



3 4456 0370127 9

oml

ORNL/TM-12312

OAK RIDGE  
NATIONAL  
LABORATORY

MARTIN MARIETTA

**Nuclear Medicine Program  
Progress Report for  
Quarter Ending December 31, 1992**

F. F. Knapp, Jr.  
K. R. Ambrose  
A. L. Beets  
A. P. Callahan  
D. W. McPherson  
S. Mirzadeh  
A. Hasan  
C. R. Lambert

OAK RIDGE NATIONAL LABORATORY  
CENTRAL RESEARCH LIBRARY  
CIRCULATION SECTION  
#560N ROOM 175  
**LIBRARY LOAN COPY**  
DO NOT TRANSFER TO ANOTHER PERSON  
If you wish someone else to see this  
report, send in name with report and  
the library will arrange a loan.  
UCR788 (2-87)

MANAGED BY  
MARTIN MARIETTA ENERGY SYSTEMS, INC  
FOR THE UNITED STATES  
DEPARTMENT OF ENERGY

This report has been reproduced directly from the best available copy.

Available to DOE and DOE contractors from the Office of Scientific and Technical Information, P.O. Box 62, Oak Ridge, TN 37831; prices available from (615) 576-8401, FTS 626-8401.

Available to the public from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

Contract No. DE-AC05-84OR21400

Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT  
FOR QUARTER ENDING DECEMBER 31, 1992

F. F. Knapp, Jr., Group Leader

K. R. Ambrose  
A. L. Beets  
A. P. Callahan  
D. W. McPherson

S. Mirzadeh  
A. Hasan  
C. R. Lambert

**NOTICE** This document contains information of a preliminary nature.  
It is subject to revision or correction and therefore does not represent a  
final report.

Work sponsored by  
DOE Office of Health and  
Environmental Research

Date Published—March 1993

OAK RIDGE NATIONAL LABORATORY  
Oak Ridge, Tennessee 37831-6285  
managed by  
MARTIN MARIETTA ENERGY SYSTEMS, INC.  
for the  
U.S. DEPARTMENT OF ENERGY



Previous reports in this series:

ORNL/TM-5809  
ORNL/TM-5936  
ORNL/TM-6044  
ORNL/TM-6181  
ORNL/TM-6371  
ORNL/TM-6410  
ORNL/TM-6638  
ORNL/TM-6639  
ORNL/TM-6771  
ORNL/TM-6916  
ORNL/TM-6958  
ORNL/TM-7072  
ORNL/TM-7223  
ORNL/TM-7411  
ORNL/TM-7482  
ORNL/TM-7605  
ORNL/TM-7685  
ORNL/TM-7775  
ORNL/TM-7918  
ORNL/TM-8123  
ORNL/TM-8186  
ORNL/TM-8363  
ORNL/TM-8428  
ORNL/TM-8533  
ORNL/TM-8619  
ORNL/TM-8746  
ORNL/TM-8827  
ORNL/TM-8966  
ORNL/TM-9037  
ORNL/TM-9124  
ORNL/TM-9343  
ORNL/TM-9394  
ORNL/TM-9480  
ORNL/TM-9609  
ORNL/TM-9707  
ORNL/TM-9784  
ORNL/TM-9937  
ORNL/TM-10082  
ORNL/TM-10238  
ORNL/TM-10294  
ORNL/TM-10377  
ORNL/TM-10441  
ORNL/TM-10618  
ORNL/TM-10711  
ORNL/TM-10839  
ORNL/TM-11014

ORNL/TM-11043  
ORNL/TM-11145  
ORNL/TM-11224  
ORNL/TM-11304  
ORNL/TM-11377  
ORNL/TM-11427  
ORNL/TM-11550  
ORNL/TM-11570  
ORNL/TM-11721  
ORNL/TM-11755  
ORNL/TM-11830  
ORNL/TM-11881  
ORNL/TM-11992  
ORNL/TM-12054  
ORNL/TM-12110  
ORNL/TM-12159  
ORNL/TM-12222

## CONTENTS

Summary .....	1
Synthesis and Evaluation of the Trans (E) and Cis (Z) Isomers of "IQNP" .....	2
Determination of Thermal and Epithermal Neutron Flux Values in HFIR Hydraulic Tube Positions .....	6
Agents for Medical Cooperatives .....	7
Other Nuclear Medicine Group Activities .....	7



