Haldan Keffer Hartline, 22 December 1903 - 18 March 1983

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HALDAN KEFFER HARTLINE

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Haldan Keffer Hartline was of genuine ‘Pennsylvania Dutch’ stock. His grandfather, James A. Hartline, a cabinet maker and also a farmer was from Reading, Pennsylvania. With his wife Hettie (Esther Ann) Schollenberger he lived as a farmer in Berks county, a Pennsylvania Dutch settlement (Dutch = Deutsch = German). One of the children of this couple was Daniel Schollenberger Hartline (b. 1866). This farmer boy rose in education to become a teacher in the natural sciences at Bloomsburg State Normal School. Clearly a man of considerable gifts he had taken a Master’s degree at Lafayette College and afterwards had spent some time (1901–1902) studying at the universities of Bonn and Heidelberg. In 1897 he married Harriet Franklin Keffer (b. 1864), daughter of Washington Henry Keffer, a violinist and orchestra leader in Lancaster, Pennsylvania, and his wife Elizabeth Ann Moss of a New England colonial-time family. Harriet Keffer taught English at Bloomsburg State Normal School and played the violin in the school orchestra. She was a skilful amateur gardener and botanist and something of a connoisseur of ferns.

The son of the two Bloomsburg teachers, Haldan Keffer (b. 1903) became the visual physiologist, known to his friends as Keffer*. He grew up in an English-speaking family but his father had still spoken the Pennsylvanian German dialect at home and learned English in school.

The naturalist boy

Keffer was brought up to become an ardent naturalist. His parents had both knowledge and enthusiasm for the education of their single child

*Quotations lacking reference in parts I–III are from Hartline’s reminiscences, as dictated during the last years of his life and kindly put at my disposal by Mrs Elizabeth Hartline.
and the country around their large house ‘Sunnyslope’ provided the rest, variety and beauty. Bloomsburg, Pennsylvania, is at a point in the Susquehanna valley where a number of brooks form the headwaters of Fishing Creek, joining the north branch of zigzag Susquehanna river which drains the Allegheny mountain plateau. Rocks, ravines and water gaps form picturesque scenery. The Pennsylvanian mountains fostered in the boy a penchant for climbing.

Keffer’s father was a competent field naturalist and a skilful teacher provided with an all-round fund of knowledge in the sciences; thus astronomy and geology enlarged a biological background that must have been of an unusual quality among teachers in schools outside the large cities. The son shared his interests. Still a child, Keffer joined him when he took his classes for a day into the country in farm wagons drawn by horses. There were planned stops at which the teacher lectured on various natural history topics and the students scattered to collect specimens and make observations. They were supposed to hand in an adequate report; failing this they risked a zero and reprimands for lack of diligence and sense of responsibility. ‘Study Nature, not books’, Louis Agassiz’s motto, hung in a visible place in the teacher’s office.

Keffer’s lively response to Nature’s wonders must have been a delight to his father. They became good companions and often went hiking together, collecting and observing. Keffer called his father ‘my first and best teacher’. Until the end he shared his father’s interest in astronomy and geology (see below) and when he finished Bloomsburg State Normal School in 1920 he was familiar with all the common insects and arthropods in the brooks and fields of Bloomsburg. That summer his father sent him to Cold Spring Harbor, Long Island, for a six-weeks course in comparative anatomy. In the autumn he entered Lafayette College.

**The years of learning**

The time had come for preliminary thoughts about his future. Keffer’s father and the much admired Professor of Biology at Lafayette, B. W. Kunkel, ‘friend and benefactor’, held medicine to be the best line to take for a young man with good background in biology. Both of them—field naturalists that they were—failed to notice the evidence already available showing Keffer to be a born biological experimenter. Some examples: when his father, having lectured on variability in plants, told Keffer to bring him one dandelion with a very short and another with a very long stalk, the boy put the one specimen to grow in a tube where it added 20 cm to its normal length of stalk. Another time when hiking with his father in the northern mountains of Pennsylvania, Keffer noticed, while they were wrapped in their blankets watching the camp fire in the dark, that the bright sparks had short tails and the dim ones much longer tails.
At home he then started experiments on flicker in order to explore the phenomenon of persistence in vision!

At Lafayette he told the sympathetic and always encouraging Kunkel that he wanted to do something scientific but did not know how to begin. Kunkel suggested a study of the land isopods. Keffer collected some but confessed to Kunkel that he did not know what to do with his cultures. Kunkel merely laughed and said ‘Well, that’s research!’. Keffer went back to his isopods and soon noticed that they avoided light, hiding in the dirt under bits of leaves. He concluded that this trait in the animals might be worth studying, then started looking up literature on avoidance responses to light in land isopods.

In the end, what put him on to doing his first published piece of original research seems to have been Jacques Loeb’s book *Forced movements, tropisms, and animal conduct*. Its special appeal was the call for quantitative work, even though to Keffer’s critical mind the interpretations were ‘simplistic, dogmatic’, in fact ‘rather vague but sounded very exact’. However, from this moment on Keffer never seriously deviated from his main line of research that came to be quantitative experiments on visual responses to light.

At this particular moment Keffer set out to guide the *Oniscus* into the centre of a circle drawn on a blackened table, and released it for a run while directing a narrow beam of light onto it. If the intensity was above threshold and not of excessive brightness the creature turned away from the light at an angle forming a linear relation with the logarithm of light intensity. Too strong lights made the *Oniscus* turn round.

In the summer of 1923, between his graduation from Lafayette and entry at Johns Hopkins University Medical School, Keffer was at Woods Hole Marine Biological Station and went to show Jacques Loeb his findings. Loeb (who died at 65 the next winter) was delighted, offered to publish the paper in the *Journal of General Physiology* and gave him an introduction to Selig Hecht. Keffer, not yet twenty, was elated at this chance of meeting one of the rising visual workers in the United States of that period. Along the lines of Loeb, Hecht had applied photochemical interpretations to quantitative observations on a light response of the clam *Mya arenaria*, a novel approach that created considerable interest at the time among students of vision. Keffer had a cordial reception from Hecht, Loeb had given him the manuscript of Keffer’s paper in advance, and a friendship was started that led to long conversations and an exchange of ideas in which Keffer in those days was the receiving partner. Later in life Keffer became critical of an approach that explained complex responses to light by deductions based on the properties of a bimolecular equation.

To Keffer himself this first taste of what science could give him suggested a future in biology rather than in medicine. His father’s teaching had taken him through Lafayette College in three years instead
of the customary four. With excellent marks he had been accepted at the Medical School of Johns Hopkins University. Then followed misgivings about this choice and he went to see Jacques Loeb hoping for advice and encouragement. But the old biologist said ‘No, no, you must go on with medicine; there is no future in biology’. And so, in the autumn of 1923 Keffer entered Johns Hopkins as a medical student, rather worried about his deficient background in physics and mathematics and pinning his hopes on the reputation of that university to encourage research. Later in life he complained of having been compelled to learn mathematics, which he liked, at a stage in his life when his ‘youthful sharpness already had been blunted’ by clinical subjects! Many of us, his friends, must have heard him jokingly maintain that he got his medical degree (1927) from Johns Hopkins on the condition that he should never take to practising medicine.

During those years of study at Johns Hopkins, Keffer seems to have had time not only for experimentation in vision but also to cultivate his major hobby, astronomy. I shall return to his hobbies later. His notes viewed in the perspective of his scientific development point to Woods Hole, its social and scientific animation, as his main source of inspiration. But he admitted that Johns Hopkins lived up to its reputation as a university encouraging research. The Department of Physiology, headed by E. K. Marshall, proved willing to do something for him and sent Keffer to Dr Charles D. Snyder who gave him the run of his string galvanometer after having taught him how to use it and how to prepare strings and to replace those that had broken. Soon Keffer was recording the retinal action potential of frogs, rabbits and cats, proving that the so-called indifferent lead could be placed anywhere on the animal’s body as long as the active lead was on the cornea. The response remained the same. This work was published in 1925 (3).* After this experience he ‘lost interest in the retinal action potential of the vertebrate eye’.

