Negative Electroretinograms in Retinitis Pigmentosa
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Purpose. Patients with typical clinical features of retinitis pigmentosa were found to have the
atypical electroretinographic finding of a negative waveform to a bright flash in the dark-
adapted state. The full-field electroretinogram (ERG) was studied in seven such patients to
understand better the pathophysiology.

Methods. Rod ERGs were isolated using blue and red flash stimuli in the dark-adapted state.
The rod ERG was assumed to be the sum of two major components, P3 and P2. A family of
delayed Gaussian functions fitted to the rod a-wave intensity series was used to estimate the P3
component. The P2 component was derived by subtracting the estimated P3 component from
the rod-isolated ERG. Long duration stimuli were used to elicit “on” and “off” components of
the light-adapted cone ERG. Oscillatory potentials were isolated by digitally filtering cone
ERGs to white flash stimuli.

Results. The estimated rod P3 component was reduced in amplitude in all patients. The derived
P2 component of the rod ERG was present but abnormally reduced relative to the P3 compo-
nent. Many of the patients had a disproportionate reduction of the “on” compared to the “off” component. Photopic oscillatory potentials were either reduced in amplitude and delayed in timing or not
detectable.

Conclusions. The ERG findings in this subset of RP patients indicate there is dysfunction not
only at the level of the photoreceptor outer segment but also at or proximal to the photorecep-

Retinitis pigmentosa (RP) is a group of inherited reti-
nal diseases that affect photoreceptors and retinal pig-
ment epithelium.1,2 The typical electroretinogram
(ERG) in patients with RP is either an undetectable
signal or a waveform with proportionally reduced a-
and b-wave amplitudes.2 The loss of a-wave amplitude is consistent with pathophysiology at the level of the photoreceptors and the proportional b-wave reduc-
tion would result from decreased photoreceptor input to bipolar cells.

We identified a number of patients who have the
typical clinical findings of RP but whose ERGs are not
typical for RP. The responses to bright flashes of light in the dark-adapted state show an expected loss of a-
wave amplitude but an unexpectedly large reduction
in the b-wave, leading to a negative waveform shape. Negative ERGs are associated with a number of retinal diseases,3-5 but are not a recognized feature of RP.

We studied the rod and cone components of the
ERGs of these patients and compared the results to those of other RP patients and normal subjects. Rod and cone a-waves, both reduced in amplitude, contributed to the negative response. Rod ERG components reflecting inner retinal function were present but were disproportionately reduced in amplitude compared to the components representing photoreceptor function. Cone ERGs showed a greater loss of the “on” response than the “off” response and there are oscil-
latory potential abnormalities. This subset of RP pa-
tients differs from other forms of RP by having ERG
evidence of dysfunction not only at the photoreceptor outer segment but also at or proximal to the photore-
ceptor terminal region.

MATERIALS AND METHODS

Subjects
The subjects in this study included RP patients with
negative ERGs (n = 7; ages 6 to 64 years); RP patients
without negative ERGs (n = 6; ages 26 to 71 years); a patient with congenital stationary night blindness (CSNB, age 45 years); and eight normal subjects (ages 22 to 60 years). RP patients without negative ERGs were selected because they had a-wave amplitudes comparable to the RP patients with negative ERGs. Patients had complete ocular examinations and underwent Goldmann kinetic perimetry, dark- and light-adapted static perimetry, and electroretinography. Informed consent was obtained from all subjects after the nature of the procedures had been explained fully. The research procedures were in accordance with institutional guidelines and the Declaration of Helsinki.

Table 1 provides some clinical characteristics of the seven patients with negative ERGs. The histories of their visual disturbances were similar to those reported by other RP patients.1,2 Patients 2 to 7 had slowly increasing nyctalopia throughout life; patients 4 to 7 also complained of peripheral and central vision losses that occurred over decades. None of the patients recalled taking medication known to be retinotoxic. Patient 3 was being treated for angina pectoris and patient 7 for hypertension; otherwise, no patients had known medical diseases.

Ophthalmoscopic examination revealed a bilateral symmetrical retinopathy in all patients. Patient 1 had only narrowing of the retinal vessels and a granular appearance of the retinal pigment epithelium in the central and midperipheral retina. The other six patients had typical abnormalities associated with RP: narrowed retinal vessels, a waxy pale appearance to the optic nerve head, and depigmentation with varying amounts of bone–spicule-like pigment in the midperipheral and/or far peripheral retina. There were pigmentary disturbances in the macula or cystoid macular edema in the patients with more severely reduced central vision. There was neither central nor peripheral retinoschisis in any of the patients.

