Some Contributions to the Cell Biology of Photoreceptors

Proctor Lecture

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If one takes on the task of studying the biochemistry of defined regions of photoreceptors, the first problem is how to gain access to all distinctive regions of these cells since, as shown in the human retina of Figure 1, substantial parts of these cells are buried in the retina vitread to the external limiting membrane. When a retina is detached from the pigment epithelium, access is obtained to the photoreceptor outer and inner segments, the regions protruding into the retinal ventricle (ie, the clinician’s sub-retinal space), but such important regions as the cell bodies and synaptic terminals remain inaccessible. Moreover, mass isolations of inner segments have not been accomplished. However, some thirty years ago, the biochemist Oliver Lowry described\(^1\) a means of sampling distinctive levels of the brain or retina for biochemistry. For eyes, this system consisted of rapidly removing and rapidly freezing an eye in liquid nitrogen near its freezing point, and then cutting 6-μm frozen tangential sections from the eye, serially cutting through the retina. Such sections could be stained for orientation or freeze-dried. Because the sections are tangential and the eye spherical, the distinctive retinal layers are spread out in the sections like broad bands of a bulls-eye target, with the composition and width of particular bands varying with the depth within the retina represented by the center of the section (Fig. 2). As the banding remains discernable and their identity known in freeze-dried sections with guidance from occasional stained sections, one can cut pieces from known retinal layers in freeze-dried sections, weigh these on quartz-fiber, fish-pole balances, and carry out assays for substrates or enzymes on these pieces using the elegant cycling techniques originally introduced by Dr. Lowry.\(^3\)

This system has some limitations. First, the bands seen in the sections rarely contain a pure cell type. Thus, outer segments and in some species, inner segments as well, may be contaminated by processes of pigment cells. Inner segments are slightly contaminated by processes of Müller cells, cell bodies more so, and photoreceptor synaptic terminals are likely to be contaminated by a variety of processes. Secondly, the system is technically demanding and time-consuming, as 2–3 weeks may be required to process a single eye. Nonetheless, it is the only system thus far devised which permits mass sampling of photoreceptor outer or inner segments, cell bodies, and terminals from intact photoreceptors.

However, if one is to expend the effort to carry out the above procedure, one should start with some idea about what sort of molecules in photoreceptors, apart from photopigment, might reward studying. For example, potential transmitters of photoreceptors would be worth investigating. In an article published in 1965,\(^4\) I suggested that by comparative biochemical studies utilizing normal versus experimentally and genetically modified retinas, one might obtain clues to molecules either notably concentrated or deficient in photoreceptors.

The above system was eventually described as a comparison of normal with “biologically fractionated” retinas and employed retinas of mice. To be compared with control retinas were photoreceptor-deficient retinas from mice homozygous for rd/rd and retinas from mice given subcutaneous injections of monosodium glutamate during their first ten postnatal days, when their blood–brain and blood–retinal barriers are deficient. The latter procedure was first described by Lucas and Newhouse\(^5\) and in mice resulted in a smaller eye and the loss of most of the retinal ganglion cells and of many amacrine cells.\(^6\) Although the retina was reduced in thickness and area, the photoreceptors appeared normal in form and concentration. Potts et al\(^7\) reported that only the “a” wave of the ERG persisted in these eyes. In contrast, the retina of the homozygous rd/rd mouse only reveals a single row of photoreceptor cell bodies in comparison with a 10-deep tier of photoreceptor
cell bodies in controls. No outer segments whatsoever are evident, but reduced inner segments with cilia may be present. However, the remaining retina appears fairly normal.

For purposes of the above comparison, an important pretense is adopted. It is assumed that the absence of the missing retinal layers of cellular elements has not affected the remaining retina. This is not likely to be true, but the pretense is justified insofar as only clues are being sought to plan subsequent definitive investigations.

