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COVER SHEET
FOR TRIP REPORTS SUBMITTED TO THE OFFICE OF ENERGY RESEARCH

Destination(s) and Dates for Which Trip Report Being Submitted: Bonn, West Germany (11/20-22/1987); Liege, Belgium (11/23-25/1987); Amsterdam, The Netherlands (11/26-27/1987)

Name of Traveler: Furn F. Knapp, Jr.

Joint Trip Report ☐ Yes ☒ No

If so, Name of Other Traveler(s): _____

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FOREIGN TRIP REPORT

ORNL/FTR-2773

DATE: December 11, 1987

SUBJECT: Report of Foreign Travel of F. F. Knapp, Jr., Group Leader, Nuclear Medicine Group, Health and Safety Research Division

TO: Herman Postma

FROM: F. F. Knapp, Jr.

PURPOSE: To participate in the International Workshop on Radioiodinated Free Fatty Acids at Amsterdam, The Netherlands, November 26-27, 1987, and to participate in joint research in Bonn, West Germany, and Liege, Belgium, November 20-25.

SITES VISITED:

11/20-22/87	Institute for Clinical and Experimental Nuclear Medicine, Bonn, West Germany	H.-J. Biersack, M.D. J. Kropp, M.D.
11/23-25/87	Cyclotron Research Center, University of Liege, Belgium	C. Brihaye, Ph.D.
11/26-27/87	Workshop, Free University Hospital, Amsterdam, The Netherlands	

ABSTRACT: The traveler participated in the Second International Workshop on Radioiodinated Free Fatty Acids in Amsterdam, The Netherlands, where he presented an invited paper describing the pioneering work at the Oak Ridge National Laboratory (ORNL) involving the design, development and testing of new radioiodinated methyl-branched fatty acids for evaluation of heart disease. He also chaired a technical session on the testing of new agents in various in vitro and in vivo systems. He also visited the Institute for Clinical and Experimental Nuclear Medicine in Bonn, West Germany, to review, discuss, plan and coordinate collaborative investigations with that institution. In addition, he visited the Cyclotron Research Center in Liege, Belgium, to discuss continuing collaborative studies with the Osmium-191/Iridium-191m radionuclide generator system, and to complete manuscripts and plan future studies.

I. VISIT TO THE INSTITUTE FOR CLINICAL AND EXPERIMENTAL NUCLEAR MEDICINE, UNIVERSITY OF BONN, WEST GERMANY

The traveler visited the Institute for Clinical and Experimental Nuclear Medicine in Bonn, West Germany, to discuss the status of collaborative studies, to plan drafts of several papers and abstracts, and to plan future studies. Routine clinical evaluation of patients with heart disease with Iodine-123-labeled fatty acids is continuing as an extension of the work the traveler conducted while on off-site assignment in Bonn during the July 1985-August 1986 period. The structurally-modified methyl-branched fatty acids developed by the traveler and his colleagues are currently used in Bonn for both evaluation in patients and also in special in vitro and in vivo model animal studies. Substrates are supplied through this collaborative program for on-site radiolabeling using procedures developed by the traveler while he was in Bonn. In addition, studies with a special isolated working rat heart system are continuing in Bonn to evaluate the metabolism, myocardial uptake and clearance of the modified fatty acids under various carefully controlled conditions. These studies will provide models and important information to interpret and predict how these agents behave in clinical studies.

Professor Hans J. Biersack, director of the institute , and his colleagues in Bonn also have extensive clinical experience in the use of radiolabeled antibodies for tumor diagnosis and therapy, primarily in multiple myeloma for patient management to monitor the effectiveness of therapeutic regimens. Rhenium-188 obtained from the new tungsten-188/rhenium-188 (W-188/Re-188) radionuclide generator system developed by the traveler and his colleagues at ORNL is an excellent radionuclide to investigate for antibody radiolabeling. Following resumption of radionuclide production in the ORNL High Flux Isotope Reactor (HFIR), generators will be supplied to the Institute in Bonn for antibody radiolabeling and testing in various animal tumor models. If these studies are successful, investigators in Bonn will apply for approval for human studies.

