Local Cone and Rod System Function in Progressive Cone Dystrophy

Karen Holopigian, William Seiple, Vivienne C. Greenstein, Donald C. Hood, and Ronald E. Carr

PURPOSE. To compare the patterns of local cone and rod system impairment in patients with progressive cone dystrophy (CD) using psychophysical and electrophysiological techniques.

METHODS. Local cone system function was assessed by measuring cone system thresholds (visual fields) and cone-mediated multifocal electroretinograms (mERGs). Rod system function was assessed by measuring rod system thresholds (visual fields) and rod-mediated mERGs. The results in a group of eight patients with CD were compared with those in an age-similar control group.

RESULTS. All the patients had abnormal cone system visual field thresholds and cone-mediated mERGs. Cone system psychophysical thresholds were elevated for targets presented within the central 10°, but were within normal limits for targets at peripheral locations. Cone-mediated mERG measures of amplitude scale and time scale were abnormal for most of the hexagons tested. Most of the rod-mediated psychophysical thresholds and mERGs were within normal limits. Rod system losses tended to be patchy and scattered throughout the area tested.

CONCLUSIONS. There was poor correspondence among local measures of cone and rod system losses in these patients with CD. The results suggest that the spatial pattern of cone system losses in this disease differs from the spatial pattern of rod system losses. (Invest Ophthalmol Vis Sci. 2002;43:2364–2373)

Progressive cone dystrophy (CD; also called progressive cone degeneration) is an inherited retinal disorder that primarily affects cone system function, with more limited involvement of the rod system. Visual function in patients with CD is most debilitated under light-adapted conditions, and the losses include reduced visual acuity, photophobia, sensitivity to glare, and abnormal color vision. Typically, fundus changes are minimal and limited to the macular area, but the fundus can also appear to be normal.

Measures of cone system function in these patients disclose both psychophysical and electrophysiological deficits. Color vision is grossly abnormal, dark adaptation curves have greatly elevated cone system thresholds, the full-field cone-mediated electoretinogram (ERG) is reduced in amplitude and delayed, and the cone-mediated mERGs are reduced in amplitude and delayed.

Although CD is primarily a disease of the cone system, rod function can be affected. Full-field rod-mediated ERG amplitudes range from normal to a 50% reduction, and implicit times may be either normal or delayed. Measures of dark adaptation have shown that final rod system thresholds may be elevated by approximately 0.5 log units. These results are consistent with relatively mild changes in rod system function.

Patients with CD often have full-field cone-mediated ERGs that, although reduced in amplitude and delayed, are still recordable. This implies that there is some sparing of the cone system. However, it is not known which areas of the retina are most affected and whether the retinotopic pattern of cone and rod system losses in this disease are correlated. In the present study, we examined the spatial relationship among local psychophysical and local electrophysiological measures of cone and rod system function. We measured local cone system thresholds psychophysically in a group of patients with CD and compared these to local cone-mediated mERG responses obtained at the same locations. We also compared local rod system psychophysical thresholds and local rod-mediated ERGs. Finally, cone and rod system results were compared, to determine whether there was local correspondence among losses in these two systems.