The first project using the above system was directed at free amino acids inasmuch as the view that certain free amino acids might have transmitter functions was being mentioned at that time in the neurobiological literature. In 1973, with the guidance of Mike McDaniel, a postdoctoral student of Oliver Lowry who was expert with amino acid analyzers, and with my newly arrived graduate student Harry Orr, the appropriate retinas were isolated and extracted with the results shown in Figures 3 and 4. All data were referred to protein. The argument was that a molecule with its highest concentration in rd/rd retinas, and lowest concentration in glutamate-modified (G-M) retinas, was likely to be a molecule normally concentrated in the inner retina. Conversely, a molecule with its highest concentration in the G-M retinas, but with lowest concentration in rd/rd retinas, was likely...
to be a molecule concentrated in the outer retina. By
this argument, the data obtained suggested that
glycine, alanine, and γ-aminobutyric acid (GABA)
were likely to be concentrated in the inner retina,
and that taurine was likely to be concentrated in
photoreceptors. Glutamate appeared to be evenly
distributed and this was somewhat true of aspartate
as well. This might mean that these were of no special
local importance or that they were important in both
the inner and outer retina. Where the rd/rd retinas
were deficient in taurine but had heightened levels of
glycine and GABA, were these differences based on
the loss of previously held molecules or on a failure
of accumulation? To test this Orr and I isolated
retinas from rd/rd and control mice of known post-
natal age. We discerned that taurine levels only
gained in controls when photoreceptors developed,
and that GABA and glycine levels only gained in rd/
rd retinas when controls formed photoreceptors, the
apparently GABA- and glycine-poor photoreceptors
diluting the inner retinal level of these molecules.
Glutamate, however, at all ages had a similar level in
normal and rd/rd retinas.

We were particularly interested in the clue strongly
indicating that photoreceptors were rich in taurine.
Using the Lowry technique Orr then carried out layer
analysis for taurine in the rabbit, cat, chick, monkey
and frog, and in all instances found taurine to have
its highest retinal levels in the layers containing
the photoreceptor inner segments and cell bodies.10 That
retinas were rich in taurine had been known for some
time, and Pasantes-Morales and her coworkers11-13
had shown that light caused the release of taurine
from retinas and also that applied taurine inhibited
the ERG. Most excitingly, only two years following
the report of our fractionated retina study which had
suggested that photoreceptors were very rich in tau-

Fig. 3. The concentrations of various amino acids in normal (striped), dystrophic (dots) and glutamate-modified (solid) retinas.

Fig. 4. The concentration of taurine in normal (striped), dystrophic (dots) and glutamate-modified (solid) retinas.
About this time data appeared in the literature suggesting that turtle photoreceptors might be using acetylcholine as a transmitter. The system employing biologically fractionated retinas seemed ideal for evaluating this suggestion. David Ross, a postdoctoral student of my Pharmacology colleague David McDougal, had been developing ultramicrobiochemical assays for choline acetyltransferase (CAT) and acetylcholine esterase (AChE), the enzymes respectively involved in synthesizing and degrading acetylcholine. Ross and I accordingly carried out these experiments with results (Fig. 5) which were totally inconsistent with the view that mouse photoreceptors used acetylcholine as a transmitter, but strongly indicating its use in the inner retina. Ross and McDougal then employed frozen eyes from many vertebrate classes on which they carried out Lowry-type layer analyses for CAT and AChE with no data supporting the view that photoreceptors might use acetylcholine as a transmitter.

The surprisingly accurate predictiveness of the biologically fractionated retina system led to my being approached by Dr. James Ferrendelli, another Pharmacology colleague. Ferrendelli was an expert in the newly emerging area of cyclic nucleotide biochemistry, and we had read that isolated photoreceptor outer segments were very rich in cyclic GMP. I was out of glutamate-modified retinas at the time but we immediately compared control and rd/rd retinas, and were not only amazed by the high level of cyclic GMP in dark-adapted control retinas, but by the exceedingly low level of this molecule in rd/rd retinas. We took this to mean that the preponderance of the retina's cyclic GMP was in photoreceptors. Moreover, we were impressed by the difference in cyclic GMP in dark versus light-adapted control retinas. Sometime later, when Gerald De Vries had joined my laboratory, we finally assayed cyclic GMP levels in dark versus light-adapted G-M retinas, and the results of both these studies are combined in Figure 6. If cyclic GMP was preponderantly in the photoreceptors of the mouse, one would have expected that, as with taurine, the levels in G-M retinas should have exceeded those in controls—but this was not the case. Obviously, some other factor was operating. Was the cyclic GMP system in the photoreceptors altered by glutamate or did glutamate cause the loss of an inner retinal pool of cyclic GMP? In any event, inspired by the earlier data, Harry Orr studied cyclic nucleotide levels in the rabbit retina, utilizing the Lowry method. He and I removed eyes from dark-adapted pigmented rabbits using infrared illumination and image converters, and similarly removed eyes from light-adapted rabbits. The results (Fig. 7) were that retinal cyclic GMP was preponderantly confined to all retinal levels containing photoreceptor regions, particularly outer segments, and were much higher in dark-adapted retinas.

