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MARTIN MARIETTA

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

F. F. Knapp, Jr.

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A. P. Callahan	C. R. Lambert
D. W. McPherson	D. E. Rice
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Health and Safety Research Division

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

F. F. Knapp, Jr., Group Leader

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SUMMARY

In this report we describe the design, synthesis and initial animal testing of a new iodine-131-labeled triglyceride analogue for the potential evaluation of clinical pancreatic insufficiency. The new agent is 1,2-dipalmitoyl-3-[(15-p-iodophenyl)pentadecanoyl]rac-glycerol (1,2-Pal-3-IPPA). Following oral administration of the iodine-125-labeled agent to rats, 34.5+8.8% of the administered activity was excreted in the urine within one day, demonstrating that radioiodinated IPPA is absorbed in the intestine after release from the triglyceride by pancreatic lipase. The final catabolic product of IPPA is then conjugated and excreted via the urinary bladder. Urine analysis following oral administration of this new agent to patients may thus be a new, simple method for the clinical evaluation of various gastrointestinal diseases.

The synthesis and the initial biological evaluation of the 3R-isomer of [¹²⁵I]IQNP are also described in this report. The separation of the (R) and (S) optical isomers of 3-quinuclidinol was accomplished with the use of (+) and (-) tartaric acid after derivatization to 3-acetoxyquinuclidine. Basic treatment of the resolved tartrate salts afforded the resolved 3-quinuclidinol. (R)-1-azabicyclo[2.2.2]octyl-3-yl- α -hydroxy- α -(1-iodo-1-propen-3-yl)- α -phenylacetate (IQNP) was then prepared in an analogous manner as the racemic compound through the use of a tributyltin intermediate. (R)-[¹²⁵I]IQNP was prepared using sodium iodide-125 with a 3% H₂O₂ solution as the oxidizing agent in 60% radiochemical yield. *In vivo* studies in rats demonstrated high uptake in the cortex (0.84% dose/gm) and the striatum (0.72% dose/gm) after 6 h. Greater than 95% of the activity in the cortex and striatum could be blocked by the preinjection of QNB.

Several agents developed in the Oak Ridge National Laboratory (ORNL) Nuclear Medicine Program were supplied to Medical Cooperative Programs for further collaborative preclinical and clinical studies. These included one tungsten-188/rhenium-188 generator supplied to the Center for Molecular Medicine and Immunology (CMMI) at the University of New Jersey School of Medicine and Dentistry in Newark, New Jersey, for radiolabeling antibodies for tumor therapy. Preliminary clinical studies with ¹⁸⁸Re-IgG for therapy of tumor patients have been initiated at CMMI.

DEVELOPMENT OF A NEW RADIOIODINATED TRIGLYCERIDE
ANALOGUE FOR THE EVALUATION OF PANCREATIC
INSUFFICIENCY BY SIMPLE URINE ANALYSIS

Diseases or conditions which compromise the availability or action of pancreatic lipase result in dietary fat (triglycerides) passing through the intestinal tract. High fat content in the stool, known as steatorrhea, is a commonly encountered clinical problem which is traditionally only effectively evaluated by chemical fecal fat analysis, an unpleasant technique. In order to have an alternative simple method, as early as 1949, radioiodinated "triolein" was introduced as an alternative which would allow the simple radioactive analysis of the stool and/or blood as an indicator of intestinal hydrolysis and absorption of dietary triglyceride. The strategy (Figure 1) was based on the well-known metabolic fate of dietary triglycerides containing long chain fatty acid residues which involves intestinal cleavage by pancreatic lipase catalyzed by bile acids, followed by adsorption of the released fatty acid in the jejunal and ileal intestinal segments. After re-esterification in the intestinal mucosa, the fatty acids are then transferred as triglycerides for storage in lipid depots or for release by lipase. Since the intact radioiodinated triglycerides cannot be absorbed by the intestinal tract, in the absence of hydrolytic activity they pass through the gut and will be excreted in the stool.

