Rod-cone interactions and analysis of retinal disease

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SUMMARY Cone flicker threshold rises as the rods dark adapt, though the cone threshold to continuous light remains constant. The rise is normally about 1 log unit, but in certain patients who complain of night blindness it may be as great as 2.5 log units. In these persons the kinetics of the rod-cone interaction are those of the recovery of rod sensitivity. The rods impose a low-pass filter on the cones. This effect is absent in congenital nystagmus and X-linked retinoschisis. We suggest that cone flicker is maintained through a feedback system involving horizontal cells, and when the rod dark current returns in dark adaptation this feedback is altered. Rod cone interaction thus tests rod dark current, and cases of abnormal interaction in patients with retinitis pigmentosa occur, which indicate that the transduction mechanism and the membrane dark current may be differentially affected.

There have been several attempts to use psycho-physical methods to localise disease conditions to given retinal layers, notably by Enoch and his collaborators,1 but the methods involved have often been complex and time consuming and have made considerable demands on the patient. However, recently Goldberg et al.3 have described an increase in the cone flicker threshold which occurs as the rods dark adapt. This inhibition of cones by rods has been known for many years,3 but in the form described the phenomenon is robust, simple to elicit, and is familiar to clinicians. The interaction is developed at a specific retinal site. It therefore promises to be of considerable use in the investigation of retinal disease. Recently properties of the rod-cone interaction have been described.46

This paper presents additional findings which help to define the nature and the site of the interaction. Equipment for a clinical test is described together with observations which show that the interaction is abnormal in a number of clinical conditions. These provide strong evidence about the site of the interaction, and suggest that study of the phenomenon will increase our understanding of various causes of night blindness.

Material and methods

Equipment

Most of the initial work was done with the computerised light-emitting diode (LED) perimeter described by Ernst et al.7 This placed 1° green or red spots of light anywhere in the visual field. In the present experiments a site 10° nasally was usually examined. Additional experiments were performed with similar equipment but manually controlled. In one version the filtered LED (light output centred at 660 nm) was attached to one end of a flexible light-pipe, the other end of which was inserted through a hole in a piece of white card, which could be illuminated to produce a dim blue surround. The (660 nm) light which was used to illuminate the surround was provided by a Grass PS22C stroboscope fitted with neutral and colour filters.8 The mean light output was altered by changing the flash rate between 40 and 60 pulses per second (pps) so that, with all the filters in place, the surround was at the rod absolute detection threshold. Under the conditions of the experiments the blue light appeared continuous.

The final equipment utilised both blue and red LEDs. These were driven by a pulse technique. The advantages of this drive, which has been developed from devices previously described in detail,7,8 are that linear output can be maintained over six decades of intensity: circuits which depend on variable current driving provide linear output over a more limited range of intensities. In addition the pulse driving circuit can provide various stimulus waveforms. Pulses, sine waves, increments, and decrements of light intensity can readily be achieved, and various spatial outputs, for example discs, annuli, chequerboards, etc., are easily realisable. In the present experiments only uniform patches of light were used, and usually flicker was produced by abruptly turning the stimulus light on and off. However, the luminance could easily be made to change in a sinusoidal fashion, and then the modulation depth of the stimulus, defined as \((I_{\text{max}}-I_{\text{min}})/(I_{\text{max}}+I_{\text{min}})\), could be varied, so that the modulation thresholds could be determined for every temporal frequency at the same mean level of illumination.

