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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1993

F. F. Knapp, Jr. Group Leader

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

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Health and Safety Research Division

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Work sponsored by
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SUMMARY

The "IQNP" agent is an antagonist for the cholinergic-muscarinic receptor. Since the IQNP molecule has two asymmetric centers and either *cis* or *trans* isomerism of the vinyl iodide, there are eight possible isomeric combinations. In this report, the systematic synthesis, purification and animal testing of several isomers of radioiodinated "IQNP" are reported. A dramatic and unexpected relation between the absolute configuration at the two asymmetric centers and the stereochemistry of the vinyl iodide on receptor specificity was observed. The E-(R)(R) isomer shows specific and significant localization (per cent dose/gram at 6 hours) in receptor-rich cerebral structures (i.e. Cortex = 1.38+0.31; Striatum = 1.22+0.20) and low uptake in tissues rich in the M₂ subtype (Heart = 0.10; Cerebellum = 0.04). In contrast, the E-(R)(S) isomer shows very low receptor-specific uptake (Cortex = 0.04; Striatum = 0.02), demonstrating the importance of absolute configuration at the acetate center. An unexpected and important observation is that the stereochemistry of the vinyl iodine appears to affect receptor subtype specificity, since the Z-(R,S)(R) isomer shows much higher uptake in the heart (0.56+0.12) and cerebellum (0.17+0.04). Studies are now in progress to confirm these exciting results *in vitro*.

We are also in the process of moving both our laboratory and office space within the ORNL complex. The office move was completed in May and our offices are now located in Building 4501, Mail Stop 6229. The telephone and facsimile numbers are unchanged. Our synthetic laboratories are expected to be relocated to renovated laboratories in the 4500-N complex in August, and new radiochemical laboratory space is expected to be completed by the end of the calendar year.

Progress has also continued during this period with several collaborative programs. The first large-scale clinical tungsten-188/rhenium-188 generator prototype (500 mCi) was fabricated and supplied to the Center for Molecular Medicine and Immunology (CMMI), in Newark, New Jersey, for Phase I clinical trials of rhenium-188-labeled anti CEA antibodies for patient treatment (D. M. Goldenberg, M.D., R. Sharkey, Ph.D., and colleagues). Collaborative studies are also continuing in conjunction with the Nuclear Medicine Department at the University of Massachusetts where a generator is in use to compare the biological properties of "direct" and "indirect" labeled antibodies (D. Hnatowich, Ph.D., et al.).

RESOLUTION, RADIOIODINATION AND *IN VIVO* EVALUATION
OF ISOMERS OF THE CHOLINERGIC-MUSCARINIC ANTAGONIST, "IQNP"

Muscarinic cholinergic receptors (m-AChR) play an essential role in many physiological and behavioral responses and it is well established that changes in m-AChR have been implicated in various disease states in addition to memory functions, learning and aging. These observations have stimulated interest in the possibility of imaging the distribution of cerebral m-AChR binding sites non-invasively *in vivo* with external imaging techniques. We have recently reported the preparation of a high affinity muscarinic antagonist, IQNP (Figure 1), which demonstrates *in vivo* selectivity and specificity for m-AChR (ORNL/TM-12110, ORNL/TM 11811 and ORNL/TM 11992 and Ref. 1). IQNP is an analogue of 3-quinuclidinyl benzilate (QNB), and is radioiodinated in high yield (> 60 %) with high specific activity from a tributylstannyl derivative. Carbon-3 of the quinuclidinyl moiety and the carbon-2 of the acetate moiety are asymmetric centers and the vinylic iodide can have either the E or Z configuration. Eight different isomeric combinations of "IQNP" are thus possible and our early studies evaluated the biodistribution (ORNL/TM-11881) and receptor reactivity and specificity of the racemic mixture.¹ Since the racemic mixture showed good specificity for the muscarinic receptor, our studies have now focused on identifying the most active component(s) from this mixture, which has required a careful and systematic synthesis of each isomer (Scheme 1). We have initiated the synthesis and biological evaluation of the various stereoisomers to determine the optimum stereochemistry which imparts the maximum affinity for m-AChR.

