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SEYMOUR KAUFMAN
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A Biographical Memoir by
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March 13 1924–June 23, 2009

BY LOUIS SOKOLOFF

THE NATIONAL ACADEMY OF SCIENCES and the biochemical community have lost another of its distinguished members. Seymour Kaufman—a member of the Academy's Section 21 and a scientist emeritus and former chief of the Laboratory of Neurochemistry of the National Institute of Mental Health—passed away at the age of 85 on June 23, 2009, after an illness of several years.

Seymour was renowned for his characterizations of the partial reactions in the chemical processes catalyzed by the mixed-function oxidases involved in the hydroxylation of aromatic amino acids. He identified tetrahydrobiopterin as the essential cofactor in the hydroxylation reactions of phenylalanine to form tyrosine, tyrosine to form DOPA, and tryptophan to form hydroxytryptophan. He identified ascorbic acid as the cofactor in the hydroxylation of the side chain of dopamine to form norepinephrine. He confirmed by direct enzyme assays in biopsied human liver tissue samples that it is indeed the lack of the phenylalanine hydroxylase enzyme that is responsible for classical phenylketonuria, the human genetic disease. Subsequently, his identification of tetrahydrobiopterin as the cofactor and his characterization of the catalytic nature of its involvement in the hydroxylation reactions made it possible for him to identify other genetic

variants of phenylketonuria resulting not from absence of phenylalanine hydroxylase activity but from deficient activity of enzymes involved in the synthesis and/or regeneration of tetrahydrobiopterin.

Seymour was born in Brooklyn, New York, on March 13, 1924, the youngest of three children, preceded by two doting sisters. His earliest interests were not at all in science, showing instead artistic talent, which encouraged him to nourish ambitions for a career as an artist. Accordingly, he applied for admission and was accepted to the prestigious New York High School for Music and Art. In the four years there he was exposed to daily art studio instruction but very little science. When, however, he compared his artistic talent to what he considered the exceptional talents of many of his fellow students, he concluded that it was unlikely that he could have a successful professional career in art.

Though poorly exposed to the sciences in the high school curriculum, Seymour read during his senior year Paul DeKruif's *Microbe Hunters* and Sinclair Lewis's *Arrowsmith.* Like so many others of his generation, his interest in the sciences was greatly stimulated by these books, and he began to consider pursuing a career in some kind of biomedical research. This new interest initially fluctuated between biochemistry and basic chemistry because he appreciated that a strong background in chemistry would also be invaluable in biochemistry.

Seymour started his college education at Brooklyn College, but after two years he applied to the University of Illinois at Urbana-Champaign because of the outstanding reputation of its Department of Chemistry and was admitted in 1941. In the course of his undergraduate studies there he took most of the courses available in organic chemistry. During his senior year he acquired considerable additional experience in synthetic chemistry by working part-time synthesizing

a variety of organic compounds needed by members of the Department of Chemistry for their research.

Despite his extensive experience in organic chemistry, however, his primary interest switched to biochemistry when in his senior year he was profoundly stimulated by W. C. Rose's course in intermediary metabolism. After graduation in 1945 he enrolled in the graduate master's degree program in biochemistry at the University of Illinois. It was there that he carried out his first experimental biochemical research under Carl Vestling, which led in 1946 to his first publication in the Journal of Biological Chemistry. His experience in this research with Vestling was so thrilling to him that it firmly fixed his interest in a research career in biochemistry, particularly in intermediary metabolism.

Seymour received his master's degree in chemistry in 1946 and decided to pursue a Ph.D. in biochemistry. It was at this point that his experience in organic chemistry paid special dividends. Hans Neurath at Duke University needed someone with a strong background in chemistry and wrote to the Department of Chemistry at the University of Illinois inquiring if they had any graduate students with a strong background in synthetic chemistry. His research needed synthetic peptides to serve as substrates for proteases whose mechanisms of action he was studying. The department recommended Seymour, and he was accepted into the Ph.D. program in the Department of Biochemistry at Duke University. There he worked together with George Schwert, John Snoke, and Elaine Elkins, another graduate student, on the enzyme activities of the proteolytic enzymes trypsin and chymotrypsin and discovered their esterase activities.

