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ORNL

FOREIGN TRIP REPORT

ORNL/FTR-2351

DATE: August 18, 1986

SUBJECT: Report of Foreign Research Assignment 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 conduct animal experiments and coordinate clinical testing of new radiopharmaceuticals at the Institute of Clinical and Experimental Nuclear Medicine, University of Bonn, Federal Republic of Germany.

SITES VISITED:			
	7/26/1985-8/1/1986	Institute for Clinical and Experimental Nuclear Medicine	H.-J. Biersack, M.D. S. N. Reske, M.D.

ABSTRACT: Work at the Institute for Clinical and Experimental Nuclear Medicine in Bonn, Federal Republic of Germany, provided the traveler with the unique opportunity to participate in the testing of new radiopharmaceuticals developed at the Oak Ridge National Laboratory (ORNL) in special animal models and to establish and coordinate the first clinical tests with several of these agents. His work in Bonn consisted of the synthesis of radioiodinated agents for testing and participation in the evaluation of the biological properties of the new dimethyl-branched fatty acid, 15-(para-iodophenyl)-3,3-dimethylpenta-decanoic acid (DMIPP) in two isolated, perfused heart systems (swine and rat). In addition, he established the radiopharmaceutical protocols for initiation of clinical testing in Bonn of iodine-123-labeled DMIPP and iridium-191m from the new osmium-191/iridium-191m radionuclide generator system. He routinely prepared iodine-123-labeled DMIPP and other fatty acids for the first testing in volunteers and patients. He also participated and coordinated the first clinical tests of heart function with the bolus application of iridium-191m in Bonn. In addition, he established and participated in collaborative programs at the clinical unit, University of Liege, Belgium, and at the Cardiology Department, Free University of Amsterdam. He also had the opportunity to visit several other institutions in central Europe, present seminars, discuss the development of

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radiopharamceuticals and establish important collaborative programs which will help advance the technology developed at ORNL. Several agents designed in the nuclear medicine research program at ORNL have reached a point where further development requires the availability of special animal models to evaluate in detail the metabolism and tissue kinetics in comparison with other agents. The results obtained from these animal experiments represent an important basis for the interpretation of clinical tests.

I. SUMMARY OF WORK AT THE UNIVERSITY OF BONN

The Institute for Clinical and Experimental Nuclear Medicine was established by C. Winkler, M.D., Ph.D., in 1962, who began his career with board certification in surgery prior to certification in radiology and nuclear medicine. The Institute is the principle clinical nuclear medicine facility in Bonn, Federal Republic of Germany (FRG), with a staff of about 25, including 6 nuclear medicine physicians. Approximately 7,000 in vivo imaging studies are performed annually, including routine studies in nuclear cardiology, kidney and lung function, cerebral perfusion, tumor localization and imaging, etc. In addition, about 17,000 in vitro tests are performed each year, including thyroid function tests, tumor antigen titers, etc.

The Institute also offers the opportunity for basic research and has close ties with the radiopharmaceutical industrial sector for initial testing of new agents. One such agent currently under study in epileptic patients is the new technetium-99m cerebral perfusion agent, "HmPAO." The traveler had the opportunity to participate in establishing the quality control procedures, and in designing experimental protocols and chromatographic analysis of metabolites in baboon studies. Another major area of investigation is the use of technetium-99m- and indium-111-labeled tumor antibodies for the localization and prognosis of tumors such as melanoma malignancies. The Institute also has a strong tradition over the last few years through the work of S. N. Reske, M.D., in both the testing in animal models and clinical evaluation of iodine-123-labeled fatty acids. Over 200 patients encompassing a variety of cardiological disorders have been evaluated with the straight-chain fatty acid, 15-(para-[I-123]iodophenyl)pentadecanoic acid (IPPA) over the last five years. Thus, the association with Dr. Reske which afforded the opportunity to participate in testing in special animal models and isolated organs and the initial clinical testing of new methyl-branched fatty acids developed at ORNL were prime factors which led to this assignment. In addition, the close proximity to other institutions where the traveler had established collaborative programs in Liege, Belgium, Essen and Julich, FRG, and Amsterdam, The Netherlands, was another attractive factor for working in Bonn.