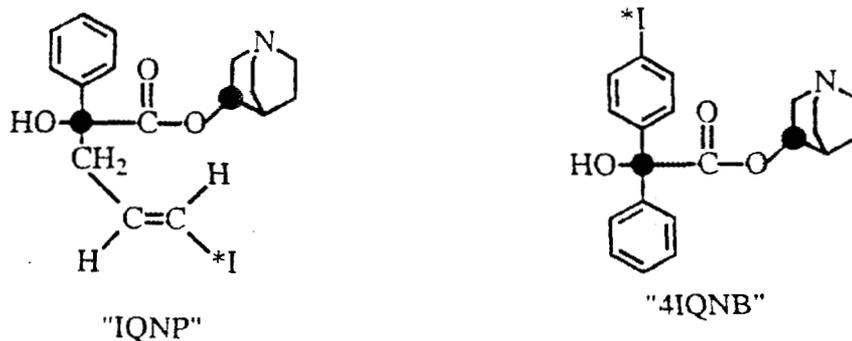
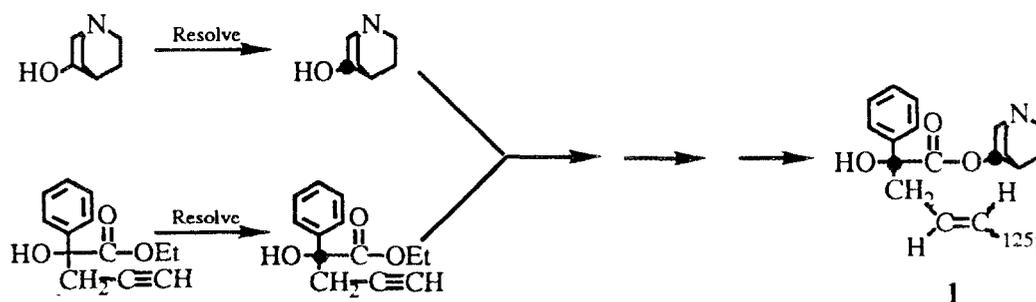


Figure 1.

Since the R configuration of the quinuclidinyl moiety has been reported to be 100 times more active than the S configuration², initially 3-quinuclidinol was resolved and (E,Z)-(R)-3-quinuclidinyl(R,S)- α -hydroxy- α -([¹²⁵I]-1-iodo-1-propen-3-yl)- α -phenylacetate[(E,Z)-(R)(R,S)-IQNP] was prepared as shown in Scheme 1 for evaluation in female rats (the first stereochemistry center refers to the quinuclidinyl moiety and the second center refers to the acetate moiety; see Figure 1). The results of our study are shown in Table 1 and illustrate that uptake in receptor rich areas of the brain (cortex, striatum) is twice the uptake observed with the racemic mixture in these regions, after 6 hours. Also, through careful separation of the racemic mixture utilizing a silica gel flash column with 98:2:1 chloroform:methanol:ammonium hydroxide mobile phase, we were initially able to isolate the E-(R,S)(S)-, (E)-(R,S)(R)-, and (Z)-(R,S)(R)- isomers of IQNP.

The iodine-125-labeled isomers were evaluated in female rats and results of these studies (Table 1) demonstrate that the (E)-(R,S)(S) isomer washes out quickly from receptor rich areas while the (E)- and (Z)-(R,S)(R) isomers are retained in the cortex and striatum. The major difference observed in the (E) and (Z) isomers of (R,S) (R)-IQNP is the relative uptake of activity in the heart and cerebellum. The heart to blood ratios of the (E) and (Z)-isomers are 1.0 to 1 and 2.5 to 1, respectively, after 6 hours. The M₂ subtype is found in the heart and cerebellum³ (low pirenzepine affinity) and these results suggest that the receptor subtype specificity may be influenced by the configuration around the double bond.



Scheme 1. Preparation of the various isomers of IQNP (1).