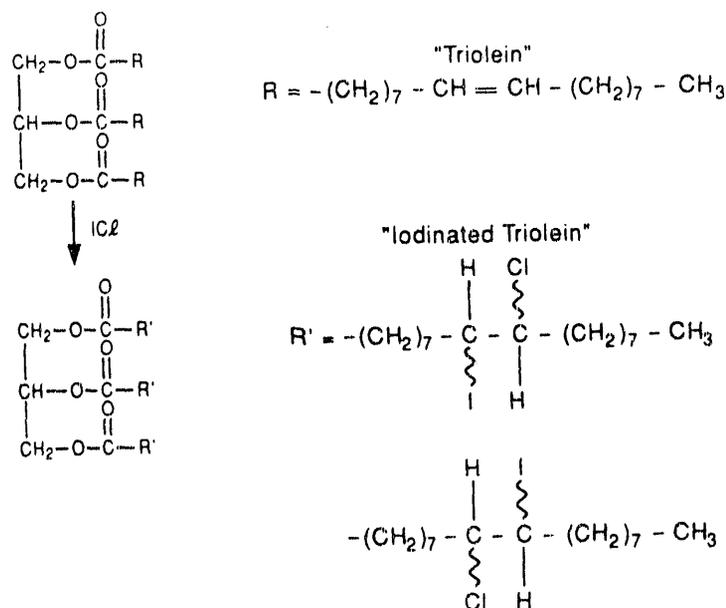
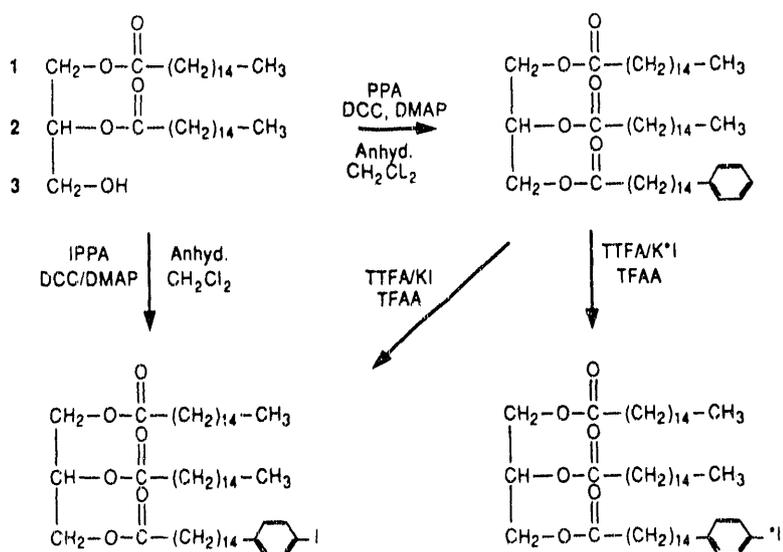


Figure 1.

Although the radioiodinated "triolein" and similar agents were investigated by many groups, the inconsistency in the results from measurement of stool and blood activity made this technique an unreliable method which was subsequently not pursued.

Because of the need for a simple, reliable technique using radioactivity for the evaluation of pancreatic lipase activity, we have re-assessed the use of triglycerides by the synthesis and evaluation of a new site specific, stable radioiodinated triglyceride analogue. Our strategy evolved from the well recognized stability of iodine attached to a phenyl ring. Thus, catabolism of 15-(p-iodophenyl)pentadecanoic acid (Figure 2) would release water soluble products which would be expected to be efficiently excreted via the urinary bladder rather than from free radioiodine, as is the case from catabolism of "iodinated oleic acid."

Our model agent was synthesized as shown in Scheme I. Acylation of 1,2-dipalmitoyl-rac-glycerol with 15-(iodophenyl)pentadecanoic acid (IPPA) was accomplished with DDC/DMAP in anhydrous methylene chloride. Iodination was then accomplished by thallation in trifluoroacetic acid followed by treatment with potassium iodide to yield the desired 1,2-dipalmitoyl-3-[15-(p-iodophenyl)pentadecanoyl]-rac-glycerol (1,2-Pal-3-IPPA). The authentic 1,2-Pal-3-IPPA was synthesized by coupling of IPPA with the 1,2-palmitoyl-3-rac-glycerol substrate.