In addition to the scientific projects described below, the traveler also served as an unofficial "editor" for the staff of the institute in Bonn, since most scientific papers of the staff are published in English. Until this experience, the traveler never appreciated the necessity for foreign scientists to have fluency in both written and spoken English. Whereas much of the state-of-the-art scientific literature was published in German 30-40 years ago, it is now a necessity for foreign scientists to both read and publish in English journals. Thus, in addition to rigorous scientific training, it is also necessary to learn English well. American scientists have a distinct advantage!

While in Bonn, the traveler also had the opportunity to meet and discuss projects of joint interest with a number of investigators from other research institutions. The traveler was invited to visit the Department of Nuclear Medicine, University Medical School in Szeged, Hungary, by Prof. L. Csernay, M.D., D.Sc. Professor Csernay is head of the Department of Nuclear Medicine at Szeged, and president of the Hungarian Society of Nuclear Medicine. Professor Csernay will be president of the European Nuclear Medicine Congress in Budapest, in August 1987. The traveler has been invited to present invited lectures at "pre-congress" symposia at the Nuclear Medicine Department, University of Aachen, FRG, and Bonn, FRG, on radiopharmaceutical development in the United States, and to also speak during the congress in Budapest.

While in Bonn, the traveler also held discussions with Herr Wolfram Lork, Programm Manager at Dornier, a FRG high technology contractor, concerning the possibility of further developing the osmium-191/iridium-191m generator system in conjunction with a multi-wire resistance-capacitance proportional camera system (RCPC) for measuring ventricular function of astronauts on one of the future European shuttle missions. The RCPC camera system is the type of imaging device used by the traveler several years ago that was developed in the Instrumentation and Controls Division at ORNL by Messrs. C. J. Borkowski and M. K. Kropp and co-workers. This lightweight, high-resolution system is ideally suited for use in space, and such an application would represent an interesting and potentially important use of the generator developed at ORNL. The traveler supplied information on the ORNL generator system and suggested approaches for evaluating this potential application further. The principal reaction of the traveler is that these scientists, and clinical investigators, are anxious for new technology, and that the new agents developed by the traveler in conjunction with his colleagues at ORNL will have important impact on these programs, and that many important contacts for continued and future collaboration were established.

A. Myocardial Kinetics and Metabolism of 15-(Iodophenyl)-3,3-dimethyl-pentadecanoic Acid (DMIPP): A New Myocardial Imaging Agent

The novel radiolabeled fatty acids that have been developed recently at ORNL may have a major impact on the design of radiopharmaceuticals for use in nulcear cardiology. The concept of myocardial "trapping" of fatty acids first demonstrated with tellurium-substituted fatty acids has now

been demonstrated with methyl-branched radioiodinated fatty acids. These unique agents appear useful to assess regional myocardial fatty acid utilization. A unique iodine-123-labeled 3,3-dimethyl-substituted fatty acid, DMIPP, has been developed at ORNL to evaluate aberrations in regional fatty acid uptake not detected by flow tracers. Applications may include the diagnosis and management of coronary artery disease, and the early diagnosis of hypertensive disease. Normal patients and patients with coronary artery disease have been studied with this agent which shows excellent properties for the evaluation of myocardial disease by single-photon emission computerized tomography (SPECT) not detected with currently-available myocardial perfusion agents. This agent closely mimics the tellurium fatty acids but can also be prepared in high specific-activity and is nontoxic. A detailed biochemical evaluation of the distribution of radiolabeled fatty acid metabolites within the various lipid pools of heart tissue is being performed to identify the mechanism of localization and retention of this novel agent.

One of the major goals of the traveler while in Bonn was to participate in studies with isolated heart systems to evaluate the effects of pharmacological intervention and reperfusion on the myocardial uptake and kinetic properties of DMIPP in comparison with IPPA. These studies consisted of work with an isolated-perfused "working" rat heart and also collaboration on an isolated-reperfused swine heart model in conjunction with Dr. Reske and two medical students in Bonn (Sigurd Kohlen and Jorn Kolkmeier). The traveler also made arrangements for the students to visit ORNL in July 1986, to set-up an isolated rat heart system for use in the nuclear medicine program.

