

NEURONS IN THE RETINA: ORGANIZATION, INHIBITION AND EXCITATION PROBLEMS¹

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Although the occurrence of excitatory and inhibitory processes in the central nervous system is well known, detailed studies of these events have in the past been largely confined to the spinal cord. The eye, a relatively exposed outpost of the brain, lends itself well to the analysis of many processes which we know to occur in different regions of the central nervous system. "Spontaneous" and rhythmic activity, a discharge pattern ever fluctuating, depending on a variety of circumstances, interaction of different areas, are examples. In this discussion emphasis will be laid on neuronal activity, probably representative of many parts of the central nervous system, rather than on problems of vision. In spite of the eye's complexity, activity in its neural network can be influenced and controlled more easily than in comparably complex portions of the central nervous system. Specific similarities with some aspects of spinal cord activity will be discussed below.

The central and principal unit of investigation has been the receptive field. This, according to Hartline (1940), is defined as the area of the retina which on illumination causes discharges in a single nerve fiber or ganglion cell. Hundreds of cells participate in the activity of each receptive field and the discharge from a ganglion cell, as from a motor horn cell in the cord, is generally the result of numerous excitatory and inhibitory influences. The latter form the principal mechanism which enables the eye to produce an exceedingly variable pattern of discharges. It will be shown that within each receptive field the distribution of inhibitory-excitatory "zones" is such that very small changes in conditions of illumination can cause very striking changes in discharge. Such an organization is apparently required to convey the complex information content from the eye through the optic nerve fibers to the central nervous system.

The exhaustive work of Granit and his collaborators on a variety of eyes, but especially on the Mammalian eye, has brought rapid progress into the field of retinal organization during recent

years (Granit, 1947, 1950). These studies and the basic contributions from Hartline's laboratory (Hartline, 1938, 1940), particularly on *Limulus* and frog, have formed the principal background to the present investigations.

RECENT TECHNIQUES OF RETINAL INVESTIGATION

A short description of some of the experimental procedures seems desirable since the present methods were developed recently (for details see Kuffler, 1953; Talbot and Kuffler, 1953). The aim was to obtain a Mammalian eye which was as normal and intact as possible for prolonged experimentation. Discharges from ganglion cells and nerve fibers were recorded through the unopened eyeball from either decerebrated cats or from animals under Urethane-Dial anesthesia. The arrangement of the set-up is shown in Figure 1. The cat's head was rigidly supported in a holder which could be moved and tilted in any desired direction. Attached to this holder was the micromanipulator arrangement. The eye was fixed to a circular ring by superficial sutures in the sclera. Some surgical procedures in the region surrounding the eyeball were necessary in order to bring the electrode holder into position. The microelectrodes were made of platinum iridium wire 5-15 μ in diameter, the tip made flush with the thin surrounding glass jacket. The micromanipulator held a hypodermic needle (#19 gauge) which penetrated the sclera behind the limbus and just protruded into the vitreous. The glass microelectrode was introduced into the eye through the bore of the hypodermic needle and it traversed the vitreous unprotected and could be advanced until it made contact with the retinal surface at required regions. The natural optical channels of the eye were not disturbed. The principal features of the "Multibeam-Ophthalmoscope" consisted of three light sources. One light (A), on upper left of the instrument in Figure 1, provided background illumination, covering an area of over 4 mm. in diameter on the retina. Its intensity could be adjusted over a wide range for required levels of light adaptation. This source also enabled observation of the fundus through an eye piece (D). Two other light sources, middle

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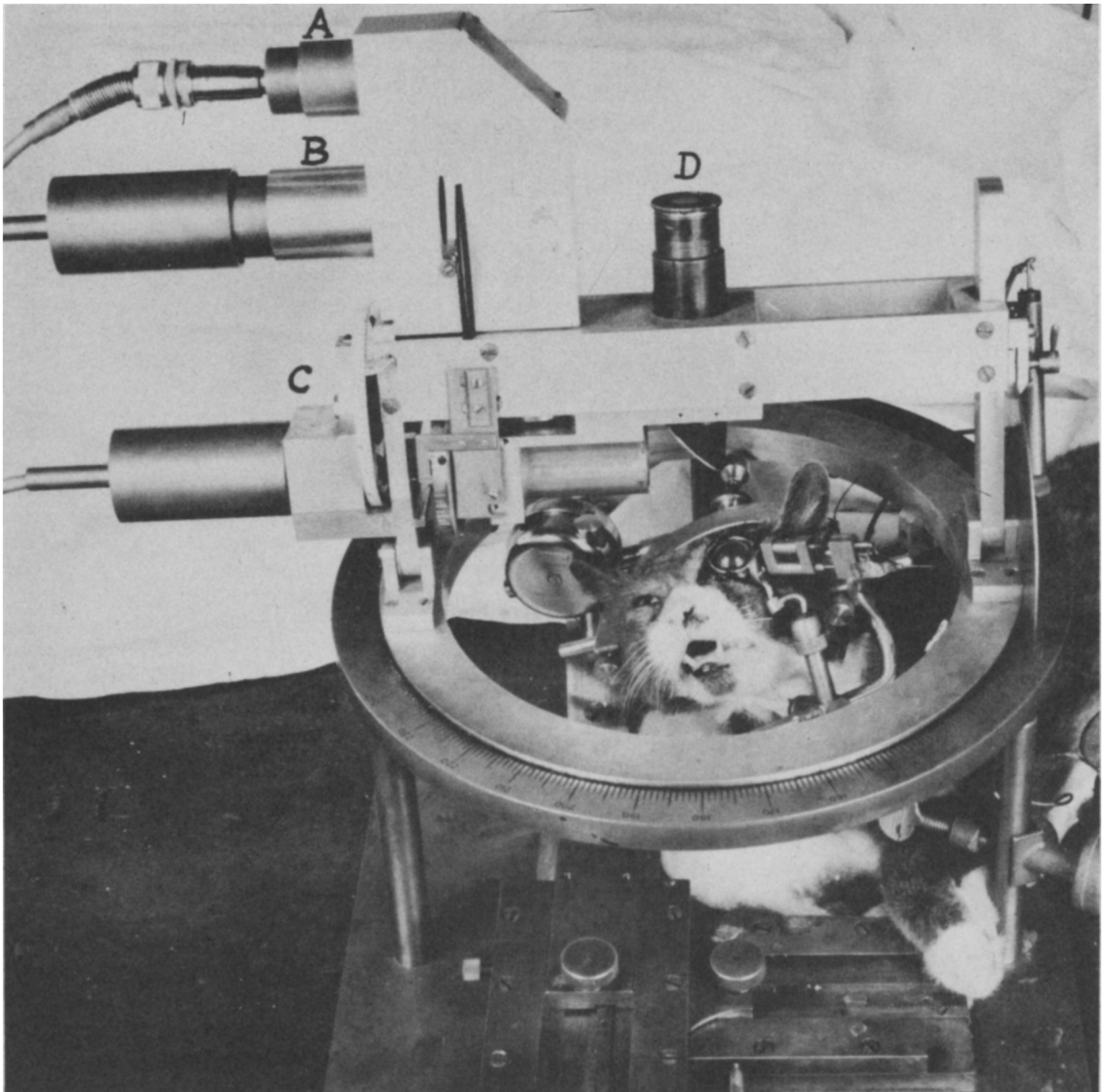


