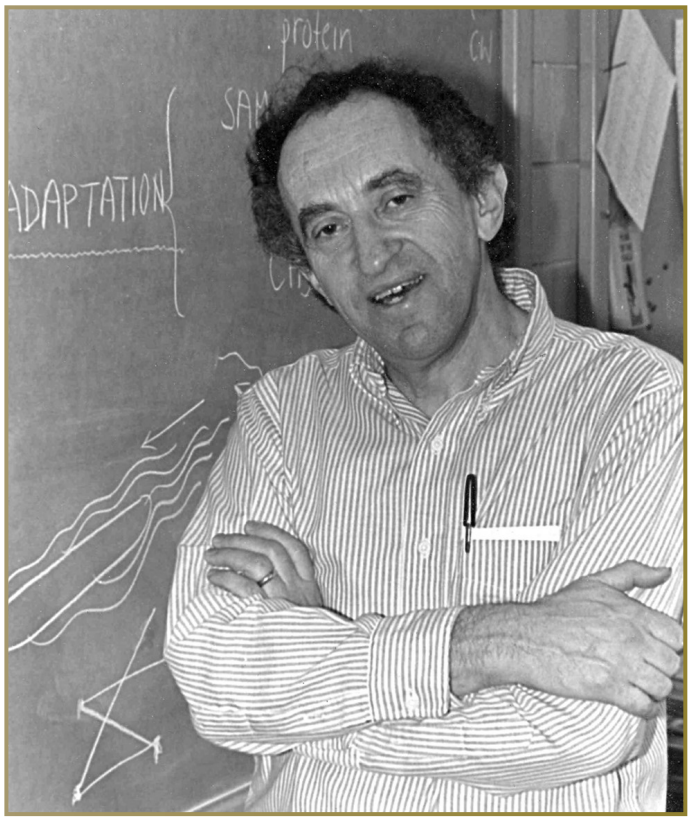
BIOGRAPHICAL MEMOIRS

Julius Adler

April 30, 1930–April 2, 2024
Elected to the NAS, 1978

A Biographical Memoir by Gerald L. Hazelbauer



Julius Adler pioneered molecular and mechanistic investigations of bacterial behavior and sensory signaling with his foundational studies of bacterial chemotaxis. He combined a boyhood fascination with butterflies and their sensory preferences with academic training in biochemistry and genetics to pursue an unconventional and innovative research direction: sensory transduction in bacteria. His publications and oral presentations were notable for their clarity. He aimed to understand behavior by studying *Escherichia coli*, a simple organism that at the time few would have considered a model for sensory phenomena. The identification of the biochemical and molecular basis of bacterial chemotaxis in his laboratory changed that perception and in doing so gave birth to the vibrant scientific field of bacterial signaling.

Articles by[1–3] and about[4–9] Julius have described his life and work. In writing this memoir, I have drawn on these sources as well as on my own experiences with him. I was a graduate student, and briefly a postdoctoral researcher, with Julius from January 1968 through August 1971. After a postdoctoral stint elsewhere, I returned to the field of bacterial chemotaxis and have been active in this area of research ever since, providing the opportunity to have regular interaction with Julius as a scientific colleague, mentor, and friend until his passing.

Early Life and Education

Julius Adler was born on April 30, 1930, to Irma (Stern) Adler and Adolph Adler in Edelfingen, a village in southern Germany where his ancestors had dwelled for 300 years. Adolph owned a butcher shop that had been in the family for generations. In a remembrance, Julius recalls that his earliest memory, at age five, was of a European swallowtail butterfly in the woods surrounding Edelfingen. The memory marks a lifelong interest in butterflies and, more broadly, nature. In 1938, like many Jewish families in Germany, the Adlers fled to the United States to escape the Nazi terror. They moved to Grand Forks, North Dakota, where some of his mother's relatives had lived since 1880, having been some of the town's earliest European settlers. There, the Adlers opened a neighborhood grocery store that they operated for thirty years. Julius entered school in Grand Forks knowing no English. Evidently, that soon changed. In high school, he was a

Figure 1 Julius (left) with his high-school debate team.