The next step of the systematic preparation of the various stereoisomers involved the resolution of α -hydroxy- α -phenyl- α -(1-propyn-3-yl)acetic acid which were resolved using quinidine and quinine. The E-(R)(R), Z-(R)(R), E-(R)(S), Z(R)(S)-isomers of IQNP were then prepared using analogous methods that had been used in the preparation of the racemic mixture (Scheme 1), and characterized by NMR, HPLC, elemental analysis and specific rotation. As a key example, (E)-(R)(R)- and (E)-(R)(S)-[¹²⁵I]-QNP were prepared and evaluated in female rats and the results are shown in Figures 2 and 3, respectively. As expected, (E)-(R)(R)-[¹²⁵I]-QNP demonstrates high uptake in receptor-rich areas of the brain while uptake in the heart, although high initially, washes out over the time period of the experiment. (E)-(R)(S)-[¹²⁵I]-QNP demonstrates rapid washout from these same areas. The dramatic effect of the absolute configuration of the asymmetric acetate center was unexpected. The (Z)-(R)(R)- and (Z)-(R)(S) isomers of IQNP were also prepared, radiolabeled and evaluated in female rats. The results of these studies are also shown in Table 1. As expected the uptake of Z-(R)(R)-IQNP was high in both the heart and resulting in a heart to blood ratio of 5.4 : 1 and cortex to cerebellum ratio of 5.4 : 1, respectively.

These results demonstrate that (E)-(R)(R)-[¹²⁵I]-QNP has high uptake and low nonspecific binding in cerebral m-AChR rich areas, while Z-(R)(R)-IQNP demonstrates high heart uptake. These are thus excellent candidates for further development as agents for *in vivo* detection of m-AChR by SPECT. In addition, in a collaboration project in association with the Department of Nuclear Medicine at the University of Chicago and George Washington University (Drs. R. Reba, and B. Zeeberg) the *in vitro* specificity and selectivity of the various isomers in comparison with QNB are being evaluated.

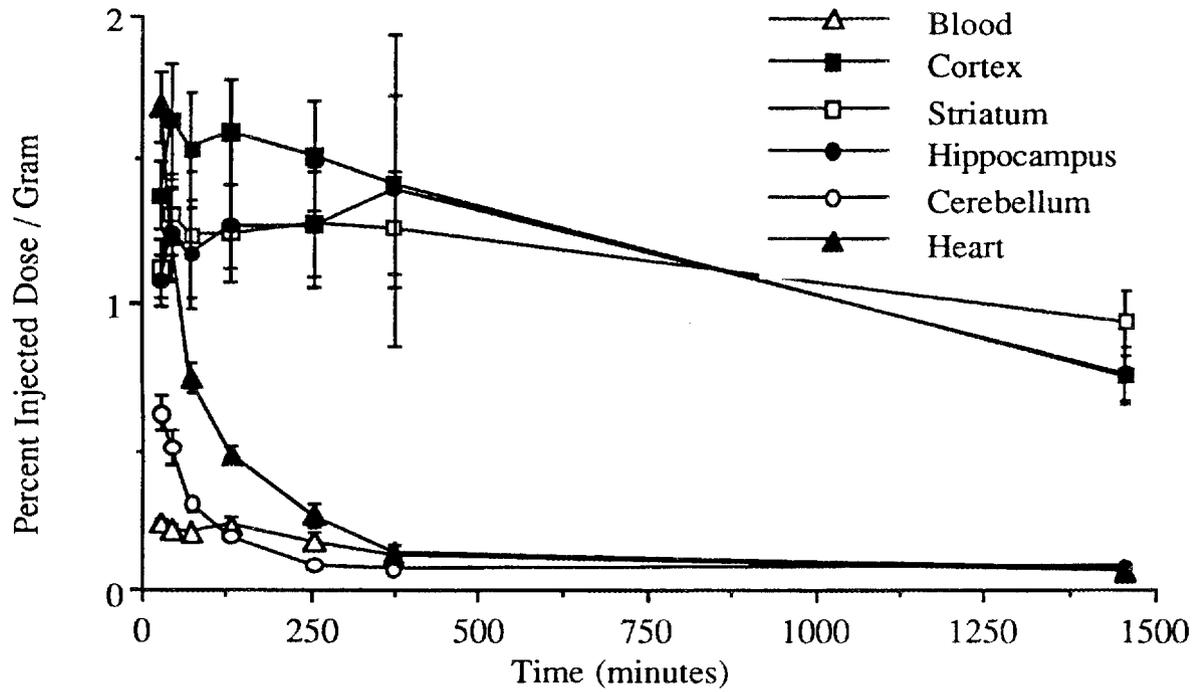


Figure 2. Biodistribution of (E)-(R) (R)[¹²⁵I]QNP in Fischer Female Rats (n=5).

