H. KEFFER HARTLINE

Visual receptors and retinal interaction

Nobel Lecture, December 12, 1967

The neuron is the functional as well as the structural unit of the nervous system. Neurophysiology received an impetus of far-reaching effect in the 1920's, when Adrian and his colleagues developed and exploited methods for recording the activity of single neurons and sensory receptors. Adrian and Bronk were the first to analyze motor function by recording the activity of single fibers dissected from a nerve trunk and Adrian and Zotterman the first to elucidate properties of single sensory receptors[1]. These studies laid the foundations for the unitary analysis of nervous function.

My early interest in vision was spurred by another contribution from Adrian's laboratory: his study, with R. Matthews, of the massed discharge of nerve impulses in the eel's optic nerve[2]. I aspired to the obvious extension of this study: application of unitary analysis to the receptors and neurons of the visual system.

Oscillograms of the action potentials in a single nerve fiber are now commonplace. The three shown in Fig. 1 are from an optic nerve fiber whose retinal receptor was stimulated by light, the relative values of which are given at the left of each record. One of the earliest results of unitary analysis was to show that higher intensities are signaled by higher frequencies of discharge of uniform nerve impulses.

In 1931, when C. H. Graham and I sought to apply to an optic nerve the technique developed by Adrian and Bronk for isolating a single fiber, we made a fortunate choice of experimental animal[3]. The xiphosuran arachnoid, *Limulus polyphemus*, commonly called "horseshoe crab", abounds on the eastern coast of North America[4]. These "living fossils" have lateral compound eyes that are coarsely faceted and connected to the brain by long optic nerves. The optic nerve in the adults can be frayed into thin bundles which are easy to split until just one active fiber remains. The records in Fig. 1 were obtained from such a preparation.

The sensory structures in the eye of *Limulus* from which the optic nerve fibers arise are clusters ofreceptor cells, arranged radially around the dendritic process of a bipolar neuron (eccentric cell)[5]. Each cluster lies behind its corneal

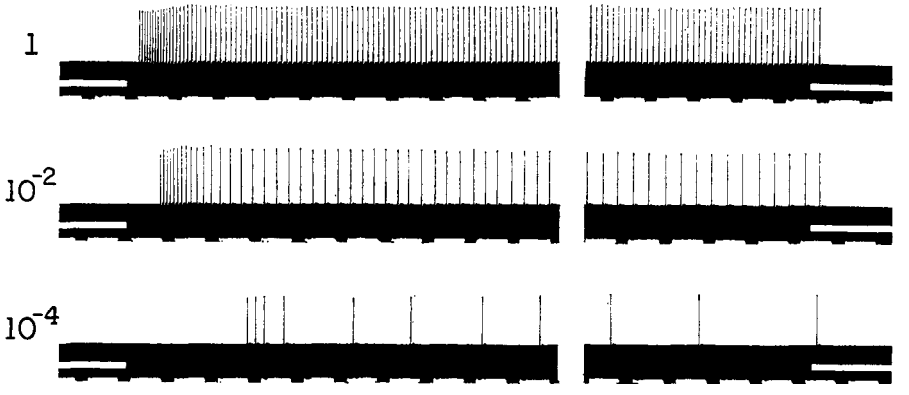

Fig. 1. Oscillograms of the electrical activity (discharge of nerve impulses) in a single optic nerve, from the lateral eye of *Limulus,* stimulated by illumination of the facet associated with its receptor. Relative values of light intensity given at left. Time marked in 1/5 sec in trace at bottom of each record; signal marking period of steady illumination blackens out the white band just above time marks. (After Hartline[11])

facet and crystalline cone, which give it its own, small visual field (Fig. 2). Each such ommatidium, though not as simple as I once thought, seems to act as a functional receptor unit. Restriction of the stimulating light to one facet elicits discharge in one fiber - the axon of the bipolar neuron whose dendritic process is in intimate contact with the light-sensitive rhabdom that is borne by the encircling retinular cells.

Many of the properties of vision that are familiar to us from behavioral experiments on animals, from psychophysical experiments with human subjects, and indeed from our own everyday visual experience find parallels in the responses of the photoreceptor units in the *Limulus* eye. Reciprocity between intensity and duration of short flashes in stimulating single receptors, the spectral sensitivity of individual receptors, the course of light and dark adaption, and threshold uncertainty as related to quantum fluctuations are examples of such parallels[6].

Two well-known and very elementary features of receptor responses appear in the records shown in Fig.1. The first is that the stimulation intensities cover a wide range; the corresponding steady frequencies ofimpulse discharge cover only a modest range. Intensity information is considerably compressed in being translated into discharge frequency of the nerve fiber. Our vision, and that of most animals, functions well over an enormous range of ambient light intensity; we may surmise that this capability results in a large measure from the inherent properties of the individual receptors.

The second feature to note in Fig. 1 is the high rate of impulse discharge which signals the onset of illumination. After this initial transient the familiar process of sensory adaption sets in to reduce the discharge to a more modest rate. By virtue of this property, a receptor can signal even small changes in intensity while still retaining its ability to function over a wide range of ambient illumination.

