Society Honors Marcus E. Raichle, MD, for Basic Science Achievement

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For the past 20 years, Marcus E. Raichle, MD, has looked into the human brain with nuclear medicine's imaging armamentarium. His efforts have uncovered many physiological properties of the body's neurologic structures and over the years have served to better connect the disciplines of nuclear medicine and neurology.

"Most of Marc Raichle's scientific achievements have consisted of utilizing the tools of nuclear medicine, most often, the application of cyclotron-produced, short-lived radionuclides and positron emission tomography [PET] to the solution of scientific problems that could not be probed by any other means," according to Michel M. Ter-Pogossian, PhD, director of the radiation sciences division of the department of radiology, professor of radiology in radiation sciences, Mallinckrodt Institute of Radiology at Washington University Medical Center, St. Louis, Missouri.

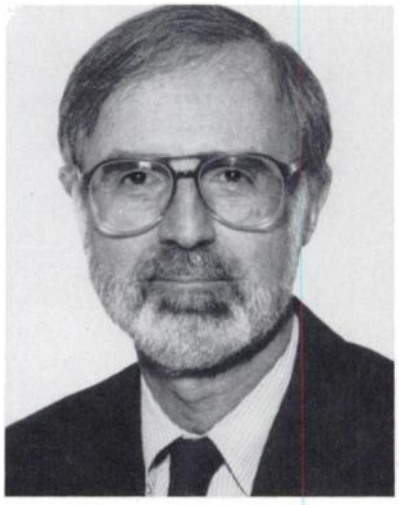
It is for his decades of interdisciplinary research that The Society of Nuclear Medicine (SNM) has selected Dr. Raichle to be the 1990 recipient of the Paul C. Aebersold Award for Outstanding Achievement in Basic Science Applied to Nuclear Medicine. Dr. Raichle, who holds professorships in neurology, radiology (radiation sciences), and biomedical engineering at Washington University, will receive the Aebersold Award during the Society's 37th Annual Meeting to be held in Washington, DC in June.

The SNM Awards Committee honors Dr. Raichle for his efforts to establish a scientific framework on which he and others can build. Chairman of the Committee, William J. MacIntyre, PhD, staff physicist in the nuclear medicine department of the Cleveland Clinic Foundation, Cleveland, Ohio, an SNM past president, says, "Dr. Raichle is one of the foremost exponents of the application of radiotracer techniques, especially as directed to the use of positron emission tomography for studies of cerebral blood flow and metabolism. His 20 years of outstanding achievements in the basic sciences applied to this important area of nuclear medicine is in the true tradition of the Aebersold Award."

In a letter nominating Dr. Raichle for the Award, William J. Powers, MD, associate professor of neurology and radiology at the Mallinckrodt Institute and chief of neurology at Jewish Hospital in St. Louis, wrote, "Dr. Raichle's many contributions to basic methodology for the application of short-lived radiotracers to the study of physiology and biochemistry in vivo have provided the sound scientific foundation necessary for the use of these techniques in the study of human disease."

Quantitative In Vivo Measurements

Dr. Raichle, who received his medical degree from the University of Washington School of Medicine, in Seattle, first studied the human brain with radioisotope techniques during his neurology residency at New York Hospital-Cornell Medical Center. After spending several years studying brain circulation in primates at the Air Force School of Aerospace Medicine, in 1971, he joined the faculty of Washington University School of Medicine as a research instructor in neurology and began to use positron-emitting, cyclotron-produced radionuclides for studies of human and other primate brains.



Marcus E. Raichle, MD

"My fascination with these tracers, which were unknown to most people in the neurosciences at the time, was that they offered the possibility of

quantitative, regional, in vivo measurements of brain circulation, metabolism, and a variety of other functions," Dr. Raichle remembers. "Our initial work was in the refinement of tracer techniques using positron-emitting radionuclides to permit regional measurements of brain circulation and metabolism with multidetector systems arrayed about the human head." Dr. Raichle explains that human studies had to be performed during angiography because a catheter in the internal carotid artery was required for radionuclide injection. "This limited us in the studies that we could perform but did not preclude a number of interesting observations during the 1970s," including the first studies of the regional relationship between oxidative metabolism, circulation, and function in the human brain, the first detailed studies of the effect of subarachnoid hemorrhage on regional hemodynamics and metabolism, the first study of regional hemodynamics and metabolism in dementia, a detailed study of regional hemodynamics and metabolism in pseudotumor, and the first of a series of studies examining the relationship of brain circulation and metabolism to occlusive disease in the carotid system.