Scheme I

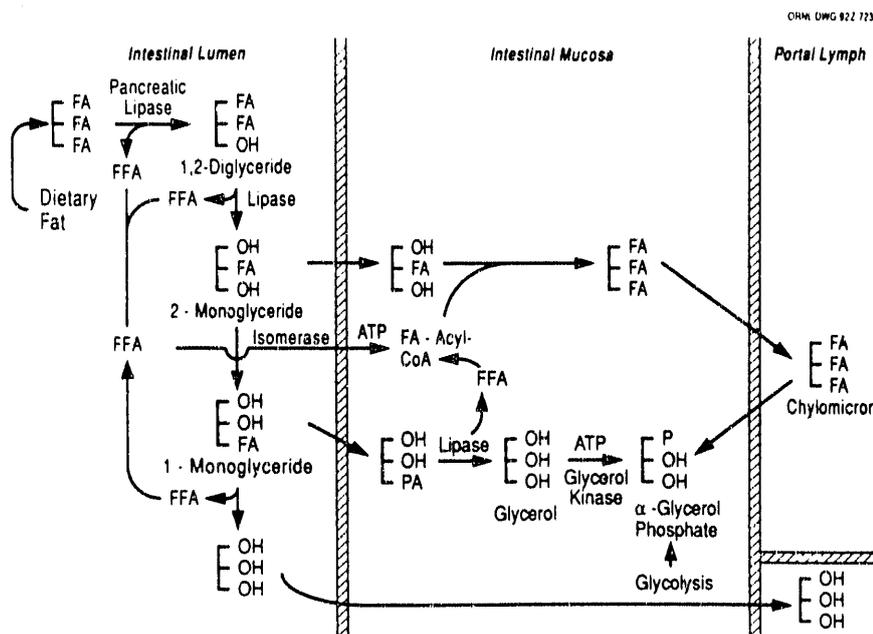


Figure 2

Radioiodination was accomplished in the same manner and the [I-131]-1,2-Pal-3-IPPA then administered to rats ($n=5$) by oral gavage. The rats were housed in special metabolism cages which permitted the separated collection of urine and feces. Within the initial 24-h period, $34.5 \pm 8.8\%$ of the administered activity was excreted in the urine, while $11.1 \pm 4.1\%$ was found in the feces (Figure 3). These results demonstrate that radioiodinated IPPA is released from 1,2-Pal-3-IPPA by lipase with subsequent intestinal adsorption of IPPA, followed by catabolism and conjugation and urinary excretion of the radioiodinated product. Urine analysis after oral administration of radioiodinated 1,2-Pal-3-IPPA may thus be a new, simple method for the routine clinical evaluation of various gastrointestinal diseases.

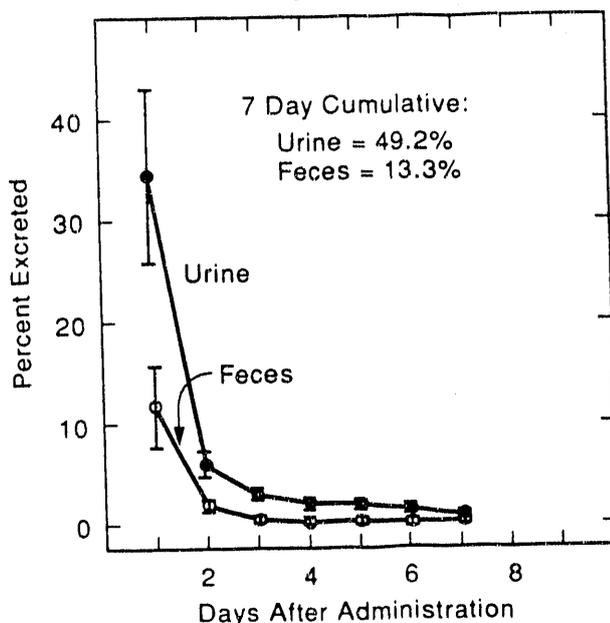


Figure 3.

