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Nuclear Medicine Program Progress Report for Quarter Ending June 30, 1995

F. F. Knapp, Jr.
K. R. Ambrose
A. L. Beets
H. Luo
D. W. McPherson
S. Mirzadeh

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Health Sciences Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING June 30, 1995

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SUMMARY

In this report we describe the first synthesis of the (-)(-) and (-)(+) isomers of 1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate ("FQNPe"). Earlier studies with the racemic FQNPe mixture had demonstrated high *in vitro* binding affinity for the muscarinic-cholinergic receptor and showed that pre-treatment of rats with this new agent significantly blocked receptor localization of subsequently injected [I-131]-Z-(-,-)-IQNP. Because of the potential important use of fluorine-18-labeled analogues for clinical evaluation of changes in muscarinic-cholinergic receptors by positron emission tomography (PET), we have now synthesized the diastereomeric isomers of FQNPe. Multi-gram quantities of ethyl-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate were prepared and then saponified into the racemic α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid mixture. The racemic acid was resolved into (-)- and (+)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid enantiomers by isolation of the (-) salt of (S)-(-)-α-methylbenzylamine and the (+) salt of (R)-(+)-α-methylbenzylamine. The resolved (-)- ($[\alpha]_D$ =-12.1°, c = 5.8, chloroform) and (+)-acetic acids ($[\alpha]_D$ = +11.6°, c = 6.0, chloroform) were fully characterized and then converted to the enantiomeric ethyl-α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetates by a four-step reaction sequence. The (-)- and (+)-ethyl-α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetates were then each transesterified with (-)-quinuclidinol to form the (-)(-) FQNPe and (-)(+) FQNPe diastereomers. These diastereomeric esters will now be evaluated in *in vitro* studies. The availability of the substrates for preparation of the fluorine-18-labeled enantiomers will now allow evaluation of the radiolabeled compounds in animals.

During this period several radioisotopes and generators were also provided to collaborators for several on-going Medical Cooperative Programs, including rhenium-186, provided to RhoMed, Inc., as part of a CRADA. In addition, tungsten-188/rhenium-188 generators were provided to Hospital de Clinica, in Montevideo, Uruguay, and the Radiopharmaceutical Research Group at the Paul Scherrer Institute in Villigen, Switzerland. Two samples of tin-117m were provided to the Medical Department at Brookhaven National Laboratory, for preparation of tin-117m for Phase II patient studies for bone palliation in conjunction with a CRADA between BNL and Diatech, Inc.

Synthesis of (-)(-) and (-)(+) Isomers of FQNPe - A Potential Ligand for Imaging of Muscarinic Cholinergic Receptors by Positron Emission Tomography (PET)

We recently reported the synthesis of the "FQNE" and "FQNPe" fluoroalkyl analogues of QNB (1 in Figure 1) (ORNL/TM-12909). This project, being pursued by Dr. H. Luo, a Distinguished Alexander Hollaender Postdoctoral Fellow working in the Nuclear Medicine Group, is based on our earlier development of "IQNP", in which the iodophenyl ring of IQNB (2) had been replaced with the iodopropenyl moiety (ORNL/TM-12110,-11811, and -11992). The FQNE (5) and FQNPe (6) analogues are based on a similar concept involving the replacement of a phenyl ring with a linear substituent in which fluorine is attached as a terminal fluoroalkyl group (Figure 1). Our initial studies of these new fluoroalkyl analogues in rats involved pre-blocking with racemic FQNE and FQNPe prior to administration of [I-131]-Z-(-,-)-IQNP. The results showed that pretreatment with the racemic fluorinated analogues blocked uptake of the radioiodinated ligand, and also indicated that FQNPe was a better blocking agent than FQNE. In addition, *in vitro* binding studies in conjunction with collaborators at the George Washington University Medical Center (Drs. B. Zeeberg and R. Reba, et al.) demonstrated higher binding affinity of FQNPe compared with FQNE for the cholinergic receptor subtypes. In addition to the more promising *in vivo* blocking and *in vitro* binding studies, results using FQNPe in comparison with FQNE, it was envisioned that fluorine-18 could be more readily incorporated into the five carbon chain-length FQNPe analogue. For these reasons FQNPe was chosen as the target compound for further study. Because of the potential importance of the new FQNPe ligand for imaging of muscarinic ligands by PET, we have now completed the synthesis and characterization of the two major diastereomeric FQNPe esters which are expected to be the major active isomers found in the racemic mixture.