METHODS

Subjects

Eight patients with CD were recruited from the practice of one of the authors (REC) for participation in this study. The patient group had a mean age of 38.8 ± 15.4 years. Relevant characteristics of the study participants are listed in Table 1. The diagnosis of CD was based on history, visual acuity, color vision, full-field ERG results (according to International Society for Clinical Electrophysiology of Vision [ISCEV] standards), and fundus examination. Patients with the cone–rod variant of RP were excluded, based on fundus findings and full-field ERG results. Visual acuity in the patients ranged from 20/20 to 20/120. Fixation was assessed with fundus photography with a fixation target and was central and steady in the tested eye. The patients either had normal findings on the fundus examination or had minimal fundus changes. They showed no evidence of cystoid macular edema and no significant cataracts or any other ocular or systemic problems. The standard full-field ERG results (see Methods and Table 1 for data) indicated that the photopic flicker responses were reduced in amplitude in all eight patients (range, 13%–24% of normal). In addition, flicker implicit times were delayed in all subjects. The scotopic rod-mediated (S1 blue) amplitudes were within normal limits in three patients and reduced in amplitude in five (range, 29%–69% of normal). The implicit times were within normal limits in three patients and delayed in the remaining five. The scotopic bright-flash (S16) amplitudes were reduced in seven patients (range, 34%–62% of normal) and delayed in six patients.
The control group consisted of eight age-similar observers with normal visual acuity and normal findings on ophthalmic examination. The control group had a mean age of 45.6 ± 11.3 years. Tenets of the Declaration of Helsinki were followed, and informed consent was obtained after the nature and possible consequences of the study were fully explained. The research protocol was approved by the Institutional Board of Research Associates of New York University School of Medicine and Bellevue Hospital.

**Apparatus and Procedure**

In all subjects, the eye with the better visual acuity was tested. If visual acuity was equivalent in the two eyes, the right eye was tested. The contralateral eye was patched. For all visual acuity was equivalent in the two eyes, the right eye was tested. The eye with the better visual acuity was tested. If visual acuity was normal visual acuity and normal findings on ophthalmic examination.

**Full-field ERGs.** For the purpose of diagnosis, ISCEV standard full-field ERGs were recorded with a photosimulator (Grass Instruments, Quincy, MA) with a ganzfeld surround. ERGs were recorded with a bipolar Burian-Allen contact lens electrode. The forehead electrode with the ipsilateral ear as ground. The full-field ERG signal was digitized at 1000 Hz, amplified (1 K; preamplifier P511J; Grass Instruments), and band-pass filtered between 10 and 300 Hz; the signal was digitized at 1000 Hz, amplified (1 K; preamplifier P511J; Grass Instruments), and band-pass filtered between 10 and 300 Hz. Subjects' vision was best corrected for the viewing distance. Two recordings were obtained (3.6 minutes each), and the first-order kernels were averaged for analysis.

**Cone-Mediated mfERGs.** After pupil dilation (1% tropicamide and 2.5% phenylephrine hydrochloride), cone-mediated mfERGs were recorded. The multifocal technique used in this study was based on the work of Sutter and Tran and has been described in detail elsewhere. Briefly, the stimulus was an array of 103 hexagons that were scaled with eccentricity. At the viewing distance of 32 cm, the hexagon display subtended 46° horizontally and 39° vertically. A central X was used for fixation. The luminance of the white hexagons was 360 cd/m²; the surround luminance was 190 cd/m². Cone-mediated mfERGs were recorded with a bipolar Burian-Allen electrode. The ipsilateral ear served as a ground. The mfERG signal was digitized at 1200 Hz, amplified (100 K; model P511J preamplifier; Grass Instruments), and band-pass filtered between 10 and 300 Hz. Subjects' vision was best corrected for the viewing distance. Two recordings were obtained (3.6 minutes each), and the first-order kernels were averaged for analysis.

**Rod System Visual Fields.** The subjects were dark-adapted for 45 minutes before the measurement of the rod system threshold visual fields. A custom computer program (Matlab; The MathWorks, Natick, MA) was used to present stimuli and calculate thresholds as a function of retinal eccentricity. The stimulus was an array of 61 equally sized white hexagons, excluding the center hexagon, which was used for fixation. The luminance of the white hexagons was 360 cd/m²; the surround luminance was 190 cd/m². Cone-mediated mfERGs were recorded with a bipolar Burian-Allen electrode. The ipsilateral ear served as a ground. The mfERG signal was digitized at 1200 Hz, amplified (100 K; model P511J preamplifier; Grass Instruments), and band-pass filtered between 10 and 300 Hz. Subjects' vision was best corrected for the viewing distance. Two recordings were obtained (3.6 minutes each), and the first-order kernels were averaged for analysis.

