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MARTIN MARIETTA

Nuclear Medicine Program Progress Report for Quarter Ending December 31, 1993

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Health Sciences Research Division

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FOR QUARTER ENDING DECEMBER 31, 1993

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SUMMARY

In this report, the results of preliminary *in vivo* metabolic studies of the iodine-125-labeled E-(R,R)-"IQNP" in rats are described. The E-(R,R) isomer demonstrates highly selective and specific localization in cerebral regions rich in the m_1 and m_4 muscarinic-cholinergic receptor subtypes and is a good candidate for potential human studies. Since the external evaluation of receptor-ligand complexes requires that only uptake of the unmetabolized agent is measured, these studies were performed to evaluate the metabolism of the radioiodinated ligand in the whole brain, heart, liver and serum from rats at several time points after intravenous administration. One group of rats was also housed in metabolism cages and urine and feces collected daily over a seven-day period. Radioactivity was very rapidly excreted in the first 24-hour period (urine = $46.33 \pm 5.28\%$; feces = $26.62 \pm 1.48\%$).

Folch extracts of the different tissue samples showed that the lipid-soluble extract from brain tissue contained 87.0 ± 1.65 of the activity up 24 hours. In the heart, $61.9 \pm 7.50\%$ of the activity was extracted in the lipid soluble extract after 30 minutes and decreased to $51.4 \pm 0.65\%$ after 4 hours. In contrast, data from other tissues studies demonstrated large amounts of either aqueous soluble activity or activity which was not extracted from the tissue pellet material [lipid extracts: liver (4h), $7.43 \pm 0.96\%$; serum (4h), $3.73 \pm 0.87\%$; urine (1d), 9.4% ; feces (1d), 16.5%]. Thin-layer chromatographic (TLC) analysis of the lipid soluble extracts indicated that only the unmetabolized E-(R,R)-IQNP was detected in brain extracts ($99.4 \pm 1.25\%$). Although the activity in the heart was determined to contain a large amount of unmetabolized ligand after 4 hours ($88.5 \pm 0.57\%$), two other radioactive products were detected and increased with time. TLC analysis of the serum lipid extracts indicated a small amount of unmetabolized E-(R,R)-IQNP present, however, the liver, serum, feces and urine lipid extracts contained only metabolites. These initial studies clearly indicate that radioactivity present in the brain after intravenous administration of radioiodinated E-(R,R)-IQNP represents only the unmetabolized ligand.

Also in this report, the predicted medical radioisotope production capabilities of the proposed Advanced Neutron Source (ANS) are discussed. The ANS is a new reactor proposed for construction at ORNL, which will replace the High Flux Isotope Reactor (HFIR), and is planned for operation late in this century. The radioisotopes production capabilities will nearly double the capabilities for the HFIR (i.e. thermal neutron flux), and will represent an important national resource for medical radioisotopes.

Metabolic Studies with Radioiodinated E-(R,R)-IQNP - A New Agent for Imaging Cerebral Muscarinic Receptors

The importance of imaging the distribution of cerebral muscarinic cholinergic receptors (m-AChR) binding sites non-invasively *in vivo* with external imaging techniques results from their essential role in many physiological and behavioral responses. In addition, changes in m-AChR have been implicated in various disease states, including memory function, learning and aging. The IQNP agent (Figure 1) is a high affinity muscarinic antagonist analogue of 3-quinuclidinyl benzilate (QNB), and is radioiodinated in high yield (> 60 %) with high specific activity from a tributylstannyl derivative. We have recently reported the *in vivo* selectivity and specificity of IQNP for m-AChR (ORNL/TM-12411). Carbon-3 of the quinuclidinyl moiety and 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. Our early studies evaluated the biodistribution and receptor uptake and specificity of the racemic IQNP mixture,¹ which showed high affinity for the muscarinic receptor. Our studies have now focused on identifying the most active component(s) from this mixture. These studies have required a careful and systematic synthesis of each isomer, and we have pursued the synthesis and biological evaluation of the various stereoisomers to determine the optimum stereochemistry which imparts the maximum affinity for m-AChR. Initial studies have shown that the R isomer of the quinuclidinyl ester is more active than the R isomer of the S configuration. We have thus prepared and investigated the 4 stereoisomers which contained the R-quinuclidinyl ester. The acetate moiety was then resolved and additional *in vitro* and *in vivo* studies demonstrated that (E)(R,R)-3-quinuclidinyl-(R)- α -hydroxy- α -([¹²⁵I]1-iodo-1-propen-3-yl)- α -phenylacetate [(E)-(R), (R)-IQNP] had high affinity for the m₁ receptor subtype. We therefore chose this isomer for initial metabolic studies in female rats.