Visual acuity and visual field measurements (Table 1) indicated a range of severity of visual loss in these patients. It varied from a wide extent of field by Goldmann kinetic perimetry (V-4e target) with normal or reduced visual acuity (patients 1 to 3), to a residual central island of function with impaired visual acuity (patients 4 to 6), to nearly complete blindness (patient 7). Dark- and light-adapted static threshold perimetry8–77 in patients 2 and 3 showed measurable rod and midspectral cone sensitivity throughout most of their visual fields. Mean rod sensitivity losses across the field were 3.1 and 2.6 log units and cone sensitivity losses were 1.3 and 0.8 log units for patients 2 and 3, respectively. Patients 4 to 6 had measurable function only within the central field; in this island, there was no detectable rod sensitivity but only impaired midspectral cone sensitivity. Patient 7's vision was too impaired to permit this testing.

Full-field ERGs to traditional stimuli using previously described methods8–10 led to the recognition that these patients differed from other patients with RP. Like many other RP patients, patients 1 to 7 had no detectable rod ERC to dim blue flashes in the dark-adapted state and their cone ERGs to single white flashes on a white background and 29-Hz flicker were reduced in amplitude (except patient 2) and delayed in timing. Unlike other RP patients, however, a mixed rod and cone ERG to a white flash (5.4 cd · s · m⁻²), dark-adapted, showed a reduced b/a-wave ratio (Table 1). There was bilateral symmetry of amplitude and

### Table 1. Clinical Characteristics of the Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age* (yr)</th>
<th>Sex</th>
<th>Genetic Type</th>
<th>Visual Acuity</th>
<th>Kinetic Visual Field Extent† (%)</th>
<th>ERG‡ Amplitude (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RE</td>
<td>LE</td>
<td>V-4e</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>M</td>
<td>Simplex</td>
<td>20/40</td>
<td>20/40</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>F</td>
<td>Multiplex</td>
<td>20/200</td>
<td>20/50</td>
<td>57</td>
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<td>3</td>
<td>46</td>
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<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>F</td>
<td>Simplex</td>
<td>20/30</td>
<td>20/30</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>Simplex</td>
<td>20/400</td>
<td>20/300</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>AR</td>
<td></td>
<td></td>
<td>U</td>
</tr>
</tbody>
</table>

AD = Autosomal dominant; AR = Autosomal recessive; LP = light perception with projection; U = unmeasurable.
* When first examined.
† Average of the two eyes expressed as a percent of normal mean; two standard deviations below normal equals 90% for V-4e and 88% for I-4e.
‡ White flash (5.4 cd · s · m⁻²) in dark-adapted state; normal b-wave amplitude (mean = 497 µV; SD = 111 µV; n = 70); normal a-wave amplitude (mean = 297 µV; SD = 65 µV; n = 70); normal b/a-wave ratio (mean = 1.7; SD = 0.3; n = 70).
§ Measured at 60 ms after the stimulus.
¶ Cataract.
∫ Pseudophakic.
waveform shape, unlike in certain retinal vascular diseases; the increase in amplitude of the single flash and flicker cone ERGs with light adaptation was no greater than in normal subjects, unlike that in patients with incomplete stationary night blindness; and S-cone ERGs were not detectable, unlike in the enhanced S-cone syndrome.