Over the same time, Dr. Raichle pursued parallel studies in monkeys on the normal regulation of small molecules through the blood-brain barrier. Dr. Powers lauded Dr. Raichle's work in this area. "...Insistence upon practically applicable methods with verifiable and validated quantitative accuracy has been the hallmark of Dr. Raichle's scientific career. The development of...novel radiotracer techniques for measuring physiology in vivo led to a variety of observations on the control of cerebral blood flow and metabolism...including the seminal discovery that the blood-brain barrier was not a static wall but a dynamic system affected by neural and other influences....Totally unexpected at the time, this observation has been confirmed and expanded by others and now forms the cornerstone of an emerging understanding of the cerebral vasculature."

Dr. Powers noted that at this time, with the advent of the intracarotid method of delivering radiotracers, Dr. Raichle began to bring these experimental radiotracer techniques into the realm of clinical research. He wrote that Dr. Raichle performed "a number of pioneering studies of neurologic diseases...that showed the importance of determining cerebral blood flow and metabolism regionally to be able to fully understand human cerebral pathophysiology. These original observations clearly demonstrated the need for the quantitative measurement of multiple different physiologic parameters in the evaluation of human disease and the capability of nuclear medicine techniques for doing so."

Brain PET Work

To find less invasive methods to study the brain, noted Dr. Powers, Dr. Raichle turned to PET. "Applying fundamental principles of tracer kinetics and extending previous work done by the intracarotid technique, he developed PET methods for the measurement of regional cerebral blood flow and metabolism. To date, they remain the only PET methods for measuring cerebral blood flow and metabolism that have been proven to be quantitatively accurate by comparison with an independent standard."

In a letter supporting Dr. Raichle's nomination, Michael E. Phelps, PhD, Jennifer Jones Simon Professor of Radiological Sciences, chief of the division of nuclear medicine and biophysics, chief of the Department of Energy Laboratory of Nuclear Medicine at the University of California, Los Angeles, School of Medicine, noted that Dr. Raichle developed techniques to measure blood flow using oxygen-15-labeled water and carbon-11-labeled butanol, and later he "led the effort to use modifications of the Kety-Schmidt approach with these diffusable tracers to develop and rigorously validate approaches for the measurement of cerebral blood flow with PET." With his colleagues, Dr. Raichle "also developed a method for the measurement of cerebral oxygen utilization and once again performed very careful validation approaches to understand and develop the measurement accuracy of this approach," added Dr. Phelps.

Seymour S. Kety, MD, senior scientist at the National Institute of Mental Health, Professor Emeritus, Harvard University, Cambridge, Massachusetts, told *Newsline* that Dr. Raichle's technique for measuring regional cerebral blood flow and his further studies in that area "have added to the evidence that regional blood flow is well correlated with functional activity....In this area, he is preeminent. There is no one whose contributions can be compared to his." According to Dr. Kety, Dr. Raichle's method, "like the deoxyglucose technique, visualizes activity throughout the brain, rather than in the cortical mantle alone, and appears likely to have a far greater impact on the study of human cognition and behavior than did the electroencephalograph. It complements the deoxyglucose technique in that it permits rapid measurements in relatively quick succession, which makes it especially suited to the study of transitory responses such as those involved in cognitive and most other physiological functions."

According to Dr. Raichle, the "development of tracer methods and data analysis strategies has been a major preoccupation" of those using PET to elucidate brain function. In addition to their measurements of blood flow, metabolism, and oxygen consumption, during the late 1970s and 1980s, Dr. Raichle, along with others at Washington University, developed and implemented techniques to measure blood volume, permeability, pH, and receptor pharmacology. "In addition to the

measurements themselves," says Dr. Raichle, "we have developed very sophisticated software that has become the key to our success in mapping the brain with PET." These software programs permit the use of neurosurgical stereotaxy to objectively localize anatomical regions of interest. In addition, the software allow for strategies that employ image subtraction and averaging procedures to localize brain blood flow changes provoked by changes in neuronal activity — with a precision of one to two millimeters. Commenting on his work, Dr. Raichle voices his conviction that "it is not just the PET scanner you have that determines what success you have but also what you do with the data once you have it."

