NEW RADIONUCLIDE GENERATOR SYSTEMS
FOR USE IN NUCLEAR MEDICINE

MASTER

by

Robert Whitehill Atcher

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

UHC-AUA-USDOE

ARGONNE NATIONAL LABORATORY, ARGONNE, ILLINOIS

Operated under Contract W-31-109-Eng-38 for the
U. S. DEPARTMENT OF ENERGY

NEW RADIONUCLIDE GENERATOR SYSTEMS
FOR USE IN NUCLEAR MEDICINE

by

Robert Whitehill Atcher

Submitted in Partial Fulfillment
of the
Requirements for the Degree

DOCTOR OF PHILOSOPHY

Supervised by
John R. Huizenga
Department of Chemistry

The University of Rochester
Rochester, New York

1979

VITAE

Robert Atcher was born in Chicago and was enrolled in primary and secondary schools in Schaumburg township, ending with his graduation from high school in 1968.

From there he went to Washington University, St. Louis, and was graduated in 1972 with a B.A. in chemistry. While there he did research on charged particle activation analysis of lead and nuclear spectroscopy with a mini-computer interfaced spectrometer.

At the University of Rochester, he began work on his Ph.D. in chemistry while supporting himself as a teaching assistant. He published two papers on the microscopic model of the nucleus and was preparing to begin his dissertation research on heavy ion reactions when he took a leave of absence.

On his leave of absence he enrolled at the University of Missouri as a graduate student in journalism. At the same time, he secured a part-time position at the university research reactor and performed flux measurements, did preliminary research on production of radionuclides for outside users, investigated new nuclear medicine programs, and researched new flux monitors for use in nuclear activation analysis. He received an M.A. in journalism from the University of Missouri in 1975.

The program to complete his journalism degree brought him to Argonne National Laboratory where he applied to the Laboratory Graduate Participantship Program. While waiting for a position to open, he joined a group researching the migration of actinides in the geosphere.

His doctoral dissertation research in Nuclear Medicine at Argonne centers on the development of generator systems with short-lived daughters (less than 40 minutes) appropriate for use in nuclear medicine. Among parent-daughter pairs investigated are W 178-Ta 178; Cd 109-Ag 109m; Pd 109-Ag 109m; Fe 52-Mn 52m; Te 118-Sb 118; and Ra 223-Pb 211. This research has included investigating production of radionuclides in reactors and cyclotrons, radiochemical separations of targets and cyclotron products, design of generators, biodistribution of the daughter radionuclides or longer lived radioisotopes, and evaluation of using portable cameras with low energy gamma ray emitters.

ACKNOWLEDGMENTS

In a multidisciplinary, multi-institutional endeavor such as this, it is inevitable that some will not be thanked. I will, however, try to include everyone in spite of space limitations.

At Rush Medical Center, I would like to thank Drs. Ernest Fordham and David Turner for guiding a neophyte into the initially murky waters of nuclear medicine. Drs. G. V. S. Rayudu and Edward Silverstein were helpful above and beyond the call of duty. The technicians, especially Pam Clark, were also helpful in the course of this work.

Dr. Richard Spencer at the University of Connecticut Health Center has been very patient and supportive on a project which took too long to get underway. I would also like to thank him for his financial support.

At Argonne National Laboratory I would like to thank Marjorie Jeschke and Shelby Miller at the Argonne Center for Educational Affairs for their spiritual and financial support while I have been affiliated with the lab. The staff of the cyclotron, chemistry glass shop and CP-5 have made the project run a lot smoother. The staff of the Chemistry Division has been extremely helpful and stimulating while I have been doing this research.

Dr. Arnold Friedman has exhibited almost saintly qualities while I have ground out this research. His patience, understanding, and help have combined an almost insurmountable number of false starts and blind alleys into a treasured learning experience.

At the University of Rochester, I want to thank Dr. Frank Buff for convincing me to stay in the racket. And I want to thank Dr. John Huizenga whose enthusiasm and interest helped both of us to chart some new areas. His guidance through this long quest is deeply appreciated.

Finally, I would like to thank Karen Peterson for typing the manuscript and all my family and friends for their support.

ABSTRACT

A current emphasis in nuclear medicine is to better match the physical lifetime of the radionuclides used in vivo for diagnosis and treatment to the biological lifetime of the diagnostic procedure or to minimize radiation dose to areas other than those to be treated. In many cases the biological lifetime is on the order of minutes.

Since the direct production of radionuclides with half lives of minutes requires the user to be near a suitable reactor or accelerator, this study was undertaken to product short-lived radionuclides indirectly. If a long-lived radionuclide decays into a short-lived radionuclide, quick separation of the daughter activity from the parent enables the user to have a short-lived daughter while freeing him from the constraint of proximity to a cyclotron. Systems where a short-lived daughter is separated from a long-lived parent are called radionuclide generators.

^{52}Fe has an 8.3 hour half life and decays to $^{52\text{m}}\text{Mn}$ which is a positron emitter with a 21.1 minute half life. A generator to remove $^{52\text{m}}\text{Mn}$ was designed using a column of anion exchange resin to adsorb ^{52}Fe . The daughter activity is eluted in 8 N HCl at a yield of 75 percent. At most, one part in ten thousand of the ^{52}Fe appears in the eluate.

^{52m}Mn can be used as a myocardial imaging agent. It clears the blood rapidly and has uptake in the myocardium comparable to other radiopharmaceuticals used for this purpose. ^{52m}Mn can also be used to assess kidney function by chelating the ^{52m}Mn . Animal studies to study both these uses are discussed.

^{223}Ra has a 11.4 day half life and decays to ^{219}Rn with a four second half life which decays through an intermediate to ^{211}Pb which has a 36.1 minute half life. ^{211}Pb decays to stability by the emission of two beta particles and an alpha particle. The short half life and the highly ionizing radiation make it an ideal candidate for in vivo therapy. Since ^{219}Rn is a gas at room temperature, a vacuum distillation apparatus was made to separate the radon from radium stearate and condense it at liquid nitrogen temperatures. ^{211}Pb grows in the radon collection vessel and is subsequently recovered in an acetate solution buffered to be physiologically compatible. The yield of the system is 10 percent and the carry-over of radium is minimal.

^{178}W has a 21.7 day half life and decays to ^{178}Ta which has a 9.3 minute half life. Recent reports of a radionuclide generator using this parent-daughter pair said that the parent was produced by a high energy proton beam. Since this is beyond the capability of medical cyclotrons, a study was done to measure production using

^3He and ^4He beams on a hafnium target. The thick target yields are 64.7 $\mu\text{Ci}/\mu\text{Ah}$ for 44 MeV ^4He beam and 23.8 $\mu\text{Ci}/\mu\text{Ah}$ for a 33 MeV ^3He beam.

^{118}Te has a half life of 6.00 days and decays to ^{118}Sb which decays primarily by positron emission with a 3.5 minute half life. The ultrashort-lived daughter has potential for use as a diagnostic tool in bloodflow studies and wall motion studies in the heart. Experiments were performed to measure thick target yields from 44 MeV ^4He bombardment in tin targets. The yield is 33.8 $\mu\text{Ci}/\mu\text{Ah}$.

$^{109\text{m}}\text{Ag}$ has a half life of 40 seconds and emits a 88 keV gamma ray in its decay to stable ^{109}Ag . Both ^{109}Cd and ^{109}Pd decay to $^{109\text{m}}\text{Ag}$. A series of studies were done to design a generator system using ion exchange resin to hold the parent while eluting the daughter. The short half life limited the eluants to physiologically compatible solutions. None of the systems investigated had yield or breakthrough characteristics suitable for clinical use.

Two generator systems were developed for use in nuclear medicine, one in diagnostic work and the other for therapeutic work. The yield and breakthrough characteristics were within the limits required to minimize unnecessary radiation exposure in patients. Two parent radionuclides were produced using ^4He beams available from medium energy cyclotrons. The yield was high enough to produce generators that would be useful in clinical applications.

TABLE OF CONTENTS

	Page
VITAE	ii
ACKNOWLEDGMENTS	iv
ABSTRACT	vi
LIST OF TABLES	
LIST OF FIGURES	
CHAPTER I. INTRODUCTION	1
CHAPTER II. PRODUCTION OF ^{52}Fe	28
CHAPTER III. ^{52}Fe - $^{52\text{m}}\text{Mn}$ GENERATOR	49
CHAPTER IV. $^{52\text{m}}\text{Mn}$ RADIOPHARMACEUTICALS	61
CHAPTER V. ^{223}Ra - ^{221}Pb GENERATOR	79
CHAPTER VI. ^{118}Te PRODUCTION	94
CHAPTER VII. ^{178}W PRODUCTION	108
CHAPTER VIII. GENERATORS PRODUCING $^{109\text{m}}\text{Ag}$	117
CHAPTER IX. SUMMARY	126
BIBLIOGRAPHY	140

LIST OF TABLES

<u>Table</u>		<u>Page</u>
I-1	Radionuclides Studied in This Work.....	25
II-1	Radionuclides of Iron.....	29
II-2	Production Reactions for ^{52}Fe	46
IV-1	Biodistribution of $^{54}\text{MnCl}_2$	
IV-2	Oxidation States of Manganese.....	67
IV-3	Biodistribution of Potential Lung Imaging Agents.....	77
VI-1	^{118}Te Production in Tin by ^4He Bombard- ment.....	103
VII-1	^{178}W Production by ^4He and ^3He Bombard- ment.....	115

LIST OF FIGURES

<u>Figure</u>		<u>Page</u>
I-1	Anger camera image of the liver.....	4
I-2	Emission tomograph image of the brain.....	8
I-3	Growth and decay in an ^{52}Fe generator.....	17
I-4	Growth and decay of an ^{52}Fe generator eluted every hour.....	18
I-5	Growth and decay of a ^{68}Ge generator eluted every three hours.....	19
II-1	Decay of ^{52}Fe and daughters.....	31
II-2	$^{52}\text{Cr}(^3\text{He},\text{xn})$ calculated excitation functions.....	39
II-3	Calculated excitation functions for ^4He reactions in chromium.....	40
II-4	$^{55}\text{Mn}(\text{p},4\text{n})$ calculated excitation functions.....	42
II-5	Calculated excitation functions for proton spallation in nickel.....	44
III-1	Distribution coefficients for iron and manganese on anion exchange resin in hydrochloric acid.....	51
III-2	Elution of $^{52\text{m}}\text{Mn}$ from a generator.....	53
III-3	Gamma ray spectrum of ^{52}Fe and daughters.....	54
III-4	Gamma ray spectrum of $^{52\text{m}}\text{Mn}$	55
III-5	Breakthrough of ^{59}Fe from a generator.....	57
IV-1	Biodistribution of $^{54}\text{MnCl}_2$	63
IV-2	Biodistribution of $^{54}\text{Mn-EDTA}$	72
IV-3	Biodistribution of $^{54}\text{Mn-DTPA}$	73
IV-4	Biodistribution of $^{54}\text{Mn-CDTA}$	74

<u>Figure</u>		<u>Page</u>
V-1	Decay of scheme of ^{235}U and long-lived daughters.....	80
V-2	Decay scheme of ^{223}Ra and daughters.....	83
V-3	Gamma ray spectrum of ^{223}Ra and daughters.....	84
V-4	Elution of ^{221}Pb from a cation exchange column.....	87
V-5	Design of ^{219}Rn distillation manifold.....	89
V-6	Photo of redesigned distillation manifold.....	91
VI-1	Decay scheme of ^{118}Te - ^{118}Sb	96
VI-2	Calculated excitation function for production of ^{118}Te by ^4He bombardment.....	99
VI-3	Calculated excitation function for production of ^{118}Te by ^3He bombardment.....	101
VI-4	Calculated and experimental excitation functions for $^{119\text{m}}\text{Te}$ and ^{118}Te production by ^4He bombardment.....	104
VII-1	Calculated excitation function for ^{178}W production by ^4He bombardment.....	112
VII-2	Calculated excitation function for ^{178}W production by ^3He bombardment.....	113
VIII-1	Distribution coefficient for ^{109}Cd on anion resin in sodium iodide.....	120
VIII-2	Distribution coefficient for ^{109}Cd on cation resin in sodium chloride.....	122

CHAPTER I

INTRODUCTION

Since the introduction of radionuclides in medicine, nuclear scientists have striven to improve the methodology with the goal of maximizing the information which can be elicited while minimizing the radiation dosage the patient receives in an imaging use; in a therapeutic use, the goal is to maximize the radiation dosage to the target organ while minimizing the exposure to non-target areas.

To date, the majority of the research efforts in nuclear medicine has been devoted to diagnostic imaging. Originally, imaging was one-dimensional consisting of a probe placed near the point of interest. Though largely supplanted by more sophisticated techniques, this methodology is still used in some studies of thyroid uptake of radioiodine, studies of kidney function and detection of deep vein thrombosis. In the thyroid study, one is interested in the percentage of a dose which ultimately, after 24 hours, is taken up by the thyroid. In the kidney study, the clearance of a radiotracer from the blood into the kidney and then into the bladder is measured. A thrombus in the leg is detected by injecting iodinated fibrinogen and scanning the leg with a probe to detect the accumulation of the fibrinogen in the clot. In all

three cases the important information developed in the study is the activity level as a function of time. This type of study can be performed with relatively simple equipment (PO71).

In order to increase the utility of radionuclide techniques, a probe is scanned over the patient's body and the activity recorded as a function of position. Thus the distribution of the radionuclide is determined throughout the patient. If a bone seeking element, such as strontium, is given to the patient, he could be scanned after the radionuclide had localized in the bone and an image of the skeleton could be obtained. In contrast to X rays, the radionuclide distribution is affected by physiological factors such as blood supply, trauma, etc. While this could overlap with radiographs, the two techniques have become largely complementary. For example, X rays can be used to detect destruction of the bone in the event of metastasis to the bone. A radionuclide scan can detect the lesion by increased bloodflow, and therefore increased activity level, to the site of the lesion.

Other diagnostic tests could be performed as well, such as imaging the perfusion of the lungs by injecting a radiocolloid which is trapped in the capillaries of the lungs. A smaller radiocolloid might be used to visualize the liver. Or a radiopharmaceutical which stays in the blood might be injected to detect internal bleeding.

Abnormalities can be detected by areas of decreased activity which represent slow or nonexistent function; a tumor in the liver might be seen as an area of little activity. Or, the radiopharmaceutical might be localized in tumors; ^{67}Ga citrate localizes in soft tissue tumors.

The scanning system has one inherent problem; the very nature of the scan reduces the uses to static ones. Changes in distribution with time are limited to rather long intervals. A study of ventilation in the lung is not possible to perform since the scanner could not complete a pass over the lung field in the time that a patient could hold his breath. Other processes involving bloodflow or time intervals on the order of a minute could not be measured using a scanner.

In the early 1960s, a new detector came into use, the Anger Camera. Instead of a single detector which scans the patient, the camera uses a large (15 inches or more in diameter) NaI crystal about 1/2 inch thick. An array of photomultiplier tubes interfaced with the crystal are wired together in such a way that an image can be obtained by electronically measuring where a photon entered the crystal and using this information to expose a piece of film to represent the distribution of activity. An example of this is shown in Figure I-1. The advantage of this system is it enables one to perform rapid sequential studies since the entire organ can be imaged. Bloodflow

Figure I-1

Anger Camera picture of the liver. A colloid which is filtered out of the blood by the liver is tagged with ^{99m}Tc . The camera is placed over the liver and a given number of events, in this case 1,000,000, are recorded. The image of the liver corresponds to its shape.

in the brain, washout of a radioactive gas from the lungs, or the initial flow of a bolus of activity in the heart can all be measured sequentially.

The advantages of the system are offset somewhat by several factors. The relatively thin crystal limits the energy of gamma rays that can be detected easily. The camera is best utilized with radionuclides emitting gamma rays of 100-200 keV. At higher energies, the gamma ray might not be entirely stopped in the crystal and be passed over electronically. At lower energies the absorption of photons in the patient is a problem. Collimation can not be quite as severe as with scanning systems, so resolution is somewhat poorer with cameras.

In fact, the ideal nuclide for imaging would have no emission other than the gamma ray to be used for imaging. Its physical half life would correspond approximately to the biological half life of the process being measured. And its production would be inexpensive.

The radionuclides which decay by particle emission are not enthusiastically embraced for several reasons. One, the particle emission increases the patient radiation dose considerably without increasing the information produced. β^- emitters, with the exception of ^{131}I , are not used for diagnosis. β^+ emitters are avoided in conventional cameras and scanners because of the increased radiation dose and the Compton scatter from the 511 keV

annihilation gamma rays tends to degrade images collected using lower energy gamma rays. The thin crystals in the cameras do not provide good images if the 511 keV gamma ray is used for the image. Finally, increased septal penetration in the collimators further degrades the image.