**Rod-Mediated mfERGs.** Rod-mediated mfERGs were recorded using the method of Hood et al. The stimulus array was the same as that used for the psychophysical procedure and was viewed through a blue filter (Wratten 47B; Eastman Kodak, Rochester, NY). At the viewing distance of 32 cm, the hexagon display subtended 42° horizontally and 38° vertically. A modified staircase procedure was used to obtain individual thresholds for 60 hexagons, excluding the center hexagon, which contained an X used for fixation.

**Table 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Fundus</th>
<th>Sex</th>
<th>Age</th>
<th>Acuity</th>
<th>S1 Blue</th>
<th>Scot. S16</th>
<th>Phot.Flicker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Salt and pepper granularity; slight vessel attenuation</td>
<td>M</td>
<td>16</td>
<td>20/50</td>
<td>108.9 µV</td>
<td>88.9 ms</td>
<td>230.1 µV</td>
</tr>
<tr>
<td>2</td>
<td>Normal, no foveal reflex</td>
<td>M</td>
<td>55</td>
<td>20/20</td>
<td>183.6 µV</td>
<td>99.6 ms</td>
<td>298.0 µV</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>M</td>
<td>40</td>
<td>20/30</td>
<td>199.3 µV</td>
<td>85.9 ms</td>
<td>306.7 µV</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>F</td>
<td>25</td>
<td>20/100</td>
<td>158.8 µV</td>
<td>74.2 ms</td>
<td>285.6 µV</td>
</tr>
<tr>
<td>5</td>
<td>Mild pigment mottling</td>
<td>M</td>
<td>34</td>
<td>20/120</td>
<td>203.9 µV</td>
<td>71.8 ms</td>
<td>302.9 µV</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>F</td>
<td>29</td>
<td>20/60</td>
<td>328.7 µV</td>
<td>70.8 ms</td>
<td>504.3 µV</td>
</tr>
<tr>
<td>7</td>
<td>Normal</td>
<td>M</td>
<td>56</td>
<td>20/30</td>
<td>146.0 µV</td>
<td>85.4 ms</td>
<td>214.9 µV</td>
</tr>
<tr>
<td>8</td>
<td>Narrowed arterioles; loss of macular RPE</td>
<td>M</td>
<td>55</td>
<td>20/20</td>
<td>78.8 µV</td>
<td>85.9 ms</td>
<td>167.5 µV</td>
</tr>
</tbody>
</table>

Scotopic S1 blue: control range, 196.0–340.0 µV; 59.1–75.9 ms; scotopic S16: control range, 361.5–619.5 µV; 37.0–45.0 ms; photic flicker: control range, 118.0–218.0 µV; 26.0–30.0 ms.
at 1200 Hz and amplified (50 K; model P511J preamplifier; Grass Instruments). To accommodate the lower-frequency components of the rod mfERG, the band-pass filter settings were changed to 1 and 100 Hz. This lower cutoff frequency may allow slow drifts into the records, but raising the cutoff frequency reduces the amplitude of the response.11

**Analysis.** The cone and rod system visual field data were converted to log threshold elevation, computed as the difference between the patient’s log threshold and the average log threshold in the control group. Values greater than 0.0 indicate elevated thresholds.

The mfERGs were analyzed using custom computer programs (Matlab; MathWorks).13 The data from the control subjects were averaged separately for the cone- and rod-mediated responses and for each hexagon to create ‘standard’ templates. The patient’s ERGs for each hexagon were then best fitted by scaling the appropriate template in both the amplitude and time domains. If the fit from a hexagon was beyond the acceptable goodness-of-fit value, the results from that hexagon were discarded. For more details on the procedure for fitting and analysis of the cone- and rod-mediated responses, see Hood and Li13 and Holopigian et al.12 The amplitude and implicit time results were measured as amplitude scale and time scale (the ratio of the patient’s response to the control subjects’ response) so that comparisons could be made between cone- and rod-mediated mfERG data, because the amplitudes and implicit times of these measures differ.