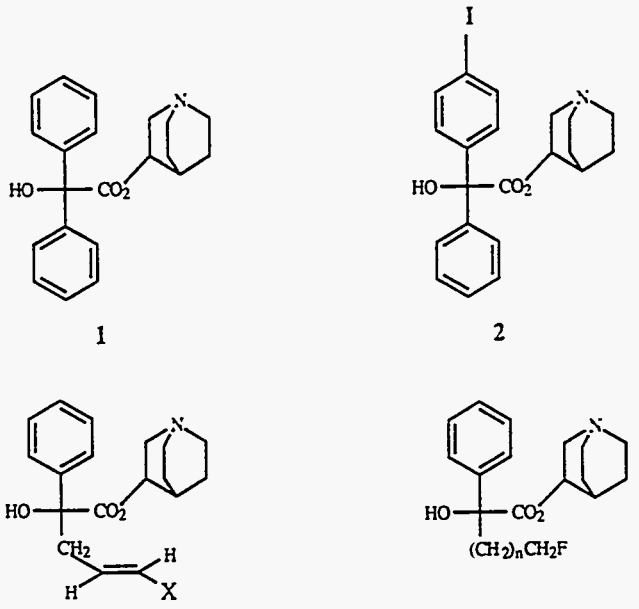

Figure 1. Structures of QNB Analogues

The synthesis of the FQNPe enantiomers is based on our earlier synthesis of the racemic FQNPe mixture (ORNL/TM-12909). Ethyl-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate was synthesized by reaction of ethylbenozylformate with phenylmagnesium bromide. The yield of the Gringard product was low (10-15 %), and attempts to prepare this key intermediate by Reformatsky conditions or other alternative routes have been unsuccessful. The products of several Grignard reactions were therefore pooled and purified by column chromatography to yield 13 grams of the purified racemic ethyl-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate which was converted to the racemic acid by basic hydrolysis. Resolution into the corresponding (-) and (+) acid isomers was accomplished by treatment of the racemic α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid mixture with (S)-(-)-α-methylbenzylamine as had been initially used in our successful resolution of the isomers of IQNP (ORNL/TM-12411). The initial crystals were re-

crystallized from H_2O:C_2H_5OH (7.5:2.5) to provide (-)-(-) diastereomer salt (Table 1). The free acid obtained from the mother liquor by treatment with dilute HCl was then reacted with (R)-(+)-methylbenzylamine to provide the (+)(+) diastereomeric salt which was re-crystallized from H_2O:C_2H_5OH (7.5:2.5)(Table 1). As expected the (-)(-) and (+)(+) diastereomeric salts had similarl rotations of opposite sign (Table 1). The final enantiomers were fully characterized.

