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**Nuclear Medicine Program Progress
Report for Quarter Ending
September 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 September 30, 1995

F. F. Knapp, Jr.

K. R. Ambrose
A. L. Beets
H. Luo

D. W. McPherson
S. Mirzadeh

Work sponsored by
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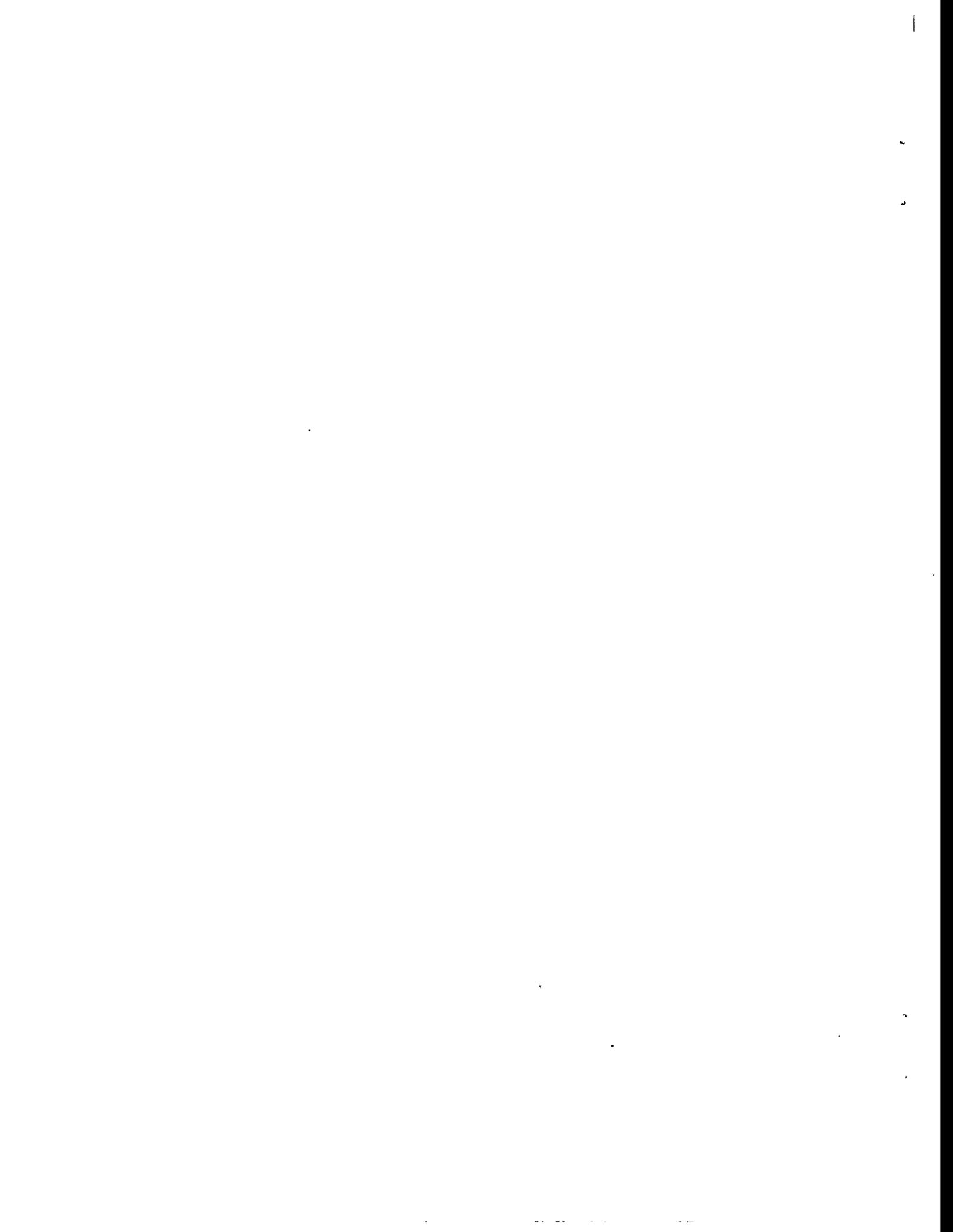
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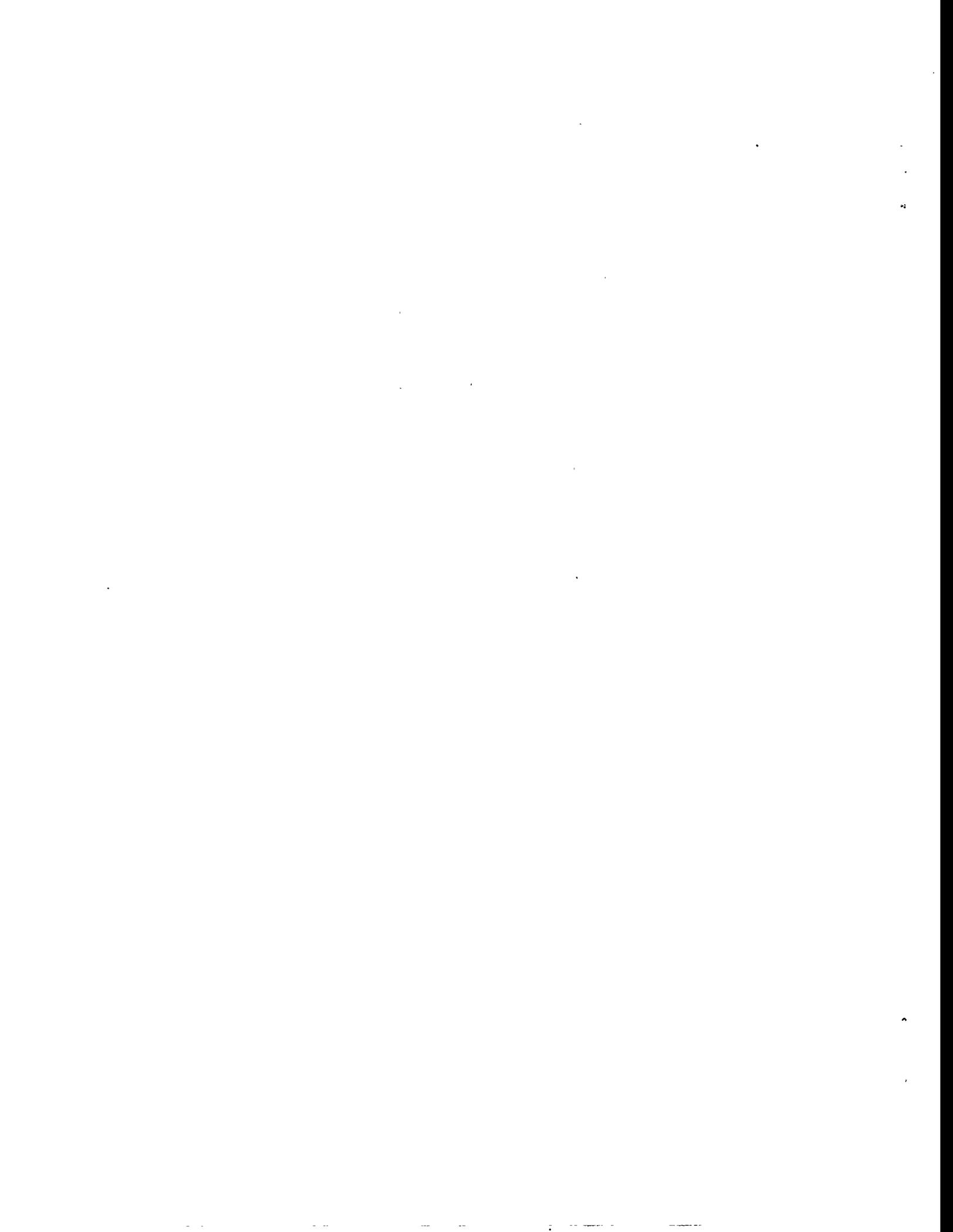
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SUMMARY

