

Perspectives in Nuclear Medicine History—

THREE DECADES OF SCIENTIFIC LIAISON BETWEEN OAK RIDGE AND BONN

Collaboration between the Institute for Clinical and Experimental Nuclear Medicine in Bonn, Federal Republic of Germany (FRG), and the Nuclear Medicine Program at Oak Ridge National Laboratory (ORNL) follows an association that began over 30 years ago when Cuno Winkler, MD, PhD worked in Oak Ridge. In 1951, Dr. Winkler, who celebrated his 70th birthday on September 30, became the first physician in Europe to use radioiodine for the treatment of metastatic thyroid carcinoma. At that time he was working at the Technical University of Aachen, but soon afterwards, he moved to the University of Bonn.

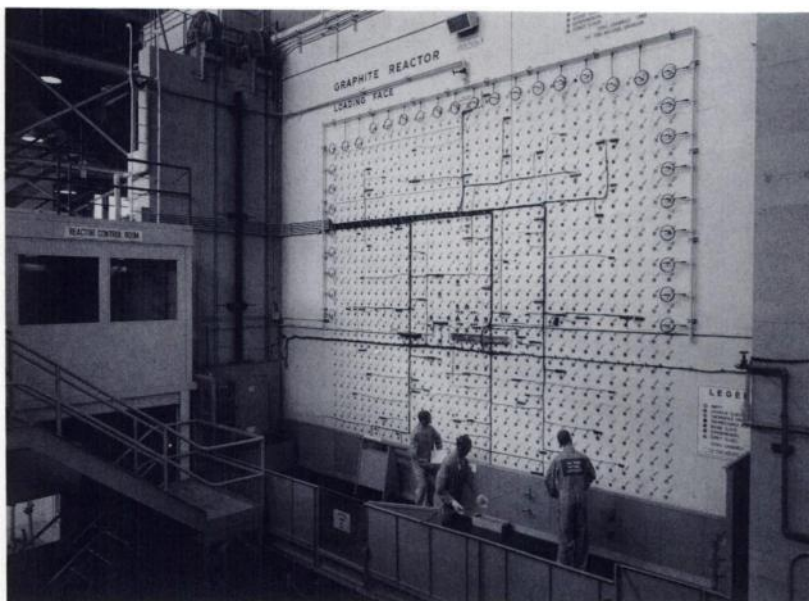
In appreciation for his pioneering work in nuclear medicine, Dr. Winkler was awarded a travel grant in 1957 by the Fulbright Commission to visit scientific institutions in the United States. His first destination was the Oak Ridge Institute of Nuclear Studies (ORINS) in Oak Ridge, Tennessee, now the Medical Division of the Oak Ridge Associated Universities. He worked at ORINS as a visiting scientist for eight months in the Medical Division, with Marshall Brucer, MD, and the late Gould Andrews, MD. Dr. Winkler's main interests at the time were protein radiolabeling, radioiodine metabolism, and the measurement of radioiodine uptake in the thyroid by gamma spectrometry. In the 1950's, fundamental studies of thyroid uptake of radioiodine had been pioneered in Oak Ridge by Dr. Brucer; at that time these thyroid studies were a major example of the unique and important

procedures that could be pursued through the emerging discipline of nuclear medicine. During his stay in Oak Ridge, Dr. Winkler participated in a course on nuclear methods at ORINS and was awarded the Institute's well-known "DRIP," or "Dabbler in Radioisotope Procedures" certificate by Ralph Overman, an ORINS instructor.

After visiting the Institute for Cancer Research in Buffalo, New York, and other institutions in the United States, Dr. Winkler returned to Germany. Collaboration between Bonn and Oak Ridge continued, and Dr. Brucer supplied phantoms that allowed Dr. Winkler to continue his radioiodine uptake studies in Ger-

many. Dr. Winkler continued his distinguished career in Bonn, forming the Institute for Clinical and Experimental Nuclear Medicine in 1972 and heading it until his retirement in 1985. As emeritus professor, he continues to work closely with Hans J. Bier-sack, MD, who succeeded him as the second director of the Institute. Since the early work of Dr. Winkler in Oak Ridge, collaboration between Oak Ridge and Bonn investigators has continued—a most effective demonstration of long-term international cooperation.