FIG. 1. Arrangement for retinal studies from the unopened cat's eye. The Multibeam-Ophthalmoscope contains three light sources, A, B, C, channelled into the eye. The fundus is observed through the ocular (D). The whole upper portion of the equipment can be freely rotated and tilted for exploration of a large region of the fundus. The cat's eye is aligned with the common optical axes of the light beams. (Note in this illustration the animal's head and eye is moved off to the right). The eye is fixed to a circular ring which is part of the microelectrode holder. (From Talbot and Kuffler, 1953).

and lower left (B and C), were used to illuminate required regions of retina. They were Sylvania argon glow tubes which could be controlled accurately and conveniently in intensity and duration of light output. They illuminated variable patterns, mostly circular patches, which were then sharply imaged on the retina. They could

be moved in relationship to each other. All three light sources were channelled into the eye through a common optical pathway and the optical axis of the eye was aligned with the illuminating system. The upper portion of the Multibeam-Ophthalmoscope containing all the optics could be detached from the base which held the animal.

When in place it could be freely rotated and tilted and directed to required portions of the retina. The eye was thus in the center of a spherical coordinate system.

The cornea was protected by a glass contact lens and stayed clear for the duration of the experiments. Details of the retinal background, such as changes in circulation, the mode of electrode contact, and projected light patterns were readily observed when the background illumination was adequate. Most experiments were performed in the region of the tapetum, a highly reflecting portion of the retina, well suited for visual observation. A magnification up to 40 times was obtained by the optical system. Figure 2 shows a view of the retina around the optic disc. The actual electrode tip is not well seen in this illustration. The upper dark line is the shadow of the electrode shaft.

For the present investigations it was particularly important to record single unit activity only. Detailed evidence in this regard has been presented before (Kuffler, 1953). The potentials derived from ganglion cells and axons were readily differentiated by their time course, size, and by the location of light stimuli which caused their discharge. The area over which excitation by a small light spot could be set up (the receptive field) was always around the electrode tip when leading was done from ganglion cells.

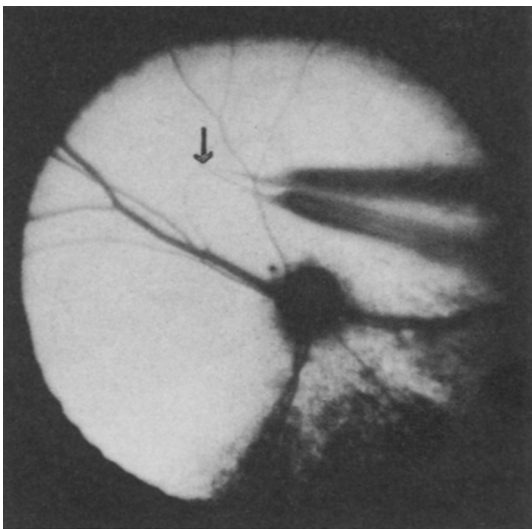


FIG. 2. View of the cat's fundus in the region of the optic disc, with electrode in position. The upper dark line on right is the shadow of the electrode shaft on the highly reflecting region of the tapetum. Arrow marks point of contact. Pigmented area of retina seen below disc. (From Talbot and Kuffler, 1953).

When axon discharges were recorded, the receptive field of a given nerve fiber could be found toward the periphery of the retina in relation to the electrode.

BACKGROUND ACTIVITY OF THE RETINA

The nervous discharge from the eye through the optic nerve fibers under different degrees of steady background illumination has not yet been analyzed sufficiently. However, an overall estimate of the extent of retinal activity can be formed if, for instance, one records simultaneously from the region of the disc discharges from many nerve fibers. The most striking observations concerned neuronal behavior in the absence of light. During dark-adaptation masses of cells discharge, the activity increasing as dark-adaptation increases. Rotation of discharge between different units can not be determined when such massed activity is recorded. In single ganglion cells, however, distinct types of behavior were clearly seen. Some ceased to discharge as the background illumination was decreased, others became intermittent, others might settle down to a discharge fluctuating between 20-50/sec. Some ganglion cells which fired during dark-adaptation ceased during low level photopic background and resumed discharging at higher intensities. From a general point of view it seems most significant that no regular steady rates were seen for prolonged periods under apparently stable conditions of illumination. This continuously shifting level of retinal activity is a striking feature of the preparation which was used, and has also previously been noted in different preparations by Granit (1947). When it became important to obtain a steady low level background discharge or complete silence in a unit this was usually achieved for limited periods by keeping the eye illuminated. The drift in thresholds was, however, continuous during such adaptation and to obtain steady discharge rates the background illumination was periodically adjusted.

