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A Biographical Memoir by

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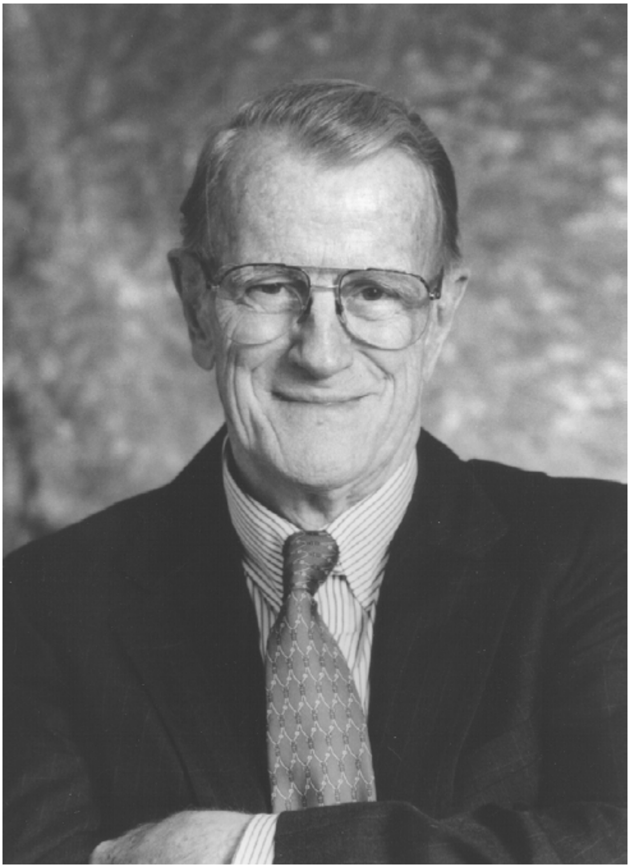
Biographical Memoir



JAMES MATHER SPRAGUE

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BY ALAN C. ROSENQUIST AND S. MURRAY SHERMAN

JAMES MATHER ("JIM") SPRAGUE, THE Joseph Leidy Emeritus Professor of Cell and Developmental Biology at the University of Pennsylvania died from leukemia on December 22, 2002, at the age of 86. Jim is survived by his wife of 43 years, Dolores, and a son, also Jim, who is a pediatric ophthalmologist. Jim Sprague was one of the pioneers in the study of the anatomy, physiology, and functions of the brain, and he was a member of the Founding Council of the Society for Neuroscience in 1970. He was elected to membership in the National Academy of Sciences in 1984.

Jim began his scientific career very early in life, largely because of his privileged upbringing. He was born into an old and wealthy New England family translocated to Kansas. His family owned a summer cottage on Mackinac Island, and this afforded Jim a wonderful base for exploring nature. He fell in love with the prospect of becoming a naturalist, and this interest helped him to develop the sort of wide-ranging, questioning mind that matured into the successful neuroscientist that Jim became. The Great Depression hit Jim's family hard, ending the bucolic, idyllic summer stays on Mackinac Island, but Jim continued his study of nature through the Boy Scouts and other public opportunities. He "tramped" the Missouri River bottoms,

the Missouri Ozarks, and the Colorado Rockies seeking the habitats of birds and mammals. This experience undoubtedly sharpened his observation skills, which served him well throughout his career.

Because of his family's struggles during the Great Depression, Jim had to get a job when jobs were extremely difficult to find. He found work as an elevator operator and janitor in an office building, earning about 30¢ per hour. But he already had ambitions to become an academic zoologist, which required an extended education. Jim finished high school with a record that he described as mediocre. Entering Kansas City Junior College in 1934, he then had to solve the problem of how to manage his education and his job simultaneously. His employer was sympathetic, allowing him to change his hours to half-time, and he secured a loan from an uncle to make up for the lost wages. His schedule was daunting. He attended classes in the mornings, worked in the afternoons, and studied in the evenings. Jim described those days as very fortunate for his continued education, because his teachers at Kansas City Junior College, while perhaps not qualified for university positions, turned out to be wonderful educators, and provided a necessary bridge in his education toward an academic career.