**RESULTS**

Figure 1 shows examples of mfERGs recorded from a control observer. The top panels show the hexagonal arrays used for the cone-mediated and rod-mediated mfERGs, and the bottom panels show the cone-mediated and rod-mediated trace arrays. There were differences in wave shape, timing, and amplitude between the cone- and rod-mediated mfERGs.

**Cone System Data**

Figures 2A and 3A show the cone system results in patients 4 and 6 (Table 1), respectively. In these figures, the upper left panel contains the mfERG trace arrays, the upper right panel contains the visual field results, and the numbers inside each hexagon represent log threshold elevation for that hexagon. The lower left panel contains the mfERG amplitude scale values and the lower right panel contains the mfERG time scale values obtained from the fit of the normal template. For the visual field and multifocal data, if the patient’s results for a particular hexagon were within the 95% confidence intervals of the control group, the hexagon is white. If the value was beyond the 95% confidence intervals, the hexagon is gray and contains the value. For the multifocal data, if the results from a hexagon were beyond the goodness of fit, the hexagon is gray, with no value shown.

The results for the two patients show the overall pattern of findings for the group. Cone threshold elevations (Figs. 2A, 3A, upper right) were highest in the central retinal areas. The magnitude of threshold elevation decreased with eccentricity, and all the subjects had cone system thresholds within normal limits for some peripheral locations. As expected, the cone-mediated mfERGs were greatly reduced in amplitude (Figs. 2A, 3A, bottom left), especially for the centermost hexagons (Figs. 2A, 3A, center and first ring). The responses in the centermost hexagons were either unmeasurable or were 10% to 20% of the control responses. Similarly, the mfERGs were delayed throughout (Figs. 2A, 3A, bottom right), and the delays were greater in the central retinal areas. In the cone system, the psychophysical thresholds were within normal limits in more hexagons than were the mfERG results.
To summarize, the results in all patients and all hexagons are shown in the next series of figures. For the cone-mediated responses, the results of six patients are shown. One patient (P1, Table 1) was unable to complete the cone system testing protocol, and another patient (P5, Table 1) had unmeasurable cone system mfERGs throughout the entire retinal area tested. Both of these patients had measurable rod-mediated mfERGs. The cone system amplitude scale and psychophysical threshold elevation data are plotted in Figure 4A. Although 86% of the responses were abnormal for amplitude scale (two lower quadrants), only 48% of the psychophysical thresholds were abnormal (right upper and lower quadrants). To determine whether there was a relationship between these two variables, regression parameters were estimated for each patient. The ANOVA statistics for the regression parameters are reported in Table 2 (top section, left column). Of the six patients with cone-mediated data, four had significant results (indicated by asterisks) indicating that, in these patients, there was a predictive relationship between these two variables (i.e., the slope of the predicted regression line was significantly different from zero).

The cone-mediated time scale values and threshold elevation data are plotted in Figure 5A. Again, more time scale...
responses (80.5%; Fig. 5A, two upper quadrants) were abnor-
mal than psychophysical thresholds (48%; Fig. 5A, right upper
and lower quadrants). Again, the regression parameters were
estimated, and the results are shown in Table 2 (middle sec-
tion, left column). In four of the six patients with cone-medi-
ated results there were significant predictive relationships be-
tween these variables; and in three of these four, as described
earlier, there were also significant relationships between
threshold elevation and amplitude scale.

