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SEYMOUR S. KETY
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A Biographical Memoir by
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SEYMOUR S. KETY

August 25, 1915–May 25, 2000

BY LOUIS SOKOLOFF

SEYMOUR SOLOMON KETY, a member of the National Academy of Sciences since 1962, died on May 25, 2000. He was an outstanding scientific statesman, but more significantly an eminent neuroscientist and pillar of biological psychiatry. He will long be remembered for his legendary scientific achievements, outstanding statesmanship, and magnanimity of spirit. I was fortunate to have known Seymour for approximately 56 years as a teacher, preceptor, collaborator, colleague, and friend, and in every one of these roles he earned an unmatched level of esteem, not just from me but also from almost everyone with whom he interacted. He graced every field in which he worked and those with whom he worked, and I know of no scientist who was so universally respected, admired, and even loved. Neuroscience and psychiatry have suffered a great loss.

Seymour was born in Philadelphia on August 25, 1915. He was raised there in rather humble but intellectually stimulating surroundings. In his childhood he suffered an automobile-inflicted injury to one foot that, though not serious, resulted in residual physical limitations that deprived him of participation in the usual athletic activities of childhood and directed him further toward intellectual pursuits. One

of his greatest interests was in chemistry, and he spent many hours carrying out chemical experiments in a laboratory he created in his home. Seymour received all his primary and secondary school education in Philadelphia, where he attended the prestigious Central High School, the city's premier high school. There he was able not only to pursue his interests in the physical sciences but also to receive a fairly broad education in the classics, including both Greek and Latin, and to be inspired by an erudite and nourishing faculty.

After graduation from high school he attended the college and then the medical school of the University of Pennsylvania, from which he graduated in 1940. He then married Josephine Gross, whom he had known from childhood, and entered into a rotating internship at the Philadelphia General Hospital. Josephine was also a medical student and eventually a physician who was particularly interested in pediatrics. It may well have been her influence that led Seymour to choose an area of research while still in medical school and to pursue further during his internship. This research led to the first of his many major contributions to medical science.

Pediatricians were at that time concerned about the many children they saw with lead poisoning, probably due to their chewing on the lead-containing paint on their cribs. Marshaling his long-time interest in and knowledge of chemistry, Seymour conceived of the idea of using citrate to treat lead poisoning, because citrate forms a soluble chelate of lead that is relatively rapidly excreted in the urine. Better and more effective chelating agents are now in use, but this was the first proof of principle that chelating agents can be used in the treatment of heavy metal intoxication.

To pursue further his interest in lead poisoning after completion of his internship, Seymour obtained a National

Research Council postdoctoral fellowship to work with Joseph Aub, a well-known researcher on lead poisoning at the Massachusetts General Hospital in Boston. The fellowship began in 1942, but by then the United States was at war, and when Seymour arrived, he found that Aub had abandoned his work on lead poisoning and switched to a more pressing problem during wartime: traumatic and hemorrhagic shock. Seymour joined the group working on that problem, and it was the research on shock that led him to develop an interest in circulatory physiology. He became particularly intrigued by the cerebral circulation that appeared to be relatively preserved in cardiovascular shock by regulatory mechanisms that adjusted the distribution of the reduced cardiac output to favor the brain, heart, and lungs at the expense of less vital circulatory beds. To pursue this new interest he elected to forego the opportunity to remain at Harvard and in 1943 returned to the University of Pennsylvania to work with Carl Schmidt, then a leading figure in the field of the cerebral circulation; Schmidt had just published his bubble-flow-meter technique for the quantitative determination of cerebral blood flow (CBF) and metabolism in anesthetized monkeys. Both Seymour and Josephine had been born, raised, and educated in Philadelphia, and their desire to return to their roots may also have been a factor in this decision.