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The block diagram and components are shown in Fig. 1. The waveform generator (Intersil 8038) provides sine, square, and triangle outputs. In the configuration shown the last is fed to a variable trigger point comparator, which thus acts as a phase detector (TLO81CP). The sine wave or pulse outputs are offset and attenuated to provide contrast and mean level controls, using standard operational amplifier techniques. The controls are 10-turn potentiometers, allowing settings to 1 part in 1000. It would be easy to provide for digital control at this stage if the equipment were to be connected to a computer. The signals alter the frequency of voltage controlled oscillators (VCOs). In the equipment, these are basically similar to the ones described by Faulkner,2,10 and for an input of 0–2.5 V provide an output from 100 Hz to 2.5 MHz, with a linearity of >1%. This is a discrete system, but a recently announced single package hybrid (Advanced Modular Concepts, 3800 series) exceeds this specification. The pulses from the VCOs are fed to edge sensitive counters (79LS390), and here divisions of 1, 2, 5, 10 . . . 10^5 are made for coarse control of light intensity. The pulses (50% duty cycle) are now fed to RS 422 line drivers, so the control equipment can be remote from the light sources. A simple digital meter inserted at this point in the circuit measures the stimulus repetition rate and also the light intensity, since this is directly proportional to the pulse frequency. Standard TTL pulse shapers and buffers are employed to produce 100 ns pulses. These drive power FETs, used as current sinks, which are sufficiently fast to pulse the necessary current and voltage through the LEDs. For all light outputs the current per pulse is constant, thus ensuring linearity. The LEDs are connected in series, and the number used depends on the supply voltage available and the forward voltage drop per LED; this varies with the type used. The peak current pulse used is very much greater than the maximum continuous forward current for the LED, and therefore high light outputs can be achieved, and of course these remain constant for the lifetime of the LED, which is much greater than for incandescent lamps or flash tubes.

In general it is possible to make the drive in such a way that various LED arrays may be plugged into the same unit, allowing for rapid interchange of light sources. The system is easily constructed, since integrated circuits are available for most components, with minimal external circuitry. Component costs are less than for a stroboscope, even for the complex version shown in Fig. 1. Further details are available from the authors. Red, orange, yellow, green, and blue LEDs are now available which will readily provide sufficient light for most physiological purposes, including electroretinography. The only disadvantage is the cost of blue LEDs (US$6 each).

Subjects and Patients

The authors and associated workers from the clinic acted as subjects. Other results were obtained on volunteers from the department who were au fait with the research and therefore could give informed consent. Other work was done in the course of normal dark adaptometry on patients who were referred for investigation of their eye condition. All observations were made after dilation of the pupil with 1% mydriate. All subjects and patients had 6/6
vision after spectacle correction, and had no visible fundus changes or complaints apart from the specific problems mentioned in the text.

**Subjects and patients** were light adapted either by using a photographic flash unit connected to a rigid light pipe, or by a tungsten-halide bulb viewed through a Fresnel lens system in maxwellian view. In both cases large areas of the retina (>1 sr) were illuminated by more than 7.5 log td s², which is sufficient to bleach almost all the rhodopsin.¹¹

**Psychophysical techniques.** In most experiments the method of ascending limits was used, with a computer providing a standard rate of increase of light intensity.¹ In a few cases this was checked by using a forced choice staircase method, with ascending and descending intensities, and the threshold was then taken as the point where the probability of correct positive and negative responses was equal. In static conditions the results obtained by the two methods were similar, but the forced choice method was laborious and not suited to measurement of changing thresholds.

**Results**

Dark adaptation curves measured with red light flashes showed a rapid increase of cone sensitivity, which was essentially complete after three minutes.¹²,¹³ After about 20 minutes rod dark adaptation might have progressed so far that even far red light was perceived best by rods, and a further slight decrease in threshold might occur.¹² Whether this is seen depends upon whether the red test flash sub-

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**Table 1  Dark adaptation in normal subjects**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Thresholds* at 10'</th>
<th>Thresholds at 30'</th>
<th>Change from 10-30'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Green</td>
<td>Red</td>
<td>Green-red</td>
</tr>
<tr>
<td>9</td>
<td>32:5±16 (16-70)</td>
<td>-0.32±0.20</td>
<td>0.41±0.51</td>
<td>0.58±0.50</td>
</tr>
</tbody>
</table>

*Light intensities expressed as log candelas m⁻². Mean values and standard deviations are given (equivalent to 3 SEMs). The differences between green and red thresholds, and the change in threshold with time in the dark, are means of the individual values.
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![Graph showing rod-cone interactions and analysis of retinal disease](image)