The cone-mediated amplitude scale values versus time scale
values are plotted in Figure 6A. The majority of the amplitude
circle scale and time scale responses (66.5%; Fig. 6A, lower right
quadrant) were abnormal, and none of the responses had both
normal amplitude and timing (Fig. 6A, bottom left quadrant).
However, 19.5% of the responses had normal timing and ab-
normal amplitude (Fig. 6A, lower right quadrant), and 14% had
normal amplitude but abnormal timing (upper left quadrant).
The regression parameters of the amplitude scale and time

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**FIGURE 3.** Cone (A) and rod (B) sys-
tem results in patient 6. Data are pre-
sented as described in Figure 2.
of eccentricity. The results for the patients shown in Figures 2 and 3 suggest that the spatial pattern of visual loss in this disease differs in the cone and rod systems. The cone system losses appeared to be more severe in the central retinal regions, whereas the rod system losses did not appear to vary with retinal eccentricity. To examine this, the cone and rod system results were summarized and compared as a function of eccentricity. For this comparison, the cone-mediated mfERG responses were reexamined with the same spatial-averaging algorithm that was used for the rod system. The values obtained for the 103 hexagons were then collapsed into 61 values corresponding to the array used for the rod system conditions. The median values for the cone and rod system data were then obtained for the center hexagon and five concentric rings.

In Figure 7 (top) the psychophysical threshold data summarized as a function of eccentricity are shown. For the cone system, threshold elevation was nearly 1 log unit greater at the centermost ring than at the most peripheral locations. A repeated-measures ANOVA indicated that eccentricity was a main effect (F(3,15) = 5.22, P = 0.011). For the rod system, threshold elevation averaged 0.54 log units and was essentially unchanged as a function of retinal location. There was not a significant eccentricity effect for the rod system data. For comparison, the same analysis is shown for a group of seven patients with retinitis pigmentosa (RP).12 The results in the patients with RP (Fig. 7, bottom) differ from the results in the patients with CD. Threshold elevation in the cone system was lower (by greater than 1.0 log unit) at the centermost ring than at the most peripheral locations. A repeated-measures ANOVA indicated that eccentricity was a main effect (F(3,15) = 5.22, P = 0.011). For the rod system, threshold elevation was also less (by nearly 0.5 log unit) at the centermost ring than at the most peripheral locations. Both cone and rod system thresholds were significantly different, as a function of eccentricity; cone: F(3,18) = 10.86, P = 0.0003; rod: F(3,18) = 4.98, P = 0.0011.

In Figure 8 (top) the amplitude scale data of the patients with CD are shown. Once again, the pattern of loss with eccentricity differed in the cone- and rod-mediated data. The cone-mediated amplitude scale values were smallest in the center ring and increased with eccentricity. A repeated-measures ANOVA showed eccentricity to be a main effect (F(4,20) = 6.99, P = 0.001). The rod-mediated amplitude scale values did not vary significantly with eccentricity. The results in the patients with RP are shown in Figure 8 (bottom). The cone-mediated amplitude scale values were largest for the center ring and decreased with eccentricity (F(4,24) = 4.53, amplitude scale. In the remaining patients, there was no significant predictive relationship between these measures (i.e., the slope of the predicted regression line was not significantly different from zero).

Rod system thresholds and rod-mediated time scale values are plotted in Figure 5B. The majority of the responses (60.5%) were within normal limits for both measures (Fig. 5B, lower left quadrant). The regression parameters (Table 2; middle section, right column) indicate that only one of the eight patients had a significant predictive relationship between these variables.

Finally, the relationship between the rod-mediated amplitude scale values and time scale values is plotted in Figure 6B. Whereas the majority of cone-mediated amplitude and timing responses were abnormal (Fig. 6A), the majority of the rod-mediated responses were normal (Fig. 6B), with more than 70% of the rod-mediated responses within normal limits for both measures (lower left quadrant). The regression parameters are shown in Table 2 (bottom section, right column). They indicate that four of the eight patients had significant regression parameters for these two mfERG measures.

