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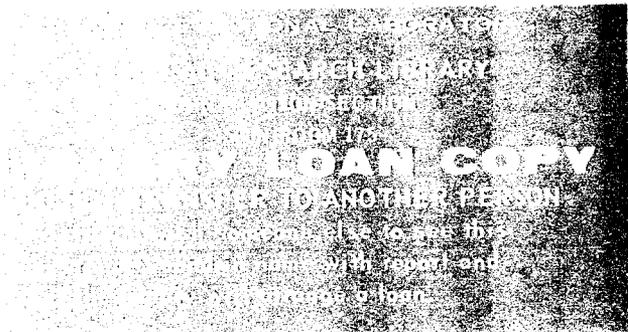
**OAK RIDGE
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MARTIN MARIETTA

**Nuclear Medicine Program
Progress Report for
Quarter Ending March 31, 1988**

F. F. Knapp, Jr.

- | | |
|----------------|------------------|
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| J. F. Allred | D. E. Rice |
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Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT
FOR QUARTER ENDING MARCH 31, 1988

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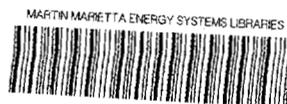
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SUMMARY

In this report the results of several studies with radioiodinated fatty acids are described. Studies with the isolated Langendorff-perfused rat heart system have continued to evaluate the distribution of [I-125]-15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (EMIPP) in myocardial lipids after 15 min of perfusion. At this time period 38-44% of the endogenous radioactivity is associated with material chromatographing in the region of triglycerides, 18-21% in the region of diglycerides and only 6-10% in the area of free fatty acids. Thus, the isolated heart mimics the in vivo studies in demonstrating that the retention of radioiodinated EMIPP is associated with lipid storage products. In addition, the synthesis of the isomeric mixture of 9- and 10-[I-125]-labeled iodooleic acid via formation of the corresponding a boronic acid intermediate is also described. The isomeric radioiodinated product mixture shows good heart uptake and retention (5 min, 3.45% dose/gm; 30 min, 2.44% dose/gm; 60 min, 2.28% dose/gm) and demonstrate that this structural perturbation does not interfere with myocardial specificity.

Also during this period [I-131]IPPA was supplied to collaborators at the Institute of Clinical and Experimental Nuclear Medicine in Bonn, West Germany, for studies with an isolated working rat heart model.

METABOLISM OF RADIOIODINATED IODOPHENYL-SUBSTITUTED FATTY ACIDS IN
ISOLATED RAT HEARTS

During this quarter, the metabolism of the monomethyl-branched iodophenyl fatty acid BMIPP was investigated using the isolated rat heart system described previously (ORNL/TM-10441, 10531). In earlier reports, we described the release of an apparent metabolite under normoxic conditions from the Langendorff-perfused rat hearts following injection of radioiodinated 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP). Our studies have continued on the identification of this polar component isolated from the perfused heart outflow.

In addition to identification of the radioactive component released by the hearts, we have investigated the profiles of the radioactive lipids remaining in the isolated hearts following injection of the radiolabeled BMIPP. At the termination of perfusion, the isolated rat hearts were removed, weighed, and counted for total radioactivity. The hearts were chilled during the brief interval (5-10 min) between removal and homogenization in chloroform:methanol (2:1) to extract the myocardial lipids. The organic and aqueous fractions were separated and counted with the remaining heart tissue to determine the efficiency of extraction of the radioactive components in the myocardium. The organic extracts were analyzed by thin-layer chromatography using triglyceride, diglyceride, and BMIPP reference standards.

The results from two representative isolated heart studies (4 hearts per study) are presented in Table 1 as the percent of radioactivity in the various lipid fractions. As expected, the majority of radioactivity extracted from the myocardium chromatographed with the triglyceride standard. A significant amount of radioactivity, however, chromatographed with the BMIPP and diglyceride standards. Previously reported lipid profiles of rat hearts injected in vivo with radiolabeled BMIPP showed a higher percentage of radioactivity chromatographing in the region of triglycerides (66% at 5 min, 76% at 30 min) and a somewhat lower percentage chromatographing in the diglyceride region (12% at 5 and 30 min).

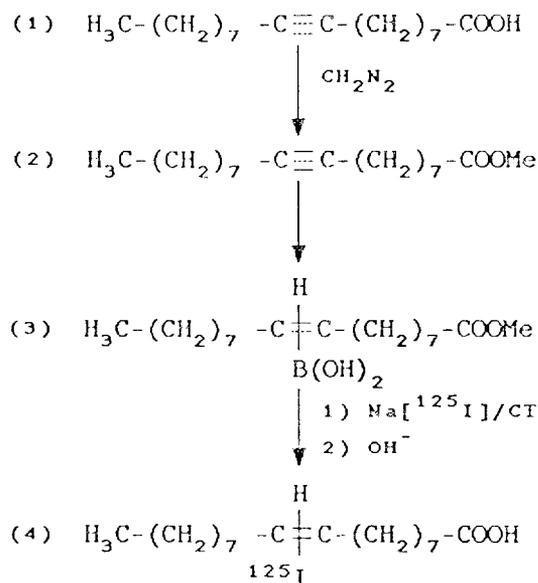
Table 1. Distribution of radioactivity in lipid pools of isolated rat hearts following perfusion with ^{125}I -labeled BMIPP.