In this report, we describe the results for study of the production of lutetium-177 (^{177}Lu) in the High Flux Isotope Reactor (HFIR). Two pathways for production of ^{177}Lu were studied which involved both direct neutron capture on enriched ^{176}Lu , $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$, reaction and by decay of ytterbium-177 (^{177}Yb) produced by the $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb}$ (β^-) reaction. Although the direct route is more straight forward and does not involve any separation steps, the indirect method via β^- -decay of ^{177}Yb has the advantage of providing carrier-free ^{177}Lu , which would be required for antibody radiolabeling and other applications where very high specific activity is required..

Substrates required for preparation of tissue-specific agents and several radioisotopes were also provided during this period through several Medical Cooperative Programs. These include the substrate for preparation of the "BMIPP" cardiac imaging which was developed in the ORNL Nuclear Medicine Program, which was provided to Dr. A. Giodarno, M.D. and colleagues at the Catholic University Hospital in Rome, Italy. Tungsten-188 produced in the ORNL HFIR was also provided to the Catholic University Hospital for fabrication of a tungsten-188/rhenium-188 generator to provide carrier-free rhenium-188 which will be used for preparation of rhenium-188-labeled methylenediphosphonate (MDP) for initial clinical evaluation for palliative treatment of bone pain (L. Troncone, M.D.). Samples of substrates for preparation of the new ORNL "IQNP" agent for imaging of muscarinic-cholinergic receptors were provided to the Karolinska Institute in Stockholm, Sweden, for preparation of radioiodinated IQNP for initial imaging studies with this new agent in monkeys and for tissue binding studies with human brain samples obtained from autopsy (C. Halldin, Ph.D.).

Evaluation of the Production of Lutetium-177 in the Oak Ridge High Flux Isotope Reactor (HFIR)

Lutetium-177g (^{177g}Lu) can be utilized for radiotherapeutic applications when chelated to tumor-associated antibodies for radioimmunotherapy. It has also been proposed as radioisotope source in brachytherapy. Lutetium-177g decays with a half-life of 6.7 d to the ground state of stable hafnium-177 (^{177}Hf) 78% of the time ($E_{\beta_1}^{\text{max}}=0.497$ MeV), to the first excited state 9.7% of the time ($E_{\beta_2}^{\text{max}}=0.384$ MeV), and to the 0.321 MeV level 12% of the time ($E_{\beta_3}^{\text{max}}=0.176$ MeV). Relevant nuclear data for ^{177g}Lu and ^{177m}Lu are summarized in Tables 1 and 2 [1,2] and a simplified decay scheme for ^{177g}Lu is shown in Figure 1. As seen de-excitation from the first excited state level (0.1129 MeV) provides a γ -ray for imaging which has an energy of 113 keV and an intensity of 6.6%. About 12% of this transition converts at the electronic shell of the Hf providing low range secondary electrons and X-rays (Table 2). The de-excitation from the 0.321 MeV level to the first excited state level provides a γ -ray at 208 keV (12%) which may be suitable for deep-organ imaging. The average β^- energy of ^{177g}Lu is 0.133 MeV and the average equilibrium dose rate constant for ^{177g}Lu is estimated to be ~ 0.5 g-rad/ $\mu\text{Ci-h}$, which is similar to that for ^{67}Cu (Table 1) [3].

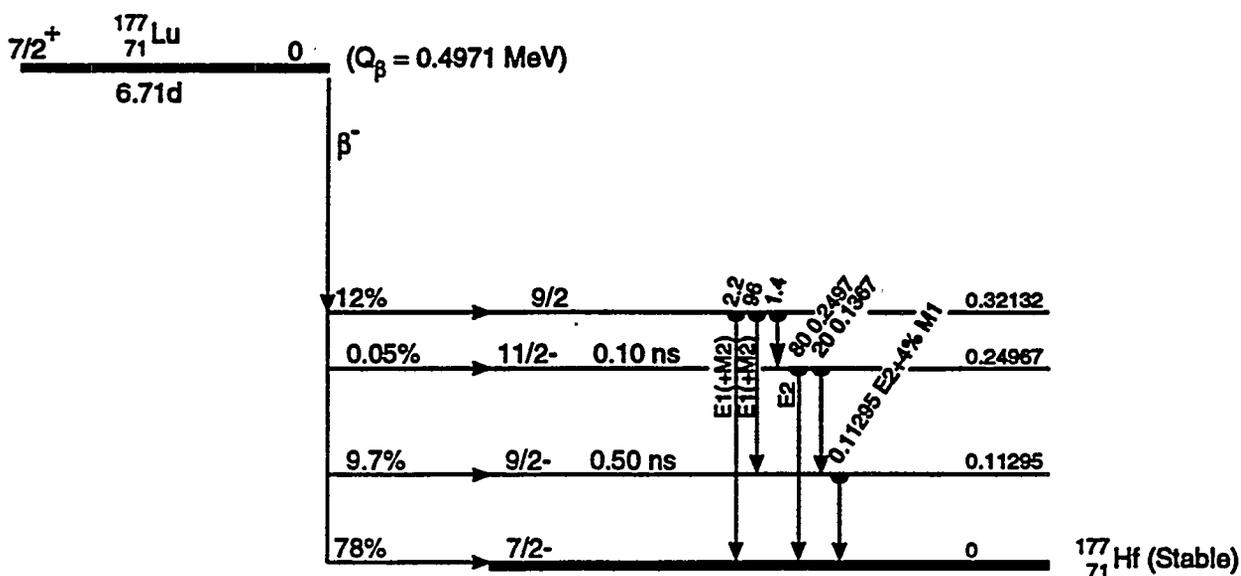


Figure 1. A simplified decay scheme of ^{177g}Lu

Table 1. Nuclear data for $^{177\text{g}}\text{Lu}$ and $^{177\text{m}}\text{Lu}$

