formed from the ^{127}I-^{14}C-3-iodotyrosine systems were only those from hydroxyl group addition and oxidation reactions.

The results from this study suggested that if a protein molecule is labeled with ^{131}I, the major reaction following the decay of the ^{131}I atom is the formation of a hydroxyl group at the iodination position. The protein chain of the molecule might be ruptured as the result of the ^{131}I decay in a small fraction of cases.

No. 103

EXCITATION FUNCTIONS, TARGETRY AND RADIOCHEMISTRY FOR ^{123}I AND ^{124}I PRODUCTION BY THE (p,2n) AND (p,n) REACTIONS ON ^{124}Te*

R. M. Lambrecht, K. Kondo, and A. P. Wolf

Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973

The purpose of this communication is to highlight new experimental results for ^{123}I production. The excitation functions for the $^{124}Te(p,2n)^{123}I$ and $^{124}Te(p,n)^{124}I$ reactions were determined by the stacked foil technique in the proton energy range of 29 to 9.9 MeV with thin films of 99.87% and 91.86% isotopically enriched ^{124}Te. The production rates and the optimum fractions of the excitation functions for obtaining the maximum radiochemical purity of ^{123}I with different isotopic enrichments of ^{124}Te were established. A target of 256 mg/cm^2 of 99.87% isotopically enriched ^{124}Te irradiated with 25.8 MeV protons results in a ^{123}I production rate of 10.6 mCi/μAH, and a radionuclidic impurity level of 0.54% ^{124}I, 0.0011% ^{125}I, 0.0014% ^{126}I and 0.031% ^{130}I. The radionuclidic impurities increase by about a factor of 2 when 91.86% ^{124}Te is irradiated under similar conditions. ^{123}I is recovered as iodide by sorption methods by using a novel platinum felt technique. A quantitative procedure for recovery of 99.9±0.1% of the ultrahigh enrichment ^{124}Te ($15.00 mg) was developed. ^{123}I can be produced at a full cost recovery of < $30.00 per mCi at EOB.

The $^{124}Te(p,n)^{124}I$ reaction can be considered as a convenient production method for ^{124}I ($T_{½}$ = 4.15 d, β^+ 25%) for double labeled radiopharmaceuticals (^{123}I + ^{124}I) and detection with a positron camera for transaxial reconstruction tomography.

*This research was performed under contract with the U. S. Energy Research and Development Administration, and partially supported by NIH Grant No. 5-P41 RR0067.

No. 104

ESTROGEN DERIVATIVES FOR THE EXTERNAL LOCALIZATION OF ESTROGEN DEPENDENT MALIGNANCY

T. Komai, W. C. Eckelman, R. Johnsonbaugh, A. Mazaitis, V. W. Jiang, and R. C. Reba

Division of Nuclear Medicine, George Washington University Medical Center, Washington, D. C. 20037

Tritiated hexestrol and estradiol have been shown to concentrate in certain experimental and human breast tumors. The concentration mechanism is related to the presence of specific estrogen receptor proteins. These receptor proteins are the same as those responsible for the concentration of estradiol in natural estrogen responsive tissues such as the uterus. Since the recent literature has shown a direct positive correlation between the presence of the estrogen receptors in malignancy and the remission of the tumor after endocrine ablation, the development of an estrogen derivative containing a gamma emitting nuclide would be useful in detecting metastases and in determining the estrogen dependency of metastatic tumors in sites which are not easily biopsied.

To this end four compounds were purchased or synthesized by standard techniques: estradiol(I), hexestrol(II), 1,3,5 estratriene, 3 ol, 17 β-yl N-[1-carbomethoxy-2-(4-hydroxypheny1)] ethyl) succinamate(III) and 1,3,5 estratriene, 3, 17 β-diol, 6 aminoxy acetyl amino-3-(4-hydroxypheny1)-propionate(IV). The compounds were iodinated using equimolar amounts of iodine and chloramine-T and analyzed by various chromatographic systems.