A very positive side effect of this project was that Seymour and Elaine married, a union that lasted until Seymour's death. From his three years of working with Neurath Seymour gained an intense interest in enzymology and knowledge

and experience with protein chemistry and the principles of separating components of complex enzyme systems.

In 1949 Seymour received his Ph.D. in biochemistry from Duke University, and after several months as a postdoctoral fellow there he accepted a position as a postdoctoral fellow with Severo Ochoa in the Department of Pharmacology of the New York University Medical School. After arriving there, he was quickly immersed in enzymology and the then fiercely competitive areas of intermediary metabolism (i.e., enzymes of the citric cycle, glycolysis, fatty acid oxidation, the hydrogen transport system, and carbon dioxide fixation). His first project was somewhat routine: separate lactic acid dehydrogenase from the then partially purified preparations of the malic enzyme. He did not find this project very stimulating but did acquire from it valuable experience in the techniques of protein separation and enzyme purification that proved so valuable in his subsequent research.

His next research project was on the enzymology of the oxidative decarboxylation of α-ketoglutarate in the citric acid cycle. The results of these studies were sensational. He found that the addition of a boiled tissue extract (Kochsaft) provided an essential cofactor that led to the α-ketoglutarate dehydrogenase-catalyzed conversion of α-ketoglutarate to succinate. The cofactor was identified as coenzyme A, and succinyl-CoA was found to be an intermediate that was subsequently converted to succinate with the associated synthesis of ATP by another enzyme, succinic thiokinase.

Seymour's findings were in spinach, but others later found that, in heart and probably also in other mammalian tissues, GDP or IDP were the primary phosphate receptors and that the GTP or ITP that were formed subsequently transferred the high-energy phosphate to ATP by the activity of the enzyme nucleoside diphosphokinase. This was the first demonstration of so-called "substrate-level phosphorylation" and showed that

the oxidative decarboxylation of α-ketoglutarate to succinate in the citric acid cycle is associated with the formation of four high-energy phosphate bonds, three coupled to the electron transport chain involved in the oxidation of the NADH formed, and the fourth from the conversion of succinyl-CoA to succinate and CoA by succinic thiokinase.

Seymour presented these findings at the 1951 meeting of the prestigious McCollum-Pratt Symposium on Phosphorous Metabolism with many of the world's leading biochemists in attendance. This was a daunting challenge, but his presentation was warmly received and proved to be an extraordinarily exhilarating experience for him. More significantly, Ochoa was sufficiently impressed by Seymour's performance that he offered him a staff position first as an instructor and then assistant professor in his Department of Pharmacology of the New York University Medical School.

Seymour spent five years in Ochoa's department that were particularly stimulating and formative in his later career. First of all, he was immersed in an atmosphere of state-of-the-art biochemical research and the most advanced techniques in enzymology that proved so valuable in his later research. Ochoa's laboratory at that time had become a magnet for a stream of prominent biochemists that visited or spent time there. In addition to Ochoa, there were many outstanding direct members and close associates of the department, including Sarah Ratner, Ephraim Racker, and Otto Loewi. There were also a number of established or future luminaries in biochemistry who spent some time there. These included F. Lynen, I. Gunsalus, T. Stadtman, W. Slater, M. Grunberg-Manago, and G. Cantoni.

Seymour was exposed to the rich scientific environment in New York City. He regularly attended the meetings of the Harvey Society and the Enzyme Club, where he was exposed to and became acquainted with distinguished scientists from

New York City and surrounding area and from around the world. It was an extraordinarily stimulating atmosphere in which a young and budding scientist could develop his career. There was also the powerful influence of Ochoa's character, personality, and modus operandi. Ochoa was completely dedicated and focused on his research and uncompromisingly rigorous in its execution. Though Seymour would probably have denied it, he later displayed some of these traits in the style and way he directed his own lab.