Now an interesting problem in photoreceptor phys-
These studies presented evidence that the numerous membranes within rod outer segments had been revealed by some of my early electron microscopic examinations of rod outer segments. The preponderant localization of photopigment is in the membrane of the disks, the likely site for light to form photorelease disks at the base of the outer segment. Since other, with the exception of a small number of membranous disks within rod outer segments were ever, Penn and Hagins, Tomita and others had shown that, in the dark, outer segments act as a sink for an external current, and that the action of light is to indirectly cause the closure of presumed channels in the plasma membrane by which this current, largely carried by sodium ions, enters the outer segment. This results in a hyperpolarization which constitutes the initial, significant electrical event in rod-signalling. Since the initial light event is in the isolated disks but the initial electrical event is in the plasma membrane, the information of the disk event must be carried to the plasma membrane, by a "messenger"—probably an ion or small molecule whose cytosol activity is modulated by the action of light on diskal photopigment. Hagins and Yoshikami proposed that light caused an increase in calcium activity in the cytosol of outer segments, and that this ion caused the closure of the membrane channels for the dark current. Calcium is still the leading candidate for this action as much data supports this view. However, with the discovery that dark-adapted rod outer segments had high concentrations of cyclic GMP, and that bright light reduced these levels, this molecule became a second candidate for a messenger.

According to this scheme, high levels of cyclic GMP in the cytosol of outer segments would somehow keep the channels for dark current in an open state, while reducing the level of cyclic GMP would allow them to close.

This led Drs. Ferrendelli, Lowry and myself to decide to further explore the behavior of cyclic nucleotides in photoreceptors. As part of this project, a system was developed for incubating isolated, dark-adapted mouse retinas in the dark and then exposing them to light. In the dark incubations cyclic GMP levels were not only maintained but slightly increased, yet a bright light reduced these dark levels by about 50%. To study the influence of external calcium levels on the cyclic GMP of such isolated retinas, the external calcium level was either sharply reduced by both omitting calcium salts from the medium and adding various concentrations of the calcium chelator EGTA, or alternatively, by simply increasing the level of calcium salt in the medium, sometimes adding a calcium ionophore. It is important to note that such manipulations of the levels of calcium activity in the external medium do not reveal what actual calcium activity levels are thereby achieved in the cytosol of the outer segment or the cell. With incubated dark-adapted retinas, lowering the external calcium level with various concentrations of EGTA gave sharp increases in the level of cyclic GMP (Fig. 8). These could be some 10-fold greater than the usual level of cyclic GMP in dark-adapted retinas. A bright light was still capable of reducing this heighted retinal cyclic GMP level by 50% while the retina was in the low calcium medium. The synapse between photoreceptors and second order neurons is known to be calcium requiring. Thus, in the very low external calcium activities achieved (approximately nM), photoreceptor signals should not have reached other neurons and, therefore, the pool of light affected by cyclic GMP must be in the photoreceptors themselves. However, to further strengthen this argument, the same experiment was performed where, in addition to the EGTA, 100 mM of the NaCl in the medium was replaced by equimolar Na aspartate, an agent which apparently suppresses contributions to the electroretinogram of retinal cells other than photoreceptors, suggesting that the electrical activity of at least some of these other neurons were no longer modulated by light. Nonetheless, the very low calcium level still markedly elevated cyclic GMP and bright light still reduced this level by 50%. The high level of cyclic GMP achieved in the dark by calcium chelation at the nanomolar level could also be reduced in the dark by returning the retinas to media with micromolar activities of calcium or restored to the normal dark level for cyclic GMP by returning the retinas to...
media with millimolar calcium levels (Figs. 9, 10). More importantly, increasing calcium in the medium to levels as high as 20 mM failed to depress the normal dark level of cyclic GMP in these retinas although 20 mM calcium is known to hyperpolarize rods in the dark, thus mimicking the effects of light.30