The same factors, with the exception of radiation dosage, that make positron emitters poor candidates for two dimensional imaging make it ideal for three dimensional imaging. Since conservation of linear momentum requires that two gamma rays be emitted 180 degrees from one another, this can be used to construct images in three dimensions. X ray computerized axial tomography (CAT scanners) use algorithms which can reconstruct images from similar data; in the case of positron emitters, the photons come from within the patient rather than from an external source. Since the photons from annihilation are emitted simultaneously, the circuits can be designed to accept events which meet the criteria of arriving at two detectors 180 degrees from one another and 511 keV in energy. This dual requirement obviates the need for collimators which reduces the amount of activity which has to be injected into the patient. The most successful design of emission tomographs has been one which used a ring with 60 to 250 detectors used in a combination of on-line and off-line data reduction by computers. The hardware and software determines coincidences between two of the detectors which

are opposite one another and uses this information to construct an image (Fig. I-2). More recently, the use of collimation has enabled one to collect data from several transaxial "cuts" of the patient rather than collecting one cut at a time and repositioning the patient after every one (PH77).

Computers have also been interfaced to two-dimensional systems to make the quantitation of phenomena studied with nuclear medicine a reality. The ejection fraction of the heart, i.e., the percentage of blood which is pumped out of the heart, can be computed using a computer for data reduction. Computers can similarly be used for image enhancement.

Ideally, the clinical data which nuclear medicine techniques can provide should be developed using radio-pharmaceuticals which are biologically active. Since the only nuclides of carbon, nitrogen and oxygen which are suitable for use in vivo are positron emitters, the development of three-dimensional imaging techniques would seem to be fortuitous.

The clinician can now use metabolites or other physiologically active molecules for diagnosis rather than labelled analogs, such as radioiodinated human serum albumin, or compounds that use part of the biochemical, e.g., ^{99m}Tc -phosphates for bone imaging.

Figure I-2

A scan from the Ortec ECAT Scanner. The radio pharmaceuticals are $^{13}\text{NH}_3$ made in an on-site cyclotron and ^{68}Ga EDTA made from a generator. The EMI scan is produced by an X ray machine.

ECATTM SCANNER

Seventy-nine year old man with cerebral atrophy consistent with age. Note apparent area of reduced perfusion ($^{13}\text{NH}_3$) and metabolism (^{18}FDG) in region of frontal fissure which is apparently due to enlargement of cerebral sulci. Good, relative agreement was observed between $^{13}\text{NH}_3$ and ^{18}FDG distribution in the various structures of the brain. EMI scan showed no mass lesion or infarct. [Phelps, M. E., Hoffman, E. J., Hung, S. C., Kuhl, D. E., ECAT: A New Computerized Tomographic Imaging System for Positron-Emitting Radiopharmaceuticals (in press)].

Fig I-2

EG&G ORTEC
Life Sciences Division

16 Offices in 49 Countries. For more information on ORTEC products or their applications, contact your local ORTEC Representative or:
United States: ORTEC Incorporated, 100 Midland Rd., Oak Ridge, TN 37830, telephone (615) 482-4411, Telex 55-7450. W. Germany: ORTEC GmbH, Munich, telephone (089) 98-11 73. United Kingdom: ORTEC Limited, Bracknell, telephone 55455. France: ORTEC S.A.R.L., Rungis-Cedex, telephone 687-25-77. Italy: ORTEC S.p.A., Milan, telephone 738-6294. Brazil: ORTEC Limitada, São Paulo, S.P., telephone 275-3943.

Unfortunately, ^{11}C , ^{13}N and ^{15}O have half lives so short (20.4 minutes, 9.97 minutes and 2 minutes, respectively) that they must be made near the hospital in which they are used. This requires, in most cases, a cyclotron and radiochemistry facilities suitable for target handling and radiopharmaceutical fabrication. The cost of a cyclotron for this type of work is about one million dollars. Such a machine is in essence a dedicated facility; the beam energy is too low, about 10 MeV deuterons, to be used for the production of fast neutrons for tumor therapy or radionuclide production for commercial sale outside the facility. If these other uses are contemplated, the cost of the machine increases to 6-10 million dollars and the requirements for shielding of the cyclotron and space for the facility increase as well.

An alternative to using an in-house accelerator is to use radionuclide generator systems. Currently, the workhorse of nuclear medicine is the ^{99}Mo - $^{99\text{m}}\text{Tc}$ generator. ^{99}Mo , 66 hour half life, is produced either by neutron capture in ^{98}Mo or by separating fission product ^{99}Mo from irradiated uranium. Both methods use a reactor for production which is inherently cheaper than using a particle accelerator. The neutron capture production produces ^{99}Mo of low specific activity necessitating large generators to effectively contain the ^{99}Mo . The large generators require large elution volumes to recover

the ^{99m}Tc . The fission product generator has some fission products other than ^{99}Mo in it, potentially increasing radiochemical contamination and also increasing radiation dose to the generator.

^{99m}Tc , half life 6 hours, is close to the ideal radionuclide for imaging. It emits a 140 keV gamma ray in 90 percent abundance; the energy is optimal for use with cameras. It decays almost exclusively by the imaged gamma ray. ^{99}Tc has a 2×10^5 year half life, essentially stable, and poses little radiation hazard to the patient since the biological half life is 20 days (DU58).

Before the introduction of this generator, many other radionuclides were used: ^{197}Hg , 64 hours; ^{198}Au , 64.8 hours; ^{131}I , 8.3 days; ^{125}I , 59.7 days; and ^{85}Sr , 65 days. Perhaps the only common factor among all these radionuclides is their relatively long half lives. ^{198}Au and ^{131}I are also β^- emitters which increases radiation dosage significantly. The obvious tradeoff is the amount of activity given to the patient is directly proportional to the dose. While one does not want to keep the patient immobile for long periods while the imaging is performed, the radiation hazard places limits on the amount of activity which can be administered.

^{99m}Tc is obviously superior to these radionuclides for these reasons. Doses can be in the tens of millicuries, whereas with some of the others doses were

limited to hundreds of microcuries. Activity (A) is related to the decay constant λ by:

$$A = \lambda N \quad (I-1)$$

where N is the number of atoms present (FR64). The decay constant is related to the half life, $t_{1/2}$, by:

$$\lambda = \ln 2 / t_{1/2} \quad (I-2)$$

For a given activity level, the number of atoms of the radionuclide is proportional to the half life; the longer the half life (the smaller λ), the greater the number of atoms that must be present. Thus over ten times more atoms of ^{197}Hg must be present, in comparison to $^{99\text{m}}\text{Tc}$, to achieve the same number of disintegrations per second. Unless the ^{197}Hg is eliminated from the body quickly, it will result in a higher radiation dosage to the patient. Thus there are real gains to be made by closely matching the physical half life of the radionuclide to the biological half life of the study.

Obviously there are limits to the half life of the radionuclide to be used in a study, unless it is immediately available from the source of production. And the financial constraints of in-house accelerators put a limit on using them directly for production. While $^{99\text{m}}\text{Tc}$ is ideal for many of the studies currently performed in nuclear medicine, there are many which are too transient

for its effective use. The search then is for radionuclides which are generator produced and have shorter half lives, yet are still suitable for use in imaging patients.

An ideal generator would have an extremely long-lived parent which could be produced easily from normally available materials and could be easily isolated from the daughter. In most cases, ion exchange columns are used as the basis of the generator. The ease of shielding and use of a column is evident. The behavior of the system over time can easily be studied and the likelihood of operator mishaps is minimal in comparison to solvent extraction or distillation.

The physical principle of a generator is quite simple. In general, the half life in isobars along a beta decay chain increases as one approaches stability along the chain. However, in some cases the half lives undergo an inversion, i.e., the parent is longer-lived than the daughter. This inversion is infrequent and, given the constraints of potential use in nuclear medicine, the useful generator pairs are few. Some have been well developed and are commercially available. Besides the aforementioned ^{99}Mo - $^{99\text{m}}\text{Tc}$, ^{113}Sn - $^{113\text{m}}\text{In}$ (115 days, 1.65 hours respectively) and ^{68}Ge - ^{68}Ga (237 days, 68 minutes) are two which have seen use in nuclear medicine. In both cases, the parent can be made in some central location in large quantities and shipped to the point of use with

little or no decay losses. ^{68}Ga is a positron emitter (88 percent) which is being used more frequently with coincidence detection systems. $^{113\text{m}}\text{In}$ decays by isomeric transition to stable ^{113}In emitting a 393 keV gamma ray (64 percent). While the energy is somewhat high for use with gamma cameras, the gamma ray can be imaged with rectilinear scanners. A great deal of work on developing radiopharmaceuticals using these radionuclides has been done because longer-lived nuclides of each, ^{67}Ga , 78 hours, and ^{111}In , 68 hours, are also used in nuclear medicine. In addition, they are members of the same group and are expected to have similar chemical properties.

The basis in nuclear theory for generator systems can be summarized by two general cases. In one, a nuclide with an even number of protons and neutrons (a stable nucleus) decays into a nuclide with an odd number of neutrons and protons (quite unstable) which subsequently decays into a nuclide with an even-even configuration. Since half life is a function of stability, the daughter would be shorter-lived than the parent. The ^{68}Ge - ^{68}Ga pair is an example of this case.

In the second case, beta decay directly to the ground state of the daughter is constrained by angular momentum differences, i.e., the change in angular momentum is larger than one unit, or there is a parity change, or both. In these cases, the decay is to a metastable

daughter rather than to the ground state which in turn either decays to the ground state (^{113}Sn - $^{113\text{m}}\text{In}$) or the metastable daughter decays by a beta process to the next isobar (^{52}Fe - $^{52\text{m}}\text{Mn}$ - ^{52}Cr).

While this is the nuclear basis for the half life inversion, the growth and decay of the parent and daughter are the basis for the generator system. In general, the decay of a radioactive species is governed by equation I-1 which can be written:

$$dN_1/dt = -\lambda_1 N_1 \quad (\text{I-3})$$

which yields on integration

$$N_1 = N_1^0 e^{-\lambda_1 t} \quad (\text{I-4})$$

N_1^0 is the number of atoms at t (time) = 0. The daughter is formed as the parent decays and in turn decays at the rate $-\lambda_2 N_2$. Thus

$$dN_2/dt = \lambda_1 N_1 - \lambda_2 N_2 \quad (\text{I-5})$$

The net rate of production is

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^0 (e^{-\lambda_1 t} - e^{-\lambda_2 t}) + N_2^0 e^{-\lambda_2 t} \quad (\text{I-6})$$

In the pairs which are the basis for a generator, the decay constant of the parent is smaller than that of the daughter. If it is so by a factor of ten or more, there results an equilibrium in the decay which is called

transient equilibrium. If there is none of the daughter present initially, and the last term in eq. I-6 is zero, the daughter will grow in rapidly and ultimately decay with the half life of the parent, which is expected since it is forming and decaying at the same rate. If the daughter fraction is separated and counted, it will decay with the half life of the daughter. The key to the generator system is that the daughter is formed at a rate proportional to its half life, but decays in the system with the half life of the parent while they are in equilibrium. In the extreme where λ_2 is much greater than λ_1 (a factor of 100 or more), the growth and decay of the daughter are essentially constant, i.e., parent decay is negligible and the system can generate the daughter at constant levels, freeing the user from having a radio-nuclide producer close at hand. For instance, the decay of ^{68}Ge is negligible on a day to day basis. A generator capable of producing 50 mCi of ^{68}Ga on Wednesday will be able to produce 49.9 mCi on Thursday.

Ultimately, the parent decays significantly which requires the parent to be replenished. In abstract terms all this is meaningless, so it might be instructive to use an example. One of the systems developed in the course of this work is the parent daughter pair ^{52}Fe - $^{52\text{m}}\text{Mn}$, 8.3 hour and 21.1 minute half lives. The decay constants are 0.0014 min^{-1} and 0.033 min^{-1} , fulfilling the requirements

for transient equilibrium, though not secular equilibrium.

As Figure I-3 shows, the parent decays at a constant rate throughout the life of the system. The daughter, absent initially, grows in and reaches saturation in about 5 half lives. After this it decays with the half life of the parent.

More realistically, the generator will be used at regular intervals and the daughter grows in until the generator is used again. Since 87.5 percent of the maximum daughter activity grows in after three half lives, one might expect that the generator would be eluted at about this interval. In this example, this would be every hour. Figure I-4 shows this case.

The obvious difference between this case of transient equilibrium and $^{68}\text{Ge}-^{68}\text{Ga}$ and secular equilibrium (decay constants are $1.68 \times 10^{-6} \text{ min}^{-1}$ and $1.02 \times 10^{-2} \text{ min}^{-1}$) is that the decay of the parent is less of a factor. Figure I-5 shows a ^{68}Ge generator eluted every three hours.

The obvious question is why bother with a system which is governed by transient equilibrium rather than secular equilibrium? As has been shown, the activity level is proportional to the decay constant and the number of atoms. Assuming that the cross section for the formation of both ^{52}Fe and ^{68}Ge is the same, i.e., an irradiation will produce the same number of atoms each, then the amount of activity produced per unit time will

Figure I-3

The growth and decay of the parent and daughter in
the ^{52}Fe - $^{52\text{m}}\text{Mn}$ generator.

FE 52 GENERATOR

○ DAUGHTER ACTIVITY

+ PARENT ACTIVITY

ACTIVITY IN MILLICURIES

18:47:02 10-11-79

Figure I-4

An ^{52}Fe - $^{52\text{m}}\text{Mn}$ generator milked every hour, approximately every three half lives.

FE 52 GENERATOR

○ DAUGHTER ACTIVITY

+ PARENT ACTIVITY

ACTIVITY IN MILLICURIES

18:42:28 10-11-79

Figure I-5

The ^{68}Ge - ^{68}Ga generator milked every three hours, about every three half lives. Note that the decay of the parent is constant over the time period, in contrast to the case in Figure I-4 where the parent decay is more of a factor.

DE 68 GENERATOR

○ DAUGHTER ACTIVITY

+ PARENT ACTIVITY

ACTIVITY IN MILLICURIES

18:51:15 10-11-79

be 820 times greater for ^{52}Fe . Since the cost of production in charged particle accelerators is usually figured as a function of time of irradiation, the cost of production per unit of activity is lower for ^{52}Fe . The shorter half life of ^{52}Fe also precludes long periods of little use which would obviously be the case for the ^{68}Ge . Thus economic arguments could be presented for short-lived parents in generators.

An additional constraint of the long half life parent is the radiation dosage to the parent in the event of breakthrough of the parent, i.e., the presence of the parent in the daughter fraction separated from the generator. Since some breakthrough is likely, the long half life tends to increase radiation exposure unless the radionuclide has a short biological half life. Also, parents that decay by beta emission increase radiation exposure compared to those that do not. This assumes that the parent is produced with a high radionuclidic purity; in most cases of cyclotron production this is true. In the high current linacs, this is not always so. ^{52}Fe made by spallation is contaminated with large amounts of ^{55}Fe and ^{59}Fe . These longer-lived nuclides pose a radiation hazard to the patient in the event of breakthrough. In general, breakthrough is kept to a minimum to avoid excess radiation exposure.

While the half life of the daughter is of primary importance in trying to match a radionuclide with a diagnostic test, other factors have to be taken into account as well. The yield of gamma rays to be imaged per unit activity is important; ^{99m}Tc has a high abundance of 140 keV gamma rays, 90 percent, and emits a 2 keV gamma ray in low abundance. ^{52m}Mn has an abundance of 197 percent for the 511 keV gamma ray. It also emits a 1434 keV gamma ray which increases radiation dosage, but not image degradation since the imaging will probably be done using coincidence techniques.

Further, the behavior of the radionuclide in vivo is important since it dictates the biodistribution of the activity. Gallium, unless strongly complexed, is taken up by transferrin and creates a blood background, if the radiopharmaceutical which is injected is labile. Manganese tends to clear the blood very rapidly and is not likely to form a blood background. If the activity in the blood could present a problem, the radiopharmaceutical using gallium must be quite stable to avoid confusing results.

Up to this point, the discussion has focused on the use of radionuclides for diagnostic purposes. In the case of generators which produce radionuclides for therapeutic use, the desired results are obviously different. One strives to deliver the maximum dosage to the patient, but only to the organ or site which is being

treated. In order to accomplish this goal, the shorter the physical half life, the less likely it is that movement from the target will occur. If the activity is made unreactive in some way, either by chemically making it inert, or by complexing it strongly, the physical decay will be the major means of its disappearance, not redistribution in the body. In addition, rather than avoiding radionuclides with particle emission, one would like to use those with energetic particle emission to maximize local dosage.

With the exception of fissioning nuclides, this can be accomplished best with alpha emitters. In contrast to radionuclides used for diagnosis, alpha emitters are nearly exclusively found in the heavy elements with nuclear charge greater than 80. In fact, the only alpha-emitting radionuclides conveniently produced by cyclotron bombardment are those of polonium and astatine. The difficult chemical problems in using polonium make astatine the only suitable choice for a cyclotron-produced alpha emitter. The most viable choice is to make ^{211}At , 7.2 hour half life, with 28 MeV alpha particles on a bismuth target, an energy in the range of medical cyclotrons. Its short half life makes it somewhat inconvenient to use far from the source of production.