Radio-nuclide	$t_{1/2}$	E_{β}^{av} (keV)	$E_{\gamma}(I_{\gamma})$ (keV)(%)	Mode of Production	Reaction Cross-sections ^a				
					Th.	I_0	Production	Burn-up Th. I_0	
$^{177\text{g}}\text{Lu}$	6.71 d	133	113(6.6)	$^{176}\text{Lu}[n,\gamma]$	2090	1087	200	400	
			208(11)	$^{176}\text{Yb}[n,\gamma]$	2.85	6.3			
$^{177\text{m}}\text{Lu}$	160 d	IT (22%) β^- (78%) < β^- >32	many low	$^{176}\text{Lu}[n,\gamma]$					
			113(21.5)	$^{176}\text{Lu}[n,\gamma]$	2.8	4.7	100	200	
			208(61.2)						
			228(36.6)						
			379(29.9)						

^aTh=thermal, I_0 =resonance integral

Table 2. Gamma-rays, K X-rays and K & L Converted Electrons In the Decay of $^{177g}\text{Lu}^a$

$E_{X,\gamma}$ (KeV)	$I_{X,\gamma}$ (%)		transition or multipolarity	e_K (%)	e_L (%)			e_{K+L} (%)
	Rel.	Abs.			L ₁	L ₂	L ₃	
52.965	57.0	1.68	Hf K _{α2} X-ray ^b	1.44x10 ⁻¹	-	-	-	-
54.070	100	2.94	Hf K _{α1} X-ray	5.14	5.77x10 ⁻¹	3.49	3.04	12.25
61.2	33.1	0.98	Hf K _{β1'} X-ray	2.79x10 ⁻²	4.57x10 ⁻³	1.93x10 ⁻²	1.72x10 ⁻²	1.11
63.0	8.6	0.25	Hf K _{β2'} X-ray	5.06x10 ⁻¹	6.93x10 ⁻²	1.21x10 ⁻²	1.11x10 ⁻²	6.0x10 ⁻¹
71.6	2.4	0.16	E1+0.03%M2	1.44x10 ⁻¹	-	-	-	-
113.0	100	6.6	E2+4%M1	5.14	5.77x10 ⁻¹	3.49	3.04	12.25
136.7	0.92	0.057	E2+10%M1	2.79x10 ⁻²	4.57x10 ⁻³	1.93x10 ⁻²	1.72x10 ⁻²	1.11
208.4	167	11.0	E1+0.5%M2	5.06x10 ⁻¹	6.93x10 ⁻²	1.21x10 ⁻²	1.11x10 ⁻²	6.0x10 ⁻¹
250.0	3.02	0.21	E2+10%M1	2.22x10 ⁻²	-	-	-	-
321.4	3.6	0.22	E1+2.8%M2	2.24x10 ⁻²	3.77x10 ⁻³	7.64x10 ⁻⁴	7.64x10 ⁻⁵	-
2.70x10 ⁻²								
Total				5.84	6.54x10 ⁻¹	3.52	3.07	13.99

a) Ref. 1,2, b) For description of the notation see Ref. 1, Appendix 12.

Because of the rather longer half-life, ^{177g}Lu is most suited for the radiolabeling of antibodies which have slow targeting kinetics, and a lower equilibrium dose rate constant makes ^{177g}Lu useful for radiotherapy of soft tissues. In addition, ^{177g}Lu has chemical characteristics suitable for protein labelling with bifunctional chelating agents such as the eight coordinate DTPA, other DTPA derivatives or DOTA. Lutetium is the heaviest member of the lanthenides but has an ionic radius comparable to Y^{3+} as the result of the "lanthenide contraction." In coordination number 6, the ionic radius of Lu^{3+} is 89.1 pm, which is about 4 pm smaller than that of Y^{3+} . At 25 °C and 0.1 M ionic strength, the equilibrium constant of the Lu^{3+} -DTPA complex (ML/M.L) is $2.51 \times 10^{22} \text{ M}^{-1}$, in comparison with $1.12 \times 10^{22} \text{ M}^{-1}$ for the Y-DTPA complex [4].

Due to a rather large cross-section ($\sigma_{\text{th}} = 2090 \text{ b}$, $I_0 = 1087 \text{ b}$), high specific activity ^{177g}Lu can be obtained directly by the $^{176g}\text{Lu}[n,\gamma]^{177}\text{Lu}$ reaction (see Figure 2). The natural abundance of ^{176}Lu is only 2.6%, however, and the highest enrichment available from the ORNL Isotopes Distribution Office (IDO) is 72% at a cost of \$ 220.95/mg. Alternatively, ^{177g}Lu can be obtained indirectly from β^- decay of ^{177}Yb ($t_{1/2} = 1.9 \text{ h}$, $E_{\beta}^{\text{max}} = 400 \text{ keV}$), as described earlier.