These initial, preliminary studies were performed using female Fisher VAF rats. For these studies [¹²⁵I]-E (R,R) IQNP was dissolved in 100 μ L of ethanol followed by 50 μ L of a 0.1 N HCl solution and diluted to 10 mL with normal saline. The [¹²⁵I]-E (R,R)-IQNP (25 μ Ci/rat) was administered by intravenous injection into a lateral tail vein to metofane-anesthetized rats. The rats were divided into 5 groups (n=3 each) and were allowed food and water *ad libitum* prior to and during the course of the experiment. One group of rats was housed in metabolism cages and urine and feces collected daily over a period of seven days. The other four groups of rats were euthanized by cervical fracture following metofane anesthesia at 30 and 60 minutes, and 4 and 24 hours after the injection of the [¹²⁵I]-E-(R,R)-IQNP. The brain, heart and liver were removed, rinsed with saline, blotted dry and weighed in tared vials.

Heparinized blood samples were obtained from the chest cavity after removal of the heart. The samples were counted in a Packard Minaxi 5000 sodium iodide auto gamma counter.

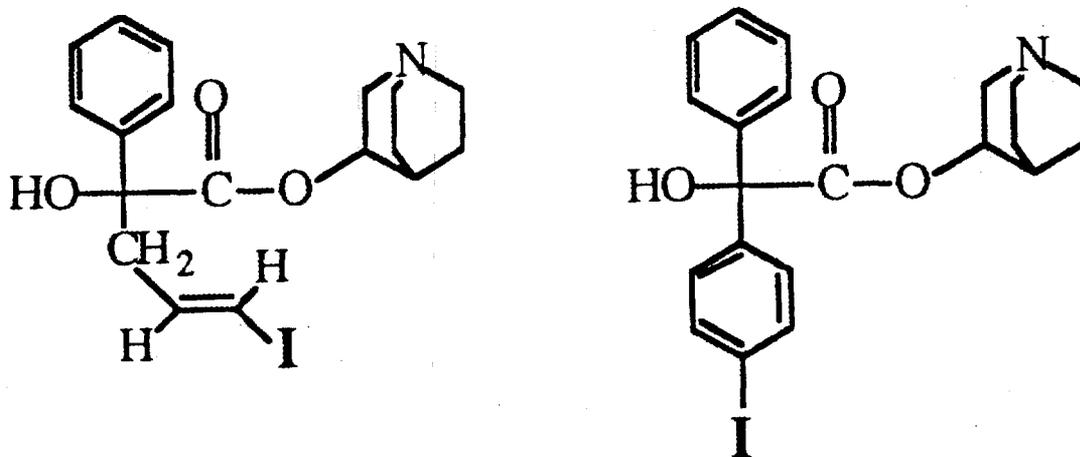


Figure 1. Chemical structures of "IQNP" and "IQNB".

Tissue samples were extracted with chloroform:methanol (2:1) by the traditional Folch technique using a loose-fitting Potter-Elmehahn ground glass homogenizer. For the brain and heart, the chilled samples were finely minced in a glass watch glass and then homogenized for 3 min in 10 mL of the 2:1 chloroform-methanol mixture. Because of the large tissue mass, the livers were weighed and then 0.5-1 gm aliquots taken and minced and extracted in the same manner. Blood samples were heparinized and centrifuged and the serum samples then homogenized and extracted. Attempted extraction of the cellular pellets by this procedure resulted in an intractable mass. A sample of [125 I]-E-(R,R)-IQNP was also subjected to the Folch extraction procedure in the same manner, and served as a control.

The extracts was filtered through filter paper into centrifuge tubes and then thoroughly mixed after addition of 2 mL of normal saline and centrifuged at low speed for 5-10 minutes to separate the organic (lower) and aqueous layers. The organic layers were filtered through a layer of anhydrous sodium sulfate and evaporated to dryness under an argon stream. The evaporated organic and aqueous fractions and the

filter paper containing the tissue pellet were then counted in a gamma counter. Aliquots of the organic residues were analyzed by TLC using silica gel-coated aluminum sheets using either 15% methanol-chloroform (System A) and 30% methanol-chloroform (System B), or chloroform acetic acid, 2:1 (System C).