Electroretinography

Three ERG methods were used to study the waveforms of the patients. The first method was used to isolate the rod ERG and its components. Responses were elicited to different intensities of blue (Wratten 47A) and red (Wratten 26) flashes in the dark-adapted state with a high intensity xenon flash tube (Vivitar mounted on an LKC ganzfeld 2503B; LKC Technologies Inc., Gaithersburg, MD; luminance of unattenuated white flash, 3000 cd·s·m⁻²; stimulus duration, approximately 1.5 ms). The intensities were selected to provide pairs of scotopically matched waveforms to blue and red flashes, which, when digitally subtracted gave a cone ERG, that was then subtracted from the response to a photopically matched blue flash (double subtraction technique). The photopic match was confirmed using 3.0 log phot·td·s blue and red flashes (3.9 and 2.0 log scot·td·s, respectively) on a 34 cd·m⁻² white background in a normal subject; the match was assumed to be valid for the other normal subjects and the patients but it was not individually confirmed. Flashes were presented every 30 seconds, and individual responses were recorded with a unipolar Burian-Allen contact lens electrode referenced to the forehead. For these recordings, the dynamic range of the 256-level digitizer was 2 mV peak-to-peak for normal subjects, and 1 mV peak-to-peak for patients (band-pass 0.5-1000 Hz). The data were sampled at 2.5 kHz for a duration of 200 ms (starting 20 ms before stimulus presentation). In normal subjects, responses to a range of intensities from 1.8 log scot·td·s to 4.6 log scot·td·s (calculated assuming a pupil diameter of 7 mm for all subjects) in approximately 0.4 log unit steps were recorded; three blue flashes and three red flashes were presented at each intensity. In patients, a more limited intensity series was recorded because of time constraints due to averaging; 8 to 12 flashes of each color were presented.

The rod-isolated ERG resulting from the double subtraction technique was assumed to be the sum of two major underlying components, P3 and P2. P3 is generated by the photoreceptors, and P2 is generated by the inner nuclear layer. The P3 component of the rod-isolated ERG was estimated by fitting a family of delayed Gaussian functions of time (equation 6.10 of Lamb and Pugh, 1992, scaled by the maximum response amplitude, .) to leading edges of the a-waves in an intensity series. This model is computationally very similar to the model fitted to the leading edge of the human a-wave by Hood and Birch. Although the rising phase of the rod photoreponse in single cell recordings is well described by this model certain assumptions were necessary to apply it to the human a-wave. First, it was assumed that at high stimulus intensities the leading edge of the rod-isolated a-wave is a good approximation of the underlying rod photoreponse. Second, it was assumed that 1 scot·td·s causes five isomerizations per rod per flash, it is likely that this will not be valid in the patients but it does not alter the conclusions of this article. The parameters of the model (, characteristic time constant of transduction; , the effective delay time) were determined in two stages. Initially, the photoreponse model was fitted by eye to the leading edge of the 3.9 log scot·td·s intensity rod ERG, a response recorded from all normal subjects and patients. The parameters were subsequently adjusted to ensure that the model describes all recorded intensities for a given subject. Rod P2 component was derived by subtracting the P3 estimate from the rod-isolated ERG. It has been shown by Hood and Birch that the derived rod P2 component produces orderly results in patients with different retinal disorders. The derived P2 component was normalized by to facilitate comparison between the different amplitudes of patients and normal subjects.

A second ERG method was used to study “on” and “off” components of the cone ERG. A continuous light source (halogen ENG projector lamp mounted on an LKC ganzfeld 2503B; maximum luminance of unattenuated white light, 1500 cd·m⁻²) interrupted by an electromechanical shutter (Uniblitz VS62, Vincent Associates, Rochester, NY; opening time, 17 ms) was used to produce white stimuli of 400 ms duration on a white background (34 cd·m⁻²). Stimuli were presented every 10 seconds and the response elicited with each stimulus was recorded individually with a bipolar Burian-Allen contact lens electrode. For these recordings, the dynamic range of the digitizer was 1 mV peak-to-peak (band pass 0.5 to 250 Hz). The data were sampled at 500 Hz for a duration of 1 second (starting 100 ms before stimulus presentation). Each waveform was carefully inspected and traces with obvious eye movement artifacts were discarded. All remaining traces for a given intensity were averaged.

The third ERG method used a flash stimulus (GS-2000 ganzfeld stimulator, Nicolet Biomedical Instruments, Madison, WI; luminance of unattenuated white flash, 9 cd·s·m⁻²; stimulus duration, approximately 100 μs) to elicit light-adapted ERGs on a white background light (34 cd·m⁻²). The responses were digitally filtered (band pass 100 to 300 Hz) to show oscillatory
potentials. Further methodologic details have been published.8

RESULTS

The negative waveforms in the seven patients included in this study are illustrated in Figure 1 and compared to waveforms from a normal subject, three other RP patients, and a patient with CSNB. In normal subjects, the ERG to this stimulus (a high-intensity blue flash of 3.9 log scot • td • s delivered to the dark-adapted eye) is a mixed rod and cone response with prominent a- and b-waves. The three RP patients (ages 26, 68, and 71 years) have differing degrees of a-wave amplitude reduction, but in all cases the b-wave appears to be proportionally reduced. The ERG from a CSNB patient illustrates the type of waveform abnormalities that occur in a retinopathy with a normal rod photoreceptor response but second-order neuron dysfunction.26,27

The CSNB waveform has a large a-wave amplitude but a reduced b-wave. Patients 1 to 7 have relatively small amplitude a-waves and disproportionately reduced b-waves.

