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HALDAN KEEFER HARTLINE

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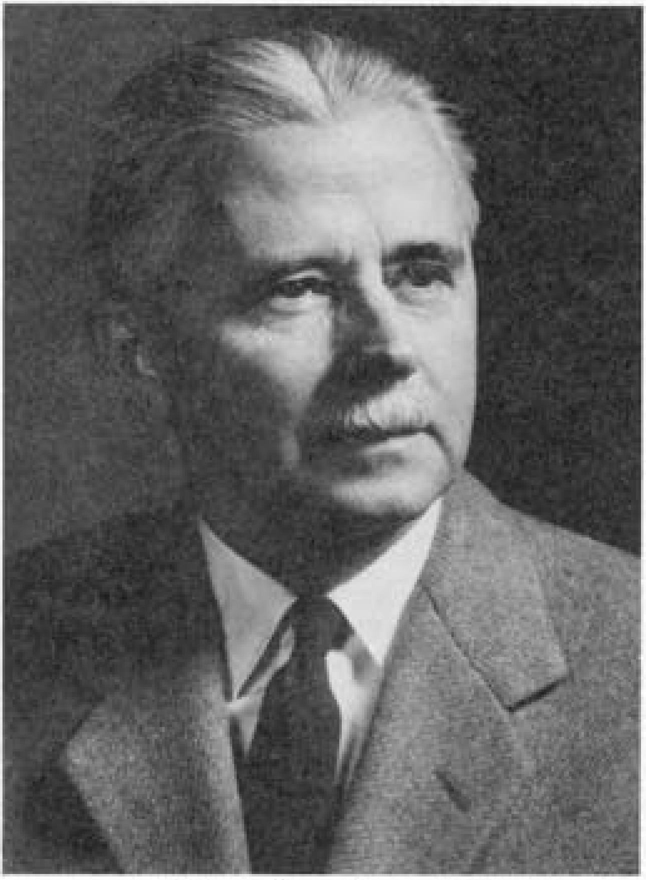
A Biographical Memoir by

FLOYD RATLIFF

Biographical Memoir



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H. K. Hartline

HALDAN KEFFER HARTLINE

December 22, 1903–March 18, 1983

BY FLOYD RATLIFF

FOR MORE THAN HALF A CENTURY Haldan Keffer Hartline, Keffer to friends and close colleagues, conducted biophysical research on vision and the retina. He studied retinas from arthropods, vertebrates, and molluscs—the three major phyla with well-developed eyes—and his investigations extended into many and diverse branches of the field. During this long career Hartline elucidated numerous fundamental principles of retinal physiology, laying the foundations for the present-day study of the neurophysiology of vision.

Hartline's four major accomplishments were all "firsts" in their respective fields: With Clarence H. Graham he recorded the activity of single optic nerve fibers. He mapped the activity of the visual receptive field to reveal a system of many convergent pathways from many photoreceptors (the foundation for modern concepts of parallel processing by specialized channels). He recorded—with Wagner and MacNichol—intracellular generator potentials. And finally, he discovered lateral inhibition in the retina and described the integrative activity of neural networks with the Hartline-Ratliff equations.

EDUCATION AND EARLY LIFE

Keffer Hartline was born on December 22, 1903, in Bloomsburg, Pennsylvania, to Daniel Schollenberger

Hartline and Harriet Franklin Keffer Hartline. His father taught science and his mother English at the Bloomsburg State Normal School (now Bloomsburg State College) where the young Hartline received his early formal education. Perhaps more significant to the young Keffer was the informal but intensive training he received at home as an only child. Both of his parents had a strong interest in the natural world around them, an interest that deeply affected the young Keffer. Indeed, he was later to refer to his father as "my first and best teacher," and the love of nature his parents instilled surely influenced his choice of experimental research in biology as his lifelong career.