debater on the state finals team, served as editor of the school newspaper, and graduated as valedictorian. (Figure 1)

Julius then entered Harvard College for his undergraduate studies and received a bachelor of arts in biochemical sciences in 1952. While there, he did research in the Department of Biological Chemistry at Harvard Medical School in Boston under the supervision of tutor G. David Novelli, a gifted biochemist in the laboratory of Fritz A. Lipmann who would receive the Nobel Prize in Physiology or Medicine in 1953. Friends Julius made as an undergraduate included future National Medal of Science honoree Thomas Eisner and future Nobel laureate Eric R. Kandel. In fall 1952, Julius began graduate school at the University of Wisconsin, Madison, where he joined the research group of Henry A. Lardy. Pursuit of his initial research project became moot when its subject drew the interest of the large group directed by Severo Ochoa, later also a Nobel laureate. Julius's response to this setback was to work on, as he expressed it, "the most obscure problem I could possibly find." Thus, he focused on elucidating the mechanism by which rat liver mitochondria catabolize the metabolite itaconic acid, which is generated by the decarboxylation of the TCA cycle intermediate *cis*-aconitate. He defended his Ph.D. thesis on this subject in 1957. Interestingly, in recent years, itaconate has been identified as a key metabolite involved in immunity, host defense, and tumorigenesis.[10]

Before beginning postdoctoral research, Julius took the legendary course in microbiology taught by Cornelius van Niel at the Hopkins Marine Station in Pacific Grove, California. There, he befriended fellow student Tetsuo Iino, who would return to Japan to help found the Japanese school devoted to study of bacterial flagella and motility. That summer Julius decided to study the behavior of bacteria. He was inspired by publications from the 1880s he discovered in the Hopkins Marine Station library, particularly those by Theodor Engelmann, a well-known German physiologist and botanist, and Wilhelm Pfeffer, another prominent German botanist and microbiologist who, among many other contributions, described what became known as bacterial chemotaxis.

Julius obtained his initial postdoctoral training (1957–59) at Washington University, St. Louis, in the laboratory of soon-to-be Nobel laureate Arthur Kornberg. There, he was involved in the laboratory's ongoing studies of DNA synthesis. He spent the next year (1959-60) in postdoctoral training under A. Dale Kaiser, who had moved from Washington University to Stanford University Medical School when Kornberg and his associates were recruited to establish a new Department of Biochemistry there. With Kaiser, who became a lifelong friend and colleague, Julius learned bacterial genetics while characterizing the *E. coli* galactose operon. That experience and some of the mutant strains he collected served him well in his seminal work using mutants in galactose metabolism and transport to demonstrate that bacterial chemotaxis was mediated by a dedicated sensory system. In the summer before joining Kaiser's lab, Julius took the renowned hands-on short courses in bacterial and phage genetics at Cold Spring Harbor Laboratory on New York's Long Island. That intense immersion greatly influenced his life and generated many lasting friendships with scientists later to become prominent, including Masayasu Nomura and his wife Junko, and future Nobel laureate Marshall Nirenberg.

Career and Groundbreaking Research

In fall 1960 Julius began his appointment as an assistant professor jointly in the Departments of Biochemistry and Genetics at the University of Wisconsin, Madison. It seems likely that each department assumed he would pursue research related to his postdoctoral research. His first five publications as an independent investigator were consistent with that assumption. Notably, one of those publications was with another faculty member who arrived in Madison in 1960, H. Gobind Khorana, shortly to be a Nobel laureate.[11] Another 1960 arrival, Howard Temin, would also receive a Nobel Prize in Physiology or Medicine in 1975. Both Khorana and Temin became Adler's lifelong friends. In his personal life, in 1963 Julius married Hilde Wohl, who had also escaped from Nazi Germany in her youth. They had two children, David and Jeane.