Seymour was an instructor in Schmidt's Department of Pharmacology when I first met him in 1944 as a student in his first class in pharmacology. He was an excellent teacher who presented lucid, stimulating lectures that emphasized the experimental procedures and results underlying the conclusions that were to be drawn. I still remember how he made even a lecture on analgesics exciting. He was popular with the students and readily accessible to them. As he was not much older than we were, he often joined some of the

members of our class on the patio of Houston Hall, the university's Student Union, where we usually congregated after lunch. It was in casual conversations on those occasions that we first learned of his interest in the cerebral circulation. He was in the process of formulating ideas about a method for measuring cerebral blood flow in human subjects that would require the sampling of cerebral venous blood from the internal jugular vein. I suspect that he might have been trying to get us to volunteer for the procedure, but if so, it was without success.

At the 1944 annual meeting of the Federation of American Societies for Experimental Biology there was a symposium on the cerebral circulation that dealt mainly with the methods of its measurement. The dominant theme was the need for a method for measuring CBF quantitatively, and preferably one applicable to unanesthetized man. There were at the time nonquantitative methods for studying CBF in man. One was the thermoelectric flow recorder, a thermocouple in the form of a needle that could be inserted into the jugular vein to detect changes in flow within the vein by recording changes in the temperature of its blood content. This technique could indicate only blood flow changes within the vein but could not measure perfusion rates within the brain tissue. Another popular method at the time was the measurement of cerebral arteriovenous O_2 differences, which should vary inversely with changes in CBF if cerebral O_2 consumption ($CMRO_2$) remained constant, but it did not actually measure CBF and could not distinguish between changes in CBF and $CMRO_2$. The only method that quantitatively determined both CBF and $CMRO_2$ was the bubble-flow technique of Dumke and Schmidt, but this method required not only anesthesia but also such extensive surgery that its use was restricted to monkeys.

Seymour attended this symposium and accepted the chal-

lenge with a unique and conceptually brilliant approach. He was aware of Cournand's application of the direct Fick principle to the determination of cardiac output in man by measuring the rate of O_2 uptake into the lungs and the difference in O_2 concentrations between blood going to and coming from the lungs. Seymour reasoned that he could apply the Fick principle indirectly by introducing into the blood a foreign, chemically inert tracer that diffused freely across the blood-brain barrier and measuring the cerebral arteriovenous difference (i.e., difference in tracer concentrations in the arterial blood going to the brain and in representative cerebral venous blood coming from the brain). He initially chose the freely diffusible gas nitrous oxide (N_2O) as the tracer and administered it in low concentrations in the inspired air.

Arterial blood is the same in all arteries, but was usually sampled in the femoral artery. Venous blood varies from vein to vein, but representative cerebral venous blood was sampled from the superior bulb of the internal jugular vein. It was necessary also to know the amount of tracer taken up by the brain. In cleverly designed experiments he showed that after about 10 minutes the concentrations in the brain and cerebral venous blood were close enough to equilibrium to allow calculation of brain N_2O concentration from the measured cerebral venous concentration at that time and the relative solubilities (i.e., partition coefficient) of N_2O in brain and blood. The same principle applied equally well to other chemically inert tracers, such as 79 krypton and 133 xenon, and these were later used sometimes instead of N_2O , because it was more convenient to measure their concentrations in blood. Another particularly valuable feature of the N_2O method was that because it required the sampling of both arterial and cerebral venous blood to determine CBF, it became relatively simple also to determine the

brain's rates of utilization or production of oxygen, glucose, carbon dioxide, and lactate by measuring their cerebral arteriovenous differences and multiplying them by the value obtained for CBF.

This ingenious conceptual approach resulted in the Kety-Schmidt method for the quantitative determination of cerebral blood flow and metabolism in unanesthetized man. The experimental work that led to its development was supported by a grant from the Scottish Rite and carried out on conscientious objectors who had volunteered to be used as subjects in medical research rather than to be inducted into the armed forces during the war. The N_2O method and five of its applications in various physiological and disease states were published in a single issue of the *Journal of Clinical Investigation* in 1948. Its impact was like a thunderclap that revolutionized research on the human brain. Numerous applications in neurology, psychiatry, and medicine led to much of our knowledge of the normal physiology, pathophysiology, and pharmacology of the circulation and metabolism of the human brain in health and disease. Carl Schmidt, in whose department Seymour developed the method, wrote,

Now, for the first time, the clinical physiologist is no longer at a disadvantage in studying the circulation in the human brain. As a matter of fact he is now able to learn more about this, and its relation to the metabolic functions of the organ supplied, than about any other organ of the body. The change is one of the small profits of the research activities of the war years and is one more example of the benefits to be expected from giving brilliant young men opportunities to develop and test out original ideas.