For a physiologist with Keffer’s inclinations, still under the influence of Loeb and Hecht, the vertebrate electroretinogram apparently exhibited a forbidding complexity. However, suddenly something occurred that gave him a fresh lead. One night he had completed his experiment with a decerebrated cat, now a carcass, when he noticed a big bluebottle fly buzzing around the dead animal. This he caught, mounted and placed electrodes as his experiments with vertebrates had taught him, the active lead on the cornea, the distant lead on the body. Cautiously he shunted the string of the galvanometer but was surprised when in spite of this precaution it disappeared upon illumination of the eye. A still heavier shunt convinced him of the fact that he actually had recorded a response of some 20 mV, probably about ten times the electroretinogram of the cat. Realizing this, Keffer’s naturalist background asserted itself and he suddenly understood that insects and arthropods would be the ideal

* Numbers given in this form refer to entries in the bibliography at the end of the text.
Haldan Keffer Hartline

preparations to tackle for quantitative work on visual receptors. It was midwinter but as soon as grasshoppers started chirping he gladly suffered the jokes that his fellow students bestowed upon his collecting of such insects in the field around Johns Hopkins.

With his considerable talents as a designer of apparatus, Keffer soon had an accurate pendulum shutter in operation and used the retinal response of the grasshopper to prove the validity of the Bunsen–Roscoe law, i.e. that for short flashes the eye responded to the product of intensity and duration (4).

At marine biological stations

In his formative years, up to 1929, Keffer generally spent his summers at marine biological stations. His father had worked at Cold Spring Harbor, Long Island, and, as mentioned, sent his son there in 1922. This gave Keffer an opportunity of handling the live equivalents of dried specimens he had seen at home. He now for the first time saw a live *Limulus polyphemus*, in whose lateral eye he was destined to take a lifelong interest. Keffer had doubted his father’s statement that a nodule on the side of its head was an eye. The live creature proved his father to have been right. Its carapace in the shape of a horseshoe has given *Limulus* its name, the horseshoe crab (though it is no crab). Another striking feature is its long spike-like tail, stiff and pointed.

At Woods Hole Keffer and his contemporaries followed M. H. Jacobs’s course on cellular permeability. Keffer found him a ‘superb teacher’ and said that he, together with his father and B. W. Kunkel, were the ones that had been most influential in forming his scientific personality. In the group following Jacobs’s course there were, among others, Francis Schmitt, John Edsall, Baldwin Lucke and Morton McCutcheon, the last two becoming his special friends. A brief deviation from Keffer’s visual line of research was collaboration with them in their project on the swelling and shrinking of *Arbacia* eggs in solutions of different tonicities. Keffer designed for these experiments a diffraction instrument that gave high accuracy. He also developed a theory that did well for the kinetics of swelling, but shrinking proved to be faster than the theory allowed for. However, this was for him a sideline that was dropped when Lucke unexpectedly died in the early 1930s.

More relevant for Keffer’s scientific development became his experiments at Woods Hole on the dark adaptation of *Limulus*, together with his growing interest in shadow reactions of available species. This was inspired by the notion that Hecht’s theory, accounting for an increase of illumination in the clam *Mya*, might hold also for a response to its decrease. The best preparation proved to be the scallop *Pecten*, which responded by a vigorous closure of the shells to a decrease of stimulus light. Keffer measured latent period of this response as a function of the
logarithm of intensity. On Hecht's theory he came out with a discrepancy of a factor of two in the slope of the plot of expected against observed values and then abandoned this type of study. Later (see below) he returned to study *Pecten* from more interesting points of view.

The work on dark adaptation of *Limulus* became, as it were, an assessment of the nature of the problems finally studied with the single-fibre preparation (see below). It did, however, mark two steps in Keffer's scientific development. One was the insight that sensitivity should be defined in relation to a criterion response; the other was his first use of amplification, in those days a new and exciting technique. Forbes & Thacher (1920) and Gasser & Newcomer (1921) had pioneered the use of amplifiers in physiological experiments on nerve action potentials. A physicist, Chaffee (1923), with some co-workers, had used amplification for investigating amphibian electroretinograms. Keffer may not at that time have been familiar with Lord Adrian's work, available in the *Journal of Physiology* from 1926, but was inspired by K. S. Cole to build an amplifier for the small Edelmann permanent magnet string galvanometer. The early results were published in 1930 (5). These are best considered in the light of his later work (see below).

### The 'Grand Tour' in Europe

Disappointed with what the regular courses at Lafayette and Johns Hopkins had given him in physics and mathematics, Keffer, suspecting that he was cut out for a career in those disciplines, used a stipend from the Eldridge R. Johnson Foundation, not yet an active institute, to go to Germany to study in Leipzig and Munich. There he found himself faced with German physics at its absolute summit: Sommerfield in Munich, Heisenberg in Leipzig! Duly impressed by these two great physicists and the qualifications of the young adepts surrounding them, Keffer soon concluded that he 'lacked the background in physics and mathematics' required for following discourses and lectures in these places. In Munich the week-ends on skis grew longer and the pages in his notebooks on Sommerfield's brilliant lectures 'showed more and more blank spots'. In the summer climbing was a noble occupation.

Keffer's impression of the rising Nazism around 1930 was that the Münchener found it ridiculous. Yet three years later came Hitler's *Machtübernahme*. One day Heisenberg's seminar at Leipzig went by train to Berlin to listen to Einstein expounding the unified field theory. Though capable of understanding the required mathematics Keffer could not grasp the intellectual content of the presentation owing, as he thought, to ignorance of the physics involved.

In spite of the disappointments, which served to teach him something about himself, Keffer considered his 1½ years in Europe well spent. He travelled a great deal, not only in the Alps, but also to England and saw
much of Italy. While skiing and climbing he made friends; he vividly recalled some of them in his last-day reminiscences. In Naples he was cordially received at the Zoological Station, was furnished with a small aquarium and a desk of his own at a window. Dr R. Dohrn, the Director, was very gracious and took him out to the house he owned in Ischia. Keffer recalled that the Naples institute was the place where F. W. Fröhlich had taken the beautiful records of the electroretinogram of the cephalopod *Eledone moschata* (published in 1914).

At the Naples Station Keffer had a chance of studying the shadow reactions of some annelids behaving like *Pecten*, with which he was familiar from Woods Hole. These annelids had long (20–30 cm) leathery tubes. Always up to a joke, he used to 'entertain visitors who would come to see this beautiful display of yellow and orange and red plumes extended in the water. I would pronounce some magic words as I passed my hand between the window and the jar containing the animals, and their disappearance as they retracted into their tubes was so fast that one had the impression that they simply disappeared.'

In England Keffer had a friend, Reginald Waterfield, with whom he had done some astronomical work at Johns Hopkins (see below). Waterfield took him to meet the Reverend T. E. R. Phillips, a notable amateur astronomer, rector of the church at Headley in Surrey and ‘a grand person in his, I guess, seventies ... an extremely agreeable person to know’. The three of them then spent some nights in Phillips’s private observatory watching Jupiter through a fine telescope on loan from the Royal Astronomical Society. Finally Keffer stayed a week with Waterfield whose father was Dean of Hereford Cathedral, and there took part in a memorable expedition to watch a tidal bore of the River Severn, vividly described in his reminiscences. Apparently he made no attempt to visit physiological laboratories.