The rod component of the mixed rod and cone ERGs to the high intensity blue flash was isolated by the double subtraction technique. Figure 2 (upper) shows the leading edge of the rod-isolated a-wave in a normal subject and in patient 4. The P3 model has been fitted to the responses from an intensity series. The model parameters are \( R_{\text{max}} = 430 \mu V, \tau = 400 \text{ ms}, t_{\text{eff}} = 3.4 \text{ ms} \) in the normal subject. Table 2 lists all P3 model parameters \((R_{\text{max}} , \tau , t_{\text{eff}})\) for patients 1–7, and for comparison, the mean and standard deviation in a group of RP patients and a group of normal subjects. \( R_{\text{max}} \) of normal subjects was significantly (Duncan’s multiple range test, \( p = 0.05 \)) larger than both the group of study patients and the group of RP patients. There were no significant differences among patients 1–7 and the other RP patients.

Figure 2 (lower) shows normalized rod P2 components from four normal subjects, four representative RP patients without negative ERGs and patients 1, 2, 4 and 7. The rod P2 components were derived by subtracting the P3 model from the rod-isolated a-wave, and then normalizing by \( R_{\text{max}} \). Table 2 lists the normalized rod P2 amplitudes for all seven patients, six RP patients without negative ERGs and six normal subjects. The patients with negative ERGs had normalized P2 amplitudes of around 1.0, whereas RP patients without negative ERGs and normal subjects had P2 amplitudes in the range of 1.4 to 2.6. P2 components of patients with negative ERGs were significantly (Duncan’s multiple range test, \( p = 0.05 \)) reduced compared to both the normal subjects and the RP patients without negative ERGs.

The a-wave, “on” and “off” components of the cone ERG were studied in the patients using 400 ms duration white stimuli on a rod-desensitizing background (Figs. 3 and 4). Figure 3 shows ERGs in response to three different intensities of 400 ms duration stimuli in a normal subject, an RP patient without a negative ERG, a CSNB patient, and patient 4. For reference, cone ERGs with a white flash (9 cd • s • m⁻²) on the same background light are shown as insets. In the normal subject, light onset elicits an a-wave followed by a positive “on” response; at light offset there is a positive “off” response. The ERG of the RP patient has reduced amplitude, but there are a-waves and both “on” and “off” components.
ROD P3 ANALYSIS

NORMAL

PATIENT 4

ROD ERG MINUS P3

NORMAL

RETINITIS PIGMENTOSA

PATIENTS

FIGURE 2. Upper: rod-isolated a-waves to different stimulus intensities in a normal subject and patient 4. The smooth curves are a family of delayed Gaussian functions best fit by eye to the leading edges of a-waves in the intensity series. Lower: normalized rod P2 components in response to the 3.9 log scot·td·s intensity stimulus in four normal subjects, four RP patients without negative ERGs, and patients 1, 2, 4, and 7.

Components have a similar relationship of amplitudes to one another as in the normal subject. In the CSNB patient, there is an a-wave at light onset but no “on” response; light offset, however, produces an “off” response. Patient 4 shows a reduced amplitude cone ERG; there is an a-wave and a definite response to light offset but there is little or no positive response to light onset.

Figure 4 shows responses to the onset and offset of the 400 ms duration light stimulus at our maximum intensity in another four patients (patients 1, 3, 5, and 7) and another normal subject. Table 2 provides amplitude and timing measurements for a-wave, “on,” and “off” components of these waveforms in all seven patients. Cone ERGs elicited with the flash are also shown in Figure 4. In patient 5, the flash ERG had normal amplitude of both the a- and b-waves but the b-wave had a prolonged implicit time. To the long duration stimulus, there was a nearly normal a-wave, a small “on” response, and a normal amplitude “off” response. In patients 1, 5, and 7, the flash ERGs showed varying amounts of a- and b-wave amplitude.
TABLE 2. Rod and Cone ERG Results