These papers were published while I was serving in the U.S. Army as a neuropsychiatrist and undecided about what to do when I was discharged. The idea of studying directly the circulation and energy metabolism of the human brain in normal and mentally ill subjects attracted me, and shortly

after leaving the Army in 1949 I joined Seymour as a postdoctoral fellow in Julius Comroe's Department of Physiology and Pharmacology in the Graduate School of Medicine of the University of Pennsylvania, where Seymour had been appointed a full professor.

It was a fantastic experience. Seymour was an inspiring leader. Despite his towering intellect, he never allowed it to overwhelm us. He was always humble and unpretentious and listened to everything we had to say. Often he would raise questions and patiently consider our comments even though, as we would later learn, he already knew the answers. His attitude stimulated us to think critically and deeply. A frequent comment of his was, "Well, think about it." He valued conceptualization, originality, and uniqueness above all. In my very first project as a research fellow, which was on the effects of hyperthyroidism on cerebral O₂ consumption in man, we were scooped in the publication of the entirely unexpected finding that the oxygen consumption of the brain remained normal despite very large increases in total body O₂ consumption. He consoled me with the comment, "Don't feel bad. It must not have been such a great idea. Someone else thought of it too"—a sentiment typical of his attitude.

Seymour's office in the department had two doors. One opened into the corridor and the other into the large room where the research fellows had their desks. The latter door was almost always open, and we constantly interrupted his work, which at that time was mainly on the preparation of his now classical and seminal *Pharmacological Reviews* article "The Theory and Applications of the Exchange of Inert Gas at the Lungs and Tissues." One day late in the summer of 1950 the door was closed all day while Seymour was meeting with two U. S. Public Health Service officers in their white uniforms.

All of us were curious, of course, because we suspected that whatever this meeting involved it would impact us. Therefore, as soon as the officers left we queried him about the purpose of their visit. It turned out that they were Robert Felix and Joseph Bobbitt, the director and the executive officer of the National Institute of Mental Health (NIMH), one of the newly formed institutes in the National Institutes of Health in Bethesda, Maryland. They had come to offer him the position of scientific director of the intramural research programs of both the NIMH and the National Institute of Neurological Diseases and Blindness (then NINDB, now National Institute of Neurological Disorders and Stroke). When we asked him if he would seriously consider leaving Penn for such an offer, he replied that would indeed, because he had always been interested in mental disease and that this offer presented a challenging opportunity to study it. We then asked why they would choose him, a physiologist and neither a psychiatrist nor a neurologist, to direct a program of research on mental and neurological diseases. His reply was that he had had the same question and had raised it with Felix and Bobbitt. They explained that it was exactly for that reason that they wanted him; they thought that the scientific director of a research program on mental and nervous diseases should be a basic scientist and not a psychiatrist or neurologist in order to ensure rigorous and scientifically sound research. Seymour did not, however, rush to a decision. After several months of agonizing rumination and frequent consultations with friends, colleagues, and undoubtedly Josephine, he accepted the appointment, and in 1951 left Penn to undertake the organization of the intramural research programs of the NIMH and NINDB.

The Clinical Center of NIH was under construction when he arrived, and Seymour, as scientific director, had what he

considered almost unlimited resources in space, budget, and positions to organize the intramural research programs of the NIMH and NINDB. He approached this responsibility in characteristic Kety fashion: cautiously, deliberately, systematically, studiously, and with great humility. He had no preconceived notions about how best to study mental and neurological diseases but had faith that more basic, fundamental knowledge of the structure and functions of the nervous system would be needed. He therefore emphasized the basic sciences and relegated most of his resources to laboratories organized along more or less traditional disciplinary lines.