Dial-Urethane or Nembutal when given to decerebrate animals had a quick and marked depressing effect on discharge rates. This was particularly obvious during "spontaneous" activity in dark-adapted eyes. The general problem of the effect of anaesthesia in altering the properties of neurons in the central nervous system, therefore, also applies to the eye.

ACTIVITY WITHIN SINGLE RECEPTIVE FIELDS

If one explores the retinal surface with a small spot of light while recording from a ganglion

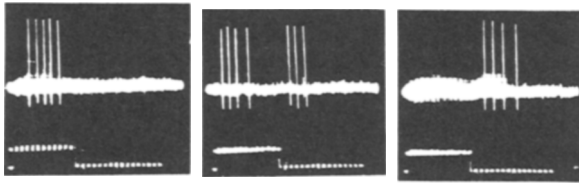


FIG. 3. Specific regions within a receptive field. Discharges recorded from a single ganglion cell when a small spot of light, 0.2 mm in diameter, is moved to three different positions within the receptive field. The recording lead is placed on the ganglion cell. The same light stimulus sets up (a) "on" responses in the vicinity of the electrode tip, while 0.5 mm away (b) only "off" discharges result. In an intermediate position "on-off" discharges (c) are set up. In this and subsequent records the second beam signals intensity and duration of the light flash. Beam intensity is modulated at 50 p.s. giving the time base. Impulses 0.5 mV. (From Kuffler, 1953).

cell, discharges will be set up within a circumscribed area in the vicinity of that cell. This area may be called the receptive field (see, however, later). The size of the receptive field as defined above, can not be determined accurately. It depends on a number of factors, such as the size and intensity of the exploring spot and the background illumination of the eye (for details see Kuffler, 1953). All these factors have previously been recognized and studied by Hartline (1940) in the frog's eye. Receptive fields in the cat are usually concentric, with the ganglion cell in the approximate geographical center. In the cat they were about 0.5 to 2 mm. in diameter when explored with a 0.2 mm. diameter light spot of about 100 meter candles (m.c.) intensity. The larger value was generally obtained with a light background of several m.c. Determination of field sizes in dark-adapted animals was difficult because under those conditions a strong "spontaneous" background discharge exists and the problem of light scatter makes measurements unreliable.

The principal new finding of recent studies concerned the detailed functional organization of receptive fields. It was observed that a small spot of light can cause different types of discharges from the same ganglion cell, depending on the subdivision of the receptive field which is illuminated. This indicated that the discharge in a single optic nerve fiber may carry a pattern which is much more flexible and fluid than has perhaps been suspected.

Figure 3 shows single ganglion cell discharges with the exploring beam at three different positions within one mm. of the recording electrode.

In *a* the cell gives an "on" discharge, i.e. it fires during illumination, in *b* the impulses occur after cessation of the light flash ("off" response), while in *c* discharges are seen while the light flashes and after it is turned off ("on-off" response). A definite pattern of organization, as revealed by discharge types, was common to all receptive fields which have been studied. Figure 4 is an example, obtained in an eye under photopic conditions. In the central area of the receptive field surrounding the ganglion cell (and electrode tip), only "on" responses were obtained, while in the periphery (diagonal hatching) the response to the same stimulus was of the "off" type. An intermediate zone (horizontal hatching) gave intermediary "on-off" discharges. In other fields the discharge type distribution was the converse, with the "off" area in the center and the "on" in the periphery. The common feature of receptive field organization was the antagonism between center and periphery. The frequency of distribution of "on-center" fields (Figure 4) and "off-center" fields is not known. The threshold to stimulation in both types was always lowest in the center. Thus, a spot-like

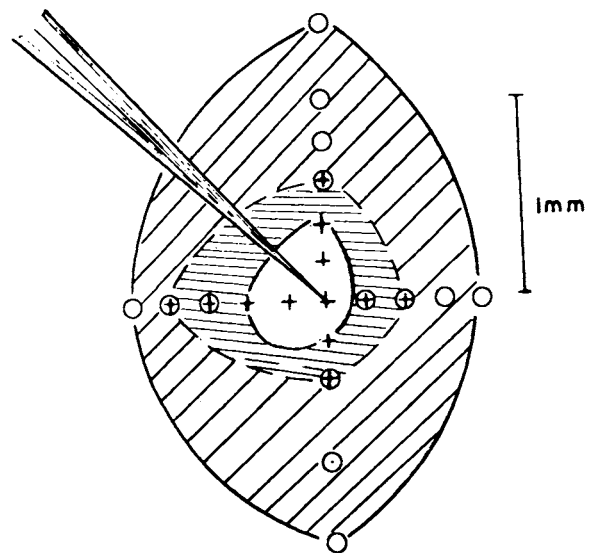


FIG. 4. Distribution of discharge patterns within the receptive field of a ganglion cell (located at tip of electrode). The exploring spot was 0.2 mm. in diameter, about 100 times threshold at the center of the field. Background illumination approximately 25 m.c. In the central region (crosses) "on" discharges were found, while in the diagonally hatched part "off" discharges only occurred (circles). In the intermediary zone (horizontally hatched) the discharges were "on-off." Note that change in conditions of illumination (background, etc.) also altered the discharge pattern distribution. (see text). (From Kuffler, 1953).

stimulus which caused one or a few discharges in the periphery, was usually several hundred times above threshold in the central region. The main reason for this appears to be the scatter of receptors in the periphery of the field rather than any threshold differences of the receptors themselves (Kuffler, 1953). The discharge pattern distribution as seen in Figure 4 was subject to change when the area of the testing spot, its intensity, position, or duration were changed. One of the most common additional variants in ordinary visual activity is the state of adaptation, determined by background illumination. Its effects on field size, pattern distribution, are striking and easy to determine. For instance, in a field with an "on" center, increased background light will first reduce the peripheral "off" fringe, i.e. the field will shrink. In the "on-off" zone the lower frequency components of the compound discharge will drop out and eventually, with a bright background, the receptive field may appear to be composed of a small "on" area only. The first changes always occur in the outer borders of the receptive field.