## SUMMARY

In this report, we describe the synthesis of the cis- and trans-iodovinyl isomers of the new ORNL cholinergic-muscarinic receptor ligand, 1-azabicyclo[2.2.2]oct-3-yl  $\alpha$ -hydroxy- $\alpha$ -(1-iodo-1-propen-3-yl)- $\alpha$ -phenylacetate ("IQNP"). This agent is prepared in high radiochemical yield, and the racemic mixture shows high specificity and selectivity for the cerebral and myocardial receptors. Since two chiral centers are present in this molecule, it is important to evaluate the importance of the absolute configuration of the two centers on receptor specificity. The tributyltin substrates were carefully separated by column chromatography, converted to the iodine-125 analogues by iododestannylation, and evaluated in rats in vivo. While the "E" (trans) isomer cleared rapidly from the receptor-rich areas of rat brain, the "Z" (cis) isomer showed high uptake in these areas but also high concentration in the cerebellum. In contrast, the E,Z-isomeric mixture showed good uptake and retention in the receptor rich areas. Studies are now in progress to determine the absolute configuration of the chiral centers in these olefinic isomers.

Also described in this report is a description of neutron flux measurements in the hydraulic tube position at the ORNL High Flux Isotope Reactor (HFIR). Also during this period, samples of [I-125]- and [I-131]-labeled racemic "IQNP" were supplied through a collaborative program with the Brookhaven National Laboratory for high resolution autoradiographic studies in rat tissues. In addition, a tungsten-188/rhenium-188 generator was provided for collaborative studies for dimercaptosuccinic acid (DMSA) radiolabeling at the University of Kent and Canterbury Hospital in England.

## SYNTHESIS AND EVALUATION OF THE TRANS (E) AND CIS (Z) ISOMERS OF "IQNP"

It has been reported that the cerebellum and heart contain a high population of the  $M_2$  receptor subtype as compared to  $M_1$  receptor subtype. We reported earlier the development of a new high affinity muscarinic antagonist, 1-azabicyclo[2.2.2]oct-3-yl  $\alpha$ -hydroxy- $\alpha$ -(1-iodo-1-propen-3-yl)- $\alpha$ -phenylacetate (IQNP, 1) (ORNL/TM-12110, -11881 and -11992). This agent is radiolabeled in high yield with high specific activity and demonstrates high specificity and selectivity for cardiac and cerebral muscarinic acetylcholine receptors (m-AChR). IQNP (1) contains 2 chiral centers; the 2 position on the acetate moiety and the 3 position on the quinuclidinyl moiety, in addition to the orientation of the iodine on the double bond (Figure 1) and therefore contains eight potential isomers.

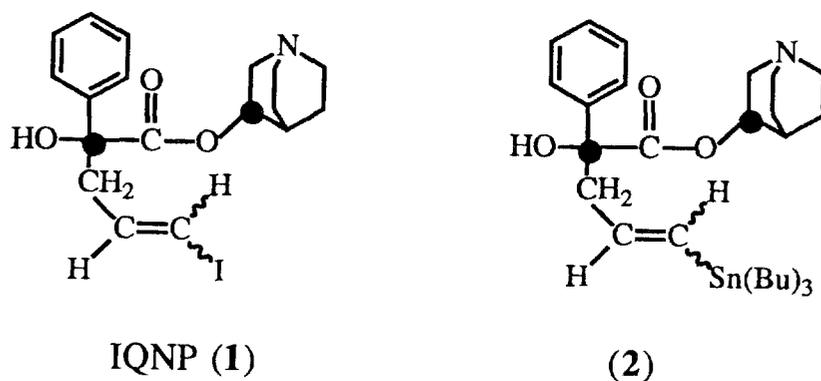


Figure 1. Structures of IQNP(1) and the tributyltin substrate (2)

We have initiated separation of these isomers to determine the best isomer for future kinetic, metabolic and imaging studies. The synthesis of the IQNP involves the preparation of the tributylstannyl intermediate (2) and TLC analysis of 2 indicated two components of similar  $R_f$ . NMR analysis of 2 indicated that this was a mixture of the E and Z isomers. Iodination of 2 resulted in 1, which chromatographed as a single component by TLC, but NMR analysis indicated this consisted of the E and Z isomers. HPLC analysis of 1 indicated that the product contained 2 components of equal amounts. After repeated flash column chromatographic purification of 2, three different compounds were isolated. NMR analysis indicated that the first isolated component was the "E-2" ( $R_f=0.31$ ), the second compound was observed to have mainly the E configuration with a slight amount of Z isomer present ( $R_f=0.27$ ), and the third contained Z-2. These isomers were then iodinated and the products analyzed by TLC, NMR, and HPLC. In all