The Institute in Bonn has been a major European center of single photon emission computed tomography (SPECT) use since the original

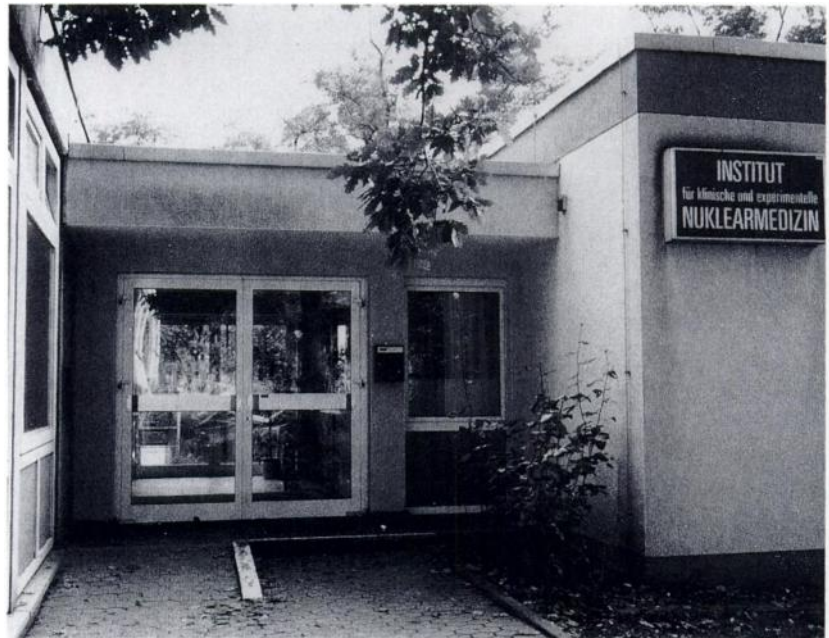


During Dr. Winkler's stay in Oak Ridge, ORNL's Graphite Reactor, now a National Historic landmark, was a principle source for production of radioisotopes used in nuclear medicine research.

multi-detector scanning system (Cleon 710) was installed in 1979. This system was replaced with a rotating gamma camera in 1980. Since 1982, Dr. Biersack and his colleagues in Bonn have employed SPECT to evaluate a large number of patients with a variety of brain disorders, using iodine-123-labeled Spectamine® (IMP). Today Bonn is recognized as an outstanding center for the evaluation of epilepsy patients using technetium-99m-labeled HMPAO.

A recent collaborative project involving Oak Ridge and Bonn was initiated at the 1981 Society of Nuclear Medicine Meeting in Miami Beach, Florida through discussions between F.F. (Russ) Knapp, PhD, who heads the ORNL Nuclear Medicine Program, and Sven Reske, MD, professor of nuclear medicine at the University of Aachen. At that time, Dr. Reske headed a group in Bonn that was one of the first to evaluate the use of ¹²³I-labeled 15-(p-iodophenyl)-pentadecanoic acid (IPPA) and SPECT for assessing myocardial metabolism in patients. The ORNL program had developed the concept of metabolic blocking of fatty acids to determine fatty acid uptake patterns by SPECT (1). Dr. Knapp worked as a visiting scientist at the University of Bonn from July 1985 through August 1986, assisting with clinical studies using two radiolabeling agents developed at ORNL.

The Institute in Bonn was interested in using the new osmium-191/iridium-191m radionuclide generator system that was developed for cardiac studies at ORNL beginning in 1983 by Dr. Knapp and Claude Brihaye, PhD, a research fellow at ORNL on leave from the Cyclotron Research Center in Liege, Belgium (2). This generator system provides ^{191m}Ir in good yields and has a long, useful shelf-life of two to three weeks. The ultrashort-lived (4.96-s half life) ^{191m}Ir is well-suited for first-pass studies evaluating ventricular func-



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tion and is especially useful for making rapid multiple views because of its very low absorbed radiation dose (3). Following his stay at ORNL, Dr. Brihaye initiated the clinical use of this generator in Europe with the assistance of Marcel Guillaume, PhD, head of the radiopharmaceutical program at the Cyclotron Center in Liege.

Because the High Flux Isotope Reactor (HFIR) at ORNL could provide the ¹⁹¹Os needed for this generator system, ORNL shipped the isotope samples produced in the HFIR to Liege, where generators were fabricated for clinical studies in Belgium from 1984 until the temporary shutdown of the HFIR in November 1986. (It is expected to resume operations within the next few months.) More than 600 patient studies have now been performed in Belgium, primarily by Philippe Franken, MD, head of nuclear cardiology at Middelheim Hospital in Antwerp and his colleagues (4). Generators prepared at ORNL (for animal and developmental studies) or in Liege (for volunteer

patient studies) are shipped to the Institute in Bonn for these applications.

The second major area of collaboration involved the use of ¹²³I fatty acids and SPECT. In 1982, the Institute of Bonn was the first facility to evaluate regional myocardial fatty acid metabolism using IPPA and SPECT. Facilities were set up in Bonn and procedures were developed for the routine in-house synthesis of ¹²³I IPPA for patient studies, which significantly reduced the cost of this radiopharmaceutical. In addition, the 3-methyl-branched fatty acid IPPA analogues developed at ORNL by Dr. Knapp and his colleague, Mark Goodman, PhD, director of radiopharmaceutical development, University of Tennessee, were radiolabeled with ¹²³I and evaluated in German hospital patients. Also during this period, collaborative studies involving ORNL and Bonn were initiated with Frans Visser, MD, at the cardiology department of the Free University in Amsterdam, where canine studies are being done to eval-

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uate the relative metabolism of various fatty acid analogues.