Giulio Cantoni was in Ochoa's lab during part of the time Seymour was there and was greatly impressed by him. Cantoni subsequently moved to Western Reserve University where he carried out his seminal research on methylation reactions and discovered and identified S-adenosylmethionine as an intermediate in these reactions. It was probably because of this work that in 1953 Seymour Kety—scientific director of the Intramural Research Programs of both the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disease and Blindness (NINDB)—offered Cantoni the position of chief of NIMH's Laboratory of Cellular Pharmacology.

Kety was the first scientific director of both institutes and, as such, had the responsibility to establish and organize the Intramural Research Programs of both institutes. I was a postdoctoral fellow with Kety at the University of Pennsylvania before he left for NIH, and he often returned to Penn to discuss the research on which we were still collaborating. During these visits he often discussed his thoughts, frustrations, and plans regarding his responsibilities at NIH. He admitted that he had no specific ideas about the best approach to study mental and neurological diseases but was firmly convinced that basic research on the nervous system would prove essential. He, therefore, chose to concentrate his efforts on the basic research of the Intramural Research

Programs of the institutes and ceded the responsibilities for clinical research to clinical directors, a psychiatrist for the NIMH and a neurologist for the NINDB. His initial task was to select the areas and disciplines for research, establish the laboratories for each of these, and recruit laboratory chiefs who would then be allowed to recruit staffs of their own choosing. He was convinced that biochemistry would be an essential discipline for progress and hoped to recruit an outstanding biochemist to direct a laboratory that would carry out biochemical research on the nervous system. It was on the basis of recommendations by Bernard Horecker and Arthur Kornberg that he offered this position to Cantoni.

Cantoni adamantly refused to commit himself to research on the brain, and though Kety felt strongly that the program should include biochemical research on the nervous system, he did not want to miss out on Cantoni. He compromised by creating a Laboratory of Neurochemistry with himself as acting chief until a permanent neurochemist could be recruited and the Laboratory of Cellular Pharmacology in the NIMH with Cantoni as its chief. Kety also divided the Laboratory of Neurochemistry into three sections and recruited Alex Rich for chief of the Section on Physical Chemistry, Roscoe Brady for chief of the Section on Lipid Biochemistry, and myself as associate chief and then chief of the Section on Cerebral Metabolism. Cantoni immediately asked Seymour Kaufman to join him at NIH. In Ochoa's lab Seymour had been required to work more or less on projects chosen by Ochoa, but Cantoni offered him complete independence and the freedom to work on research projects of his own choosing. This was an offer that Seymour could not refuse, and he accepted.

All of us arrived at various times in 1954, usually before our labs were completed and ready for operations. While waiting for completion of our labs, we spent our time on

ordering equipment and supplies and interviewing and selecting research fellows and technical staff. After sufficient professional staff had arrived, Cantoni organized a biochemical journal club. The club met every Friday at lunch during which its members rotated to present published articles for discussion. The original round of meetings was devoted to each of us presenting the research we had done before coming to NIH. It was this round that led to my close association with Seymour.

At my presentation I reported on the effects of thyroid hormones on cerebral oxygen consumption: that hyperthyroidism in human adults had no effects on cerebral oxygen consumption even when total body oxygen consumption was increased by as much as 70 percent. Others had shown that thyroid hormone administration in rats raised cerebral oxygen consumption in early life during the brain development but no longer after the brain had reached maturity. As a result of these observations, an exhaustive review of the literature, and various other considerations, I arrived at the hypothesis (provocative at the time) that the action of thyroid hormones in vivo was to stimulate protein synthesis and not on uncoupling of oxidative phosphorylation, which was the popular belief at that time.

Following my presentation Seymour approached me and expressed his opinion that from entirely different considerations he had arrived at a similar hypothesis and suggested that we collaborate on studies of the effects of thyroid hormones on protein synthesis. This led to a collaboration over a number of years during which we did, in fact, find that thyroid hormones stimulated protein synthesis. This collaboration also led to the development of a close friendship between us and our families that has survived even to today.

