'Conceptually Continuous' Research

SEYMOUR S. KETY, LOUIS SOKOLOFF TO RECEIVE HEVESY PIONEER AWARD

Two prominent investigators in the area of brain blood flow and metabolism, Seymour S. Kety, MD, associate director for the Basic Research Intramural Program of the National Institute of Mental Health (NIMH), Bethesda, Maryland, and Louis Sokoloff, MD, chief of the Laboratory of Cerebral Metabolism, also at NIMH, will receive the 29th Georg Charles de Hevesy Nuclear Medicine Pioneer Award from the Society of Nuclear Medicine (SNM) at its 35th Annual Meeting in San Francisco, California in June.

The award recognizes two careers that are notable for their fecundity. Dr. Kety's pioneering work in measuring cerebral blood flow attracted Dr. Sokoloff, who sought out Dr. Kety and worked as a post-doctoral research fellow with him at the University of Pennsylvania. They have made significant discoveries in their own right, and Drs. Kety and Sokoloff have helped provide others with the tools needed to explore human brain function.

Louis Sokoloff, MD

Seymour S. Kety, MD

NAS Award

This year the two researchers are also the first winners of the Neuroscience Award of the National Academy of Sciences (NAS), Washington, DC, which Academy officials said is "in recognition of their extraordinary contributions to progress in the field of neuroscience." The $15,000 prize is supported by the Fidia Research Foundation of the Italian-based Fidia S.p.A., a pharmaceutical company. The NAS presented the award to the pair at its annual meeting in late April "for developing techniques in brain blood flow and metabolism—valuable tools in the study of brain function that have major applications in clinical medicine."

In his letter nominating them for the NAS Neuroscience Award, Gunther Stent, PhD, chairman of the neurobiology section of the NAS and chairman of the department of molecular and cellular biology at the University of California at Berkeley, explained why the two researchers should receive the award together. "Drs. Kety and Sokoloff have made a series of epochal contributions to the understanding of brain blood flow and metabolism, starting in the 1940s with the Kety-Schmidt technique for measuring blood, and culminating in recent years with Sokoloff's development of the 2-deoxyglucose technique for monitoring localized changes in brain activity," he wrote. "These contributions are especially noteworthy for their having led to breakthroughs both in fundamental neurophysiology and in clinical neurology. A joint award is justified, moreover, because Sokoloff was one of Kety's early collaborators and the work of both men is conceptually continuous."

The SNM award will be presented to the pair by David Kuhl, MD, professor of internal medicine and radiology and chief of the division of nuclear medicine at the University of Michigan Medical Center in Ann Arbor. Dr. Kuhl is also well-known for the study of brain blood flow and metabolism, and has worked with Dr. Sokoloff on studies with fluorodeoxyglucose (FDG).

The Nuclear Medicine Pioneer Award was established in 1960. In 1979, to honor the contributions of the late Georg Charles de Hevesy, PhD, MD, the Hungarian chemist who developed the radiotracer technique, the title of the award was modified to include his name.

Both Dr. Kety and Dr. Sokoloff

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were born in Philadelphia, Pennsylvania, in 1915 and 1921, respectively, and both earned their baccalaureate and MD degrees at the University of Pennsylvania. After receiving the MD in 1940, Dr. Kety served a two-year internship at Philadelphia General Hospital, worked as a National Research Council Fellow at Harvard University and Massachusetts General Hospital in Boston until 1943, and then returned to the University of Pennsylvania to the Departments of Pharmacology and Physiology of the Undergraduate and Graduate Medical Schools, where he stayed until 1961. In 1951 he was appointed the first scientific director at the National Institute of Mental Health and Neurological Diseases and Blindness, establishing the intramural research programs at these institutes. From 1956 to 1967, he directed the Laboratory of Clinical Science at the NIMH, and he served as Henry Phipps Professor of Psychiatry at Johns Hopkins, Baltimore, Maryland, from 1961 to 1962, and as a research professor of psychiatry at Harvard Medical School from 1967 to 1983. From 1984 to 1985 he also served as senior science advisor in alcohol, drug abuse and mental health for the United States Public Health Service.

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Lead Poisoning Treatment

In 1942 Dr. Kety proposed a new treatment for lead poisoning based on his basic studies of the lead citrate complex. This was a forerunner of the modern treatment of the condition with chelating agents. Three years later he developed a technique for the measurement of cerebral blood flow in humans based upon his examination of the principles of capillary-tissue exchange and, with collaborators, he applied this to studies of the circulation and metabolism of the human brain in health and disease. In 1951, Dr. Kety published his mathematical expression for the exchange of inert tracers between blood and tissue, which has become the basis for measurement of local blood flow throughout the brain in animals and humans. His interest in the role of biological mechanisms in psychiatric illness led him and his collaborators to demonstrate the importance of genetic factors in the transmission of schizophrenia.

Dr. Kety traces his interest in the human brain back to his high school days, when he attended Central High School in Philadelphia, a magnet school that attracted students interested in science. "I've always been interested in the brain and mind," Dr. Kety said. "I went to medical school not because I expected to practice but because I was interested in research."