Again, it is advantageous to examine the possibilities of utilizing a generator system to product a short-lived

alpha emitter. In fact, two such systems are possible, each in the decay of naturally occurring radionuclides. ^{211}Pb , 36.1 min. half life, is a member of the ^{235}U decay chain. ^{212}Pb , 10.6 hour half life, is a member of the thorium decay chain. In both cases, the bismuth daughter of the lead radionuclide is an alpha emitter. Also, the decay to stability in both cases includes two beta emissions; both have low gamma fluxes, minimizing dosage outside the area of administration.

An additional constraint to the use of alpha emitters is that they are almost all bone seekers in vivo; migration from the site of administration irradiates a particularly sensitive organ. This is another reason to keep the half life of the administered radionuclide as short as possible.

Many of the beta emitters commonly used in therapy have half lives on the order of days. This presents obvious problems of keeping the activity at the target for much longer periods of time.

The advantages of using short-lived radionuclides are obvious, both for diagnostic and therapeutic uses. This study has examined many systems with varying degrees of success. The first requirement was that the parent half life should be longer than 5 hours and the daughter half life be between one and thirty minutes, although half lives up to one hour were acceptable.

Parent-daughter pairs which fell in this group are shown in Table I-1. None had been explored successfully. The only alpha emitter, ^{211}Pb , was also the only product of a naturally occurring radionuclide. All the rest were produced by charged particle bombardment or neutron capture.

Production schemes of the radionuclides were assessed and the production rate was determined if no data had been published previously. Production of ^{109}Cd was measured to compare costs with commercially available sources. Production of ^{178}W and ^{118}Te by helium ion bombardment was also measured.

The production rates and cross sections were compared with predictions from the computer code Overlaid ALICE (BL76). A model which accurately predicts excitation functions is quite valuable in decisions on target thickness, optimal bombarding energy and assessing potentially problematic competing reactions.

After these studies were finished, target-parent separations schemes were explored for the radionuclides produced in the cyclotron since reactor production does not entail such a separation. In general, these investigations were limited to processes which were compatible with remote manipulation since the radiation levels of the targets after irradiation are quite high, often hundreds to thousands of rads per hour.

TABLE I-1
Parent Daughter Pairs for Use in Generators

<u>Parent</u>	<u>Half Life</u>	<u>Decay Mode</u>	<u>Daughter</u>	<u>Half Life</u>	<u>Decay Mode</u>
$^{52}_{\text{Fe}}$	8.27 hours	β^+ , E.C.	$^{52\text{m}}_{\text{Mn}}$	21.1 minutes	β^+
$^{109}_{\text{Pd}}$	13.5 hours	β^-	$^{109\text{m}}_{\text{Ag}}$	39.2 seconds	I.T.
$^{109}_{\text{Cd}}$	453 days	E.C.	$^{109\text{m}}_{\text{Ag}}$	39.2 seconds	I.T.
$^{118}_{\text{Te}}$	6.0 days	E.C.	$^{118}_{\text{Sb}}$	3.5 minutes	β^+
$^{178}_{\text{W}}$	21.5 days	E.C.	$^{178}_{\text{Ta}}$	9.4 minutes	E.C.
$^{223}_{\text{Ra}}$	11.4 days	α	$^{211}_{\text{Pb}}$	36.1 minutes	β^- (α)

Generator design was undertaken with several factors in mind: is the generator product to be injected directly into the patient?; is the half life long enough to permit radiochemical manipulations?; and is the generator to be reused or will it be a single use system. Yield of the daughter, breakthrough of the parent and behavior of the generator as a function of time and elutions were determined. From these measurements, optimal conditions for the operation of the generator were deduced.

Animal biodistribution studies were undertaken for the generator product, or a biologically compatible form of the radionuclide which could be prepared quickly. Other radiopharmaceuticals were also investigated to determine if biodistribution could be significantly altered to visualize other organs than those seen in the baseline study.

The baseline study consisted of injecting a biologically compatible form of the generator product to establish biodistribution. Then effects of chemical changes could be determined. Since the generator products had relatively short half lives, the time scale for the biodistribution studies was short, often shorter than published data. Since the animals were usually dissected and counted rather than imaged, the short half life daughter was not used; longer lived carrier-free isotopes were used.

The procedure used in the study of the ^{211}Pb generator was the same as that used for the diagnostic generators. After the generator was operational, the ^{211}Pb was injected into animals and its biological effects were measured.

The biological studies were deemed necessary to insure that the medical community was aware of the potential of the systems which were developed. Those less active in research are sometimes less perceptive to advances in basic sciences applied to nuclear medicine.

PRODUCTION OF ^{52}Fe

^{52}Fe has been recognized as a suitable radionuclide for use in nuclear medicine for a number of years (RA73, KN76, AN64). Other radionuclides of iron do not have suitable half lives, decay characteristics for detection outside the body, or radiation dosages which are too high to be used in vivo (Table II-1). In particular, iron tracers have been used for visualizing bone marrow and other metabolic processes using iron.

^{52}Fe has not been used extensively in nuclear medicine to date, primarily because it and its daughters decay by positron emission and its daughters emit high energy gamma rays not easily detected in conventional two dimensional imaging systems. Its half life, 8.3 hours, is relatively short for a cyclotron product to be used widely in nuclear medicine. Commercial vendors have not provided ^{52}Fe on a routine basis. While the 169 keV photocons from the decay of ^{52}Fe would be ideal for imaging, the Compton scattering from higher energy gamma rays coupled with the septal penetration in the collimator by the higher energy gamma rays degrade the image considerably.

We used ^{52}Fe as the parent for a generator system which separates the daughter $^{52\text{m}}\text{Mn}$. The advantages of this

TABLE II-1

<u>Nuclide</u>	<u>Half life</u>	<u>Decay mode</u>	<u>Gamma Rays</u>
^{52}Fe	8.3 hours	β^+ 56.5% e.c. 43.5%	169 keV (100%)
^{53}Fe	8.5 minutes	β^+ 98%	378 keV (42%)
$^{53\text{m}}\text{Fe}$	2.5 minutes	IT	701 keV (99%) 1012 keV (85%) 1328 keV (85%)
^{55}Fe	2.6 years	e.c.	none
^{59}Fe	45.6 days	β^-	1095 keV (56%) 1292 keV (44%)

are two-fold; ^{52m}Mn is almost a pure positron emitter and is well suited for use in the new emission computed tomography systems; and the separation of the parent and daughter reduces the radiation dosage to the patient.

The decay scheme for ^{52}Fe is shown in Figure II-1. ^{52}Fe decays by positron emission (56 percent, 0.80 MeV) and electron capture (LE78). Both decay modes deexcite through the 169-keV level in ^{52m}Mn , emitting a gamma ray with 100 percent abundance. Though it is not useful for imaging, the 169-keV gamma ray is a convenient means of detecting breakthrough from the generator using a high resolution gamma ray spectrometer.

The daughter, ^{52m}Mn , decays by positron emission (98 percent, 1.63 MeV maximum) and isomeric transition to ^{52}Mn with a half life of 5.6 days. The high flux of 511 keV annihilation radiation, 197 percent, makes the nuclide ideal for imaging in emission computed tomography instruments which have been introduced as commercial machines recently. The decay also includes deexcitation by emission of a 1434-keV gamma ray, 100 percent abundance.

^{52}Mn decays 66 percent of the time by electron capture and by emission of a positron with a maximum energy of 0.575 MeV. ^{52}Mn also emits a 1434 keV gamma ray which is 100 percent abundant, and also emits relatively abundant gamma rays at 744 keV (90 percent) and 935 keV (94 percent) which are the strongest. While ^{52}Mn increases radiation

Figure II-1

The decay scheme of ^{52}Fe and its daughters.

dosage, only 52 nanocuries are formed per millicurie of ^{52m}Mn . A generator left overnight would have to be pre-eluted to remove the ^{52}Mn which had built up from the growth and decay of ^{52m}Mn .

^{52}Fe can be produced by a number of nuclear reactions. The most likely to be used in an institution with an in-house cyclotron is ^4He or ^3He bombardment of natural chromium. Natural chromium has an isotopic content of: 50, 4.3%; 52, 83.8%; 53, 9.6%, and 54, 2.4%.

Originally, ^{52}Fe was made by ^4He bombardment of chromium. Yano and Anger (YA65) used the reaction to demonstrate the production and chemical processing for medical use. They used a 65-MeV beam on a chromium powder target which had been pressed into a disc. This disc was enclosed in aluminum and irradiated with a 12 microampere (μA) beam. They reported a yield of 8 microcuries per microampere-hour ($\mu\text{Ci}/\mu\text{Ah}$) per gram of chromium. Their separation scheme involved ether extraction from hydrochloric acid and took 6-7 hours to produce a biologically compatible solution of ferrous citrate. The chemical yield was 99 percent if carrier iron was used.

^{55}Fe , produced by $^{52}\text{Cr}(^4\text{He},n)^{55}\text{Fe}$, is about 5-6 percent of the ^{52}Fe produced at the end of bombardment (EOB). ^{55}Fe with its long physical half life, 2.6 years, is a significant radionuclidic contaminant. The biological half life, i.e., the time it takes for half of the element or compound

to be eliminated from the body, of iron is 600 days which means that ^{55}Fe will decay in the body and not be eliminated quickly (DU58). The presence of the iron in the hemoglobin results in irradiation of a particularly sensitive organ.

Thakur et al. (TH71) used the 30-MeV ^4He beam at the Hammersmith Hospital to produce ^{52}Fe using an internal target irradiated with a 500 μA beam current. They used chromium electroplated onto a copper backing which first had been electroplated with nickel. This highly conducting backing enabled them to bombard with high current without destroying the target or experiencing evaporation losses.

The yield was 3.3 $\mu\text{Ci}/\mu\text{Ah}$, somewhat more than predicted by Yano. ^{55}Fe was 14 percent of ^{52}Fe (EOB). The chemical yield from target processing was 100 percent and took 1 1/2 hours. They point out that ether extraction should be done from hot acid which enables them to operate without carrier iron.

Greene et al. (GR70) used 45.5-MeV ^3He beam to produce ^{52}Fe by $^{52}\text{Cr}(^3\text{He}, 3n)^{52}\text{Fe}$. The yield for this reaction was 50 $\mu\text{Ci}/\mu\text{Ah}$. Natural chromium electroplated on an internal target holder to a 0.25 mm depth was tilted in the cyclotron to achieve an effective depth of 0.56 mm. They also used an ether extraction to recover the product. ^{55}Fe was estimated at 0.001 percent (EOB).

At Argonne, a 33-MeV ^3He beam is used in an external target of natural chromium plated on copper (RA73). The yield was 20 $\mu\text{Ci}/\mu\text{Ah}$: ^{55}Fe was measured to be less than 0.072 percent (EOB). The target is dissolved in hydrochloric acid, treated with concentrated nitric acid to oxidize the iron to the III oxidation state, and the ^{52}Fe is adsorbed on a column of anion exchange resin (BioRad AG1x8, 100-200 mesh, chloride form). The chromium from the target and the manganese radionuclides formed are washed through the column in 8 N HCl. The ^{52}Fe strip is done in deionized water at a yield of 95-100 percent.

Murakami (MU73) did a comparative study and concluded that ^3He is superior to ^4He for production of ^{52}Fe . Their data agreed with past studies on reaction yields at a given energy. In fact, if one is able to increase the ^3He beam energy from 30 to 40 MeV, the ^{52}Fe yield increases by a factor of four, whereas ^{55}Fe yield increases by 10 percent. They separate iron by solvent extraction into di-isopropyl ether; no chemical yield is given.

For groups with access to higher energy cyclotrons, production using protons is an alternative which has some advantages. The target, manganese, is monoisotopic which should limit the problems of radionuclidic contamination if target thickness and beam energy are chosen judiciously. While most accelerators which produce high energy protons are dedicated to research in physical science, there is a

growing interest in using them on radionuclide production (SE78). The major limitation is the low currents available from such machines.

The growth of high energy physics, and the large accelerators used for the experiments, has provided the research community in nuclear medicine with a new source of radionuclides. At Brookhaven National Laboratory the second stage of the alternating gradient synchrotron (AGS) is a linear accelerator which accelerates protons to 200 MeV at currents of 70 μ A. This proton beam, when not injected into the AGS, is used in the Brookhaven Linac Isotope Producer (BLIP). BLIP has been in operation for several years and is producing a wide variety of radionuclides.

At the Los Alamos Meson Physics Facility (LAMPF) protons are accelerated to 800 MeV with currents of 300 μ A to produce mesons (SE78a). Since the beam is not used constantly for high energy experiments, a target facility was built in the beam dump area. The high energy and large current available at LAMPF makes it ideal for isotope production.

Saha (SA71) studied the (p,4n) reaction on manganese dioxide irradiated with 65-MeV protons at 0.5 μ A. Typically, the irradiation lasted for one hour and produced 80 μ Ci, a yield of 160 μ Ci/ μ Ah. ^{52}Fe was separated by dissolving the MnO_2 in HCl and eluting through an anion

exchange column: ^{52}Fe was stripped in distilled water and the separation repeated. The separation took two hours and the chemical yield was 70-80 percent. They estimate the ^{55}Fe production to be less than 3 percent (EOB).

BLIP routinely produced ^{52}Fe for in vivo use by irradiating 2.5 g/cm^2 manganese targets (RI78). The proton energy is degraded from 70 to 50 MeV in the target. An irradiation at 70 μa for 15 hours will produce 115 mCi of ^{52}Fe (EOB). ^{55}Fe is less than 0.7 percent (EOB). This contamination level is low enough to allow administration to patients.

^{52}Fe can also be produced by spallation. A target of atomic number higher than iron is irradiated in a beam of medium energy protons (greater than 100 MeV). The incident protons knock out a number of protons and neutrons. While this mode of production is less specific, increasing the radionuclidic contamination, the amounts of activity which can be produced are much higher.

Sodd (SO74) used targets of manganese, cobalt, nickel, and copper to measure the production of ^{52}Fe . The ^{52}Fe was extracted from HCl into ether. The cross section for the reaction with nickel was 1.35 millibarns, about a factor of ten higher than for cobalt or copper. The targets were irradiated with an external beam of 588-MeV protons at a current of 50 nA, monitored by ^{24}Na production in aluminum. The ^{55}Fe yield is 3.3 percent and ^{59}Fe yield

is 0.16 percent (EOB). Radiation dosage from ^{59}Fe is high because it decays by β^- emission and emits several high energy gamma rays as well as having a long half life of 45 days.

A trial spallation run was done at BLIP (RI78). A 20 mil nickel foil was irradiated by 200-MeV protons, degrading the beam about 1.5 MeV. A 15 hour irradiation at 70 μA produced 70 mCi (EOB). The relative production of ^{55}Fe and ^{59}Fe was 2.0 and 0.15 percent, respectively. Obviously, a thicker target would increase the yield significantly. The foil was relatively impure and introduced a large amount of stable iron into the final product, a problem which prevents the ^{52}Fe from being used in a compact generator system.

At LAMPF, the cross section for spallation on a nickel target was measured at 800 MeV at an integrated current of 1 μAh . They reported cross sections of 1.54 mb for ^{52}Fe and 0.306 mb for ^{59}Fe . The chemical yield for the separation is 96 percent (GR78). They project an ^{52}Fe yield of 8.3 Ci at half saturation, assuming a target thickness of 2.3 cm and a 300 μA current. Recently, a stack of foils was irradiated and processed producing 1 Ci (EOB) after a 16 hour irradiation (OB78). The intensity of the beam passing through the target was not known since the beam spot was larger than the target. The processed ^{52}Fe was shipped to the West Coast in less than 24 hours from end

of bombardment.

As a test of the predictive power of Overlaid ALICE, the excitation functions for all the reactions examined here were generated using the Sigma 5 computer in the Chemistry Division.

Since various reactions can be used for radionuclide production, a theoretical basis for selection of one or another of the production modes would decrease the time spent measuring reaction cross sections and comparing production schemes. In addition, the accurate prediction of excitation functions could aid in selection of target thickness and bombarding energy, especially in cases where competing reactions produce unwanted radionuclides.

In the case of ^{52}Fe production, one wants to minimize production of ^{55}Fe and, in the case of spallation, ^{59}Fe . This can be accomplished if the excitation functions can be accurately predicted. In Figures II-2 and II-3 the excitation function for ($^3\text{He}, \text{xn}$) and ($^4\text{He}, \text{xn}$) reactions calculated by Overlaid ALICE are shown.

For these two reactions, as we have seen, the ^3He reaction is superior; it has the peak of the excitation function within the range of most machines, the desired reaction takes place with the most abundant isotope of chromium and the reaction minimizes radionuclidic contamination from ^{55}Fe .

Figure II-2

The excitation function predicted by ALICE for $^{52}\text{Cr}(^3\text{He}, 3n)^{52}\text{Fe}$ using experimental and calculated binding energies are compared to experimental results (MU73). The use of calculated binding energies better fits the experimental data. The cross section is corrected for the abundance of ^{52}Cr in natural chromium.