The use of receptor systems is an important technique to screen new drug derivatives. The estradiol receptor binding affinity of the four compounds to be iodinated was determined. Quantities of I, II, III and IV were added to the receptor assay system containing rabbit uterine cytosol. Compound I was most effective (50% inhibition at 2.9x) in displacing ^{3}H estradiol followed by II (50% inhibition at 6.4x) and III (50% inhibition at 200x). Compound IV could not displace ^{3}H estradiol from the receptor even at 200 fold excess.

In contrast iodinated I could not displace ^{3}H estradiol from the receptor. Monoiodinated II could displace ^{3}H estradiol, although a 100 fold excess was required to decrease the binding of ^{3}H estradiol by 50%. Compounds III and IV were not tested in the iodinated form.

Sucrose gradient centrifugation patterns using immature rat uteri gave similar results. Tritiated estradiol showed a distinct peak which corresponds to the 8S region. This peak disappeared when excess unlabeled estradiol was added to the cytosol. The iodinated form of compounds I and III showed no binding in the 8S region but did show binding in the 4S region. This binding was not decreased by addition of excess unlabeled estradiol. However, the radioiodinated form of compound II showed a small peak in the 8S region where ^{3}H estradiol binds. This peak diminished to zero in the presence of excess estradiol indicating a specific interaction with the estradiol binding protein. Similar *in vitro* results for iodohexestrol have been obtained by Katzenellenbogen *et al.*

The radioiodinated forms of Compound I, II and III were then evaluated as diagnostic radiopharmaceuticals by comparing their distribution in immature female rats. The uterus-to-blood ratio was used as an index of the value as a diagnostic agent. In agreement with the *in vitro* experiments, the radioiodinated form of compound II showed a higher uterine concentration (1.69% D/g) than either the

radioiodinated form of compound I (0.29% D/g) or compound III (0.17% D/g). However the uterus-to-blood ratio for compound II, although the highest of the three compounds, was still less than 2. The preinjection of thyroxine before the injection of the radioiodinated form of compound II produced an increase in the uterine concentration and a decrease in the blood concentration. The uterus-to-blood ratio was 10.4 at 2 hr after injection. In contrast, the effect of thyroxine on the uterus-to-blood ratio for the radioiodinated forms of compounds I and III was minimal.

Although many diagnostic radiopharmaceuticals result in high rates of detection, they are not specific. In an attempt to develop specific diagnostic agents for the detection of hormone regulated tumors, four iodinated derivatives of estrogens were prepared. One of these, iodinated hexestrol, showed specific binding with the estradiol binding protein. However, non-specific binding with thyroxine binding proteins prevented high differential uptake unless thyroxine was administered. Attempts must be made to design derivatives which retain their affinity for estradiol binding protein but do not bind in a non-specific manner.

No. 105

BY-PRODUCTS IN THE RECOIL LABELING OF 1,1,1-TRIFLUORO-2-CHLORO-2-BROMOETHANE WITH ^{82}Br

Kiyoshi Hoizumi, Terutomi Mogi, Hiroshi Kudo, and Takashi Moriya

Japan Atomic Energy Research Institute, Tokai-mura, Naka-gun, Ibaraki-ken, Japan

In order to satisfy the requirement for the biological research, the authors have been examined to prepare fluothane-^{82}Br(1,1,1-trifluoro-2-chloro-2-bromo-ethane-^{82}Br) by means of a recoil labeling, and then obtained it in 38% or more of the radiochemical yield.[1,2] In this preparation, many byproducts are observed on a radiogas chromatogram of neutron irradiated fluothane. CF_3CHBr_2 stand out clearly from other byproducts because of its high radiochemical yield. Our attentions are focused on radiolysis of fluothane and its resulting byproducts.

More than 20 chemical species, which were originated in fluothane irradiated with neutrons for 3 hr, had a detectable concentration by a thermal conductivity detector of gas chromatograph. About half of these byproducts were identified by means of the gas chromatograph and mass spectrometer (GC-MS). The following chemical formula were of the byproducts giving comparatively high yields.