Seymour arrived at NIMH before his lab was ready. The delay allowed him to deliberate without distractions on the choice of what was to be his first completely independent research project. It was a time when he and I met almost every afternoon for coffee in the NIH cafeteria, and at these times he usually expressed his thoughts on the selection of a research project. Several considerations were playing a part in these deliberations. First, he had a very strong background and interest in organic chemistry. Second, he had developed very strong interests and experience in intermediary metabolism and enzymology. Third, he still retained his youthful ambition to contribute to biomedical research.

NIMH had been established specifically to support research on mental disorders, but its scientific director had assured investigators in the Intramural Basic Research Program that they would not be obligated to work on problems directly related to mental disease or even the brain. Nevertheless, the fact that Seymour was in NIMH probably influenced his final decision. The research problem he finally decided on was the enzymatic hydroxylation of phenylalanine to tyrosine, a problem that met all three considerations. First, Seymour was curious about how nature managed to hydroxylate the benzene ring of phenylalanine, a reaction that, as an organic chemist, he had no idea how to achieve. Second, the reaction was a fundamental one with broad implications in biochemistry and intermediary metabolism. Third, an inherited recessive mental disorder, phenylketonuria, characterized by mental deficiency, was attributed to a failure in this reaction; therefore, the project had relevance to mental disease.

As soon as Seymour's lab became available for experimental work, he initiated work on this project and eventually developed a cell-free system that converted phenylalanine to tyrosine in vitro. The system consisted of partially purified enzymes from rat liver and sheep liver, but in addition to

oxygen, it required NADPH or a NADPH-generating system. The reaction occurred only when a boiled rat liver extract (i.e., Kochsaft) was added. This indicated that a nonprotein cofactor was also essential for the reaction. He then concentrated on a long and intensive effort to identify this essential cofactor. He tried to substitute for the Kochsaft one after another of many possible compounds that might have been the cofactor.

By chance, I happened to be present when he made a critical advance in this effort. I was in his lab sitting on a stool and discussing with him something that I no longer remember while he was standing at the bench stirring the contents of test tubes sitting in a water bath. Suddenly, he became silent and turned pale; thinking that he had become ill, I asked what was wrong. He replied, "I think I found the cofactor." Of all the test tubes that contained various potential candidates that could replace the Kochsaft, the only one in which phenylalanine was successfully hydroxylated to tyrosine was the one that contained tetrahydrofolic acid. That was a major discovery. Although it did not prove that tetrahydrofolic acid was the cofactor, it did tend to narrow the search to tetrahydropteridines. This discovery was made some time in 1957 or 1958, after which Seymour continued his effort to identify the cofactor.

In 1960-1961 Seymour spent a sabbatical year in the laboratory of Professor Ernst Hadorn in the Zoological Institute of the University of Zürich. Hadorn was a zoologist, and Seymour's choice to spend his sabbatical year in a zoological laboratory might seem strange. I cannot document this, but I have a vague memory that he once told me that Hadorn was working on the colors of butterfly wings, which involved pteridines, and it may be that his decision to join him was based on the wish to learn more about pteridines. In any case, after his return to NIMH, he eventually established

the identity of the cofactor as tetrahydrobiopterin. And in a series of classical experiments he purified and characterized the components and the partial reactions in the phenylalanine-hydroxylating system. One enzyme is phenylalanine hydroxylase that hydroxylates phenylalanine to tyrosine in the presence of tetrahydrobiopterin. In that reaction the tetrahydrobiopterin is oxidized to 7,8-dihydrobiopterin, and the second enzyme, dihydrobiopterin reductase, catalyzes the NADPH-dependent regeneration of dihydrobiopterin back to tetrahydrobiopterin so that the hydroxylation reaction can continue.

Seymour, subsequently, found that tetrahydrobiopterin is also an essential cofactor in other aromatic amino acid hydroxylations i.e., the hydroxylation of tyrosine to dopamine by tyrosine hydroxylase in the synthetic pathway of the catecholamine neurotransmitters, dopamine, norepinephrine and epinephrine, and in the hydroxylation of tryptophan to hydroxytryptophan in the synthetic pathway of another major central nervous neurotransmitter, serotonin. In contrast, Seymour and some of his research fellows found that the hydroxylation of the side chain of DOPA to form dopamine required ascorbic acid instead of tetrahydrobiopterin as the essential reducing cofactor.