SYNTHESIS AND BIOLOGICAL EVALUATION OF (R)-[¹²⁵I]-1-AZABICYCLO-
[2.2.2]OCT-3-YL (R,S)- α -HYDROXY- α -(1-iodo-1-propen-3-yl)- α -
PHENYLACETATE (R-[¹²⁵I]IQNP)

We have previously reported the preparation and *in vivo* animal studies of a new muscarinic antagonist, IQNP, an analogue of QNB (ORNL/TM-11881, ORNL/TM-11992). These studies have shown that IQNP, when labeled with iodine-125 in high specific activity, has high uptake in muscarinic rich (m-AChR) tissues of the brain and heart. Blocking studies carried out with a series of established receptor specific ligands demonstrated only muscarinic antagonists blocked the uptake of activity in areas of the brain which contain a high concentration of m-AChR.

IQNP contains two chiral centers in addition to two regional isomers around the double bond (Figure 4). Studies with QNB have shown that the R isomer of the quinuclidine portion of the molecule has a 100-fold higher affinity for the receptor than the S isomer.¹ Studies have also evaluated the effect of the stereochemistry around the acetate center and the R isomer has been reported as the most active isomer.² We have therefore initiated the separation of the optical isomers of 3-quinuclidinol and the preparation of the (R) and (S)

isomers of IQNP to determine the effect of this center on the affinity of the ligand for m-AChR.

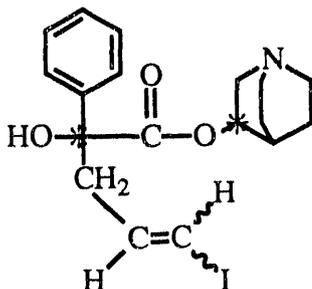
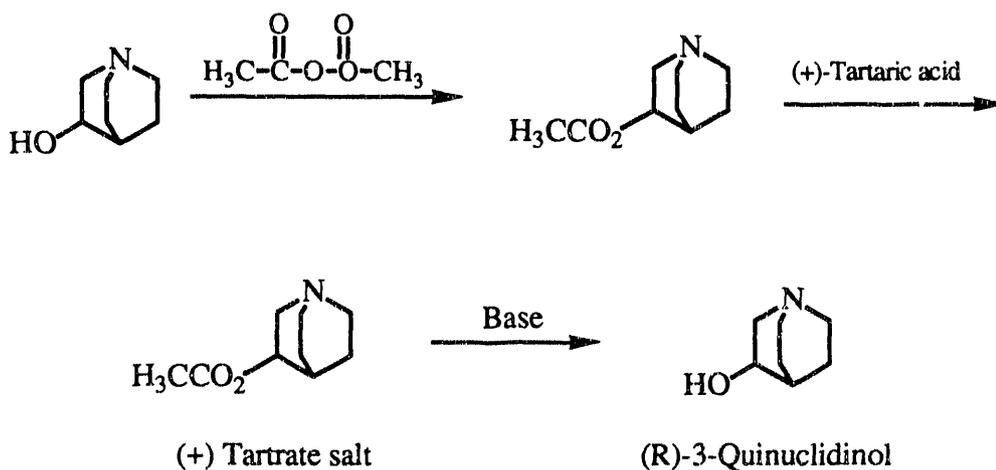


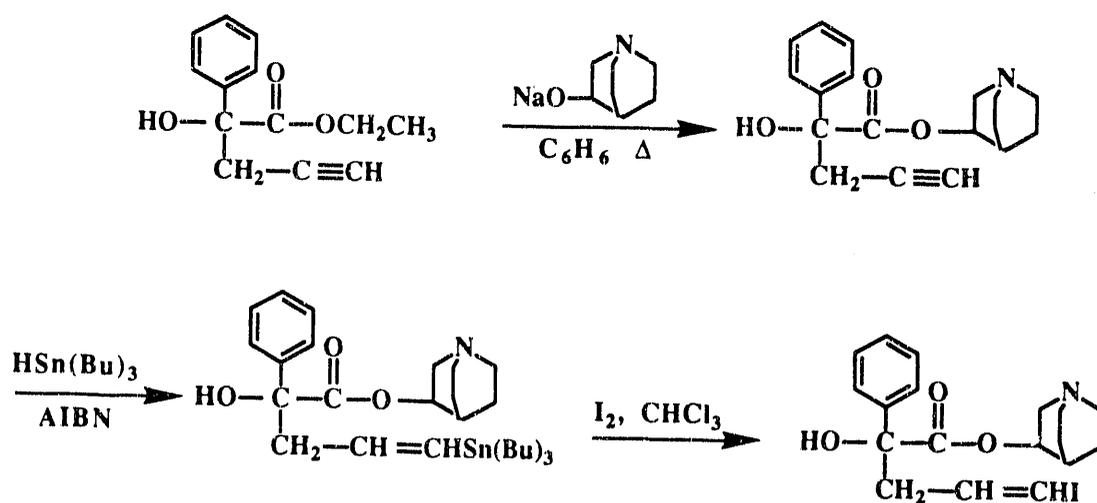
Figure 4.