II. ENTERING THE JOHNSON FOUNDATION

D. W. Bronk who, after a *séjour* in England with A. V. Hill and E. D. Adrian (1955 Baron of Cambridge), had been offered the post as Director of the Eldridge R. Johnson Foundation at the University of Pennsylvania, had no more difficulties in persuading the frustrated theoretical physicist to join the new venture as Fellow in Medical Physics, an ideal position for Keffer. He arrived in 1931 and stayed till 1949 with a brief intermission in 1940–1941 at Cornell University Medical School in New York. He returned to Pennsylvania as Professor of Biophysics. When he arrived in 1931 there were already W. A. H. Rushton and myself on two-year appointments since 1929. By a curious coincidence Hartline, Rushton and I independently went in for experimentation in the field of vision, Keffer for a lifetime, I for the first, and Rushton for the second half of his life as an experimenter.
In the autumn of 1931 Keffer started his Fellowship by building a three-stage battery coupled amplifier with screen grid tubes that fed into a power stage driving a Matthews oscillograph. The rest of his apparatus could safely be left in the hands of the excellent engineer, Arthur Rawson, whom Bronk had engaged to run the workshop. At that time Bronk, a skilful experimenter, was starting his work on recording impulses from the Pacini bodies and the carotid sinus. Rushton, with simple tools, carried out the decisive tests destroying Louis Lapicque’s ideas on ‘isochronism’ between a nerve and its muscle, and I was engaged in applying flicker fusion of intermittent stimulation as an index of excitation and inhibition, to supplant psychophysical notions by neurological ones. Clarence Graham, then a student of experimental psychology, worked with me and, after my departure, with Keffer.

Gradually Bronk filled the institute with a staff of physiologists. He himself later took to administration on a grand scale but whatever position he reached, be it President of Johns Hopkins, Professor at Cornell Medical School, or President of the Rockefeller Institute, Keffer followed him loyally. Bronk was a genius at raising funds for everything that his fertile administrative imagination thought worth developing or preserving. He always saw to it that Keffer was adequately supported, both with ample funds for research as well as with a good personal allowance. Keffer never had to ask for a rise in his salary. The Johnson Foundation called forth the best traits in Bronk’s personality and he and Hartline eagerly read and criticized each other’s papers.

The single-fibre optic nerve preparation of Limulus

In the summer of 1931 Keffer went with Graham to Woods Hole for work on *Limulus*. He selected young animals, 5–6 cm across the carapace, whose optic nerves were easy to dissect. These had shiny clear eyes and responded well to light, both with retinal action potentials and discharges in the nerve. Ralph Gerard, who at this time was at Woods Hole, suggested splitting the nerves to obtain single-fibre impulses, as had been done for the first time by Adrian & Zotterman (1926) in a fundamental paper with the nerve from a frog stretch receptor. Hartline and Graham used fine glass needles of a kind developed by Robert Chambers, an expert at microdissection. They had no luck. Even their thinnest strands of fibres always gave composite discharges. Work was frustrating and gradually the summer drew to an end. Finally, with only two days left and only two large mature animals remaining in the aquarium, they ‘were rewarded with a beautiful set of absolutely single-fibre responses’ from the first of them. The second adult *Limulus* behaved in the same way. And to Keffer’s last day it remained inexplicable why it should be so difficult to split nerve bundles in the young *Limulus* and so much easier to
do it in the adults. Be that as it may, once this technical problem had been solved, Keffer had a preparation for a lifetime of work on visual reception.

The *Limulus* eye responded with a frequency variation of impulses over an intensity range of 1 to 1,000,000. The initial maximal discharge was logarithmically related to stimulus intensity. In this eye there are some 300 large, coarsely spaced ommatidia each consisting of 14–16 sense cells (retinular cells) surrounding a central light-sensitive rhabdom. At the time Keffer still thought they had recorded an uncomplicated receptor–nerve-fibre response. They wrote a brief paper that can be said to have initiated Keffer’s creative period of visual research with an eye—as he jokingly used to maintain—that very likely was not used at all for seeing. However, it did serve to elucidate some fundamentals of phototransduction.

The first problems to be solved at the single-fibre level were taken from the arsenal of classical psychophysics. To this category belonged the verification of the Bunsen–Roscoe law, the course of dark adaptation, the spectral distribution of sensitivity. The latter proved to reproduce the human visibility curve in dark adaptation, determined by the absorption spectrum of rhodopsin. However, in *Limulus* there was no shift of ‘visibility’ with state of adaptation as in man (Purkinje shift), suggesting ommatidial homogeneity. This work, carried out at the Johnson Foundation, did not require single-fibre spikes, though the new technique added precision to the conclusions and elegance to the records. At the time Keffer still thought that there was a direct connection between photoreceptors and nerve fibres.

That notion had to be given up. For this there were two reasons, one anatomical, the other experimental. Keffer had sat down to give proper attention to Grenacher’s (1879) early description of the *Limulus* retina and he soon realized that he had neglected to consider the numerous clumps of neuropile, charged with synaptic regions, clustering around the dendrites of a somewhat eccentric cell, so also named. In his laboratory Miller (1957) confirmed and extended Grenacher’s study. The experiments had shown that dimming the light of the room increased the firing rate of the spike. In due course Keffer understood that the eccentric cell was indeed a second order neuron and when, after the move to Johns Hopkins, G. Ling arrived to pull out micropipettes for intracellular recording, full confirmation was obtained by direct comparison of the generator potential of the eccentric cell with the firing rate of its discharge.

With the new insight came a new creative period in Keffer’s thinking and experimentation, releasing his full capacity of original scientific work. In retrospect (1974) he spoke about a change of attitude to his experimentation as follows: ‘The second development in our studies of the *Limulus* eye turned my attention away from receptor mechanisms. Once alerted I could easily show that shading the regions of the eye
neighbouring the receptor whose nerve fibre I had isolated restored its activity.' And so was born the important concept of lateral inhibition, first presented in 1949 (37). Realizing that he had now discovered an inhibitory process in a relatively simple organism, Keffer decided that it would be worth his while to give it a detailed experimental evaluation (see § IV).

A more critical attitude to photochemical explanations of complex neural events was an early consequence. Thus, for instance, when he and McDonald (34) had found that dark adaptation in Limulus greatly slowed down after strong light adaptation, they attributed this effect 'to a decrease in the concentration of the photochemical substances by photoysis and to its regeneration by chemical mechanisms that are independent of light'. Partly true or the whole truth? The new attitude is illustrated by what Hartline, Wagner & MacNichol wrote in 1952: 'Sensory adaptation is a universal property of receptors of all kinds. It scarcely seems reasonable to ignore this and ascribe all of the sensitivity changes in the visual receptor to alterations in its highly specialized photochemical component' (41). It is known that large drops in sensitivity of vertebrate eyes may coincide with negligible effects on rhodopsin concentration.

**Isolation of single fibres in the eye of the frog**

His success with Limulus stimulated Keffer to attempt isolation of single fibres also in a vertebrate retina. For this he chose the eye of the bullfrog. Recalling suddenly—during a flight in his own aeroplane—that the optic nerve is split naturally where the fibres from different regions course towards the blind spot, he saw an opening to a solution of the technical difficulties. He had a background of experience, manipulative dexterity, and skill as a craftsman as his three major assets. Philip Davies, in a comment to Mrs Hartline, has described the instrumentation of Keffer, 'the Master Grinder'. The tips of his scissors, looked at under the microscope, met exactly. The same held good for his 'real masterpiece, the tweezer-type microscissors which he invented for dissecting single fibres from the optic nerve of the limulus. He made them completely from scratch.' The long process of shaping them was complete when they could be used to 'cut neatly through just half of a single cotton fibre, and it was a treat to see Keffer perform this operation'.