CF_3Br	CF_3CHBr_2	$CF_3CHCl\ CHCl\ CF_3$
	CF_3CH_2Br	$CF_3CHCl\ CHBr\ CF_3$
	CF_3CHCl_2	$CF_3CHCl\ CClBr\ CF_3$
	CF_3CH_2Cl	$CF_3CHBr\ CClBr\ CF_3$
	CF_3CCl_2Br	

It was confirmed that there was a certain regularity between the structure of these compounds and their retention time in the gas chromatograph.

Polyhalogenated methane, ethane, and butane were predominant in the byproducts, but polyhalogenated propane and higher alkanes than pentane were not detected. Consequently, the seemingly structural units in common with the byproducts were CF_3CHCl, CF_3CHBr, and CF_3CClBr, and others were scarce. The CF_3 group of fluothane was contained in many byproducts, and the C-F bond cleavage were only in part. These results indicate that the C-Br, C-Cl, and C-H bonds of the parent molecule had much chance to be broken, and that C-F and C-C bonds had less chance.

Associations of CF_3CHCl and CF_3CHBr groups with bromine, which is continuously generated in the reaction system, correspond to the reproduction of parent molecule and to the formation of CF_3CHBr_2. This reproduction will not be independent of the fact that the recoil labeling is successfully applied to fluothane being considered to be labile to radiation. This suggests the higher adaptability of the recoil labeling than expected.

On the other hand, both chemical and radiochemical yield of polyhalogenated butanes increase with increasing neutron irradiation time, while those of parent compound, fluothane, decrease over 3 hr of neutron irradiation. Consequently, the constitution of the byproducts changed during a prolonged neutron irradiation. Since ^{82}Br-labeled polyhalogenated compounds are usually difficult to be prepared, there may be some cases, where the byproducts are successfully used for trace experiments.

References

(1) K. Hoizumi, T. Mogi, and H. Kudo, J. Labelled Compounds, 10 (1974) 437.
(2) H. Kudo, T. Mogi, and K. Hoizumi, Bull. Chem. Soc. Japan, 47 (1974) 2162.

No. 106

THE SYNTHESIS OF 6-DEOXY-6-^{18}F-α-D-GALACTOPYRANOSE FOR METABOLIC STUDIES

David R. Christman, Zlata Orhanovic, and Alfred P. Wolf

Chemistry Department, Brookhaven National Laboratory,
Upton, New York 11973

Carbohydrates labeled in a position not normally involved in initial metabolic processes are of considerable potential interest for both organ scanning and for studying their metabolism in disease states, if the compounds should either accumulate in specific organs or should show altered metabolism when disease states are present. The 6 position in certain common carbohydrates is such a position, and in many cases it has been found that substitution of fluorine for the hydroxyl group in the 6 position does not cause a major perturbation in the tissue transport properties as compared to those of the parent compound[1]. As an example, galactose is known to accumulate in the liver[2] and to show altered metabolic patterns in the case of certain liver diseases. The synthesis of the 6-deoxy-6-^{18}F galactose analog was therefore undertaken in the hope that it would prove of value in such cases.

The unlabeled compound has been prepared by several groups, and the approach of Taylor and Kent[3] was investigated. The method involves the displacement of a standard leaving group from the 1,2:3,4-di-O-isopropylidene-6-O-R-α-D-galacto-pyranose compounds with KF in ethylene glycol. We have tried the reaction with R being mesyl, tosyl, iodo, and p-nitrobenzylsulfonyl groups, and with K^{18}F alone, K^{18}F plus 18-crown-6 crown ether, and tetraethylammoniumfluoride as displacing agents, using ethylene glycol or acetonitrile as solvent. Reaction times ranged from 1-24 hours and reaction temperatures from 85-200°C.