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Rod</th>
<th>Normalized P2 Amplitude</th>
<th>Cone</th>
<th>Implicit Time (ms)</th>
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<tbody>
<tr>
<td></td>
<td>Rmax (µV)</td>
<td>τ (ms)</td>
<td>toff (ms)</td>
<td>A-wave</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>490</td>
<td>3.2</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>580</td>
<td>4.4</td>
<td>1.1</td>
</tr>
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<td>3</td>
<td>31</td>
<td>560</td>
<td>3.6</td>
<td>1.1</td>
</tr>
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<td>4</td>
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<td>650</td>
<td>3.4</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>420</td>
<td>3.8</td>
<td>1.0</td>
</tr>
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<td>3.5</td>
<td>0.9</td>
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<td>7</td>
<td>40</td>
<td>650</td>
<td>4.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Retinitis pigmentosa
Mean ± SD
99 ± 74 | 452 ± 114 | 3.6 ± 0.6 | 1.9 ± 0.4 | 20 ± 8 | 23 ± 9 | 21 ± 10 | 28.9 ± 2.5 | 60.0 ± 1.6 | 52.8 ± 5.0
Normal
Mean ± SD
458 ± 50 | 380 ± 28 | 3.3 ± 0.1 | 1.6 ± 0.2 | 65 ± 8 | 56 ± 21 | 64 ± 11 | 25.8 ± 0.4 | 42.8 ± 2.3 | 44.7 ± 1.2

* a-wave measured from baseline to peak; on-wave measured from trough to peak; off-wave measured from baseline at time of stimulus offset to peak.
† a-wave and on-wave measured from stimulus onset, and off-wave from stimulus offset.
‡ Not detectable within the noise of the recording.
§ n = 6 for rod responses; n = 4 for cone responses.
¶ n = 6 for rod responses; n = 5 for cone responses except the off-wave, which is n = 3.

...reductions and b-wave timing delays. With the long duration stimulus, patient 1 had a reduced a-wave and "on" component but the "off" response approached normal amplitude. Patients 7 and 5 had a-waves and "off" components that are reduced in amplitude and there is no discernible "on" component in the waveforms. Table 2 indicates that six of seven patients, despite having different amplitudes of the cone ERG, showed a relatively reduced "on" component compared to the "off" component. In the normal subjects and in four other RP patients studied, there was little difference between the amplitude of these components.

Figure 5 shows white flash cone ERGs that were digitally filtered for oscillatory potentials (OPs) in patients 1 to 4 compared with results from a normal subject and an RP patient without a negative ERG. The cone ERGs without digital filtering had different a-wave amplitudes but are displayed at gains that nearly equate them in size. The relationship between display gains for the cone ERGs and the digitally-filtered waveforms was kept constant to permit an estimate by inspection of OP amplitudes relative to a-wave amplitudes. The normal subject showed at least four positive and three negative OP components. The RP patient had OPs although they appear reduced in amplitude and delayed in timing. Patient 3 had OPs of similar amplitude to those of the RP patient but very delayed in timing. Patients 1, 2, and 4 had no measurable OPs.

DISCUSSION
We identified a subset of RP patients with an unusual pattern of ERG findings. Like other RP patients, these patients had a cone a-wave and an estimated rod P3, ERG components attributable to the level of the photoreceptor, that are reduced in amplitude. Unlike other RP patients, these patients had a derived rod P2 component, which reflects the activity of inner nuclear layer cells, which is decreased in amplitude relative to the rod P3 component. There is also a disproportionate reduction in the amplitude of the "on" component of the cone ERG compared to the "off" component in most of these patients. The abnormalities in the derived rod P2 and the more pronounced abnormality in the "on" versus "off" response in the cone ERG suggest a greater defect in transmission between photoreceptors and depolarizing bipolar cells, which subserve the rod- and cone-mediated "on" components of the ERG, than hyperpolarizing bipolars. In addition, there are abnormalities in the photopic oscillatory potentials, wavelets that also reflect inner retinal function.