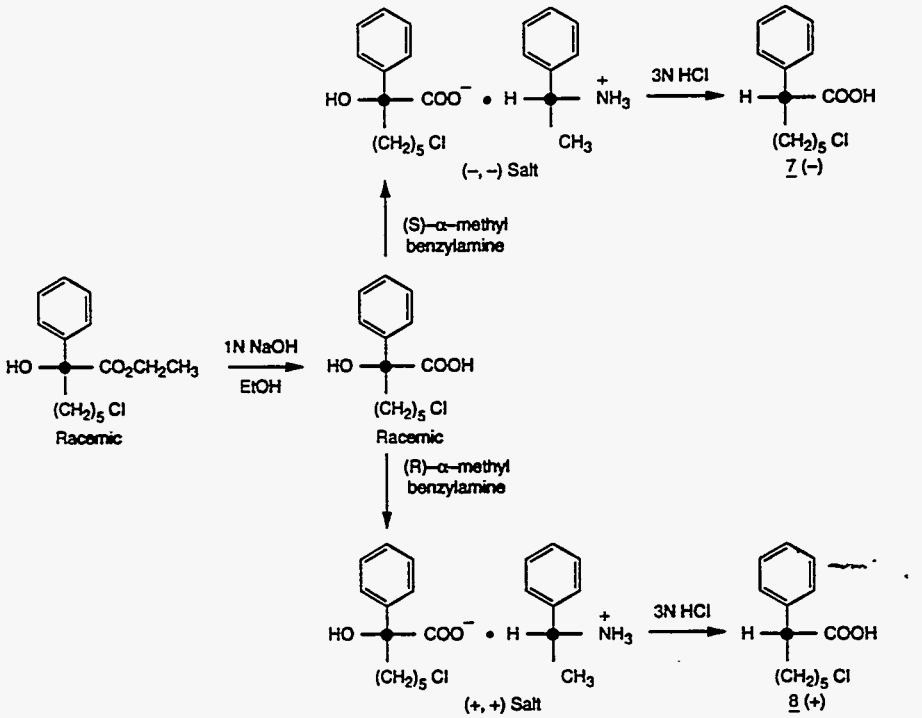

Figure 2. Synthesis of enantiomers of α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid

Analysis of the proton NMR spectra of the (-)(-) and (+)(+) diastereomeric salts provided additional information which could be used to differentiate the configuration of the acetate moiety of the two diastereomeric salts (Figure 3). While the chemical shift of the *ortho* aromatic proton in the ^1H spectrum of the (+)(-) salt exhibited a resonance at 7.51 ppm, this two proton pattern was observed at 7.41 ppm in the spectrum of the (+)(+) salt. This assignment was confirmed by freeing the (+) acid from the (+)(+) salt and forming the (+)(-) salt with the (S)-(-)-α-methylbenzylamine. Similarly, while the chemical shift of the *ortho* aromatic proton in the ^1H spectrum of the (-)(+) salt exhibited a resonance at 7.51 ppm, these two protons

were moved to 7.42 ppm in the spectrum of the (-)(-) salt. This assignment was also confirmed by freeing the (-) acid from the (-)(-) salt and forming the (-)(+) salt with the (R)-(+)-α-methylbenzylamine. The specific rotation values and melting point of these four diastereomeric salts are summerized in Table 1. The configuration at the acetate center as well as an indication of the diastereomeric purity can thus be assessed by examination of the chemical shift of the *ortho* aromatic protons from the benzene ring of the acetic acid moiety in the proton NMR spectra.

Table 1. Specific Rotation* ($[\alpha]_D$) and Melting Point of Four Diastereomeric Salts

Diastereomeric Salts	$[\alpha]_D$ (°)	c gm/ml	MP (°)
(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (S)-(-)-α-methylbenzylamine salt	-7.27	1.10	155-156
(+)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (R)-(+)-α-methylbenzylamine salt	+6.06	1.15	155
(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (R)-(+)-α-methylbenzylamine salt	-11.15	1.44	112-113
(+)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (S)-(-)-α-methylbenzylamine salt	+11.30	1.51	116-117