The use of K^{18}F under all conditions gave either no reaction or very low yields of impure product. By far the best results were obtained using the tosyl group as leaving group, with Et$_4$N^{18}F in acetonitrile in a molar ratio of about 1:2.6. A small pressure bottle was used for the displacement at a temperature of 170°C for 2 hours. Total time for the reaction, including acid hydrolysis of isopropylidene groups and extraction with ether, with a final evaporation and dissolution in an appropriate solvent, was 3½ to 4 hours. The overall radio-chemical yield was 15%. From an initial activity of 100 mCi of ^{18}F$^-$, about 4 mCi in about 0.2 mg of product should be available at the end of the synthesis.

References

(1) J. E. G. Barnett, W. T. S. Jarvis, and K. A. Munday, Biochem. J. 109, (1968) 61.
(2) W. Shreeve, et al., J. Nucl. Med. 15 (1974) 532.
(3) N. F. Taylor and P. W. Kent, J. Chem. Soc. (London) 872 (1958).

No. 107

PRODUCTION AND USE OF ^{11}C-LABELLED PHOSGENE

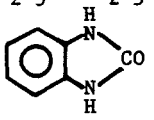
D. Roeda and B. van Zanten

Department of Organic Chemistry, Vrije Universiteit,
c/o Radionuclidencentrum de Boelelaan 1083a, Amsterdam, The Netherlands

Phosgene reacts with a broad spectrum of organic functional groups, its reactions at a nitrogen, oxygen or sulfur centre are well-known. The formation of reactive agents like isocyanates and chloroformate proceeds easily and rapidly, and substituted carbonates, urea derivatives and other compounds can be prepared in a short period of time in excellent yields. In our opinion the production and use of $^{11}COCl_2$ should open up many new ways for the preparation of ^{11}C-labelled pharmaceuticals.

We developed a flow-type system suitable for the production of $^{11}COCl_2$ from cyclotron-produced $^{11}CO_2$. In our present experiments about 0.1 to 1 ml of CO_2 is introduced into a stream of dry helium or nitrogen (25 ml/min). The CO_2 is quantitatively reduced to CO by reduction with zinc at 400°C and the formed CO is converted into $COCl_2$ by reaction with $PtCl_4$ at elevated temperature. The amount of conversion is a function of the temperature, 30% conversion is obtained at 270°C and about 100% at 320°C. Because even at 270°C the $PtCl_4$ starts to decompose, liberating some chlorine gas, experiments with antimony absorbers for the trapping of Cl_2 are underway.

The yield of the $COCl_2$ production is determined by bubbling the gas stream through an alcoholic solution of sodium ethanolate. The amount of formed diethyl carbonate is measured by a quantitative glc-analysis. Up till now the in-flow production has been carried out of the following compounds:

Urea	:	$NH_2.CO.NH_2$
s.Diphenyl-urea	:	Ph.NH.CO.NH.Ph
Chloroformate	:	C_2H_5OCOCl
Diethyl carbonate	:	$C_2H_5OCOOC_2H_5$
o-Phenylene urea	:	

Thus far our results indicate that in-flow reactions with phosgene basically are suitable for a rapid preparation of biologically interesting compounds.

Experiments with ^{14}C are now in progress in order to check the feasibility of the phosgene production system for in-flow reactions on a micro-scale (less than 0.001 mmole).

Experiments with ^{11}C will start the end of this year in cooperation with dr. Comar from the French Nuclear Research Centre C.E.A.