This is further illustrated in Fig. 3, which shows the response of a *Limulus* receptor to an increment in light intensity imposed shortly after adaptation to a stronger background light had taken place. This oscillogram was obtained by means of a micropipette electrode thrust into the eccentric cell of the ommatidium[7]. It shows both the slow depolarization of the cell - the "generator potential", to use Granit's term[8] - and the train of superimposed nerve impulse spikes that are generated in the axon by the local currents from the depolarized cell[9]. Both features of the response-the graded depolarization and the frequency of impulse discharge - display exaggerated transients at the onset and cessation of the incremented step in light intensity. The basic mechanism of the receptor is one that emphasizes change.

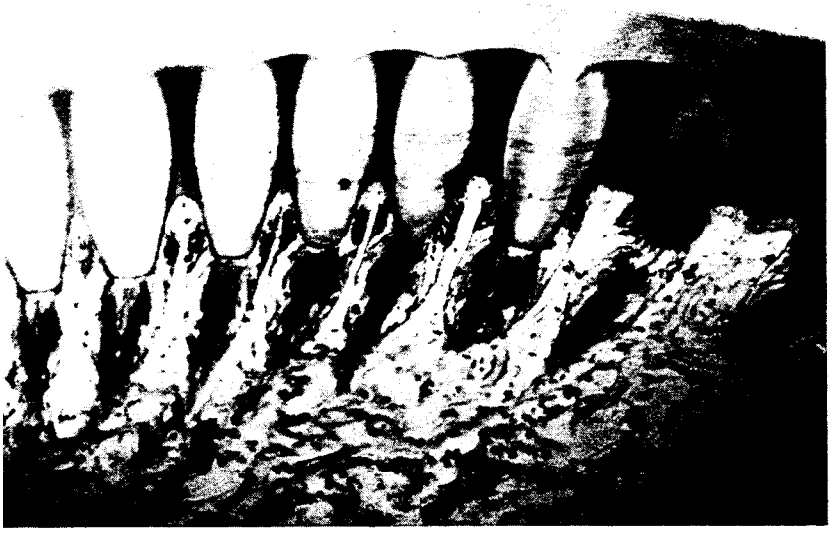

Fig. 2. Section perpendicular to cornea through a portion (approx. 1.5 mm) of the lateral (compound) eye of *Limulus,* showing 7 ommatidia: the cornea is above; the crystalline cones project downward to the sensory portions of the ommatidia, which have been partially bleached to reveal the retinulae. Fibers of optic nerve and plexus show faintly below. Micrograph by W. H. Miller (*cf.* ref. 7).

The response patterns of Figs. 1 and 3 are not faithful representations of the light stimuli, which were simple steps ofintensity. To some extent, the receptor mechanism distorted the sensory information. This illustrates the broad principle established by the earliest studies of single sensory endings: receptors, by virtue of their inherent properties, operate upon the information they collect from their surroundings to favor certain features of it. The processing of sensory data begins in the receptors.

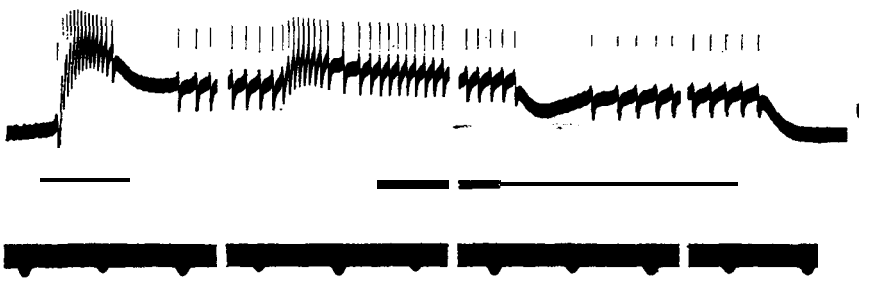

Fig. 3. Oscillogram of the electrical activity of a receptor unit in the lateral eye of *Limulus,* recorded by a pipette microelectrode in the eccentric cell of an ommatidium, showing "generator potential" and superimposed nerve impulse "spikes". Stimulation by light signalled by black lines above the (1/5 sec) time marks. Light shone steadily, starting near the beginning of the record; in the middle of the record the light was incremented by approx. 50%, marked by second black lime. Calibration deflection at right = 10 mV. Baseline at beginning of record *ca.* 50 mVnegative with respect to outside cell.

Successful recording from single fibers in the optic nerve of *Limulus* emboldened me to apply the same methods to the vertebrate eye. The optic nerve of a vertebrate is very different from that of *Limulus;* dissection of bundles of fibers from it seemed a quite hopeless task. Moreover, this was before Granit and his colleagues developed micro-electrodes for retinal recording. But Nature has provided a ready-made dissection of the opticnerve, spreading it in a thin layer over the vitreous surface of the retina. Picking up small bundles from the exposed retina of a frog's eye was easy; splitting one of them until only a single active fiber remained was not too difficult.

The findings were unexpected: different optic nerve fibers responded to light in different ways (Fig. 4). Some fibers gave discharges much like those in *Limulus,* some responded vigorously at onset and again at cessation of illumination or when slight changes in intensity were made, and were otherwise silent. Still other fibers gave no response during illumination, firing a vigorous and prolonged train of impulses only when light was dimmed.