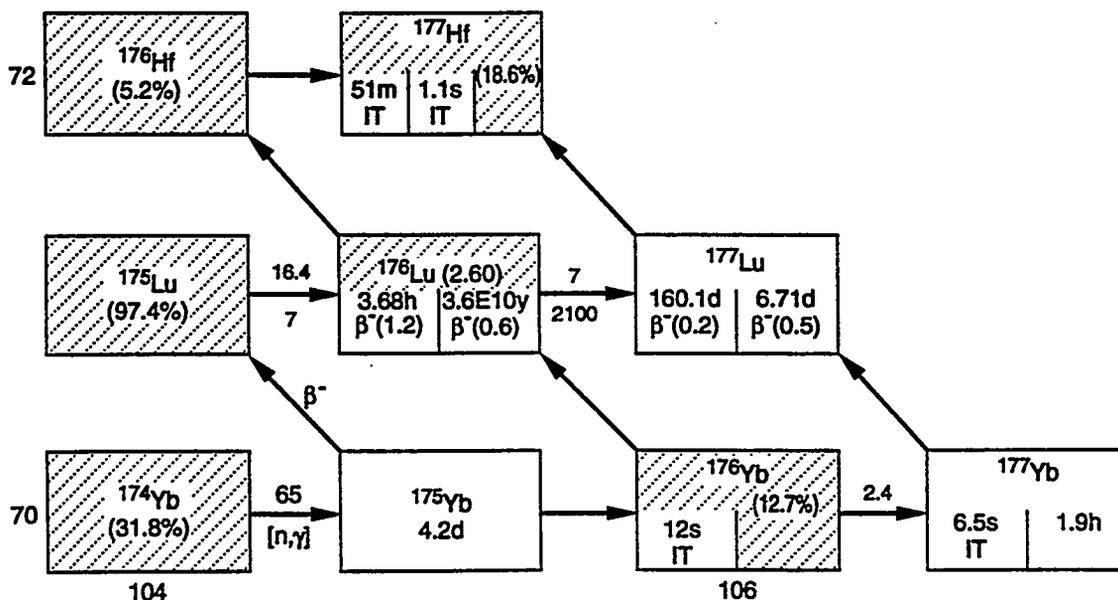


Figure 2. Scheme for Production of ^{177g}Lu

In this case, the ^{177}Yb parent nuclei is produced in a fission nuclear reactor with neutron capture on ^{176}Yb which has a natural abundance of 12.7%. Ytterbium-176 enriched to 97.79% is also available from the IDO at a cost of \$ 17.40/mg. Obviously, the indirect route yielding carrier-free ^{177g}Lu is the desired production route if Lu can be separated efficiently from the Yb target material. We have recently reported similar separation of carrier-free holmium-166 (^{166}Ho) from milligram quantities of dysprosium (Dy). In certain applications, such as protein labelling, the use of a high specific activity radioisotopes is often essential. In addition, the indirect route produces ^{177}Lu which is free from the 160-d ^{177m}Lu . This radioisotope is unavoidably co-produced with ^{177}Lu by the $^{176}\text{Lu}[n,\gamma]^{177m}\text{Lu}$ reaction.

For a one-hour irradiation of two natural Lu targets (as Lu_2O_3 , see Table 3 for composition) in position #4 of the HFIR, the experimental yield of ^{177}Lu is $(2.44 \pm 0.20) \times 10^3$ MBq/mg of Lu, corresponding to a value of $(9.42 \pm 0.99) \times 10^4$ MBq/mg of ^{176}Lu . The ratio of the $^{177m}\text{Lu}/^{177g}\text{Lu}$ in this case is $4.8 \times 10^{-3}\%$. Under similar conditions, the yields from two 43% enriched ^{176}Lu targets were $(4.18 \pm 0.59) \times 10^4$ MBq/mg of Lu and $(9.46 \pm 1.29) \times 10^4$ MBq/mg of ^{176}Lu with a $^{177m}\text{Lu}/^{177g}\text{Lu}$ ratio of $4.6 \times 10^{-3}\%$. The averaged yield from natural and 43% enriched target was $(9.44 \pm 0.78) \times 10^4$ MBq/mg of ^{176}Lu in comparison to the theoretical yield of 5.69×10^4 MBq/mg of ^{176}Lu for a $Y_{\text{Exp.}}/Y_{\text{Theo.}}$ of 1.66. The theoretical yield of ^{177g}Lu as a function of the irradiation time is shown in Figure 3. From these data it is clear that saturation will be reached within 4 days in HT#4 or #6 with an expected yield of $\sim 3 \times 10^6$ MBq (~ 80 Ci) per mg of ^{176}Lu . Since the $^{177m}\text{Lu}/^{177g}\text{Lu}$ ratio will increase with the irradiation time (Figure 4), for a 4-d irradiation the fraction of ^{177m}Lu at the end of irradiation (EOI) is expected to be less than 0.01% for a 4-d irradiation period.

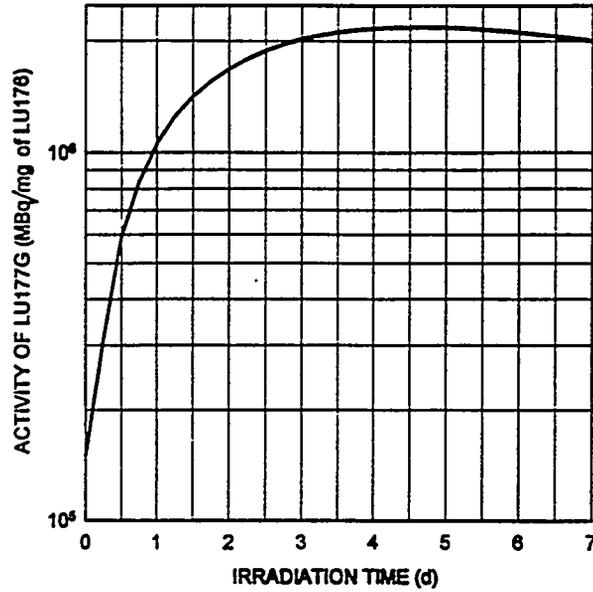


Figure 3. Direct production of ^{177g}Lu - theoretical yield of ^{177g}Lu as a function of the irradiation time. HT#4 or 6, $\phi_{\text{th}} = 1.76 \times 10^{15}$, n.s.⁻¹.cm⁻², th/epi=26.

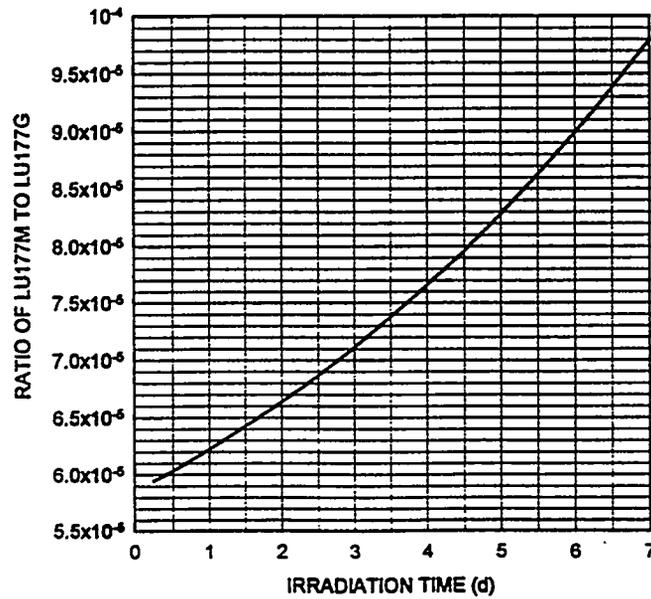


Figure 4. The ratio of ^{177m}Lu to ^{177g}Lu as a function of irradiation time at the HT#4 or 6. $\phi_{\text{th}} = 1.76 \times 10^{15}$, n.s.⁻¹.cm⁻², th/epi=26.