At this time a new building was being constructed in the center of town and during the excavation, fossils were found in large numbers. Jim petitioned the contractor and received permission to go into the pit and carry out a backpack of fossils. He identified these fossils of pelecypods, brachypods, crinoids, and ferns using library books, and he placed them carefully on shelves in his room next to his collection of American Indian artifacts, bird nests, animal skulls, and minerals.

Upon completion of his two years in junior college, good luck struck Jim in the form of two wealthy, powerful, and generous family friends who secured a job for him at the Natural History Museum in Kansas City and provided tuition for him to attend the University of Kansas. Again he faced a grueling schedule, having to find time both to be a productive university student and to do his work at the museum. His job entailed field work to obtain new fossils for the museum collection and teaching various courses in comparative anatomy, evolution, and ecology. Some of Jim's colleagues at the museum, like Jim, went on to distinguished careers in comparative zoology and paleontology.

After four years Jim had earned baccalaureate and master's degrees in zoology, the latter under the supervision of Edward Taylor. Jim's thesis was a study of the rodent hyoid bone that attaches to the base of the skull and supports the tongue and pharynx. His description of his methodology for this work is quite revealing: Starting with rodents trapped during his various field trips, he skinned them, treated them chemically, and placed the carcasses in boxes with dermestid beetles, insects that devoured the soft parts of the carcasses, leaving complete, articulated skeletons, including the delicate hyoid bone complex. This work acquainted Jim with the writings of some of the great European comparative anatomists and led to his desire to pursue the doctorate.

Jim then turned his attention to further his education with a Ph.D., and one of his chief targets was Harvard University, largely because of the presence there of the noted vertebrate paleontologist Alfred Romer. Again, his family stepped in and supported a visit to Harvard, which marked the beginning of Jim's transformation from a Midwesterner to an Easterner. Jim interviewed with Professor Romer at Harvard in 1940, and this interview reflected the remark-

ably good fortune that characterized Jim's career and allowed him to overcome so many obstacles. Professor Romer greeted Jim "by chanting with full body participation" the football cry of the University of Kansas. It seems that Jim and his future mentor were both proud Kansas alumni, and this happy coincidence cemented a relationship that had much to do with Professor Romer's offer of a position at Harvard and an opportunity for Jim's Ph.D.

Jim initially intended to train himself as a future museum curator, and Professor Romer was an early model for him. As it happened, Harvard's Museum of Comparative Zoology had an extensive collection of "pickled" bats, to which Jim was quickly introduced. Not surprisingly, he chose for his Ph.D. dissertation to study their hyoid structure, culminating in a scholarly thesis in which this was carefully and thoroughly described for 39 species of 32 genera of bats. Jim received his Ph.D. in 1942: his thesis was published in the *American Journal of Anatomy* in 1943.

His plans were to continue on the track as a museum curator, and Professor Romer arranged for Jim to get a position at the Field Museum in Chicago. At this point the actual career trajectory that led Jim to become such an important figure in experimental neuroscience seemed far fetched, but fate intervened. World War II imposed itself on Jim's career plans. His sought-after post in Chicago was never realized, and Jim was instead drawn toward the general field of medicine because of the perceived national need for more physicians during wartime.

Jim decided to be trained to teach medical students and after graduation took a course at Harvard involving dissection of the human body. This gave him the bare rudiments required to teach human anatomy to first-year medical students; with this rather limited training he was able to secure a medical teaching post at Johns Hopkins University.

As it happened, Jim's home at Johns Hopkins was the Department of Anatomy, a place where the study of neuroanatomy was heavily emphasized. This afforded Jim his first real exposure to neuroscience; as they say, the rest is history.