OR 52 (HE 3,3N) EXCITATION FUNCTIONS

- ALICE CALCULATION EXPERIMENTAL BINDING ENERGIES
- ALICE CALCULATION CALCULATED BINDING ENERGIES
- ◇ EXPERIMENTAL CROSS SECTION

00:05:34 10-12-79

Figure II-3

The calculated excitation functions for the reactions $^{52}\text{Cr}(^4\text{He},4\text{n})$, $^{50}\text{Cr}(^4\text{He},2\text{n})$ and $^{52}\text{Cr}(^4\text{He},\text{n})^{55}\text{Fe}$. Again the use of calculated binding energies better fits the data than the experimental binding energies. In this case, the production of ^{55}Fe at low energy would limit the use of ^{52}Fe produced in this manner to generators. The cross sections in the ALICE calculation are corrected for isotopic abundance.

FE 52 PRODUCTION BY HE 4 BOMBARDMENT OF CHROMIUM

- ALICE CALCULATION CR 52 (HE4,N)
- ALICE CALCULATION EXPERIMENTAL BINDING ENERGIES CR 52 (HE4,4N)
- ⊠ ALICE CALCULATION EXPERIMENTAL BINDING ENERGIES CR 50 (HE 4,2N)
- ALICE CALCULATION CALCULATED BINDING ENERGIES CR 52 (HE 4,4N)
- ALICE CALCULATION CALCULATED BINDING ENERGIES CR 50 (HE 4,2N)
- ◇ EXPERIMENTAL CROSS SECTION

18:58:05 10-12-78

For a case such as this, the information is contained in the literature. If, however, one is working with a system which has not been explored previously, then one wants to be able to predict this behavior from a theoretical model.

Overlaid ALICE can calculate the excitation functions from input consisting of the mass and charge of the target and projectile and the energy released in the reaction (Q). There is also a provision to input the binding energies of neutrons, protons, and alphas for all the nuclides produced in the reaction. Alternatively, the program can calculate these masses. Both of these options were used; binding energies were found in Wapstra and Bos (WA77).

While the shape predictions for the excitation functions are reasonable, within a few MeV, the absolute value of the calculation is high by a factor of nearly 70 for ^3He and 15 for the ^4He reaction if experimental binding energies are used. If the program calculates binding energies, the results are better, agreeing for ^3He within a factor of 5 and for ^4He by a factor of 2.

The excitation function for the $^{55}\text{Mn}(p,4n)$ reaction is shown in Figure II-4. None of the experiments determined excitation functions for the reaction. The average cross section can be determined from the yield data quoted. In the case of BLIP production, the average from 50-70 MeV is 0.48 mb. In the other study, the production is con-

Figure II-4

The calculated excitation function for the $^{55}\text{Mn}(p,4n)^{52}\text{Fe}$ reaction using experimental and calculated binding energies. Estimates of the cross section at a few energies show that the fit is better using the calculated binding energies.

MN 55 (P,4N) EXCITATION FUNCTIONS

- ALICE CALCULATION EXPERIMENTAL BINDING ENERGIES
- ◇ ALICE CALCULATION CALCULATED BINDING ENERGIES

00:27:26 10-12-79

sistent with a cross section of 3.4 mb for the energy range of 65 MeV and lower. Since the target dimensions are not expressly described it is hard to estimate the beam degradation in the target.

The ALICE calculation with calculated binding energies obviously provides better agreement for the proton reaction. The maximum of the excitation function is predicted to be 6.6 mb at 55 MeV with a full-width at half maximum (FWHM) of 14 MeV. In the case of the experimental binding energies, the peak of the excitation function is 100 mb at 50 MeV with a FWHM of 18 MeV. Since the ^{55}Fe production is relatively low at these higher energies, any ^{55}Fe produced is by scattered or re-emitted protons. BLIP figures indicate that it is less than 0.7% at end of bombardment.

Finally, the spallation reactions provide little information on specific reactions since the yield contributions come from a number of reactions on the nickel isotopes. The predicted excitation function for the ^{58}Ni and ^{60}Ni is shown in Figure II-5. These two isotopes comprise 94 percent of nickel. Since the maximum energy that the ALICE program can input is 200 MeV, the higher energy cross sections cited earlier can not be compared to calculations. In this case again, the calculated binding energies produce excitation functions that are a factor of 10 lower than the excitation function produced

Figure II-5

The excitation functions for the spallation reactions on ^{58}Ni and ^{60}Ni . The broadness of the excitation functions provides little information on the competing reactions that produce other iron isotopes. The calculation does enable the experimenter to gauge the optimal target thickness and beam energy.

ALICE CALCULATION FE 52 PRODUCTION

- NI 58 SPALLATION REACTION EXP. BINDING ENERGIES
- NI 58 SPALLATION REACTION CALC. BINDING ENERGIES
- ◇ NI 60 SPALLATION REACTION EXP. BINDING ENERGIES
- + NI 60 SPALLATION REACTION CALC. BINDING ENERGIES

using actual binding energies.

While no cross section is quoted for the spallation production at BLIP, the yield for a thin target is consistent with a figure of 1.78 mb, which is higher than the predicted value. Since the excitation functions are less peaked and more spread at these energies, the calculation is of little value in helping to minimize radionuclidic contamination. The calculation can help the experimenter to decide what is the minimum energy for production of the isotope in question. In this case it is about 50 MeV.

Since ^{52}Fe produced for medical use has, until now, been for in vivo application, the constraints on radionuclidic purity have been stringent. The use of ^{52}Fe in a generator system relaxes these somewhat, unless the other radionuclides produce daughters which increase the dose without any beneficial effects. Fortunately, both ^{55}Fe and ^{59}Fe decay to stable daughters, so this is not a problem. The specific activity of the radionuclide, i.e., the activity per unit weight of the element present, is crucial since the size of the generator is dictated by it.

The production capabilities of the reactions are summarized on Table II-2. The spallation reaction has the largest yield and is best suited to the production of ^{52}Fe for use in a generator system. The high radionuclidic contamination would be problematic if the product were

TABLE II-2
 ^{52}Fe Production Reactions

<u>Particle</u>	<u>Reaction</u>	<u>Particle Energy</u>	<u>Thick Target Yield $\mu\text{Ci}/\mu\text{Ah}$</u>	<u>Reference</u>
^3He	$^{52}\text{Cr} (^3\text{He}, 3\text{n})$	45.5	50	GR70
	$^{52}\text{Cr} (^3\text{He}, 3\text{n})$	33	20	RA73
	$^{52}\text{Cr} (^3\text{He}, 3\text{n})$	40	50	MU73
^4He	$^{50}\text{Cr} (^4\text{He}, 2\text{n})$	65	8	YA65
	$^{50}\text{Cr} (^4\text{He}, 2\text{n})$	30	3.3	TH71
p	$^{55}\text{Mn} (\text{p}, 4\text{n})$	65	160	SA71
	$^{55}\text{Mn} (\text{p}, 4\text{n})$	70	~110	RF78
	Ni (p, spallation)	200	$67^{\dagger}$	SO74
	Ni (p, spallation)	588	700**	GR78
	Ni (p, spallation)	800	3300**	OB78

† Thin target yield.

**Estimated from cross section measurement.

not used in a generator. With breakthrough at most one part in ten thousand, a one hundred millicurie generator produces 200 nCi of ^{55}Fe and 15 nCi of ^{59}Fe at maximum.

The large targets required by the higher energy machines require longer workup times and greater volumes of reagents. It is imperative that these be ultrapure in order to hold levels of carrier iron to a minimum, and thus keep specific activity as high as possible. An additional problem is that the radiopharmaceuticals most likely to be used with manganese are those developed using DTPA-labelled proteins (KR77). The low number of chelate binding sites also dictates that the contaminants be kept to a minimum.

Since the high current machines are capable of production by spallation, it is unnecessary to produce ^{52}Fe by bombarding manganese, unless the beam energy had to be kept below 50 MeV. Even relatively low energy machines could be used to produce ^{52}Fe in smaller quantities.

Cyclotron Corporation makes a cyclotron, the CS-15, which is not inordinantly expensive and is found at some medical centers around the country. The CS-15 is capable of producing an internal current of 300 μA for ^3He . Even at its low energy of 24 MeV, it is still able to produce 1.5 mCi of ^{52}Fe per hour, or 12 mCi in 8 hours, enough for a generator of useful size.

The threshold for the ^4He reaction on chromium, 15 MeV, prevents the use of the CS-15 for ^{52}Fe production since this is the maximum energy of the ^4He beam. If a cyclotron has a higher beam energy, the ^4He reaction could be used since ^{55}Fe production presents no problem if the ^{52}Fe is used in a generator. Machines with a beam energy of 30 MeV can produce 3.8 $\mu\text{Ci}/\mu\text{Ah}$; at 40 MeV they can produce 8.2 $\mu\text{Ci}/\mu\text{Ah}$ (MU73).

Thus the many production schemes available for the production of ^{52}Fe make it feasible for development of the generator system since many sources of the parent radionuclide are available.

^{52}Fe - $^{52\text{m}}\text{Mn}$ GENERATOR

Considering the ease with which ^{52}Fe can be made, the development of a generator was undertaken. In most instances, the physical half life of the $^{52\text{m}}\text{Mn}$ is the limiting factor rather than the biological half life of the phenomenon studied.

Since iron is unique among the transition elements in its ability to form a very strongly anionic chloride complex, a separation based on this was devised. The two systems which are most applicable are extraction into ether and isolation on an anion exchange resin. Since the use of a column has advantages over extraction procedures, e.g., stationary phase adsorbent, simpler shielding requirements and ease of operation, the system based on the anion exchange resin was developed.

^{52}Fe produced in Argonne's 60-inch cyclotron and at Brookhaven's BLIP was used to test the generator. The BLIP radionuclide had been reduced to the ferrous state with ascorbic acid and made physiologically compatible with a citrate buffer. The ^{52}Fe from BLIP was treated with concentrated nitric acid and hydrogen peroxide and evaporated to dryness. This was sufficient to oxidize iron to the III oxidation state.

For these studies, about 2 mCi of ^{52}Fe was used in the generator tests. The ^{52}Fe was dissolved in 8 N HCl and percolated through an anion exchange resin (Bio Rad AG1x8), 100-200 mesh, chloride form, which had been pre-equilibrated with 8 N HCl. The resin was held in a 2 mm i.d. column and supported by glass wool plugs at the top and bottom. The column height was 40 mm (125 μl volume). Unless a large amount of carrier iron was present in the ^{52}Fe from reagents or the target, this column size was sufficient to bind the ^{52}Fe completely. The kinetics of the adsorption are fast enough to bind the iron while the sample flowed through the column. The distribution coefficients for Fe(III) and Mn(II) as a function of HCl concentration are shown in Figure III-1 (KR56). $^{52\text{m}}\text{Mn}$ was eluted from the generator in 8 N HCl. Two column volumes were sufficient to elute the bulk of the activity. Studies at 6 N HCl and 9 N HCl were also performed.

The yield of the generator was determined by gamma ray spectroscopy using a Ge(Li) detector and a multichannel analyzer. A spectrum from the column before elution and of the eluate after elution was taken using the same geometry. The yield was determined by integrating the 1434-keV photopeak in both spectra. Since both the $^{52\text{m}}\text{Mn}$ and ^{52}Mn decay through this level in ^{52}Cr the yield of all of the radio-manganese generated is determined. Breakthrough was determined by the 169-keV photopeak either at elution or

Figure III-1

The distribution coefficients of iron and manganese on anion exchange resin as a function of hydrochloric acid concentration.

after the ^{52m}Mn had decayed, approximately three hours later.

The eluate was evaporated to dryness to remove the HCl. The ^{52m}Mn was dissolved in a 0.2 M acetate buffer, pH 5, for administration to animals.

In order to test the behavior of the generator over many elutions, one was loaded with ^{59}Fe in the form of FeCl_3 and the generator was eluted 100 times in succession, the eluate collected in a sample changer and counted in a separate sample changer. A typical generator would not be used this many times in regular use.

A typical elution curve is shown in Figure III-2. The yield falls off rapidly as a function of volume. The maximum breakthrough observed was one part in ten thousand of the ^{52}Fe on the column. In general, ^{52}Fe levels were lower than this if detected at all. In 9 N HCl, the yield was 60 percent and breakthrough negligible. In 6 N HCl, the yield increased to 89 percent, but breakthrough increased to a maximum of four parts in ten thousand.

Figures III-3 and III-4 show Ge(Li) spectra of the generator before elution and of the eluate. The 169-keV peak from the ^{52}Fe decay is not seen in the eluate. Additional information on the ^{52}Fe breakthrough was obtained by counting the samples after the ^{52m}Mn had decayed, three hours or more after elution. Correcting for ^{52}Fe decay, the breakthrough was less than one part in ten thousand,

Figure III-2

Elution of ^{52m}Mn from a generator in 8 N HCl. Column volume is 125 μl .

Figure III-3

A spectrum from a Ge(Li) detector was collected in a multichannel analyzer. Both the parent and the daughter are present in the generator.

FE 52 COLUMN 23:47

COUNTS (ARBITRARY UNITS)

Figure III-4

After elution of the generator in the previous figure, a Ge(Li) spectrum was recorded of the eluate in the same geometry. Note the absence of the 169 keV peak from the ^{52}Fe .

MN 52 ELUTION 4 23:50

COUNTS (ARBITRARY UNITS)

10^4

10^2

10^0

511 keV

200

CHANNEL

1200

as assayed by integration of the 169 photopeak.

Figure III-5 shows the results of the column loaded with $^{59}\text{FeCl}_3$ which was eluted 100 times. With few exceptions, the breakthrough is less than one part in ten thousand. In the majority of cases, no breakthrough was detected. This column was later loaded with ^{52}Fe and performed as well as the others; yield was 75 percent and the breakthrough was negligible.

As was seen in the previous chapter, cyclotron production of ^{52}Fe produces a product of high radionuclidic purity. Proton reactions produce enough ^{55}Fe and ^{59}Fe to present potential breakthrough problems. Even the maximum breakthrough, one part in ten thousand, is low enough to present little radiation hazard to the patient. The important point is that the long half lives of the radionuclidic contaminants means that their relative concentration in the eluate increases with respect to ^{52}Fe and, therefore, $^{52\text{m}}\text{Mn}$.

This potential problem from the longer-lived activity dictates that breakthrough be held to a minimum. The HCl-anion exchange resin system has the highest distribution coefficient (K_d) for iron of any of the commonly used eluants or exchange resins. Iron is barely adsorbed from HF; K_d is a maximum of three at low concentrations (FA60). Iron is not adsorbed from nitric acid (BU60). In 0.01 N H_2SO_4 , the K_d is 54 (ST67). While adsorption is high in

Figure III-5

A generator was loaded with $^{59}\text{FeCl}_3$ and eluted 100 times. The initial breakthrough of activity may be due to carrier iron present in the reactor irradiated sample.

oxalic acid-HCl mixtures, the presence of the toxic oxalic acid makes this system unattractive (ST72). Cation exchange in HCl approaches a maximum of 1000 in concentrated HCl (NE64).

In 8 N HCl, the K_d for iron is 10,000, an anion exchange resin near its maximum of 40,000 in 10 N HCl. Thus breakthrough problems will be minimal at these concentrations of HCl.

In 8 N HCl, the K_d for manganese is less than one, enabling one to recover nearly all the ^{52m}Mn on the column. In fact, the ratio of the distribution coefficients of Fe(III) and Mn(II) goes through a maximum in 8 N HCl. Hydrochloric acid also has the advantage of being easily evaporated and yielding manganous chloride, a stable form of manganese. Manganese stays in the II oxidation state in acidic chloride media, whereas nitric acid or other oxidants might oxidize the manganese to the IV state, MnO_2 , which is an insoluble colloid. The chloride left after the evaporation of the excess hydrochloric acid presents no toxicological hazard to the patient.

In 9 N HCl, the reduced breakthrough of iron is offset by the decreased yield; conversely 6 N HCl increased the yield of Mn, but at increased breakthrough.

In the test of using ^{59}Fe , breakthrough could be due to the carrier iron. This isotope is reactor produced and consequently has stable iron as well. The initial elution

of a peak of activity supports this concept.

In an effort to reduce breakthrough of ^{52}Fe from a generator loaded with activity obtained from BLIP, hydrogen peroxide was added to the eluant to insure that all the iron was in the III oxidation state. Breakthrough decreased, and an increase in yield to 100 percent was noted. Since manganese has many oxidation states, it was possible that some of the activity was born in a higher oxidation state than the II and, instead of being reduced to II by the chloride, was forming an anionic chloride in a higher oxidation state or was forming an insoluble colloid.

A later experiment, using cyclotron produced ^{52}Fe , used 8 N HCl to which hydrogen peroxide was added to make it 0.1% in concentration. The yield decreased to 50 percent and breakthrough increased to one part in one thousand. No explanation for this behavior was evident and this course of study was abandoned.

Recently the group at Brookhaven presented the results of their experiments with the same generator system (KU79). They use a smaller mesh (200-400) resin in a larger column, 600 μl . Since all other parameters are the same, the higher yield they report, 90 percent in 2 ml of 8 N HCl, is due to a combination of these factors. They also report no breakthrough of ^{52}Fe which indicates that the column size used for this study is at the limit of retention

capacity.

