The exact action and its effects upon visual phenomena are about the biggest remaining mystery in the physiology of the retina. With these words, Gordon Walls concluded a brief discussion of the function of amacrine cells in his extensive book on the vertebrate eye in 1942. There was little cause to alter this view in the next two decades. The gap between experimental physiology and anatomy was thus immense and long-standing: around the turn of the century, Ramon y Cajal had confirmed earlier observations on the existence of a prominent class of cells in the inner retina which had no obviously identifiable axon. Cajal named them amacrine cells (without an axon), went on to provide a wealth of information concerning their structure in various vertebrates, and speculated on their function: "It can only be said that they must exert some influence on the clusters of ganglion cells and also on clusters of bipolar cells."

The anatomic view of the amacrine cell, due to Cajal and other light microscopists, was considerably extended when the electron microscope was applied to the study of the inner retina in the 1960's. Reciprocal synapses between amacrine and bipolar cells, serial synapses between adjacent amacrine cells, and synapses between amacrine and ganglion cells were then described in several species. This work rekindled a general awareness of amacrine cells and contained some new and provocative hypotheses about their function. But at that time there was still no convincing electrophysiologic work to complement the anatomy. Recent intracellular recordings from identified amacrine cells therefore constitute a landmark in the study of the retina, and it is of interest to sketch some findings and implications of this work.

Amacrine cells of the on-off type were first identified in the mudpuppy and have since been found in other species. They respond with graded depolarizing potentials at both the onset and offset of a light flash or whenever an object moves in or out of their receptive field. These responses, being predominantly transient, differ significantly from the more sustained responses of bipolar and receptor cells. So on-off amacrine cells seem to be the first neurons in the visual pathway which are primarily designed to selectively emphasize dynamic aspects of the visual environment. Two important hypotheses have been advanced about on-off amacrine cells. The first holds that they serve as interneurons...
between bipolar and ganglion cells and are thereby responsible for shaping the transient responses of on-off ganglion cells. It has since been shown that some ganglion cells synapse almost exclusively with amacrine cells, but direct physiologic evidence showing that on-off amacrine cells drive on-off ganglion cells is still needed. The second hypothesis suggests that the amacrine-bipolar synapse may function as a recurrent inhibitory pathway and is thereby responsible for the transient nature of the amacrine cell response. This hypothesis remains appealing but has yet to receive a critical test and alternative mechanisms have been suggested. So the very basic issue of the mechanism(s) responsible for the generation of the on-off amacrine cell response is not yet resolved.

Cajal identified several anatomic varieties of amacrine cells. A comparable variety is now emerging in the electrophysiology. Thus, in addition to the common depolarizing on-off type, a hyperpolarizing on-off type is sometimes found. There are other amacrine cells which respond with a relatively sustained depolarization (on type) or hyperpolarization (off type). And in goldfish, there is a sustained type which is hyperpolarized by red and depolarized by green light. This is consistent with Svaetichin's views and implicates, but falls short of clearly defining, a role for amacrine cells in color coding. Center-surround antagonism seems weak or absent in the types discussed so far. But it is well-developed and forms the basis for identifying two additional types in the carp: on-center and off-center amacrine cells. If center-surround antagonism is characteristic of all bipolar cells, its absence in some amacrine cells must be clarified in terms of mechanism and functional consequences. Of similarly unsettled significance is the finding that some amacrine cells generate nerve impulses and others do not.

The results just summarized show that there are several functional classes of amacrine cells and raise the possibility that specific functional types may be assigned to specific anatomic types. The first such evidence is at hand: in catfish retina, stratified amacrine cells apparently respond in a sustained manner while amacrine cells with spindle-shaped cell bodies generate transient on-off responses. More evidence of this sort will be very important and hopefully soon forthcoming. We may also hope that correlations can soon be extended to the ultrastructural level and, among other benefits, clarify the relation between amacrine-bipolar synapses and amacrine response modes. Neurochemical differentiation among amacrine cells is likely, for there is already evidence that GABA, glycine, catecholamines, and acetylcholine are present in the amacrine cell layer. Firmly establishing the full set of interrelations between the anatomy, electrophysiology, and neurochemistry of amacrine cell specialization thus defines a central and most challenging goal.

The classic view that amacrine cells are important agents of lateral interaction seems obvious from the prominent lateral processes which some amacrine cells display and seems further reinforced by the discovery of serial synapses between adjacent amacrine cells. But testing and refining this idea requires methods which can dissociate the lateral influences of amacrine cells from those of horizontal and bipolar cells. One such approach has recently been attempted and yields evidence that on-off amacrine cells impress an antagonistic lateral influence upon on-off ganglion cells. But this effect is small near threshold and there is as yet no comparable data for other classes of amacrine cells. Intracellular stimulation of amacrine cells may provide a useful means to isolate their lateral effects.

Several quantitative indices of amacrine cell synaptic relations vary across species. The hypothesis of a link between these anatomic variations and the "complexity" of ganglion cell responses remains intriguing. But no critical tests have yet emerged and there is need of more refined criteria for ganglion cell complexity. Recordings from mammalian amacrine cells, now apparently within technical reach, should
prove important for this and other questions about amacrine cell function. Efferent innervation of amacrine cells is a classic anatomic finding which cries for functional interpretation, and it has been reported that antidromic stimulation of the optic nerve evokes an excitatory postsynaptic potential in amacrine cells. Work in avian retinas, known to have a well-developed amacrine cell population and efferent system, may give more insight into how the brain uses amacrine cells to communicate with the retina.

Looking at the present state of the electrophysiology of amacrine cells, Cajal and Walls would certainly perceive the elements of remarkable progress along with the seeds of an exciting future in which painstaking research may deprive the amacrine cells of much of their remaining mystery.

Dwight A. Burkhardt
Vision Laboratory
Department of Psychology
University of Minnesota
Minneapolis, Minn. 55455

REFERENCES

The importance of the mucopolysaccharides in intraocular pressure regulation

Although our knowledge concerning the aqueous humor outflow has advanced during the last few years, the subject is still evolving because of the application of new research techniques, among which the following must be mentioned:

1. Electron microscopy,¹ which makes it possible to study seriated sections of the...