cases the NMR analysis of each compound was identical to the racemic mixture except in the vinyl region where the difference in isomers could be detected. The first compound, "E-1", was isolated as a white solid, mp, 118-119°C,  $R_f=0.35$ . NMR analysis of the vinyl regions shows a multiplet at 6.50 ( $J = 6.35$  Hz) and a doublet at 6.20 ( $J = 14.57$  Hz). The second compound, "E,Z-1", was isolated as a white solid, mp, 150°C,  $R_f=0.34$ . NMR analysis of the vinyl regions shows a multiplet at 6.50 ( $J = 6.35$  Hz) and a doublet at 6.20 ( $J = 14.57$  Hz) in addition to a multiplet at 6.30 corresponding to a "Z" configuration. The third compound, "Z-1", was isolated as a pale oil,  $R_f=0.32$ . NMR analysis of the vinyl regions shows a multiplet at 6.37-6.22. HPLC analysis of these isomers indicated that these were three distinct compounds with "E-1" eluting first, "E-Z-1" eluting next and "Z-1" eluting last.

These isomers were then radiolabeled with iodine-125 and their uptake in selected tissues was evaluated in female rats. The results of these studies are shown in Figures 2-4. Initial uptake of "E-1" was high, but cleared rapidly from the areas of interest (Figure 2). "E,Z-1", however, demonstrated substantial uptake in the cortex, striatum, and hippocampus, which are rich in muscarinic receptors (Figure 3). In addition, uptake of activity in the cerebellum (receptor poor) was low after 6 hours, with a cortex to

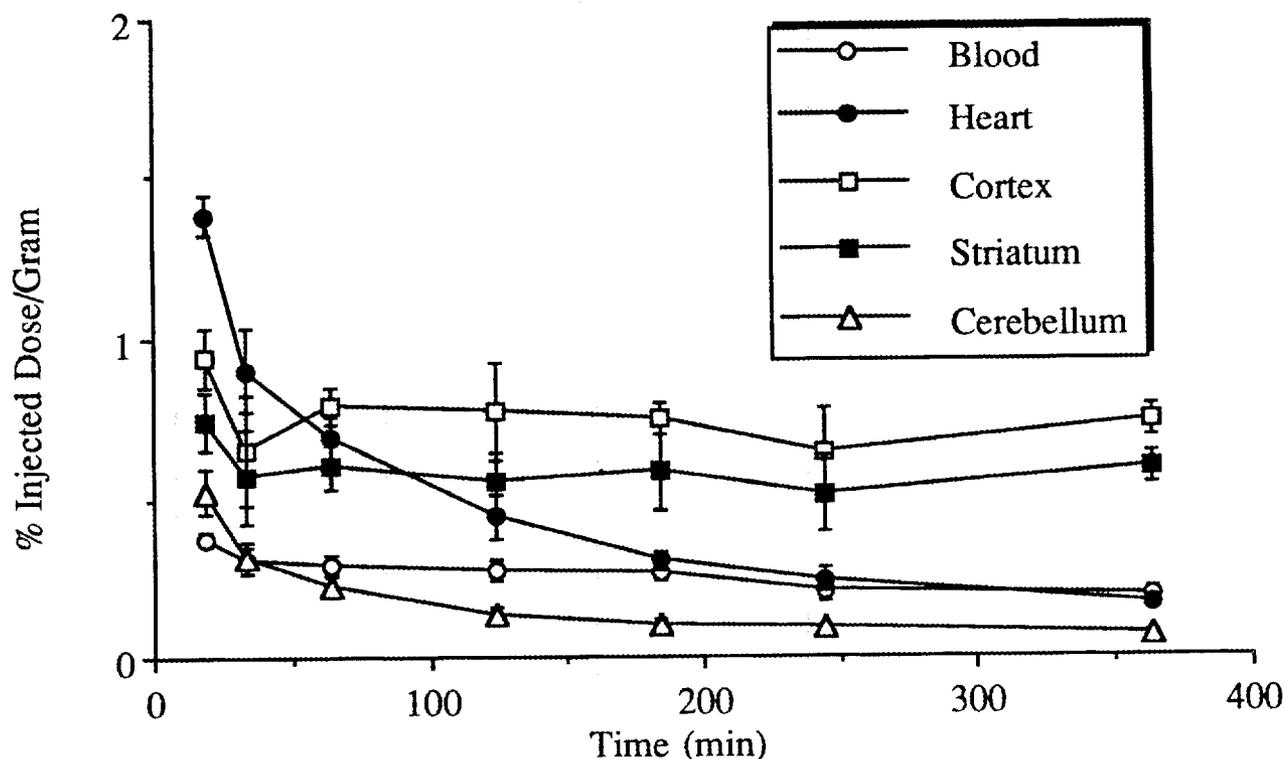


Figure 2. Biodistribution of "E-1" in female rats.

cerebellum ratio of  $\sim 20:1$ . The uptake of activity in the heart rapidly cleared during the time course of the experiment. "Z-1" demonstrated similar uptake in the cortex, striatum, and hippocampus as was observed for "E,Z-1", however, it also demonstrated higher uptake in the cerebellum (Figure 4). It was also observed that the cardiac uptake of this isomer was higher than that observed for the "E,Z-1" isomer with a heart to blood ratio of  $\sim 3:1$  after 6 hours.