The short half life of the ^{52m}Mn presents a problem only if one wants to perform extended radiochemical manipulations to increase or change the biodistribution. The high yield of manganese, low breakthrough and excellent performance of the generator make its utility dependent only on the increased availability of three-dimensional imaging devices.

^{52m}Mn RADIOPHARMACEUTICALS

The high yield of the generator, up to 90 percent, coupled with the low breakthrough, less than one part in ten thousand, enabled us to pursue the development of radiopharmaceuticals using radiomanganese. Our initial interest in the system was prompted by the suggestion that carrier free manganese had potential use as a myocardial imaging agent (CH77).

The work of Chauncey et al. was originally undertaken to investigate the use of manganese as a tumor imaging agent (CH76, HA76). The high uptake in the myocardium indicated that it would be useful to investigate it for this use as well. Since the radionuclide currently used for this purpose, ^{201}Tl , has a long half life, 73 hours, the time scale for their study was relatively long; the first data point in their experiment was at 30 minutes. Since this is much longer than one would use for short-lived ^{52m}Mn , we investigated uptake on a much shorter time scale.

Animal biodistribution studies were performed using the longer lived ^{54}Mn , 303 days, to eliminate the problems associated with counting short-lived activity in animals. The manganese was treated in the same way as the generator

product; it was evaporated to dryness, redissolved in acetate buffer, passed through a bacteria filter and injected into the tail vein of ICR strain white female mice, 20-30 grams, about eight weeks old. The total time from evaporation to injection was 5 minutes.

Three mice each were sacrificed at 5, 10, 20 minutes and two hours after injection. The mice were dissected and the organs counted in a NaI well detector. About 1 μ Ci was injected into each animal.

The results are shown in Figure IV-1 and in Table IV-1. The percent of the total dose which is detected in the organ is divided by the weight of the organ to yield the percent dose per gram of tissue. In imaging, the ratio of these values is important if two organs are relatively close, such as the heart and liver. For a blood rich organ like the heart, the ratio of activity in the blood to activity in the organ is important since the origin of the image must be clear.

The biological half life, the time it takes half the activity to clear the organ, for blood is one minute (S078). Since one wants to use ^{52m}Mn as a myocardial imaging agent, it is important that blood background be minimal. With this rapid clearance, a study was performed 5 minutes after administration of the activity. The activity level shown for the blood in Figure IV-1 is the tail of the rapid clearance component.

Figure IV-1

The biodistribution of radiomanganese as a function of intravenous injection. The rapid blood clearance is well suited for myocardial imaging. The high liver uptake presents difficulty in two-dimensional imaging, but three-dimensional imaging avoids this problem.

TABLE IV-1

Tissue Concentration of Mn-54 in Mice

Percent of Total Dose/Gram of Tissue

<u>Time Post Injection</u>	<u>5 min.</u>	<u>10 min.</u>	<u>20 min.</u>	<u>2 hrs.</u>
<u>Organ</u>				
Blood	0.18 ± .14	0.13 ± .13	0.06 ± .01	0.04 ± .02
Myocardium	17.34 ± 1.10	16.53 ± 1.02	13.00 ± 2.84	12.85 ± 3.12
Liver	14.82 ± 5.89	11.38 ± 1.49	11.60 ± 5.29	13.18 ± 4.51
Kidney	40.57 ± 2.94	37.89 ± 1.25	34.90 ± 7.24	33.57 ± 8.67
Lung	8.25 ± 1.32	7.03 ± 0.48	4.67 ± 0.16	6.07 ± 1.41

Ratios of Percent Total Dose/Gram of Tissue

Myocardium/Blood	97.5	123.5	236	328.9
Myocardium/Liver	1.17	1.47	1.12	0.97
Myocardium/Lung	2.12	2.36	2.78	2.12
Myocardium/Kidney	0.43	0.44	0.37	0.38

Any changes in the biodistribution after 5 minutes are most likely due to physical losses from decay. Chauncey et al. produced an infarct in a dog's heart, injected the animal with ^{54}Mn and sacrificed the dog. The heart was sectioned and counted. They found that uptake in the heart was reduced in the area of the infarct; activity levels at the center of the infarct were 25 percent of those in normal tissue. They also pointed out that the ratio of activity levels in the myocardium to those in the blood were equal to or exceeded those of ^{201}Tl .

Previous studies showed that manganese concentrates in organs of high metabolic activity (MA55). In these studies uptake was shown to be intracellular with a majority of the activity going to the mitochondria. Nearly three-fourths of the activity is found in the organelles of the cell.

The rapid blood clearance of manganese is especially suited to a radionuclide with a short physical half life. In a myocardial study currently performed with ^{201}Tl , the patient is injected with the radionuclide and an image is taken while he is at rest. Then the patient is exercised and the imaging is repeated under stress. Thallium will redistribute in the heart to reflect areas of ischemia, decreased bloodflow. Consequently, patients who have adequate bloodflow to the heart at rest, but who experience problems while under stress can be imaged to

determine the extent of ischemia.

The drawback is that the half life of ^{201}Tl is 73 hours. This is obviously long compared to the biological lifetime of bloodflow to the heart. $^{52\text{m}}\text{Mn}$ is much better suited for these studies. If $^{52\text{m}}\text{Mn}$ is found to redistribute, the exercise study could be performed immediately after the rest study. If it does not redistribute, an exercise study can be performed 4 hours after the rest study; the rapid blood clearance allows the patient to be injected while exercising and would not extend the length of the study.

While the application for myocardial imaging was the most immediate and direct use of the generator product, other studies were performed to test the use of $^{52\text{m}}\text{Mn}$ for other diagnostic purposes.

In order to use $^{52\text{m}}\text{Mn}$ for other tests, the bio-distribution of the activity must be altered. The approach which seemed to have the most promise was to change the biodistribution by using different oxidation states of manganese.

Table IV-2 lists some of the oxidation states of manganese in both acidic and alkaline media. Manganese is in Group VII-B and is an analogue of technetium and rhenium. Perhaps the most significant difference in these elements is the oxidation potential of the higher oxidation states. Manganese, as manganic(III),

TABLE IV-2
Oxidation States of Manganese

In Acidic Solution

Mn (II)	MnCl_2
Mn (III)	MnCl_3
Mn (IV)	MnO_2
Mn (VII)	MnO_4^-

In Basic Solution

Mn (II)	Mn(OH)_2
Mn (III)	Mn(OH)_3
Mn (IV)	MnO_2
Mn (VI)	MnO_4^{--}
Mn (VII)	MnO_4^-

manganate(VI) and permanganate(VII), is a powerful oxidizing agent. Manganese dioxide is a relatively inert compound soluble only in HCl. In fact, chloride in acid medium acts as a reducing agent for all oxidation states higher than II; one of the advantages of using HCl as an eluant of the generator is that it insures the activity will be in a single oxidation state.

If the manganese, once eluted, can be oxidized to higher states, the possibility of using this to form radiopharmaceuticals is apparent. Preinjection of stannous tin into the blood followed by injection of pertechnetate is a means of in vivo labelling of red blood cells (PA77). Since the permanganate is a stronger oxidizing agent, it is possible that the manganese directly labels the red blood cells. Or another possible reduction site is human serum albumin (HSA). In both cases, the activity remains in the blood instead of clearing rapidly. The advantages of a short-lived blood pool imaging agent are obvious. Most phenomena involving blood flow are short lived, often a matter of seconds. Diagnostic tests using a long-lived activity, like ^{99m}Tc , create high backgrounds if later tests are to be performed. The tests also require high activity levels since the data must be collected over a short time span. Thus when the movement of a bolus of activity in first pass studies in the brain and heart takes place on the order of 10 seconds, radionuclides

with a half life of 6 hours are counterproductive.

Several methods are available for the oxidation of Mn(II) to Mn(VII). A solution of manganous ion is made acidic with HNO_3 and an oxidizing agent is added. Any of the following agents are suitable, namely, KIO_4 , Pb_3O_4 , $\text{K}_2\text{S}_2\text{O}_8$, NaBiO_3 . Sodium bismuthate was used for two reasons; the reaction takes place at room temperature, and the unreacted bismuthate is insoluble. The insolubility enables the excess reagent to be removed by filtration or centrifugation. Several attempts were made to produce microspheres tagged by the precipitation of MnO_4^- on them. In every case, the biodistribution indicated that a colloid had formed, i.e., uptake was in the liver instead of the lung.

These studies were discontinued for several reasons. A large percent of the activity was found in the centrifuged bismuthate after centrifugation. Since MnO_2 is the only oxidation state in acid that acts as a colloid, it is likely that this is the oxidation state formed. The behavior of a carrier free oxidizing agent like permanganate was uncertain, especially since the reduction step can lead to the more labile Mn(II) rather than Mn(IV). The oxidation step itself may produce Mn(IV) rather than Mn(VII). And finally, the presence of trace amounts of chloride ion made the experimental conditions even more complicated since it too takes part in the oxidation-

reduction steps. Attempts to remove it by precipitation as AgCl proved fruitless.

The attempts to make MnO_2 were more successful; the material behaved as a radiocolloid and localized in the liver. In this case, one could just as easily use the standard, commercially available sulfur colloid kit to form the liver scanning agent. The longer preparation time, about 20 minutes, is offset by the higher localization, about 90 percent.

The uptake in the intracellular components by the manganous ion especially in the kidney would enable two diagnostic tests to be performed. One could examine bloodflow and metabolic function in the kidney by injecting $MnCl_2$ and scanning a few minutes later.

Secondly, by complexing the manganese with a chelating agent, one could also measure the glomerular filtration rate of the kidney, a test now done with Tc-DTPA among other compounds. Manganese normally excretes through the bowels. Since the biological half life in a normal subject for this test is about 20 minutes for filtration from the blood and excretion into the bladder, ^{52m}Mn is well suited for this diagnostic test as well.

Three chelating agents were tested for this procedure. Ethylenediamine tetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA) and 1,2-cyclohexylenedinitrioloacetic acid (ODTA) were used.

All three were dissolved in sterile water and diluted to physiologically tolerable levels, about 1 mg/ml.

$^{54}\text{MnCl}_2$ in pH 5 acetate buffer was added and the solutions mixed for a few minutes to allow the manganese to be complexed by the chelate. These solutions were then bacteria filtered and injected into the tail vein of mice. The mice were sacrificed and dissected at 5, 10, 20 and 30 minutes post injection. The organs were counted in a NaI well counter.

The results are shown in Figures IV-2 to IV-4. As is evident, the CDTA is superior for this application. A higher percentage of the activity passes through the kidneys and into the bladder.

This result is consistent with the stability constants for the three compounds (BJ57). The stability constants, measured in 0.1 N KNO_3 at room temperature are: EDTA, 13.8; DTPA, 15.1; and CDTA, 16.8.

The structure of the chelates influences the stability. EDTA, with its short alkyl chain, has the flexibility to coordinate all four positions on a manganese atom. The short chain, however, also provides little constraint to the movement of the acetate groups, enabling the bonds to be easily broken. The longer alkyl chain in DTPA hinders this movement and provides a stronger complex.

CDTA, by contrast, is constrained to a fixed position by the cyclohexane backbone. In addition it is sterically

⌘ BLADDER

□ LIVER

○ BLOOD

◇ KIDNEY

MN 54 - NA EDTA BIODISTRIBUTION IN MICE

22:19:38 04-26-78

Figure IV-2

Biodistribution of ^{54}Mn -EDTA in mice.

Figure IV-3

Biodistribution of ^{54}Mn DTPA in mice.

✠ BLADDER

□ LIVER

○ BLOOD

◇ KIDNEY

MN 54 - CR DTPA BIODISTRIBUTION IN MICE

22:25:35 04-26-79

Figure IV-4

Biodistribution of ^{54}Mn CDTA in mice.

▣ BLADDER

□ LIVER

○ BLOOD

◇ KIDNEY

MN 54 CDTA BIODISTRIBUTION IN MICE

22:42:54 04-26-79

impossible for the acetate groups to rotate and bind two ions simultaneously (MA63). Thus, a manganese ion which is chelated by the CDTA molecule is most likely coordinated by all four acetate groups.

The use of chelating agents for the development of other radiopharmaceuticals has recently been proposed (KR77, SU74). Sundberg et al. used a bifunctional analogue of EDTA to synthesize metal chelates on macromolecules. 1-(p-benzenediazonium)EDTA was synthesized and coupled to several proteins. Studies with HSA-EDTA tagged with ^{111}In showed that the activity remained bound to the albumin rather than being bound to the transferrin, the blood component which normally takes up the indium. The drawback to this system is the rather long synthesis, about one week, to make the diazonium salt.

Krejcarek and Tucker use a peptide synthesis to attach DTPA to macromolecules. The total synthesis takes about a day and one half and can be done without some of the extreme conditions which are required to form the diazonium salt. Tests in animals of the chelate attached to albumin showed that its biodistribution is the same as iodinated HSA.

$^{52\text{m}}\text{Mn}$ would also be ideal for use as a lung scanning agent. Current procedure is to form either microspheres or macroaggregates (MAA) of HSA, both of which are commercially available, tag them with a radionuclide and

inject into the patient. Localization in the lung is rapid (first pass) and perfusion defects are readily seen. Since the localization is rapid, the half life of the radio-nuclide is the important parameter in radiation dose to the patient.

Studies with ^{68}Ga (HN76) and ^{111}In and $^{113\text{m}}\text{In}$ (HA78) indicated that HSA microspheres are labelled quickly (10 minutes) and efficiently (~100 percent yield). Therefore, attempts to label microspheres and MAA were attempted with ^{54}Mn .

The HSA microspheres or MAA were suspended in a buffer, the activity added, and the mixture sonicated for 15 minutes. The results for the most successful cases are shown in Table IV-3. The microspheres proved to be difficult to label, even when attempts were made to label with MnO_4^- .

The macroaggregates were more prone to be labelled, yet the total dose per organ is low while the dose per gram is high. The only explanation for this is that a hydroxide of manganese is precipitated in the macro-molecule; the high percentage of activity that is in the lung follows the biodistribution of the macroaggregates.

Obviously, one can also use the method of Krejcarek and Tucker to attach chelating groups to the microspheres or MAA. Samples of DTPA microspheres prepared by Krejcarek were mixed with ^{54}Mn and injected into mice.

TABLE IV-3

Mn HSA MAA Prepared at pH 5

<u>Organ</u>	<u>Dose-%/Gram S.D.</u>	<u>Dose-%/Organ S.D.</u>
Blood	0.52 ± 0.271	1.09 ± 0.595
Liver	8.67 ± 5.094	9.63 ± 4.539
Lung	70.27 ± 28.214	13.10 ± 5.601
Kidney	14.86 ± 9.685	4.41 ± 2.997
Heart	6.69 ± 3.169	0.71 ± 0.318
Spleen	3.46 ± 2.138	0.52 ± 0.361
Muscle	1.13 ± 0.359	14.24 ± 4.483
S. Intest	4.78 ± 2.495	9.15 ± 2.889

Mn HSA MAA Prepared at pH 9

The Average Dose for 3 Mice

<u>Organ</u>	<u>Dose-%/Gram S.D.</u>	<u>Dose-%/Organ S.D.</u>
Blood	0.63 ± 0.700	0.93 ± 0.944
Liver	7.21 ± 1.899	8.62 ± 1.503
Lung	139.93 ± 24.410	20.85 ± 1.372
Kidney	11.23 ± 2.028	2.82 ± 0.367
Heart	5.48 ± 1.649	0.49 ± 0.100
S. Intest	3.62 ± 0.587	6.48 ± 0.899
Muscle	0.68 ± 0.612	6.04 ± 5.166
Bone	0.84 ± 0.498	1.83 ± 1.008

Mn MAA Prepared at pH 10

The Average Dose for 3 Mice

<u>Organ</u>	<u>Dose-%/Gram S.D.</u>	<u>Dose-%/Organ S.D.</u>
Blood	0.69 ± 0.794	1.02 ± 1.193
Liver	19.76 ± 2.285	20.08 ± 1.787
Lung	116.96 ± 14.798	16.23 ± 0.974
Kidney	14.21 ± 0.734	3.67 ± 0.212
Heart	6.24 ± 3.843	0.48 ± 0.306
S. Intest	4.64 ± 0.608	8.49 ± 0.911
Muscle	1.75 ± 1.801	16.12 ± 16.570
Bone	4.09 ± 4.547	3.76 ± 9.867

The results indicated that the activity was not taken up by the chelating groups. It is likely that contaminants in the reaction solution had complexed all the chelates; a microgram of iron is sufficient to bind all the DTPA in the preparation and it forms a stronger complex than manganese.

Attempts to attach the chelate to microspheres gave inconsistent results. There is evidently some crucial step which was not forming the bond properly between the macromolecule and the DTPA. The promise of the technique and the wide applicability of the radiopharmaceuticals should most likely induce a commercial vendor to make a chelate-macromolecule mixture available commercially.

^{223}Ra - ^{211}Pb GENERATOR

As was pointed out in the introduction, many of the advantages of using short-lived activity in diagnostic uses also applies to therapy. Since our initial study was directed toward use of the alpha activity in vivo in a direct administration, the system with the shortest half life daughter was used, ^{223}Ra .