<u>Experiment #</u>	<u>Percent of total radioactivity</u>		
	<u>Triglyceride</u>	<u>Diglyceride</u>	<u>BMIPP</u>
1	44.42 \pm 3.79	21.07 \pm 2.31	5.79 \pm 1.07
2	38.99 \pm 4.75	18.10 \pm 2.33	10.36 \pm 1.86

Future studies with the isolated heart system will evaluate the relationship of tissue lipid distribution patterns and global release of radioactivity in the outflow with the effects of various interventions, including hypoxia, lactate infusion, and glucose-insulin infusion.

SYNTHESIS AND TISSUE DISTRIBUTION STUDIES OF IODINE-125 IODOLEIC ACID ANALOGUE

Oleic acid (OA), 9-octadecenoic acid, is a naturally occurring fatty acid. Radiolabeling of this agent is of interest since fatty acids are principal nutrients for the normoxic heart and an evaluation of their uptake and release offer the opportunity to detect biochemical as well as metabolic defects in the myocardium in addition to coronary blood perfusion. Tissue distribution studies using carbon-14 and iodine-131 labeled oleic acids have been reported by Ryo and co-workers and by others.^{1,2} Since these studies provide no synthetic details or information to accurately determine the structure of [^{131}I]radioiodinated oleic acid for correlation with tissue distribution data, we have synthesized [^{125}I]OA and performed tissue distribution studies in laboratory rats. The synthetic route, shown in Scheme I, involves the synthesis of a boronic acid intermediate, methyl-9(10)-borono-9-octadecenoate (3), prepared via the diazomethane esterification of the commercially available stearolic acid [9-octadecynoic acid, (1)] to provide (2), followed by hydroboration.



Scheme I

We have investigated in detail the synthesis of trans (E)-boronalkenes prepared by hydroboration of alkynes such as (2) using catechol borane. However, the alkynes such as (2) containing ester functional groups are prone to undergo the reduction of the ester to provide the corresponding alcohol as a side product. To inhibit this side reaction, the hydroboration of (2) was performed using dibromoborane dimethylsulfide complex. The chloroamine-T and Na[¹²⁵I] iodination of the boronic acid (3) followed by basic (NaOH) hydrolysis provided the desired 9(10)-[¹²⁵I]iodooleic acid (4). The radiochemical purity was determined by TLC comparison of (4) with the unlabeled standard which was prepared similarly and characterized by TLC, ¹HNMR, ¹³CNMR and mass spectral analyses. The tissue distribution of ([¹²⁵I]4) was performed in fasted Fischer 344 female rats, and the data are given in Table 2. Our data indicate the heart uptake by ([¹²⁵I]4) is similar to that shown by C-14 oleic acid but approximately two-fold greater than I-131 oleic acid as reported by Ryo and co-workers.^{1,2}

Table 2. Distribution of radioactivity in tissues of Fischer 344 female rats following intravenous administration of [^{125}I]iodooleic acid.^a

Tissue	Percent injected dose per gram of tissue		
	Time (min)		
	5	30	60
Heart (H)	3.45 ± 0.13	2.44 ± 0.40	2.28 ± 0.17
Blood (B)	0.72 ± 0.12	0.88 ± 0.11	0.68 ± 0.10
Liver	12.63 ± 0.77	11.08 ± 0.70	10.01 ± 0.59
Lungs	1.06 ± 0.06	1.01 ± 0.09	0.97 ± 0.09
Kidneys	1.31 ± 0.00	1.15 ± 0.03	1.12 ± 0.04
Thyroid	13.76 ± 3.23	28.77 ± 3.90	52.96 ± 15.05
Heart/Blood ratio	4.79	2.77	3.35

^aThree fasted female rats for each time period were used.

LITERATURE CITED

1. W. H. Beierwaltes, R. D. Ice, M. J. Shaw, and U. Y. Ryo "Myocardial Uptake of Labeled Oleic and Linoleic Fatty Acids, "J. Nucl. Med., 16, 842 (1975).
2. J.-L. Piette, M. C. Pardon, G. Delfiore, L. Quaglia, J.-M. Peters, C. DeLandsheere, and P. Rigo "Synthesis and Biodistribution of ^{11}C -Labeled Unsaturated Fatty Acids," Seventh Int. Nat. Symp. on Rad. Pharm. Chem., Groningen, The Netherlands, July 4-8, 1988.

AGENTS FOR MEDICAL COOPERATIVES

One shipment of eluants from an Os-191/Ir-191m generator was supplied to the University of Tennessee Hospital, Knoxville, TN (Dr. K. Hubner), for subacute toxicity studies in rats. One shipment of [^{131}I]IPPA was supplied to the University of Bonn, Bonn, West Germany (Dr. J. Kropp), for collaborative studies with an isolated rat heart system.