It was concluded from the above studies that while calcium activity can sometimes influence the level of cyclic GMP, the reduction of cyclic GMP in rods by light was not likely to be triggered by an increase in cytosol calcium.31 The increase in cyclic GMP produced by low levels of external calcium appears to be due to the fact that guanylate cyclase, the enzyme required for the production of cyclic GMP, is inhibited by calcium. Thus, very low external calcium disinhibits this enzyme.32-34

It is now well known that light reduces cyclic GMP by a system termed the cyclic GMP cascade, and that calcium is not required to trigger this sequence. In the cascade, one molecule of bleached photopigment can successively activate many molecules of a GTP-binding protein (GBP), and one molecule of GBP can activate (by disinhibition) many molecules

of cyclic GMP phosphodiesterase, which destroys cyclic GMP.

However, all the preceding data on cyclic GMP had been achieved with retinas where rods were the numerically preponderant photoreceptor. What of cones? Gerald De Vries in my laboratory proceeded to investigate cyclic nucleotide levels in strata of the retinas of the 13-lined ground squirrel, where 97% of the photoreceptors are cones. After carrying out the Lowry technique on dark-adapted eyes of these animals, the eyes being obtained under infrared illumination using image converters, the results were compared with results from similarly processed eyes from light-adapted animals. We were surprised to observe that although, as in rod-dominated retinas, those strata of the retina containing photoreceptors had high levels of cyclic GMP, with the peak occurring at the level including the outer segments, light adaptation had no effect on this level.35 A similar result for cyclic GMP of isolated retinas from dark- and light-adapted ground squirrels was seen in a study from another laboratory.36 To follow up on this result, De Vries and Ferrendelli used the layer analysis technique to compare the distribution of guanylate cyclase (the enzyme involved in cyclic GMP synthesis)
in both the retinas of the ground squirrel and rabbit (94% rods), and similarly Lowry’s laboratory studied the distribution of cyclic GMP phosphodiesterase (the enzyme involved in cyclic GMP destruction) in strata of the same retinas. In both the rabbit and ground squirrel a sharp peak in the activity of these enzymes was seen in the strata containing outer segments. The distribution of adenylate cyclase activity was also similar in these two retinas, however, in the strata relating to photoreceptors, the peaks for adenylate cyclase, in contrast to that for guanylate cyclase, were at the inner segment and outer plexiform levels.

If the outer segments of this cone-rich retina contain a high level of cyclic GMP and the enzymes for its synthesis and degradation, why is no effect of light adaptation evident? It is of course possible that no cyclic GMP cascade occurs in cones, but the explanation may lie elsewhere. It is known that for a given background of illumination, cones have an operating range of about 1,000 times their threshold, but that this range rapidly shifts for different backgrounds of illumination. Thus, it might be that the cyclic GMP level rapidly accommodates to new backgrounds.

Indeed, Nelson Goldberg et al. have recently presented data showing that rod-dominated rabbit retinas present no measurable loss of cyclic GMP when exposed to light in the scotopic (rod) range, and that only brighter lights produce measurable losses of cyclic GMP. In the rod physiological range only an enhanced turnover of cyclic GMP was evident. It could well be that in any operating range of cones only an enhanced turnover of cyclic GMP occurs in response to light superimposed on a background.

The levels of cyclic GMP are generally measured by radioimmune assay. Sensitive as this analytical technique may be, it is also possible that in the physiological ranges for rods or cones, losses of cyclic GMP are simply hard to detect above the “noise” inherent in the assay. In a recent study in which compared levels of cyclic GMP or cyclic AMP after dark-adapted mouse retinas had been exposed to IR filtered white light of differing intensities for 6 min, no significant losses were observed in the scotopic range, but such were readily seen with brighter lights. In these experiments, a HEPES-buffered medium was used which contained 5 mM Ca++ for the dual purpose of elevating dark levels of cyclic AMP (but not cyclic GMP), and for blocking the photoreceptor synapse in order to confine the effect of light to photoreceptors, assuming that these are the only retinal cells with photopigment.

While there is much ongoing research on the elements of the cyclic GMP cascade and on the relation of cyclic GMP levels and its changes to transduction and adaptation, there is no consensus on exactly what role cyclic GMP plays in the function of outer segments, although all investigators appear convinced that the elaborateness of the system predicts its importance. Certainly the data generated by our Washington University laboratories do not speak to its role in photoreceptors.