Fig.4. Oscillograms of the electrical activity of single optic serve fibers, dissected from the vitreous surface of the retina of a frog's eye. Recording as in Fig.1 (After Hartline[10], 1938)

Further study of these responses of single retinal ganglion cells revealed interesting properties. Slight movements of a small spot or shadow elicited responses in some optic nerve fibers if they were within the square millimeter or so of retinal area that is the receptive field of the fiber's ganglion cell (Fig. 5). Convergence of excitatory and inhibitory influences was found to take

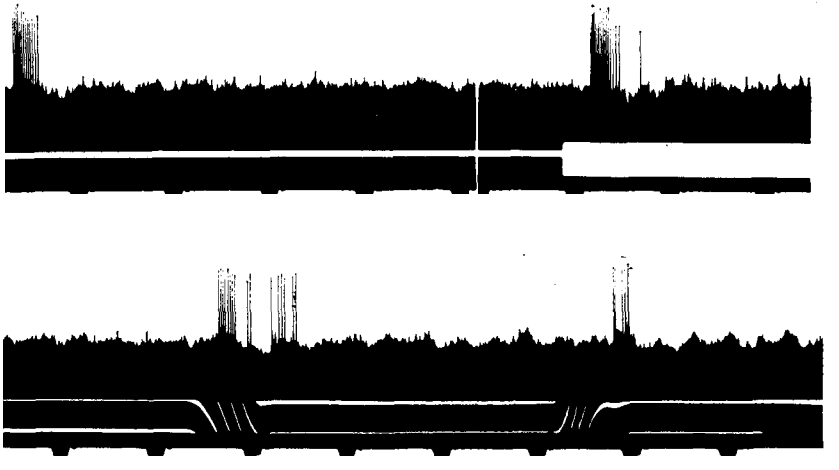

Fig. 5. Discharge of impulses in a single optic nerve fiber in the frog's retina in response to movements of a spot of light on the retina. Lower record: a small spot (50μ diam.) was moved twice within the fiber's receptive field, about 30μ each time, as signalled by the white lines crossing the blackened band just above the 1/5 sec time marks. Upper record: same fiber responded only to light going on and off, when no movement of the spot took place. (Steady light signalled by blackening of band above time marks.) (After Hartline[10], 1940)

place within the receptive fields of fibers, and summation of excitation was demonstrated. Receptive fields of fibers were shown to overlap extensively; a given small area of the retina is held in common within the confines of many receptive fields, belonging to fibers of greatly diverse response characteristics[10,11]. Thus there is interaction in the retina, as Granit had shown, and as Adrian and Matthews had demonstrated earlier. It is evident that a great deal of elaborate and sophisticated "data processing" takes place in the thin layer of nervous tissue that is the retina.

Since those early observations a wealth of new knowledge has been obtained by workers in many laboratories. From studies of the retinas of mammals as well as cold-blooded vertebrates, from recordings of units, for example, in the ganglionic layers in the eyes of crustaceans and insects, and by the use of various patterns of light, moving and stationary and of various colors, new and surprising properties of retinal neurons have been and are constantly being discovered[12]. It is now clear that the retina is even more powerful in the integrative tasks it performs than my early experiments had intimated.

Can we understand how these diverse and complex response patterns, highly specialized for specific tasks, are generated in the retina? Broad Sherringtonian principles can guide us - the interplay of excitatory and inhibitory influences in convergent and divergent pathways, with various spatial distributions, thresholds, time courses[8]. But the application of broad principles to specific cases of such complexity is not easy. It is here that comparative physiology can help. The animal world is rich in its variety of visual systems, built in different ways and with different degrees of complexity, although all governed, we are confident, by the same universal, basic principles.

In this, *Limulus* has again proved to be a valuable experimental animal. It, too, has a retina, although a much simpler one than those of the vertebrates or higher invertebrates. Interaction in the *Limulus* retina is complex enough to be interesting, yet simple enough to be analyzed with relative ease.

When I first worked with *Limulus,* I thought that the receptor units acted independently of one another. But I soon noticed that extraneous lights in the laboratory, rather than increasing the rate of discharge of impulses from a receptor, often caused a decrease in its activity. Neighboring ommatidia, viewing the extraneous room lights more directly than the receptor on which I was working, could inhibit that receptor quite markedly[13]. With my colleagues H.G. Wagner and F. Ratliff, I undertook the investigation of this inhibitory process[14].

An experiment illustrating inhibition in the *Limulus* retina is shown in Fig.

Fig. 6. Inhibition in the eye of *Limulus*. The train of impulses from a receptor, elicited by steady illumination, was slowed by illumination of a group of 20-30 neighboring receptors in an annular region surrounding it (signalled by blackening of the white band above the 1/5 sec time marks). (From Hartline *et al.* [7])

6. Illumination of a small group ofommatida (20-30) in the neighborhood of an arbitrarily chosen, steadily illuminated test receptor caused a substantial slowing of its discharge. After the light on the neighboring receptors was turned off, there was prompt recovery, followed by a small but distinct overshoot - a post-inhibitory rebound.

The basic properties of the inhibition in the *Limulus* eye are quickly summarized. The brighter the light on neighboring receptors, the greater is the slowing of the discharge of a receptor being tested. The greater the number of neighboring receptors illuminated, the greater is their effect: there is spatial summation of inhibitory influences. Receptors close to a given receptor inhibit it more strongly, on the average, than do distant ones. Each ommatidium in the eye has its surrounding field of inhibition. The influences are mutual: each receptor, being a neighbor of its neighbors, inhibits and is inhibited by those neighbors. Interaction in the *Limulus* eye, as far as is yet known, is purely inhibitory. Ratliff and I, with many colleagues in our laboratory, have been engaged over the past decade and a half in the analysis of this processis.