The joint fatty acid studies begun in Bonn have now been expanded to include evaluations of the viability of myocardial regions following coronary bypass surgery and percutaneous transluminal coronary angioplasty (PTCA). Administering ^{123}I and the methyl-branched fatty acid analogues developed at ORNL as labeling agents before and after these procedures has demonstrated that this technique can determine the viability of myocardial regions more accurately than flow markers such as thallium-201. The most recent clinical fatty acid studies in Bonn are being carried out by Joachim Kropp, MD, staff physician at the Institute in Bonn, who also recently worked at ORNL as a guest researcher. Andreas Bockisch, PhD, MD, staff physician at the Institute in Bonn, on leave for a scientific stay at the University of Tennessee Hospital (UTK) in Knoxville, collaborated with Edward Buonocore, MD, chief of radiology, UTK, and Karl Hubner, MD, chief of nuclear medicine, department of radiology, UTK, on research projects using the UTK 0.5 and 2.0 Tesla nuclear magnetic resonance tomographs and the new positron emission tomography camera.

An advantage of initiating clinical studies of new agents in Europe is that the time required there for approval of clinical testing of radiopharmaceuticals in humans is shorter than the United States requirement. Our experience also shows that international collaboration on important research problems often has a catalytic effect and speeds not only the research progress but the rate of technology transfer in nuclear medicine. The long-standing collaboration between ORNL's basic radiopharmaceutical research programs and the Institute for Clinical and Experimental Nuclear Medicine in Bonn has

been very effective and mutually beneficial. New work underway in this ORNL/Bonn collaborative arrangement includes evaluation of rhenium-188 for possible use in radiolabeling antibodies and their fragments for therapeutic applications using a tungsten-188/rhenium-188 generator developed at ORNL.

Investigators at the Bonn Institute have completed evaluations of the effectiveness of such agents against TPA, CEA and CA 19/9 human tumor antigens in experimental (transplanted) tumors in rodents. In these studies, researchers measured the tumor uptake of those antibodies and evaluated their ability to block reaction of the antisera with epitopes on normal tissue by preinjection of "cold" antibodies as a means of decreasing background activity and thus whole body irradiation. In clinical studies, antibodies or their fragments chosen on the basis of an antigenic profile of the resected primary tumors have been used against CEA, TPA, CA 19/9, CA 125, HFMG2, Beta HCG and melanoma. Currently, a variety of antibodies labeled with $^{99\text{m}}\text{Tc}$, indium-111, or ^{123}I are being evaluated by SPECT imaging, which allows a more precise visualization of tumorous tissue. The goal in the collaboration studies is to attach ^{188}Re and copper-67, using new methods being developed at ORNL, to representative antibodies for radioimmunotherapy.

In 1989, ORNL and the Institute in Bonn forged another link in their close association when the international journal *NucCompact, European-American Communications in Nuclear Medicine* expanded and began distribution in the United States. U.S. editors on the expanded editorial board include Dr. Knapp of ORNL, Aldo N. Serafini, MD, professor of radiology and medicine, University of Miami School of Medicine, and Henry N. Wellman, MD, chief of nuclear medicine, University of Indiana

Medical Center. Andreas Hotze, MD from Bonn was recently appointed to the European Editorial Board.

In 1957, Dr. Winkler traveled for 10 days to reach Oak Ridge; since 1988, computer links between Bonn and Oak Ridge have facilitated exchange of scientific results and reports within minutes. Through this long collaborative history, these joint approaches for the advancement of nuclear medicine research have changed. These changing, continuing joint efforts, will benefit patients far into the future.

H.J. Biersack, MD
F.F. Knapp, Jr., PhD
C. Winkler, MD, PhD

References

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2. Brihaye C, Butler TA, Knapp FF, et al. A New Osmium-191/Iridium-191m Radionuclide Generator System Using Activated Carbon. *J Nucl Med* 1989; 27:380-387.
3. Franken PR, Dobbeleir AA, Ham HR, et al. Clinical Usefulness of Ultrashort-Lived Iridium-191m from a Carbon-Based Generator System for the Evaluation of Left Ventricular Function. *J Nucl Med* 1989; 30:1025-1035.
4. Ibid.

SNM Executive Director Appointed

Torry Mark Sansone has been appointed Executive Director of The Society of Nuclear Medicine. Mr. Sansone joins the Society from the Emergency Nurses Association where he had held the post of Executive Director since 1981. Prior to that, he was the American Student Dental Association's first Executive Director, holding that position from 1972-1980. Mr. Sansone will assume his post on November 1, 1989. ■