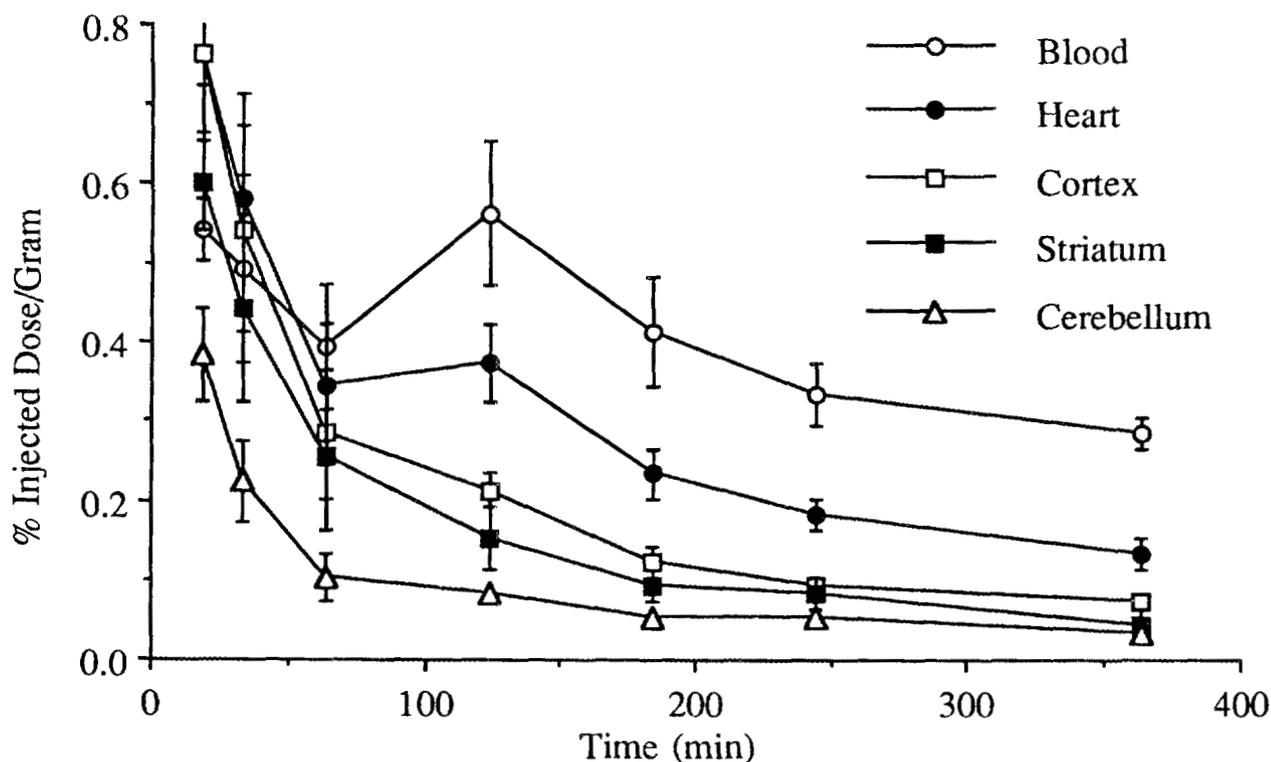


Figure 3. Biodistribution of "E,Z-1" in female rats.

Autoradiography of "E,Z-1" was performed by Dr. P. Som and co-workers at the Brookhaven National Laboratory and a typical ARG is shown in Figure 5. These studies were performed using  $[^{131}\text{I}]$ -"E,Z-1" and the slices obtained one hour post-injection. High uptake of activity was observed in the cortex, striatum, olfactory bulb, and hippocampus with very low uptake of activity in the cerebellum.