* All samples were dissolved in chloroform

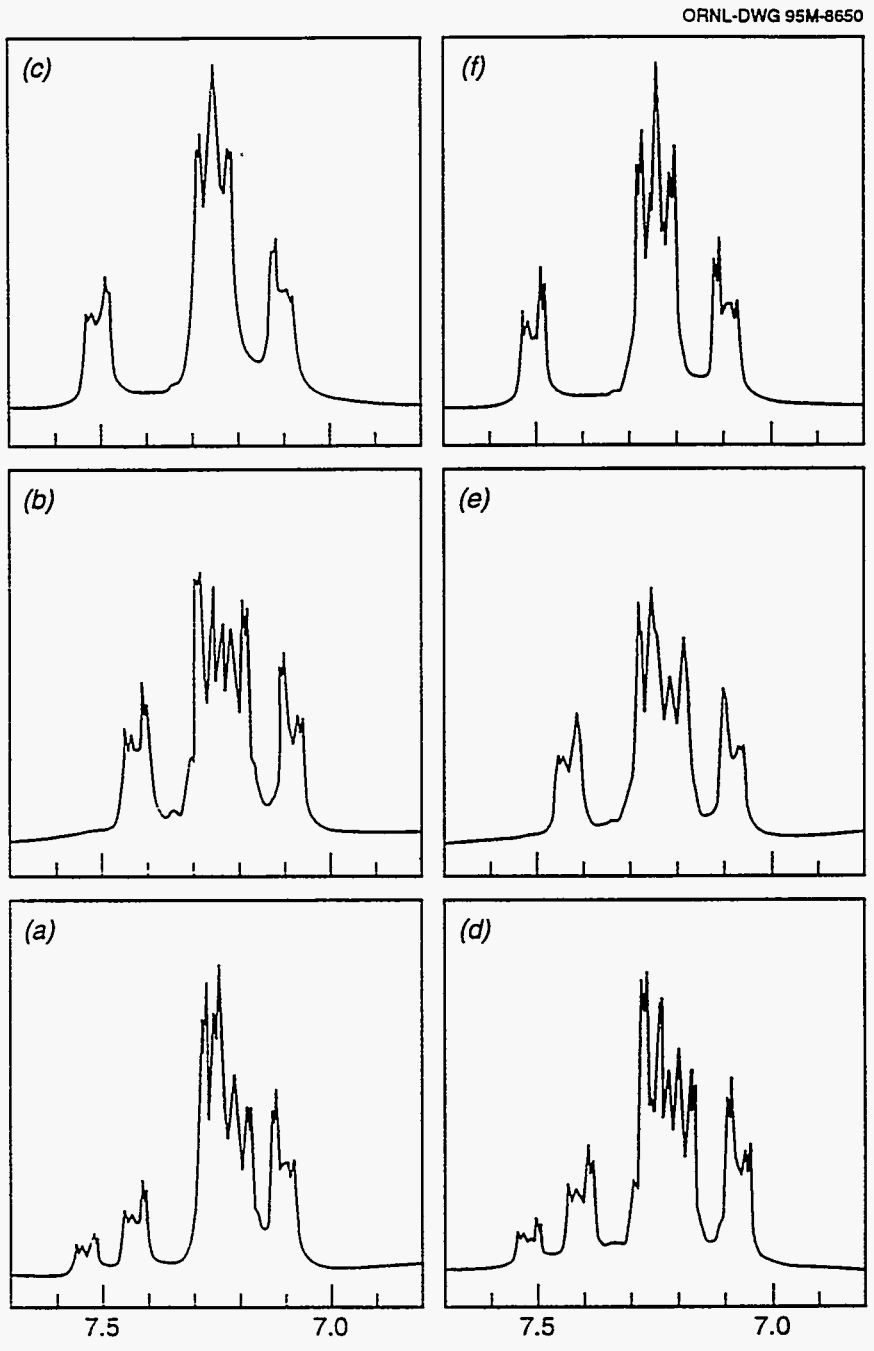

Figure 3. Selected downfield regions of the proton NMR spectra of initial impure (-)(-)- salt (a), purified (-)(-) salt (b), (+)(-) salt (c), initial impure (+)(+) salt (d), purified (+)(+) salt (e), and (-)(+) salt (f).

The two enantiomeric acetic acid moieties were then released from the diastereomeric salts to provide the (+)- and (-)- α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid isomers, which were each converted to the corresponding ethyl α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate enantiomers (9 & 10 in Figure 4) by esterification in ethanol. The stepwise treatment of 9 and 10 with sodium iodide, silver p-toluenesulfonate, and tetrabutylammonium fluoride afforded the desired fluorinated ethyl α-hydroxyester enantiomers (11 & 12). The proposed structures of each intermediate were confirmed by NMR (see Table 2). The final step in the preparation of the (-)(-)- and (-)(+)-1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate isomers [(-)(-)- and (-)(+)-"FQNPe"] involved transesterification with (-)-quidnuclidinol. The racemic quinuclidinol was resolved into (+) and (-)-3-quinuclidinol isomers as described earlier by treatment with tartaric acid (ORNL/TM-12909). Synthesis of the diastereomeric quinuclidinol esters was then accomplished as shown in Figure 4. Both diastereomeric quidnuclidinol esters have been fully characterized, and all data are consistent with the proposed structures.