Michael Posner, PhD, professor of psychology at the University of Oregon, in Eugene, says Dr. Raichle and his colleagues have been instrumental in developing the software and other parts of the "infrastructure" required to effectively employ PET technology.

Using these same PET strategies in humans, the Washington University researchers have engaged in various other avenues of neurological study. In the early 1980s, Dr. Raichle and others conducted some of the earliest PET studies of newborns to determine how prematurity and neonatal asphyxia affect the subsequent development of brain damage. The investigators have also continued to examine the physiological and clinical significance of hemodynamically significant carotid artery disease and have extended their studies of blood flow, metabolism, and receptor pharmacology to patients with Parkinson's disease and dystonia, a hereditary disease characterized by disordered muscle tone.

Psychiatric Disorders

Since the mid 1980s, Dr. Raichle has worked to apply PET to the study of psychiatric disorders. Using this technology to study panic disorder, the Washington University researchers found that in the non-panic state, individuals with this disease have an abnormality in the limbic system in the right parahippocampal gyrus. In further studies, they found that the panic state was physiologically manifested by highly localized bilateral changes in the temporal lobes. "These were exciting observations for us and prompted us to study normal anxiety in the form of anticipatory fear," Dr. Raichle told *Newsline*. "This study revealed, again, highly localized bilateral changes in the temporal cortex and strongly suggests that work with imaging techniques will contribute to a better understanding of human emotions."

Dr. Posner told *Newsline*, Dr. Raichle has "been able to provide the most convincing evidence for the localization of both cognitive and affective (or emotional) processes" in studies of patients with panic disorder and normal subjects in an anxiety state. The results, he adds, "provide stronger support that a common, underlying neural system is involved."

More recently, using PET, Dr. Raichle has focused on developing functional maps of the brain areas involved in sensory and language information processing. While some of this work builds on and confirms earlier efforts, Dr. Raichle notes, "our work on language has provided a new perspective on the organization of language in the human brain and the potential of PET to explore such complex and uniquely human processes." Dr. Phelps notes, "These studies have illustrated the way that one can examine subsystem organizations of the brain in dealing with different components of a task."

Furthermore, notes Dr. Posner, Dr. Raichle and his colleagues have uncovered "very specific areas of the brain that code for visual and auditory aspects of specific words. This kind of localization might be possible for higher mental functions."

As an offshoot of this work, the group has studied the relationship between brain blood flow, brain metabolism, and neuronal activity. "We discovered that functional changes in neuronal activity are supported by nonoxidative glycolysis. Oxygen, although present in abundance, is not used."

"In the coming years," Dr. Raichle says, "I will continue to apply PET techniques to gain further understanding of the human brain, with the hope that eventually we can understand diseases that affect human performance and behavior." He adds that studies of the human brain are "uniquely at a crossroads." Major advancements are centered in the neurosciences, and "these kinds of nuclear medicine techniques are allowing an entry point," facilitating those advances.

Dr. Kety agrees that "It is in [the] important processes of thinking and feeling that the study of the human brain has no comparable analogy in lower animals and where the most important approaches to future understanding lie."

In his nominating letter, Dr. Powers stressed Dr. Raichle's attention to detail and accuracy and his efforts to educate the public and the rest of the medical world about nuclear medicine—admirable traits in an outstanding basic scientist. "Dr. Raichle has made major contributions to the field of nuclear medicine in his application of basic radiotracer principles to the study of human physiology and disease. His work has involved taking these tracers from theory to practical applications that are based on careful validation of quanititative accuracy. This has provided a sound scientific foundation for the use of radiotracer techniques such as PET in clinical research...His untiring efforts [to teach] both lay and medical personnel ...the value of quantitative nuclear medicine techniques have led to a more widespread appreciation of the scientific value of nuclear medicine in both basic and clinical research."

Sarah M. Tilyou