In this model a coronary artery of the isolated-perfused swine heart is ligated and (iodine-125) DMIPP administered. Since the initial distribution pattern is frozen, the use of DMIPP allows an accurate method to evaluate the fatty acid uptake pattern. After release of the ligation and reperfusion, a second fatty acid (iodine-131 IPPA) is then administered, the heart dissected and the distribution of the two fatty acids then determined by regional tissue counting. If regions are "salvaged" following reperfusion, the second fatty acid will show the same distribution pattern and DMIPP before reperfusion. An important requirement and unique property of DMIPP is the absence of wash-out or redistribution. By determining this difference as a function of different ligation periods, the viability of reperfused regions was evaluated. In addition, extraction and chromatographic analysis of lipids provided insight of how the two fatty acids were metabolized. When ligation periods were short (15-30 min), the reperfused regions showed the same uptake patterns with IPPA, demonstrating "salvage" or viability of these regions. With more prolonged ligation periods (45-60 min), the regions supplied by the ligated artery showed significantly reduced IPPA uptake in comparison to control regions, since these areas were now necrotic. These data are now being analyzed and demonstrate that the use of "trapped" fatty acids such as DMIPP can be used to evaluate uptake patterns before and after reperfusion. The practical significance of these results is the

possibility of evaluating reperfusion by either angioplarty (coronary bypass) or enzymatic reperfusion (streptokinase) with SPECT with successive administrations of (iodine-123) DMIPP.

B. Clinical Evaluation of Iodine-123-Labeled Fatty Acids

One of the major goals of the traveler was to coordinate and initiate the clinical testing of the new iodine-123-labeled DMIPP in Bonn. The interest expressed by Dr. Reske in studying this agent was one of the primary factors in selecting Bonn as the site for assignment. After equipping a small radiochemical facility, the micro-scale iodine-123 labeling of DMIPP was optimized and a detailed procedure for the synthesis, purification and formulation of DMIPP was written. High purity iodine-123 produced in Karlsruhe by proton irradiation of enriched xenon-124 by the xenon-124(p,2n)iodone-123 reaction was used for these studies. This is a new commercial production technique which gives very high purity iodine-123 with only very low levels of iodine-125 radiocontaminant (< 0.05%) and no iodine-124. Thus, this high purity iodine-123 produced by this route is far superior to production by the tellurium-124(p,2n)iodine-123 route, since the problems associated with image degradation and increased radiation dose by iodine-124 are eliminated. In addition, production by this route is also superior to iodine-123 produced by the iodine-127(p,5n)iodine-123 route, since potential problems associated with high local dose from iodine-125 are also eliminated. The iodine-123 DMIPP was prepared weekly for studies in a variety of patient groups consisting of coronary artery disease (CAD) and hypertension, and to evaluate the effects of calcium blocker therapy, a widely used pharmacological intervention for patients with ischemic heart disease. The DMIPP distribution was evaluated by SPECT and demonstrated, for the first time, that this agent shows the expected prolonged retention which allows the acquisiton of high-quality SPECT images since there is no wash-out or redistribution during the 15-20 minute imaging period.

A preliminary report describing these first clinical results with iodine-123 DMIPP has been recently published, "Results of Myocardial SPECT with Fatty Acids in Coronary Artery Disease," Nuklarmedizin, 25, 90-98 (1986) (S. N. Reske, F. F. Knapp, Jr., J. Nitsch, J. Kropp, K. Reichman, and C. Winkler). A second detailed review describing the animal studies and development work performed by the traveler and his colleagues in Bonn has been accepted by the new American journal, The Journal of Physiologic Imaging, entitled "Phenyl Fatty Acids in Heart Disease. I. Experimental Studies" (S. N. Reske, F. F. Knapp, Jr., and C. Winkler).

A second important application that was demonstrated for the first time was the effect of calcium blocker therapy on regional fatty acid uptake. This is a very important observation, since it may represent the first quantitative method for prognosis of this widely used technique. Calcium blockers, such as Nifedipine or Veraprimil, are administered for several days to improve the quality of life of patients with ischemic heart disease. The effectiveness of the therapy is determined

subjectively, by the increase of comfort, decrease of pain, etc., of the patient. A protocol was established where patients were evaluated with iodine-123 DMIPP before therapy and often large defects in the uptake pattern were observed. Five days after therapy the procedure was repeated, and it was observed that often the lesions had become much smaller, and sometimes completely filled. This is the first demonstration of an imaging technique that may have prognostic value in assessing the effectiveness of calcium blocker therapy. Similar results have been obtained in collaborative studies between the traveler and investigators at the Brookhaven National Laboratory (A. B. Brill, M.D., Ph.D., et al.) where the distribution of iodine-131 DMIPP in the hearts from cardiomyopathic hamsters either before or after therapy have shown similar decrease in lesion size. The results of these clinical studies in Bonn are currently being analyzed and the results will be submitted to a cardiology journal for publication.