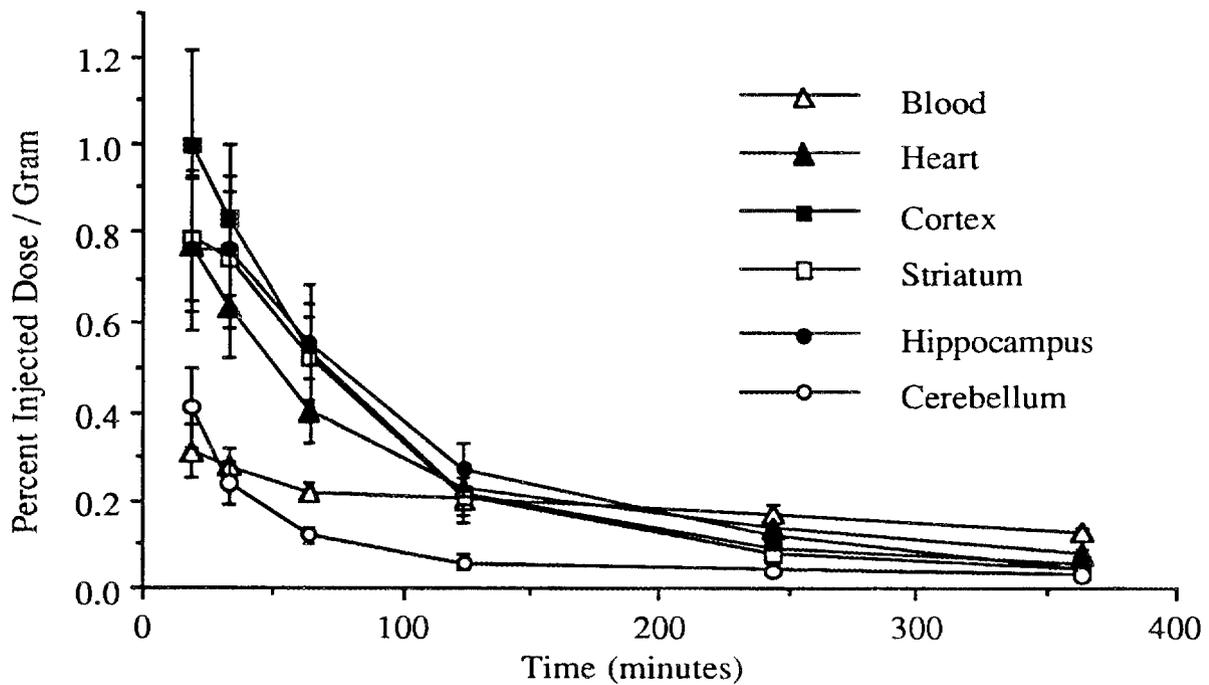


Figure 3. Biodistribution of (E)-(R) (S)[¹²⁵I]QNP in Fischer Female Rats (n=5).

Table 1. Evaluation of Various Isomers of [¹²⁵I]-QNP in Female Fischer Rats at 6 Hours (n=5).

	(E,Z)			(E)			(Z)		
Mean Percent Injected Dose/Gram in Standard Deviation									
Tissue	Racemic Mixture	(R)(R,S)	(R,S)(S)	(R,S)(R)	(R)(R)	(R)(S)	(R,S)(R)	(R)(S)	(R)(R)
Cortex	0.47 ±0.06	0.84 ±0.17	0.06 ±0.00	0.71 ±0.05	1.38 ±0.31	0.04 ±0.00	0.73 ±0.18	1.15 ±0.17	1.52 ±0.25
Striatum	0.41 ±0.07	0.72 ±0.09	0.03 ±0.02	0.56 ±0.05	1.22 ±0.20	0.02 ±0.02	0.59 ±0.14	0.97 ±0.16	1.32 ±0.22
Cerebellum	0.06 ±0.01	0.08 ±0.02	0.02 ±0.01	0.03 ±0.01	0.04 ±0.01	0.01 ±0.01	0.17 ±0.04	0.10 ±0.02	0.28 ±0.05
Heart	0.17 ±0.02	0.24 ±0.05	0.12 ±0.02	0.13 ±0.01	0.10 ±0.02	0.06 ±0.01	0.56 ±0.12	0.34 ±0.05	0.70 ±0.15
Blood	0.21 ±0.02	0.14 ±0.03	0.27 ±0.02	0.16 ±0.02	0.09 ±0.02	0.11 ±0.01	0.20 ±0.04	0.12 ±0.02	0.13 ±0.02
Cortical/ Cerebellar Ratio	7.8	10.5	3.0	23.7	34.5	4.0	4.3	11.5	5.4
Heart/Blood Ratio	0.81	1.7	0.44	0.81	1.1	0.55	2.8	2.8	5.4