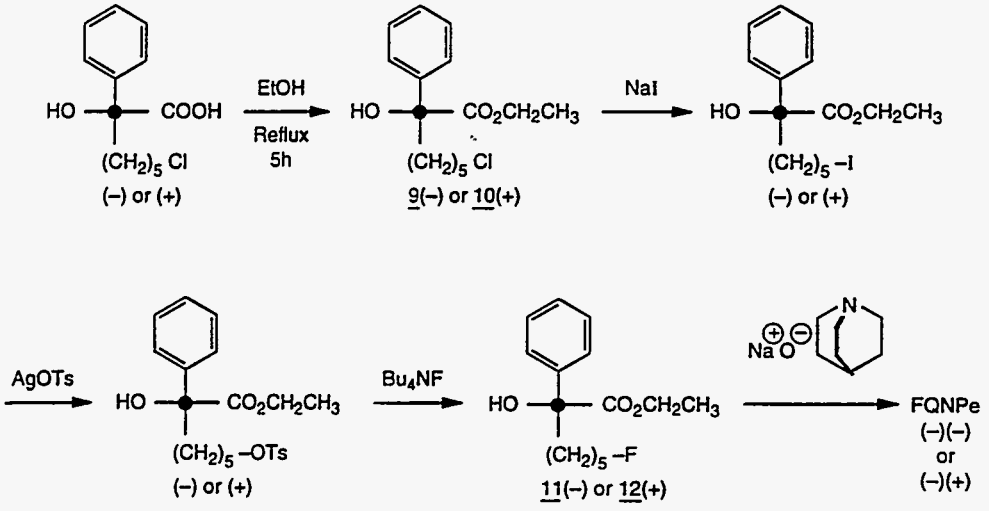

Figure 4.Synthesis of (-)(-)- and (-)(+)-diastereomers of 1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate [(-)(-)- and (-)(+)-("FQNPe"]

Table 2. Specific Rotation Values for intermediators and FQNPe Diastereomers*

Compound		$[\alpha]_D$ (°)	c 10mg/ml
(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid	(-)	-12.1	5.80
	(+)	+11.6	6.05
ethyl-(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-17.4	8.06
	(+)	+19.3	9.31
ethyl-(-)-α-(1-iodopent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-14.1	11.30
	(+)	+15.5	9.66
ethyl-(-)-α-(1-tosyloxypent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-12.0	8.30
	(+)	+12.2	6.56
ethyl-(-)-α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-23.7	1.31
	(+)	+23.7	1.14
(-)(-)-1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate, (-)(-)-FQNPe	(-)	-11.72	1.28
(-) (+)-FQNPe	(+)	+24.14	1.16

* All samples were dissolved in chloroform

HFIR Production of Molybdenum-99

Because the fission route produces high levels of radioactive waste, there are distinct long-term advantages for the routine production of ^{99}Mo via neutron capture by an enriched ^{98}Mo target. For fabrication of $^{99}Mo/^{99m}Tc$ generators, the principal issue which differentiates fission-produced ^{99}Mo from the direct neutron capture route is specific activity. The specific activity of ^{99}Mo attainable at HFIR via neutron capture reaction are summarized in Table 2. These data indicate that specific activities of 50-100 mCi/mg of ^{98}Mo can be reached within 3 days of irradiation in the hydraulic tube of the HFIR.

Although molybdenum-99 used in the United States is produced in Canada from fission of uranium, there are distinct long-term advantages for routine production of molybdenum-99 by neutron activation of enriched molybdenum-98 targets. For fabrication of molybdenum-99/technetium-99m generators, the principal issue which differentiates fission-produced Mo-99 from neutron-activated production of molybdenum-99 is specific activity. Since the fission route produces high levels of radioactive waste, the preferred route for molybdenum-99 production would be expected to be neutron-activation, if sufficient specific activity could be attained. With its very high neutron flux, the HFIR offers an opportunity for routine production of molybdenum-99 by neutron activation with high enough specific activity for generator fabrication. Experimental production yields are summarized in Table 3. A comparison of the experimental and theoretical data is shown in Figure 5. Theoretical calculations were performed for position 5 of the HT with thermal neutron flux of 2.0×10^{15} $n.s^{-1}.cm^{-2}$ and thermal-to-epithermal ratio of 25. Contributions from burn-up of ^{99}Mo and depletion of ^{98}Mo were included in the computation. For sake of comparison, the experimental yields were adjusted to represent the yields expected for position 5 of the HT.