No. 108

MODIFICATIONS OF CONVENTIONAL CHEMICAL PROCEDURES IMPOSED BY RADIOPHARMACEUTICAL PREPARATION

K. A. Lathrop and P. V. Harper

Franklin McLean Memorial Research Institute, University of Chicago, 950 East 59th Street, Box 420, Chicago, Illinois 60637

When a radiochemical is to be used as a radiopharmaceutical the chemical production is made more rigorous by the imposition of pharmaceutical limitations, but, at the same time some chemical restrictions may be relaxed. The pharmaceutical limitations are sterility, apyrogenicity, lack of biologic toxicity, and, in some instances, the volume of the final product and the time permitted to carry out the reaction. The usual chemical procedures that may be unnecessary are isolation, purification, and quantitative production of the chemical. Sterility may be achieved for filterable preparations by passage through membranes of suitable pore size, but the pyrogenic products of bacterial metabolism will remain in solution. The chemical reaction in itself can accomplish both sterility and apyrogenicity if appropriate reagents are used, provided that care is used to prevent subsequent contamination after removal of the radiochemical from such medium. When use of such chemicals is impossible, reagents pretested for microorganisms and pyrogens may be employed in a clean, closed system. Biologic toxicity, as well as quantitative biologic distribution, which will be determined by the amounts of substances present, are usually controlled best by using micro quantities of chemicals. Several options available for limiting the patient dosage to around 1 ml, when desirable, include small volumes of reactants, extraction into a small volume of solvent, rapid evaporation from a volatile solvent and subsequent solution into a small volume. Isolation and purification of the radiochemical will not be necessary if other radioactive products are insignificant and if nonradioactive materials are nontoxic. The above considerations apply to syntheses with short-lived radionuclides (a few seconds to a few hours). Some requirements may not be mutually compatible, and, in addition the established chemical methods may require impossibly long reaction times so that new procedures must be invented, thoroughly challenging the chemist.

No. 109

SELENIUM-73 AND NEW POTENTIAL RADIOPHARMACEUTICALS

M. Guillaume, Centre de Recherche Cyclotron

L. Christiaens, and M. Renson, Institut de Chimie Organique

Université de Liège, Belgium

In cases where specific new organo-seleno compounds do provide a feasible and reliable tumor visualization, it would be a major advantage to substitute the selenium-75 by a more suitable radioisotope. The more convenient nuclear properties of selenium-73 ($T_{\frac{1}{2}}$ = 7.1 hr, β^+ = 65%, EC = 35%, γ = 66 keV (0.65), 359 (0.99), 511 (1.30)) suggest that ^{73}Se may be a more useful radioselenium label for *in-vivo* medical applications. The comparison of the calculated absorbed radiation dose to the liver between ^{73}Se and ^{75}Se shows an approximate ratio of 1:50, respectively. These fundamental reasons were incitements to incorporate ^{73}Se into radiopharmaceuticals with specificity for the pancreas or brain as required not only for the anatomic imaging, but also for dynamic measurements and interpretation of physiological functions.

Our present experimental work has been developed in two complementary directions. Firstly, the feasibility of the selenium-73 production with a low energy ^3He beam available from a compact medical cyclotron has been considered. ^{73}Se was produced by the $^{72}Ge(^3He,2n)^{73}Se$ nuclear reaction by irradiation of a 1.2 mg/cm^2 compressed natural germanium oxide pellet with a 29 MeV ^3He beam. A yield of 2.5 mCi was obtained after a 1 hr bombardment with a 10 µA beam. A rapid chemical separation of the carrier-free selenium-73 was successfully achieved by means of a simplified thermochromatographic method by taking advantage of the difference in the vapor pressures of metallic germanium and selenium at 600°C. The easy remote-controlled instrumental procedure gives (with argon used as carrier-gas) a high radionuclidic purity (^{75}Se < 0.8%; ^{72}Se < 0.2%) and a reproducible radiochemical yield of 70-75%.

In a second part, the labelling of new aromatic seleno compounds with radioselenium (^{75}Se) has been considered. The choice of the seleno compounds has been dictated by the fact of the large requirement for exogenous amines and amino acids of the pancreas and, on the other hand, because proteins containing selenium are known to be essential components of enzyme systems. The synthesis of a new class of selenium-containing amines and amino acids has been undertaken where the selenium can either be bioisosteric replacement for sulfur in the heterocyclic structure (benzoselenophene amines and amino acids) or incorporated in an aliphatic substitution group (-$SeCH_3$ for example).