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1. McPherson, D. W., DeHaven-Hudkins, D. L., Callahan, A. P., and Knapp, F. F., Jr., J. Med. Chem., 36, 848-854 (1993).
2. Meyerhoffer, A., J. Med. Chem., 15, 994-995 (1972).
3. Sawada Y., Hiraga, S., Francis, B., Patlak, C., Pettigrew, K., Ito, K., Owens, E., Gibson, R., Reba, R., Eckelman, W., Larson, S., and Blasberg, R. G., J. Cereb. Blood Flow etab., 10, 781-807 (1990).

STATUS OF NEW LABORATORY AND OFFICE FACILITIES
FOR ORNL NUCLEAR MEDICINE PROGRAM

The office and laboratory facilities of the ORNL Nuclear Medicine Program are in the processing of moving to new locations. Our offices were recently moved from Building 3047 to Building 4501 and the new Mail Stop number is 6229. The telephone [(615) 574-6223] and facsimile [(615) 574-6226] numbers are unchanged. Renovations and installation of new hoods are in progress in laboratories in the main 4500-N complex for our non-radioactive synthetic laboratory and instrument room. This move is expected to be complete in August 1993. Because of the classification of our radioisotope laboratories in Buildings 3047 and 3026-C to the "Environmental Restoration" list, laboratories are also being renovated for our radioisotope processing, radionuclide generator and radiopharmaceutical synthesis and animal testing activities in Building 4501. These renovations and relocation of these aspects of our program are expected to be complete before the end of the calendar year. Together, these new facilities represent an important resource for the continued growth of our program.

AGENTS FOR MEDICAL COOPERATIVES

During this period a tungsten-188/rhenium-188 generator was fabricated for an ongoing preclinical collaborative program with the Nuclear Medicine Department at the University of Massachusetts (D. Hnatowich, Ph.D., et al.) for comparison of the properties of rhenium-188 "indirect" and "direct" labeled tumor specific antibodies. In addition, the largest clinical prototype

generator to date (500 mCi W-188) was supplied for initial antibody radiolabeling and Phase I patient studies to the Center of Molecular Medicine and Immunology (CMMI) in Newark, New Jersey (D. M. Goldenberg, M.D. and R. Sharkey, Ph.D.). Tin-177m prepared by the $^{117}\text{Sn}(n,n,\gamma)^{117\text{m}}\text{Sn}$ reaction was supplied for patient studies in a collaborative program between the Nuclear Medicine Department at Stonybrook University (H. Adkins, M.D.) and the Medical Department at BNL (L. Mausner, Ph.D.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

McPherson, D. W., Dehaven-Hudkins, D. L., Callahan, A. P., and Knapp, F. F., Jr. "Synthesis and Biodistribution of Iodine-123-Labeled 1-Azabicyclo[2.2.2]oct-3yl α -hydroxy- α -1-iodo-1-propen-3-yl)- α -phenyl acetate - A New Ligand for the Potential Imaging of Muscarinic Receptors by Single Photon Emission Computed Tomography," *J. Med. Chem.*, **36**, 848-854 (1993).

Meeting Presentations

Several papers were presented and co-authored by members of the Nuclear Medicine Group at both major national and international meetings:

Society of Nuclear Medicine 40th Annual Meeting, Toronto, Canada, June 7-11, 1993

McPherson, D. W., DeHaven-Hudkins, D. L., Callahan, A. P., Lambert, C. R., Mohn, K., Trankle, C., Holzgrabe, U., Biersach, J.-J., Wang, G.-J., Som, P., and Knapp, Jr., F. F. "*In Vitro and In Vivo* Evaluation of IQNP: A High Affinity Muscarinic Antagonist," *J. Nucl. Med.*, **34**, 54 (1993).

McPherson, D. W., Callahan, A. P., Hudkins, R. L., and Knapp, Jr., F. F. "Synthesis, Radioiodination and *In Vivo* Evaluation of (I-125)-Iodocaramiphen (ICAR) - A Candidate for Muscarinic Receptor Studies," *J. Nucl. Med.*, **34**, 236 (1993).