These combined results suggest that the E and Z configuration around the double bond may enhance the receptor subtype selectivity of IQNP (1). The uptake of "Z-1" is higher in these regions as compared to "E,Z-1" which contains only a small fraction of a Z isomer. We are currently separating the chiral centers of IQNP to obtain the best

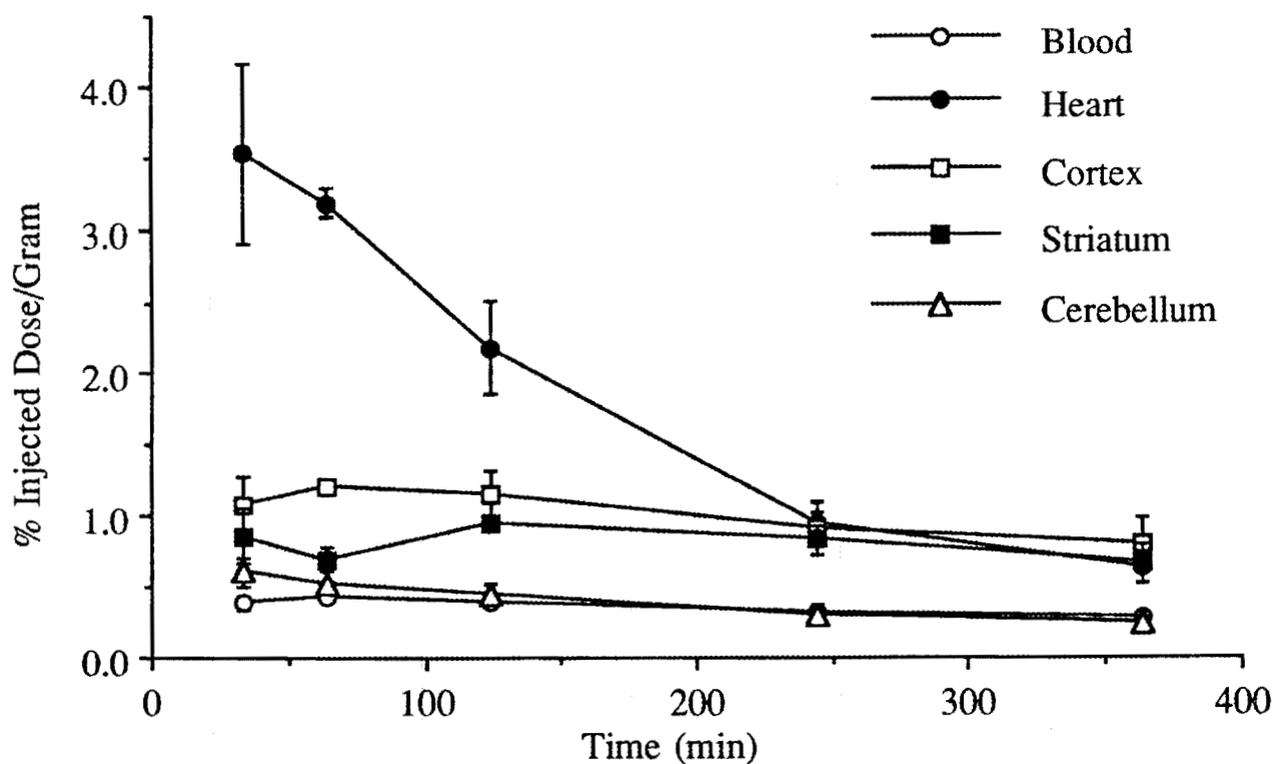


Figure 4. Biodistribution of "Z-1" in female rats.

candidates for future studies and to determine if a selective subtype isomer can be isolated.

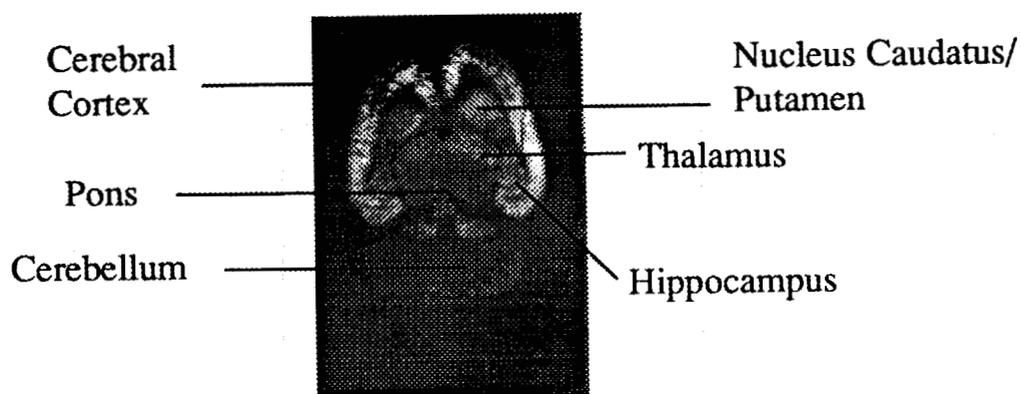


Figure 5. Autoradiographic studies of [ $^{131}\text{I}$ ]-"E-Z"-IQNP in rats.