AGENTS PREPARED FOR COST-RECOVERY THROUGH
THE ORNL ISOTOPES DISTRIBUTION OFFICE

One shipment each of Pt-195m was supplied to Beth Israel Hospital, Boston, MA (Dr. Kolodny), New York University Medical Center, New York, NY (Dr. T. Reich), and Rambam Hospital, Haifa, Israel (Dr. D. Front) on a cost-recovery basis.

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

United Nations Development Program Off-Site Assignment:

P. C. Srivastava completed off-site assignment sponsored by the United Nations Development Program (UNDP) at the Central Drug Research Institute (CDRI), Lucknow, India, for the period of November 1 to December 31, 1987. The main aim of the UNDP Award, in cooperation with CSIR, is to invite distinguished scientists for limited periods to participate in well defined projects and programs supporting India's development endeavors, leading to transfer of knowledge, special skills, or techniques. During this assignment he visited several institutions in India, where he presented seminars on the topics currently being pursued at ORNL. The presentations were as follows:

All India Institute of Medical Sciences, November 2, 1987. "Malimide Probes for Labeling Antibodies."

Chemistry Department, University of Jaipur, Jaipur, November 18, 1988. "Boronic Acid Precursors for Radioiodinations and Radiopharmaceutical Development."

Central Drug Research Institute, Lucknow, November 27, 1987. "Synthesis and Chemotherapeutic Activity and Mechanism of Action of Tiazofurin and Selenazofurin Nucleosides."

Bhabha Atomic Research Center, Bombay, December 14, 1987.
"Development of Radiopharmaceuticals at ORNL for Diagnostic and
Therapeutic Applications."

New Staff:

Sheri Blystone joined the Nuclear Medicine Program as a postdoctoral fellow on January 11 following the completion of her doctoral studies in organometallic chemistry at Case Western Reserve University in Cleveland, Ohio. On January 18, Carla Rogers joined the program as a Biological Laboratory Technician. She is now responsible for conducting tissue distribution studies and care and maintenance of animals. Daniel McPherson, Ph.D., a synthetic organic chemist formerly from the Nova Pharmaceutical Company in Baltimore, Maryland, accepted a staff position and joined the Nuclear Medicine Program on March 7. Dr. McPherson completed two years of postdoctoral work at the Brookhaven National Laboratory with Drs. A. Wolf and J. Fowler. He will be working on the development of new radiopharmaceuticals.

Visitors:

Ms. Rebecca Pearl, the new medical editor, and Mr. Frank Munger, from the Knoxville News Sentinel, visited for an overview of the Nuclear Medicine Program on January 21.

Publications:

Srivastava, P. C., Knapp, F. F., Jr., and Pruitt, C. D. "Potential Cerebral Perfusion Agents. Synthesis and Evaluation of a 1,4-Disubstituted Dihydropyridine Analogue," J. Heterocyclic Chem., 25, 667-669 (1988).

Papers:

Two papers co-authored by members of the Nuclear Medicine Group, describing collaborative studies with the University of Liege, Belgium, and the Nuclear Medicine Department at the University Hospital in Aachen, West Germany, were presented at the 20th International Bad Gastein Symposium in Bad Gastein, Austria, on January 11-14, 1988:

Reske, S. N., Knapp, F. F., Jr., Nitsch, J., Kolkmeier, J., and Kohlen, S. "Sustained Cardiac I-123-Phenylpentadecanoic Acid (IP) Uptake After Reversible Coronary Occlusion: A Possible Marker of Myocardial Salvage."

Brihaye, C., Guillaume, M., and Knapp, F. F., Jr. "A New Osmium-191/Iridium-191m Generator System for Medical Studies."

Miscellaneous:

In conjunction with the Division of Nuclear Medicine at the University of Tennessee (UT) Memorial Research Center (M. M. Goodman, Ph.D., and K. Hubner, M.D.), fluorine-18 from the new UT cyclotron has been used for the first time in a collaborative project with the Nuclear Medicine Group for the synthesis of new F-18-labeled fatty acid analogues. These agents show promise for the evaluation of heart disease by positron emission computerized tomography (PET). A new methyl-branched fatty acid analogue is being prepared at UT, and the heart uptake and retention are being evaluated in rats in vivo and in an isolated rat heart model. A grant to the NIH for extension of these collaborative studies has been submitted.

Meetings and Lectures:

F. F. Knapp, Jr., visited the Carlyle Fraser Heart Center, Crawford Long Hospital, at the Emory University Medical Center, on February 24-25, and presented an invited seminar describing the development of radioiodinated fatty acids for applications in nuclear cardiology. This visit was coordinated by Randall E. Patterson, M.D., Medical Director of Nuclear Cardiology, with whom a Medical Cooperative Program has been

established. The goal of the collaborative studies at Emory is to take advantage of the unique retention properties of the methyl-branched fatty acids developed at ORNL to evaluate myocardial salvage after reperfusion using an open chest canine model. The iodine-123 BMIPP agent was synthesized and the first SPECT imaging study conducted at Emory. It is anticipated that this work will be extended to a large number of dogs and joint support will be pursued through the NIH.

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