The significance of Seymour's contributions to neuroscience and to the research program of the NIMH was recognized by his appointment in 1969 as chief of the Laboratory of Neurochemistry in its Intramural Research Program. This greatly expanded his research resources, not only with laboratory space but also with professional and technical personnel. This enabled him to extend his research from basic biochemistry to collaborative research with clinicians within and outside NIH, who provided him with liver biopsies from patients. This led to his definitive demonstration by direct enzyme assays in the biopsy samples that classical

phenylketonuria is indeed due to the genetic lack of activity of the phenylalanine hydroxylase enzyme. He also found that, though less frequent, other atypical types of phenylketonuria exist that are due to deficiencies in other enzymes in the overall phenylalanine hydroxylation process.

One atypical phenylketonuria was found to be due to the genetic absence of the dihydrobiopterin reductase that is required to synthesize the cofactor tetrahydrobiopterin. Other variants of phenylketonuria that were identified were those resulting from enzyme deficiencies in the pathway of biopterin synthesis. These were found to be treatable by biopterin administration. The clinical applications and usefulness of his fundamental biochemical research were a source of immense satisfaction to Seymour.

The biochemical journal club that had been organized by Giulio Cantoni in the 1950s lasted for approximately 30 years. At first, it included only the staff of his own Laboratory of Cellular Pharmacology, later renamed the Laboratory of General and Comparative Biochemistry, and of the sections on Cerebral Metabolism, Physical Chemistry, and Lipid Biochemistry of the Laboratory of Neurochemistry of the NIMH and NINDS Intramural Research Programs. It eventually expanded considerably to include a number of members of other NIH institutes. A few of the many who participated for various periods during its existence, in addition to Cantoni, Kaufman, and myself, were Alex Rich, Jack Dunitz, Sidney Bernhard, Bruce Ames, Bernard Agranoff, Werner Klee, Claude Klee, Harvey Mudd, John Giovanelli, Howard Nash, and David Neville. It met every Friday at lunchtime, and members rotated to present published papers of their choosing.

The presentations were informal and widely open to continual interruptions by others with questions, criticisms, or opinions. Though scheduled to last for only one hour,

the meetings often lasted much longer, depending on the interest and discussion elicited by the presentation. One example is the session in which Peter Mitchell's chemiosmotic hypothesis for the mechanism of oxidative phosphorylation was presented. Oxidative phosphorylation was then a subject of intense interest in biochemistry, and Mitchell's hypothesis was, to say the least, enormously controversial at the time. This session lasted for several hours with almost everyone participating in the discussion and expressing an opinion.

In these journal club sessions Seymour usually said little, but when he did, it was usually decisive and people listened. He was not inclined to verbalize speculations. He dealt only with facts. For him a speculation or hypothesis was only for experimental testing and not for debate. This was also his style in his research. He was never satisfied with evidence that only supported a conclusion. He sought absolute truths. As one of his first postdoctoral fellows, Ephraim Levin, once appropriately wrote about him, "The one word which best comprises Seymour Kaufman's approach to research is *careful*. He felt that to publish an erroneous datum or draw an unjustified conclusion would be a disaster, because it might deflect the progress of science. He once said that he spent 10% of his time being 90% sure, and the remainder being 99.9% sure."

In the 1980s there was a progressive change in the nature of the Intramural Research Program of the NIMH. The program was originally designed and organized in the early 1950s by its first scientific director, Seymour Kety, whose background was in physiology. He believed that progress in the understanding of the causes and treatment of mental diseases would require more basic research on the nervous system and, accordingly, distributed program resources (e.g., space, positions, and budget) mainly to basic science laboratories and sections. Laboratory space for experimental work

with animals was limited mainly to these basic laboratories and sections, and clinical branches had no laboratory space of their own.

Clinicians interested in doing research requiring laboratory space and facilities had to do so in collaboration with basic laboratories. This was entirely acceptable to the clinical branches because psychiatry at that time was largely dominated by psychoanalysis and had little interest in laboratory research on biological processes. This arrangement was more or less maintained until the 1980s by successive scientific directors who also came from basic science research backgrounds.