The optical isomers of 3-quinuclidinol were separated in the classical manner³ by use of (+) and (-) tartaric acid as shown in Scheme II. 3-Quinuclidinol was first derivatized into its acetoxy analogue to increase its solubility in various organic solvents. The R isomer was then crystallized as the tartrate salt using (+)-tartaric acid. 3-Acetoxyquinuclidine, which was mainly the S isomer was recovered from the mother liquor and crystallized as the tartrate salt using (-)-tartaric acid. Recrystallization of each tartrate salt from 80% ethanol twice afforded pure R and S isomers of the tartrate salts. Treatment of each tartrate salt with 2 M NaOH solutions followed by saturation of the solution with potassium carbonate and extraction with hot benzene then afforded the R and S isomers of 3-quinuclidinol.



Scheme II.

R-IQNP was synthesized as shown in Scheme III. This method is analogous to that used in the preparation of racemic IQNP. Studies performed on several QNB analogues have shown the transesterification step allows the molecule to retain the chirality at the 3-position of the quinuclidinyl moiety.⁴ The radiolabeling was also accomplished in an analogous manner as the racemic compound using sodium iodide-125 and hydrogen peroxide as the oxidizing agent in 60% radiochemical yield.



Scheme III.

In vivo animal experiments were performed using female Fischer strain rats over a 6-h time period. Following intravenous administration of a saline solution (1.4 μCi) of (R)-[¹²⁵I]IQNP in a lateral tail vein of the metofane anesthetized rats, at the designated time points the animals were then anesthetized and killed by cervical fracture. The various organs were removed, rinsed with saline, blotted dry, and weighed in tared vials. Blood samples were obtained from the heart cavity after removal of the heart. Samples were then counted in a Packard Miniaxi 5000 sodium iodide auto gamma counter. Blocking studies were performed by the injection of a saline solution of the blocking agent (5 mg/kg) into a lateral tail vein 1 h prior to the injection of (R)-[¹²⁵I]IQNP. Three hours postinjection of (R)-[¹²⁵I]IQNP the animals were anesthetized and killed by cervical fracture and analyzed as above.

The biodistribution of (R)-[¹²⁵I]IQNP is shown in Figure 5. It was observed that the uptake of R-IQNP in the muscarinic rich areas (cortex, striatum, and heart) was higher than observed for racemic IQNP. The cortex to cerebellum and the striatum to cerebellum ratios increased to 12:1 and 10:1, respectively, after 6 h. The results of the blocking studies are shown in Figure 6. For this study ketanserine, a serotonin antagonist, and QNB, a muscarinic antagonist, were used as the blocking ligands. We observed that QNB blocks greater than 95% of the activity in muscarinic rich areas while ketanserine has no effect on the uptake of activity. Further blocking studies utilizing other receptor specific ligands are planned to determine the selectivity of (R)-[¹²⁵I]IQNP for m-AChR.