Jim's colleagues at Johns Hopkins included some of the great neuroscientists of the day: Bill Strauss, Marion Hines, Louis Flexner, Vernon Mountcastle, Jerzy Rose, Reginald Bromiley, and Clinton Woolsey. Soon after arriving at Johns Hopkins, Jim developed his deep fascination with the brain that was to endure for the remainder of his days. Experimental approaches were new to Jim, however, and he suffered several unproductive forays into experimental problems of the brain. Then he found a practical problem worthy of his talents: He successfully mapped the locations in the primate spinal gray matter of the motor neurons that innervated the myotonic or lateral plate muscles. This arduous task was completed by cutting the dorsal or ventral rami and noting the locations of chromatolytic neurons. These were the days before the advent of the sensitive retrograde tracers that are in use today.

Jim then developed a series of collaborative arrangements that furthered his breadth and competence in neuroscience. Many of these were with distinguished neuroscientists at other institutions, which showed Jim's ability to network; for instance, Jim worked with Professor Donald Barron of Yale on a project to describe the development of the sheep spinal cord. He then arranged a collaboration with Professor Horace Magoun of Northwestern University, which led to spending much of the spring of 1948 in Chicago working with Magoun on the neurophysiology of the reticulospinal control of stretch reflexes.

Later in 1948, with a Guggenheim Fellowship in hand, Jim boarded the *Mauritania* for a journey that led him to the United Kingdom and to both Oxford and Cambridge Universities. At Oxford under the direction of Sir W. E. Le Gros Clark, he learned the Glees silver technique for staining degenerating axoplasm and applied it to the study of hippocampal connections in the rabbit. At Cambridge in the physiology laboratory of Bryan Matthews, he was surprised to learn that investigators were expected to do everything for themselves and that very few general facilities were available. Jim began, along with Michael Fourtes, by building an amplifier that he described as a "pile of junk" but one that worked! While in the U.K., Jim also had the pleasure of visiting with Lord Adrian and Sir Charles Sherrington.

Jim returned to Johns Hopkins University for only one year, a year that was in many ways frustrating for him. His home department had new leadership that Jim found less than supportive, and he discovered that the very promising Glees technique that worked so well in Oxford failed to work at all in Baltimore. Undaunted, Jim reverted to old standby techniques of retrograde chromatolysis and Marchi degeneration to tackle his next problem, the anatomical location of the cells of origin and axonal course of the ventral spinocerebellar tract.

In 1950 he eagerly accepted a position at the University of Pennsylvania. Here under the leadership of Dr. William Windle and in collaboration with Bill Chambers and John Liu, Jim continued his studies of the spinocerebellar tracts and the structure and function of the cerebellum. Using the newly devised silver degeneration techniques of Walle Nauta and his collaborators, Jim, Chambers, and Liu expanded on the earlier studies of Jan Jansen and Alf Brodal on the efferent projections of the cerebellar cortex and deep nuclei. This work showed that there were three differ-

ent systems of cerebellar output, organized in mediolateral "zones," and this naturally resulted in Jim pondering the question of function: What is the functional significance of these three systems? The pursuit of this question led to an approach that marked much of the remainder of Jim's career: testing structure and function by evaluating the behavioral deficits associated with specific brain lesions.

To address the functional questions concerning the cerebellum, Jim and Chambers placed cerebellar lesions or stimulating electrodes into each of the three mediolateral cerebellar zones of the cat, and showed that the vermis and fastigal nucleus are involved with gross postural tone, equilibrium, and locomotion of the entire body. They further showed that the intermediate zone is involved with skilled movements and tone of the ipsilateral limbs, and that the lateral zone (lateral cerebellar cortex and dentate nucleus) is involved in skilled movements of the ipsilateral limbs but without effects upon posture and tone. These were seminal studies of the functional organization of the cerebellum that have largely stood the test of time.

