

Seymour S. Kety, MD (1915-2000)

When Seymour Kety died quietly and peacefully on May 25, 2000, at age 84 years, he left a legacy of scientific accomplishments in the elucidation of human brain function in health and disease. He brought the methodological rigor of basic science and his extraordinary insights into studies of the human brain that have led to major advances in neurophysiology, cognitive science, and allied disciplines, and launched neuroscience on its royal road to solving many of the mysteries of psychopathological and neuropathological conditions. Although Kety contributed substantively to many areas of physiology and neuroscience, he will be most remembered for developing methods to measure cerebral blood flow (CBF) and metabolism, for providing the evidence for the genetic transmission of schizophrenia, and for having established the first national mental health research effort at the National Institutes of Health (Bethesda, Md).

When he was 13 years old, Kety was given a chemistry set by an aunt, and from that moment his attraction to chemistry became so strong that he built a formidable laboratory in his basement. He would save his lunch money to buy chemicals from a chemical supply house near his high school. While attending college at the University of Pennsylvania (Philadelphia) he got a job assisting a toxicologist in the study of lead and was assigned the task of analyzing lead in the urine of workers. Kety used the standard procedure of precipitating the lead as an insoluble salt and then redissolving it with sodium citrate, which formed a soluble lead chelate. It occurred to Kety that it might be possible to treat lead poisoning with citrate, which might solubilize the lead and accelerate its excretion. He successfully tested this idea in experiments in rats and established the basis for the modern treatment of lead poisoning.

His work on lead gained him a fellowship at Massachusetts General Hospital (Boston) with Joseph Aub, MD, who was a leading authority on lead, but with the start of World War II, Aub switched his research agenda from lead poisoning to traumatic shock. Aub's group recognized that there were homeostatic circulatory reflexes operating in the body during shock that served to preserve blood flow to the brain, heart, and lungs, while reducing flow to other organs. The coronary, cerebral, and pulmonary vessels were not constricted by the increased sympathetic nervous activity in traumatic shock as were the vessels supplying the skin, kidneys, and viscera. Consequently, as cardiac output

declined, it was redistributed to favor the brain, heart, and lungs because brain and heart tissues could survive only a short time without blood flow, whereas kidneys, skin, muscles, etc, could withstand circulatory insufficiency for much longer times.

At this point, Kety read an article by Dumke and Schmidt¹ that described the measurement of



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CBF in the anesthetized rhesus monkey by means of a bubble flow meter inserted in the cerebral arterial system. This was the first time anyone had measured quantitatively the flow of blood through the brain. Challenged by the idea of measuring CBF in unanesthetized humans, Kety decided to return to the University of Pennsylvania to work with Schmidt. He felt that the human brain is unique among organs for its complexity as well as its capacity, versatility, and plasticity, its ability to conceptualize, to create, to experience ecstasy and deep grief, and to describe to outside observers the results of its inner processes. It also falls prey to serious disorders of these functions, for which no animal models exist. It seemed to him that the study of the circulation and metabolism of the human brain while it was engaged in these functions might teach us something about these processes, and such studies in disease might be of benefit to those suffering from neurological or mental disorders.

Kety was aware of the applications of the classic Fick principle in the determination of cardiac output and of hepatic and renal blood flow. Cournand² had calculated cardiac output from the steady-state oxygen uptake by the lungs and the difference in oxygen contents in the blood entering and leaving the lungs, each of which could be measured independently. In determining blood flow in the liver and kidney, investigators took advantage of the ability of these organs to excrete a specific foreign substance into the blood at rates that could be measured. There was, however, no known natural or foreign substance that the brain selectively removed from or excreted into the blood that could be accurately measured. Kety reasoned that he could apply the Fick principle indirectly by introducing an inert gas into the blood, which the brain could take up by simple diffusion. He originally chose nitrous oxide (N₂O) as the tracer, administered in inspired air in low concentrations while its arteriove-

nous differences across the brain were measured. In ingenious experiments he showed that after about 10 minutes of inhalation, brain and blood concentrations of N₂O were almost at equilibrium, allowing him to determine the brain N₂O concentration from the cerebral venous concentration at that time. He could measure the concentrations of the gas in arterial and mixed cerebral venous blood and integrate the difference over time. Because the measurement of cerebral blood flow required sampling arterial and representative cerebral venous blood, it was simple to also measure the brain's rates of consumption of any metabolic substrates or production of any metabolic products that could be detected in the blood (eg, oxygen, carbon dioxide, lactate). The method and several of its applications were published in 1948 in 5 separate articles in a single issue of the *Journal of Clinical Investigation*, leading to the widespread application of the method to treat a variety of physiological and pharmacological conditions and disease states, and revolutionizing research on the human brain.