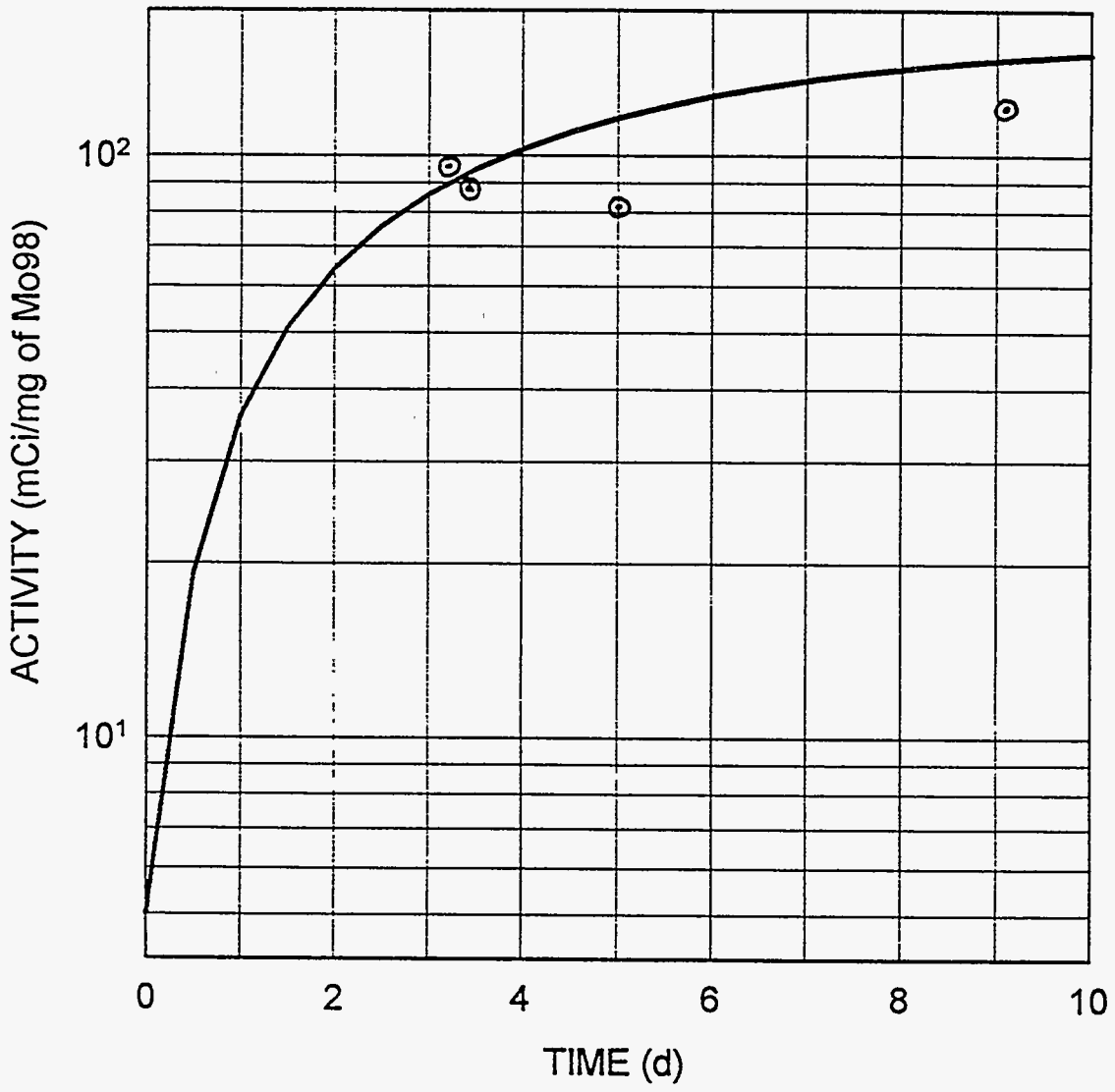

Figure 5. Comparison of experimental values (data points) and the theorectical curve for HFIR production of molybdenum-99 from irradiation of molybdenum-98. Experimental values are extrapolated to position number 5.

Table 3. Summary of HFIR Production of ^{99}Mo [a]

Expt. No.	^{98}Mo Target as MoO_3 Mass (mg)	Enrich. (at. %)	HT Level	T_{irr}	Yield at EOB ($mCi.mg^{-1}$) Exp.	Exp./Theo.
1	11.5	98.5	(2)	9.1d	$6.58x10^{1}$	0.90
2	11.5	97.6	(8)	5.0 d	$5.30x10^{1}$	0.71
3	9.6	97.3	(8)	3.2 d	$6.23x10^{1}$	1.10
4	7.3	97.3	(4)	3.3 d	$7.88x10^{1}$	0.97

[a] Reactor power level = 98 MWt

Literature Cited

1. Luo, H., et al, Nucl. Med. Biol, *in press.*

Other Nuclear Medicine Group Activities

Publications

Knapp, F. F. Jr. and Kropp, J. "Iodine-123-Labeled Fatty Acids for Myocardial Single-Photon Emission Tomography: Current Status and Future Perspectives, "*Invited Review*, Eur. J., Nucl. Med., 22, 361-381 (1995).