**Fig. 3** Increment thresholds in a second subject with an exaggerated rod-cone interaction. The background was a 10° disc illuminated by 460 nm light (see 'Material and methods'). The subject dark adapted, and then visual threshold was determined for the background. The right hand ordinate gives the intensity in multiples of this threshold. Note that the threshold for detecting the red light (at 15 Hz, the sensation evoked is of a continuous constant luminosity) is unchanged by the rod background until, with four log units of filter removed, the threshold rises slightly. In contrast, the flicker threshold for red light drops when the background is increased. Other conditions similar to those for Fig. 2.

tends a large area, and is placed in a region of high rod density. However, if the stimulus is a 15 Hz square wave flicker, and the subject is asked to report not when he sees the light but when he sees it 'flicker', a very different result occurs. From about the 10th to the 25th min after the beginning of dark adaptation the flicker threshold rises, by over half a log unit.2 Table 1 gives the range for our 'normal' subjects. The slow time course of this change and the fact that it began almost at the moment of the rod-cone break suggests very strongly that the rod dark adaptation was causing the loss of sensitivity of cones.

In some persons the rise is much greater. We have found three of these, and all complained of difficulty with night vision, specifically in driving at night. Fig. 2 shows the result obtained in a patient aged 30, who had been seen for 10 years. No abnormality had ever been detected, but the patient, who is medically qualified, was positive he and other members of his family were visually impaired in dim light conditions. Since cone and rod thresholds were normal by a Goldmann-Weekers adaptometer, a possible psychogenic disturbance had been discussed. However, the threshold for detecting cone flicker rises by about 2.5 log units as the rods adapt, and because the effect is so large its kinetics are easy to study. The dashed curve in Fig. 2 gives the reciprocal of rod threshold, and it can be seen there is good agreement between it and the cone threshold data. Similar results have been found on other subjects (Fig. 6). One of these, a laboratory technician aged 39, volunteered that she had difficulty in driving at night and in seeing kerb markings. Another of our colleagues, hearing these results, suggested he should be tested, and he also had a large rise of flicker threshold. However, another subject who claimed he had the same disability had a threshold rise of only 0.6 log unit.

The appearance of the cone inhibition can be reversed by using a background which stimulates only rods. Fig. 3 shows this, again on a subject with an exaggerated effect. It can be seen that 3 log units of background were required before the cone flicker threshold abruptly fell. At visual threshold only a small fraction of the rods—perhaps one in a hundred—absorbed a quantum of light per second. Thus the
illumination which causes the fall in cone flicker threshold is one where all the rods are continuously stimulated, but the rod dark current is reduced but not abolished. The rapid increase of the cone threshold when the rod background is turned off is what would be expected under such circumstances. Such a background, while effective in stimulating rods, is still subthreshold for the red cones. Note that 4 log units suprathreshold light was required to increase the cone flash threshold.

The inhibition of the cone signal occurred only at higher temporal frequencies. Fig. 4 presents the modulation curves for two subjects, and it can be seen that, while for low frequencies (1 Hz) the threshold modulation was unaffected by the background, for higher frequencies the effect became progressively greater: Dark adapted rods seemed to interpose a low-pass filter into the cone pathway.

The effect of backgrounds is not critically dependent on the light intensity used in the red test. Fig. 5 shows results obtained when it is set at 1, 3, and 4-3 log units above the 1 Hz detection threshold. For all these values the effect of the background was to decrease the depth of modulation required to see the flicker. The ability to detect the flicker was much greater for the stimulus which was 3 LU above threshold, but the further increase caused little change either in the dark adapted condition or in the presence of a background. Thus the effect of the background cannot (within these limits) be mimicked by increasing the intensity of the test light. These observations are incompatible with the idea that the effect is somehow spurious and produced by subliminal stimulation of the cones by the rod stimulus.

Another observation which shows that a novel form of interaction is occurring is that the rise of flicker threshold was seen only if the red test field was relatively small: the rise of approximately 2 LU shown in Fig. 6 was totally absent if a 50° field was used as a test target (Fig. 6).