C. Development of Protocols and Initiation of Clinical Studies with Iridium-191m from the New Osmium-191/Iridium-191m Generator

Improved diagnosis and evaluation of a variety of cardiac disorders are possible with the short-lived iridium-191m radioisotope (4.9 sec half-life) obtained from a new system developed at ORNL in conjunction with investigators at the Cyclotron Center, University of Liege, Belgium. This new improved osmium-191/iridium-191m generator system which gives good iridium yields, low osmium-191 parent breakthrough and has a useful clinical shelf life of 2-3 weeks has been developed. The screening of several osmium species of various valence states with 39 potential adsorbents identified osmium(IV) potassium hexachloroosmate adsorbed on activated carbon as the most attractive generator system. The activated carbon osmium-191/iridium-191m generator system developed at ORNL may be of significant importance in the diagnosis of heart and vascular disease using nuclear medicine techniques.

The generator system has entered clinical trials through our medical cooperative program in Belgium, in which over 100 patients have been evaluated through June 1986. First-pass (bolus-mode) studies have been performed for the evaluation of both right and left ventricular ejection fraction; perfusion of the cerebral, femoral, and renal arteries; and evaluation of occlusions of the leg veins. The ultrashort-lived iridium-191m radioisotope (4.9 sec half-life) may also be used for the detection and evaluation of abnormal blood-flow (shunts) between the heart chambers of pediatric patients. Important unique features of this system include a very low absorbed radiation dose which is about 1/50 that of an equivalent dose of technetium-99m, now widely used for such studies. In addition, repeat studies can be conducted only a few moments apart. The consistent performance of the generator over a 2-3 week period may make this system available to a large clinical population at a cost competitive with currently-available nuclear medicine procedures. Presently, a variety of carbon adsorbents and various generator geometries are being evaluated to increase yields to prolong the useful shelf life. At the same time,

generators are routinely supplied in the United States to investigators at the Massachusetts General Hospital in Boston, for evaluation of regional myocardial perfusion by constant infusion in animals, and it is expected that clinical studies will soon be initiated at these institutions.

The traveler coordinated the shipment of osmium-191 from ORNL to Liege, Belgium, and traveled to Liege for fabrication of the generators which were then shipped to Bonn. A detailed protocol for clinical use, daily quality control, etc., was written and sterility and pyrogen testing determined to insure that the generators were safe prior to approval for human use. Following initial studies in several volunteers, approval was received in June 1986, from the German Health Ministry for use of the new activated carbon osmium-191/iridium-191m generator system in Bonn in an initial group of 50 patients for first-pass heart studies. This international collaborative effort established by the traveler will continue and involves production of osmium-191 in the ORNL High Flux Isotope Reactor (HFIR) and shipment to the University of Liege, Belgium, where generators are prepared for clinical testing in Belgium and for transporation to Bonn for these new clinical studies.

II. RESEARCH AT OTHER INSTITUTIONS

Belgium

While at off-site assignment in Bonn, the traveler also regularly visited the Cyclotron Research Center at the University of Liege, Belgium, for fabrication and evaluation of osmium-191/iridium-191m generators prior to shipping to Bonn. He worked with Claude Brihaye, Ph.D., a co-developer of the generator who had worked with the traveler at ORNL as a guest scientist in 1982. The collaboration between the traveler, Dr. Brihaye, and his colleagues in Liege, has been very effective. Osmium-191 produced in the ORNL HFIR is shipped to Liege for these generator patient studies in Belgium and Bonn. Thus far over 100 patients have been evaluated with iridium-191m from the new ORNL generator in Belgium, and one goal of the traveler was to coordinate and initiate patient studies in Germany. In Liege, the traveler also initiated and coordinated a collaborative project for clinical evaluation of the new iodine-123-labeled dimethyl-branched fatty acid agent (DMIPP). These studies were performed at the clinical section of the Center for Cyclotron Research at the University of Liege, Belgium, in conjunction with C. DeLandsheere, M.D., and R. Rigo, M.D., where he visited regularly and prepared this agent for clinical studies. Four patients have been evaluated through August 1986 by SPECT with promising results similar to those obtained in Bonn, FRG. The DMIPP agent shows good heart uptake with only very slow wash-out which permits the acquisition of high quality SPECT analysis of regional uptake patterns. Such clinical studies have not been possible with earlier iodine-123 fatty acids. The traveler recommended one major application which will be pursued in Liege. These studies will involve the evaluation of regional myocardial viability by comparison of SPECT images before and after