Analysis of the brain extracts clearly indicated that essentially all the activity was extracted into the organic layer (Table 1). The TLC and HPLC analyses of brain lipid extracts (Figure 2) demonstrated that only unmetabolized IQNP is identified in brain tissue, while the other tissues analyzed contained other components. As an example, the heart extracts contained primarily the unmetabolized IQNP but two minor components, one more polar and one less polar than IQNP slowly increased with time. The identify of these two components is not known but the time dependence of their increase would indicate that they may be metabolites of IQNP. In contrast, the majority of activity remained in the aqueous extracts of the liver samples (Table 2).

Urine and feces were collected daily for seven days, which demonstrated rapid and high excretion of radioactivity in the urine and feces with about 60% of the excretory activity in the urine (Table 3). We presume the fecal activity represents hepatobiliary excretion of radioiodinated IQNP metabolites. Samples of the urine from Day 1 and Day 2 were applied to silica gel plates and analyzed in the three solvent systems. For the feces, small aliquots from Day 1 were homogenized as described above. Both the organic extract and aqueous layers were analyzed using the three solvent systems. The organic layer was then analyzed in System A. These analyses demonstrated that the urine and feces contained metabolites more polar than IQNP.

Table 1. Summary of Distribution in the Organic, Aqueous and Pellet Fractions of Tissues Analyzed After Administration of [¹²⁵I]-E-(R,R)-IQNP*

Tissue	Time	Total Activity			Soluble Activity	
		Organic Mean % ± SD	Aqueous Mean % ± SD	Filter/Pellet Mean % ± SD	Organic Mean % ± SD	Aqueous Mean % ± SD
Control		87.2±4.78	6.56±0.32	6.29±4.46	93.0±0.61	7.0±0.61
Brain	30 min	72.8±8.10	1.56±1.25	25.6±6.98	97.8±2.00	2.16±2.04
	60 min	87.2±1.14	1.03±0.25	11.7±1.39	98.8±0.31	1.17±0.53
	4 h	82.9±1.99	2.40±0.46	14.7±1.92	97.2±0.53	2.80±0.53
	24 h	87.0±1.65	1.13±0.15	11.8±1.75	98.7±0.21	1.17±0.12
Heart	30 min	61.9±7.50	11.5±1.58	26.6±8.09	84.3±2.02	15.7±2.02
	60 min	72.0±1.22	12.5±0.70	15.4±1.35	85.1±0.74	14.9±0.74
	4 h	51.4±0.65	20.5±1.33	28.2±1.89	71.5±1.09	28.5±1.09
	24 h	47.7±3.03	25.2±2.19	28.9±1.65	67.3±4.80	32.7±4.81
Liver	30 min	23.4±0.92	16.2±1.78	60.4±1.16	59.1±3.59	40.9±3.53
	60 min	14.5±1.29	9.60±1.45	75.8±1.65	60.3±4.76	39.7±4.76
	4 h	7.43±0.96	4.80±1.55	87.8±1.55	60.8±1.22	39.2±1.22
	24 h	7.76±0.55	3.06±0.35	89.1±0.87	71.8±1.15	28.2±1.15
Blood Serum	30 min	8.96±3.71	51.43±15.1	39.6±13.1	15.7±8.53	84.3±5.83
	60 min	6.73±3.95	53.97±8.95	39.3±12.8	10.5±4.06	89.5±4.06
	4 h	3.73±0.87	64.1±5.88	32.1±6.37	5.46±0.99	94.5±0.98

* Three female Fischer rats for each time point.