Well prepared by these preambles, he tried to lift fine bundles of the naturally split optic nerve on cotton wick electrodes and to separate single fibres from the lot. Though 'successful in only a very small percentage of trials' (22), his findings represented a great step forward in our coming to grips with the details of retinal organization. In his own words the results were 'exciting surprises' (80). He classified the individual response patterns into three categories: 'on', 'off' and 'on-off' fibres. Today we
would speak of response types rather than of fibre types and, perhaps, emphasize that the major conceptual advance was that the single fibre gave access to a study of its receptive field. Keffer himself, contemplating his work in 1974, said humbly: ‘Successes were exasperatingly few, but they were welcome at the time, before Granit and his colleagues had developed their microelectrode for retinal recording’.

The term and concept ‘receptive field’ had been introduced by Adrian (1932) for the area innervated by a single skin afferent. In the retina a receptive field has a complex organization. It is composed of those receptors, horizontal cells, bipolar cells and amacrine cells that are capable of shaping the discharge of a single ganglion cell sending its message upwards through its fibre in the optic nerve. It is thus a small organized structure and in this regard conceptually closer to Sherrington’s (1906) ‘reflex receptive field’, which in the end came to refer to a single motor axon.

The size of the receptive field in the bullfrog retina depended on stimulus intensity. Explored by a small spot of light at moderate intensities its diameter was of the order of 1 mm. The strongest response was always obtained from its central portion. There was a considerable amount of overlap between adjacent fields, just as in Adrian’s (1932) pictures of the receptive fields in the frog skin. Spatial summation in the retina was found to be restricted to the area of the receptive field. Keffer also noted inhibitions from adjacent fields on the on–off type of response. Barlow (1953) was the first to discover surround inhibition on the receptive field, a feature apparently more prominent in mammalian eyes where it was described in 1953 by Kuffler (45), and since studied in many ways in many laboratories. Regrettably Keffer himself gave up working on the vertebrate retina after having pioneered so brilliantly this profitable field of study. From talks and correspondence, then and later, I conclude that he found the vertebrate retina too complex for his particular attitude to experimentation that was bent on quantitative interpretations. He wanted analysable material, preferably facts that could be handled mathematically. And there, round the corner, was Limulus providing an analysable inhibition!

Returning to the eye of Pecten

One feature of the unitary responses of the bullfrog retina continued to intrigue Keffer, the pure off-fibre. It reminded him of his early interest in ‘shadow reactions’. So he decided to return to Pecten irradians, this time in an attempt to record from its optic nerve. Ratliff (1974) has given a brief and precise summary of Pecten as a preparation facing the experimenter: ‘Not content with a mere hundred eyes, the scallop has a double retina in every eye with each of the two retinas served by a separate optic nerve. The eyes are extremely small, of course, being only about one
millimeter in diameter. The two retinas and their optic nerves, which are located on the outer end of a tentacle-like structure, appear to be easily accessible in anatomical drawings. In actual practice, however, the flexible tentacle is most difficult to dissect.

Keffer succeeded in recording from both optic nerves, even to the extent of isolating single fibres. He found that the inner layer of the retina responded with a type of discharge to light reminiscent of that of Limulus, a lasting on-response. The outer retinal layer conformed to his expectations from the animal’s ‘shadow reaction’; it gave a pure off-response. The question now arose of whether the off-reaction was the consequence of synaptic interaction between the two seemingly isolated retinal layers, or a direct response of the receptors in the outer layer. Anatomically the latter do not look like typical visual receptors, being short and round, whereas the on-response of the inner layer originates in characteristic rod-like structures. However, both are receptors and no synaptic layer has been identified between them. Accepting this evidence Keffer realized that he had discovered a new type of receptor, probably hyperpolarizing during illumination and discharging to its cessation or diminution with a firing rate dependent on intensity and duration of stimulation. The analogy with the frog off-fibre was striking and suggested synaptic interaction as an explanation of the off-response. Keffer put forth both alternatives, and Ratliff, reviewing the literature 36 years later, still shows some hesitation in deciding between them. It is, however, easier today than in 1938 to believe in a receptor being polarized by light and depolarized at its cessation, to set up a generator potential directly exciting its nerve fibre.

III. HOBBIES, HOME AND PERSONALITY

I have tried to outline the development of Keffer Hartline, analytical experimenter by inclination, trained from birth to be a naturalist, into a distinguished scientist specializing in the field of biophysics of vision. The account of his last phase at the Rockefeller University, culminating in the masterly studies of lateral inhibition and other properties of the ommatidial eye, has been left to his long time co-worker, Professor Floyd Ratliff, in New York. Finally I add some words about the man I had the privilege to be joined with in a friendship lasting just over half a century. It began over some ‘mint juleps’ in his home in Philadelphia in 1931 and never lost the cordial note thus introduced.

Keffer’s secretary, the wife of his colleague Frank Brink, hit the nail upon the head when characterizing him in a letter to Mrs Hartline: ‘One way or another Keffer always seemed to enjoy life . . . never unfair, intolerant, or even abrupt in any of his dealings with the working staff . . . (but) I think he was allergic to office work’. He knew well what to
appreciate, what to neglect and what to detest. When he received the
Nobel Prize in 1967 a journalist telephoned him in New York and said:
'What did you do when you heard about having had the Nobel Prize?'
Keffer: 'I was having my breakfast.' The journalist in excitement: 'And
what did you do when you knew that you had gotten the Nobel Prize?'
Keffer: 'I finished my breakfast.' In Stockholm Betty and Keffer took
great delight in the old-world ceremonies surrounding the award. The
previous year another great honour, much appreciated, had made him a
Foreign Member of the Royal Society.

Keffer's most serious scientific interest outside his professional field
was astronomy. His father, responsible for so much in his upbringing,
woke him one night in early May 1910, a little before dawn, to see
Halley's Comet. This was a great experience to which he returns several
times in his autobiographical notes. Apparently they had a wonderful
view of it; in Keffer's words 'a great sight . . . most spectacular'.

At Johns Hopkins in 1927 he met Reginald Waterfield, a British
haematologist whose main interest really was astronomy, possibly in­
erited from Sir John Herschel of whom he was said to be a great-
nephew. Keffer had returned to his university on a National Research
Fellowship to study physics and mathematics. In downtown Baltimore
they discovered the university telescope, a Hastings-Brashear 9½ inch
refractor, equatorially mounted and clock-driven. Keffer's boyhood
enthusiasm had been sustained by the use of his father's 3 inch refractor.
Now, stimulated by Waterfield, it burst out into a flame that did not
subside until supplanted by the equally passionate engagement in visual
experimentation. Waterfield never gave up astronomy and became the
author of well-known popular books in the field and of communications
to the Royal Astronomical Society.

Everything in the old place could be dusted off or properly cleaned and
after that the two friends spent much time on trips to the observatory,
enjoying with friends diverse common sights, the moon, Jupiter, double
stars, clusters, nebulae. In the spring of 1928 they succeeded in persuad­
ing the university authorities to build a new observatory to their design
on the Homewood Campus, to where the university had moved. This
became ready in the autumn of that year, 'in fine shape, a great credit to
those who did the work'. After alignment of the instrument they started
observing in earnest, Mars in particular being on the programme. It is
impossible here to allow more space to their happy companionship in a
virtually private observatory. Apparently it represented some kind of
fulfilment for Keffer, to judge by the boyish excitement that pervades his
old-age reminiscences, page after page, from that time.