Recently, however, some additional tests as to the potential importance of cyclic GMP for vision have become possible. These involve the use of two mutant mouse strains, one homozygous for rd, the other for rds. Both situations result in retinas with photoreceptors lacking outer segments.

The first of these, the rd mutant, has long been studied, and the remarkable aspect of this animal is that considerable evidence exists to the effect that in spite of the mutation it possesses vision at a high light threshold for months. Sanyal and Bal noted a retarded differentiation of the photoreceptors on the 4th postnatal day. The beginning of structural deterioration of the photore-
receptors was seen on the 8th postnatal day. On the 21st postnatal day only one layer of photoreceptor cell bodies persisted, in contrast to a 10 to 11 deep tier of such cell bodies in controls, but the persistent somata had truncated inner segments with cilia and synapses. All the residual photoreceptor cell bodies appeared to be those of cones after 36 postnatal days, and inner segment organelles were now found in the somata. Some cilia persist and any persistent synapses were cone-like. On the 14th postnatal day rd/rd retinas had an abnormally high level of cyclic GMP which subsequently fell sharply. The rhodopsin content of the retina (by difference spectroscopy) was "almost zero" on the 19th postnatal day, and the ERG was progressively abnormal, becoming extinct between 20 and 28 days. Yet, at 150 days the animals seemed able to detect light and distinguish vertical from horizontal slits; the threshold being increased some 100,000 times. In a more recent study at 95 days, vertical rectangles could be distinguished from horizontal rectangles. Finally, Ursula Drager and David Hubel successfully recorded visual receptive fields from the tectum for about 150 days, and found the responses compatible with cones being the detectors.

The rds mutation occurs on the 17th chromosome. The mice fail to form outer segments and no rhodopsin could be detected by difference spectroscopy at 21 days. A slow loss of photoreceptors ensues from about 14 days until all are gone by 1 year. The surviving inner segments possess cilia.

If vision persists for months in the rd mutant, would a light-modulated cyclic GMP metabolism also persist in their surviving photoreceptor somata? The same question can be raised for the rd mutant although testing for persistent vision in these mice has not, as yet, been reported. To approach this question one must first attempt to demonstrate the presence of cyclic GMP in the retina or to cause its appearance pharmacologically, then to test for any effect of light on the level of cyclic GMP, and finally to try to determine if such an effect is occurring in the residua of the photoreceptors. One first uses isolated retinas from dark and light-adapted mice for direct assay for cyclic GMP. One can then try to increase retinal cyclic GMP by exposing dark-adapted retinas to the phosphodiesterase inhibitor IBMX, or to the much more potent procedure of exposing such retinas to very low levels of external calcium, or to both IBMX and low calcium. If IBMX alone suffices to raise cyclic GMP levels, this can be employed in HEPES-buffered media with synaptic blockers present, such as 5 mM Co ++ or Cd ++ , to see if light can modify the elevated cyclic GMP levels. If low calcium medium with EGTA is required to elevate cyclic GMP, then one cannot use Co ++ or Ca ++ as blockers of calcium-requiring synapses since EGTA will chelate these cations, although as noted earlier, the very low calcium levels themselves may well result in synaptic blocking, but this has not been adequately studied. The remaining approach in low Ca ++ media is to flood the dark-adapted, isolated, incubated retinas with one of a number of molecules mimicking the action of the transmitter normally liberated by photoreceptors in darkness. These molecules include the L and D forms of glutamate and aspartate, kainic acid, and N-CH3-D-aspartate. Kainate is reputed to be a strong glutamate agonist while N-CH3-D-aspartate is reputed to be a potent aspartate agonist. In addition, as argued by my former student, John Olney, in elevated concentrations the excitatory amino acids and their analogues are highly cytotoxic, and many second and third order retinal neurons appear to have receptors for such molecules, as recently described for the mudpuppy retina. Aspartate has been used to isolate photoreceptor responses by Sillman et al. Dowling and Ripps, and Winkler. Hampton et al have shown the resistance of rabbit photoreceptors to the toxic effects produced by kainate on other retinal neurons.