Knapp, F. F. Jr., "Mycardial Metabolish of BMIPP," *Invited Editorial*, J. Nucl. Med., 36, 1051-1054 (1995).

Knapp, F. F. Jr., Franken, P. and Kropp, J., Cardiac SPECT with Iodine-123-Labeled Fatty Acids - Evaluation of Myocardial Viability with BMIPP," *Clinical Commentary*, J. Nucl. Med., 36, 1022-1030 (1995).

Presentations

Dr. F. F. Knapp, Jr., Group Leader of the ORNL Nuclear Medicine Program, presented *Invited Lecture* at the special symposium on "Basic and Clinical Findings with Iodine-123-BMIPP", hosted by Nihon Medi-Physics, Inc. in conjunction with the Second International Symposium of Nuclear Cardiology, held in Cannes, France on April 22-28, 1995. On May 7-12, 1995, he presented a lecture on reactor-produced medical radioisotopes for therapeutic applications at the "International Conference on Isotopes," held in Beijing, China, and also served as co-chairman for the Radiopharmaceutical Session. In addition, during this period he presented invited lectures at the clinic for Nuclear Medicine at the medical university in Shanghai, and at the Institute for Nuclear Research, presented an Invited Lecture on the ORNL development and

evaluation of new radiopharmaceuticals for evaluating muscarinic-cholinergic receptors, at the Fifth Meditteranean Symposium on Nuclear Medicine and Radiopharmaceuticals, held in Athens, Greece, on May 22-28, 1995.

Dr. D. W. McPherson, a staff member of the ORNL Nuclear Medicine Program who worked as a Guest Scientist at the Clinic for Nuclear Medicine in Ulm, Germany during the June 1994- June 1995 period, presented a lecture on the development of new radiohalogenated legands for imaging muscarinic-cholinergic receptors on March 29, 1995, at the Department of Imaging Research in Pharmacology and Physiology, at the Hospital Frederic Joliot, of the French Atomic Energy Agency in Orsay, France.

Medical Cooperative Shipments

During this period several HFIR-produced radioisotopes and radioisotopes generator systems were provided to collaborators. Samples of tin-117m were provided to the Medical Department at the Brookhaven National Laboratory on April 18 (600 mCi) and May 9 (400 mCi) for preparation and patient use of Sn-117m-DTPA for palliative treatment of bone pain. On April 27, 100 mCi of rhenium-186 perrhenate solution was provided to RhoMed, Inc., for peptide radiolabeling through a DOE-supported Cooperative Research and Development Agreement (CRADA). Tungsten-188/rhenium-188 generators were provided for collaborative research projects to the Paul Scherrer Institute in Villigen, Switzerland (A. Schubiger, Ph.D.) to provide carrier-free rhenium-188 for labeling new ligands with Re(I) and to the University Hospital in Montevideo, Uruguay (Gaudiano, M.D.) for optimization of phosphonate radiolabeling in anticipation of initiation of clinical trials for bone palliation.

Visitors and Guest Assignments

Several visiting scientists and students joined the Nuclear Medicine Program during this period. Joachim Kropp, M.D., who has collaborated with the ORNL Nuclear Medicine Program since 1986, visited for one week beginning June 5, to complete several manuscripts and protocols for on-going collaborative studies. On May 1, Ekaterina Dadachova, Ph.D., a radiochemist from the Australian National Science and Technology Organization (ANSTO), joined the ORNL Nuclear Medicine Program for six months to work on joint collaborative projects. On May 29, Qun Lin, Associate Professor at Xavier University in New Orleans, Louisiana, began working for a three month period on the synthesis of radiopharmaceutical substrates. Students who joined the program for the summer included Jason McAllister (Duke University), Donald Marsh (University of Tennessee) and Pedro Rivera Matos (University of Puerto Rico). In addition, visitors included Elena S. Kalevich, Prof. Yeugeny A. Karelin, and Dr. Rostislav A. Kuznetzoo from the research reactor in Ulyanovsh, Russia.

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