The anatomical basis for the inhibitory influences that are exerted mutually in the *Limulus* eye is a network of nerve fibers - a true retina-lying just behind the layer of ommatidia, and interconnecting them (Fig. 7). It is over this plexus of fiber bundles that run laterally from ommatidium to ommatidium that the inhibitory influences pass: cut these bundles, and the inhibition vanishes. Fibers in these bundles arise as branches of the sensory axons from the ommatidia that traverse the plexus on their way to become the optic nerve; scattered profusely through the plexus are clumps of neuropil, rich in synaptic regions and packed with synaptic vesicles[16].

Electrophysiological evidence confirms the synaptic nature of the inhibitory interaction in the *Limulus* retina. Hyperpolarizing potentials are observed by intracellular recording in the eccentric cell of an ommatidium, coincident with inhibition of the receptor[16,17]. Analysis of these and the accompanying conductance changes indicates that these are inhibitory post-synaptic potentials like those met with elsewhere in nervous systems[18,19].

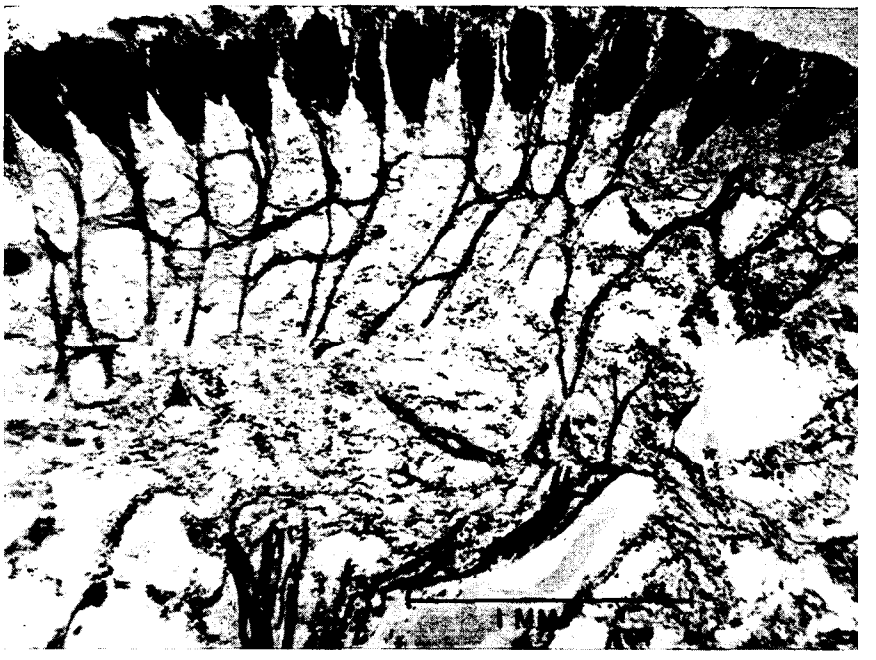

Fig.7. Section, perpendicular to the cornea, through part of a lateral eye of an adult *Limulus.* At the top of the figure are shown the heavily pigmented sensory portions of the ommatidia. Bundles of nerve fibers are shown emerging from the ommatidia, with the plexus of interconnecting fibers, and a portion of the optic nerve below. Samuel's silver stain. The chitinous cornea and crystalline cones that appear in Fig. 2 were stripped away prior to fixation. Prepared by W.H. Miller. (From Hartline *et al.* [14])

Before proceeding to a detailed consideration of inhibitory interaction we may ask what roles it might play in vision. One role is enhancement of contrast. Strongly excited receptor elements in brightly lighted regions of the retinal image exert a stronger inhibition on receptors in more dimly lighted regions than the latter exert on the former. Thus the disparity in the actions of the receptors is increased, and contrast enhanced. Since inhibition is stronger between close neighbors than between widely separated ones, steep intensity gradients in the retinal image-edges and contours-will be accentuated by contrast.

"Simultaneous contrast", "border contrast", and the like are well known in visual physiology[20]. A century ago Ernst Mach correctly ascribed them to inhibitory interaction in the visual system. Most of us have noted the fluted appearance of uniform steps in intensity, as those in shadows cast by multiple light sources as, for example, a cluster of candles. The Mach bands flanking a

simple gradient are also familiar "illusions" in which contrast is overemphasized by the use of a special pattern of light. Such "distortions" of sensory information ordinarily serve a useful function to accent and "crispen" important features of the visual scene and to sharpen spatial resolution. It is possible to demonstrate analogous distortions of spatial patterns of optic nerve activity in *Limulus,* when its eye views similar patterns of light (Fig. 8). These phenomena are all the result of inhibitory interaction in the visual system.