Achim Kropp, M.D., a staff member in the institute, is responsible for routine clinical cardiology studies, including evaluations with the iodine-123-labeled fatty acids. Routine studies involve the evaluation of the effectiveness of re-vascularization by coronary graft surgery and percutaneous transmural angioplasty (PCTA) on reperfusion of ischemic areas of the myocardium. The PCTA technique is commonly utilized by cardiologists for reperfusion (resumption of flow to threatened areas) and involves the use of an inflatable ballon on the end of a catheter which is positioned in the region of the coronary obstruction. The evaluation of uptake and clearance kinetics of iodine-123 fatty acids before and after the reperfusion has been shown in Bonn to be a good technique to predict the eventual recovery of mechanical function (contraction) to the ischemic zones. Arrangements are being made for Dr. Kropp to work in the Nuclear Medicine Group at ORNL for a six-month period beginning in about July 1988. He will expand the current work with the isolated rat heart study to evaluate the effects of various interventions on the uptake and clearance of modified fatty acids currently under development.

II. VISIT TO THE CYCLOTRON RESEARCH CENTER, UNIVERSITY OF LIEGE, BELGIUM

In route to Amsterdam, the traveler visited colleagues in Liege (Drs. Claude Brihaye and Marcel Guillaume) with whom he developed the carbon-based Osmium-191/Iridium-191m (Os-191/Ir-191m) radionuclide generator system beginning in 1983. Routine clinical studies are expanding at several institutions in Belgium and an "Iridium User Group" has been formed consisting of clinical investigators from five Belgium institutions. This group meets every 3-4 months to discuss the progress of clinical studies, new improvements in the use of the generator system, and future plans. Because both personnel and facilities for preparation of Os-191/Ir-191m generators in Liege for clinical studies are limited, only two generators are prepared each month. An effective program has thus been coordinated between several institutions to allow the most effective use of generators. The generators are shared between several institutions by transportation. New processing facilities are being constructed in Liege, and it is anticipated that in the spring of 1988 generators can be prepared weekly for studies in Belgium and expanding into West Germany, where the traveler initiated a collaborative program and initial volunteer studies in Bonn in 1986. Approval has now been received in Bonn for routine clinical testing.

Recent developments on the Os-191/Ir-191m generator system in Liege include the design of a new automated elution system which allows consistent, reproducible elution of the generator system. One of these units has been supplied to ORNL through this collaborative program. The very low adsorbed doses to patients continues to be a major advantage of Ir-191m. Clinical investigators have raised the question, however, of the radiation exposure to personnel working with the Os-191/Ir-191m generator system during the elution of successive 100 mCi boluses required for adequate count rates in the left ventricle and peripheral arterial circulation. Recent calculations by Dr. Brihaye have indicated that even at the surface of the intravenous line, exposure from 10 boluses of 100 mCi each would result in a total radiation exposure of only 2 mRad, thus demonstrating that exposure to personnel is not a problem.

In addition to their interest in ultrashort-lived radionuclide generator systems, the center in Liege has a clinical unit and routinely prepares various agents radiolabeled with positron emmitting radioisotopes for clinical evaluation by positron emission computerized tomography (PET). They have extensive experience in the design and development of automated synthetic devices for the rapid, automated preparation of radiopharmaceuticals labeled with short-lived positron emitters such as carbon-11 ($T_{1/2}$ 20 min) and fluorine-18 ($T_{1/2}$ 120 min). As an extension of collaboration with the traveler at ORNL, an automated device for preparation of F-18-labeled 2-fluoro-2-deoxyglucose (FDG) and fluoro fatty acids and other agents will be supplied for collaboration with the PET program at UT Hospital.

Other interests at Liege include the evaluation of regional coronary blood flow (perfusion) in patients with heart disease. One radioisotope which has excellent characteristics for evaluation of regional myocardial perfusion by PET is rubidium-82, which is the daughter available from the strontium-82/rubidium-82 (Sr-82/Rb-82) radionuclide generator system. Because of the extremely high cost of Rb-82 ($27/mCi) available from the producers in the U.S. (Los Alamos Scientific Laboratory), the costs associated with a 100 mCi generator (approximately $4,200; including shipping costs), has necessitated the use of an alternative radionuclide. The center in Liege, thus, utilizes potassium-38 (K-38) produced by alpha particle bombardment of natural chlorine-36 [Cl-36(α,n)K-38].