angioplasty (coronary by-pass). Such a technique may allow a new, and useful tool to evaluate the success of this widely used surgical procedure in restoring regional myocardial function after restoration of flow. Studies in isolated swine and rat hearts (vide ante) have demonstrated that this application may be possible.

The Netherlands

In conjunction with the Department of Cardiology (Franz Visser, M.D., and colleagues), the traveler was able to establish and participate in a research program involving the evaluation of the new radioiodinated dimethyl-branched fatty acid agent (DMIPP) developed at ORNL in a special open chest canine model. Studies were conducted and will continue at the Radionuclide Center (RNC) at the Free University of Amsterdam. The RNC is a unique center that was opened in 1976 where radioisotope research is conducted in many fields, including radiopharmaceutical development and testing, geochemistry, environmental science, etc. The center is quite unique and has a permanent staff of 17 and about 40 "guest scientists" from other departments at the Free University and other institutions within the Netherlands. There are 20 radiochemical laboratories and two fully-equipped surgical suites that are reserved for special experiments involving radioactivity. In addition to a gamma camera, these suites are fully equipped with the necessary physiologic monitoring and fluoroscopic equipment, etc.

The canine experiments conducted in Amsterdam involve the simultaneous evaluation of the myocardial kinetics and metabolism of DMIPP in comparison with two other fatty acid analogues radiolabeled with iodine-125 and iodine-123 in an open chest dog model. This unique animal model, where the heart is exposed in vivo, allows serial myocardial biopsy samples to be obtained followed by lipid analysis to evaluate the metabolism of the new dimethyl fatty acid agent (DMIPP) in comparison with other fatty acids under controlled normoxic conditions, and interventions such as ischemia, hypoxia and pharmacological stimulation. Studies involved the simultaneous evaluation of fatty acid uptake and wash-out kinetics and metabolism using three fatty acid analogues labeled with different iodine radioisotopes (iodine-123, iodine-125 and iodine-131). For these studies, the traveler prepared iodine-131 DMIPP in Liege, Belgium, which was then shipped to Amsterdam. A second fatty acid agent (IPPA) was radiolabeled with iodine-125 by colleagues at ORNL and also shipped to Amsterdam, and the third agent, radiolabeled with iodine-123, was obtained commercially. Since there is often difficulty and controversy in comparing the results of studies reported in the literature with these different agents which were performed in different groups of animals under different controlled conditions, the triple-label studies in Amsterdam provide a powerful and unique opportunity to compare these agents under exactly the same conditions. The studies involve 5-6 dogs for each experimental group to obtain adequate statistics. The traveler participated in the evaluation of the three fatty acids in five normoxic control dogs, and in the first dog studied with a glucose/lactate infusion aimed at evaluating global fatty acid kinetics under altered substrate

conditions. The other intervention that will now be studied also include isoproterenol stimulation global hypoxia, and ischemia. It is anticipated that these studies will continue for the next year. The results of these studies will demonstrate the relative retention of the three agents under a variety of interventions which are directly applicable to the use of DMIPP agents in clinical situations. The data obtained thus far are being analyzed, future intervention studies being planned and it is anticipated that the results from these will be submitted for publication to Circulation.

United Kingdom

The traveler attended and participated in the European Nuclear Medicine Congress 1985, held in London, England, on September 3-6, 1985, and presented a poster presentation entitled "Clinical Potential of a New High Performance Osmium-191/Iridium-191m Generator" (C. Brihaye, M. Guillaume, F. E. Delcourt, H. Ham, F. F. Knapp, Jr., and T. A. Butler). The traveler and his colleagues at ORNL also co-authored two additional abstracts entitled "Myocardial Scintigraphy Using 15-p-(Iodine-123)-Iodophenyl-β-Methyl-Pentadecanoic Acid (βMPPA)" (R. Dudczak, P. Angelberger, R. Schmoliner, K. Kletter, F. F. Knapp, Jr., and M. M. Goodman), and "Effects of 3-Methyl-Branching on Heart Uptake and Metabolism of 15-(p-Iodophenyl)pentadecanoic Acid Analogues" (F. F. Knapp, Jr., M. M. Goodman, and K. R. Ambrose).