Soon after arriving in Madison, Julius began investigations of bacterial chemotaxis. He presented his preliminary work at the 1965 Cold Spring Harbor Symposium on Sensory Receptors.[12] The following year he published a single-author paper in *Science* describing bacterial chemotaxis using *E. coli* as the model organism.[13] That publication included a striking illustration of chemotaxis: cells inoculated in the center of a soft-agar plate containing metabolizable attractants would consume the compounds locally, forming gradients that chemotactic cells would follow, creating a ring of cells that moved through the plate consuming the compound as they went, forming a perfect, expanding circle. The paper noted

Figures 2a & 2b Julius and son David in the mid-1960s with Gobind Khorana (left), and with Howard Temin and child (right).

that the laboratory had used this phenomenon to enrich for mutants that, although motile, were non-chemotactic—that is non-responsive to the attractants—by harvesting cells that remained at the point of inoculation. Furthermore, the *Science* paper suggested that there could be specific chemoreceptors for each kind of stimulating chemical and a "coordinating system" to translate recognition by such chemoreceptors to control the functioning of the bacterial flagella. These hypotheses were the outline for research in the Adler laboratory for many years thereafter. In addition, the paper drew a parallel between sensory phenomena and the features of metabolism and genetics shared by all organisms to suggest "Is it not possible that all organisms also share common mechanisms for responding to stimuli by movement?" This notion informed much of Julius's research. The paper also posed the question: "Can bacteria learn?", a question that fascinated him throughout his career.

In 1967, Julius and John Armstrong, his first graduate student to work on chemotaxis, described isolation and characterization of generally non-chemotactic mutants, the first behavioral mutants in *E coli.*[14] Next came a seminal work in 1969 as another single-author *Science* paper.[15] It summarized an impressive body of data in five categories that convincingly demonstrated that *E. coli*, and presumably all other chemotactic bacteria, had dedicated chemoreceptors that recognized attractants independent of the transport or metabolism of the attractant molecules. The paper argued that if bacteria had chemoreceptors, then they should also contain a specific machinery that received information from the chemoreceptors and in turn regulated flagellar action. All this machinery was presumably composed of proteins and thus would be encoded by genes. This proposal meant that the behavior of bacterial chemotaxis could be dissected using the tools of *E. coli* genetics and biochemistry.

The first example of such dissection was published in the *Proceedings of the National Academy of Sciences* (PNAS) almost concurrently with the 1969 *Science* paper.[16] In this article, I, fellow graduate student Bob Mesibov, and Julius described *E. coli* mutants defective in chemotaxis toward specific chemicals, that is, mutants in the postulated chemoreceptors. Chemoreceptor mutants defective specifically in galactose chemotaxis became the tools for identification of the galactose receptor as the periplasmic galactose-binding protein (MglB), work published by me and Julius in 1971 in *Nature New Biology* (see my 2012 paper[17] for the unexpected ways the mutant isolation and receptor identification occurred). The promise of using the power of *E. coli* genetics and biochemistry to dissect behavior was being fulfilled. But there was much left to do, and Julius had the vision to see what was needed. He distributed major projects—from chemoreceptors through flagellar structure and motility—among the half-dozen or so lab members. This plan was an audacious one for a small research group, but Julius outlined it to us in his typical energetic manner, making lists and drawing diagrams on the constantly used blackboard in his office. As students, we assumed it would all work out as outlined. In large part, it did.

To understand chemotactic behavior, Julius realized that he needed to understand bacterial flagella, both structure and function. At the time, little was known about either. The subject was assigned to graduate student Melvin DePhamphlis, who after many agonizing years succeeded in isolating and imaging what we now know to be a major portion of the flagellar rotary motor. His work was described in 1971 in four papers in the *Journal of Bacteriology*, three coauthored with Julius, that provided the best images of the motor for the next eighteen years.[18-21] As to flagellar function, in 1974 Julius and graduate student Steve Larsen collaborated with

Figure 3 Julius (right) with Ching Kung (left) planning experiments at Lake Mendota in the winter.