^{223}Ra is the product of the decay of ^{235}U , a naturally occurring isotope. The decay of ^{235}U is shown in Figure V-1. ^{227}Ac , half life 21.6 years, is the best grandparent for the ^{223}Ra . The relatively long half life of ^{227}Ac makes it a "constant" source of ^{223}Ra . Obviously, smaller quantities of material are handled if ^{227}Ac is the grandparent rather than some of the longer lived grandparents. Since the separation of naturally occurring ^{227}Ac requires large amounts of pure ^{235}U , an alternative method of production is to produce ^{227}Ra by neutron capture in ^{226}Ra . ^{227}Ra with a half life of 41 minutes beta decays to ^{227}Ac . The cross section for neutron capture, 20 barns, is high enough that 20 mg of ^{226}Ra irradiated in a reactor at a flux of 10^{14} neutrons/cm²-sec for one month would produce 100 mCi of ^{227}Ac .

Figure V-1

The decay scheme for ^{235}U and its long-lived daughters.

U 92	U ²³⁸ , AcU (actinouranium) 7.13 × 10 ⁸ years				
Pa 91	α	Pa ²³¹ , Pa (protactinium) 3.48 × 10 ⁴ years			
Th 90	Th ²³¹ , UY (uranium Y) 25.6 hours	β	α	Th ²²⁷ , RdAc (radioactinium) 18.17 days	
Ac 89		Ac ²²⁷ , Ac (actinium) 22.0 years	β (98.8%)	α	
Ra 88			Ra ²²⁶ , AcX (actinium X) 11.7 days		

^{223}Ra can be separated from ^{227}Ac by a number of methods. Since the radiation levels from ^{227}Ac and its daughters are quite high, the separation should involve a minimum amount of handling. Two methods using columns were attempted. ^{227}Ac and its daughters were adsorbed on a cation exchange column which is heated to 60°C in hydrochloric acid (CA59). The lead, bismuth, and francium daughters are eluted in 6 N HCl. The radium is eluted in 3 M HNO_3 . The actinium is eluted in 6 N HNO_3 . The thorium daughter can be left on the column or it can be eluted in lactic or formic acid.

^{223}Ra can also be separated by extraction of ^{227}Ac and ^{227}Th into di(2-ethylhexyl)orthophosphoric acid (HDEHP) in a non-miscible solvent such as heptane from 0.01 N HNO_3 . The high radiation levels from the ^{227}Ac and daughters makes this suitable for low levels of activity; attempts at using this system led to rapid breakdown of the organic phase. Impurities in the actinium we used also precluded the use of a column of an inert support which was saturated with HDEHP since the small capacity of the column was exceeded by the contaminants.

For the production of a generator, approximately 20 mCi of ^{227}Ac was purified and used. The radiation level of this amount of activity is about 2 Rads per hour; this level of activity made manipulation by hand quite difficult.

The decay of ^{223}Ra and its daughters is shown in Figure V-2. Only the major decay chain is shown. Two separation schemes for the generator were attempted, one using the ^{219}Rn and the other using the ^{211}Pb .

^{223}Ra , half life 11.4 days, decays to ^{219}Rn , half life four seconds, by alpha emission to a number of levels in ^{219}Rn . The gamma spectrum is complex (Figure V-3).

^{219}Rn decays to ^{215}Po , half life 2 milliseconds, which by alpha emission decays to ^{211}Pb , the generator daughter. The ^{219}Rn decays to several levels in ^{215}Po ; ^{215}Po decays almost entirely to the ground state of ^{211}Pb , half life 36.1 minutes.

^{211}Pb decays by beta emission to several levels in ^{211}Bi ; the beta energy is 1.36 MeV maximum. ^{211}Bi decays by alpha emission almost entirely to several levels in ^{207}Tl ; the energy is 6.62 MeV. ^{207}Tl de-excites to the ground state by emitting a 351-keV gamma ray, 12.7 percent abundance.

The ^{207}Tl daughter, half life 4.77 minutes, decays by beta emission with a maximum energy of 1.431 MeV to the ground state of ^{207}Pb , which is stable.

The generator product, ^{211}Pb , thus decays by the emission of two beta particles and one alpha particle to stability. These particle emissions are almost the entire source of the radiation dose since the gamma emission is

Figure V-2

The decay scheme for ^{223}Ra and its daughters. The generator products are ^{211}Pb and its daughters.

^{223}Ra decay

Figure V-3

A Ge(Li) spectrum of ^{223}Ra and its daughters. Except for the peaks indicated by arrows, the gamma rays are not seen in the generator product.

RA 228 BREAKTHROUGH 8-20-70 1 KEV / CHANNEL

limited to the 351-keV gamma ray in ^{207}Tl and weaker transitions from the ^{211}Bi at 405, 427, and 832 keV.

The radiation dosage for the radionuclides is calculated using the reaction:

$$\frac{\text{rads}}{\text{g-hr-mCi}} = \frac{\text{dis/hr} \times \text{average particle energy} \times 1.6 \times 10^{-6} \text{ erg/MeV}}{100 \text{ ergs/g-rad}}$$

The contribution to the total dosage is: ^{211}Pb , 861 rads/gram-hour; ^{211}Bi , 1.41×10^4 rads/gram-hpur; and ^{207}Tl , 1022 rads/gram-hour. The initial total dose rate is 1.6×10^4 rads/g-hour per millicurie of activity. Assuming the activity decays in place, the total integrated dose is 1.39×10^4 rads/gram (DO79).

Thus large dosages can be administered to the site of interest. The range of an alpha particle of this energy in water is less than 1 mm. Therefore over 90 percent of the radiation dosage will be at the site of decay.

Since the initial separation of the ^{223}Ra includes elution of the short-lived daughters in HCl, a generator based on this system was constructed. A column 2 mm i.d. x 80 mm was filled with Bio Rad AG50x8, 100-200 mesh, hydrogen form. The column was held inside a jacket through which heated water could be circulated. The column was run at 60°C.

The ^{223}Ra was put on the column in dilute HCl and the column was washed with 5 column volumes of the same con-

centration. Since lead exhibits its most anionic character in 2 N HCl, this was used as the eluant (KR56). The bismuth also is strongly anionic at this concentration.

An elution curve is shown in Figure V-4. The activity elutes in one column volume. The problem which developed is that the breakthrough is about 3-10 percent of the eluted activity which is unacceptably high. In order to improve the breakthrough, 0.5 N HCl was used to elute the daughters. The effect of this was to lower the yield of the generator by a factor of 2 or more, but breakthrough also decreased to 1 percent or less of the eluted activity. Another effect of the lower acidity is a separation of the lead and bismuth activity. The bismuth is eluting preferentially since it is much more anionic at the lower chloride concentration.

Finally, elution in 0.1 N HCl was tried. The yield fell to about 1 percent of the levels in 2 N HCl. The breakthrough was minimal at this concentration.

Since the results of this system were so poor, a generator was constructed which distills the short-lived ^{219}Rn from the ^{223}Ra parent.

Wahl and Daniels (WA58) precipitated ^{223}Ra with barium stearate to test the emanation of short-lived activity from the stearate precipitate. They were measuring the yield of short-lived gases from fission

Figure V-4

The elution of ^{211}Pb from a cation exchange column in 2 N HCl. The activity elutes in the first column volume.

01:18:57 10-15-78

and needed a matrix which allows the gas to escape to enable its daughters to be counted separately from those that formed directly from fission.

The radium and barium can be precipitated two ways; by neutralization of an alcoholic solution of stearic acid with aqueous barium hydroxide or by mixing warm aqueous solutions of sodium stearate and barium chloride. Though Wahl used the latter system, the small tubes in which the precipitate was held prevented easy heating. A compromise solution was to use sodium stearate and barium chloride, both dissolved in methanol. Excess solution was evaporated instead of filtered because there was some evidence that the radium may be concentrating in the solution.

The precipitate was transferred to a manifold which could be evacuated (Figure V-5). The radon was collected in a tube, cooled to liquid nitrogen temperatures, which detaches from the system. The tubing was 1 cm i.d. and all valves and connections used O-ring seals to minimize the grease present to absorb the radon. This early design proved workable, but the yield was low, 100 μ Ci per elution. A few animal studies were attempted with this level of activity but the results were inconclusive. The yield represented approximately 5-10 percent of the activity in the tube. Several reasons for this were proposed. The small diameter of the tube created problems with the precipitate since it was several millimeters deep.

Figure V-5

The radon still used to separate ^{219}Rn from ^{223}Ra . The radium stearate is precipitated in a tube which fits inside the tube on the left. After the system is pumped down to a vacuum of 50 microns or less, the pump is isolated from the system and the radon distills into the receiving cone.

^{219}Rn still & manifold

Secondly, the short half life, 4 seconds, may have contributed to a significant decay loss while the gas was in the tubing. Finally, the three valves in the assembly provided sites for the radon to be absorbed.

A new generator was designed which diminished these problems (Figure V-6). The tubing was 2.5 cm i.d. and the distance from the radium to the receiver was decreased. Two of the valves were eliminated to decrease the number of O-rings present in the system. A vacuum gauge was added to the system to insure that the vacuum in the system was maintained.

The yield increased to 10 percent, still lower than expected, but the larger diameter tubing enabled us to put a larger ^{223}Ra source in the manifold by precipitating the stearate in a platinum crucible; the glass tubes which were inserted into the first generator were subjected to extremely high radiation doses.

A number of trials were undertaken to determine the optimum conditions for extraction of the activity from the receiver. It was noted that a solution frozen into the receiver cone increased the chemical yield significantly. The activity apparently reacts with the vessel walls and resists etching with strong acid.

The yield is highest if ~2 N HCl is used to withdraw the ^{211}Pb . This system proved unsatisfactory in later experiments with animals, even though the acid had been

Figure V-6

The still which is currently in use. The inner diameter of the tube was increased to 2.5 cm, and two valves were eliminated. In addition, a gauge was installed in the system to monitor the vacuum. The larger size tube also accommodates a platinum crucible which holds the activity.

- note to be taken

evaporated to dryness and the activity dissolved in pH 5 acetate buffer. Consequently, the later experiments were done with the acetate buffer frozen into the cone; the yield decreased to 65 percent of the ^{211}Pb distilled.

Since the acetate does not form a strong complex with the lead, the buffer was made up with sulfate to complex the lead. The final concentration of K_2SO_4 was 10^{-4} molar. This proved satisfactory as a masking agent.

The system can be pumped down to 5 microns (Hg) and it is stable as long as the receiver is kept at liquid nitrogen temperatures. At this low pressure the breakthrough or carry-over of radium increases. This may be due to turbulence when the system is brought to atmospheric pressure. The numerous gamma rays in the decay of radium make it easy to detect any breakthrough.

The animal studies performed to date were undertaken to demonstrate the effect of the particle emission in tissue. Mice were injected in the thigh muscle (using the other thigh as a control). The histological examination indicates muscle damage from the radionuclide.

The next step in the program is the injection of activity into the peritoneal cavity. Since most of this activity is taken up by the liver one can assess the damage there. Finally, the ^{211}Pb will be mixed with an agent which localizes exclusively in the liver to determine any differences between this and the i.p.

administration.

The ultimate goal of the use of these short lived alpha emitters is for therapy. Two potential uses have been identified. Treatment of malignant lesions has been proposed. Both chemotherapy and immune therapy are more effective with small tumor masses. The administration of the alpha emitter, with its short range, intensely ionizing radiation, serves two purposes; one, to shrink the tumor mass and two, to liberate products from the tumor which could possibly stimulate an immune response. The activity can be administered by direct injection into superficial lesions or by catheterization into deeper tumors.

The other potential use of the alpha emitter is in therapy of hypertrophied synovium, the lining of the joints. There has been interest in treatment of this condition with intraarticular colloids bearing a beta emitter. The isotopes used for this work to date have been relatively long lived beta emitters since they were made and packaged away from the hospital. Since the half life is long, some of the beta emitter leaves the site of treatment, possibly through the lymphatic system and irradiates distant sites (R078). The alpha emitter irradiates only locally and its short half life decreases the likelihood of it leaving the treatment area.

PRODUCTION OF ^{118}Te

The current interest in using nuclear medicine techniques for dynamic studies of blood flow and the cycle of the heart has opened the way for use of radionuclides with half lives on the order of tens of seconds. In particular, the recent development of generators that produce ^{82}Rb , with a half life of 1.25 minutes (GR78a), ^{178}Ta , 9.3 minute half life (NE78), and $^{191\text{m}}\text{Ir}$, 4.9 second half life (HN77), has been prompted by the advantages of using these ultrashort-lived radionuclides for dynamic studies.

The problem associated with all of the above generator produced radionuclides has been the inability to use them for anything but the most rudimentary procedures. Rubidium localizes in the myocardium and is an excellent agent for locating ischemia since it acts like potassium. Recently it has also been proposed as an agent for measuring blood-flow in the kidney (BI79).

Tantalum has been proposed as a blood pool imaging agent and has shown itself to be useful for this purpose. The tendency to form colloids, unless strongly complexed, is a drawback to using it for other purposes unless the characteristics of the colloid make it more useful. For

example, if a colloid is to be used for imaging the liver, then this radionuclide might be useful except for its low photon energy.

The extremely short half life of the iridium also precludes its use as anything other than a blood pool imaging agent. Many of the uses of the generator have been limited to pediatric nuclear medicine since the transit time from an arm vein to the heart creates serious decay losses in adults.

These limitations in the above ultra-short lived generator products prompted us to investigate another system based on the parent daughter pair ^{118}Te - ^{118}Sb with half lives of 6.00 days and 3.5 minutes respectively (LE78).

The decay scheme is shown in Figure VI-1. ^{118}Te decays by electron capture to the ground state of ^{118}Sb . Since no gamma rays are emitted, breakthrough from a generator must be detected by the persistence of the daughter beyond 10 half lives, almost 35 minutes.

^{118}Sb decays by electron capture and positron emission, the majority of the decays going directly to the ground state. The remainder of the decays as can be seen, go to a number of excited states. A number of gamma rays result from the deexcitation of these excited states; the most abundant are the 1229 keV (2.5%), 1267 (0.58%), 528 (0.4%) and 827 keV (0.4%).

Figure VI-1

The decay scheme for ^{118}Te - ^{118}Sb .

Since the radionuclide decays by positron emission 75 percent of the time, the weaker gamma rays do not pose problems if a coincident detection technique is used. The maximum energy of the positron is 2.67 MeV.

The advantage of this system over the others mentioned earlier is the two oxidation states of the daughter, III and V. The possibility of performing quick radiolabelling by reduction of the Sb(V) to Sb(III) is unique to this system. If the reduction occurs in vivo, it is likely that some component of the blood is labelled; the reduced antimony might adhere to serum proteins or the ion might be taken up by transferrin as is Ga(III) or In(III).

Studies with the tellurium-antimony parent daughter pair were undertaken to investigate the use of anion exchange resin to separate different oxidation states of antimony (MO62). A small column, 2 mm x 70 mm, was used to isolate the carrier-free tellurium and antimony activities from a spallation reaction in CsCl. The activity was adsorbed in 6 N HCl and the ^{118}Sb was eluted in 1.7 N HCl. The tellurium activity was eluted in 0.5 N HCl and the other, longer lived antimony activity were eluted in 0.2 M NH_4OH and 0.2 M $\text{NH}_4\text{CH}_3\text{COO}$.

Moskvin proposes that the longer lived antimony activities are reduced by the resin which will retain Sb(III) in any acidic chloride media. The short lived ^{118}Sb is not reduced and elutes in HCl with a normality

less than two. To demonstrate this conclusively, Moskvina allowed a mixture of ^{119}Te and ^{118}Te to come to equilibrium with the daughter activities in 6 N HCl. The mixture was transferred onto a column of anion exchange resin and then washed with 1.7 N HCl. Only the ^{118}Sb eluted under these conditions. After the tellurium was stripped from the column in dilute HCl, the ^{119}Sb eluted in a solution of the ammonium salts.

The possibility of using this system as the basis of a generator prompted us to investigate the production of ^{118}Te in the ANL cyclotron.

All studies published to date have utilized protons or deuterons to produce ^{118}Te . Since the minimum energy required for these reactions is beyond the maximum energy of the ANL cyclotron, bombardments of tin targets with ^4He particles were used.

The excitation functions calculated by ALICE are shown in Figures VI-2 and VI-3. Since the production of ^{118}Te from ^3He and ^4He is not restricted to a single tin isotope, but rather has contributions from ^{116}Sn to ^{119}Sn , the excitation function was constructed by adding together the cross section for the reactions at each energy weighted for the isotopic abundance of the tin isotope in natural tin. The objective of this study was to use readily available target materials for radionuclide production. The isotopic abundances are: ^{116}Sn , 14.8

Figure VI-2

The calculated cross sections for the indicated reactions in the production of ^{118}Te are shown as a function of bombarding energy of ^4He . The solid line is the excitation function which results from adding the values of the cross section for all reactions at each energy. The cross section is corrected for isotopic abundance.