Figure 5 shows how an "on" discharge, obtained by illumination of an area about 0.3 mm from the field center, can be converted into an "on-off" type, by changing the area (I), intensity (III), position of the stimulus (IV), or by changing (reducing) the background light which falls on the receptive field (II). Under usual conditions of vision most of these parameters of illumination fluctuate simultaneously. Figure 5, however,

illustrates adequately the inherent flexibility of discharge patterns arising in a receptive field, when only one of many possible changes is made while other variants are kept constant. In the cat no receptive field has as yet been found to give a uniform discharge pattern over its whole area, since with careful scrutiny and adjustment of illumination conditions both "on" and "off" components were always present. The ratio of areas giving different discharge contributions was, however, very variable in different receptive fields.

FUNCTIONAL RELATIONSHIP BETWEEN AREAS WITHIN THE RECEPTIVE FIELD

The presence of "off" responses has long been correlated with inhibitory processes by Hartline (1938) and by Granit (1947). Since now both "on" and "off" areas have been demonstrated within the same receptive field, a first step towards a closer study of the interaction of functionally antagonistic neuron chains in the retina could be taken. These receptive field subdivisions, as in Figure 4, should not be regarded as "pure" or uniform. They always represent a mixture of "on" and "off" pathways, but with one or the other predominating (Kuffler, 1953). Figure 6 illustrates the clearest example of some of the inherent possibilities within this organization. The experiment is set up in the following manner: Two small test stimuli are projected onto two separate regions of a receptive field. All parameters of illumination, except

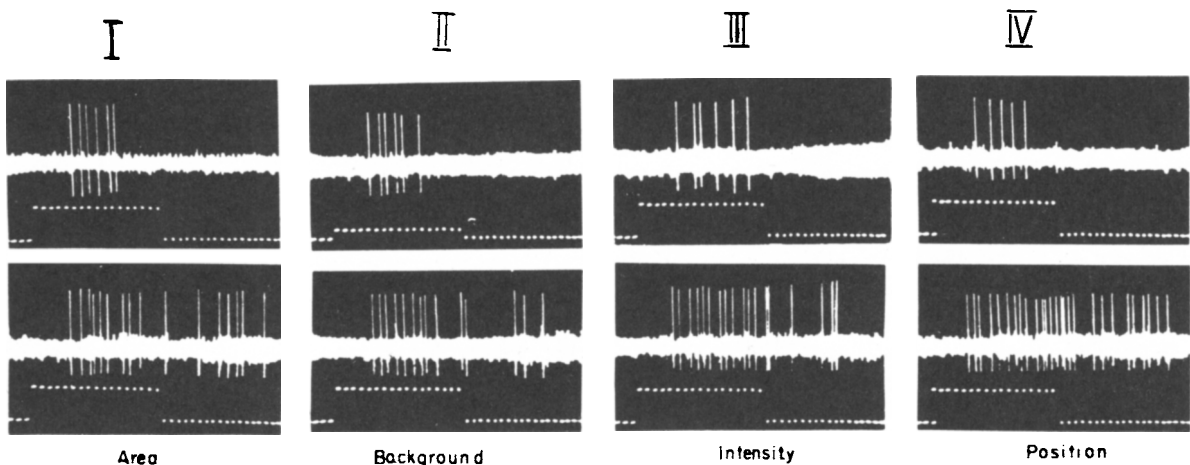


FIG. 5. Factors influencing change in discharge patterns within a receptive field. In the upper records "on" discharges from a ganglion cell were obtained by a small, 0.2 mm diameter, light spot projected onto the central region of a receptive field. These discharges were converted into "on-off" types in I by increasing the illuminated area (expanding the spot diameter), in II decreasing the background illumination from 19 m.c. to 4 m.c. without change in stimulus intensity and in III by increasing the stimulus spot intensity (in III intensity scale of second beam different). In IV, the exploring spot was shifted by about 0.4 mm into the more peripheral part of the receptive field. Intensity modulation 50 p.s. (From Kuffler, 1953).