As indicated in Table 3, the yield from the indirect route (from decay of ^{177}Yb) is $(7.46 \pm 0.50) \times 10^1$ MBq/mg of ^{176}Yb (2.0 mCi/mg of ^{176}Yb) for a 1 h irradiation in HT#5. This experimental yield is $\sim 20\%$ lower than the theoretical value using calculations which allow for a 12-h decay period post irradiation. The activity of ^{177g}Lu in the irradiated Yb target decayed by a factor of more than thousand fold with a half life of 6.7 d, results in an estimated value for the $^{177m}\text{Lu}/^{177g}\text{Lu}$ ratio of $\leq (1.0 \pm 0.5) \times 10^{-4} \%$. The theoretical yields of both ^{177}Yb and ^{177g}Lu as a function of time are shown in Figure 5. In this case, the yield of ^{177g}Lu will reach a saturation value of $\sim 1.5 \times 10^4$ MBq (411 mCi)/mg of ^{176}Yb within 21 days of irradiation in HT#5. A 3D graph showing the theoretical yields of ^{177g}Lu as a function of the irradiation time and total time (sum of the irradiation time and post-EOI decay period) is depicted in Figure 6. As seen, the post-EOI contribution from the decay of ^{177}Yb to the total activity of ^{177g}Lu decrease rapidly as a function of irradiation time. As shown in Figure 7, this contribution becomes negligible ($< 1\%$) for irradiation time of more than 20 hours. Although the yield of the indirect route is lower than the direct route by a factor of 1000, the specific activity of ^{177}Lu from both routes will be almost the same assuming carrier-free Lu can be separated from Yb in 1 part per thousand. Studies are currently in progress to evaluate various ion exchange methods for the separation of carrier-free ^{177}Lu from carrier ^{176}Yb .

Table 3. Summary of HFIR Production of ^{177g}Lu

No.	Target			^{177g}Lu Yield at EOB		^{177m}Lu fraction at EOB (%)
	Mass (mg)	Enrich. (at.%)	Chem. Form	HT Level	MBq.mg ⁻¹ of Lu	
1A	9.1	(Nat., 2.6%)	Lu_2O_3	(4)	$(2.24 \pm 0.26) \times 10^3$	
1B	4.8	(Nat., 2.6%)	Lu_2O_3	(4)	$(2.64 \pm 0.44) \times 10^3$	
				Av.	$(2.44 \pm 0.20) \times 10^3$	4.8×10^{-3}
2A	0.70	44.23	$^{176}\text{Lu}_2\text{O}_3$	(6)	$(3.60 \pm 0.15) \times 10^4$	
2B	0.5	44.23	$^{176}\text{Lu}_2\text{O}_3$	(6)	$(4.77 \pm 0.53) \times 10^4$	
				Av.	$(4.18 \pm 0.59) \times 10^4$	4.6×10^{-3}
				Grand Av.	$(9.46 \pm 1.29) \times 10^4$	$(4.7 \pm 0.4) \times 10^{-3}$
				$Y_{\text{Exp.}}/Y_{\text{Theo.}}$	1.66	
3A	5.0	96.43	$^{176}\text{Yb}_2\text{O}_3$	(5)	$(7.13 \pm 0.77) \times 10^1$	
3B	3.8	96.43	$^{176}\text{Yb}_2\text{O}_3$	(5)	$(7.26 \pm 0.57) \times 10^1$	
				Av.	$(7.19 \pm 0.48) \times 10^1$	$(1.0 \pm 0.5) \times 10^{-4}$
				$Y_{\text{Exp.}}/Y_{\text{Theo.}}$ ^b	0.79	

^aReactor power level = 85 MWt, Irradiation time=1 h. ^bAllowed a 12-h post EOB decay

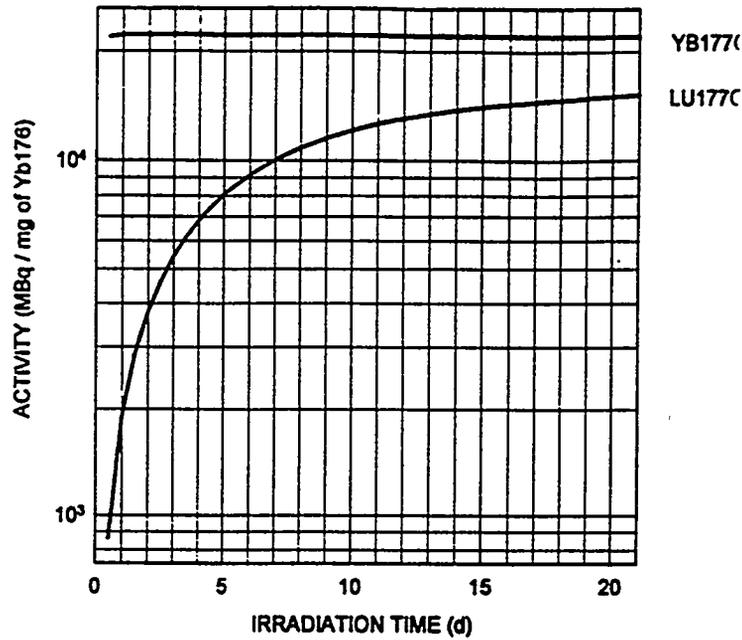


Figure 5. Indirect production of ^{177g}Lu - theoretical yields of ^{177}Yb and ^{177g}Lu as a function of irradiation time. HR#5, $\phi_{\text{th}}=2.05 \times 10^{15}$, $\text{n.s.}^{-1} \cdot \text{cm}^{-2}$, $\text{th/epi}=20$.

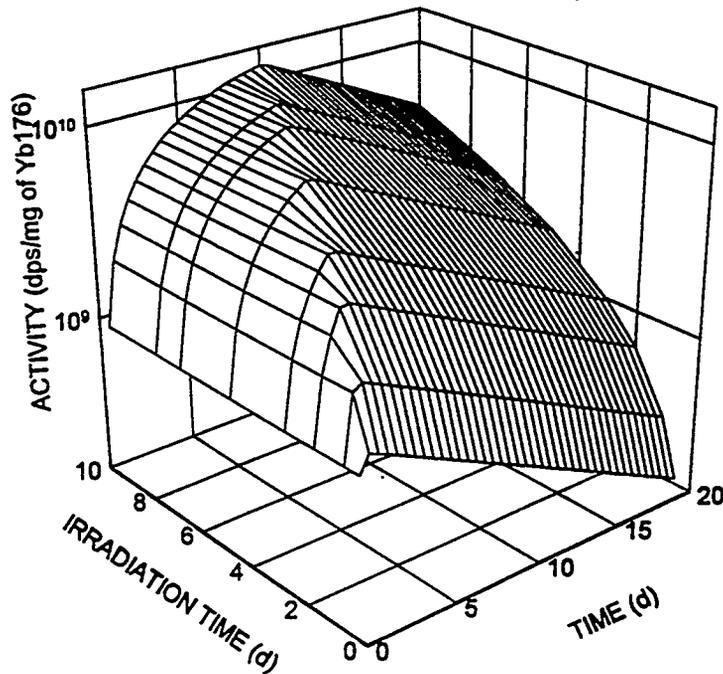


Figure 6. Indirect production of ^{177g}Lu - a 3D graph of the theoretical yield of ^{177g}Lu as a function of the irradiation time and total time.