As shown in Figure 11, when retinas were rapidly removed from dark- or light-adapted mutant or control mice of 21 days of age and immediately frozen prior to chemistry, the dark-adapted control retinas showed substantial levels of cyclic GMP, while light-adapted retinas had significantly lower levels. Despite their lack of outer segments, while the levels of cyclic

![Fig. 11. The cyclic GMP levels of dark- and light-adapted retinas obtained from 21-day-old control pigmented (C57) or albino (BALB/c) mice, versus those obtained from albino mutant (rd/rd) animals.](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933344/)
GMP in the dark-adapted rds retinas were much lower than those of normal controls, light-adapted rds retinas had still lower levels. The rd retinas, on the other hand, showed no difference in their very low levels of cyclic GMP in either dark or light-adapted retinas.

However, as shown in Figure 12, when dark-adapted rd retinas were isolated and incubated in media with very low levels of calcium, significant levels of cyclic GMP accumulated in the dark-adapted retinas, but significantly less if the last 2 min of incubation were under a bright IR-filtered light. Surprisingly, these effects were exaggerated if the medium contained 100 µM kainic acid, and more so if both kainate and IBMX were present. If 21-day dark-adapted rds retinas were incubated in physiological media containing 1 mM IBMX, as shown in Figure 13, this agent markedly increased the dark levels of cyclic GMP and if the last 2 min of incubation were under a bright light, a significant reduction in cyclic GMP was obtained. All the same phenomena were observed if the medium contained, in addition, 5 mM levels of Ca++ or Cd++ or Mn++. Similarly, very low calcium medium significantly elevated cyclic GMP in dark-adapted 21-day rds retinas with the levels achieved being increased by kainate and/or IBMX. Neither kainate nor various levels of aspartate interfered with a significant reduction of this level by light (Fig. 14). Figure 15 shows the results of an experiment using 90-day dark-adapted rd and rds retinas. The physiological incubation medium had the usual very low calcium level but contained in addition 100 µM kainate. For both mutant retinas the low calcium level caused increases in the dark level of cyclic GMP, but significantly lesser levels if the last 2 min of incubation were in the light. Surprised by the persistence of biochemical light effects in 90-day rd retinas, a more extensive experiment was carried out as shown in Figure 16. The dark-adapted rd retinas, in addition to their exposure to very low calcium, were additionally exposed to either 100 µM kainate, or 10 mM levels of either D or L forms of glutamate and aspartate, or to 1 mM...
N-CH₃-D-aspartate. None of these agents hindered the effect seen if the last 2 min of incubation were under a bright light.

The above data show that pharmacological manipulations can increase cyclic GMP levels in the dark-adapted mutant retinas, and that light can reduce the levels achieved. Thus, both mutant retinas must contain a cyclic GMP metabolism which can be influenced by very low calcium or IBMX. In addition, both retinas must contain a photopigment whose light activation, directly or indirectly, influences cyclic GMP levels. If we assume that only the residual photoreceptors among retinal cells contain photopigment (which deserves to be proven by some sensitive, independent means) and that at least some of the strategies taken to prevent the light-modulation of post-photorceptoral cells were successful, then the phenomena observed mean that the resida of the photoreceptors still have a functional cyclic GMP system.

These results raise the question of whether normally photoreceptors have some photopigment and cyclic GMP cascade molecules outside the outer segment, perhaps in the cilium or membrane of the inner segment. Jan and Revel in an immunocytochemical study localizing rhodopsin in mouse rods, did find some evidence for photopigment in the plasma membrane of the inner segment. Alternatively, the absence of outer segments may promote the accumulation of these molecules elsewhere, but the photopigment as an intrinsic membrane protein, and the extrinsic membrane proteins of the cyclic GMP cascade must be in close proximity in order to interact. Are the extrinsic cascade proteins normally transported, bound to the membrane of the opsip transport system so that they locate in proximity to each other?

Another question raised by the result with the rd retinas relates to the fact that at 90 days current evidence points to the residua of the photoreceptors as being residua of cones. Is the cyclic GMP of mouse cones normally reduced by light or has the abnormality disturbed the adaptive situation in these cells to where light effects on cyclic GMP levels of cones are now revealed?

Finally, these data may have some clinical implications. Obviously, it was possible to pharmacologically manipulate levels of molecules potentially important for vision in severely damaged photoreceptors. Clearly it becomes important to study in model systems not only how deleterious genes damage photoreceptors, but also the biochemistry of what persists. Perhaps such studies could lead to improving and/or prolonging residual vision.

**Key words:** photoreceptors, transmitters, amino acids, cyclic nucleotides, mutant retinas

**References**

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