DETERMINATION OF THERMAL AND EPITHERMAL NEUTRON FLUX VALUES  
IN HFIR HYDRAULIC TUBE POSITIONS

The shift from isotope production to material testing in the HFIR since restart of the HFIR in 1991 has perturbed the neutron fluxes and spectra. In addition, during the HFIR shut down, the hydraulic tube facility, which was originally located in the center of the flux trap, was relocated to an off-center position. For prediction of the production rates of radioisotopes of interest to us, it is very important to have an accurate knowledge of the neutron flux values of the hydraulic tube position, and a systematic "mapping" of the flux values was thus initiated. With the help of a summer student, a computer code was developed for the above purpose, and the thermal neutron fluxes were measured in all positions of the hydraulic tube (Figure 6.). A report is under preparation describing these activities. Currently with collaboration with two other divisions at ORNL, we are in the process of mapping the epithermal and fast neutron fluxes in the hydraulic tube.

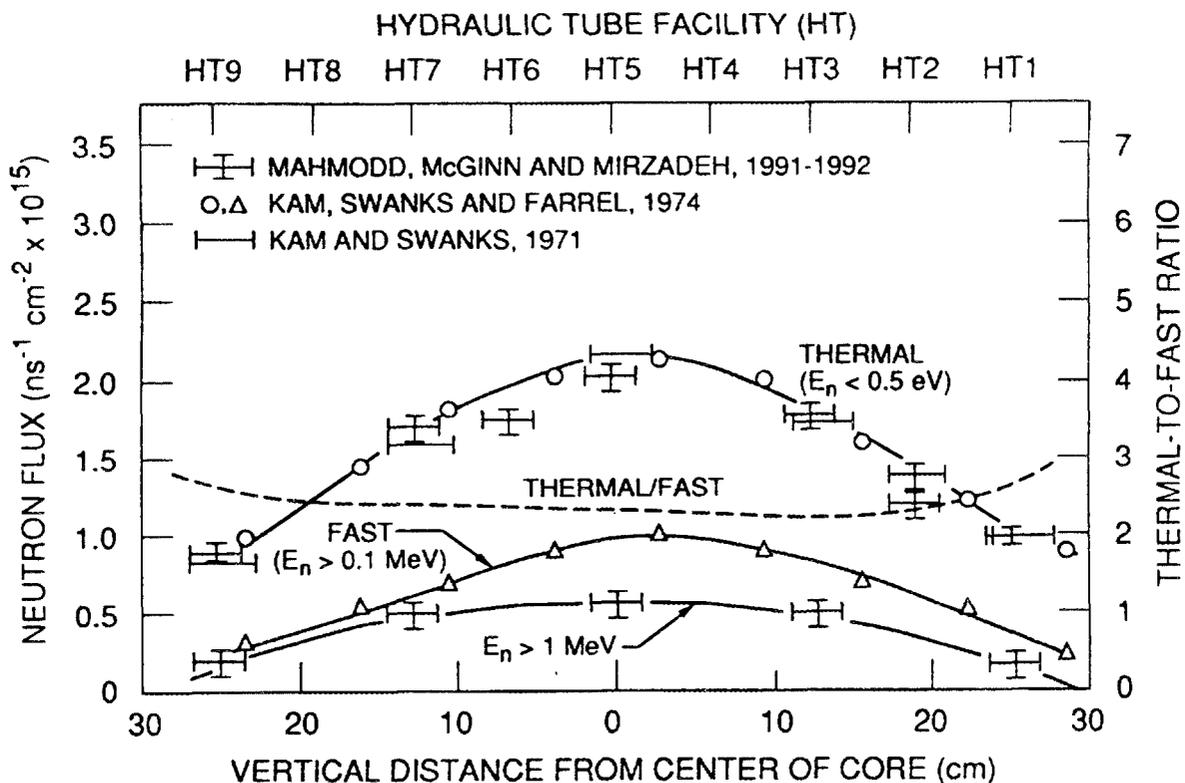


Figure 6. Neutron flux values measured in HFIR hydraulic tube positions

## AGENTS FOR MEDICAL COOPERATIVES

In a continuation of collaborative studies to evaluate the regional uptake in cerebral structures by high resolution autoradiography (ARG), samples of I-125- and I-131-labeled "IQNP" were supplied to the Brookhaven National Laboratory (P. Som, D.V.M.). One of the ORNL tungsten-188/rhenium-188 generators was supplied for preclinical studies in a collaborative program with the University of Kent and Canterbury Hospital in England (P. J. Blower, Ph.D.).

## OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

### Publications

A new electrochemical technique has been developed to provide radioisotopes of copper for applications in nuclear medicine by the processing reactor-irradiated zinc targets. This technique represents an important improvement in providing carrier-free copper-67 for therapeutic applications and copper-64 for diagnostic use with positron emission tomography (PET).

Mirzadeh, S. and Knapp, Jr., F.F., "Spontaneous Electrochemical Separation of Carrier-Free Copper-64 and Copper-67 from Zinc Targets," *Radiochim. Acta*, 57, 193-199 (1992).

An "Editorial" was recently authored by F.F. (Russ) Knapp, Jr., S. Mirzadeh and A. P. Callahan, in a special issue of the journal, Radioactivity and Radiochemistry (Vol. 3, No. 4, 1992), which introduced sixteen papers from the "Symposium on Radionuclide Generator Systems for Nuclear Medicine Applications". The Symposium was organized by the ORNL researchers at the Annual Meeting of the American Chemical Society (ACS), held in Washington, D.C., on August 24-28, 1992. The symposium encompassed state of the art presentations on radionuclide generator systems for diagnostic and therapeutic applications in nuclear medicine.

Members of the ORNL Nuclear Medicine Group have published the first comprehensive overview summarizing the production capabilities of U.S. reactors for medical radioisotopes. The 190 page survey summarizes the production capabilities of nine U.S. reactors and will be an important resource for DOE staff, nuclear medicine researchers, and students.

S. Mirzadeh, R. E. Schenter, A. P. Callahan and F. F. (Russ) Knapp, Jr., "Production Capabilities in U.S. Nuclear Reactors for Medical Radioisotopes," ORNL/TM-12010.

### **Nuclear Medicine Group Technician Receives Certification**

Carla Lambert, a Laboratory Technician in the Nuclear Medicine Group, has recently been certified as a Laboratory Animal Technician by the Animal Technician Certification Board of the American Association for Laboratory Animal Science (AALAS). This certification follows six months of preparatory course work, laboratory animal procedure training, laboratory exercises, and successful completion of the Laboratory Animal Technician examination. This is the first AALAS certification to be awarded to a member of Health and Safety Research Division and is an important accomplishment consistent with increased emphasis by federal agencies and by the ORNL Animal Care and Use Program on the training and certification of personnel involved with animal studies.

### **Presentation**

Members of the ORNL Nuclear Medicine Group co-authored a recent paper describing the use of radioiodinated fatty acids for cardiac imaging to evaluate heart involvement in patients with myopathies of skeletal muscle which was presented at the *Annual Meeting of the American Heart Association*, held in New Orleans, Louisiana, on November 16-19, 1992. The collaborative studies were conducted by J. Kropp, M.D., and colleagues at the Clinic for Nuclear Medicine at the University of Bonn, Germany.

Kropp, J., Koehler, U., Zierz, S., Knapp, Jr., F.F., and Biersack, H.-J. "Radionuclide Imaging of Myocardial Oxidative Metabolism in Patients with Systemic Myopathies."

## INTERNAL DISTRIBUTION

- |       |                          |        |                          |
|-------|--------------------------|--------|--------------------------|
| 1.    | K. R. Ambrose            | 18.    | S. Mirzadeh              |
| 2.    | A. L. Beets              | 19.    | B. Patton                |
| 3.    | B. A. Berven             | 20.    | G. Prosser               |
| 4.    | A. P. Callahan           | 21.    | D. W. Ramey              |
| 5.    | E. D. Collins            | 22.    | D. E. Reichle            |
| 6.    | K. F. Eckerman           | 23.    | P. S. Rohwer             |
| 7.    | R. N. Hamm               | 24.    | S. Stafford              |
| 8.    | A. Hasan                 | 25.    | S. J. Wolfe              |
| 9-13. | F. F. Knapp, Jr.         | 26-27. | Central Research Library |
| 14.   | C. R. Lambert            | 28.    | Document Record Section  |
| 15.   | E. C. Lisic (Consultant) | 29-30. | Laboratory Records Dept. |
| 16.   | D. W. McPherson          | 31.    | Lab. Records, ORNL RC    |
| 17.   | J. C. Miller             | 32.    | ORNL Patent Section      |