Seymour then exhaustively consulted leaders in these disciplines to identify outstanding candidates and succeeded in recruiting a truly impressive array of laboratory chiefs. Some of these were Wade Marshall, chief of the Laboratory of Neurophysiology; William Windle, chief of the Laboratory of Neuroanatomical Sciences; Giulio Cantoni, chief of the Laboratory of Cellular Pharmacology; Kenneth Cole, chief of the Laboratory of Biophysics; David Shakow, chief of Psychology; and John Clausen, chief of the Laboratory of Socio-Environmental Sciences. He retained for himself the position of acting chief of the Laboratory of Neurochemistry while he was trying to recruit an outstanding biochemist with interest in the nervous system; he also reserved for himself within that laboratory the Section on Cerebral Metabolism in which he could carry out his own research.

Seymour did not pretend to be expert in all these disciplines in the program. Once these laboratory chiefs were appointed he gave them full authority and support to direct their own laboratories as they chose, but provided them with his advice, counsel, and assistance in recruiting their staffs. The laboratory chiefs were selected not because they had been working in the latest most fashionable, so-called

“hot” research areas but because they had demonstrated originality and conceptual ability in their choice, design, and execution of their previous research. He was unimpressed by mere descriptive research or research driven more by ambitious, wish-fulfilling (though unrealistic) goals than by insight. His acumen in his selection of laboratory chiefs, as well as some members of their staffs that he had helped to recruit for them, was eventually confirmed; one won a Nobel Prize, at least three received Lasker awards, and at least a dozen, if not more, were eventually elected to the National Academy of Sciences.

While engaged in the organization of the intramural research programs of the NIMH and NINDB, Seymour collaborated with several biochemists in Europe and the United States (e.g., Heinrich Waelsch, Paul Mandel, Derek Richter, Henry McIlwain) in efforts to bring greater recognition and respect to and interest in the field of neurochemistry. Their efforts resulted in the initiation in 1954 of biennial neurochemical symposia, later transformed into the International Society for Neurochemistry, the founding of the *Journal of Neurochemistry* in 1956, and the establishment of the International Brain Research Organization (IBRO) in 1960.

Seymour allocated to his own Section on Cerebral Metabolism a modest amount of laboratory space in which to conduct his own research. Because his nitrous oxide method measured only average blood flow and metabolic rates in the brain as whole, it could not localize changes in these functions in discrete regions of the brain. He therefore undertook the development of a method to measure local cerebral blood flow based on his theory of inert gas exchange between blood and tissues that he had previously developed and published in 1951. With the help of several research fellows (i.e., William Landau, Walter Freygang, Lewis

Rowland, and myself) he ingeniously translated his theories into an operational method for measuring local CBF. The method could be used with any chemically inert tracer that could diffuse freely across the blood-brain barrier, but they selected ^{131}I -labeled trifluoroiodomethane ($^{131}\text{I}[\text{CF}_3\text{I}]$), a gas with the requisite properties. Localization within the brain was achieved by a unique quantitative autoradiographic technique that limited its use to animals. The method and its use to determine local CBF in individual structural and functional units of the brain in conscious and anesthetized cats was first reported in 1955. When used to examine the effects of visual stimulation, the autoradiograms clearly visualized the increases in CBF in the various structures of the visual pathways and led to the very first published demonstration of functional brain imaging, a field now enjoying enormous popularity.

Because the trifluoroiodomethane method was designed for use with autoradiography, it could be used only during uptake of tracer by the tissues. The underlying principles on which it was based were, however, equally applicable to clearance of the tracer from tissues after they had been pre-loaded with the tracer. Seymour had in fact used the clearance approach to determine blood flow in muscle of human subjects. He had injected $^{14}\text{NaCl}$ directly into the muscle and measured its clearance from its site of injection with a Geiger counter. The publication in 1949 that described these experiments included a detailed description of the theory and procedure for calculating local blood flow from the rate of clearance of the tracer. The $^{24}\text{NaCl}$ clearance method could not, however, be used in brain because $^{24}\text{NaCl}$ is not freely diffusible in either direction across the blood-brain barrier, but Niels Lassen, David Ingvar, and colleagues later adapted it by using radioactive gases, first radioactive krypton (^{85}Kr) and subsequently $^{133}\text{xenon}$.