Responses as a Function of Eccentricity

Rod-mediated results in patients 4 and 6 are shown in Figures 2B and 3B, respectively. Patient 4 showed scattered rod-mediated threshold elevations (Fig. 2B, upper right) of 0.7 to 0.9 log units. Patient 6 had normal thresholds throughout the area tested (Fig. 3B, upper right). In both patients, the rod-mediated mfERG was abnormal for both amplitude scale and time scale values in some hexagons. These abnormal responses appeared to be scattered across the area tested.

Rod system thresholds and rod-mediated amplitude scale values in the eight patients are plotted in Figure 4B. The majority of the responses (66.9%) were normal for both measures (Fig. 4B, upper left quadrant), whereas 16.2% of the responses were abnormal for both (Fig. 4B, lower right quadrant). For these data, the ANOVA statistics for the regression parameters for each patient are shown in Table 2 (top section, right column). Of the eight patients with rod-mediated results, only one had a significant relationship between thresholds and parameters for each patient are shown in Table 2 (top section, right column). Of the eight patients with rod-mediated results, only one had a significant relationship between thresholds and.

Responses as a Function of Eccentricity
where the electrophysiological responses could be abnormal. And normal cone system thresholds for some of the peripheral cone system thresholds for the more centrally located targets areas in our patients with CD. All the patients had abnormal difference between central retinal areas and peripheral retinal areas.

For the psychophysical cone system thresholds, we found a 2.2, P = 0.14

Figure 9, top, shows the time scale data examined in the same manner. In the patients with CD (top), the cone-mediated time scale values showed a significant decrease as a function of eccentricity (F(4,19) = 6.25, P = 0.002). The rod-mediated time scale values did not vary significantly with eccentricity. The results of the patients with RP are shown in Figure 9 (bottom). The time scale results are similar to the amplitude scale results, in that cone-mediated time scale varied significantly with eccentricity; (F(4,24) = 12.98, P < 0.0001) and rod-mediated time scale did not.

**DISCUSSION**

**Local Cone and Rod System Topography in Patients with CD**

For the psychophysical cone system thresholds, we found a difference between central retinal areas and peripheral retinal areas in our patients with CD. All the patients had abnormal cone system thresholds for the more centrally located targets and normal cone system thresholds for some of the peripheral targets. These normal cone system thresholds were in areas where the electrophysiological responses could be abnormal. Brown et al. examined Goldmann visual fields in a family with X-linked cone-rod dystrophy and found central and paracentral scotomas with normal peripheral fields in all patients, regardless of age. In the present study, the size of the area with normal thresholds varied among the patients, ranging from 10% to almost 90% of the tested locations.

As expected, the cone system mERGs showed large reductions in amplitude and significant delays over much of the tested area. These results are consistent with the findings of Kretschmann et al. who examined cone-mediated mERGs in five patients with cone dystrophy. The mERGs in our patients with CD were abnormal in more hexagons than were the psychophysical thresholds. In addition, the mERGs from the

P = 0.007). Rod-mediated amplitude scale, however, did not vary significantly with eccentricity.

**FIGURE 5.** The relationship between psychophysical threshold elevation and mERG time scale values. (A) Cone-mediated and (B) rod-mediated results. Data are presented as described in Figure 4.