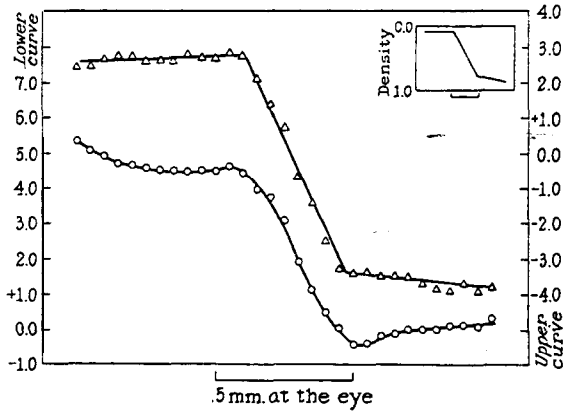

Fig. 8. Contrast phenomena, analogous to Mach bands, demonstrated by patterns of optic nerve fiber activity in the eye *of Limulus.* The discharge of impulses from a receptor was recorded as the eye was caused to scan slowly a pattern of illumination containing a simple gradient of intensity shown in the inset, upper right. When all the receptors were masked except the one from which activity was being recorded, a faithful representation of the actual physical distribution of light was obtained (upper graph, triangles). With the mask removed, so that all the receptors viewed the pattern, the lower graph (circles) was obtained, with a maximum and a minimum where Mach bands are seen by a human observer viewing the same pattern. (From Ratliff and Hartline[21])

Inhibitory interaction in the retina is a simple neural mechanism that operates on the sensory data supplied by the receptors, modifying spatial features just as the inherent mechanism of the receptors modifies temporal characteristics. Both of these "data processing" operations are integrative functions taking place in the earliest phases of the visual process.

Enhancement of contrast is but one consequence of inhibitory interaction. Inhibition plays a pervading and subtle role, in vision as elsewhere in nervous function. To the basic excitation furnished by light, retinal inhibition adds a molding influence, increasing temporal and spatial resolution and supplying a mechanism for increased versatility of response. The opportunity to analyze

this process in a retina that is much simpler than those of higher animals should prove helpful in understanding the more complex functions of more complex visual systems.

We begin this analysis[22] with an experiment showing the interaction of just two ommatidia (Fig. 9). Illuminated together, each of these receptor units discharged impulses at a lower rate than when it was illuminated by itself For each illuminated alone, its frequency of discharge measures its excitation, *e,* at the particular intensity being used on it. When both are illuminated together, at the same intensities, we will call their responses *r.* Analysis shows that the lowering of frequency of each, *e - r,* is to be related quantitatively to the concurrent frequency, r, of the other. It is the output of a receptor unit - its rate of discharge of nerve impulses that determines how much inhibition

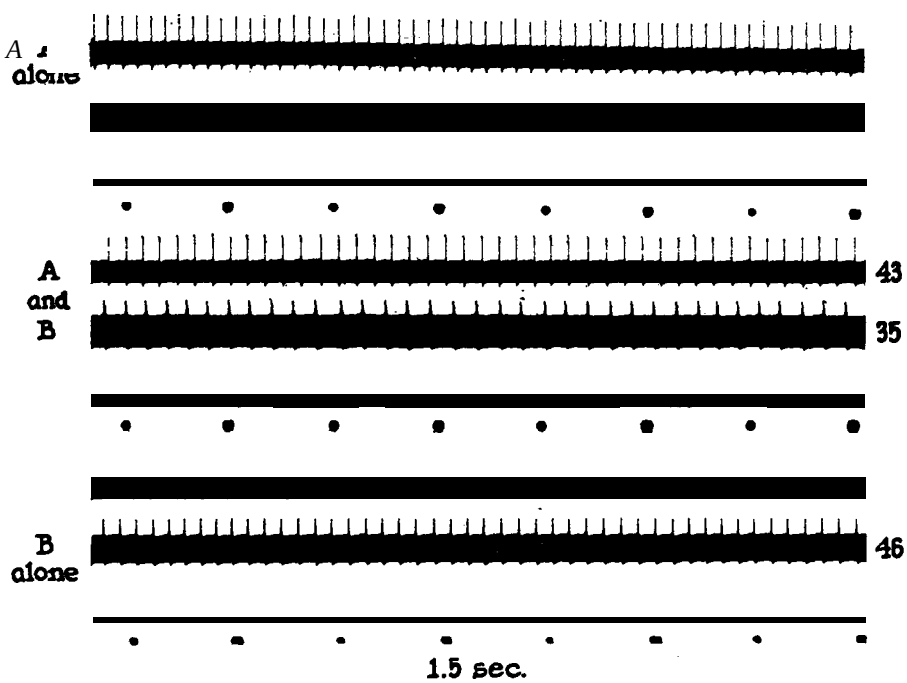

Fig. 9. Mutual inhibition of receptor units in the eye of *Limulus*. Nerve impulses recorc simultaneously from two optic nerve fibers, showing the discharges when their respective ommatidia were steadily illuminated, separately and together. The numbers on the right give, for the respective cases, the total number of impulses discharged in the period of 1.5 sec shown. The inhibitory effect on A, 53-43, is to be associated with the concurrent frequency of B, 35; likewise the effect on B, 46-35, is to be associated with the concurrent frequency of A, 43. Time in 1/5 sec. (From Hartline and Ratliff[22])

it exerts on other units. A receptor that inhibits another receptor affects the very output that in turn inhibits it. Thus the inhibitory interaction is recurrent in its operation, as may be visualized schematically, for just two elements, by Fig.10. Mathematically, the mutual interaction of two units can be expressed by a pair of simultaneous equations. Measurements of the response of two interacting receptor units, stimulated by various intensities of light in various combinations, permit the construction of two graphs shown in Fig. II, in which the lowering of frequency of each, $e - r$, is plotted against the concurrent response, r of the other. Evidently the two simultaneous equations that describe the relationship between the responses of the two interacting receptors are piecewise linear. Considered over the entire range, each relationship is highly non-linear as a result of the fairly abrupt threshold, r^0, below which the steady firing of a receptor exerts no inhibition on its neighbors.