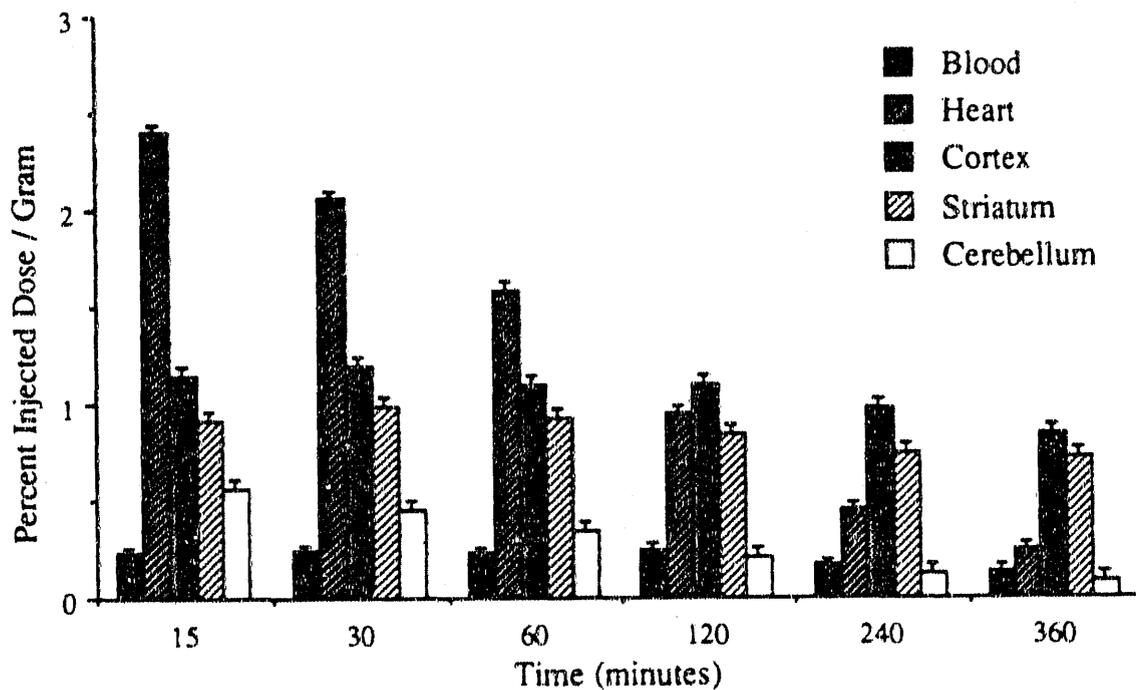


Figure 5.

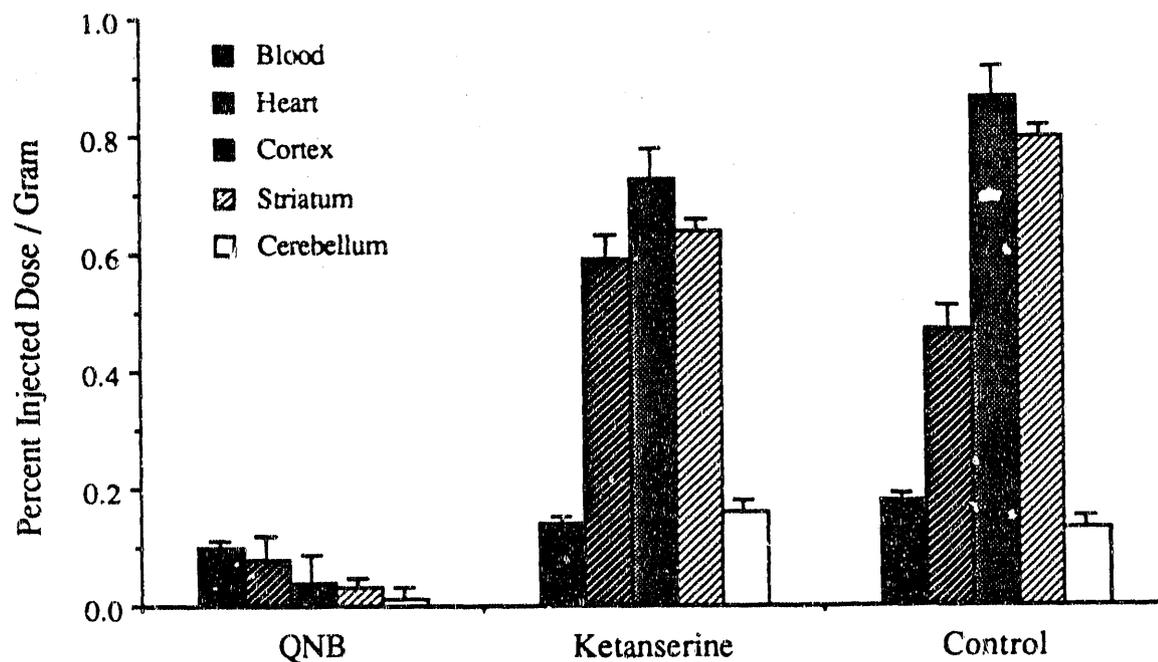


Figure 6.