In collaboration with John Liu, Bill Chambers, Eliot Stellar, and postdoctoral fellows Tom Meikle, Mel Levitt, and Ken Robson in the 1950s, Jim undertook to amplify the work of Moruzzi and Magoun on the functions of the brainstem reticular activating system (RAS). Earlier work was limited to acute descriptions of lesion effects, and Jim and his collaborators extended these studies by studying the long-term effects of brainstem lesions, employing a large battery of behavioral tests. These studies contributed to a much better understanding of the roles of RAS and direct sensory pathways to attentive, adaptive, and affective behaviors than the short-term studies alone. In the course of these studies Jim noted that lesions placed below the superior colliculus that interrupted collicular afferents and

efferents had caused unexpected visual deficits that included visual neglect. He hypothesized that these attentional and other deficits involved the superior colliculus. It is for this work and much subsequent work on the roles of cortical and collicular pathways in visual functions that Jim is most remembered.

Nonetheless, before committing to studying visual pathways, Jim was involved in one last, important study of spinal circuitry. The background to this was a controversy as to whether the 1a dorsal root afferents made monosynaptic, inhibitory connections onto ipsilateral antagonist muscle motoneurons or whether they affected their inhibition on these motoneurons via local, inhibitory interneurons. The importance of this question is linked to a key hypothesis that still endures: a single neuron must produce the same transmitter(s) at all of its presynaptic terminals. That is, there was already strong evidence that 1a afferents monosynaptically excited ipsilateral motoneurons, and for the same axons to inhibit contralateral motoneurons would seem a violation of this hypothesis. (We now know that a single axon can inhibit some target neurons and excite others, but this is via different postsynaptic receptors activated by the same neurotransmitter.)

Jim's first attempt to determine the projections of these 1a afferents was the result of yet another collaboration that took Jim to the Rockefeller Institute for Medical Research (now Rockefeller University) in New York City to work with David Lloyd. This occurred during a sabbatical in 1955. This project was purely anatomical and produced ambiguous results regarding the main question. Undaunted, Jim then teamed up with Karl Frank a few years later to reinvestigate the problem using physiological techniques of intracellular recording of motoneurons and latency analysis of EPSPs elicited by 1a afferent stimulation. They found that

the contralateral pathway had a longer latency consistent with an extra synaptic delay; they thus concluded that the 1a inhibition of contralateral motoneurons was disynaptic and involved an inhibitory interneuron.

At the beginning of the 1960s Jim, in reanalyzing his lesion studies of the brainstem, began to recognize a relationship between lesions involving the superior colliculus and vision disorders. He decided to follow this up. It is relevant to note that at the time, when vision research was coming under the domination of David Hubel and Torsten Wiesel at Harvard University, the field had a decided cortical bias; this led to the prevailing view that any important visual capacity must be cortical in nature and not, for instance, involve subcortical structures, such as the superior colliculus, for any but the most mundane reflex-like functions.

Jim began by making various lesions of the superior colliculus, with the general thread that these interfered with detecting and orienting to objects, and again this view challenged the cortical chauvinism of the day (that persists still!). Then, in 1966 Jim published a seminal paper in *Science* that described a remarkable visual recovery phenomenon in the cat that has since been called the "Sprague effect." Jim had shown that a large unilateral visual cortical lesion produces an enduring hemianopia (i.e., blindness in half the visual field) in the side opposite to the lesion. This by itself was an old story and part of the lore that elevated cortex to a prominent, unique role in vision. However, when the superior colliculus contralateral to the cortical lesion was ablated or when the commissure between the two colliculi was transected, there followed a dramatic recovery of the cat's visual orienting ability to visual stimuli presented in the previously blind hemifield. Later studies showed that this restored visual capability was subserved by the remain-

ing superior colliculus, ipsilateral to the original cortical lesion. This remarkable observation should serve as a red flag to the interpretation of all lesion studies, since in this case a second lesion partly ameliorated the effects of a first lesion, perhaps because any lesion, in addition to directly removing neuronal circuitry, may have widespread secondary effects on other, apparently intact neuronal structures. It is the depression of these secondary structures that leads to the lesion-evoked impairment. Thus the structure/function relationship from lesion studies can be misinterpreted.