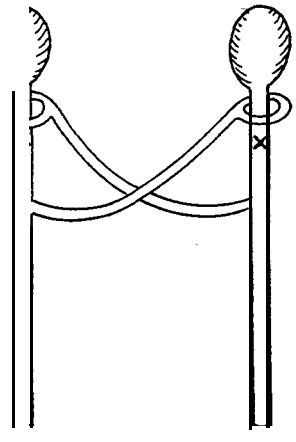

Fig.10. Schematic representation of the recurrent nature of mutual inhibition of two receptor units. Excitation of each generates trains of impulses which originate near the point of emergence of the axon from the cell body, marked x. Influences pass back up the recurrent branches of each to exert inhibition on the other at synapses at or near the points emergence. (From Ratliff *et al.* [17])

Above this threshold, however, a linear relation holds to a fair degree of approximation. The slope of each graph, K, is the inhibitory coefficient measuring the strength of the influence of each element, respectively, on the other.

To describe the interaction of more than two elements, more equations are required. For a group of n interacting receptor units a set of n simultaneous equations, piecewise linear, must be written, and in the equation for each

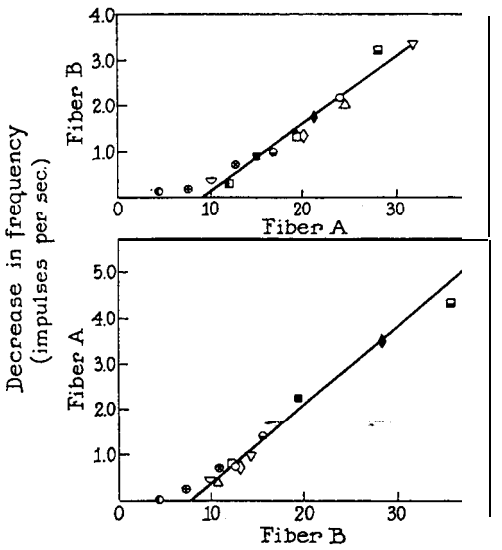

Fig.11. Mutual inhibition of two receptor units in the eye of *Limulus*. In each graph, the magnitude of the inhibitory action (decrease in frequency of impulse discharge) exerted on one of the ommatidia is plotted (ordinate) as a function of the concurrent frequency of the other (abscissa), as explained in the legend of Fig. 9. The different pairs of points (identified by the same symbols in the two graphs) were obtained by using various intensities of illumination on the two ommatidia, in various combinations. (From Hartline and Ratliff[22])

unit inhibitory terms must be introduced and summed to express the inhibition on that particular unit by all of the units that act upon it:

$$r_p = e_p - \sum_{j=1}^{n} K_{p,j}(r_j - r^0_{p,j}) \qquad p = 1, 2, \cdots n$$

In this set of equations, r_p is the response of the p^{th} receptor, which if free of inhibition would have discharged impulses at a rate e_p, but which is subjected to the summed inhibitory influences expressed by the linear terms on the right. In each term Kp,j is the inhibitory coefficient measuring the action of the j^{th} receptor on the p^{th}; $r^0_{p,j}$ is the associated threshold of that action[23].

In the eye, receptors are deployed spatially, in a mosaic, and the strength of their interaction, as already noted, depends on their separation. In general the coefficients K decrease and the thresholds r^0 increase with increasing separation of interacting ommatidia in the eye. The spatial distribution of values of the coeffkients in the inhibitory field surrounding a small group of receptors

has recently been mapped in detail by R. Barlow[24]. Such maps will be indispensable in the analysis of the spatial properties of retinal interaction.

The set of simultaneous equations written above provides a succinct and useful description of steady state inhibitory interaction in the retina of *Limulus.* Quantitative measurements of the activity of interacting receptors and groups of receptors, in various configurations, are satisfactorily accounted for[17]. With measured or postulated inhibitory fields, spatial patterns such as Mach bands are successfully represented as. Ratliff's recent book treats this subject in detail[20]. Von Békésy, using mathematically equivalent formulations to represent inhibitory interaction, has discussed in his recent book[26] the applications to other sensory systems.

Up to this point we have restricted our discussion of inhibitory interaction to the steady state of receptor activity, after all the mutual interactions have come into balance. Whenever, as in the natural world, changes occur in the patterns of light and shade on the retinal mosaic, receptor transients occur, new distributions of excitation are established, and readjustments of the inhibitory interactions are mediated over the retinal network. The interplay of excitation and inhibition is a dynamic process.