Sharkey, R. M., Goldenberg, D. M., Levine, G., Vagg, R., Ahmad, M., Pawlyk, D., Siegel, J. A., Griffiths, G. L., Hasen, H. J., Callahan, A. P., and Knapp, Jr., F. F. "Phase I Radioimmunotherapy (RAIT) Using a Rhenium-188-Labeled Murine Monoclonal Antibody (MAb)," *J. Nucl.*, 34, 54 (1993).

Som, P., Wang, G.-J., Oster, Z. H., McPherson, D. W., and Knapp, Jr., F. F. "Wholebody Distribution of a New Selective Muscarinic Antagonist: Radioiodinated IQNP," *J. Nucl. Med.*, 34 197 (1993).

Visser, F. C., Sloff, G. W., E.F.I., Comans, Knapp, Jr., F. F., "Metabolism of Radioiodinated Heptadecanoic Acid in Normal, Ischemic and Hypoxic Canine Myocardium," *J. Nucl. Med.*, 34, 15 (1993).

First International Conference on Nuclear Cardiology, Cannes, France, April 25-28, 1993

Kropp, J., Koehler, U., Zierz, S., Knapp, F. F., Jr., Von Smekal, A., and Biersack, J.-J. "Evaluation of Myocardial Involvement in Patients with Systemic Myopathies with 15-(p-iodophenyl)pentadecanoic acid (IPPA) SPECT."

Kropp, J., Joergens, M., Glaenger, K., Knapp, F. F., Jr., and Biersack, H.-J, "Evaluation of Ischemia and Myocardial Viability in Patients with CAD with the Fatty Acid 15-(p-iodophenyl)-3-R,S-methylpentadecanoic Acid (BMIPP)."

Wang, G. J., Som, P., Oster, A. H., Knapp, F. F., Jr., Volkow, N. D., and Sacker, D. F., "Cocaine-Induced Regional Myocardial Metabolic Changes in Hypertensive Rats."

Annual Meeting of the Belgium Nuclear Medicine Society, May 9, 1993

Clinical studies with an ORNL cardiac imaging agent describing collaborative studies between the ORNL Nuclear Medicine Program and the Free University of Brussels were recently discussed at the Annual Meeting of the Belgium Nuclear Medicine Society on May 9, 1993.

De Geeter, F., Franken, P., De Sadeleer, C., Knapp, F. F., Jr., and Bossuyt, A., "Relative Myocardial Distribution of Tc-99m-MIBI and I-123- β -methyl-15-(p-iodophenyl)pentadecanoic Acid (BMIPP) in Myocardial Infarction."

Guests Assignments

Hollander Postdoctoral Fellowship Awarded for Research in ORNL Nuclear Medicine Program

A prestigious Alexander Hollander Distinguished Postdoctoral Fellowship has been awarded to Huimin Luo, Ph.D., to work in the ORNL Nuclear Medicine Program on the development of receptor ligands for the imaging of cerebral and cardiac receptors. Dr. Luo completed her doctoral work at the University of Tennessee and is expected to initiate her postdoctoral studies at ORNL in August. The award is supported by the Office of Health and Environmental Research (OHER), U.S. Department of Energy.

Collaborator Joins ORNL Nuclear Medicine Program Through INER

B.-T. Hseih, Ph.D., a radiochemist from the Institute of Nuclear Energy Research (INER) in Lung-Tan, Taiwan, joined the ORNL Nuclear Medicine Program for a six-month collaborative research assignment to conduct radioisotope generator research under the auspices of the AIT-CCNAA Civil Nuclear Cooperative Active Working Item between the U.S. and Taiwan.

NATO Grant Received for Collaborative Research

F. F. Knapp, Jr., has received a renewal for a NATO Collaborative Research Grant in conjunction with J. Kropp, M.D, at the Clinic for Nuclear Medicine at the University of Bonn, Germany, for continuing studies of the development and clinical use of radioiodinated fatty acid analogues for the evaluation of cardiac disease and gastrointestinal disorders.

Participation in Neuro-PET Symposium

D. W. McPherson presented an invited lecture at the April 23 Symposium describing the ORNL Nuclear Medicine Program development of new radioiodinated antagonists which bind to the cholinergic-muscarinic receptor. These agents are being developed for the evaluation of changes in receptor activity or density in various neurological diseases.

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