Keffer's major recreations were climbing, sailing and flying. In
October 1934 he gained his Private Pilot's Licence and could fly to see his
parents, to Woods Hole, or fly for sheer enjoyment. In another respect,
too, it was a momentous year because a young gifted psychologist,
Elizabeth Kraus, arrived to work at the Johnson Foundation. She was a nature lover, like himself interested in biology, brought up in a scientific milieu. Her father was the notable chemist Charles A. Kraus, Professor at Brown University, Providence, Rhode Island. They were married in April 1936 and lived happily together until his death. Their three sons, Daniel, Peter and Fred, all went in for scientific careers in biology.

Keffer's sailing in the States was chiefly done during holidays with the Bronk family, up the coast to Maine as soon as Bronk had advanced to boats big enough for open waters. A small sloop on the Delaware was the humble beginning of Bronk's seamanship. A couple of times Keffer sailed with me among the islands in the Baltic. My memory retains a vivid picture from 1938: Keffer and Betty had been climbing the Jotunheim mountains in Norway, then had taken the train from Oslo to Stockholm and the boat to Mariehamn, capital of the Åland islands. With my wife and son (then 8 years old) I had sailed there in our uncomfortable 6 M R-yacht to meet them. Alexander Forbes, who had had a large and comfortable wishbone ketch built at Burmeister & Wain in Copenhagen, arrived that same evening in this ship with his family as crew. Our ships were badly matched, I fast on the tack, he doing his best with the wind from behind. In the two ships we sailed together for several days having meals together anchored or, more often, landing at suitable skerries. Captains and crews, however, were well matched and enjoyed themselves thoroughly. Forbes and Hartline were both highly competent sailors. From our island home both went to Zürich for the Physiological Congress, Keffer to present his paper on single fibres in the frog eye under the chairmanship of Adrian. A steamer moved Forbes's ship, the 'Stormsvala', to the United States where he kept it in the harbour of the family island, Naushon, opposite Woods Hole.

Keffer's enjoyment of life was infectious and spread to those surrounding him. It was based also on his gentle manners and willingness to like—as he once said to me—people of all races and creeds, adding with his quizzical humour 'except vegetarians'. He would go out of his way to help anyone in a laboratory where no one else reached his superb manual skill. When J. Z. Young at Woods Hole showed him what was to become the well-known squid axon, Keffer undertook to confirm this notion by making it discharge impulses, leaving matters at that. In 1932 he gave me a coupling diagram for a d.c. amplifier to be used with the permanent magnet string galvanometer, apparently the one he had got from K. S. Cole. He helped Baldwin Lucké, as described above, and numerous other people. At their home in Turtlewood Keffer and Betty kept open house, informally, for friends and colleagues and there were no 'lateral inhibitions'. Being deeply devoted to the movement of nature preservation they could not think of setting up house in New York. Keffer had rooms there but lived in his laboratory and 'commuted' to Maryland for the week-ends.
In 1948 the trustees of Johns Hopkins University asked Detlev W. Bronk, then Director of the Johnson Foundation, to succeed Isaiah Bowman as President of Johns Hopkins (see Adrian 1976 and Brink 1979). Bronk’s acceptance, in 1949, was predicated, among other things, upon the establishment of a biophysics department on the Homewood Campus. Bronk immediately appointed Hartline the first Professor of Biophysics and Chairman of the newly created Thomas C. Jenkins Department of Biophysics. There Hartline continued his earlier close association with Henry G. Wagner and E. F. (Ted) MacNichol, Jr. Other collaborators during Hartline’s four years at Johns Hopkins were: Lloyd Beidler, N. A. Coulter, O. Sten-Knudsen, Leo Lipetz, William H. Miller, Koitu Motokawa, Floyd Ratliff, Lorrin Riggs, Paul Stonesifer, John (Smokey) Stover, Tsuneo Tomita, Myron Wolbarsht and Stephen S. Yeandle. Electronics engineer John P. Hervey and instrument maker Walter Biderlich provided valuable support services.

The generator potential

As early as 1935 Hartline had recorded, with external electrodes, the local ‘action current’ of a single ommatidium 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 precursor of the impulses. Indeed, Granit (1947) proposed that the retinal action potential be called the ‘generator potential’. The development, by Graham & Gerard (1946) and Ling & Gerard (1949), of micropipette electrodes with tips small enough to penetrate cells, opened the generator potential to direct study and rekindled Hartline’s early interest in this topic. Using micropipettes, Hartline, Wagner & MacNichol (41) recorded intracellular generator potentials for the first time. Hartline and his colleagues emphasized the similarity between externally recorded action current and internally recorded depolarization. They wrote,

'We are encouraged to believe that the use of the micropipette enables us to observe directly a depolarization of the sensory element under the action of light, a depolarization that is intimately related to the initiation of nerve impulses and that is manifested externally as the retinal action potential.'

This important conclusion was reinforced by further observations by MacNichol, Wagner & Hartline (43) and by later more detailed studies by MacNichol (1956), who showed 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. Tomita (1956) soon...
demonstrated that the depolarization resulted from an increase in membrane conductance that short-circuits the resting potential of the cell.

In Hartline’s laboratory at Johns Hopkins, Stephen Yeandle (1957) discovered minute fluctuations in the generator potential. Each of these fluctuations was believed to result from the absorption of one photon of light, and they were given a rather inelegant name: ‘quantum bumps’. These phenomena were later studied extensively by several of Hartline’s students and colleagues at Rockefeller, including Alan Adolph, F. A. Dodge, Jr, Bruce W. Knight, Jr, Jun-ichi Toyoda and Fulton Wong. The stimulus for much of this work was W. A. H. Rushton’s (1959) proposal that the generator potential resulted from the superposition of the quantum bumps and, further, that the potential became smoother at higher intensities because the bumps became smaller. Indeed, this was the origin of the ‘adapting bump model’ formulated by Bruce Knight in Hartline’s Rockefeller laboratory, where some work on the ‘bumps’ is still in progress. Hartline himself did only one further study on the generator potential after moving to Rockefeller in 1953, relating the inter-impulse variability to variations in the generator potential with light and dark adaptation (71). Nevertheless, Hartline maintained a strong interest in the generator potential and contributed much to the direction of the continuing research on it by colleagues and students in the laboratory.

The ‘lateral effect’

As pointed out above, one of Hartline’s most important contributions to the physiology of vision was his discovery of lateral inhibition in 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 (37) on this pattern of central excitation and surround inhibition was long delayed, but even so it pre-dated the discovery of the centre-surround organization of the vertebrate retina.

In 1950 Floyd Ratliff joined the Hartline laboratory at Johns Hopkins as a National Research Council Postdoctoral Fellow. Ratliff was immediately attracted to the lateral inhibition in the Limulus eye, which was still ‘on the shelf’ at that time. (Hartline and his other colleagues were preoccupied then with the generator potential.) The academic year 1950–51 was spent on a detailed study of the general properties of the lateral inhibition in Limulus, but the work did not appear in print until five years later (48).

Tsuneo Tomita (Keio University) spent the following year in Hartline’s laboratory. Tomita was very surprised by Hartline’s easy-going ways. Even today, more than thirty years later, he finds it hard to believe that Hartline gave him a master key to the new Jenkins
Laboratory on the day of his arrival and told him to come and go when and as he pleased and to work on whatever interested him. But this was characteristic of Hartline, who always saw to it that his colleagues—no matter what their rank—enjoyed the same freedom in their research that he himself did. Within a few months Tomita demonstrated that antidromic stimulation of the optic nerve resulted in essentially the same lateral inhibition as that produced normally by light. In addition to helping to elucidate physiological mechanisms of the inhibition, this work furnished a productive new technique for the study of lateral inhibition. Hartline was delighted with Tomita’s findings and told him, ‘Until you go home you don’t have to do anything else.’ Following the ‘custom’ of the laboratory, this work was not published until many years later (Tomita 1958).