Table 2. Summary of Per Cent of IQNP Identified by TLC in the Organic Extracts of Tissues After Administration of [¹²⁵I]-E-(R,R)-IQNP*

Tissue	Time	Per Cent Total Activity in IQNP ± SD
Brain	30 min	99.4±0.19
	60 min	99.7±0.25
	4 h	99.4±0.73
	24 h	98.4±1.25
Heart	30 min	97.7±3.93
	60 min	92.3±0.83
	4 h	88.5±0.57
	24 h **

* Three female Fischer rats for each time point

** Insufficient radioactivity for analysis.

*** Remainder of radioactivity streaked on TLC plates with no clearly identified radioactive peaks.

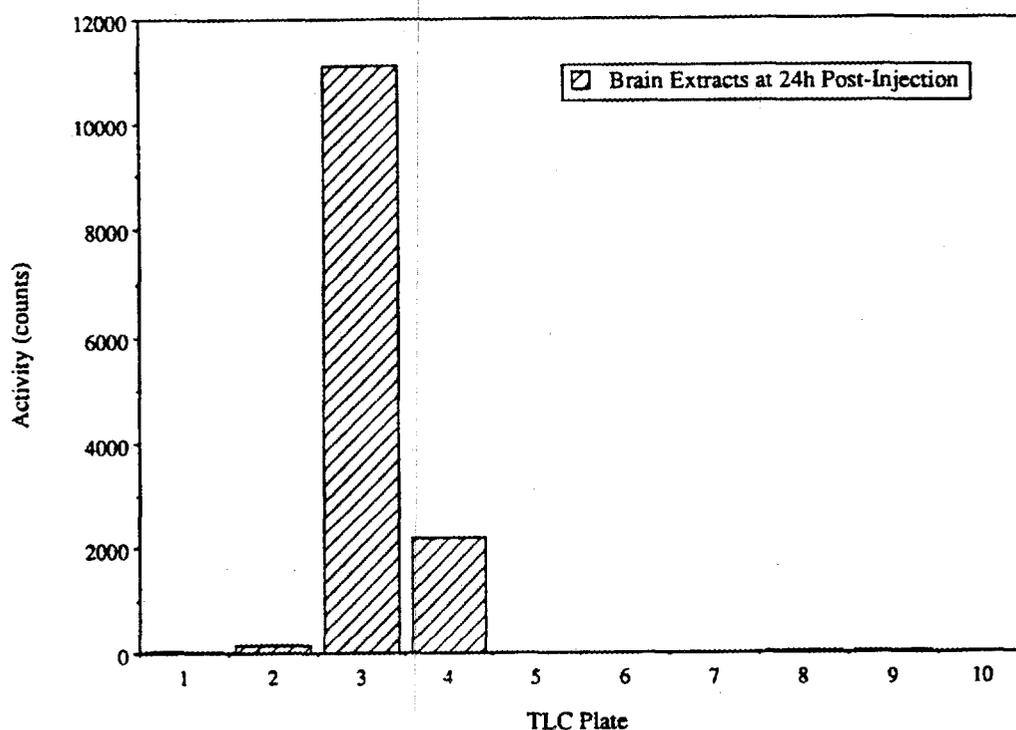


Figure 2. Thin-layer chromatogram of radioactivity in Folch-extracted lipids from whole brains of rats four hours following intravenous administration of [125 I]-E-(R,R)-IQNP (n=3).

Our recent studies have demonstrated that E (Trans)-(R,R)-IQNP has high affinity for those regions of the brain which have the greatest concentration of the muscarinic-cholinergic receptor and identified this isomer as the best candidate to study the cerebral m1 receptor and for possible human evaluation. Our goal in the current study was to study the metabolism of the radioiodinated E-(R,R) isomer in rat tissue *in vivo* in order to determine the metabolic fate of the ligand and the time course of formation of metabolic products. In these initial studies global analysis of the brain contents indicated that unmetabolized IQNP was the sole radioactive component of brain extracts analyzed by TLC and HPLC. Analysis of the excretory products animals housed in metabolism cages also provided an opportunity to analyze excretion over a seven-day period and to obtain some information on the chromatographic properties of the excretion products.

Table 3. Radioactive Contents in Urine and Feces After Intravenous Administration of ^{125}I -E-(R,R)-IQNP to Rats*

Mean \pm SD Per 6 Day

Days After Injection	Urine	Feces	Cumulative Mean Total Excreted
1	46.33 \pm 5.28	26.62 \pm 1.48	72.9%
2	1.90 \pm 0.16	6.33 \pm 2.19	81.1%
3	1.15 \pm 0.30	1.44 \pm 0.14	83.7%
4	0.58 \pm 0.16	0.66 \pm 0.15	84.9%
5	0.49 \pm 0.20	0.56 \pm 0.17	85.9%
6	0.33 \pm 0.11	0.34 \pm 0.08	86.6%
7	0.25 \pm 0.05	0.25 \pm 0.09	87.1%