A simple method for introducing radioselenium into the radiopharmaceutical with a 85-90% chemical yield has been obtained. The reproducibility of such a fast radiochemical procedure using the powdered gray allotropic form of selenium and sodium borohydride in aqueous solution has been determined. This procedure enabled to begin with the multistep synthesis of the first term of the series, i.e. the benzoselenotryptamine. A chemical yield of 25% has been obtained on a 50-100 mg scale. Specific activities of 50-100 µCi/mM have been achieved, but have not yet been optimized. *In-vivo* distribution studies on animals are planned.

No. 110

A METHOD OF DETERMINING CALIBRATION SETTING NUMBERS FOR A COMMERCIAL RADIOISOTOPE CALIBRATOR

Arata Suzuki, Marcia N. Suzuki, and Arthur M. Weis

Capintec, Incorporated, 136 Summit Avenue, Montvale, New Jersey 07645

Radioisotope calibrators are routinely used to assay activity levels of commercially available and the new medical isotopes, and to dispense radiopharmaceuticals in the clinic. It may be desirable to use a calibrator for the assay of a radioisotope which is not commonly used and therefore, whose calibration number is not given by the manufacturer of the calibrator. A method of determining a calibration setting number is described.

It is very convenient to express the response of the detector to a radioisotope, A, relative to that of a standard reference material, e.g. ^{60}Co

$$R_A \equiv \frac{\dfrac{\text{Detector Output due to Sample A}}{\text{Activity of Sample A}}}{\dfrac{\text{Detector Output due to SRM}^{60}\text{Co}}{\text{Certified Activity of the SRM}^{60}\text{Co}}} \qquad (1)$$

The sensitivity of the detector for a photon of energy E_i is defined as:

$$S_i \equiv \frac{\text{Detector Output due to } 3.7 \times 10^{10} \text{ Photons of } E_i}{\text{Detector Output due to one Curie of } ^{60}\text{Co}} \qquad (2)$$

The detector response and the sensitivity have the following relation

$$R_A = \sum_i I_i S_i \qquad (3)$$

where I_i is the intensity of the photon whose energy is E_i.

The procedure is to measure the response of the detector to all the available primary standard samples and to establish the sensitivity of the detector as a function of photon energy so as to satisfy equation (3) for all the standards. Once the sensitivity curve has been determined, the response of the detector to any radioisotope may be calculated using equation (3), provided that the decay data are known.

The relationship between the response of the detector and the gain setting (relative to that for ^{60}Co, in order for the instrument to give a direct reading of the activity) is given by

$$G_A = \frac{1}{R_A} \qquad (4)$$

In order to derive the calibration number for a particular type of calibrator, one may have to refer to the manual or literature of the calibrator of interest. An example of the sensitivity curve for a tall argon filled aluminum ionization chamber is given in Figure 1.

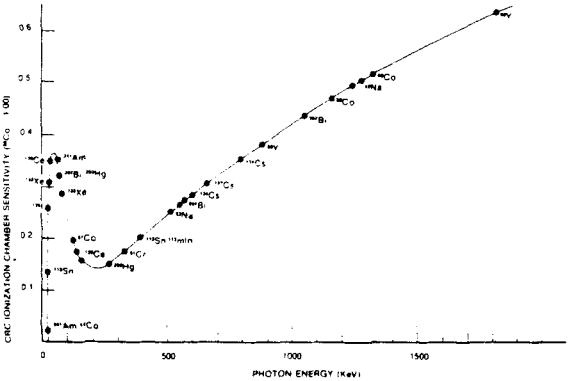


Fig. 1. The sensitivity of the Capintec Radioisotope Calibrator as a function of photon energy.
Sensitivity is normalized by the chamber response to Cobalt-60 radiations.