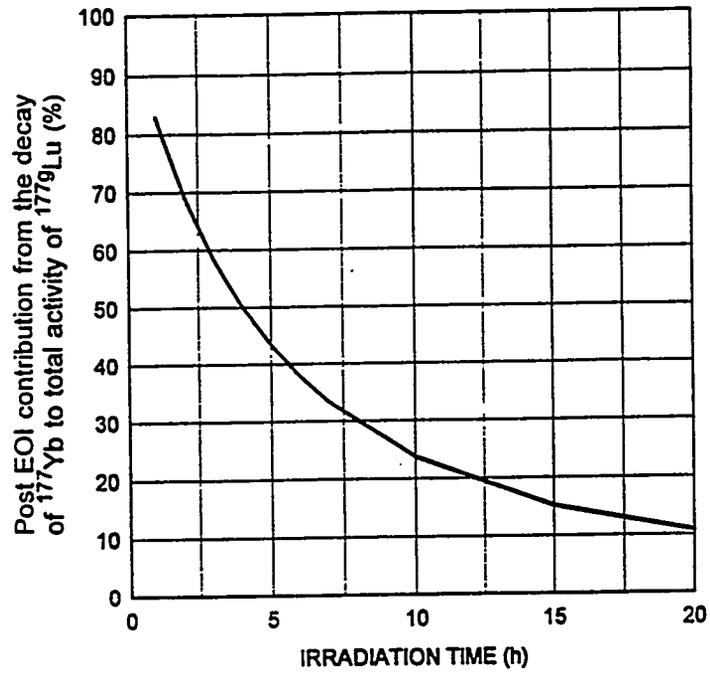


Figure 7. Indirect production of ^{177}Lu -- post EOI contribution from the decay of ^{177}Yb to total activity of ^{177}Lu as a function of the irradiation time.

Literature Cited

1. Lederer, C. M., and Shirley, V. S., Editors, *Table of Isotopes*, 7th Ed., John Wiley & Sons Inc., New York 1978.
2. Reus, U. and Westmeier, W., *Catalog of Gamma-rays from Radioactive Decay*, At. Data and Nucl. Data Tables. Parts I and II, **29**, 1983.
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Erratum

The following corrections are for section in ORNL/TM-13053, published September 1995:
Page 7, Line 3. Phenylmagnesium bromide should be corrected to the original agent prepared from 1-bromo-5-chloropentane.

Other Nuclear Medicine Group Activities

Publications

Wang, S. J., Lin, W. Y., Hsieh, B. T., Shen, L. H., Tsai, Z. T. and Knapp, F. F., Jr., "Rhenium-188 Sulfur Colloid as a Radiation Synovectomy Agent," *Eur. J. Nucl. Med.*, **22**, 505-507 (1995).

Gilfer, M. S., Boulay, S. F., Sood, V. K., McPherson, D. W., Knapp, F. F. (Russ) Jr., Zeeberg, B.R. and Reba, R. C. "Characterization of *in vivo* brain muscarinic acetylcholine receptor subtype selectively by competition studies against (R,R)-[¹²⁵I]-IQNB," *Brain Research*, **687**, 71-78 (1995).

Presentations

ORNL Nuclear Medicine Program Staff members D. W. McPherson and S. Mirzadeh participated in the recent International Symposium on Radiopharmaceutical Chemistry held in Vancouver, Canada, on August 13-17, 1995. The following papers were presented and co-authored by members of the ORNL Program:

E. Dadachova, S. V. Smith, N. DiBartolo, P. F. Schmidt, S. Mirzadeh and E. L. Hetherington, "Labeling of Proteins with ^{166}Ho ."

E. Dadachova, S. V. Smith, P. F. Schmidt and S. Mirzadeh, "Electrochemical Reduction of ^{188}Re for Protein Labeling."

D. W. McPherson, H. Luo, A. L. Beets, B. Zeeberg, V. Sood, R. C. McRee, R. C. Reba and F. F. Knapp, Jr. "Preparation, *In Vitro* and *In Vivo* Evaluation of New Fluoroalkyl QNB Analogues as Potential mAChR Ligands for PET Studies."

S. Mirzadeh, A. L. Beets and F. F. Knapp, Jr. "HFIR-Produced Radioisotopes of Current Medical Interest."

A. Schaffland, S. Guhlke, F. F. Knapp, Jr., P. O. Zamora and H. J. Biersack, "Pre- and Post-Conjugate Labeling of Amies and Peptides with ^{188}Re Using the MAG_3 Chelate."

V. Strijckmans, D. W. McPherson, F. F. Knapp, Jr., C. Loc'h and B. Maziere, " ^{76}Br]-Z-(R,R)-QNP: A High Affinity PET Radiotractor for Central Muscarinic Receptors."

F. F. (Russ) Knapp, Jr. attended the European Association of Nuclear Medicine (EANM) Congress held in Brussels, Belgium, on August 26-30, 1995. In addition to participating in this meeting and assisting the staff of the Department of Energy Isotope Production and Distribution Program (IPDP), he also met as an editorial board member with the Editorial Board of the European Journal of Nuclear Medicine. Members of the ORNL Program co-authored the following papers at the EANM Congress:

Grillenberger, K., McPherson, D., Hartung, T., Knapp, Jr., F. F. and Reske, S.N.
"An Improved Method for Labeling MAB with Carrier-Free Rhenium-188."

Hosono, M., Hosono, M., Haberberger, T., Zamora, P., Gohlke, S., Bender, J.,
Knapp, Jr. F. F. and Biersack, H.-J. "Targeting of Small-Cell Lung Cancer by
Octreotide Labeled With I-125, In-111, and Re-188 in a Mouse Model."

Lin, W., Chen, M., Wang, S., Hseih, B., Tsai, Z, Ting, G. and Knapp, Jr., F. F.
"Biodistribution of Rhenium-188 Lipiodol in Rats Following Hepatic Arterial
Injection."