TE 118 PRODUCTION CALCULATED

- EXCITATION FUNCTION FOR NATURAL TIN
- ⊠ ALICE CALCULATION SN 119
- ALICE CALCULATION SN 118
- ALICE CALCULATION SN 117
- ◇ ALICE CALCULATION SN 116

CROSS SECTION (MILLIBARNS)

percent; ^{117}Sn , 7.75 percent; ^{118}Sn , 24.3 percent; and ^{119}Sn , 8.6 percent.

The excitation function shown in Figure VI-2 for ^4He bombardment has a threshold of 20 MeV for the reaction. The excitation function is nearly flat from 28 to 42 MeV. Above 42 MeV the large cross section in the $^{118}\text{Sn}(^4\text{He},4n)$ reaction increases the excitation function above this plateau. The maximum energy for ^4He is 44 MeV so this reaction contributes little to the production.

The excitation function calculated from ALICE for ^3He reactions is shown in Figure IV-3. The excitation function is much more sharply peaked in this case; most of the peak results from the contribution of the $^{118}\text{Sn}(^3\text{He},3n)$ reaction. The maximum energy of the ANL cyclotron for ^3He particles is 33 MeV. This sharp excitation function and the lower beam current available for ^3He led us to measure only the cross section for the ^4He beam on a natural tin target.

A stack of 25.4 micron tin foils was irradiated at an integrated current of 1 μAh . The foils were removed from the cyclotron and the short-lived activity was allowed to decay for one week. The foils were counted with a Ge(Li) detector interfaced to a multichannel analyzer. The yield of ^{118}Te was measured by integrating the 1229 keV photopeak.

Figure VI-3

The calculated cross sections for ^{118}Te in the indicated reactions are plotted as a function of bombarding energy of ^3He . The solid line represents the excitation function resulting from the addition of all the cross sections at a given energy. The cross sections are corrected for isotopic abundance.

TE 119 PRODUCTION BY HE 3 BOMBARDMENT

- ⌘ EXCITATION FUNCTION FOR NATURAL TIN
- ALICE CALCULATION SN 119
- ALICE CALCULATION SN 118
- ◇ ALICE CALCULATION SN 117

18:14:48 10-12-78

The ^4He reactions also produce $^{119\text{m}}\text{Te}$ which has a half life of 4.7 days and ^{119}Te with a 16 hour half life. Both of these radionuclides decay to ^{119}Sb which has a half life of 38.0 hours. The daughter, if eluted from the generator, will increase radiation dose to the patient without adding any information since it does not decay by positron emission. While the study by Moskvina indicated that ^{119}Sb is reduced on the resin, the increased radiation dose to the generator dictates that the production of the parents be minimized.

The yield of $^{119\text{m}}\text{Te}$ was determined by integrating the 1212 keV photopeak; the ^{119}Te had decayed before the yield was determined. The results for this the ^{118}Te and $^{119\text{m}}\text{Te}$ production are shown in Table VI-1.

The calculated and measured excitation functions for ^{118}Te and $^{119\text{m}}\text{Te}$ production are plotted in Figure VI-4 for ^4He reactions. In both cases, the fit between the calculation and the experiment is fair. Features in the excitation function are not reproduced well, although the cross section is accurate above 35 MeV for $^{119\text{m}}\text{Te}$. The poor fit to the ^{118}Te data is not easily explained. The excitation function should be flatter at the high energies since it is in this energy range that many reactions are contributing to the production of ^{118}Te .

The ALICE calculation does indicate that both ^{118}Te and $^{119\text{m}}\text{Te}$ will be produced in good yield and that both

TABLE VI-1
 ^{118}Te Production Experiment
 ^4He Bombardments

<u>Foil Number</u>	<u>Average Beam Energy</u>	<u>Microcuries</u>	<u>Millibarns</u>	$^{119\text{m}}\text{Te}$ <u>Microcuries</u>
1	43.4	2.66	70	15.8
2	41.9	5.21	136	12.4
3	40.2	7.07	184	12.0
4	38.4	6.08	159	7.88
5	36.6	4.92	128	5.28
6	34.8	4.47	117	4.79
7	32.9	2.33	61	5.20
8&9*	29.8	1.02	27	6.52
10		--	--	0.04

*Foil 8 and 9 melted together.

Figure VI-5

The calculated excitation functions are compared with the experimentally determined ones for production of ^{118}Te and $^{119\text{m}}\text{Te}$ using ^4He beams. While the quantitative fit is not good, the predictive value of the model is apparent, i.e., both radionuclides will be produced in comparable quantities in the same energy range.

EXPERIMENTAL VS. CALCULATED EXCITATION FUNCTIONS

- ⌘ TE 119M PRODUCTION BY HE 4 BOMBARDMENT OF TIN
- TE 119M EXCITATION FUNCTION CALCULATION
- TE 118 PRODUCTION BY HE 4 BOMBARDMENT OF TIN
- ◇ TE 118 EXCITATION FUNCTION

will be produced in the same energy range.

Thick target yield for ^{118}Te is 33.75 $\mu\text{Ci}/\mu\text{Ah}$. At a current of 40 μA , one can produce 1.4 mCi/hr. Thus a 50 mCi generator can be produced after 37 hours of irradiation.

The literature for separation of tin, antimony, and tellerium is dominated by separation of fission products. Unfortunately, all the separations which were found use carrier tellerium to achieve a good yield. Since the object of the study was to keep generator size as small as possible, especially with a short-lived daughter, several attempts were made at carrier free separations.

Distillation techniques using the volatile halides or hydrides were not attempted since both the target and the products will distill. Most extraction procedures were also not used since both tin and tellerium extract under the same conditions. Similarly, precipitants of tin also precipitate tellerium.

Some authors claim that anion exchange columns can be used to separate tin and tellerium (SM55). The separation, though not of carrier free radionuclides, used 0.1 M oxalic acid to elute the tellerium, 0.1 M oxalic acid neutralized to pH 4.3 to elute the antimony and 1 M H_2SO_4 to elute the tin.

Attempts to duplicate this work failed. The tellerium did not separate in a well-defined peak from the column;

the activity dribbled off, never amounting to more than a few percent of the tellerium activity in one column volume. In addition, no clear separation from the other activities was noted.

Anion exchange resin was also used in an HCl system. The activity and target were adsorbed in 6 N HCl and an attempt was made to elute the tellerium with 1 N HCl. Again the tellerium activity did not elute in a peak, but dribbled off at a few percent per column volume.

In order to insure that the tellerium activity was separable from the tin target, 0.5-1.0 mg of tellerium carrier was added to the target and the tellerium precipitated as the metal. The precipitation can be carried out either by bubbling SO₂ into the HCl which was used to dissolve the target, or, if enough Sn(II) is present in the solution, by reduction by Sn(II). In both cases, over 99% of the tellerium activity is precipitated.

¹¹⁸Te can be produced in good yield using a medium energy ⁴He beam, 44 MeV. While contamination from ^{119m}Te presents some problems, the radionuclidic contamination can not be minimized using this production scheme. The major problem is increased radiation dose to the generator since the ¹¹⁹Sb daughter has a long half life and can be pre-eluted. In addition, evidence suggests that ¹¹⁹Sb is reduced by the anion exchange resin and is adsorbed in 1.7 N HCl. Thus a generator will produce only the ¹¹⁸Sb.

While it is not desirable, tellerium can be separated from the target by precipitation with small amounts of carrier tellerium. Therefore it is possible to produce and separate ^{118}Te in large enough quantities to produce a generator for clinical use.

PRODUCTION OF ^{178}W

The research for this dissertation was originally prompted by the obvious need for a generator product to be used in studies of the heart, both in assessing blood-flow and myocardial distribution. Blood flow studies are currently done using $^{99\text{m}}\text{Tc}$ tagged to human serum albumin (HSA). First pass studies can detect shunts in the vascular system. Once the activity comes to equilibrium in the blood, studies of the heart cycle can be used to determine ejection fraction, the amount of blood that the heart pumps out as a percent of the total blood in the ventricle, and to detect aneurysms which can lead to heart failure.

The alternative to a nuclear medicine study is to catheterize the patient, inject a dye into the heart and use X rays to examine heart function. Since the catheter involves surgical intervention, this procedure is called an invasive procedure. In addition, the dye is toxic and causes complications. Finally, most patients who require this procedure are gravely ill and invasive procedures poses serious threats to their life.

The study using a blood pool agent like $^{99\text{m}}\text{Tc}$ HSA is much simpler. The technetium is complexed with the

HSA and injected intravenously in an arm vein. This is a non-invasive procedure and poses little risk to the patient.

The drawback to this study is the half life of the radionuclide ^{99m}Tc which is 6 hours. In this case, the blood pool studies have a biological half life of minutes and the first pass studies are on the order of seconds. If a radionuclide with a shorter half life is used, the advantages are obvious. The radiation dose to the patient is lower, the radionuclide decays more quickly allowing repeat studies to be performed sooner and more activity can be administered allowing the studies to be finished more quickly.

But, as was pointed out in the introduction, such a short half life necessitates either proximity to a cyclotron or the use of a new generator system.

Our initial efforts were directed at the parent daughter pair ^{178}W - ^{178}Ta . ^{178}W , half life 21.5 days, decays by electron capture with no gamma ray emission. The daughter, half life 9.3 minutes, decays by electron capture (98.9 percent) and positron emission. The decay branches through several levels in the stable ^{178}Hf ; 4 percent of the decays goes to levels between 1175 and 1772 keV, 34 percent of the decays feeds the first excited state at 93 keV and 62 percent of the decays goes directly to the ground state. The abundance of the 93 keV gamma ray is 5.9 percent; it is obviously internally converted. The

greatest photon yield is from the X rays of hafnium between 54.5 and 65 keV.

While this energy is somewhat low for use in gamma cameras, the proximity of the heart to the anterior chest wall reduces the absorption of photons which is the major drawback to the use of low energy photons in imaging. The low yield of the 93 keV gamma ray precludes its use for imaging since large amounts of the parent must be produced and the economic consideration of such expensive bombardments takes precedence.

While this investigation was underway, another group from Harvard reported on the development of a ^{178}W - ^{178}Ta (NE78) generator. The system was developed specifically for use in conjunction with a new camera design, the low energy multiwire proportional camera. Subsequent studies have shown that the generator product can be used with conventional equipment and produce images of the same quality as those made with $^{99\text{m}}\text{Tc}$ in first pass studies (HO79).

The production scheme for the reported generator uses proton bombardments of tantalum to produce ^{178}W by $^{181}\text{Ta}(p,4n)^{178}\text{W}$ (HO78). The cross section reported from other experiments is about 770 mb at the peak in the excitation function at 36 MeV bombarding energy. Calculations with the ALICE code reported in the paper and performed here at Argonne predict a peak in the (p,4n)

cross section at 34 MeV. While the authors profess concern over radionuclidic purity from competing reactions producing ^{177}W , with a half life of 135 minutes, and ^{179}W , with a half life of 38 minutes, the short half life of these radionuclides means they decay in a day. This short cooling time would have little effect on the amount of ^{178}W with its much longer half life.

The proton energy used for production is far above the energy available in medical cyclotrons. Further, the cyclotrons currently in place with the capability for these energies are usually low current machines and are impractical for use in radionuclide production. Of course, the high current linacs at BLIP and LAMPF could easily produce this radionuclide.

For those with access to a cyclotron which has a high current capability for helium bombardment, we investigated the ($^4\text{He}, \text{xn}$) and ($^3\text{He}, \text{xn}$) reactions on hafnium to produce ^{178}W . The reactions contributing to the production from alpha bombardment are $^{176}\text{Hf}(^4\text{He}, 2\text{n})$, $^{177}\text{Hf}(^4\text{He}, 3\text{n})$ and $^{178}\text{Hf}(^4\text{He}, 4\text{n})$. For ^3He bombardment they are $^{178}\text{Hf}(^3\text{He}, 3\text{n})$ and $^{179}\text{Hf}(^3\text{He}, 4\text{n})$.

The excitation functions calculated for these reactions using ALICE are shown in Figures VII-1 and VII-2. In both cases the excitation function was constructed by adding the contribution for each isotope weighed for its natural abundance. They are: ^{176}Hf , 5.2 percent, ^{177}Hf , 18.6

Figure VII-1

The calculated excitation function is plotted as a function of bombarding energy for reactions of a ^4He beam in natural hafnium. The points represent the cross section for the indicated reaction, corrected for the isotopic abundance of the target nucleus. The solid line is the sum of all the cross sections at a given energy.

H 178 PRODUCTION BY HE 4 BOMBARDMENT OF HAFNIUM

- EXCITATION FUNCTION HE 4 BOMBARDMENT
- ⊠ ALICE CALCULATION HF 178
- ALICE CALCULATION HF 178
- ALICE CALCULATION HF 177
- ◇ ALICE CALCULATION HF 176

CROSS SECTION (MILLIBARNS)

18:21:43 10-12-78

Figure VII-2

The calculated excitation function is plotted as a function of bombarding energy for reactions of a ^3He beam in natural hafnium. The points represent the cross section for the indicated reaction, corrected for the isotopic abundance of the target nucleus. The solid line is the sum of all the cross sections at a given energy.

W 178 PRODUCTION BY HE 3

- EXCITATION FUNCTION FOR NATURAL HAFNIUM
- ALICE CALCULATION HF 178
- ◇ ALICE CALCULATION HF 178

18:06:33 10-12-78

percent, ^{178}Hf , 27.1 percent, and ^{179}Hf , 13.8 percent.

The excitation function for production of ^{178}W using ^4He shows a threshold at 20 MeV with a quick rise to 30 mb from the $^{176}\text{Hf}(^4\text{He}, 2n)$ reaction. The excitation function dips slightly between the peak of this reaction and that for $^{177}\text{Hf}(^4\text{He}, 3n)$. At 36 MeV the excitation function rises because the cross section for the $^{178}\text{Hf}(^4\text{He}, 4n)$ reaction is much higher and ^{178}Hf is more abundant.

The excitation function for the production of ^{178}W by the $(^3\text{He}, xn)$ reactions is much lower, peaking at 170 mb at 28 MeV. The major contribution to the excitation function is from reactions in ^{178}Hf and ^{179}Hf ; the cross section for the other reactions is negligible.

The experimental excitation functions were determined by irradiating a stack of 2.5 mil hafnium metal foils at an integrated current of 1 μAh . An irradiation was done using a 44 MeV ^4He beam and a 33 MeV ^3He beam in the ANL cyclotron. The thickness of the foils was greater than one would want for such a study, but was the thinnest available from commercial sources.

The experimental results are shown in Table VII-1. The results from the ALICE calculation are shown in the last column. The experimental values agree qualitatively with the predictions of ALICE. In the ^4He reactions the large cross section at high energy diminishes at low energy as the threshold for the $^{178}\text{Hf}(^4\text{He}, n)$ reaction

TABLE VII-1
Production of ^{178}W

^4He Bombardment

<u>Foil number</u>	<u>Beam energy</u>	<u>Yield $\mu\text{Ci}/\mu\text{Ah}$</u>	<u>Experimental cross section millibarns</u>	<u>Theoretical cross section millibarns</u>
1	44	33.5	1050	500
2	37.8	21.2	664	380
3	31.0	4.98	156	30
4	23.2	5.07	159	35

^3He Bombardment

1	33	12.8	401	135
2	24	10.6	332	200
3	15	0.45	14	-

is passed and the only contribution is from less abundant target isotopes.

The thick target yield is 64.7 $\mu\text{Ci}/\mu\text{Ah}$. Using a 40 μA current, 2.5 mCi can be produced in an 8 hour bombardment.

The results of the ^3He bombardment show a broad peak in the excitation function from 16 MeV to 33 MeV. This agrees qualitatively with the ALICE calculation. The yield is much lower for the ^3He reactions, 23.8 $\mu\text{Ci}/\mu\text{Ah}$.

No satisfactory separation of carrier-free ^{178}W from the hafnium target was developed. The only separation that worked was precipitation of tungstic acid with carrier tungsten in the form of sodium tungstate. The presence of carrier increases the generator size to accommodate the stable tungsten.

Attempts to separate the tungsten and hafnium on anion exchange resin were unsuccessful. The similarity of behavior of the two elements in HF, HCl and mixtures of the two resulted in no satisfactory separation.

The use of ^3He and ^4He to produce ^{178}W broadens the potential use of this radionuclide in generator systems. The ability to use cyclotrons with intermediate energy beams of these bombarding particles to produce ^{178}W during periods of little use (nights and weekends) can make this radionuclide more readily available.

GENERATORS PRODUCING ^{109m}Ag

A generator system that can be used with conventional cameras has obvious advantages over the positron emitters since it can be used in almost any medical center in the United States. The major drawback to the ^{178}W system is the low abundance of the high energy gamma rays.

^{109m}Ag , half life 39.8 seconds, decays by isomeric transition to the stable ground state, emitting a 88.0 keV gamma ray in 3.6 percent abundance. While the low yield is a disadvantage, the higher energy is more compatible with conventional cameras than the X rays of hafnium.

The radionuclide is produced in the decay of ^{109}Pd and ^{109}Cd . ^{109}Pd has a 13.4 hour half life and is produced by neutron capture in ^{108}Pd , abundance 26.7 percent. The cross section for the reaction is 12 barns to the ground state, and 0.2 barns to ^{109m}Pd , half life 4.7 minutes, which decays by isomeric transition to ^{109}Pd . The large cross section makes reactor production quite easy; the low cost of reactor production, when compared to charged particle reactions, is another positive factor.