Upon completion of his studies at Bloomsburg in 1920, Hartline spent the summer at the marine laboratory in Cold Spring Harbor, Long Island, taking a six-week course in comparative anatomy. That fall he entered Lafayette College to study biology and was encouraged by Professor B. W. Kunkel to do research. Hartline was much impressed by Jacques Loeb's quantitative work on tropisms, and his very first experiments—phototropic responses of land isopods—were along the same lines. At Woods Hole in the summer of 1923 he showed the results of his experiments to Loeb, who encouraged him to publish the work in the *Journal of General Physiology*. Loeb also introduced Hartline to the biophysicist Selig Hecht, who was just coming into prominence in the field of vision research. That fall, Hartline entered the Johns Hopkins University School of Medicine.

Finding time at Hopkins to continue his research, he came under the influence of E. K. Marshall, head of the Department of Physiology, and, even more strongly, of Charles D. Snyder. Snyder taught Hartline how to use and replace the inevitable broken strings on a string galvanometer, then gave him free access to that delicate instrument. Hartline bore out his confidence and soon thereafter published pioneering work on the retinal action potential he had recorded from a variety of species, including humans. His early research helped lay the groundwork for modern electroretinography. In 1927, Hartline received the M.D. degree from Hopkins but—clearly more interested in research—never went on to practice medicine.

Remaining at Hopkins for two years as a National Research Council Fellow, Hartline decided, after a brief exposure to quantitative experimental biology, to study mathematics and physics. Drawn to these disciplines, he went so far as to consider a career in either one or the other. On a Johnson Research Scholarship from the Eldridge Reeves Johnson Foundation, he went to Germany to study under Arnold Sommerfeld at Munich and under Werner Heisenberg at Leipzig. It soon became evident, however, that Hartline lacked the background for these advanced courses and lectures, and—disappointed with the outcome of this venture—he returned to the United States after one year to take up his first appointment in biology. Hartline's interest in mathematics and physics never waned, and his approach to experimental biology remained rigorously quantitative and based on sound physical principles.

PROFESSIONAL CAREER

Detlev W. Bronk, director of the Eldridge Reeves Johnson Foundation at the University of Pennsylvania from 1929, was quick to recognize genius and soon offered Hartline a position as a fellow in medical physics. This proved ideal for the frustrated theoretical physicist, and Hartline remained at the Johnson Foundation from 1931 until 1949 (except for a brief and unsuccessful move, with Bronk, to Cornell University Medical College from 1940 to 1941).

While at the Johnson Foundation, Hartline met a number of investigators who later became prominent in vision research. Among these were psychologists Clarence H. Graham and Lorrin A. Riggs, who became his research collaborators, and physiologist William A. H. Rushton, who turned to vision research in his later years. It was also at the Johnson Foundation that Hartline first met the neurophysiologist Ragnar Granit. While at Woods Hole he became acquainted with the biochemist George Wald. Hartline, Granit, and Wald each went his independent way in vision research, following the work of the other two closely and admiring it, but never working together in collaboration. They little dreamed that—a quarter of a century later—they would share the Nobel Prize.

In 1949, Bronk accepted the presidency of the Johns Hopkins University on the condition (among others) that a biophysics department be established on the Homewood campus. He appointed Hartline the first professor of biophysics and chairman of the new Thomas C. Jenkins Laboratory of Biophysics. There Hartline continued his earlier close association with Henry G. Wagner and E. F. (Ted) MacNichol, Jr., while electronics engineer John P. Hervey and instrument maker Walter Biderlich provided valuable support services. I first met Hartline in 1950 when I joined his laboratory on a one-year National Research Council fellowship. We felt an instant rapport and would work together in close collaboration for the next twenty-five years.

In September of 1953, Bronk became president of the Rockefeller Institute for Medical Research (later The Rockefeller University) and immediately appointed Hartline a member and head of the Institute's Laboratory of Biophysics. Within the year, Hartline invited me to leave Harvard for The Rockefeller, and I immediately accepted. Over the next few years we were joined by William H. Miller, Bruce W. Knight, Jr., Frederick A. Dodge, Jr., and electronics engineer Norman Milkman. When the Rockefeller Institute became

The Rockefeller University, Hartline was appointed professor and head of laboratory. He never left The University thereafter for any extended period, except for a sabbatical leave as George C. Eccles Professor at the University of Utah in 1972. That same year, he was named Detlev W. Bronk Professor at The Rockefeller, the post he held until his retirement until 1974.