Bob Hogg, at Case Western Reserve University, and his student J. Jay Gargus to identify the energy source for bacterial flagellar motion as the protonmotive force, the electrochemical gradient across the bacterial cytoplasmic membrane, and not, as was then commonly assumed, ATP.[22] In the same year, three back-to-back papers in *Nature* demonstrated that bacterial flagella rotated (and did so in both directions), rather than waved or contracted.[23-26] One of those papers, by Julius and graduate students Steve Larsen, Ed Kort, and Wung-Wai Tso, and postdoc Bob Reader, took advantage of the laboratory's collection of generally non-chemotactic mutants to demonstrate that chemotaxis required not only flagellar rotation, but also rotation in both directions, as well as switching between them.[27] They found that counter-clockwise rotation correlated with smooth swimming and clockwise rotation with tumbling. The implication was that the pattern of smooth swimming and tumbling in the biased random walk of *E. coli* reflected alternation between counterclockwise and clockwise flagellar rotation. These insights were a major advance in the understanding of chemotaxis.

The following year, the Adler laboratory made another major advance. It had long been known that methionine was required for chemotaxis, but the reason was a mystery. In a 1975 PNAS paper, the laboratory (Julius and graduate students Ed Kort, Michael Goy, and Steve Larsen) described methylation of membrane proteins involved in chemotaxis and named them methyl-accepting chemotaxis proteins (MCPs).[28] A dozen papers followed from the Adler laboratory that defined many aspects of the methylation and demethylation reactions.[29-40] These included identification of the methylated proteins as the products of the genes for two classes of chemoreceptor mutants,[41] and convincing demonstrations that methylation was the central mechanism of sensory adaptation in bacterial chemotaxis.[42-45]

A remaining issue was how chemoreceptors communicate with the flagellar rotary motor. Julius's lab pursued multiple possibilities, including cGMP,[46] calcium,[47] and ion fluxes,[48] all signaling modalities in eukaryotes. Yet, it was none of these, but rather protein phosphorylation, as discovered in Melvin I. Simon's laboratory.[49] But Julius was particularly fascinated by the possibility that ion fluxes across the membrane were somehow involved in chemotaxis. To pursue that possibility, he had many discussions with Ching Kung, who had arrived in Madison in the mid-1970s and was an expert on electrophysiology of ciliated microbe *Paramecium*. These discussions evolved into collaborative experimentation. The result was the first electrophysiological studies of *E. coli* membranes and the discovery of mechanosensitive ion channels in a bacterium.[50] This collaborative work found no link between ion flux and chemotactic signaling, but it did open up an entirely new research area.[51-54]

Mentor, Scholar, Colleague, and Friend

Julius thought widely and deeply about many subjects. He had seemingly unlimited enthusiasm for the wonders of nature and science. He had comparable enthusiasm in his interactions with his many friends and colleagues. He was always interested in *what* you were doing and *how* you were doing. Julius was a creative and groundbreaking scientist who was the antithesis of a verbally facile, fast-thinking researcher. In conversation, whether with a friend, a scientific peer, or a beginning student, he focused intensely and often appeared lost in thought. After what could be an uncomfortably long silence, his response was often a question or observation that revealed an unconventional perception of the subject at hand. Perhaps because of that pattern of considered thought, his seminars and lectures were impressive in their clarity. His scientific publications had the same features. Those regularly went through multiple revisions after Julius collected comments and criticisms from scientific friends and colleagues. He was famous in the laboratory for considering and then reconsidering every detail of a draft manuscript. His desk and the floor around it were regularly scattered with reprints, but their order was in his mind.

Julius trained and mentored many students and postdoctoral fellows. Besides guiding them to do meticulous science, he provided a striking example of ethical behavior, honesty, and kindness. He was generous in giving credit and professional exposure to his students and postdoctoral fellows. For instance, while I was still a student and attending my first Gordon Research Conference, Julius insisted that I present part of his invited talk. His love of nature prompted him to take his students on canoe trips and hikes. Daily, he walked along the shore of Lake Mendota from his home to his laboratory and back, noticing and studying all aspects