V. The Rockefeller University, 1953–83

In September 1953 Detlev W. Bronk became President of the Rockefeller Institute for Medical Research. He immediately appointed Keffer Hartline a Member of the Institute and Head of the Laboratory of Biophysics. Within the year, Hartline invited Floyd Ratliff (then at Harvard) to join the laboratory at Rockefeller.

There was an instant rapport between Hartline and Ratliff when they first met in 1950, and they became close friends almost immediately. They had rather different approaches to science: Hartline preferred to focus his attention on one problem at a time and to elucidate carefully one basic principle; Ratliff preferred to consider several different but related problems at once to elucidate general principles. These different approaches, both with a quantitative bent, nicely complemented one another and Hartline and Ratliff worked harmoniously in close collaboration for over three decades. Both their friendship and their collaboration was based upon and nurtured by a strong bond of mutual understanding and respect for one another. A harsh word never passed between them.

The Hartline–Ratliff equations

Georg von Békésy, at Harvard, had pointed out to Ratliff the similarity between lateral inhibition in the eye of *Limulus* and the inhibitory interactions in the retina hypothesized by Mach, in 1865, to account for various contrast effects in human vision, including the so-called Mach bands seen at the edges of half-shadows. This work of Mach, expressed in a quantitative form, had a significant influence on all of the subsequent work by Hartline and Ratliff on lateral inhibition (see Ratliff 1965, 1974, 1976). Indeed, in their first studies carried out at Rockefeller, Hartline and Ratliff focused their efforts on a quantitative account of the inhibitory
interactions in the eye of Limulus (46, 47, 49, 54, 59). They were able to express the reciprocal interactions between two ommatidia in the steady state with a pair of simultaneous equations. Although these equations were strongly nonlinear overall, they were, as Hartline put it, ‘mercifully, piecewise 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.

The subsequent discovery by Hartline & Ratliff (49) of the phenomenon of ‘inhibition of inhibition’ enabled them to extend their mathematical description to any number of interacting units. This inhibition of inhibition—or disinhibition as they preferred to call it (following Pavlov)—confirmed the notion they had already expressed in their pair of simultaneous equations describing the interaction of two elements, i.e. that the interaction was both mutual and recurrent. With this knowledge Hartline and Ratliff 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, in the form of one integral equation. At first the phenomenon of disinhibition was thought to be unique to the Limulus retina, but it has since turned out to be a general principle of neural organization, widespread in other species and in other neural systems.

William H. Miller, who had worked briefly with Hartline at Johns Hopkins, joined the Rockefeller laboratory in 1955. Miller made many important contributions to the understanding of the microanatomy of the Limulus retina. For example, using the newly available electron microscope he showed in detail the extremely fine fibres and their synaptic endings in the lateral plexus of interconnections in the Limulus retina. It is not yet known how this plexus conducts the lateral inhibition, but it is known that the inhibition is mediated by the plexus. Hartline demonstrated this early on by means of one of the many extraordinary feats of microdissection, by hand, for which he was famous. Using a pair of his home-made scissors, with the blades well honed and the tips well adjusted, Hartline carefully cut the plexus of lateral connections to a single optic nerve fibre. This completely abolished the lateral inhibition.

The computer

The measurement of oscillographic records and the calculation of interactions among two or three neurons in the retina was a formidable task with instruments available in the 1950s. All sorts of shortcuts were devised. One of Hartline’s favourites was the so-called hyperbolic sweep, invented by E. F. MacNichol and J. A. H. Jacobs, to calculate electronically the reciprocals of intervals between impulses and display them as a
Haldan Keffer Hartline

graph of 'instantaneous rate' on an oscilloscope. Later, electronics
engineer L. Eisenberg and Ratliff constructed an automatic interval
counter that printed intervals in milliseconds on the recording film
alongside the corresponding impulses. But, as Hartline often complained,
'If one has a graph, one always wants the numbers; if one has the
numbers, one always wants a graph.'

Automation was not new to the laboratory. At Johns Hopkins, John
Hervey had constructed a bank of five timers for Hartline that could be
pre-programmed to trigger one another and to control electromagnetic
shutters in three independent beams of light. These high-speed shutters,
designed for Hartline by A. J. Rawson on the principle of a polarized
relay, were of extraordinary quality. They opened and closed in less than
a millisecond and would operate thousands of times, at rates up to 100 per
second, without failure—provided that Hartline himself, who alone in the
laboratory had the necessary patience and 'touch', had adjusted them.

Laboratory-sized digital computers were just beginning to become
available in the early 1960s, and Hartline and Ratliff began to explore the
possibility of getting a computer for the laboratory. Hartline was ever-
cautious, however, and decided to get experience on one in another
laboratory. At week-ends, when he went to his home in Maryland, he
would take with him several rolls of punched tapes of data, laboriously
transcribed from photographic records on a Flexowriter. In Maryland
Hartline would visit Werner Love, at Johns Hopkins, who was the proud
owner of an LGP-30 computer. Analysis of the data on punched tapes
showed that the computer could do in seconds or minutes what the more
primitive techniques then in use required hours or days to do, or could
not do at all. Now confident that they were going in the right direction,
Hartline and Ratliff obtained funds, in 1962, to purchase a Control Data
Corporation 160-A computer (with a 4000 word core memory). Hartline
was fascinated by the great potential of the digital computer, and was one
of the few neurophysiologists of his generation who made 'hands on' use
of a computer in his research. Even more unusual for a scientist of his age
at that time was the fact that he wrote his own programs (in machine
language). The new computer made possible the proper study of the
dynamics of neural networks and set the work of the laboratory on a new
course, which it is still following today.

The dynamics of lateral inhibition

The earliest studies of the dynamics of lateral inhibition by Hartline
and Ratliff were purely empirical. Quantitative theoretical approaches to
the dynamics of neural mechanisms were 'in the air', however. In the
early 1960s, for example, one of Hartline's students, Alan R. Adolph,
developed a stochastic model (based on those originally applied to the
statistical description of 'shot noise' in electron tubes) for the quantum
bumps in *Limulus* photoreceptors at various stages of adaptation. At the same time another student, Robert Devoe, applied Fourier methods to the study of the dynamics of the electroretinogram of the wolf-spider. A third student, Charles F. Stevens, used a mathematical analysis of responses of the *Limulus* retina to step-transients to demonstrate that there must be a self-inhibitory loop in the network. (Fortunately Hartline and Ratliff had left this possibility open in their original steady-state equations.) Thus in the early 1960s the stage was set for a proper quantitative analysis and theoretical account of the dynamics of lateral interactions in a real neural network.

First attempts by Ratliff, Hartline and Miller (62) merely introduced a simple delay into the earlier steady-state equations. Despite the crude nature of this first approximation, it did give a reasonable account of various phenomena such as the damped oscillations following step-transients in illumination and the paradoxical ‘backward inhibition’ in which lateral effects seemed (at first sight) to occur before their causes. A short time later, a graduate student, Richard L. Purple, directly recorded both self- and lateral-inhibitory synaptic potentials. Purple and Fred Dodge then formulated a dynamic model of the concurrent operation of excitation and self and lateral inhibition in a single ommatidium (essentially a series of dynamic linear filters). Another graduate student, G. David Lange, collaborated with Hartline and Ratliff on a more extended study of the dynamics of the horseshoe crab’s eye (67–69). Their quantitative account of the inhibitory interactions was expressed as a computer program, an impulse-by-impulse calculation of self and lateral inhibition on responses to changing levels of illumination. (The program was equivalent to the integral form where individual impulses are expressed as delta functions.) At about this time another graduate student, Robert M. Shapley, returned to the quantitative analysis of inter-impulse variability in the discharge of impulse in the optic nerve of *Limulus*. Shapley extended the previous analyses to include the indirect effects of lateral inhibition, as well as the direct effects of light, on the ‘noise’ in the discharge of a particular receptor unit. Again the treatment of the system as a concatenation of linear filters led directly to the use of Fourier analysis of the fluctuations in both theory and experiment.