MAJOR SCIENTIFIC CONTRIBUTIONS

Single Optic Nerve Fibers

In 1927, Edgar D. Adrian and Rachel Matthews successfully recorded electrical activity in an optic nerve, though—in this early work (on the eye of the eel)—they were only able to record the massive discharge of the whole nerve trunk. Adrian and Bronk later managed to dissect and isolate a single fiber of the phrenic nerve and record its activity.

Inspired by their success, Hartline and Graham undertook similar studies on the optic nerve of the horseshoe "crab," *Limulus*. The compound eye of this venerable animal, with its large photoreceptors and long optic nerve, was ideally suited for this study, and in 1932 they were able to record the activity of single optic nerve fibers for the first time. Their research showed that impulses transmitted by an optic nerve fiber are essentially identical and that information about the intensity of light incident on the photoreceptor is coded in terms of the rate of discharge of impulses rather than the shape or amplitude of individual impulses. Here began the direct, quantitative, experimental investigation of information-processing in the visual system.

The techniques used by Hartline and Graham also provided an indirect but proximate method for studying the physical and chemical events in the photoreceptor that give rise to nerve impulses. In 1935, for example, the two researchers used it to determine the spectral sensitivity of the *Limulus* photoreceptor. Later, with P. R. McDonald, they measured light and dark adaptation. Twenty-five years later Ruth Hubbard and George Wald confirmed the precision and reliability of Hartline's early spectral measurements by extracting the photopigment from the eye of *Limulus* to determine its spectral absorption by direct methods. The two curves agreed almost point for point.

The Receptive Field

In his early research at the Johnson Foundation and later at Johns Hopkins and Rockefeller, Hartline nearly always worked in collaboration with other investigators. In all of these collaborations, however, there was never a question in anyone's mind about who was the master and who the apprentice. Though unquestionably a brilliant collaborator, Hartline's extraordinary ability and unique talents produced the most startling results during the period of his thirties and forties when he worked alone. The single-handed investigations, mainly on the vertebrate retina, of those years are perhaps his most significant contribution to science.

With his exquisite microdissection technique, Hartline was able to isolate single optic nerve fibers of the vertebrate retina and, for the first time, record their activity. He found that the response of the whole nerve resulted from the summated activity of fibers whose individual responses differed markedly. Some fibers discharged steadily in response to steady illumination, some in response to the onset and cessation of illumination, others only to its cessation. Many fibers showed extreme sensitivity to moving patterns of light and shade. Mapping the "receptive fields" of some of them in detail showed that a retinal ganglion cell can receive excitatory and inhibitory influences over many convergent pathways from many photoreceptors. The optic nerve fiber arising from the retinal ganglion cell is simply the final common pathway.

Hartline found that the processing of visual information begins in the retina with the specialized activity of diverse types of ganglion cells, thereby laying the foundation for modern concepts of parallel processing by specialized channels. "The study of these retinal neurons has emphasized the necessity for considering patterns of activity in the nervous system," he remarked in his 1942 Harvey Lecture. "Individual nerve cells never act independently; it is the integrated action of all the units of the visual system that gives rise to vision" (1942,1).

The Generator Potential

As early as 1935 Hartline, using external electrodes, had recorded the local "action current" of a single photoreceptor unit in the compound eye of *Limulus*. Simultaneous records of the propagated impulses in the optic nerve suggested that this retinal action potential might be the generator of the impulses. When micropipette electrodes with tips small enough to penetrate cells were developed, opening the generator potential to direct study, Hartline's earlier interest in this hypothesis was rekindled.

Using the new micropipettes, Hartline, Wagner, and MacNichol recorded intracellular generator potentials for the first time and were able to study the photoreceptor as a biological transducer—relating nerve impulses to a generator potential, and generator potential to the light incident on the photoreceptor.

MacNichol, Wagner, and Hartline further observed that the rate of discharge of impulses was approximately linear with depolarization of the cell—whether induced by light or by current passed through the electrode—and that spontaneous activity was suppressed by hyperpolarizing current.

Hartline's colleague, Tsuneo Tomita, soon demonstrated that the depolarization resulted from an increase in membrane conductance short-circuiting the resting potential of the cell. The way was now open to a proper biophysical understanding of the generation of impulses by sensory receptor cells.