No. 111

GENERATION OF KRYPTON-81m FOR INFUSION AND VENTILATION STUDIES

L. W. Mayron, E. Kaplan, A. M. Friedman, and J. E. Gindler

Veterans Administration Hospital, Hines, Illinois 60141 and
Argonne National Laboratory, Argonne, Illinois 60439

^{81m}Kr is a radioactive noble gas, inert both chemically and biologically. It has a monoenergetic gamma emission at 190 keV and a 13 second half-life. Continuous generation of this gas from ^{81}Rb allows its continuous elution by air or by 5% dextrose-in-water from a minigenerator of our own design; its placement into any organ or tissue in the body, by means of a 150 cm minibore catheter, results in excellent imagery of the perfusion of that organ or tissue, inasmuch as the flow of krypton follows the flow of body water.

We have produced ^{81}Rb in the Argonne National Laboratory 60-inch cyclotron by irradiation of Cu_2Br_2 (^{79}Br) as the target of alpha irradiation, and by irradiation of krypton gas (^{82}Kr) as the target of deuteron irradiation. These target materials produce a rubidium preparation that is free of sodium ions; we have determined that sodium ions, at concentrations greater than 1.5×10^{-4} M, will displace ^{81}Rb from the cation-exchange resins commonly used in krypton generators. Because sodium ions do displace rubidium ions from the generators, saline may not be used to elute the ^{81m}Kr from the generator. Other investigators eluted the ^{81m}Kr with water, followed by mixing of the eluate with hypertonic saline to obtain an isotonic solution; we avoid these manipulations by eluting directly with isotonic, non-polar, 5% dextrose-in-water, thus decreasing delivery time and intersystem volume.

By keeping sodium ions out of the system, the volume of resin required to hold the ^{81}Rb is kept to a minimum; thus, the use of a stainless steel elution tube (E. R. Squibb and Sons, Inc.) with internal dimensions of 2.5 mm I.D. and 22 mm long, as a receptacle to hold 0.08 ml of Dowex 50-X8 (100-200 mesh), was more than adequate to retain the ^{81}Rb. This size generator bore also kept to a minimum the elution volume and the delivery time to the patient. Amicon polypropylene inert porous filter support was used on the bottom and the top of this cylindrical generator base in order to contain the resin. The outlet was tapered to a 22 gauge needle, 3/8-inch long. Attached to the outside of the column at the inlet was the lower 2/3 of a plastic disposable tuberculin syringe, which acts as a reservoir, and which has a built-in plastic Luer-lok. To this is connected the thick-walled tygon tubing from an infusion pump (Electrocraft Corp., Model E650-048), through which air or 5% dextrose-in-water is pumped in order to continuously elute the generator.

The requirements of the ^{81m}Kr system are such that a catheter of extremely small bore is necessary to permit the krypton to reach its destination in the body in sufficient flux to be detectable by the scintillation camera. In addition, the catheter had to be sufficiently stiff to allow its insertion into a blood vessel and its intravascular passage to distant organs. These requirements were satisfied by the use of Becton-Dickinson TWX 012 or UTX 015 teflon tubing, 150 cm in length.

For intravenous or intraarterial insertion and infusion, the above minigenerator and delivery system is complete. For use in ventilation studies, an inhaler system was devised in which the ^{81m}Kr was fed directly into the inhaler and was washed into the patient by inspiratory air. The distal end of the teflon catheter was placed into and through a Tuohy female luer-slip adapter. The female luer-lok on the distal end of this Tuohy adapter is then connected to a male luer-lok adapter on a piece of nylon rod, 19 mm in diameter and 23 mm long, tapered on

the distal end to 18.2 mm diameter. The 1/16-inch hole of the metal luer-lok was extended through the nylon rod. In a circle 2 mm from the perimeter of the rod, eight holes were drilled through the rod. A plastic mouthpiece from a Medi-Physics Xenon-133 kit was then placed over the distal end of the nylon adapter to complete the inhaler unit. An individual taking a breath through this mouthpiece will pull air through the 8 perimeter holes in the nylon adapter, thus washing krypton into the mouth and lungs from its flow point into the mouthpiece.