III. VISITS TO OTHER LABORATORIES

Federal Republic of Germany

The traveler visited the Institute for Health Physics and Radiation Biology at the Medical School, University of Essen, to discuss joint projects and to present a seminar describing the development of iodine-123-labeled structurally-modified fatty acids at ORNL. The IPPA straight chain agent was originally developed at Essen so these investigators have interest in the development and potential new fatty acid agents. In May the traveler visited the Institute of Medicine at the Federal Research Center in Julich to discuss joint projects and present a similar seminar.

Austria

The traveler was an invited speaker at the "Symposium on the Assessment of Myocardial Metabolism by Cardiac Imaging" in Vienna, Austria, on October 26, 1985, to describe the results of studies conducted at ORNL to investigate the metabolism of the new methyl-branched fatty acid agents, BMIPP and DMIPP (vide ante). During this period he also had the opportunity to visit the Nuclear Medicine Department, University of Vienna (R. Dudczak, M.D.) and the Austrian Research Center in Seibersdorf-Vienna (P. Angelberger, Ph.D.). The traveler had previously established a multi-center Medical Cooperative arrangement where substrates for the radioiodination of the new methyl-branched fatty acids

developed by the traveler and his colleagues at ORNL are supplied for iodine-123-labeling of BMIPP and DMIPP for clinical studies in Vienna. The first clinical studies of BMIPP were performed by Dr. Dudczak which indicated this agent showed the expected more prolonged myocardial retention in comparison with the IPPA straight-chain analogue and may have some advantages for evaluation of specific aspects of fatty acid uptake and metabolism. The clinical studies with DMIPP have just begun in Vienna.

The Seibersdorf Research Center is located about 20 miles south of Vienna and was established in 1960. It is the largest non-academic research institution in Austria with a staff of about 530, including about 80 students and postdoctoral fellows. Similar to ORNL, the original goals were to study nuclear energy and to use nuclear technology for peaceful purposes. The center has a small research reactor (8 megawatts). Areas of research include agriculture, chemistry, biology, electronics, metallurgy, physics and health physics. The radiopharmaceutical research group headed by Dr. Angelberger is in the Department of Chemistry. While little basic research involving the development of new agents is conducted in this program, the major emphasis is on the adaptation of preparation of important new agents for routine production and then distribution to clinical and research investigators within Austria. Thus, revenue is generated by sale of these agents which include compounds radiolabeled with technetium-99m, iodine-131, indium-111, iodine-123, etc., for applications in cardiology, renal function, cerebral blood flow, tumor localization, etc. In addition, custom syntheses with carbon-14 and sulfur-35 are conducted. Dr. Angelberger and his colleagues routinely prepare radiopharmaceuticals for Dr. Dudczak in Vienna, such as the new methyl-branched fatty acids which are now under clinical testing.

The traveler also co-authored an abstract at the Annual Badgastein Symposium in Austria on January 3-6, 1986, entitled "Evaluation of Structure Effects on the Pharmacological Behavior of Radioiodinated Phenylpentadecanoic Acids."

Switzerland

The traveler visited several colleagues in Switzerland and presented seminars describing the development and use of radioiodinated structurally-modified fatty acids and the new osmium-191/iridium-191m radionuclide generator system. He was a guest of the staff of the Radiopharmaceutical Development Department at the Eidgenossisches Institut fur Reaktorforschung (EIR) in Wurenlingen, on April 24, 1986, and the Cardiology Department, University of Geneva Hospital, on April 25. The EIR is a facility of the Swiss government with a staff of about 700. The principal production facilities include a 8×10^{13} neutrons·square centimeter/sec flux reactor and a high energy 300 keV cyclotron. This program is primarily involved in development, production and distribution of radiopharmaceuticals and is not involved in basic radiopharmaceutical research. Major products include iodine-123-labeled agents such as iodohippuran (kidneys), iodoamphetamine (brain), various kits, antibodies, etc. The iodine-123 is produced at a rate of about 4 Ci/week with sales of