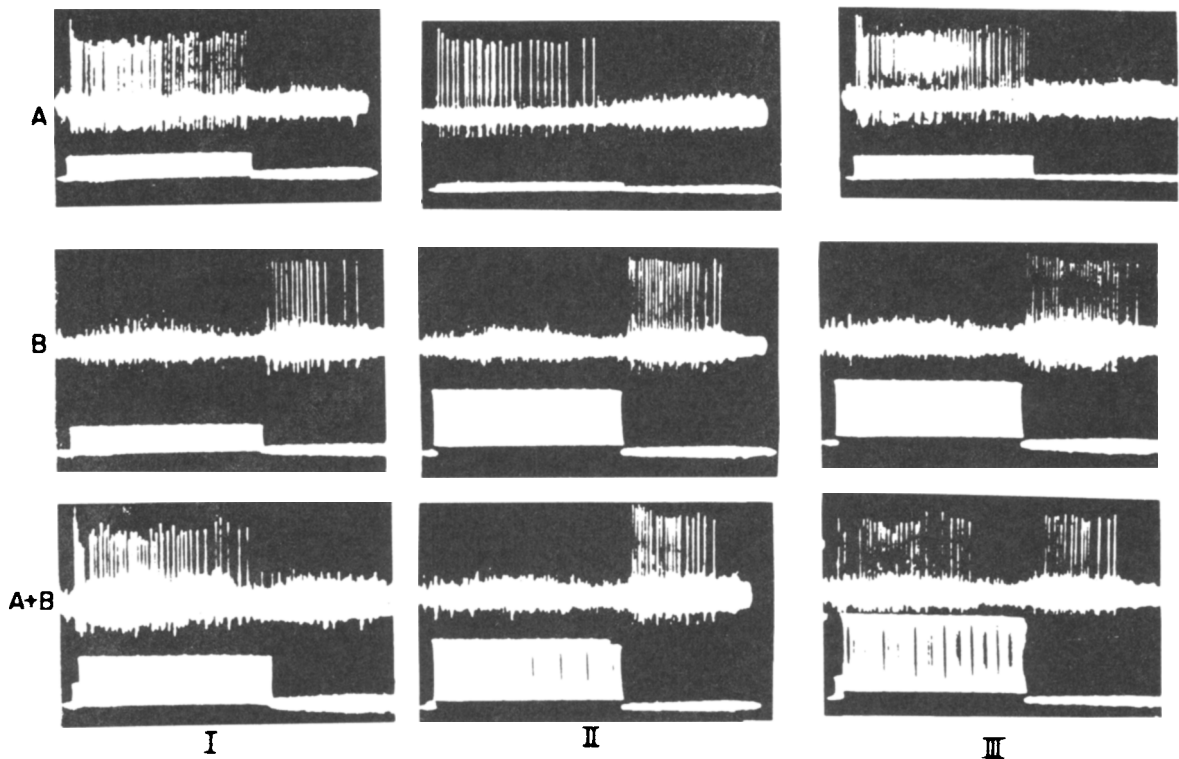


FIG. 6. Interaction of two separate light spots. Single ganglion cell discharge during background illumination of 20 m.c. Spot A, 0.1 mm. in radius, was placed in the center of the receptive field at the tip of the recording electrode. Spot B, 0.2 mm. in radius, was 0.6 mm. away in the surround. Flashed separately they set up "on" (A) and "off" (B) responses. With a simultaneous flash, A+B in column I, the "off" response was suppressed and at the same time the number of "on" discharges in A+B was slightly reduced as compared with A. In II, the intensity of spot A was reduced, while spot B was increased (note flash strength indication on second beam). As a consequence B suppressed "on" discharge of A. In III, both spots were "strong." When flashed together (A+B) they reduced each other's discharges. The flash duration was 0.33 sec., the potentials were 0.3 mV. (From Kuffler, 1952).

stimulus strength, remain constant. Spot A, within the central region causes "on" discharges, while spot B in the periphery sets up "off" discharges in the same ganglion cell. If both light stimuli are flashed simultaneously, the resulting discharge depends on the intensity relationship between the two. In I, where B was relatively weak, both light stimuli (A+B) set up an "on" discharge only, with the "off" suppressed. If, however, the intensity relationship is reversed without moving the light spots and B is made stronger, the relatively weak effect of A in the center will be suppressed by the effect of B in the periphery of the field (Fig. 6 II, A+B). If both test flashes are adjusted to give an approximately equal discharge (Fig. 6, column III, A and B), then their interaction results in a mutual suppression or reduction of each others effect, giving a relatively weak "on-off" response (A+B).

Numerous observations on interaction do not appear to fit into a "simple" explanation of

equal excitatory and inhibitory influences cancelling each other (see later). A general rule has, however, emerged, namely that within receptive fields the periphery and center are functionally antagonistic. In this competitive set-up the central area is the dominant fraction, taking the receptive field as a whole. Its contribution is the last to be suppressed by such changes as strong background light. Conversely, when conditions of illumination are altered in the opposite direction, as during reduction of background illumination, the peripheral contribution emerges and contributes progressively in the determination of the discharge through the common neuron, the ganglion cell and its axon.

GENERAL COMMENT

One of the principal tasks of neurophysiological studies at present is to determine the mechanism of inhibition-excitation at synapses. This approach is likely to clarify the most outstanding question in retinal organization, namely, how

the different discharge patterns come about. Within the confines of single receptive fields, there is given a functional arrangement—probably representative of central nervous system behavior—by which relatively uniform types of stimuli can be converted into an extraordinary variety of discharge patterns.

The simplest response which can be obtained from the Mammalian eye is the sustained “on” response which lasts for the duration of light stimulation. This is the type of discharge found in *Limulus* eyes when a single facet is excited and probably no junctions are involved (Hartline, 1940). This is also the discharge type characteristic of simple sense organs, for instance stretch receptors, where relatively little accommodation intervenes to reduce the sustained train of impulses. It will be assumed here that during the sustained “on” response the three-neuron system of the Mammalian eye—primary receptor, bipolar cells and ganglion cells—carries through fairly directly the excitation which is impressed on the photoreceptors. The ganglion discharge is directly related to photochemical changes in the receptors. Changes in simple discharge patterns have long been attributed, on theoretical grounds and by analogy with other structures, to the interneuron network interfering with and modifying activity between receptors and ganglion cells. Some observations on this problem are mentioned here.

The transient “on” response, which is prominent only when light is turned on but does not continue in spite of maintained illumination, is one of the commonest responses in the eye (Granit, 1947). Evidence has recently been presented that this transient discharge can be the result of inhibition superimposed on the sustained “on” type. For instance, sustained “on” responses were obtained by restricted spot stimulation of the “on” center of a receptive field. The responses could be converted into a transient “on” or into an “on-off” type by either applying a second stimulus to the inhibitory surround of the receptive field, or by making the stimulus to the central region larger. In both instances part of the “off” periphery (Fig. 4) was added. This type of observation gives experimental support to the notion that deviations from the simple “on” responses are due to collateral interference in the “direct” pathways, presumably three-neuron chains. In fact, recent work on *Limulus* also suggests collateral interference. Hartline, Ratliff and Wagner (1952) report that the response from illumination of one facet of this compound eye, giving the well known maintained discharge

during illumination, can be inhibited by exciting surrounding facets. Apparently even in this eye there exists a linkage between nervous elements of different facets. However, the nature of the interference and the type of connection between nerve fibers is not known. Experiments as just mentioned, and those of the interaction type (Fig. 6) between different zones of receptive fields, furnish a tool by which varieties of discharges can be produced, almost at will, by suitably changing parameters of illumination.