^{109}Cd can be produced in two ways. ^{109}Ag or natural silver can be bombarded with protons or deuterons to produce ^{109}Cd , half life 453 days. The product is carrier free which reduces the size of the generator required to hold the parent.

Alternatively, ^{109}Cd can be produced by neutron capture in ^{108}Cd , abundance 0.9 percent. The low abundance in natural cadmium and lower cross section, 3 barns, make this a less attractive production scheme unless a target is used which is enriched in ^{108}Cd .

In order to compare production in the Argonne cyclotron with purchase from commercial vendors, a thick target was irradiated with deuterons with an integrated current of 10 μAh . The yield was 45.2 μCi for the bombardment, or 4.52 $\mu\text{Ci}/\mu\text{Ah}$. The cost of ^{109}Cd is \$200 per mCi from New England Nuclear, North Billerica, MA. Irradiation time in the ANL cyclotron is \$125/hr, so the cost is \$275 per mCi, assuming the maximum beam current of 100 μA is used. The commercial vendor is cheaper.

If an enriched target of ^{108}Cd was used for production in a reactor, a 100 mg target of 75 percent enriched ^{108}Cd irradiated to saturation (12.5 years) produces 1 Ci of activity, the amount needed to make a useful generator. By contrast, a high current (300 μA) cyclotron produces the same amount of activity in 800 hours.

Obviously, the cost of this type of generator is quite high. The interest in this system is prompted by the parent daughter pair ^{107}Cd - $^{107\text{m}}\text{Ag}$, half lives 6.5 hours and 44.3 seconds, respectively. This generator can be used instead of the ^{109}Cd system since the $^{107\text{m}}\text{Ag}$ decays by the emission of a 93 keV gamma ray, 4.6 percent abundance. Assuming that the cross section for production is the same, deuteron production of ^{107}Cd is 7.5 mCi/ μAh . An 8 hour irradiation produces 6 Ci.

Similarly, studies of the generator production of $^{109\text{m}}\text{Ag}$ can be applied to the ^{109}Pd parent as well as the ^{109}Cd parent. The longer half life of ^{109}Cd makes it easier to use.

A number of systems using both cation and anion exchange were used to test the generators. Yano and Anger (YA68) reported on the use of alumina to adsorb the ^{109}Cd . The best separation was achieved in 2.5% NaI; yield was 32 percent and breakthrough was one part in ten thousand. The low yield made this system unattractive. The eluant was also not physiologically compatible. The short half life of the generator product prevents any manipulation of the eluant.

The distribution coefficients (K_d) for cadmium as a function of iodide concentration on anion exchange resin was measured and is shown in Figure VIII-1. The strongly anionic character of the CdI_4^{--} complex makes

DISTRIBUTION COEFFICIENT

00:55:14 10-15-78

Figure VIII-1

The distribution coefficient for ^{109}Cd is shown as a function of NaI concentration on Bio Rad AG1x8. The high values above 0.05 M NaI are sufficient to keep breakthrough of ^{109}Cd very low.

it an ideal candidate for use in anion exchange columns. This is borne out by the large K_d in concentrations above 0.05 M NaI. The ^{109m}Ag produced by the decay of the ^{109}Cd combines with the iodide to form a neutral complex which elutes from the column.

Column tests of this system proved that premise wrong. The yield was negligible, often little over background. The silver was evidently forming an anionic complex in the presence of such a large excess of iodide and remaining bound to the column.

Similar attempts were made with cation exchange resin. The K_d as a function of chloride concentration was measured as shown in Figure VIII-2. In the concentration range 0.08 M to 0.10 M, the K_d is 300-1000. It was in this range that the generation of ^{109m}Ag vs. breakthrough of ^{109}Cd was optimal. Initially the yield was about 20 percent and breakthrough was about one part in one thousand. The breakthrough rapidly increased as more eluant passed through the column until the activity in the eluant was almost entirely due to ^{109}Cd stripping from the column. Trials with other masking agents for silver also produced negative results. In most cases, the yield was negligible, or the agent itself, such as ammonia, was not physiologically compatible.

Another system which was tested was a column of HDEHP loaded on celite, an inert support (HO75). The

DISTRIBUTION COEFFICIENT

01:03:45 10-15-78

Figure VIII-2

The distribution coefficient of ^{109}Cd is shown as a function of chloride concentration on Bio Rad AG50x12. Elution of $^{109\text{m}}\text{Ag}$ is optimal at 0.1 M NaCl, where the K_d is 300.

K_d for cadmium in 0.0025 N HNO_3 is 2000 and for silver it is 20. The trace of nitrate can be removed by elution through an anion exchange column in the acetate form. This would increase the pH of the eluant and introduce a more physiologically compatible anion.

The trials with this system produced negative results. The ^{109}Cd was initially adsorbed, but elutes more quickly than the K_d of the cadmium indicates. Either impurities in the carrier free ^{109}Cd were at fault, or the kinetics of the column were being exceeded. The results were discouraging in the face of more promising results reported by Horowitz.

The experiments with ^{109}Pd also proved to be discouraging. Since palladium does not easily stay in solution as a cation, the study was confined to ion exchange in anionic systems.

The presence of the carrier palladium naturally increased the generator size needed to contain the activity of the parent. If the system had proved workable, the size can be reduced by the use of 95% enriched ^{108}Pd , which costs \$1.60 per mg. The column size decreases by a factor of four, at a slight increase in cost. A sample irradiated in a flux of 3×10^{13} neutrons/cm² to saturation (6 days) to produce 1 Ci requires only 19 mg of material. Unless breakthrough is very high, this material can be recovered after the ^{109}Cd had decayed.

Previous authors had indicated that palladium was adsorbed on Dowex 1 anion exchange resin from chloride (KR56) and nitrate (BU61) media. Both of these systems were tried.

A 10 mg sample was irradiated in CP-5 at a flux of 3×10^{13} for one hour. The sample was allowed to cool for one hour and the ^{109m}Pd decayed to the ground state. About 5 mCi were made per irradiation.

The irradiated sample was dissolved in hot concentrated nitric acid. The nitrate system was tested using aliquots of the irradiated sample. The chloride sample was made using an aliquot of the irradiated sample which was added to a solution of 10 N HCl.

In both cases, the breakthrough was larger than was expected from K_d data in the literature. Breakthrough ranged from 1 to 10 percent of the eluted activity. This was unacceptably high for a beta emitter.

Recently, a report of a ^{103}Pd - ^{103m}Rh generator was made (MA78). The palladium is isolated from deutron irradiated rhodium and put on a column of Dowex 2 in the chloride form. Elution in 2 N HCl produces 90 percent of the ^{103m}Rh ; radionuclide purity is 99.99%.

Assuming such a generator was developed for use with the ^{109}Pd system, a calculation was performed to estimate patient dose from the breakthrough of the system, 4.7×10^{-5} . Assuming that a 1 Ci generator is used, enough

activity is produced to make the system competitive with a ^{99m}Tc study. Using the relation from Chapter V for dosage of particle emitters, the breakthrough of 47 μCi of ^{109}Pd when injected into the patient produces a dose rate of 34 rads/g-hr. Since this is fairly high, the system requires a much lower breakthrough to insure that the patients are not exposed to unnecessarily high levels of activity.

The system has obvious advantages, but its serious breakthrough problems must be solved before it can be used in humans.

SUMMARY

This research project was undertaken to develop generator systems that produced daughters with short half lives. Of the many systems investigated, the most successful is the ^{52}Fe - $^{52\text{m}}\text{Mn}$ system. The yield is high, 75 percent, and breakthrough is less than one part in ten thousand; often no breakthrough is detected. The generator product can be evaporated and redissolved in a physiologically compatible solution in 5 minutes with minimal decay losses. The parent can be produced in large enough quantities, up to 8 Ci, to limit the disadvantage of its relatively short half life, 8.3 hours.

Animal studies showed that carrier-free radiomanganese can be used directly as a myocardial imaging agent. The concentration of activity in the myocardium is approximately the same as that seen in ^{201}Tl which is currently used for this purpose. The rapid blood clearance makes $^{52\text{m}}\text{Mn}$ ideal for use in exercise studies where the blood flow to the heart is examined under stress.

If the radiomanganese is complexed with a chelating agent, studies of kidney function can be performed. The chelating agent CDTA binds the manganese strongly and is primarily excreted through the kidneys. Manganese

acetate or chloride is excreted through the intestines, so any excretion in the urine is a definite change in biodistribution.

Other radiopharmaceuticals can be made by attaching chelates to proteins in human serum albumin, human serum albumin microspheres or macroaggregates. The manganese can also be made into a colloid for use as a liver scanning agent.

The renewed interest in nuclear medicine techniques in therapy has pointed out the advantages of short-lived particle emitters, particularly alpha emitters. The highly ionizing radiation and short path length of the alpha particles guarantees that the radiation dose will be delivered close to the site of administration.

A system was developed to separate ^{211}Pb from its grandparent ^{223}Ra . Distillation of an intermediate, ^{219}Rn , enables one to cleanly separate the ^{211}Pb from ^{223}Ra . The low yield, 10 percent, can be overcome by using large quantities of ^{223}Ra in the still. The system maintains very good vacuums at liquid temperatures, 5 microns (Hg), for one hour or more, time enough to collect about three-fourths of the theoretical maximum of ^{211}Pb . A physiologically compatible solution can be frozen into the collecting vessel to allow direct administration of the generator product after the solution has been warmed sufficiently.

The recent development of a generator that produces ^{178}Ta will create a need for production of the parent, ^{178}W . The ^{178}W has been produced using 40 MeV protons, but beams of this energy are not readily available. ^{178}W was produced using both ^3He and ^4He beams on thick targets in sufficient quantities, 23.8 $\mu\text{Ci}/\mu\text{Ah}$ at 33 MeV and 64.7 $\mu\text{Ci}/\mu\text{Ah}$ at 44 MeV, respectively, to make its production in medical cyclotrons possible.

Another system that produces an ultrashort-lived daughter, ^{118}Te - ^{118}Sb , has potential for use in studies of phenomena with short lifetimes such as bloodflow in various organs or first pass studies in the heart. ^{118}Te can be produced by ^4He bombardment of natural tin metal targets. The thick target yield at 44 MeV is 33.8 $\mu\text{Ci}/\mu\text{Ah}$.

The computer code Overlaid ALICE was used to determine the predictive powers of the program for radionuclide production. Calculations were compared to experimental results for ^{52}Fe , ^{118}Te and ^{178}W . While quantitative predictions of cross sections were fair, qualitative predictions, i.e., peaks in the excitation function and threshold of reactions, were fairly accurate. This code can be used to determine optimum target thickness, maximum effective bombarding energy and can also be used to assess competing reactions that produce significant radionuclidic contaminants.

Finally, systems that produce $^{109\text{m}}\text{Ag}$ from the parents

^{109}Pd and ^{109}Cd were examined. Both anion and cation exchange resins were used to adsorb the parent activity. In the ^{109}Cd system, yield was too low if the parent is adsorbed on anion exchange resin. The $^{109\text{m}}\text{Ag}$ evidently forms an anionic complex with the large excess of iodide present in these studies. In the cation exchange systems, the tendency of ^{109}Cd to form anionic complexes with those anions used to elute the daughter creates breakthrough problems.

In the systems using ^{109}Pd and anion exchange resin, the high breakthrough poses serious radiation hazards to the patients since the parent is a beta emitter. The low cost of producing the parent in a reactor makes this system attractive for further study.

BIBLIOGRAPHY

- AN64 Anger HO, Van Dyke DC: Science 144, 1587 (1964).
- AT78 Atcher RW, Friedman AM, Huizenga JR et al.:
J. Nucl. Med. 19, 689 (1978).
- BI79 Bingham JB et al.: J. Nucl. Med. 20, (1979).
- BJ57 Bjerrum J, Schwarzenbach G, Sillen LG: Stability
Constants, Part I, Organic Ligands, London, The
Chemical Society, 1957.
- BL76 Blann M, Overlaid ALICE, Report COO-3494-29, 1976.
- BU61 Buchanan RF, Faris JP: Radioisotopes in Physical
Sciences and Industry, Geneva, 1961.
- CA59 Cabell MJ: Can. J. Chem. 37, 1094 (1959).
- CH76 Chauncey DM et al.: Read before the first annual
regional meeting of the Society of Nuclear Medicine,
San Francisco, 1976.
- CH77 Chauncey DM et al.: J. Nucl. Med. 18, 933 (1977).
- DO79 Dolecek EH, private communication.
- DU58 Dummer JE: Los Alamos Handbook of Radiation
Monitoring (LA 1835), 3rd ed., 1958.
- FA60 Faris JP: Anal. Chem. 32, 520 (1960).
- FR64 Friedlander G, Kennedy JW, Miller J: Nuclear and
Radiochemistry, Second Ed., New York, John Wiley &
Sons, 1964.
- GR70 Greene MW et al.: Int. J. Appl. Radiat. Isot. 21,
719 (1970).
- GR78 Grant PM et al.: Proceedings of the Second
International Symposium on Radiopharmaceutical
Chemistry, Oxford, England, 1978.
- GR78a Grant PM et al.: J. Nucl. Med. 19, 1250 (1978).
- HA76 Hagan PL et al.: Read before the first annual
regional meeting of the Society of Nuclear Medicine,
San Francisco, 1976.

- HA78 Hagan PL et al.: J. Nucl. Med. 19, 1055 (1978).
- HN76 Hnatowich DJ et al.: J. Nucl. Med. 17, 57 (1976).
- HN77 Hnatowich DJ et al.: Radiology 123, 189 (1977).
- HO75 Horwitz EP, Bloomquist CA: J. Inorg. Nucl. Chem. 37, 425 (1975).
- HO78 Holman BL et al.: J. Nucl. Med. 19, 510 (1978).
- HO79 Holman BL et al.: Radiology 131, 525 (1979).
- KN76 Knopse WH, et al.: Cancer 37, 1432 (1976).
- KR67 Krause KA, Nelson F: P/837 Proceedings of the International Conference on the Peaceful Uses of Atomic Energy, Geneva, 7, 113 (1956).
- KR77 Krejcarek GE, Tucker KL: Biochem. Biophys. Res. Comm. 77, 581 (1977).
- KU79 Ku TH et al.: J. Nucl. Med. 20, 682 (1979).
- LE78 Lederer CM, Shirley VS: Table of Isotopes, Seventh Edition, New York, John Wiley & Sons, 1978.
- MA55 Maynard LS, Cotzias GC: J. Biol. Chem. 214, 489 (1955).
- MA63 Marjerum DW, Bydalek TJ: Inorg. Chem. 2, 683 (1963).
- MO62 Moskvina LN: Soviet Radiochemistry 4, 452 (1962).
- MU73 Murukami Y et al.: Radiopharmaceuticals and Labelled Compounds, Vienna, IAEA, 1973.
- NE64 Nelson F et al.: J. Chrom. 13, 503 (1964).
- NE78 Neirinckx RD et al.: J. Nucl. Med. 19, 514 (1978).
- OB78 O'Brien HA, private communication, 1978.
- PA77 Pavel DG, Zimmer AM: J. Nucl. Med. 18, 305 (1977).
- PH77 Phelps ME: Seminars in Nucl. Med. 7, 337 (1977).
- PO71 Powsner ER, Raeside DE: Diagnostic Nuclear Medicine, New York, Grune & Stratton, 1971.
- RA73 Rayudu GVS et al.: Int. J. Appl. Radiat. Isot. 24, 451 (1973).

- RI78 Richards P, private communication, 1978.
- SA71 Saha GB, Farrer PA: Int. J. Appl. Radiat. Isot. 22, 495 (1971).
- SE78 Serafini AN, Beaver JE: Medical Cyclotrons in Nuclear Medicine, Basel, S. Karger, 1978, p. 16.
- SE78a ibid, p. 34.
- SM55 Smith GW, Reynolds SA: Anal. Chim. Acta 12, 151 (1955).
- SO74 Sodd VJ et al.: Med. Phys. 1, 25 (1974).
- SO78 Som P, private communication, 1978.
- SP78 Spencer RP: Therapy in Nuclear Medicine, New York, Grune & Stratton, 1978.
- ST67 Strelow FW, Bothma CJ: Anal. Chem. 39, 595 (1967).
- ST72 Strelow FW et al.: Anal. Chem. 44, 2352 (1972).
- SU74 Sundberg MW et al.: J. Med. Chem. 17, 1304 (1974).
- TH71 Thakur ML et al.: Int. J. Appl. Radiat. Isot. 22, 481 (1971).
- WA58 Wahl AC, Daniels WR: J. Inorg. Nucl. Chem. 6, 278 (1958).
- WA77 Wapstra AH, Bos K: Atomic Data and Nuclear Data Tables 19, 215-276 (1977).
- YA65 Yano Y, Anger HO: Int. J. Appl. Radiat. Isot. 16, 153 (1965).
- YA68 Yano Y, Anger HO: J. Nucl. Med. 9, 2 (1968).