The spectacular advances being made in neuropsychopharmacology, molecular biology, and molecular genetics eventually resulted in the reorientation of psychiatry toward biological psychiatry, and research-minded psychiatrists became more interested in laboratory research. These influences affected the organization of the NIMH's Intramural Research Program, and in the middle 1980s a clinical psychiatrist was for the first time selected to be its scientific director. From then on, there was a progressive redistribution of the resources from the basic laboratories to the clinical branches that acquired experimental research laboratory space and staff of their own, largely at the expense of the basic laboratories. Most of the basic laboratories lost space, positions, budget, etc. Cantoni's and Kaufman's laboratories were among the first to suffer the greatest attrition until, eventually, both decided to retire.

Seymour retired in 1999 and was granted emeritus status by NIH, a status that provided him with office space, access to the NIH computer network, library privileges, and the right to search for a parking place on the NIH campus. He used these privileges for several years until about 2005, when he became ill, progressively more disabled, and eventually bedridden at home until he passed away in 2009.

Seymour's outstanding research contributions and his status in the world of biochemistry were widely recognized and honored. In addition to his many invited lectureships, he was selected to serve two terms on the Editorial Board of the American Journal of Biochemistry, a number of years on the Editorial Board of the Archives of Biochemistry and Biophysics, and was elected to the National Academy of Sciences (in 1986) and the American Academy of Arts and Sciences. He received the Meritorious Presidential Rank Award of the U.S. Government and the Hillebrand Prize of the American Chemical Society.

Seymour also had strong interests other than science to which, typical of him, he was passionately devoted. Although he had artistic talents, he decided early in his life that he lacked the talent to be a successful artist but never lost his interest in art. He occasionally practiced it, particularly in the preparation of woodblock prints. He also acquired an impressive art collection. His house was filled with works of art that included a number of original lithographs by one of his favorite artists, Toulouse-Lautrec. He also owned a number of sculptures by his daughter Emily, a prominent sculptor, one of whose works is on display at the Hirshhorn Museum in Washington, D.C.

Tennis was another of his passions. He lacked natural athletic talents and never received any formal coaching, but he developed a quite creditable tennis game, mainly because of his intensity and strong competitive nature. He hated to lose.

As a child, Seymour had suffered from mastoiditis and had been treated with bilateral mastoidectomies which left him with hearing deficiencies that troubled him throughout his life. He had a strong appreciation of classical music and for many years attended most of the performances of the Washington (D.C.) Opera.

He also developed an intense appreciation of good food, not of its preparation but of its consumption. I believe that I was present at its conception. In the summer of 1958 Seymour Kaufman and I attended in succession 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 in Rome, Italy. Seymour Kety, then our scientific director at NIMH, also attended these meetings. During the meeting in Strasbourg, Kety asked Kaufman and me whether, if he bought a car, we would be willing to ride with him to the subsequent 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.

Kety had never previously eaten at any of the three-star restaurants in the *Guide Michelin*, the almost biblical guide to the best restaurants in France—only 12 at the time. He, therefore, planned a route that led us to four of the twelve. Because of time constraints, we ate in four consecutive days: dinner at Baumanière in Les Baux, Provence; dinner at La Pyramide in Vienne, Burgundy; lunch at the Hostellerie de la Poste in Avallon, Burgundy; and dinner at La Tour d'Argent in Paris. Kaufman and I were thoroughly saturated with food. Those restaurants probably represented the epitome of the traditional French haute cuisine, and though we had eaten more than enough of it in too short a time, it inoculated both Seymour and me with an appreciation of fine food and wine that we shared thereafter.

Seymour passed away on June 23, 2009. He had been ill for several years during which he never lost his zest for life. He is survived by his wife Elaine; son Allan; daughters Emily and Leslie; three grandchildren Lisa, Joshua, and Amanda Kaufman; and two sisters Lilly Wolfe and Dottie Laiserin.

He will be greatly missed not only by them but also by his many friends, colleagues, and members of the scientific community.

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