A relatively simplified scheme for the functional organization of the neural network within receptive fields implies that by addition of activity in inhibitory pathways the maintained “on” response is modulated. Thereby simple discharge patterns could be converted into more complex ones. On such a view the activity in the final common path of the retinal network, the ganglion cell and its nerve fibers, will be determined by the ratio at which “on” and “off” contributors are thrown into action. Special properties of receptors (including spectral sensitivity) will have a primary role in instituting activity in neuron chains which give required discharge patterns.

The scheme of altering maintained “on” discharges by the modulating action of collateral inhibitory surrounds, would produce a very great variety of discharge patterns. Such a pattern would, however, lack all the features of the “off” discharges and in respect to mechanisms, it reveals but one aspect of the inhibition problem. While “off” zones are stimulated and no discharges occur, excitation is stored somewhere in the neural network, since on release of the stimulus, discharges are set up. Their frequency and number is related to the intensity and duration of preceding stimulation. The “off” mechanism then does not simply interrupt “on” excitation but also places a barrier or a “lid” at a required location in the pathway, where excitatory processes can be built up and stored, as discussed by Hartline (1938). To achieve this it may be preferable to place the principal site for inhibition at the common ganglion cell and not merely the bipolar level. With inhibition at the latter level it would be more difficult to account for mutual cancellation of “on” and “off” discharges (Fig. 6) set up at distinct locations, occasionally as far as one mm apart, within receptive fields. At such distances it becomes less likely that many bipolars are shared by “on” and “off” pathways. Intracellular recording from different cells (or a two neuron retina) may furnish information on this point.

Consideration should also be given to the possibility of the existence of specific primary inhibitory receptors which produce "off" responses of the type found in *Pecten* (Hartline, 1938). Further, receptors may produce during illumination positive potentials and hyperpolarization and thereby inhibition (Parry, 1947). The PIII response in the electroretinogram may indicate such a function (Granit, 1947).² Interaction experiments as in Figure 6, however, do not appear to favor a direct inhibitory role of receptors in the mammalian retina. They rather suggest that during cessation of the discharge, while illumination lasts, many interneurons are actually active but are somehow unable to fire the ganglion cells. This certainly seems the case when during inhibition "on" regions are also excited but their effects are suppressed (Fig. 6 II, A+B). If a positive potential arising in receptors were to account for inhibition one would have to assume that it acted at appreciable distances. While this is not unreasonable, the electrotonic spread would in addition have to be confined to specific pathways and act across synapses which seems quite unlikely. If the spread occurred more diffusely, crossing cell boundaries in line with known electrotonic spread phenomena, it would be hard for one ganglion cell to be excited, while at the same time an adjoining one is inhibited. It has been seen quite frequently that two ganglion cells quite close to each other, within the recording range of a microelectrode, gave opposing discharge types to the same stimulus. "Diffuse" electrotonic spread as a mechanism for "off" inhibition could hardly account for the precise and finely balanced discharge mechanisms which are seen. It is also recalled that "off" discharges in *Limulus* are obtained only from nervous elements beyond the synaptic regions of the optic lobe (Wilska and Hartline, 1941). Unless contrary evidence is obtained it is then reasonable to assume that primary receptors connected to "off" pathways discharge during illumination, probably in a similar manner as receptors connected to "on" pathways. Polarization experiments of the retina also seem to contraindicate specific "off" receptors (Gernandt and Granit, 1947; Granit, 1948). In analogy with cord inhibition it is preferable to consider specific nervous connections leading to a synaptic mechanism of inhibition, with hyperpolarization at

specific locations in cells, in line with the results of Brock, Coombs and Eccles (1952).

The problem regarding "storing" excitatory or inhibitory processes can be analyzed somewhat further and two alternatives explored. Is the "off" discharge the result of excitatory processes, brought about by contributions through the "on" pathways, while the cell was prevented from firing; or is the "off" discharge the result of a special process which emerges following activity in inhibitory pathways? On the first assumption one may regard each receptive field composed of "on" and "off" pathways distributed in varying densities. The "on" paths, although their effect is suppressed or dammed up during illumination, would then be essential in bringing about the "off" discharge. Such a scheme is contraindicated by the following experiments: "Off" regions were stimulated at a fixed strength of illumination and "on" regions were added at varying intensities. The added "on" pathways did not cause stronger "off" discharges, but in fact reduced them. Further, if the "off" discharges were due to "stored" activity in "on" channels, one would expect them to be reinforced if "on" regions are excited *during* an "off" discharge. Such a summation, however, need not occur (see below).

As the simplest alternative to the above view one may assume that stimulation of "off" pathways prevents ganglion cells (or bipolars) from firing, perhaps by a process of hyperpolarization (Brock, Coombs and Eccles, 1952). The "off" discharge would then represent a "release" or rebound phenomenon. The latter, in turn, could be inhibited by the opposing depolarization caused by "on" impulses, explaining the suppression of "off" discharges as seen in Figure 6 I, A+B. While the neuroanatomical arrangements allow a wide scope for formulation of alternative hypotheses, no other experiments bearing directly on this particular point are available.

As mentioned before, interaction experiments do frequently yield different results than those expected from a "simple" scheme of inhibition-excitation. For instance, two small regions in "on" zones (Fig. 4) when excited simultaneously do not necessarily sum or facilitate each other, although that is the rule. In fact, one "on" response may block another one. Again, at what level the interference occurs is not known. Some related experiments on the spinal cord by Hunt (1952) may be mentioned. By selective stimulation of spindle afferents through small-nerve

²During this Symposium, Svaetichin presented evidence which would place all the components of the electroretinogram in the receptor layer.