The Hartline-Ratliff Equations

One of Hartline's most important contributions to the physiology of vision was his discovery of lateral inhibition in the retina of the compound eye of *Limulus*. It is uncertain when the discovery of this "lateral effect" (as it was first called) was actually made, although—according to Hartline's best recollection—it was the late 1930s. The first published report (1949,1) on this pattern of central excitation and surround inhibition was long delayed, but even so it predated the discovery of the analogous center-surround organization of the vertebrate retina.

In our first studies carried out at Rockefeller, Hartline and I focused on a quantitative account of the inhibitory interactions in the eye of *Limulus*. We were able—with a pair of simultaneous equations—to express the reciprocal interactions between two photoreceptor units in the steady state. Although these equations were strongly nonlinear overall, they were, as Hartline put it, "mercifully, piece-wise linear, to a good approximation." These so-called "Hartline-Ratliff equations"—actually based upon, and testable by, direct electrophysiological measurements—provided the first mathematical description of the integrative activity of a *real* neural network.

Our subsequent discovery of the phenomenon of "inhibition of inhibition" enabled us to extend the mathematical description to any number of interacting units. This inhibition of inhibition—or *disinhibition* as we preferred (following

Pavlov) to call it—confirmed the notion we had already expressed in our pair of simultaneous equations describing the interaction of two elements: the interaction was both mutual *and* recurrent. With this knowledge, Hartline and I could now express the interactions among not just two units, but any number *n*—either with a set of *n* simultaneous equations, or, if the number was large enough, with integral equations. The phenomenon of disinhibition first thought to be unique to the *Limulus* retina has since turned out to be a general principle of neural organization, widespread in the other species and neural systems.

Our earliest studies of the dynamics of lateral inhibition—with William H. Miller and G. David Lange—were purely empirical, but quantitative, theoretical approaches to the dynamics of neural mechanisms were in the air. Attracted by the symmetry of responses of the *Limulus* eye to equal increments and decrements, Bruce W. Knight, Jr., a physicist and applied mathematician, joined the Laboratory in 1961. Knight realized that the *Limulus* eye appeared to be a "time-invariant linear system" that could be treated as a system of linear transducers, and that the several transductions could all be characterized by transfer functions.

The transduction from light to generator potential, generator potential to impulses, and impulses to self- and lateral-inhibitory potentials were directly measured and characterized as transfer functions, enabling the Laboratory to make successful theoretical predictions of responses to a wide variety of stimuli. These experiments—performed mainly in collaboration with Bruce Knight, Jun-ichi Toyoda, and Fred Dodge—showed the appropriateness of treating the *Limulus* eye as a system of linear transducers over a wide range of experimental conditions. But Hartline remained wary. "The trouble with theories," he once said, "is that after a while one begins to believe them."

A SENSE OF HUMOR

Hartline's wry humor often produced unexpected and telling remarks. Capping a discussion of a new laboratory building on campus much criticized by the scientists who had to use it, he said drily that "it must have been designed by an architect." He was also given to telling tall tales with a straight face, many of which were taken for truth. His often repeated assertion that he was "awarded the M.D. on the condition that he never practice medicine," for instance, was widely believed. But Hartline's humor was a two-way street, and he often quoted my own description of his untidy laboratory as "a slightly disorganized, but extremely fertile, chaos."

HONORS AND AWARDS

While still in medical school Hartline received the William H. Howell Award in Physiology. Experimental and physiological psychologists were among the first to recognize the importance of his later work to an understanding of human visual perception, and the Society of Experimental Psychologists awarded him the Howard Crosby Warren Medal in 1948. That same year saw his election to the National Academy of Sciences. He was elected to the American Philosophical Society in 1962, received Case Institute of Technology's Albert A. Michelson Award in 1964, became a foreign member of the Royal Society in 1966, and, in 1969, received the Lighthouse Award for Distinguished Service.

In 1967 the Nobel Prize in Physiology or Medicine was awarded jointly to Ragnar Granit (Karolinska Institute), Haldan Keffer Hartline (The Rockefeller University), and George Wald (Harvard University) "for their discoveries concerning the primary physiological and chemical visual processes in the eye."