Vision itself is a dynamic process. There is little in the world that stands still, at least not as imaged in our retinas, for our eyes are always moving. The visual system is almost exclusively organized to detect change and motion. How can we explain this? How are we to understand, for example, the exquisite sensitivity of some of the frog's retinal fibers to slight movements of the shadow of a fine wire across their receptive fields? Or, what mechanisms can explain the responses that are so highly specific to certain features of the moving pattern, such as curvature of a boundary, size of an object, direction of its motion, etc., as Lettvin and his colleagues[27], and others, report? Study of visual dynamics in a retina as simple as that of *Limulus* can hardly solve such problems, but it may suggest principles that can be applied toward their solution[28].

If responses are recorded from representative receptors in two interacting groups in a *Limulus* eye, and one group subjected to a small increment in intensity, the other, steadily illuminated, will be disturbed only by the inhibitory influences exerted by the first[29].

Experiments of this kind furnish good examples of dynamic responses that might be encountered in nature. However, they are not suited to quantitative analysis, because the time courses of photoreceptor discharges are difficult to control and those features that are contributed solely by the dynamic proper-

ties of the inhibitory interaction are hard to distinguish. Fortunately, lateral inhibition of a receptor unit can be produced artificially by electrical stimulation of the optic nerve fibers from the receptors' neighbors, as Tomita first showed[30]. This affords an exact control of temporal factors that is not possible when the neighbors are excited naturally by light.

By this method, sinusoidally modulated inhibition can be exerted on a receptor, and if the influences are above all thresholds, linear systems-analysis can be applied[31]. Alternatively, abrupt stepwise increments of inhibition can be generated artificially to excite transients of inhibitory systems. Since the latencies and transients of the photic mechanism are thereby avoided, the dynamics of the inhibition itself are revealed (Fig. 12). Inhibition is then seen to set in after an appreciable delay of its-own, and often, though not always; with a transient undershoot at the beginning. After the cessation ofinhibition, no matter how it is produced, the post-inhibitory rebound we have already noted always occurs; it is a true <off> response[33].

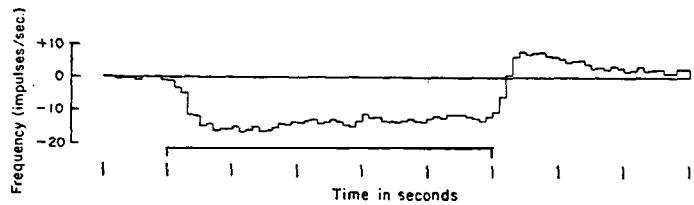

Fig.12. Inhibition of a steadily illuminated receptor, elicited artificially by electrical shocks applied to optic nerve fibers from neighboring receptors to generate a train of antidromic volleys of impulses at constant frequency. Frequency of discharge of impulses from the receptor during an experimental run of 9 sec that included the 5 sec period of inhibition (signalled by step at bottom) is plotted as ordinate (vs. time as abscissa) after subtracting the frequency of discharge during a "control" run taken over a comparable period, but with no inhibition. The ordinates are given as impulses per second above or below control. Experiment by Lange[32].

The delayed onset of lateral inhibition as a simple consequence, which appears when a large area of the receptor mosaic is suddenly illuminated (Fig. 13). The first part of the strong <on> transient of each receptor escapes the action of lateral inhibition from its neighbors. After the delay, however, mutual inhibition quickly sets in, sometimes suppressing the discharge for a fraction of a second, before the steady discharge is established, often withminor oscillations, as the receptor adapts and as mutual interactions come into balance[16]. This "crispening" of the <on> response is an augmentation of the sensory adaptation that is an inherent property of each individual receptor.

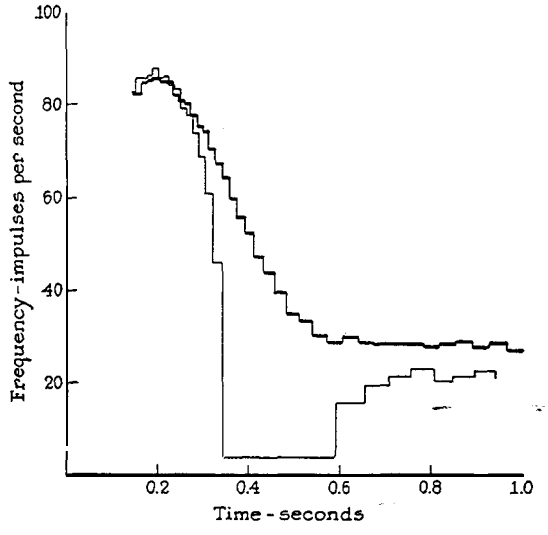

Fig. 13. "Crispening" of the <on> transient of the discharge of a receptor unit by the inclusion of neighboring receptors in the area illuminated. The upper, heavy curve gives the frequency of discharge of a "test" receptor when it was illuminated alone. The lower curve gives the frequency of discharge of the same receptor when the area of illumination (same intensity as before) was enlarged to include neighboring receptors; the time delay of their inhibitory action on test receptor was long enough that the initial peak of the discharge was unaffected, only the subsequent discharge being reduced to thesteady level that reflected the steady state interaction within the entire group. (From Hartline *et al.* [16])

Related to this is the emphasis a short delay in the development of lateral inhibition can give to light fluctuations of a certain frequency occurring over a large retinal area in which there is strong mutual interaction. When the frequency of the fluctuation is such that a minimum of excitation occurs just as the delayed inhibition from the previous maximum comes to its full value, the net fluctuation of the response may actually be amplified, compared to what it would have been had the area been small, with no large numbers of receptors to supply mutual inhibition. The eye of *Limulus* shows such an amplification of response, at about 3 cycles per sec, to a sinusoidally modulated light shining on a large area?[34].