fibers, a motoneurone could be made to discharge. The same cells also responded monosynaptically following a muscle nerve stimulus. The monosynaptic reflex could occasionally be inhibited by spindle afferent stimulation which under other circumstances was excitatory. Another observation related to this problem is the following: Although stretch could bring motorhorn cells to a maintained discharge, the same cells could at the same time be blocked to monosynaptic excitation at that particular level of muscle stretch. In the latter case the situation—being a two neuron arc—is simpler than in the retina, since the interaction must occur on a specific cell. If, however, one assumes an analogy with the retina then in both instances a cell, while actually firing to one excitatory stimulus, was not responsive to another one. Refractoriness or post-excitatory inhibition was excluded, since the

cells were ready to fire at much higher frequencies when stimuli were made stronger or repeated. An example is shown in Figure 7. Two light spots were placed on adjoining regions within an "on" area and their interaction was tested. When stimulated together, spot A which was practically subthreshold did not add to B, but in fact reduced the combined response. When the two spots were superimposed, they reinforced each other's discharge. Another frequent finding was related to the "off" discharge. While a ganglion cell discharge was in progress subsequent to withdrawal of a stimulus to an "off" zone, stimulation via another pathway to this cell, through an "on" channel, was either ineffective or greatly reduced. At the same time the "off" discharge rate could be increased by making the preceding stimulus stronger. On the basis of the above observations one may conclude that while in the retina there is good evidence that certain pathways are exclusively inhibitory on a cell, other evidence suggests that stimuli may be either excitatory or inhibitory depending on the background activity reaching that cell. The second type inhibition has been particularly marked when two excitatory pathways converged on a cell. It may be speculated that with a particular distribution of two sites on a cell each leads to a discharge when stimulated separately, while a combined stimulation of the sites may be less effective. An additional related finding in the spinal cord may also be mentioned. Brock, Eccles and Rall (1952) could inhibit the discharge of a motoneurone by a homosynaptic afferent volley which by itself was subthreshold for motoneuron discharge.

It is difficult to speculate about the actual neural connections which underlie the complex but apparently well organized receptive fields. Information in that direction should be obtained from a careful analysis of discharge patterns in foveal regions where histological evidence is clearer (Polyak, 1941). Since all types of discharge patterns are equally found in dark and light adapted states, it seems safe to assume that rods or cones are not exclusively associated with "on" or "off" discharges. This does naturally not imply that they do not have special properties. It may rather be speculated that special interconnections serve the two discharge functions.

It should be emphasized at this point that the present and past investigations on the retina have dealt with a rather select population of neurons, namely those which converge on the large ganglion cells. Further, investigations

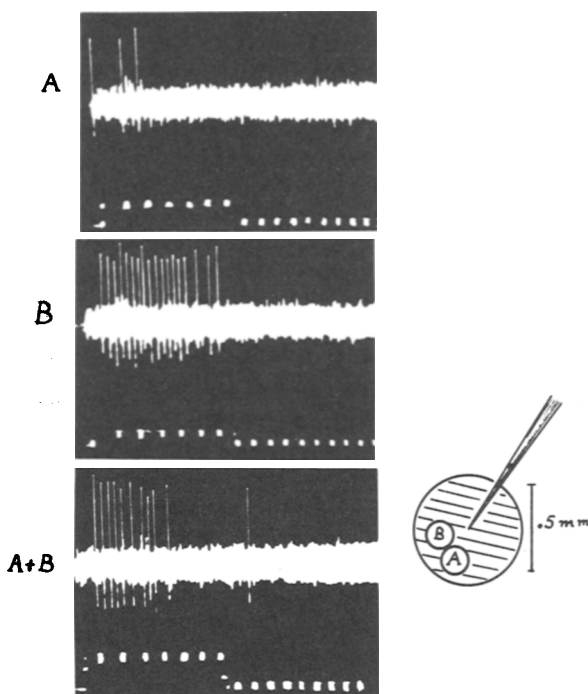


FIG. 7. Inhibition of "on" discharge by another "on" stimulus. Electrode tip on ganglion cell. Background illumination of about 5 m.c. Two circular light spots of 0.16 mm diameter placed within "on" zone of receptive field. Spot A was made practically subthreshold, caused two impulses (the first impulse was "spontaneous," occurred before light flash). Increasing its intensity set up a high frequency burst during the flash of 0.35 seconds. Spot B alone caused 18 impulses. A and B together set up 10 discharges only. When the spot A was moved and superimposed on B their effects summed. "On-off" and "Off" zones outside shaded area (as in Fig. 4) are not drawn. Frequency modulation 20 p.s.

have mainly been concerned with the responses to relatively sudden changes and nothing is known about the factors which lead to the rather striking "spontaneous" activity of neurons in complete darkness.

Psychophysical interpretations are outside the scope of this paper, and only some comment related to receptive field size and composition are made. Although a receptive field may be large, it can not convey information concerning spatial separation of stimuli which reach it, since all information has to pass through one nerve fiber and only its discharge pattern can be changed. Field size with its related change of "on" and "off" area ratios, will, however, have an important effect on the nature of the output from a given cell. Since receptive fields overlap, even the smallest light spot will excite numerous ganglion cells. For such reasons psychophysical conclusions based only on individual cell responses will have to remain limited. It is obvious, however, how the plasticity of receptive field properties serves as a convenient tool to furnish discharge pattern changes. The variety of "zones" makes available an amplification system which makes each unit very sensitive to changes in the parameters of illumination. All these properties should be useful in such functions as perception of contrast or movement.

In respect to possible interconnections between wider regions of the retina, no work has yet been done. The boundaries of receptive fields, as obtained with present methods, may not correspond to the distribution of all nervous elements which have functional connections. There may be regions which can facilitate or inhibit a ganglion discharge at a distance, without being able to initiate activity. It is difficult at present to locate all such regions (for details see Kuffler, 1953). If the wider definition is adopted, the usefulness of the "receptive field" concept may largely be lost, if it should really include a very large area.

That the retinal discharge is the result of inhibitory-excitatory influences has been discussed at length by Granit and his co-workers and these papers should be consulted (Donner and Willmer, 1950; Granit, 1947, 1950). By their different experimental procedures they have also shown the plasticity of discharge types. This paper merely stresses one new approach in the analytical study of these complex phenomena. In any event, all these problems show that the retinal neurons may be worth analyzing to a similar extent, and with similar prospects, as spinal neurons have been in the past.