Ironically, the Nobel Prize for Hartline's contributions to vision research coincided with a decline in his direct participation in such research. Slowly failing eyesight, a result of senile macular degeneration, made it increasingly difficult for Hartline to read and write, to use a microscope, and to perform the highly skilled manual techniques for which he was noted. "The loss of central vision is bad enough in itself," he once remarked, "but to be prematurely labeled senile only adds insult to injury."

HOME AND FAMILY

In 1936 Hartline married Elizabeth Kraus, daughter of the eminent chemist C. A. Kraus, and, at that time, instructor in comparative psychology at Bryn Mawr College. Mrs. Hartline shared her husband's interest in nature and later became a dedicated conservationist. Their three sons Daniel Keffer, Peter Haldan, and Frederick Flanders—tutored by their father as he had been by his—all became biologists.

When Hartline accepted a position at Johns Hopkins in 1949, the family purchased a house near Hydes, Maryland, about twenty miles from Baltimore. This country house, which they called Turtlewood, is still the family home. In 1953, Hartline became a member of the Rockefeller Institute and moved to an apartment in New York City. Leaving Mrs. Hartline and their three sons in Maryland, Hartline returned home for long weekends and holidays, viewing the New York apartment as little more than a "winter camp" in the city. The family's "summer camp" was the Kraus family place on Old Point, just across Frenchman Bay, northwest of Bar Harbor, Maine.

CONCLUDING REMARKS

Hartline enjoyed good health throughout most of his life and, despite his slight stature and rather frail appearance, was an active outdoorsman. When young he enjoyed mountain climbing and had some first ascents to his credit in the Wyoming Rockies. He piloted his own open-cockpit plane around the country. He enjoyed sailing—with Bronk near their summer home in Maine and, on occasion, with Ragnar Granit in the Baltic.

Continuing his outdoor activities even into old age, Hartline decided in his seventies to take a long-postponed rafting trip through the Grand Canyon. His cardiologist recommended against the trip, but Hartline decided that it was now or never, basing his decision (according to one of his apocryphal stories) on a favorable second opinion from a dermatologist. In any event, he and Mrs. Hartline took the trip and—except for being too cold and wet on the raft in the rapids and too hot and dry on the desert shore—both enjoyed it immensely.

In his late seventies Hartline's chest pains became more frequent and severe, and on March 18, 1983—as he was entering his eightieth year—he died of a heart attack at the Fallston General Hospital in Maryland.

Keffer Hartline achieved great distinction in every phase of his half-century of research on the physiology of vision and was awarded the highest of all honors in science. Yet he remained modest and unassuming throughout and was somewhat embarrassed by fame and public acclaim. He specifically requested that there be no official memorial service or organized tribute to him at The Rockefeller University, suggesting rather that one of the University concerts—which he had enjoyed so much over so many years—would be an appropriate memorial, bringing joy to others rather than sorrow. On March 7, 1984, the Stuttgart Chamber Orchestra, with Karl Münchinger conducting, played to a full house in a performance dedicated to Keffer Hartline's memory.

Keffer Hartline and I worked together day after day, year after year, for more than a quarter of a century. The strong bond of friendship between us transcended all time and place, and all human frailty. To such a friend, the truest tribute is one enshrined in memory and thought, unspoken.

INFORMATION ABOUT HARTLINE'S life and work during the period of 1903–1950 came from his own reminiscences dictated during the last years of his life and transcribed by his long-time secretary, Maria Lipski. The period of 1950–1983 is based primarily on my own records and firsthand knowledge. For other accounts, see: John E. Dowling and Floyd Ratliff, "Nobel Prize, Three Named for Medicine, Physiology Award," *Science*, 158(1976):468–73; Ragnar Granit and Floyd Ratliff, "Haldan Keffer Hartline, 1903–1983," *Biographical Memoirs of Fellows of the Royal Society*, 31(1985):262–92; and Floyd Ratliff, "Haldan Keffer Hartline (1903–1983)," *Year Book 1984* (Philadelphia: American Philosophical Society), pp. 111–120.

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