**MEDICAL RADIOISOTOPE PRODUCTION
IN THE ADVANCED NEUTRON SOURCE (ANS)-
A PROPOSED NEW RESOURCE FOR THE UNITED STATES**

A major area of current interest is the treatment of various types of cancer with therapeutic radioisotopes. In this manner, cancer can be treated using therapeutic antibodies attached, for instance, to antibodies specific for tumor cells ("Radioimmunotherapy"). Other therapeutic applications include treatment of arthritis of the fluid-filled joints ("Radioisotope Synovectomy") and treatment of bone pain associated with metastasis of cancer to the skeleton ("Palliation"). Most therapeutic radioisotopes of current interest are reactor-produced, and for this reason the ORNL High Flux Isotope Reactor (HFIR) is an important resource. The proposed ANS will also be expected to play an important role in making a greater source of therapeutic radioisotopes available. The ANS may play another potentially important role in the production of molybdenum-99. There are currently no commercial or U.S. Government reactors with the facilities required for processing fission-produced molybdenum-99. Production of molybdenum-99 by neutron activation of enriched molybdenum-98 is an attractive alternative, if the neutron flux and thus the production yields are sufficiently high. The ANS will be more considerably more powerful than the HFIR (e.g. higher neutron flux), and may thus represent a unique opportunity to produce molybdenum-99 by the neutron activated route (e.g. activation of enriched molybdenum-98) rather than the fission process. In this manner, the major logistical and expense problems associated with the disposal of the waste involved in processing fission products can be avoided. Thus, the ANS may represent an important facility for routine production of molybdenum-99 for medical applications well into the future.

The ANS and Medical Radioisotope Research and Production

Most radioisotopes that are or can be produced by a nuclear reactor can be produced by the ANS. In general, higher levels and higher specific activity (e.g. units of radioactivity per mass of target material; Curies/Gram) products can be produced by the ANS because of the greatly increased neutron flux. Tables 4-6 summarize key examples of reactor-produced radioisotopes. The current production capabilities of the HFIR and the anticipated production capabilities of the ANS are important where a high neutron flux is required. For the isolation of radioisotopes from fission products or radioisotopes which have a short half-life and a large production cross section, reactors with the lower thermal neutron flux are usually sufficient and high thermal neutron flux is not required.

**Table 4. Examples of Reactor-Produced Radioisotopes Currently Used
for Clinical Applications and Distributed Commercially**

Radioisotope	Application
<u>Diagnostic Applications:</u>	
Molybdenum-99	Decays to Technetium-99m which is the most Widely Used Radioisotope in Clinical Nuclear Medicine
Xenon-133	Used for Lung Ventilation Studies
<u>Therapeutic Applications:</u>	
Californium-252	Cancer Therapy
Rhenium-186	Bone Cancer and Tumor Therapy
Palladium-103	Treatment of Prostatic Cancer
Phosphorus-32/33	Cancer Therapy and Important Application in Genome Research
Strontium-89	Recently approved by the FDA for routine Clinical Use to Treat Bone Cancer
Strontium-90	Decays to Yttrium-90 - Used for Cancer Therapy

The highest flux available is required, however, for production of long-lived radioisotopes, many radioisotopes which require a very high specific activity, and in particular those which are produced by double neutron capture. An example of a radioisotope for therapy produced by single neutron capture which is of current interest is rhenium-186, where the highest specific activity possible is required for radiolabeling tumor-specific antibodies.

High neutron flux is an especially important requirement to optimize yields of radioisotopes produced by successive double neutron captures, where the production yields are a function of the square of the

neutron flux. Tungsten-188 and dysprosium-166 are two key examples which are efficiently produced in the HFIR, and one would predict even higher affinity in the ANS.

In terms of projecting through this decade into the next century, it is also important to stress that the HFIR has a finite operational life. When the HFIR is no longer operational, a new alternative reactor such as the ANS must be available to provide a source of many of the radioisotopes which are expected to be of interest for nuclear medicine. If an alternate, new, state-of-the-art reactor is not available, research on reactor-produced radioisotopes and reactor production of medical radioisotopes in the U.S. would be expected to be significantly impaired, and therefore would have significant detrimental effects on both health delivery in the U.S. and continued medical radioisotope research.