## EXTERNAL DISTRIBUTION

33. H. L. Atkins, M.D., Radiology Dept., State Univ. of New York, Stony Brook, NY 11794-8460
34. H. J. Biersack, M.D., Director, Klinik fuer Nuklear Medizin, Der Universitat Bonn, Sigmund Freud Strasse 25, 5300 Bonn 1, West Germany
35. C. Brihaye, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
36. A. B. Brill, M.D., Ph.D., Dept. of Nuclear Medicine, Univ. of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655
37. T. F. Budinger, M.D., MS 55/121, Lawrence Berkeley Laboratory, 1 Cyclotron Road, Berkeley, CA 94720
38. J. G. Davis, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
39. S. J. DeNardo, M.D., Univ. California, Davis Medical Center, Sacramento, CA 95817
40. R. F. Dannals, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205-2179
41. R. Dudczak, M.D., Dept. Nuclear Medicine, I. Medizinische Universitatsklinik, A-1090 Wien, Lazarettgasse 14, Vienna, Austria
42. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
43. L. Feinendegen, Institut fur Medizin, Forschungszentrum Julich GmbH, Postfach 1913, D-5170, Julich 1, Germany
44. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
45. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103
46. G. Goldstein, Ph.D., DOE-OHER, Washington, DC 20585
47. M. M. Goodman, Nuclear Medicine Section, Department of Radiology, University of Tennessee Medical Center, 1924 Alcoa Highway, Knoxville, TN 37920-6999
48. M. Guillaume, Chef de Travaux, Centre de Recherches du Cyclotron, Universite de Liege, Belgium

49. D. R. Hamilton, Director, Division of Technical Development, OTA/CDRH/FDA, 1901 Chapman Avenue, Rockville, MD 20857
50. J. Hiltunen, Managing Director, MAP Medical Technologies, Inc., Otakaari 3 A, SF-02150 Espoo, Finland
51. K. Hubner, M.D., Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
52. A. Jones, HMS Radiology Dept., Shields Warren Radiation Laboratory, 50 Binney Street, Boston, MA 02115
53. G. W. Kabalka, Chemistry Department, University of Tennessee, Knoxville, TN 37996-1600
54. G. Kirsch, Department of Chemistry, Universite de Metz, Metz, France
55. J. Kropp, M.D., Klinik fuer Nuklear Medizin, Der Universitat Bonn, Sigmund Freud Strasse 25, 5300 Bonn 1, West Germany
56. 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.
57. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
58. D. J. Maddalena, FRACI, Department of Pharmacology, Sydney University, NSW 2006, Sydney, Australia
59. H. J. Machulla, Eberhard-Karls-Universität Tübingen, Radiologische Universitätsklinik, Pet-Zentrum, Röntgenweg 11, 7400 Tübingen, Germany
60. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
61. R. Patterson, M.D., Nuclear Cardiology, Crawford Long Hospital, 550 Peachtree Street, NE, Atlanta, GA 30365-2225
62. C. L. Partain, M.D., Professor and Vice Chairman, Dept. Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232
63. R. C. Reba, M.D., 5841 S. Maryland Ave., U.C. Hospital Box 429, Chicago, IL 60637
64. S. N. Reske, University Clinic, Dept. of Nuclear Medicine, Steinhoevelstrasse 9, D-7900, Ulm, Germany
65. M. Robbins, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
66. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
67. R. E. Schenter, HO-37, Westington Hanford Co., P.O. Box 1970, Richland, WA 99352
68. S. K. Shukla, Prof., Servizio Di Medicina Nucleare, Ospedale S. Eugenio, Pizzale Umanesimo, 10, Italy
69. F. Snyder, ORAU, Oak Ridge, TN 37831
70. A. Solomon, M.D., UT MRCH, 1924 Alcoa Highway, Knoxville, TN 37920-6999
71. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
72. P. C. Srivastava, DOE-OHER, Washington, DC 20585
73. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
74. H. W. Strauss, M.D., Vice President, Diagnostics, Pharmaceutical Research Institute, Bristol Meyers Squibb, Rt. 202 Provinceline Rd., PO Box 4000, Princeton, NJ 08543-4000
- 75-85. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831
86. F. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands

87. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, 615 N. Wolfe Street, Baltimore, MD 21205-2179
88. A. P. Wolf, BNL, Upton, NY 11973
89. R. Wolfangel, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
90. D. V. Woo, Centocor, 244 Great Valley Parkway, Malvern, PA 19355
91. R. W. Wood, Jr., DOE-OHER, Washington, DC 20585
92. S. Wynchank, Research Institute for Medical Biophysics (RIMB), Republic of South Africa
93. Y. Yonekura, M.D., Kyoto University Faculty of Medicine, Shogoin, Sakyo-kuy Kyoto, 606-01, Japan