Before we can understand fully the dynamics of inhibitory interaction, we must consider a new feature of the inhibitory process in the *Limulus* eye : the inhibition of a receptor unit by its own discharge. This was first analyzed by Stevens[35] and has recently been studied by Purple and Dodge[36]. They present evidence that this "self-inhibition" may be a synaptic process like lateral inhibition: following each impulse discharged by an ommatidium, a hyperpo-

larizing potential appears. Whatever the mechanism underlying it, self-inhibition forms a substantial component of the adaptation process in the *Limulus* receptor, and by tending to oppose any change in the discharge rate of a receptor unit, has a strong influence on the dynamics of receptor action and interaction.

The rise of inhibition, as successive impulses contribute their additive effects, and its decay, resulting presumably from removal or inactivation of inhibitory transmitter, determine the form of the transients exhibited by the interacting system as it adjusts to changing influences. When lateral inhibition is suddenly applied and builds up on a receptor unit, so that its discharge rate drops, its self-inhibition subsides to a new equilibrium, opposing the full effects of the lateral influence. Lateral-inhibition has an inherently shorter time constant than self-inhibition, hence the transient in the discharge of a receptor usually is an undershoot when lateral inhibition increases, and a post-inhibitory rebound when it decreases. Non-linearities introduced by the thresholds of lateral inhibition increase the delay in the onset of the inhibition, diminish the undershoot and augment the rebound. Fig. 14 illustrates the two cases, linear and non-linear, by means of a computer simulation, like one devised by Lange[37].

For all of the modifications introduced by inhibitory interaction, patterns of optic nerve activity in *Limulus* remain not too grossly distorted representations of the patterns of light and shade on the receptor mosaic. Although significant integration of sensory data is prominent, the effects are mild, compared to what takes place in more complex retinas. Even in *Limulus,* however, the potentiality for more extreme modifications of optic patterns can be demonstrated. Ratliff and Conrad Mueller[38], by careful adjustments of patterns of light, were able to elicit, from a perfectly normal receptor in *Limulus,* <on-off> and pure <off> responses, shown in Fig. 15. Here, by a contrived interplay of excitation (by light on the receptor) and inhibition (by light on its neighbors), taking advantage of time delays and post-inhibitory rebounds, response patterns simulating some of those observed in the vertebrate retina were "synthesized" What Ratliff and Mueller contrived more or less artificially resembles the dynamic interplay we believe takes place naturally as a result of the complex neural organization in more highly developed retinas and higher visual centers.

The unitary analysis of visual function has yielded substantial knowledge about receptor properties, and about dynamic integrative mechanisms in the retina. In the eye of *Limulus,* the relative simplicity ofretinal interaction facili-

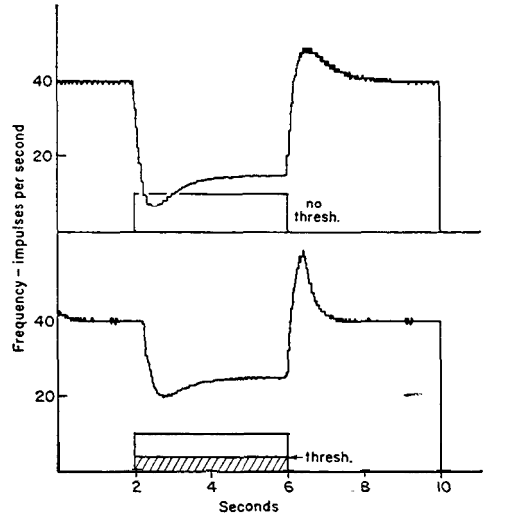

Fig.14. Simulations by means of a computer program of the responses ofa steadily excited receptor subjected to a period of constant inhibition fromneighboring receptors, as in the actual experiment of Fig.12. The decay constants assigned to the self-inhibitory and lateral-inhibitory influences were respectively 1 sec and 0.4 sec. For the upper tracing, a threshold of zero was assigned to the lateral inhibition; for the lower tracing, a threshold was introduced that was unrealistically large, considering the strong lateral influence that was assigned. This served to exaggerate, for illustrative purposes, the asymmetries of onset and cessation of inhibition, especially the "post-inhibitory rebound". *Cf.* ref. 28.

Fig.15. Response of a receptor in the eye of *Limulus* imitating the <on-off> and <off> discharges of vertebrate optic nerve fibers. Obtained by the use of special patterns of stimulation under special conditions of adaptation that suppressed the steady discharge but retained the transient at <on> and <off>, the latter the consequence of post-inhibitory rebound. Steady illumination of receptor signalled by blackening of white band above 1/5 sec time marks. (Record by Ratliff and Mueller, *cf.* ref. 38)

tates its analysis. In more highly organized retinas, a vastly richer integration takes place. Many workers, in many laboratories, are engaged in the study of the diverse and highly specialized responses generated by visual neurons as neural information is processed for transmission to still higher centers. I am confident that the familiar neurophysiological concepts that were needed in the analysis of the simple interaction in the *Limulus* retina will prove useful in elucidating these very complex and very interesting features of visual physiology.

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