The Fick Principle

While in Boston Dr. Kety saw a paper by Carl Schmidt, MD, who had used a bubble flow meter inserted in monkey brains to measure cerebral circulation. He was also influenced by the work of Nobel laureate Andre Cournand, MD, who was using indirect techniques to measure cardiac output in humans. "I became fascinated by the possibility of measuring human cerebral circulation" because of its relationship to metabolism, he said. He also felt that measuring circulation in the brain was more important than doing so for the heart. "The human brain is really unique, it's a quantum jump from the animal brain, even the brain of the higher apes," he points out. "It suffers from a number of diseases for which there are no animal models."

Dr. Kety extrapolated from the work of Dr. Cournand and modified the Fick Principle to measure blood flow to the brain. But he knew he couldn't use oxygen as a tracer because the amount used by the brain varies with the organ's activity. Instead he selected the non-metabolized, inert gas nitrous oxide as a tracer, and applied this technique to various kinds of coma and to studies of schizophrenia, in which he discovered that overall brain blood flow and oxygen consumption is the same in schizophrenics as in normal people. This meant either that there wasn't any difference, or that changes were taking place in discrete regions of the schizophrenic brain that were obscured in the brain as a whole.

'Beautiful' Autoradiograms

Soon thereafter Dr. Kety devoted a year to understanding inert gas exchange. He derived equations that helped explain the uptake of gases used in anesthesia, such as ether and chloroform, and this work contributed to anesthesiology and helped provide a framework for later studies of the uptake of radioactive gases by the brains of animals. In the mid-1950s he and a group of colleagues, including Dr. Sokoloff, ad-

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ministered the gas trifluoroiodomethane labeled with iodine-131 intravenously to cats, sacrificed the animals after one minute, and produced sections of the frozen brain tissue. Autoradiograms, which showed varying degrees of exposure depending on the concentrations of the inert radioactive gas, were produced at low temperatures. Dr. Kety concluded that these autoradiograms could measure blood flow with an accuracy of ± 10%. These were the first measures of regional blood flow to the brain. Dr. Sokoloff went on to use photic stimulation to produce what Dr. Kety calls "beautiful" autoradiograms clearly showing markedly increased blood flow in the visual cortex and superior colliculi of the cat after five minutes of exposure to flashing light. This demonstrated that regional blood flow and metabolism are associated with functional activity in the brain.

Since then Dr. Kety has expanded his research in many areas, such as explorations of the sleeping brain. He continues to study cerebral blood flow and is looking for a better tracer technique for PET than oxygen-15 water. He remains interested in the genetic and environmental factors that lead to schizophrenia, the condition he first explored with Dr. Schmidt in the 1940s.

The Deoxyglucose Method

Dr. Sokoloff, who describes himself as "a physiologist who works on the biochemistry of the brain—a physiological chemist," said he first became interested in neuropsychiatry while working as a physician in the United States Army in the late 1940s. After working with Dr. Kety in the 1950s and 1960s, he went on to study many other related areas, but remained interested in a non-invasive technique, which unlike autoradiography, would permit the study of regional function in the human brain.

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By the 1970s, physics and engineering had caught up with the biological theories as PET instrumentation appeared. As part of a research team including Martin Reivich, MD, Dr. Kuhl, Al Wolf, PhD, Michael Phelps, PhD, and several others, Dr. Sokoloff proposed the now well-established deoxyglucose method in 1977. Dr. Kety said this technique is superior to nuclear magnetic resonance (NMR) and computed tomography (CT) scans when applied to brain tumors not only because it provides good images, but also because it measures the degree of metabolic activity of the tumor.

In the years since, Dr. Sokoloff has studied many aspects of brain function, including the effects of aging and hormones. Currently he's working on further adaptations of the deoxyglucose method. But he is also studying cell cultures to learn more about how carbohydrates are transported and metabolized at the cellular level. This work is indicative of a commitment to basic research that Dr. Sokoloff, who has published more than 300 papers, believes is essential to scientific productivity and application. "Everything I do, I draw always on my background in basic scientific principles. Whatever contributions I've made have been based on basic science," he said. "Applications are often just the trivial fallouts from good, solid, basic science." For example, he noted that the deoxyglucose method came out of work aimed at understanding the chemistry of the brain.

Grounding in Basic Science

Consequently, Dr. Sokoloff believes that those preparing for a career in science need a solid grounding in biology, chemistry and physics, and thinks medical schools should adjust their curricula so that they accept students who are well-grounded in basic science. "Everybody is in a hurry, they want it all and they want it now, instead of preparing for the future," he said.

But, he adds, facts alone are not enough. Quoting from another source, Dr. Sokoloff pointed out that a house is composed of a pile of stones, but a pile of stones does not make a house; in the same way, science is composed of a collection of facts, but a collection of facts does not make science. "Science is an understanding based on actual facts," he said, "but it's an understanding of how nature carries out its things. You must ask intelligent questions, meaningful questions, and they'll direct you to the facts. Often you don't have the methods to acquire those facts, so you develop them. But eventually the facts fall into place and answer the questions, and then the practical applications fall out."

Karla Harby