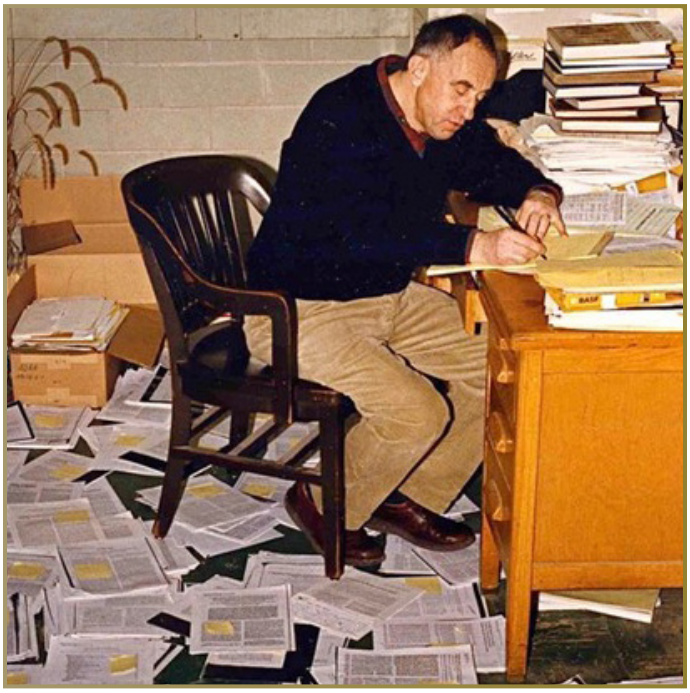


Figure 4 Julius working in his office at the University of Wisconsin-Madison.

of nature along the way. When one visited after moving on from his laboratory, Julius would often propose a walk to a nearby grove or along picnic point. He did the same with faculty colleagues. On his own, he explored the wilds of Wisconsin. Farther afield, he went on safari in Africa and made several trips to the Amazon, often with the aim of sighting butterflies.

As a faculty member, Julius was interactive with his colleagues and supportive of them. He and his wife Hilde hosted at their home evening gatherings of faculty colleagues for discussions and presentations of research. The two of them were sensitive to the challenges facing new faculty members who arrived in Madison knowing few in the university or community. They regularly took such individuals under their wing, particularly those who were otherwise alone. In the wider community, for fifty-five years Julius presided over large Chanukah parties and Passover Seders at the Adler home.[55]

In 1996, Julius retired from his faculty position, but not from research. His laboratory first continued investigations of bacterial behavior and then transitioned to searches for behavioral mutants in the fruit fly *Drosophila melanogaster.* With an approach reminiscent of his laboratory's early enrichment strategy for *E. coli* chemotaxis mutants, Julius and a stream of enthusiastic undergraduates searched for *Drosophila* mutants defective in responses to stimuli[56] and, ultimately, in learning as tested using a simple experimental set-up reminiscent of his early demonstration of bacterial chemotaxis.[57] For more than twenty years, many undergraduate students were trained in the logic of experimental design and interpretation that was a hallmark of Julius's approach to science.

Awards and Honors

For his research contributions, Julius received many awards and honors. These accolades include election to the National Academy of Sciences (1978), American Academy of Arts and Sciences (1976), Gesellschaft für Biologische Chemie (1986), and American Philosophical Society (1989). He was a fellow of the American Association for the Advancement of Science, American Academy of Microbiology, Nordrhein-Westfalische Akademie der Wissenshaften, and Wisconsin Academy of Sciences, Arts, and Letters. He received the Pasteur Award from the Illinois Society for Microbiology, the Selman A. Waksman Award in Microbiology from the National Academy of Sciences, the Otto Warburg Medal of the German Society for Biological Chemistry, the Abbott-American Society for Microbiology Lifetime Achievement Award, and the William C. Rose Award from the American Society for Biochemistry and Molecular Biology. He was also honored with honorary doctoral degrees and lectureships from institutions around the world.

Julius died of congestive heart failure a month before his ninety-fourth birthday. He is survived by Hilde, his wife of sixty years, son David Adler (Mary Elizabeth), daughter Jeane McMahon (Dan), two grandchildren, and many other family members. Julius Adler had the courage to pioneer a new area of research and the determination and creativity to be successful in that endeavor. As Hilde wrote, "Julius heard his own drummer and lived exactly to his own beat. Nothing got in his way. He was unfailingly kind, generous and loving (and knew how to be completely charming when called for!!!!)." He was an original.

Acknowledgments

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