**ROD–CONE INTERACTION IN PATIENTS WITH ABSENCE OF ROD B WAVES**

The site of the interaction between the rod and cone pathway can be investigated by utilising clinical pathology. In nyctalopia there is a failure of synaptic
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Transmission by rods, though rhodopsin is present, and there is electroretinographic evidence that only the rod receptor potential is developed.\textsuperscript{11} \textsuperscript{14} \textsuperscript{15} Consequently, if the rod-cone interaction occurs at a site which precedes the development of the b wave, it should be developed in nyctalopes. Fig. 1 in Arden and Hogg's paper\textsuperscript{1} shows that in one patient this is not the case. Various forms of nystagmia have been described\textsuperscript{11} \textsuperscript{14} \textsuperscript{15} \textsuperscript{16} \textsuperscript{17} and our patients fall into two groups —those with and those without elevation of the cone flicker threshold. Table 2 shows the thresholds after 5 minutes and 20–30 minutes of dark adaptation in this group. All the patients had classical electroretinograms, consisting of rod PIII and some cone b wave. The mean rise in the flicker threshold is $-0.025$ LU.

The appearance of an isolated rod PIII also occurs in some cases of X-linked retinoschisis.\textsuperscript{15} \textsuperscript{16} In young patients vision is well preserved, and schisis at the posterior pole is patchy, so large cysts such have been reported in the literature are not formed. The fundus photograph of the eye is shown in Fig. 7. Dark adaptation thresholds are normal or moderately elevated. In cases such as these (see the caption to fig. 8 for further details) the cone flicker threshold does not rise during rod dark adaptation (Fig. 8). However, in one family, the results are variable, and this is not surprising, for so too is the degree of schisis. The cases we have seen differ from the nyctalopes in one respect, that rods continue to function though there may be an elevation of the dark adapted threshold.

**Rod-cone interaction in retinitis pigmentosa**

In some cases where there is no detectable rod function (type 1, see Arden et al.,\textsuperscript{9} Massof and Finkelson\textsuperscript{10}) rod-cone interaction has not been seen, though cone threshold was not significantly elevated. In one patient with type II disease and well preserved rod function the effect was present, though reduced (Fig. 9). In another patient with type II disease there

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**Fig. 5** Modulation thresholds as a function of test light intensity, without a background (left) and with a background (right). Note that for test lights 3 and 4-3 log units above the detection threshold the high frequency modulation thresholds are not greatly different, but there are large effects of the 460 nm background, which is 3 log units above the rod threshold.
was slowed dark adaptation, and a normal sized increase in the cone flicker threshold occurred at a time when the patient’s rods were very insensitive. No further change occurred as they gradually recovered (Fig. 10) and threshold for green light fell to nearly normal limits.

Discussion

The rod-cone interaction described is a very robust phenomenon, and can easily be measured by a simple modification of most dark adaptometers. It is consequently a practical clinical test. Patients easily comprehend the idea of distinguishing between the appearance of a light and the development of a sensation of flicker. The threshold for detection of a red light flickering at 15 Hz is little different from that of a non-flickering red light, and during the early part of the cone plateau the thresholds for detection and recognition of flicker in most patients are nearly the same. Consequently, even if the adaptometer is modified so that the red test spot always flickers, there is no loss in terms of the information available, and there are the gains described above, in terms of diagnosis of complaints of loss of night vision.

One of the new findings made in the course of the investigation is that there are persons in whom the rod cone interaction is exaggerated, and that these persons either present with the complaint or volunteer the information that they have difficulty in seeing at night. Although in many cases where no retinal cause can be found subjective nyctalopia may be due to aging processes, which reduce retinal illumination or cause glare, or to night myopia, there remains a core of patients in whom, as demonstrated above, dark adapted rods seem to cause gross inhibition of the sensation caused by small, rapidly changing objects. The task which one would predict would be
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Fig. 7A: Fundus photograph of patient with X-linked retinoschisis, case 13011, whose ERGs and dark adaptation curves are shown in Fig. 8. B: Early phase fluorescein angiogram of peripheral retina in same subject.

difficult for such persons is night driving, and this is the presenting complaint. It is therefore plausible that abnormally active rod-cone interaction can be a hitherto unsuspected cause for referral to an ophthalmologist. In the absence of other signs and symptoms, and before the demonstration that all people such as those whose results are shown in Fig. 2–6 have actual visual disability, it is premature to suggest that the test has uncovered a new disease.