### Table 2. Regression Parameters

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cone</th>
<th>Rod</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude scale vs. threshold elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>F(1,100) = 11.7, P &lt; 0.001*</td>
</tr>
<tr>
<td>2</td>
<td>F(1,100) = 11.7, P &lt; 0.001*</td>
<td>F(1,46) = 0.11, P = 0.74</td>
</tr>
<tr>
<td>3</td>
<td>F(1,101) = 0.91, P = 0.34</td>
<td>F(1,49) = 0.56, P = 0.45</td>
</tr>
<tr>
<td>4</td>
<td>F(1,100) = 48.0, P &lt; 0.001*</td>
<td>F(1,44) = 0.70, P = 0.41</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>F(1,31) = 1.5, P = 0.24</td>
</tr>
<tr>
<td>6</td>
<td>F(1,99) = 53.2, P &lt; 0.001*</td>
<td>F(1,45) = 0.08, P = 0.78</td>
</tr>
<tr>
<td>7</td>
<td>F(1,94) = 0.03, P = 0.87</td>
<td>F(1,42) = 0.16, P = 0.69</td>
</tr>
<tr>
<td>8</td>
<td>F(1,101) = 36.4, P &lt; 0.001*</td>
<td>F(1,33) = 1.52, P = 0.23</td>
</tr>
<tr>
<td>Time scale vs. threshold elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>F(1,46) = 2.2, P = 0.14</td>
</tr>
<tr>
<td>2</td>
<td>F(1,96) = 0.73, P = 0.39</td>
<td>F(1,49) = 3.2, P = 0.08</td>
</tr>
<tr>
<td>3</td>
<td>F(1,101) = 1.76, P = 0.19</td>
<td>F(1,49) = 0.46, P = 0.50</td>
</tr>
<tr>
<td>4</td>
<td>F(1,100) = 8.2, P = 0.005*</td>
<td>F(1,44) = 7.2, P = 0.01†</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>F(1,31) = 0.57, P = 0.46</td>
</tr>
<tr>
<td>6</td>
<td>F(1,99) = 22.2, P &lt; 0.001*</td>
<td>F(1,45) = 1.73, P = 0.20</td>
</tr>
<tr>
<td>7</td>
<td>F(1,94) = 22.6, P &lt; 0.001*</td>
<td>F(1,42) = 1.20, P = 0.28</td>
</tr>
<tr>
<td>8</td>
<td>F(1,101) = 5.92, P = 0.017†</td>
<td>F(1,33) = 1.52, P = 0.23</td>
</tr>
<tr>
<td>Amplitude scale vs. time scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>F(1,47) = 0.46, P = 0.50</td>
</tr>
<tr>
<td>2</td>
<td>F(1,95) = 38.5, P &lt; 0.001*</td>
<td>F(1,50) = 9.2, P = 0.004*</td>
</tr>
<tr>
<td>3</td>
<td>F(1,101) = 154, P &lt; 0.001*</td>
<td>F(1,50) = 0.82, P = 0.37</td>
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<td>4</td>
<td>F(1,100) = 60.4, P &lt; 0.001*</td>
<td>F(1,45) = 0.91, P = 0.34</td>
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<td>5</td>
<td>NA</td>
<td>F(1,44) = 18.5, P &lt; 0.001*</td>
</tr>
<tr>
<td>6</td>
<td>F(1,99) = 23.7, P &lt; 0.001*</td>
<td>F(1,46) = 9.6, P = 0.003*</td>
</tr>
<tr>
<td>7</td>
<td>F(1,94) = 0.03, P = 0.86</td>
<td>F(1,42) = 1.05, P = 0.31</td>
</tr>
<tr>
<td>8</td>
<td>F(1,101) = 20.1, P &lt; 0.001*</td>
<td>F(1,35) = 10.2, P = 0.003*</td>
</tr>
</tbody>
</table>

* P < 0.01.
† P < 0.05.
peripheral retina were less impaired than the responses from the central retina; four of the patients had some normal mfERG responses in the peripheral retina.

To determine whether there were significant predictive relationships among our three measures of cone function, regression parameters were calculated (Table 2). Of the six patients with cone system data, all six had significant relationships in one set of our measures of cone system function; four of the patients had significant relationships in all three sets of measures. Therefore, retinal areas with relatively elevated threshold responses would be more likely to have lower mfERG amplitudes and delayed mfERG timing. This correspondence among the electrophysiological and psychophysical measures of cone system function suggests that there may be some overlap of function between these measures of cone system activity in patients with CD.