SUMMARY

A brief account is given of recent methods for the investigation of single cell discharges from the unopened eye of cats. The discussion is mainly confined to neuronal rather than visual problems. The striking background activity of the retina in the absence of illumination and under varying degrees of illumination is noted. Emphasis is laid on the functional organization of receptive fields—those areas which on illumination give discharges in ganglion cells or nerve fibers. Discharge patterns from individual receptive fields show a very great fluidity, depending on the conditions of illumination. The general organization of fields is the following: They contain three zones in an approximate concentric arrangement around ganglion cells, i.e. "On," "Off" and "On-Off" zones. "On-center" receptive fields have a central region where predominantly "On" discharges are set up, with "Off" discharges arising from the periphery. "On-Off" zones are always in an intermediate region. "Off-center" fields have a converse organization. The extent of receptive fields and the discharge pattern distribution within them varies over a wide range. Factors leading to these conditions are discussed.

Functionally the central and peripheral regions of receptive fields are opposed. The discharge from the common effector organ, the ganglion cell, is determined by interaction of excitatory and inhibitory neural chains. All types of discharge patterns and combinations can usually be produced under experimentally controlled conditions from one receptive field. These preparations seem well suited for the study of central nervous system organization patterns and of inhibitory-excitatory phenomena. It is thought that two modes of inhibition, based on different mechanisms, can be distinguished in the retina.

Analogies with spinal neurons are pointed out and conjectures are made regarding neural pathways.

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DISCUSSION

GALAMBOS: The results of Dr. Kuffler's use of the retina as a model of the nervous system parallel in a remarkable way what those of us who have been similarly using the auditory system have managed to uncover. In both models the receptor cell is exquisitely sensitive, and the adequate stimulus (light for rods and cones, sound for hair cells) appears to evoke large electrical potentials from it. The retinal bipolars may be compared to the eighth nerve fiber, and at this point the auditory model-maker, unlike Dr. Kuffler, considers the activity of this link in the chain to be most highly important. All the information that ever gets to the nervous

system must be channelled through the bottleneck of these fibers, and it seems quite clear that detailed knowledge of this first neural event is a *sine qua non* for the understanding of subsequent ones. To date, unfortunately, no one has succeeded in providing the fundamental facts here for either the eye or the ear.

At the level of the first synapse, auditory physiologists have described responses which, it is interesting to note, agree even in detail with what Dr. Kuffler reports for the ganglion cell in the retina. Spontaneous activity is a common finding; tones and white noise can excite or inhibit auditory neurons; two tones—each stimulating a different place on the basilar membrane just as two lights stimulate different retinal places—have been shown to produce neural interaction. In only one important respect do the data from eye and ear differ: true "off-effects" have not been described for auditory stimuli except at the medial geniculate level.

Dr. Kuffler, and Dr. Granit before him, have focused their attention throughout upon the retinal ganglion cell. This is natural since the retinal neural data are limited to responses from it. Dr. Kuffler's basic assumption would appear to be that all such cells belong to the same population, i.e., that they behave in an essentially similar manner. With the auditory model we feel that this cannot be so since anatomists clearly show that the auditory cells comparable to the visual ganglion cell fall into at least two major categories. The first group, located in the dorsal cochlear nucleus, receive afferents from dozens, if not hundreds, of different primary afferent neurons, while the second group, in the ventral nucleus, receive afferents mainly from only one fiber at the extraordinary end-bulbs or calices of Held. On the basis of anatomy alone, therefore, it is to be expected that two major categories of physiological events will be found at the first synapse in the auditory system. Since it is clear from Polyak's description of the retinal anatomy that a variety of ganglion-cell types also exist, it is perhaps not unreasonable to expect that a variety of retinal ganglion-cell activities will also be described.

My final point is to raise the question of whether studying the retina as a model for the integrative action of the nervous system is more likely to inform us or to confuse us. My own bias is probably obvious, since I work with the auditory model, but in support of the bias the following may be said. Banishment to the periphery is a disgrace unique, among complex interacting neural units, to the retina. For this

reason the retina must possess highly specialized properties, and in developing them, it may have suppressed important unspecialized ones. One cannot profitably pursue such thoughts very far, yet it seems likely that the bipolars have a larger mission than that of simply feeding the ganglion cells with impulses. The bipolars must process the incoming signals in much the same way that all interacting neural elements—including the bipolars—go about their mysterious business. If we agree with Dr. Kuffler that retinal interactions occur importantly only at the ganglion cell, then we do indeed have here a good model. If, on the other hand, we require a clear definition of the input to the ganglion cell from the bipolar layer, then we are certainly no better, and possibly we are considerably worse off with the retina than with most other models. To understand what goes on in the bipolar layer is going to be something of a task.

Probably the most important feature of the neural interaction problem is to come to specify both the input to, and the output from, the neuron with a high degree of certainty. Micro-electrodes give us the output, and the soma spike tells us reliably whether or not a synaptic event has successfully been consummated. The next problem for solution is to come to specify afferent influences upon that soma with comparable accuracy. A glance at Polyak's pictures will

convince most people that the retinal ganglion cell is not the best place to start.

KUFFLER: Since this work was done on ganglion cells the paper emphasized some of those phenomena which could be reasonably assumed to occur at the ganglion level. It is not implied that inhibition-excitation and a good deal of interaction do not take place at the bipolar level, especially in view of the known neural connections, such as the different horizontal cells or amacrine cells. While it is most desirable to know more about the processes at the bipolar level, some interaction experiments can be devised in which modification of excitation by bipolars seems of relatively little significance.

I agree with Dr. Galambos that our sampling of ganglion cells was restricted to a relatively small population of large and medium size ganglion cells. It is almost certain that with more refined methods a variety of ganglion cells of different behavior remains to be uncovered. I further subscribe to Dr. Galambos' opinion that a study of the retina is likely to confuse us, but only if we regard this structure as *the* model of integrative action of the nervous system. This is not claimed for the present preparation and, in fact, no single model could fulfill such a task. The present experiments do, however, show one of many possible samples of integrative action in a complex nervous structure.