However, it is possible that in one of our patients, the condition is familial.

MECHANISM OF ROD–CONE INTERACTION

Depending on the cause of the interaction, the test can shed light on the pathophysiology of disease, and for this reason our first investigations have been directed to this end. In the mammalian retina there are numerous gap junctions between rods and cones, and these may allow a certain degree of electrical communication between the different photoreceptor classes. It is possible that in the first instance a normal interaction is a necessary consequence of the basic mammalian retinal architecture.

Table 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
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<th>EOG</th>
<th>ERG</th>
<th>Thresholds*</th>
<th>Rod-cone interaction†</th>
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<tr>
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<td></td>
<td></td>
<td>At cone plateau</td>
<td>Final value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Green</td>
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<td></td>
<td></td>
<td>Red</td>
<td>Green</td>
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<tr>
<td>13011</td>
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<td>117</td>
<td>-ve</td>
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<td>0.35</td>
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<td>11806</td>
<td>46</td>
<td>6/60</td>
<td>178</td>
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<td>13565</td>
<td>59</td>
<td>6/60</td>
<td>—</td>
<td>-ve</td>
<td>0.45</td>
<td>0.5</td>
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<td>13331</td>
<td>48</td>
<td>6/60</td>
<td>—</td>
<td>-ve</td>
<td>0.15</td>
<td>-0.25</td>
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<td>13493</td>
<td>10</td>
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<td>200</td>
<td>reduced b waves</td>
<td>0.10</td>
<td>-0.65</td>
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<tr>
<td>13494</td>
<td>6</td>
<td>6/6</td>
<td>240</td>
<td>reduced b waves</td>
<td>-0.25</td>
<td>-0.25</td>
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Summary of data on patients with stationary night blindness‡

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>VA</th>
<th>EOG</th>
<th>ERG</th>
<th>Thresholds*</th>
<th>Rod-cone interaction†</th>
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<td>At cone plateau</td>
<td>Final value</td>
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<td>Green</td>
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<td>Green</td>
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<tr>
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<td>6/6</td>
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<tr>
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<td>6/18</td>
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<td>0.50</td>
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<tr>
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<td>—</td>
<td>-ve</td>
<td>0.30</td>
<td>0.35</td>
</tr>
<tr>
<td>14085</td>
<td>22</td>
<td>6/12</td>
<td>—</td>
<td>-ve</td>
<td>2.10</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Threshold values in log cd.m⁻².
†Normal interaction is given a +ve sign.
‡All patients had full fields with no scotomata, no ophthalmoscopic changes in the fundus, a history of nyctalopia for many years, and no evidence of repeated visits of any progressive disorder.
cones, so that presynaptic interaction is possible. The results with nyctalopia provide good evidence that the interaction is postsynaptic. The absence of the interaction in patients with retinoschisis, who are not night blind, implies that the bipolar cell—ganglion cell pathway itself cannot mediate the interaction. The finding that the interaction imposes a low pass filter in the cone pathway, but that this effect is absent or reduced when the cone test stimulus has a very large subtense, suggests strongly that the rod interaction occurs via a lateral interaction with a large spatial summation pool, and the earliest site for this to happen is the horizontal cell, which has such characteristics. In mammals horizontal cells are known to form synapses with both rods and cones, and the axon terminations receive predominantly rod inputs. All S potentials recorded contain rod and cone components, but the potentials are additive. The inhibition of cones by rods is not directly explicable from such observations. However, an inhibitory action which is well known involves the feedback to cones from horizontal cells. This has been demonstrated only in turtles and amphibia, where intracellular recordings from photoreceptors is possible, but the synaptic appearances in the primate outer plexiform layers suggest a similar organisation. The effect of the feedback is to reduce the cone receptor potential waveform after a delay, so that the flash evoked response reaches its peak and then suddenly decreases. As expected, this feedback improves the high frequency response of the cone system.
The simplest explanation of the findings described under 'Results' is that late in dark adaptation the cone feedback system becomes relatively inefficient, so that the high frequency responsiveness of the photopic system is decreased. Horizontal cells, like photoreceptors, are depolarised in darkness and are supposed under these conditions to liberate continuously an inhibitory transmitter. Hence when a stimulus hyperpolarises the cones, and the horizontal cell membrane hyperpolarises in turn, there is a small proportional decrease in the concentration of the inhibitory feedback transmitter. When rods hyperpolarise, the horizontal cell follows suit, the concentration of the inhibitory feedback transmitter declines, and the fractional change in transmitter caused by the same cone signal increases. In addition it is possible that the relationship between horizontal cell membrane potential change and the rate of liberation of feedback transmitter is optimised for the light adapted state. A given cone signal would then cause a maximal change in feedback transmitter.
output when the horizontal cell was partially hyperpolarised.