The preparation of (S)-IQNP is currently in progress and the *in vivo* study of (S)-[¹²⁵I]IQNP will be performed to study the effect of stereochemistry of the 3-quinuclidinol center on the receptor-specific interactions.

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AGENTS FOR MEDICAL COOPERATIVES

During this period a tungsten-188/rhenium-188 generator was supplied to Immunomedics, Newark, New Jersey (Dr. Gary Griffiths). One shipment of barium-140 and calcium-45 was made to the University of Rhode Island, Narragansett, Rhode Island (Prof. S. S. Mitra), and one shipment of the iodine-125-labeled fatty acid analogue, 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) was made to Brookhaven National Laboratory, Upton, New York (Dr. Prantika Som).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

F. F. (Russ) Knapp, Jr., was appointed to the Abstract Review Committee and was requested to serve as co-chairman of a Scientific Session at the "9th International Symposium on Radiopharmaceutical Chemistry," Paris, France, on April 6-10, 1992. These meetings are held every two years and are the major international forum for the discussion of new developments in radiopharmaceutical research and production and processing of radioisotopes for nuclear medicine applications.

He was also invited to present an Invited Lecture entitled "New Radioiodinated Agents for Imaging Cerebral Receptors by Single Photon Emission Tomography," at the Second Mediterranean Symposium on Nuclear Medicine and Radiopharmaceuticals, to be held in Athens, Greece, on April 7-12, 1992. A book chapter for the "Proceedings" will be co-authored by D. W. McPherson, a staff member in the Nuclear Medicine Program. In addition, he was also appointed to the "Board of Editors" of the *European Journal of Nuclear Medicine*, the official journal of the European Association of Nuclear Medicine. The journal

has an international circulation of over 3,000 and is a major organ for publication of papers on both clinical and research studies in nuclear medicine.

P. C. Srivastava has been invited to organize a session on "Radiolabeled Nucleosides – Metabolism and Biomedical Applications" at the Tenth International Round Table on Nucleosides, Nucleotides and Their Biological Applications, to be held September 1992 in Park City, Utah. Topics of the meeting include molecular design, nucleoside, nucleotide, RNA, and DNA synthesis, and development of chemotherapeutic agents. The meeting proceedings will be published in *Nucleosides and Nucleotides*.

Publications

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Clinical Studies Initiated with ORNL Agent

Clinical studies have been initiated for the treatment of cancer patients using the rhenium-188 radioisotope obtained from the ORNL tungsten-188/rhenium-188 prototype generator system developed in the Nuclear Medicine Program. The generator system provides high yields (85-90%) of the rhenium-188 daughter radioisotope with low tungsten-188 parent breakthrough. The generator has a useful shelf-life of several weeks. In addition to the therapeutic use of the high energy beta particle emission with a maximum energy of 2.12 MeV for cancer treatment, rhenium-188 also decays with the emission of a 155 keV gamma photon which permits gamma camera imaging to evaluate organ distribution, pharmacokinetics and estimation of tissue absorbed radiation dose.

Generators are being used through a Medical Cooperative Program in collaboration with David Goldenberg, M.D., and his colleagues at the Center for Molecular Medicine and Immunology, New Jersey College of Medicine and Dentistry, Newark, New Jersey, where the rhenium-188 is being attached to antibodies which concentrate in tumor cells. The studies are designed to accumulate sufficient levels of the rhenium-188-labeled antibodies (Re-188-IgG) in tumors of patients for radioimmunotherapy. The first patient received two fractionated doses of Re-188-IgG three days apart. A total of five patients are planned for the initial group to evaluate the therapeutic effectiveness of this new approach.

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