The symmetry of responses of the *Limulus* eye to equal increments and decrements (62) had attracted the attention of Bruce W. Knight, Jr, a physicist and applied mathematician, who had 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. Early experimental and theoretical results in the temporal frequency domain were very successful. 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, and successful predictions of responses to a variety of stimuli were made. These experiments by Bruce Knight, Jun-ichi Toyoda and Fred Dodge showed the appropriateness of treating the \textit{Limulus} eye as a system of linear transducers over a wide range of experimental conditions.

Some very interesting and (to most people) completely unexpected consequences of lateral inhibition were the ‘tuning and amplification’ observed in the study of the dynamics of the retina of \textit{Limulus} (70). The effect of simple delays of inhibition on ‘tuning’ and ‘gain control’ is now recognized as a general principle, probably common to practically all neural networks.

All of this theoretical and experimental work culminated in a study entitled ‘Fourier analysis of dynamics of excitation and inhibition in the eye of the \textit{Limulus}: amplitude, phase and distance’ (78). This research was Hartline’s final direct contribution to the quantitative analysis of the dynamics of the interaction of excitation and inhibition in the eye of \textit{Limulus}. Further extension of the work from the temporal frequency domain to the spatial frequency domain required several technical advances, however, to which Hartline continued to make important contributions with the aid of instrument makers Nils Jernberg and Carl Tiden. One of these advances was the development of fibre optics devices and special manipulators for illuminating the hemispherical eye of \textit{Limulus}, which was very difficult to illuminate over its full extent with conventional planar-image lens systems. This advance was initiated by Hartline’s graduate student R. B. Barlow, Jr, in his thesis research on the spatial characteristics of the inhibitory field. The subsequent development of a special fibre optics taper by Walter P. Siegmund, of the American Optical Corporation, made it possible to focus a plane image sharply on the curved surface of the \textit{Limulus} eye. With this device and with new electronic controls for visual displays (Milkman, Shapley & Schick 1978) the \textit{Limulus} retina could be completely characterized in both the spatial and temporal domain by means of a spatiotemporal transfer function (Brodie, Knight & Ratliff 1978). It was then possible to calculate the response of the whole retina to an arbitrary stimulus varying in both space and time. Hartline was very pleased with these results, because they proved the generality and adequacy of a logical extension of the original, much simpler, Hartline–Ratliff equations (49) for the steady state.

Hartline did no further work on the vertebrate retina after he came to Rockefeller in 1953. He did continue his interest in the vertebrate visual system, however, and encouraged others in the laboratory to do research in that area. Gradually, techniques of stimulus control and data analysis, derived from the study of linear interactions in the eye of \textit{Limulus}, were applied to the more complex nonlinear visual systems of higher vertebrates. As in times past, a common feature of all the recent work in the
laboratory has been an emphasis on lateral interactions. Also, as in times past, recent advances in the laboratory have depended strongly upon the development of new electro-optical means of stimulus control (Milkman et al. 1980) and upon the use of the most appropriate methods of applied mathematics (Victor et al. 1977). For example, using newly developed methods of optical displays, coupled with special techniques of nonlinear analysis, Shapley & Victor (1979) have shown that in the cat retina small nonlinear subunits that excite the so-called Y cells can exert a strong influence on the 'gain' or amplification of a neighbouring X cell with a simple linear receptive field. Thus, even at the retinal level, there is interaction between, as well as within, neural networks. These complex interactions are reminiscent of the much simpler lateral interactions first studied by Hartline in the 1930s and 1940s. Indeed, many of the new lines of work in the Hartline–Ratliff laboratory during the past decade are logical extensions of Hartline's original studies and are based upon the same fundamental principle that he expressed so well and so succinctly in his Harvey Lecture (30): 'Individual nerve cells never act independently; it is the integrated action of all the units of the visual system that gives rise to vision.'

The Nobel Prize

In 1967 the Nobel Prize in Physiology or Medicine was awarded jointly to Ragnar Granit (Karolinska Institute), Haldan Keffer Hartline (Rockefeller University) and George Wald (Harvard University) 'for their discoveries concerning the primary physiological and chemical visual processes in the eye'. Hartline was, of course, very pleased and greatly honoured by the worldwide recognition of his work and, by extension, that of his laboratory and of his many close collaborators over the years. He accepted this high honour with his usual grace and humility. In the Foreword to a collection of papers from his laboratory that were assembled nearly ten years later to honour his seventieth birthday (Ratliff 1974), he looked back on his life's work and wrote:

'If there is any merit in republishing a collection of papers extending back over forty years, it lies in exhibiting a short segment of a thread of work that is now woven almost unrecognizably into the fabric of visual science. This thread is spun of many strands, whose origins are easily traced to the beginnings of modern science—the optics of Kepler, the 'animal electricity' of Galvani. The influence of Helmholtz, of course, and of Mach is clear. Adrian's influence is fundamental to this entire study, and Adrian and Bronk's technique and their inspiration and example invited its development. Sherringtonian concepts pervade its later phases basically, spurred by Granit's interpretations. The early retinal electrophysiologists contributed much, but it would be hard to sort out specific influences.
And it is almost as hard to recognize the ideas contributed by one's contemporaries, interacting with one's own. Origins of ideas soon become obscured, just as the ideas developed in these papers will inevitably share the anonymity that soon graces most of the contributions of individual workers as patterns in the fabric of understanding emerge.

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, resulting from 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 labelled senile only adds insult to injury.') The overall result was that Hartline gradually began to lose touch with work in progress by students and collaborators, and a few years after his 'official' retirement at the age of 70, he began to feel almost like an outsider in his own laboratory.

Hartline the laboratory scientist

Hartline was a scientist's scientist: he spent his time working in the laboratory. As far as possible he left the administration of University affairs and, indeed, the administration of his own laboratory, to others. He seldom answered his mail promptly, and he had not one but two files labelled procrastinate, for matters requiring a decision but which he hoped might take care of themselves if left unattended. He was never happier than when he came across an item on his desk for which a deadline or due-date had long since passed. 'Good,' he would say, 'Now we won't have to do anything about that.' Hartline's good sense about what was worth attending to and his infectious sense of humour made his laboratory a delightful place to work.

Hartline never travelled on the 'lecture circuit'. He rarely attended regular professional meetings during his years at Rockefeller, although he did participate in a number of symposia on topics in his own field (to which he was specially invited). Indeed, he seldom gave public lectures except on those rare special occasions when it was impolite or impolitic to refuse. Although Hartline was friendly and charming in public, and well known to and well liked by many, he was in fact a very private person.

Hartline often attended and greatly enjoyed the meetings of the American Philosophical Society 'held in Philadelphia for the promotion of useful knowledge'. Occasionally he attended the meetings of the National Academy of Sciences, but he stayed out of the politics of science altogether. He did serve (somewhat reluctantly) on two major advisory groups. Just before the creation of the National Aeronautics and Space
Biographical Memoirs

Administration, Hartline was one of the group of leading scientists composing the Space Science Board of the National Academy of Sciences—National Research Council and served as chairman of its committee on biological sciences. Hartline also served on the so-called Clemence Committee of the National Academy of Sciences, appointed to evaluate the Condon Report on unidentified flying objects—in Hartline’s words ‘a somewhat sticky and bizarre task’. In later years Hartline served on the Board of the National Society to Prevent Blindness and on the Advisory Panel of Research to Prevent Blindness, Inc.