1 Ci/week. The price is currently 74 SF/Ci, which is competitive with iodine-123 in the FRG and Belgium. Also, iodine-131 is produced in the reactor by the usual n,γ route and radiolabeled products such as capsules for thyroid therapy and m-iodobenzylguanidine (MIBG) for therapy of adrenal pheochromocytoma tumors are regular products. Since the EIR is a Swiss national company, they can directly market products only in Switzerland and arrangements for sale in other countries in the European community are made through private, licensed companies, such as Squibb in the FRG, etc. In many ways, the EIR is similar to ORNL. One major and interesting difference is the mechanism to finance capital improvements. The funds are provided through the Swiss government as a loan, with arrangments for payback over 10 (equipment) or 20 years (buildings). The traveler found this to be an interesting and innovative means of financing major improvements. A positron emission computerized tomographic (PET) project is also being established at the EIR as a regional diagnostic center with patient referrals for special procedures from local hospitals. The staff also indicated to the traveler interest in gadolinium-153, how it is produced, purified, etc., since they have had numerous requests for this isotope for bone densitometry measurments.

Finland

During the May 12-16 period, the traveler visited several institutions in Finland to present lectures describing the development and use of the new osmium-191/iridium-191m radionuclide generator system, and to discuss and coordinate collaborative studies with this generator and the new iodine-123-labeled dimethyl fatty acid (DMIPP) recently developed by the traveler and his colleagues at ORNL. The traveler presented seminars at the Reactor Research Laboratory in Espoo (Helsinki) and the Nuclear Medicine Department at the University Medical School in Kuopio, and also visited the departments of Nuclear Medicine and Cardiology at the University Hospital in Helsinki. It is interesting that the actual organizational unit in Kuopio performing nuclear medicine studies is typical in about 30% of hospitals in Finland and is designated as the department of "Clinical Physiology." The current state of the art of nuclear medicine is directed at the measurement of "in vivo biochemistry" and physiology in addition to anatomical abnormalities. The designation "clinical physiology" is thus very appropriate. Such a designation in the United States would more accurately reflect the clinical applications of our specialty and remove the hysteria often associated with the term "nuclear," but also would perhaps delete a key descriptive phrase. Whether such a designation would be more readily accepted in the United States is difficult to access, but it is important to note that clinical applications of nuclear magnetic resonance are now widely and almost generally designated as magnetic resonance imaging. In many ways, this may well reflect the competition between nuclear medicine and radiology departments for this high revenue-producing speciality, but may also reflect a marketing decision to remove the term nuclear.

Despite a relatively small (5 million) population in Finland, nuclear medicine procedures are widely used. Finnish colleagues indicated that nuclear medicine in the Soviet Union is evidently much less advanced than in Finland. Most of the radiopharmaceuticals used in Finland are either purchased directly from central European suppliers (Amersham-Buechler, FRG, EIR, Belgium, etc.), or are prepared at the Espoo Facility. For example, molybdenum-99/technetium-99m generators are prepared from molybdenum-99 purchased from the German Democratic Republic. The reactor at Espoo has a low neutron flux, and thus has a limited capability for production of many radionuclides, such as the parent osmium-191 for the osmium-191/iridium-191m radionuclide generator system. The traveler had the impression that routine nuclear medicine practice in Finland is generally up to Western standards, and that nuclear cardiology in general is an important modality and that there is interest and effort for the use of new agents. Examples include the technetium-99m HmPAO cerebral perfusion agent developed by Amersham, iodoamphetamine by Medi-Physics and the mercury-195m/gold-195m generator system by Mallinckrodt. In addition, this institution has specific interest in use of the new osmium-191/iridium-191m generator system and [iodine-123]DMIPP fatty acid agent both developed at ORNL.

IV. SUMMARY AND RECOMMENDATIONS

The traveler gained valuable experience while in Bonn, participated in a variety of important projects which were extensions of the ORNL medical cooperative programs, and was able to effectively stimulate European collaborative programs. Such an off-site assignment is a very valuable experience for the individual scientist. The experience gained, opportunity to participate in various projects, and contacts that were established by the traveler will be important in insuring the continued success in his leadership of the ORNL nuclear medicine program. The medical cooperative programs that were established will continue to be an integral, important aspect of nuclear medicine research at ORNL.