Sloof, G., Visser, F. C., Comans, E. and Knapp, Jr. F. F. "Correlation of
Heterogeneous Blood Flow and Uptake of a DiMethyl-Branched Iodo Fatty Acid
in the Normal and Ischemic Dog Heart."

Wang, S., Chen, M., Lin, W., Hseih, B, Tsai, Z, Ting, G, and Knapp, Jr. F. F.
"Rhenium-188 Labeling of Lipiodol for Hepatoma Therapy."

Wang, S., Lin, W., Hseih, B, Tsai, Z, Ting, G. and Knapp, Jr. F. F. "Studies on Re-
188 Sulfur Colloid for Use as a Radiation Synovectomy Agent."

Medical Cooperative Shipments

During this period several radioisotopes were provided to collaborators for ongoing research projects through our Medical Cooperative Programs which included tungsten-188 which was provided to Sorin Biomedica in Milan, Italy for fabrication of a sterile tungsten-188/rhenium-188 generator under GMP's to obtain rhenium-188 for preparation of rhenium-188-MDP for initial clinical evaluation of rhenium-188-MDP for bone palliation studies at the Catholic University Hospital in Rome, Italy (L. Troncone, M.D.). Tungsten-188/rhenium-188 generators were also provided to RhoMed, Inc. through a CRADA arrangement for radiolabeling of peptides and somatostatin analogues for tumor therapy (B. Rhodes, Ph.D. and P. Zamora, Ph.D., et al.) . Tungsten-188 (1 Ci) was provided to Nordion, Inc. through the UPDP. Scandium-47 and tin-117m which were supplied to the Medical Department at the Brookhaven National Laboratory (L. Mausner, Ph.D. and S. C. Srivastava, Ph.D.). The scandium-47 is being used for antibody labeling for animal studies and the tin-117m is used in Phase II patient studies for evaluation of bone palliation with tin-117m-DTPA complex in a CRADA with Diatech, Inc.

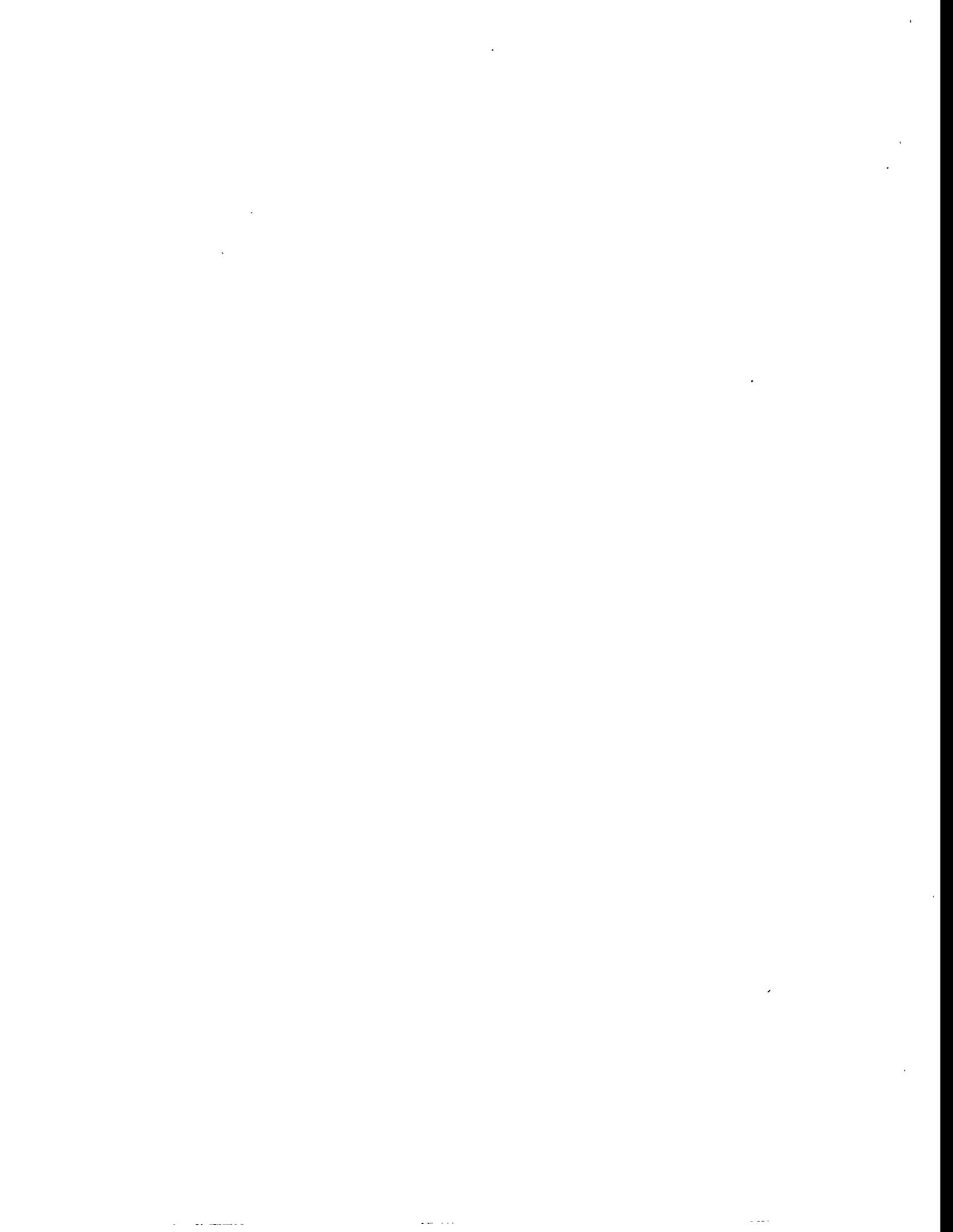
Visitors and Guest Assignment

During the July 1-September 30, 1995, several guests who joined the Nuclear Medicine Program included Florian Mokler, a medical student from the University of Mainz, Germany, who will work at ORNL for the September 1995-February 1996 period to evaluate the metabolism of new cardiac imaging agents. Several visitors during this period included:

