Michigan Brain Imaging Researcher Receives 1990 Tetalman Memorial Award

The Education and Research Committee of The Society of Nuclear Medicine (SNM) has given the tenth annual Tetalman Memorial Award to Kirk A. Frey, MD, PhD, a leading researcher in positron emission tomography (PET) brain imaging, at a presentation held at SNM's Annual Meeting in Washington, D.C. Dr. Frey is an assistant professor in internal medicine and neurology at the University of Michigan Medical Center, Ann Arbor, Michigan.

In a letter nominating Dr. Frey for the Award, David E. Kuhl, MD, professor of internal medicine and radiology and chief of the division of nuclear medicine at the Medical Center, wrote, "his accomplishments and promise are so impressive at such an early time in his development. He chooses important subjects, is innovative in his approach, and presents data carefully and with concern for his audience." Dr. Kuhl also pointed to the fact that, although it is early in his career, Dr. Frey has already published over 20 scientific papers related to nuclear medicine in prestigious journals like *Science, The Journal of Neuroscience, Proceedings of the National Academy of Sciences,* and *The Annals of Neurology.*

Furthermore, Dr. Kuhl wrote, "[Dr. Frey] has established an international reputation concerning the study of in vivo neuropharmacology and cerebral metabolism using nuclear medicine procedures such as [PET]. His future is bright for an outstanding academic career in nuclear medicine."

In another letter of support, Albert Gjedde, PhD, associate coordinator of brain imaging and professor at the department of neurology and neurosurgery at McGill University, Montreal, Canada, lauded Dr. Frey for the significance of his achievements, particularly in the area of quantitative in vivo studies of neuroreceptors in the brain. "It is likely that his contributions will lead to important new findings in this field," wrote Dr. Gjedde. Marveling at Dr. Frey's versatile academic foundation, Dr. Gjedde commented, "His unique background combines the rigor of an education in a branch of physics with the biological insights of a medical man."

Progress in Cerebral Imaging

Dr. Frey obtained an S.B. (Bachelor of Science) degree in electrical engineering from the Massachusetts Institute of Technology (MIT) in 1977. There, he encountered his initial experiences in brain imaging, which culminated in an undergraduate dissertation entitled "Local changes in brain metabolism during temporal lobe seizure in the rat." This study focused on carbon-14 glucose autoradiography of amygdala-kindled seizures in the rat.

After graduating from MIT, Dr. Frey entered the joint MD/PhD program at the University of Michigan, where he first met his mentor, Bernard W. Agranoff, MD, professor of biological chemistry and psychiatry at the University of Michigan and director of the University's Mental Health Research Institute.

Dr. Frey's association with Dr. Agranoff led to one of his most important contributions to the evolution of PET cerebral imaging. In 1983, Dr. Frey produced a scientific article in which he suggested an effective mechanism for using pharmacologic intervention to detect malfunctioning brain tissue with PET imaging. In the paper

Kirk A. Frey, MD, PhD

— published in *Science* and entitled "Barbiturate-enhanced detection of brain lesions using [14C]-2-deoxyglucose autoradiography" — Dr. Frey reported on the use of barbiturate anesthesia in conjunction with the administration of carbon-14-deoxyglucose in the rat. This study showed that when the animal was awake, a caudate lesion appeared as an autoradiographic region of diminished glucose utilization. If, however, the animal was deeply anesthetized prior to the injection, neuronal metabolism was reduced, and the lesion region in the caudate remained unchanged, thus appearing as a hot spot.

According to Dr. Kuhl, this paper proposed for the first time that barbiturates can enhance detection of pathology in PET cerebral metabolic imaging. Commenting on the study in a letter supporting Dr. Frey's candidacy for the Award, Dr. Agranoff wrote, "This demonstration opened the way for subsequent human PET studies using a test-retest design to detect malfunc-

tioning brain tissue, particularly tumors."

Dr. Frey's doctoral thesis, entitled "The in vivo determination of ligand binding with the central nervous system," dealt with the development of a quantitative method for the imaging and measurement of the local densities of muscarinic receptors in the brain. He put his theoretical developments into practical use by developing an in vivo equilibrium model in the rat using tritiated hydrogen-3-scopolamine. Afterward, he developed a kinetic rat model and eventually extended his tracer technique studies of muscarinic receptors to the human brain using carbon-11-scopolamine in conjunction with PET. In addition, this research used radiotracer methods for the autoradiographic localization and quantification of cerebral blood flow, amino acid uptake, protein synthesis, glucose utilization, and neurotransmitter receptor binding.

"These studies exemplify his careful, quantitative approach," wrote Dr. Agranoff. "Currently, he is exploring other ligands that will doubtless improve the method further. It has great promise for the study of psychiatric, neurological, and gerontologic disorders." Louis Sokoloff, MD, chief of the laboratory of cerebral metabolism at the National Institute of Mental Health in Bethesda, Maryland, adds, "This work on imaging muscarinic receptors in the central nervous system is outstanding and is generally so recognized throughout the world."

A year after receiving both his medical doctorate from the University of Michigan School of Medicine and a PhD in neurosciences from the University's Rackham School of Graduate Studies, in 1985, Dr. Frey produced a study entitled "Quantitative in vivo receptor binding III: Tracer kinetic modeling of muscarinic cholinergic receptor binding." This paper, which was part of a landmark effort to quantify neuroreceptors with PET, was published in *The Proceedings of the National Academy of Sciences*. "This was an extremely important contribution," wrote Dr. Kuhl. Commenting on the significance of this study, he added, "[Dr. Frey's] tracer kinetic effort gained him international recognition for in vitro and in vivo receptor studies of the brain, explored first with quantitative autoradiographic techniques and then extended to the study of human subjects using PET."