Table 5. Examples of Reactor-Produced Radioisotopes Which Have Applications Developed and Established Clinical Studies and Expected to Have Broad Commercial Market in the Near Future

Radioisotope	Application
<u>Diagnostic Applications:</u>	
Copper-64	Various Diagnostic Agents
Osmium-191	Decays to Iridium-191m - Used for Heart Function Tests
Platinum-195m	Pharmakokinetic Studies of Antitumor Agent
<u>Therapeutic Applications:</u>	
Copper-67	Cancer Therapy
Dysprosium-165	Arthritis Therapy
Dysprosium-166	Decays to Holmium-166 For Cancer Therapy
Erbium-169	Arthritis Therapy
Gold-199	Used for Arthritis and Cancer Therapy
Holmium-166	Cancer Therapy
Iridium-192	Cancer Therapy
Rhenium-186	Cancer Therapy, Treatment of Arthritis
Samarium-145	Treatment of Ocular Cancer
Samarium-153	Palliative Treatment of Bone Cancer Pain
Tin-117m	Palliative Treatment of Bone Cancer Pain
Tungsten-188	Decays to Rhenium-188 for Treatment of Cancer and Arthritis

Neutron Activation Production of Molybdenum-99

As discussed earlier, there may be distinct long-term advantages for routine production of molybdenum-99 (Mo-99) by neutron activation of enriched molybdenum-98 targets. For fabrication of Mo-99/Tc-99m generators, the principal issue which differentiates fission-produced Mo-99 from neutron-activated production of Mo-99 is specific activity. Since the fission route produces high levels of radioactive waste, the preferred route for Mo-99 production would be expected to be by neutron-activation, if sufficient specific activity could be attained. With its very high neutron flux, the ANS may offer for the first opportunity the routine production of Mo-99 by neutron activation with high enough specific activity for generator fabrication. A comparative method was used for calculation of the projected molybdenum-99 production yields from neutron irradiation of enriched molybdenum-98 shown in Figure 3. These calculations consider the higher neutron flux of the ANS relative to the HFIR, assuming that the ANS has at least two times the thermal neutron flux than the HFIR (e.g. Hydraulic tube position #4 of the ANS is expected to have a peak thermal flux which is 100% greater than the maximal flux available in the HFIR). The calculations also account for the resonance integrals (epithermal neutrons) for neutron capture by the molybdenum-98 target atoms.

Table 6. Examples of Reactor-Produced Radioisotopes Currently Under Preclinical Evaluation and Expected to Have Potential Medical Applications

Radioisotope	Application
<u>Therapeutic Applications:</u>	
Arsenic-77	Cancer Therapy
Osmium-194	Decays to Iridium-194 - For Cancer Therapy
Einsteinium-253	Antibodies for Cancer Therapy
Fermium-255	Antibodies for Cancer Therapy
Lutetium-177m	Cancer Therapy
Silver-111	Cancer Therapy

Production of Tungsten-188

Reactor-produced tungsten-188 is a radioisotope of widespread interest since it is used to prepare a generator in which the rhenium-188 radioisotope, formed from decay of the tungsten-188, can be readily obtained for attachment to therapeutic agents such as molecular antibodies. The ANS is expected to produce at least 100% more of the tungsten-188 in a much shorter irradiation time compared to the HFIR, as shown in Figure 4. Increased production capabilities will also conserve target material and greatly reducing the unit costs of this important medical radioisotope.