Hartline was not secretive about work planned or in progress. The Hartline–Ratliff laboratory, as it became known at Rockefeller, was always open. Visitors for a day, a week or a year were always welcome. Neither rank nor experience were prerequisites. Many high-school students and college undergraduates could always be found in the laboratory serving as unpaid volunteers to get started in the field, especially in the summertime. It was not difficult to keep everyone busy; Hartline’s head was always full of new ideas, and his files were full of old but incomplete experiments. Indeed, Hartline often joked that the unpublished research in his files probably equalled or exceeded his published research. Much of the work that was published was only in the form of brief abstracts of projects that were undertaken in an exploratory manner and then put aside for further study later on. ‘Later on’ frequently turned out to be ‘never again’. For example, the study by Wilska & Hartline (29) on the optic lobe of *Limulus* was published as a one-page abstract. It lay dormant for more than a quarter of a century until it was taken up by D. Max Snodderly, Jr, for his thesis research. Important studies by Hartline and Riggs on flicker in the eye of *Limulus* (which laid groundwork for later studies in the laboratory on the dynamics of the eye) were never published (cf. Riggs 1984). Work on quantum fluctuations at threshold in *Limulus* photoreceptors (closely related to the pioneering work on humans by Hecht, Shlaer & Pirenne in 1942) was published only as a one-page abstract (33). The simple fact was that Hartline preferred to do experiments rather than to write about them. Also, Hartline was a perfectionist: for him, experiments were always incomplete and conclusions drawn were always tentative. Furthermore, any gaps remaining were best filled with data rather than hypotheses. ‘The trouble with theories’, he once said, ‘is that after a while one begins to believe them.’

The city and the country

When Hartline accepted a position at Johns Hopkins and the family moved to Maryland, they purchased a house near Hydes, about 20 miles from Baltimore. This country house, which they called Turtlewood, is still the family home. In 1953, when Hartline became a Member of what was then The Rockefeller Institute for Medical Research, he moved to an
apartment in New York City, near the Institute. Mrs Hartline and their three sons Daniel Keffer, Peter Haldan and Frederick Flanders (now all biologists) stayed in Maryland and Hartline went home for long weekends and holidays. The New York apartment was little more than a 'winter camp' for the family in the city. Their 'summer camp' was on the Kraus family place on Old Point just across Frenchman Bay to the northwest of Bar Harbour, Maine.

The Hartlines preferred country life to city life, and neither spent any more time in Manhattan than they had to. Indeed, attractions of the city had little appeal for Hartline. In his thirty or so years in and out of Manhattan, he probably did not go to theatres, museums, concerts, operas, art galleries and the like more than once a year, on average, and then usually in the company of out-of-town visitors and for their entertainment rather than his own. Hartline did, however, greatly enjoy the series of classical music concerts held on the Rockefeller campus, which he attended regularly. An amateur violin player, he loved music and listened regularly to WQXR, the local 'good music' station. He disliked the morning programme 'Piano personalities' intensely, and would not go to a university concert if it were to be a piano solo. Hartline read extensively on American history and was quite knowledgeable about the period of the American Revolution. He kept up with new developments in physics, astronomy and geology and greatly enjoyed long discussions with Bruce W. Knight, Jr, on these topics and on various aspects of applied mathematics.

The last years

Hartline enjoyed good health throughout most of his life. Despite his slight stature and rather frail appearance, he enjoyed outdoor activities even into his old age. Indeed, in his seventies Hartline decided to take a long-postponed trip on a raft down the Colorado River through the Grand Canyon. Unfortunately he was now having some problems with his heart, and his cardiologist recommended against the trip. But Hartline decided that it was now or never. 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 Hartline’s late seventies his chest pains became more frequent and more severe. On 18 March 1983, as Hartline entered his 80th year, he died of a heart attack at the Fallston General Hospital in Maryland. He did not live, as he had long hoped he would, to see the return of Halley’s comet in 1986.

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

The photograph reproduced was taken in 1966.

**Career and Honours**

**Education**

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<tr>
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<td>1927</td>
<td>M.D., Johns Hopkins University</td>
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<td>1927-29</td>
<td>National Research Council Fellow at Johns Hopkins University</td>
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<td>1929-31</td>
<td>Travelling Research Scholar in physics at Universities of Leipzig and Munich</td>
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**Profession**

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<td>1941-43</td>
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<td>1936-40</td>
<td>Associate Professor, Cornell University</td>
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<td>1931-36</td>
<td>Fellow, Johnson Foundation, University of Pennsylvania</td>
</tr>
<tr>
<td>1974-</td>
<td>Professor Emeritus, The Rockefeller University</td>
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<td>1972-74</td>
<td>Detlev W. Bronk Professor, The Rockefeller University</td>
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<td>1972</td>
<td>George C. Eccles Professor, University of Utah</td>
</tr>
<tr>
<td>1953-72</td>
<td>Professor, The Rockefeller University</td>
</tr>
<tr>
<td>1949-53</td>
<td>Professor and Chairman of Department of Biophysics, Johns Hopkins University</td>
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<tr>
<td>1948-49</td>
<td>Professor, Eldridge Johnson Research Foundation, University of Pennsylvania</td>
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**Honorary degrees**

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<th>Year</th>
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<tr>
<td>1959</td>
<td>Sc.D.(hon.), Lafayette College</td>
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<tr>
<td>1969</td>
<td>LL.D.(hon.), Johns Hopkins University</td>
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<tr>
<td>1971</td>
<td>Sc.D.(hon.), University of Pennsylvania</td>
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<tr>
<td>1972</td>
<td>Doctor of Medicine (hon.), Albert Ludwig University Freiburg im Breisgau</td>
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<tr>
<td>1976</td>
<td>Sc.D.(hon.), The Rockefeller University</td>
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<tr>
<td>1978</td>
<td>Sc.D.(hon.), University of Maryland and Baltimore County</td>
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<td>1979</td>
<td>Sc.D.(hon.), Syracuse University</td>
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**Awards**

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<tr>
<td>1927</td>
<td>William H. Howell Award in Physiology</td>
</tr>
<tr>
<td>1948</td>
<td>The Society of Experimental Psychologists’ Howard Crosby Warren Medal</td>
</tr>
<tr>
<td>1964</td>
<td>The Albert A. Michelson Award from the Case Institute of Technology (now known as Case Western Reserve University)</td>
</tr>
<tr>
<td>1967</td>
<td>The Nobel Prize in Physiology or Medicine</td>
</tr>
<tr>
<td>1969</td>
<td>The Lighthouse Award for Distinguished Service</td>
</tr>
<tr>
<td>1980</td>
<td>Honorary Member of the Optical Society of America</td>
</tr>
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</table>
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(3) The electrical response to illumination of the eye in intact animals, including the human subject; and in decerebrate preparations. Am. J. Physiol. 73, 600–612.
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(20) 1937 The discharge of impulses in the optic nerve fibers of the eye of Pecten irradians. (Abstract.) Am. J. Physiol. 119, 328.
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(38) 1953 (With F. J. Marhold) The frequency of seeing at low illumination. P. 800.


(41) 1956 (With F. J. Marhold) Fields of inhibitory influence of single receptor units in the lateral eye of Limulus. Science, Wash. 126, 1234.


Haldan Keffer Hartline

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