Regarding the rod-mediated mfERG results, the losses in amplitude and timing were much less pronounced than those of the cone system. For example, the amplitude scale values for the rod-mediated responses were significantly larger in amplitude (47%–62% of normal) than were the cone-mediated responses (11%–26% of normal). The majority of the rod-mediated responses in these patients were within normal limits for amplitude, timing or both. The lessened impairment of the rod mfERGs in these patients, relative to the cone mfERGs, is consistent with the full-field ERGs recorded in these and previously examined patients with CD.2–4

The relationships among the measures of rod system function were also examined in these patients. In the rod system, there was little or no relationship between performance on the psychophysical threshold measures and performance on the electrophysiological measures, because only one patient in eight had significant regression parameters (Table 2, top and middle sections). In the remainder of the patients, there was no relationship between rod system psychophysics and rod-mediated mfERGs. In addition, in the rod system results, there was no consistent change in the degree of impairment as a function of eccentricity (Figs.7, 8, 9). Similar to our psychophysical findings, Birch and Anderson14 examined rod system visual fields in patients with cone–rod degeneration and found that overall sensitivity was reduced (i.e., thresholds were elevated) but the pattern of loss did not vary with eccentricity.
Comparison with RP

How do the cone and rod system psychophysical and electrophysiological findings in our patients with CD compare with the same measures obtained in patients with RP? In most of the patients with RP and CD, there were significant relationships among the psychophysical and electrophysiological measures of cone system function that were not detectable in the corresponding measures of rod system function. This effect was not due to the size of the rod system responses, because, although the rod responses were unmeasurable in many of the areas in the patients with RP, they were easily measurable in the patients with CD. It is not clear why the correspondence in the rod system is so poor in both of these diseases.

Regarding regional correspondence, in the patients with CD, cone system central responses were the most impaired, and the degree of impairment decreased with eccentricity, whereas in the patients with RP peripheral responses were the most impaired (Figs. 7, 8, 9). In addition, the patients with CD had greater disease-related losses in cone system function than in rod system function. The patients with RP did not exhibit a relative sparing of either cone or rod system function. More interesting, however, is the pattern of change between the cone and rod systems for the different measures in these two diseases. In the patients with RP, we predicted that there would be regional correspondence between cone and rod system abnormalities, given that the degeneration of cones has been shown to follow directly from the degeneration of rods. In the psychophysical results, we were able to demonstrate regional correspondence; however, we could not demonstrate any such correspondence in the mfERG results. In the patients with CD, we found a different pattern of eccentricity-related loss in the cone and rod systems with both the psychophysical and electrophysiological measures. These results suggest that the degenerative processes in CD and RP may be more complex than would occur with a straightforward apoptotic mechanism.

Histologic Findings

Gregory-Evans, et al. examined retinal histology in donor eyes of patients with disorders of the central retina, including one patient with cone–rod dystrophy, with minimal involvement of the rod system. This patient showed a loss of cone photoreceptors throughout the retina. The loss was most pronounced in the macula and in the far periphery, with a relative...
preservation of cone numbers in the midperiphery. The cone pedicles were enlarged and distorted, and there was a thickening of some cone axons. This was most pronounced in the central retina, where the cone pedicles were twice the normal size. The cone pedicles in the periphery were distorted, but to a lesser extent. Double-labeling experiments indicated that all cone types had abnormal synapses. The Müller cell processes surrounding the abnormal cone pedicles were swollen and pale, and the postsynaptic outer plexiform layer processes were also abnormal. Most rod and cone outer segments were slightly shortened, but rods were morphologically normal in all other respects throughout the retina. In our study, we found that the loss of cone system function was greatest in the central retinal areas, consistent with the histologic findings of more pronounced loss of cone photoreceptors in the macular area. In addition, we found that cone system function, especially psychophysical function, was less impaired in the outer rings (Figs. 7A, 8A, 9A). This finding is also consistent with the histologic findings. Regarding the rod system results, we found relatively mild impairment (relative to the cone system) and no change in the degree of impairment as a function of eccentricity. This agrees with the histologic findings of relatively normal rod morphology throughout the retina.

References