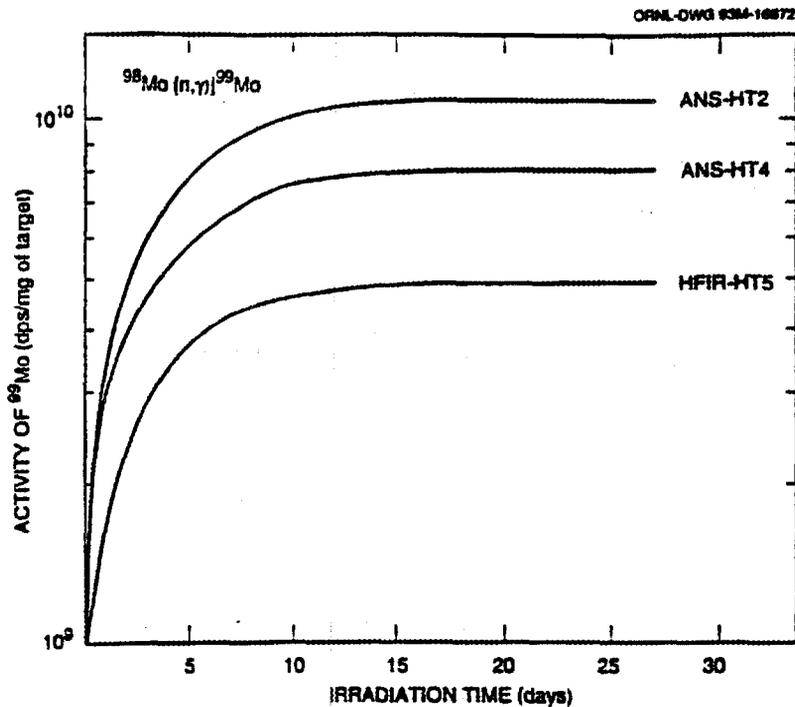


Figure 3. Comparison of Calculated Production Yields of Molybdenum-99 in the HFIR and ANS.

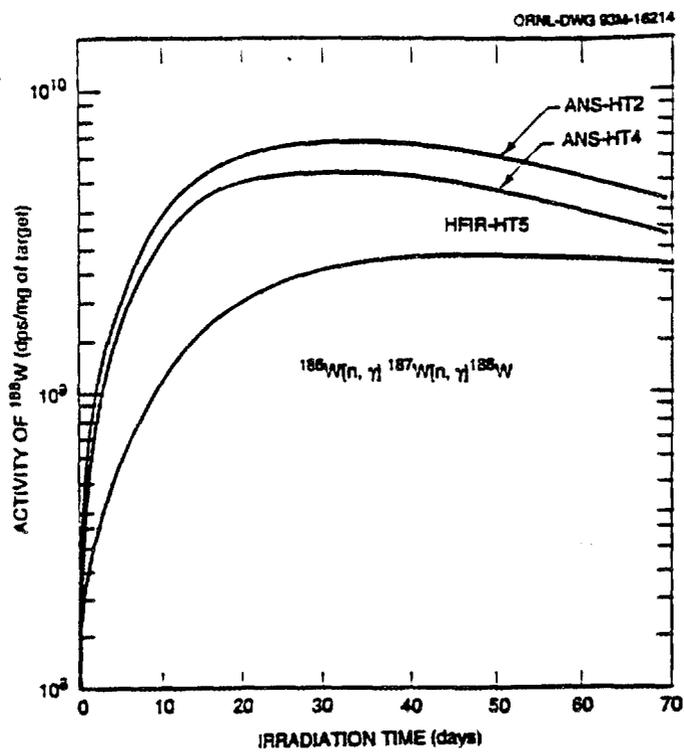


Figure 4. Comparison of Calculated Production Yields of Tungsten-188 in the HFIR and ANS.

Dysprosium-166 decays to Holmium-166 and is also produced by a double neutron capture process, and is another example of the important increased production capabilities of high flux reactors such as the HFIR and ANS, as illustrated in Figure 5.