July 25, 1995, George B. Crawford, Scintillation Technologies, Knoxville, TN

July 25, 1995 Prof. Nicholas Schad, Passau, Germany

August 17, 1995, Prof. E. S. El'Ashray (Medical Chemistry) Alexandria, Egypt



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31. A. Bockisch, Ph.D., M.D., Klinik und Poliklinik fuer Nuklearmedizin, Postfach 39 60, Langenbeckstrasse 1, 55101 Mainz, Germany
32. C. Brihaye, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
33. A. B. Brill, M.D., Ph.D., Dept. of Nuclear Medicine, Univ. of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655
34. T. F. Budinger, M.D., MS 55/121, Lawrence Berkeley Laboratory, 1 Cyclotron Road, Berkeley, CA 94720
35. A. P. Callahan, Route 1, Box 305, Harriman, TN 37748
36. J. S. Carty, Isotope Production and Distribution Program, U.S. Department of Energy, NE-46, GTN, Room B-419, Washington, D. C. 20585-1290
37. D. Cole, Medical Applications and Biophysical Research Division, ER-73, Department of Energy, GTN, Washington, D.C. 20585-1290
38. B. Coursey, National Institute for Standards and Technology, Building 245, RM C214 Gaithersburg, MD 20899

39. J. G. Davis, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
40. R. F. Dannals, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205-2179
41. S.J. DeNardo, M.D., University of California, Davis Medical Center, 4301-X Street, FOCB II-E Sacramento, CA, 95817
42. R. Dudczak, M.D., Dept. Nuclear Medicine, I. Medizinische Universitätsklinik, A-1090 Wien, Lazarettgasse 14, Vienna, Austria
43. G. Ehrhardt, Missouri University Research Reactor, University of Missouri, Research Park, Columbia, MO 65211
44. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
45. L. Feinendegen, Medical Department, Brookhaven National Laboratory, Upton, NY 11973
46. J. Fowler, Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973
47. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
48. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103
49. G. Goldstein, DOE-OHER, Washington, DC 20585
50. G. Griffiths, Immunomedics, Inc., 300 American Rd, Morris Plains, NJ 07950
51. J. Hiltunen, Managing Director, MAP Medical Technologies, Inc., Elementitie 27, SF-41160 Tikkakoski, Finland
52. Bor-Tsung Hsieh, Ph.D., Institute of Nuclear Energy Research, (INER) Lung-Tan, Taiwan, Republic of China
53. K. Hubner, M.D., Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
54. J. M. R. Hutchinson, Ph.D., U. S. Dept. of Commerce, National Institute of Standards and Technology, Gaithersburg, MD 20899-0001
55. B. Johannsen, Ph.D., Forschungszentrum Rossendorf e.V. Postfach 51 01 19, D-01314 Dresden, Federal Republic of Germany.
56. A. Jones, HMS Radiology Dept., Shields Warren Radiation Laboratory, 50 Binney Street, Boston, MA 02115
57. G. W. Kabalka, Chemistry Department, University of Tennessee, Knoxville, TN 37996-1600
58. G. Kirsch, Department of Chemistry, Universite de Metz, Metz, France
59. J. Kropp, M.D., Klinik für Nuklearmedizin, der Medizinischen Akademie, Fetscher - Str. 74, 01307 Dresden, Germany
60. D. E. Kuhl, M.D., Division of Nuclear Medicine, University of Michigan Hospitals, University Hospital BIG 412/0028, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0028
61. R. Lambrecht, Ph.D. Pet-Zentrum des Universitätsklinikum, Eberhard-Karls-Universität Tuebingen, 15 Roentgenweg, Tuebingen 72076, Germany
62. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
63. E. C. Lisic, Ph.D., Department of Chemistry, Tennessee Technological University, Cookeville, Tennessee 38505
64. J. Lister-James, Ph.D., Director, Research Administration, Diatech, Inc., 9 Delta Drive, Londonderry, New Hampshire 03053
65. O. Lowe, Isotope Production and Distribution Program, U.S. Department of Energy, NE-46, GTN, Room B-419, Washington, D. C. 20585-1290
66. G. Limouris, Nuclear Medicine Department, Areteion University Hospital, Athens Medical School, Athens, Greece

67. D. J. Maddalena, FRACI, Department of Pharmacology, Sydney University, NSW 2006, Sydney, Australia
68. John Maddox, 4608 Flower Valley Drive, Rockville, MD 20853-1733.
69. H.-J. Machulla, Eberhard-Karls-Universität Tübingen, Radiologische Universitätsklinik, Pet-Zentrum, Röntgenweg 11, 7400 Tübingen, Germany
70. Frederick J. Manning, National Academy of Sciences, Institute of Medicine, 2101 Constitution Ave., M.W., Washington, D.C. 20418
71. M. Meyer, M.D., Biomedical Research Foundation, P.O. Box 38050, Shreveport, LA 71133-8050
72. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
73. G. Notohamiprodjo, M.D., Ph.D., Institute of Nuclear Medicine, Heart Center North Rhine-Westphalia, Bad Oeynhansen, D-4970, Germany
74. C. L. Partain, M.D., Professor and Vice Chairman, Dept. Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232
75. R. C. Reba, M.D., Department of Radiology, 5841 S. Maryland Ave., MC 2026, Chicago, IL 60637
76. S. N. Reske, M.D., Klinik für Nuklearmedizin, Ärztlicher Direktor der Nuklearmedizin, Klinikum der Universität Ulm Oberer Eselsberg, D-7900, Ulm, Germany
77. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
78. R. E. Schenter, HO-37, Westington Hanford Co., P.O. Box 1970, Richland, WA 99352
79. A. Serafini, Nuclear Medicine Division (D-57), University of Miami School of Medicine, P. O. Box 016960, Miami, FL 33101
80. S. K. Shukla, Prof., Servizio Di Medicina Nucleare, Ospedale S. Eugenio, Pizzale Umanesimo, 10, Rome, Italy
81. S. Smith, Biomedicine & Health Program, Australian Nuclear Sci. & Tech. Org., Lucas Heights Research Laboratories, Private Mail Bag 1, Menai NSW 2234, Australia
82. J. Smith, Ph.D., Research & Development, DuPont Merck Pharmaceutical Company, 331 Treble Cove Rd., North Billerica, MA 01862
83. A. Solomon, M.D., UT MRCH, 1924 Alcoa Highway, Knoxville, TN 37920-6999
84. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
85. P. C. Srivastava, DOE-OHER, Washington, DC 20585
86. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
87. G. Strathearn, Isotope Products Laboratories, Inc., 3017 N. San Fernando Blvd., Burbank, CA, 91504.
- 88-90. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831
91. E. A. van Royen, M.D., Ph.D., Head, Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam ZO, The Netherlands.
92. F. C. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
93. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, 615 N. Wolfe Street, Baltimore, MD 21205-2179

94. R. Wolfangel, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
95. J.-I. Wu, Ph.D., Senior Research Representative, Nihon Medi-Physics Co., Ltd., 2200 Powell Street, Suite 765, Emeryville, CA 94608.
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97. Y. Yonekura, M.D., Fukui Medical School, 23 Shimoaizuki, Matsuoka, Fukui 910-11, Japan.