III. PARTICIPATION IN THE "WORKSHOP ON RADIOIODINATED FREE FATTY ACIDS", FREE UNIVERSITY HOSPITAL, AMSTERDAM, THE NETHERLANDS

The 1987 "Workshop" is the second in this series initiated in 1984, and the new structurally-modified agents developed by the traveler and his colleagues at ORNL have received extensive recognition and participation at these meetings. The program in Amsterdam consisted of 25 invited speakers from the major research programs in eight countries working in this area. Presentations and discussions focused on the development and synthesis of structurally-modified fatty acids (FA), the evaluation of FA myocardial uptake and clearance in various animal models of ischemia and reperfusion, and clinical applications. The traveler presented an invited talk entitled "Synthesis and Biological Properties of Radioiodinated Methyl-Branched Fatty Acids," which described the synthesis of modified fatty acids, studies with the isolated rat heart system to understand the metabolism of these agents and the synthesis and potential importance of 3-R,S-hydroxy fatty acid intermediates in ischemia. An important aspect of this meeting, and an important indicator of the leadership impact the ORNL Nuclear Medicine Program has had on this international area of research, is that 9 of the 25 presentations described the use of the 3-monomethyl-branched fatty acid, 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) agent developed at ORNL.

The traveler also had the opportunity to discuss collaborative interests with investigators from the Department of Physiology at the University of Limburg in Maastricht, The Netherlands. These investigators (Drs. G. J. van der Vusse and J. F. C. Glatz) have isolated and characterized the myocardial cell fatty acid binding protein (FABP) which is an important entity in transfer of fatty acids from plasma to the intracellular sarcolemmar site for activation to the acyl-coenzyme A derivatives. An evaluation of the effects of structural modifications of fatty acids on the binding to FABP may explain and even predict the myocardial specificity, uptake and clearance of the radioiodinated fatty acids being developed for myocardial imaging. Samples of fatty acids developed and synthesized at ORNL will be supplied to these investigators for these collaborative studies. It would be very useful to develop an in vitro binding system that could predict the myocardial uptake and retention of new analogues.

IV. SUMMARY AND RECOMMENDATION

Attendance at the Second International Workshop on Radioiodinated Free Fatty Acids in Amsterdam was important since it allowed and stimulated important collaborative ties with institutions involved in joint research efforts. It also provided the opportunity for a continuing leadership role by the traveler and his colleagues at ORNL in the development of these important agents. Because of the constraints encountered in the U.S., new radiopharmaceuticals can be tested much more quickly in Europe. Collaboration allows the rapid transfer of technology and the evaluation of new agents developed at ORNL. In addition, collaboration with investigators working in the fields of cardiology, oncology, etc., is important for the continuation of state-of-the-art research at ORNL. Such collaboration has proven to be particularly effective in pursuing new initiatives, initiating clinical studies and should be encouraged to continue.

APPENDIX

Itinerary

11/19/1987	Travel from Oak Ridge, Tennessee, to Bonn, West Germany
11/20/1987-11/22/1987	Institute for Clinical and Experimental Nuclear Medicine, Bonn, West Germany
11/23/1987-11/25/987	Cyclotron Research Center, University of Liege, Belgium
11/26/1987-11/27/1987	Workshop on Radioiodinated Free Fatty Acids, Amsterdam, The Netherlands
11/28/1987	Travel from Amsterdam, The Netherlands, to Oak Ridge, Tennessee

Persons Contacted

West Germany

1. University of Bonn
   - H. J. Biersack, M.D.
   - A. Bockish, Ph.D. M.D.
   - A. Kropp, M.D.

Belgium

1. University of Liege
   - C. Brihaye, Ph.D.
   - C. DeLansheere, M.D.
   - M. Guillaume, Ph.D.

The Netherlands

1. Amsterdam
   D. R. Elmaleh, Ph.D.
   J. F. C. Glatz, Ph.D.
   J. Kropp, M.D.
   R. Lerch, M.D.
   S. N. Reske, M.D.
   P. Som, D.V.M.
   G. J. Van der Vusse, Ph.D.
   F. Visser, M.D.
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