The ^{133}Xe method has been extensively and very effectively used as a clinical and research tool for several decades. More recently the trifluoriodomethane method has been resurrected for human use, but with ^{15}O -labeled water as the tracer and PET scanning in place of autoradiography, and is now widely used in the functional brain imaging of cognitive processes in humans. All these fantastic new developments in neurobiology were derived from Seymour's pioneering work.

In 1956 Seymour stepped down from the position of scientific director to become the chief of the Laboratory of Clinical Science. Having completed organization of the basic research components of the intramural research programs of NIMH and NINDB and being too humble to feel that he should or could direct or interfere with the research of the outstanding and diverse cadre of laboratory chiefs that he had assembled, he no longer found the position of scientific director sufficiently challenging. As he put it, he no longer enjoyed the role of "deciding where to put the broom closets." There were also other reasons; he was anxious to become more immersed in his own research in new areas in which he had become interested. He had been impressed by developments in psychopharmacology, particularly those involving the monamine neurotransmitters and the actions of psychotomimetic drugs, such as LSD, mescaline, indole derivatives, and the like. There were suggestions at the time that abnormal metabolites of amino acids or of epinephrine might be involved in schizophrenia. There were also a few published studies, which though flawed and inconclusive suggested genetic influences in schizophrenia. All this reinforced Seymour's suspicion that schizophrenia might be a biochemical disorder that was at least partly inherited. He therefore established in the Laboratory of Clinical Science a program of research on the

biology of schizophrenia. One of his projects was to examine the hypothesis that abnormal disposition of epinephrine might be involved in schizophrenia, and to facilitate this study he contracted for the first commercial synthesis of radioactive epinephrine and norepinephrine. The labeled compounds later proved to be of immense value to Julius Axelrod, a member of the laboratory, in his Nobel Prize-winning research. Although no definitive evidence of a biochemical defect linked to schizophrenia was derived from these studies, they did serve to organize Seymour's thinking about the subject and led to his publication of several critical and heuristic papers in *Science* that almost certainly laid the foundation for modern biological psychiatry. He was quite amused by my quip that he had transmuted psychiatry from psychoanalysis to urinalysis.

His research at NIMH was interrupted in 1961, when he accepted the position of chairman of the Department of Psychiatry at Johns Hopkins University. He had, however, never received formal training in clinical psychiatry, and he felt very uncomfortable being in the position of psychiatrist in chief at Johns Hopkins University Hospital. Therefore, after one year he resigned and returned to his position as chief of the Laboratory of Clinical Science at NIMH and resumed his research on schizophrenia, this time focused on the question of genetic contributions to the disease.

Previous studies of siblings and monozygotic and dizygotic twins had suggested a genetic influence, but they had failed to disentangle convincingly the roles of "nature and nurture." He conceived the brilliant idea of studying the adoptive and biological family lines of schizophrenics who had been adopted at birth. The necessary data were available in the Danish Case Registry, and he in collaboration with colleagues, mainly David Rosenthal and Paul Wender at NIMH and Fini Schulsinger in Denmark, initiated such

studies. In 1967 he left NIMH for Harvard University, where he first became director of psychiatric research at the Massachusetts General Hospital, then director of the Laboratories for Psychiatric Research, Mailman Research Center, McLean Hospital, and finally professor of neuroscience in the Department of Psychiatry. In 1983 he retired from Harvard and returned to NIMH from which he retired once again in 1996.

Throughout all these decades and all his moves he continued his studies on adopted schizophrenics. The results demonstrated far greater incidence of the disease in the biological than in the adoptive family lines and thus provided unequivocal evidence of a major genetic component in the etiology of schizophrenia. The conclusions were not readily accepted by many committed to a social and/or environmental basis for the disease. Seymour acknowledged that schizophrenia was not a purely genetic disease, like phenylketonuria or Huntington's disease, only that there was an inherited susceptibility in a group of patients that fell within what he called a "schizophrenia spectrum." He responded to sometimes severe criticism with his characteristic wit and wisdom. For example, in response to the statement "Schizophrenia is a myth," he wrote, "If schizophrenia is a myth, it is a myth with a strong genetic component." The adoption studies contributed not only to our understanding of schizophrenia but also their underlying strategy and design provided a research model that has been and continues to be followed in studies of a number of other psychiatric disorders.