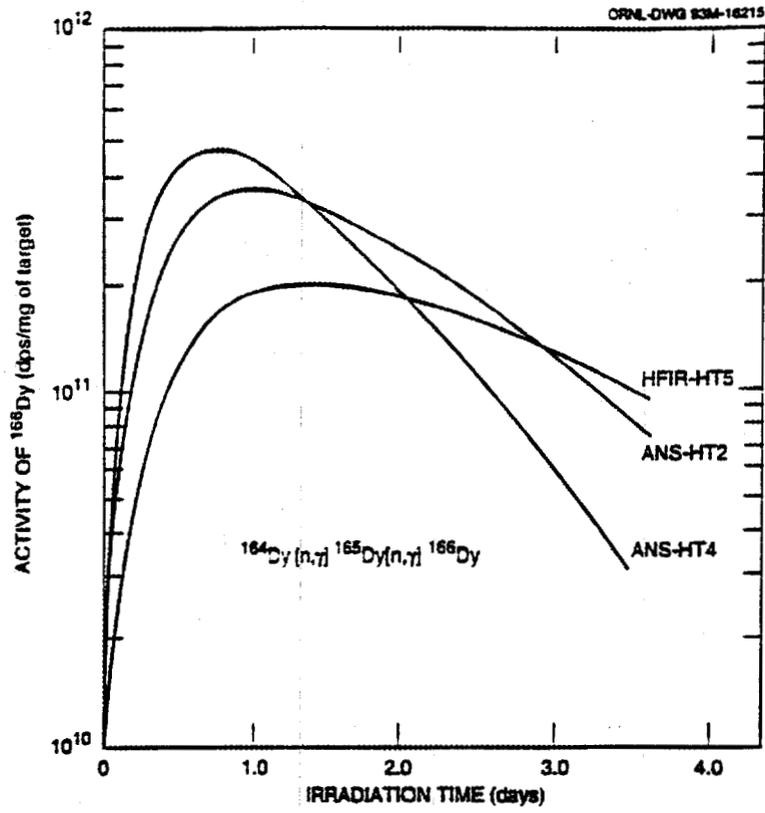


Figure 5. Comparison of Calculated Production Yields of Dysprosium-166 in the HFIR and ANS.

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1. McPherson DW, DeHaven-Hudkins D L, Callahan AP, Knapp FF, Jr., *Med. Chem* 1993; 36:848-854.
2. Gibson RE, Schneidau TA, Cohen VI, and et al. *In Vitro* and *In Vivo* Characteristics of [Iodine-125] 3-(R)-Quinuclidinyl (S)-4-Iodobenzilate. *J. Nucl. Med.* 1989; 30:979-1087.

AGENTS FOR MEDICAL COOPERATIVES

During this period tungsten-188/rhenium-188 generators were supplied to collaborators for various research projects, including the evaluation of rhenium-188-labeled colloids for treatment of arthritis and rhenium-188-labeled NCA antibody for bone marrow ablation at the Department of Nuclear Medicine at the University of Ulm, Germany (Professor S. N. Reske, M.D., et al.). A generator was also supplied for collaborative studies to the Clinic for Nuclear Medicine at the University of Bonn, Germany, to evaluate the radiolabeling of rhenium-188-HEDP for bone marrow pain ablation and various peptides and antibodies as potential antitumor agents (Professor H.-J. Biersack, M.D. et al.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

F. F. Knapp, Jr., "The Development of Radioiodinated Fatty Acids for Myocardial Imaging," Proceedings, 17th New Town Conference on Nuclear Cardiology, Tokyo, Japan, December 1993, pp. 7-12.

Meetings

D. W. McPherson presented a paper at the 10th International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan, October 25-28, 1993. Members of the Nuclear Medicine Program also co-authored several other papers.

McPherson, D. W., Lambert, C. R., Jahn, K., Knapp, F. F., Jr. "Preparation and Biological Evaluation of the Stereoisomers of 3-quinuclidinyl α -hydroxy- α -([¹²⁵I]-1-iodo-1-propen-3-yl)- α -phenylacetate (IQNP). A Novel Ligand for the Imaging of Muscarinic Receptors by SPECT."

Mirzadeh, S., Hetherington, E., Knapp, F. F., Jr., Lambrecht, R. M. "Carrier-free ¹⁶⁶Dy/¹⁶⁶Ho Biomedical Generator System."

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F. F. (Russ) Knapp, Jr., participated in the Annual Congress of the European Association of Nuclear Medicine held in Lausanne, Switzerland, on October 11-15, 1993. He was also an *Invited Professor* in the Nuclear Medicine Department at the University of Ulm, Germany, during the period of October 18-22, 1993, and then visited the Clinic for Nuclear Medicine at the University of Bonn, Germany, to coordinate on-going collaborative projects.

Members of the ORNL Nuclear Medicine Program co-authored several papers describing collaborative clinical studies at the European Nuclear Medicine Congress, which was held in Lausanne, Switzerland, on October 11-15, 1993.

P. R. Franken, F. De Geeter, P. Dendale, F. F. Knapp, Jr., and A. Bossuyt, "Beta methyl-15-(p-iodophenyl)pentadecanoic Acid (BMIPP) and MIBI SPECT to Identify Stunned Myocardium: Correlation with Low-Dose Dobutamine-Gated NMR."

F. F. Deeter, P. Franken, C. De Sadeleer, F. F. Knapp, Jr., and A. Boosuyt, "Relative Myocardial Distribution of Tc-99m hexaMIBI and I-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic Acid in Myocardial Infraction."

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