When the cone stimulus covers a large retinal area, it produces larger horizontal cell responses than when it subtends a small visual angle, and therefore the feedback may still be effective in the dark adapted eye. In the first few minutes after intense light adaptation, the rat rod receptor potential is maintained in the hyperpolarised state, but later the dark current returns once more along a time course that (in axolotl rods) approximates to, but is not identical with, that of the recovery of sensitivity to light, thus accounting for the attenuation of the cone flicker signal during rod dark adaptation.

Following intense bleaching there is a large afterhyperpolarisation in cat horizontal cells, which lasts for many seconds, but the time course of recovery may be faster than the rate of rhodopsin regeneration. In turtle cones the horizontal cell feedback is best seen and operates between different classes of cones, but it has been reported that in man the interaction occurs only between rods and red cones; little is known about the feedback in mammalian or primate receptors. An alternative hypothesis is that the rods control the horizontal cell membrane potential indirectly, through an interplexiform cell feedback.

CLINICAL IMPLICATIONS

The appearance and magnitude of the rod-cone interaction described above would, on our hypothesis, depend upon the time and extent of the rod dark current. In those persons with exaggerated effects, perhaps the effectiveness of the rod transmitter in depolarising the horizontal cells is greater than normal. In our cases of X-linked schisis the reduction of the inhibition of cones by rods implies that the horizontal cell feedback must be reduced, but the relationship to pathological changes is not certain. In elderly persons cystic degeneration affects the outer retina, so that in the end a few bipolar cells mark the limits of the cysts, and it is entirely plausible that the lateral connections of horizontal cells are disrupted. In X-linked schisis the split is supposed to be in the nerve fibre layer or the inner plexiform layer. However, the evidence is not conclusive, and the patients from whom the histological results were derived were not investigated by ERG, so it is not known if they were of the type we have seen. The lesions were much more severe than in our patients.

If the hypothesis advanced above is correct, this form of rod-cone interaction measures the integrity of the outer plexiform layer and also provides an index of the function of the rods which is independent of whether visual transduction occurs normally. Thus in retinitis pigmentosa we can show that in some cases, although there is a moderate reduction in sensitivity, the interaction is present. This would be consistent with the idea that there was a reduced rod dark current input to horizontal cells. In one case change in cone sensitivity is dissociated (Fig. 8) from the change in rod sensitivity, and hence on this argument dissociated from the rod membrane current. Therefore it is likely that in this patient the plasma membrane processes may be normal, while the intracellular mechanisms which control rod sensitivity are affected by the condition. Detailed analysis of selected patients is under way to determine whether reduction in membrane current and reduction of rhodopsin concentration run in parallel. This might answer the question whether rods in retinitis pigmentosa are shortened or disorganised.

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References

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