Kety used the method to examine several conditions, including schizophrenia, essential hypertension, diabetic acidosis, anesthesia, and normal sleep. To his surprise, he found that the brains of schizophrenic patients had the same blood flow and oxygen utilization as those of normal subjects. He suspected that the pathological processes in the brains of schizophrenic patients were too localized to reveal themselves in the average CBF and metabolism of the brain as a whole, which is what the N₂O method measured. This led him to develop a method for the measurement of regional blood flow within the brain, called the [¹³¹I] trifluoriodomethane method. This method was based on an equation he had derived in his development of the principles of inert gas exchange between blood and tissues. He employed quantitative autoradiography to achieve localization within the brain. This method was later adapted for use in humans with ¹⁵O water and positron emission tomography, now widely used to visualize local functional activity in the brain. The field of functional brain imaging was thus ushered in, revolutionizing the study of mental, cognitive, and emotional processes.

In 1950, Robert Felix, MD, the first director of the newly established National Institute of Mental Health (Bethesda), approached Kety regarding the open position of the first scientific director of what Felix, perhaps not too hyperbolically, described as the greatest program of research on the brain and behavior that the world has ever seen. The position was offered to Kety despite the fact that he was not a psychiatrist and, in fact, because he was not a psychiatrist. Felix wanted a researcher with a proven track record to head the new national research effort into the causes of mental illnesses. Kety was convinced that basic research was of fundamental importance in this effort and that much better understanding of brain physiology, biochemistry, neuropharmacology, genetics, sociology, and psychology, as well as understanding of clinical psychiatry was needed before testable hypotheses about the causes of mental illnesses could be con-

structed. In creating a research program of unprecedented magnitude and quality, he recruited outstanding established scientists and promising young scientists with assurances of complete scientific freedom. He believed that supporting these people and leaving them to carry out their programs would yield the best research. His selection of scientists was so astute and the atmosphere he created so generative that more than 20 among those he appointed were ultimately elected to the National Academy of Sciences (Washington, DC), and one received a Nobel Prize.

In the early 1960s Kety turned his focus to the issue of the genetics of schizophrenia. Although there was much evidence that schizophrenia ran in families, in the 1950s and earlier most psychiatrists, psychologists, and sociologists believed that schizophrenia was a condition learned from one's parents, and the only prescribed treatment, therefore, was educational, psychological, and sociological manipulation. The atmosphere in American psychiatry and psychology in the 1950s and early 1960s was rigidly biased against recognizing genetic factors in the development of schizophrenia. Consider R. D. Laing's 1967 book, *The Politics of Experience*, in which he wrote, "It seems to us that *without exception* the experience and behavior that gets labeled schizophrenic is a *special strategy that a person invents in order to live in an unlivable situation.*"³(pp114,115) Theodore Lidz, wrote "It seems unlikely . . . that the cognitive disorder can be transmitted genetically . . . , rather than experientially."⁴(p12)

In tackling this problem, Kety, with his collaborators, gathered a national sample of adopted individuals in Denmark and identified those with schizophrenia among them. If Lidz and Laing were correct, the adoptive parents of individuals with schizophrenia would be found to have schizophrenia. Two crucial conclusions from these studies remain unchallenged. First, children born to a mother with schizophrenia and reared in an adoptive family without schizophrenia become schizophrenic at the same rate as those reared by the biological mother. Second, biological relatives of an adopted child with schizophrenia are found to have chronic schizophrenia in their families, whereas the adoptive family members of that child have a rate of chronic schizophrenia no higher than that in an adoptive family of a child without schizophrenia. The studies thus confirmed that schizophrenia was confined almost exclusively to the biological families of the adopted children with schizophrenia, and that the adoptive relatives of these children, as well as the relatives of adopted children without schizophrenia, show the low rate of schizophrenia that is found in the general population.

Kety also found increased rates of conditions that seemed to be much less severe forms of schizophrenia in the biological family of the adopted children with schizophrenia, but not in the adoptive family members. Bleuler⁵ had called these conditions latent schizophrenia. It has many of the symptoms of schizophrenia except that they are neither as disabling nor as obvious. Kety and his group adopted Bleuler's term to denote this condition, which in the *DSM-IV* is called

schizotypal personality disorder. Because Kety found this condition in the biological but not in the adoptive relatives of schizophrenic patients, the adoption strategy gave this finding a genetic basis. Kety thus confirmed that there is another syndrome like schizophrenia that is genetically related to schizophrenia. This finding was the beginning of the idea of the “schizophrenia spectrum,” which presumes that there are several conditions that, although not recognizable as a schizophrenic psychosis, nevertheless seem phenotypically related to the psychotic condition.

Seymour Kety truly opened the door to the understanding of the basic processes not only of normal brain functioning, but also of how the body, brain, and mind function when disease attacks. He was a giant among us, but his tread was soft, graceful, and unobtrusively dazzling. Our field owes much to him, and it is with pride

and humility that we say, “Thank you, Seymour. We are privileged to have been touched by your brilliance and friendship.”

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