Indeed, Jim's interpretation of the Sprague effect is as follows. There is a large ipsilateral projection from the visual cortex to the superior colliculus, and the result of the first cortical lesion removes this input, leaving a depressed colliculus; this depression is largely subserved by the remaining fibers coursing through the collicular commissure, and the second lesion of the other colliculus or transaction of the commissure removes this depressing input, releasing the untouched colliculus for action. It should be noted that the visual function subserved by the remaining colliculus is done so by a wounded colliculus, since many of its normal inputs are removed, suggesting that in the normal animal the colliculus may subserve even more visual functions that are much more than vestigial reflex functions.

Jim continued his involvement in the Sprague effect into the 1990s in collaboration with Alan Rosenquist and Steve Wallace at the University of Pennsylvania. Together they showed that the crossed inhibitory connections to the colliculus arose from the substantia nigra, pars reticulata. The mechanism underlying the Sprague effect has since been further elaborated by Rosenquist and his collaborators. Our current understanding is best summarized by Jim in his autobiography published by the Society for Neuroscience:

The mechanism appears to work as follows. Visual input from the retina reaches extrastriate cortex, which projects to the striatum and there activates a striatonigral path (using glutamate), which terminates in the substantia nigra, pars reticulata. This system (using GABA) exerts a controlling influence on nigral neurons which project to the superior colliculus by way of a nigrotectal tract. The nigrotectal path is a tonically active GABAergic tract that suppresses firing of the orienting neurons in the colliculus; these nigral neurons are phasically inhibited by GABAergic activity in the striatonigral path, thus releasing the colliculus to trigger contralateral orienting responses.

In 1966 Jim took a sabbatical to work at the Institute of Physiology in Pisa with Giovanni Berlucchi, a young protégé of the director, Giuseppe Moruzzi, who had worked as a young man with Magoun at Northwestern. At Pisa Sprague and Berlucchi began a warm and lasting friendship and a decades-long collaboration aimed at understanding the roles of cortical and midbrain visual areas in visual form and pattern discrimination and interhemispheric transfer. They used a split-brain approach, making a combination of cortical and midbrain lesions differing on each side, to maximize information from each cat. These experiments, which led to a string of research publications, established an unexpected role for the midbrain in pattern vision.

While in Italy, Jim also collaborated with Giacomo Rizzolatti and Lorenzo Marchiafava in conducting some of the earliest single-cell recordings of the feline superior colliculus.

Jim's longstanding interest in cat visual psychophysics stemmed from his collaborations with Mark Berkley at Florida State, which began in 1972. From 1984 to 1995 this interest took the form of a rich and fulfilling collaboration with Guy Orban, Erik Vandenbusshe, and others at the University of Leuven, Belgium. Jim loved to visit Leuven and did so twice annually for many years. He and Dolores especially liked living in the beautiful facility (the Begijnof) owned by the University of Leuven.

Jim will long be remembered for his important contributions to a wide range of biological and neuroscience areas. His work on the cerebellum, spinal cord, brainstem reticular formation, superior colliculus, and the multiple visual cortical areas and pathways will remain his legacy and seminal contribution to the field of neuroscience. Jim will also be remembered for his contributions to the University of Pennsylvania as one of the founders and as director of the Institute of Neurological Sciences (1973-1980). He also served as chair of the Department of Anatomy (now the Department of Cell and Molecular Biology) from 1968 to 1975.

Both authors of this memoir were students and later colleagues of Jim Sprague and both of us greatly lament his loss of a role model, mentor, and close personal friend. He will be missed but never forgotten by us, or by the hundreds of younger neuroscientists who will continue to amplify and extend the discoveries that are his legacy.

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