Seymour Kety's legacy encompasses at least three different areas of endeavor. As a physiologist he made extraordinary contributions mainly to the field of cerebral circulation and metabolism but also to general circulatory and respiratory physiology. As a wise and adroit statesman he

developed at NIMH and NINDB outstanding research programs in neuroscience, contributed substantially to the recognition of neurochemistry as a respectable and important field of neuroscience, was a powerful force for the development of biological psychiatry, and was a sage counselor on countless advisory boards and committees. As a psychiatric geneticist he conceptualized and developed a methodological approach for separating the contributions of nature and nurture in the etiology of mental disease and used it to prove the existence of a strong genetically determined vulnerability to schizophrenia.

There is, in addition, Seymour Kety the man. His professional achievements gained him enormous international recognition and acclaim. He received many awards, honorary degrees, and honorary titles and was elected into some of the most honorific societies, such as the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. In 1999 he received his last award, the Lasker Award for Special Achievement in Medical Science, which touched him deeply. None of these honors changed him. He remained the same humble, modest, self-effacing, unselfish, considerate, kind, generous, and warm human being that he was when I first met him 56 years earlier. He always remained readily accessible to all and never used his razor-sharp intellect to overwhelm or intimidate. He was intensely loyal and supportive of his colleagues and truly relished their successes whenever they occurred. Perhaps his wife, Josephine, a master of one-liner repartee, kept him humble. For example, Seymour once expressed to her his surprise that a newly arrived research fellow from India did not appear to be very impressed when Seymour had proudly escorted him through NIH's newly opened Clinical Center, the world's largest all-brick building furnished with the most modern hospital facilities. Her

response was, "Did you ever hear of the Taj Mahal?" When Seymour was scientific director of NIMH, psychoanalysis was a powerful influence in psychiatry, and the NIH administration felt that the director of its research program should undergo a personal psychoanalysis. Seymour resisted, but finally, when they offered to pay for it, he was inclined to accept. Josephine's comment was, "Suppose they offered you a free appendectomy. Would you take it?"

The Ketys were generous and genial hosts and would often entertain at their home. These were always delightful experiences full of scintillating conversation and humor from guests with a wide variety of backgrounds. Seymour had an enormous reservoir of jokes and amusing anecdotes that he enjoyed telling and occasionally using to make a point. The Ketys were also great art lovers, and Seymour was enamored of good food and wine. Seymour Kaufman and I, both of us in the intramural program of NIMH, were present at what was probably the zenith of his experience with the French cuisine. In the summer of 1958 the three of us attended in sequence an International Neurochemical Symposium in Strasbourg, France, an International Biochemical Congress in Vienna, Austria, and finally the inaugural meeting of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Rome, Italy. During the meeting in Strasbourg Kety inquired from Kaufman and me whether, if he bought a car, we would be willing to ride with him to these meetings and then onto Paris, France. We, of course, gratefully accepted, but it was not until we reached France on the leg from Rome to Paris that we learned his intentions. He had longed to but had never previously eaten at any of the three-star restaurants in the almost biblical *Guide Michelin*. He had, therefore, planned a route that led us to four of only twelve such restaurants in all of France so honored at that time by the guide. Because

of time constraints we ate in four consecutive days at Baumanière in Les Baux, Provence; De La Pyramide in Vienne, Burgundy; Hostellerie de la Poste in Avallon, Burgundy; and La Tour d'Argent in Paris. Kaufman and I were thoroughly saturated with food but not iron-man Kety, who attributed our weakness to lack of stamina due to our youth. Those restaurants probably represented the epitome of the traditional French haute cuisine with its rich, flavorful sauces that he had come to admire so much. He later lamented the subversion of the classical French sauces by the advent of the nouvelle cuisine and cuisine minceur.

Seymour is survived by his wife, Josephine; daughter, Roberta Kety; son, Lawrence Kety; and two grandchildren. He will be greatly missed not only by them but also by his many colleagues and friends whose lives he so greatly influenced and enriched.

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