Versatile Post-Doctoral Career

Dr. Frey moved on to serve an internship in internal medicine at Ann Arbor's St. Joseph Mercy Hospital, and then he returned to the University of Michigan to start his post-doctoral research career. He entered the neurology residence training program under Sid Gilman, MD, chairman of the department of neurology, and subsequently served as a fellow in nuclear medicine under the direction of Dr. Kuhl, who considers Dr. Frey, "the most brilliant nuclear medicine fellow I have encountered during my career."

While performing his neurology residency, Dr. Frey continued his neuroscience research under the direction of Dr. Agranoff, and was appointed research investigator at the Mental Health Research Institute. According to Dr. Frey, working in Dr. Agranoff's laboratory allowed him the time to explore basic issues in tracer kinetics and to develop approaches to in vivo radioligand binding methods, which are the current focus of his research activities. In Dr. Agranoff's laboratory, Dr. Frey was able to extend the results of his doctoral thesis by developing an in vivo model for the quantitative measurement of receptors in the human brain. Dr. Kuhl says, "This model was carried forward from the rat to noninvasive studies in humans. This major contribution is considered among the most significant that have come from the Michigan PET program thus far."

According to Dr. Frey, his initial studies with lipophilic tracers for in vivo imaging of myelin distribution introduced him to "the possibility of applying radiotracer methods to clinical neuroscience problems." In addition, his experiments in Dr. Agranoff's laboratory on regional cerebral glucose utilization "revealed unanticipated metabolism associated with non-neuronal processes in experimental brain lesions. These studies have been extended to evaluation of stroke and brain tumor in humans." Another experiment in Dr. Agranoff's laboratory led to the development of a quantitative receptor autoradiographic method that provided binding parameters from tissue sections. According to Dr. Frey, this approach, refined and modified by others, is currently in use in a number of neuroscience laboratories.

Appointed to assistant professorships in both the nuclear medicine and neurology departments at the University of Michigan Hospitals in 1989, Dr. Frey now has regular assignments teaching neuroscience to medical students and clinical nuclear medicine to residents in radiology, nuclear medicine, and internal medicine. Along with teaching responsibilities, Dr. Frey conducts regular lectures on the basic science of nuclear medicine and oversees the resident training program within the division of nuclear medicine, where he has responsibility for all cerebral radionuclide studies, particularly PET scans.

He also leads the nuclear medicine division's neuropharmacologic effort in PET research. According to Dr. Frey, Michigan's neuropharmacology laboratory is prominent "in the development and characterization of new radiopharmaceuticals for brain imaging. The researchers are focused on physiologic and pharmacologic investigation of ligand distribution." Dr. Frey has explored methods for in vivo characterization of muscarinic cholinergic synapses for several years. In his application for the Award, Dr. Frey

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have emphasized its failure to find radiation-induced breast cancer in highly exposed atom bomb survivors over 40.

Solutions to such scientific and public health problems require a realistic evaluation of the risks associated with low doses of radiation delivered at low dose rates. All too often those concerned with radiation and other environmental issues present worst case scenarios based, perhaps, on the theory that it is better to be overprotective. However, it must be appreciated that in the cases just cited and in a number of other instances of omissions in the BEIR V Report and other similar reports, selective reporting may actually interfere with the presentation of a balanced viewpoint and contribute to a phobic rather than a rational approach to assessing potential problems associated with exposure to low doses of ionizing radiation delivered at a low dose rate.

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wrote that these studies led to "new observations on the regulation of muscarinic receptors in experimental animals, as well as in the development of tracer kinetic methods for determination of in vivo muscarinic receptor binding." Dr. Frey pointed out that the emphasis of his work has been on isolation and extraction of receptor binding information from other ligand distribution processes — blood flow and nonspecific binding — in kinetic PET studies.

Future Endeavors

Dr. Frey will continue to work on the characterization of the normal and pathologic human brain with emission tomographic techniques. This work will consist of both basic research in experimental animals for the selection and development of new tracer techniques as well as clinical research studies applying these methods to normal and diseased populations.

Noting the influential role of nuclear medicine in his clinical and research activities, Dr. Frey wrote, "[nuclear medicine] facilitates the synthesis of my major scientific interests in brain imaging and neurochemistry and is uniquely situated to provide insights into the biochemical disturbances underlying neurologic and psychiatric diseases. Few of these disorders have known pathophysiology or etiology. Autopsy studies are unable to provide data on early or initial changes which may be essential to complete understanding of the diseases process. In this setting, emission tomographic studies will provide insight into the mechanisms of disease in addition to providing potential diagnostic applications."

According to Dr. Kuhl, Dr. Frey plans to explore the pathogenesis of cerebral disease, especially altered neurotransmitter systems, using clinical nuclear medicine imaging. "Although his age is only 34 years, Dr. Frey already is well on his way to becoming an important leader in nuclear medicine as he seeks to develop new ways to image cerebral physiological processes based on neurochemistry," adds Dr. Kuhl.

Summing up Dr. Frey's skills, Dr. Sokoloff wrote "[he] is one of the truly bright young men who will in the near future dominate the field of brain imaging. He has already demonstrated a mastery of the fundamentals of modeling physiological and biochemical processes in vivo and has shown considerable ingenuity and imagination in [that] application."

Presented each year to the most promising nuclear investigator under the age of 36, the Tetalman Memorial Award commemorates Marc Tetalman, MD, a highly respected clinician and researcher, who was murdered during a robbery while attending SNM's 1979 Annual Meeting in Atlanta.

Palash R. Ghosh