The mechanism leading to the unusual pattern of ERG findings in these patients is not known. One speculation is that they have photoreceptor disease, but unlike forms of RP caused by abnormalities in photoreceptor outer segment proteins (for example, rhodopsin and peripherin35), the phenotype results from an abnormal gene product critical to structure and/or function at the photoreceptor terminal region. This could lead to defective signal transmission between photoreceptors and bipolar cells; the outer segment disease would be ascribed to secondary degenerative processes. It is of interest that negative ERGs have been found in a strain of Norwegian elkhounds with inherited retinal degeneration and morphologic stud-
Negative ERGs in RP

Another speculation is that this phenotype is caused by disease expression at both receptor and postreceptoral sites in the retina, possibly resulting from a defective gene product critical to normal structure and/or function of both photoreceptors and inner retinal cells. A final speculation is that the inner retinal dysfunction in these patients could be a secondary effect. This notion results from the recent finding in patients with melanoma-associated retinopathy that there are autoantibodies to bipolar cells, the putative dysfunctional cell type in the melanoma-associated retinopathy. It could be hypothesized that autoantibodies to certain retinal antigens following blood–retinal barrier breakdown lead to inner retinal dysfunction in some RP patients. Antibodies to many retinal antigens have been found in the sera of RP patients.

Both rod and cone photoreceptor responses were abnormal even in the youngest patients examined in this study. We examined the relationship between rod and cone receptor responses to determine if there was greater dysfunction in one of the systems. We plotted the rod P3 maximum response amplitude ($R_{max}$) against cone a-wave amplitude (graph not shown, data in Table 2); the amplitudes were normalized to the mean normal amplitude (Table 2) and expressed in log units, as has been done to examine rod and cone ERG
FIGURE 4. Cone ERGs in response to a white flash (9 cd \cdot s \cdot m^{-2}) and to a 400 ms duration white light, both stimuli on a white background light (34 cd \cdot m^{-2}), in a normal subject and patients 1, 3, 5, and 7. For the long duration stimulus, the first 100 ms after light onset and offset are shown. Vertical calibrations are in microvolts; horizontal calibrations are in milliseconds.

relationships in other retinal degenerations.\textsuperscript{9,39,40} Although it cannot be determined with certainty from our results which receptor may be primarily involved in the study patients' disease, this comparison of rod and cone ERGs showed a greater rod than cone dysfunction in all study patients.

An important question that follows from the finding of inner retinal dysfunction by ERG testing in these patients is whether or not they have more severe visual loss than other RP patients. To try to answer this question, we used psychophysical data to match our most severely affected four patients (patients 4 to 7) with other severely affected RP patients and then compared the ERG results elicited with a white flash (5.4 cd \cdot s \cdot m^{-2}) in the dark-adapted state. We surveyed the ERG results in 100 other RP patients (aged 7 to 86 years) with autosomal inheritance who, like patients 4 to 7, also had no measurable visual field peripheral to the 10° isopter by kinetic perimetry (V-4e target) and impaired rod and cone sensitivity in the residual central island by static threshold perimetry. Ninety-three patients had no detectable responses to the white flash and seven had a very reduced amplitude response (mean a-wave amplitude = 23 μV; SD = 11 μV; n = 7; b/a ratio > 1.25). This survey suggests that patients 4 to 7 in this study have larger a-wave amplitudes than most other RP patients with a comparable degree of visual loss. Future studies that will use rod- and cone-isolated a-wave amplitudes to match these patients to other RP patients (who have rod b-waves and cone “on” responses) and then compare their psychophysically measured rod and cone sensitivity should clarify this issue further.

The RP phenotype described here should now be considered among the retinopathies that are associated with a negative ERG.\textsuperscript{3-5} The other disorders with negative ERGs can be distinguished from this subset of RP patients by clinical evaluation and retinal function testing. For example, CSNB patients can be distinguished by their normal fundi and normal (or nearly normal, depending on degree of myopia) a-wave amplitudes. Incomplete CSNB patients also have normal fundi and their dark-adapted ERGs to bright light flashes have a normal a-wave; also, there is an exaggerated increase of the cone flicker ERG amplitude with light adaptation.\textsuperscript{12,26,30} Juvenile X-linked retinoschisis, optic neuropathies, and retinal vascular disorders should be distinguishable clinically. The enhanced S cone syndrome, including the Goldmann-Favre syndrome, can present as a retinal degeneration with a negative ERG.\textsuperscript{13,41,42} Our patient 1 was originally referred to us to rule out this diagnosis. The diagnosis of this entity is made by finding that ERGs elicited in the light-adapted state with photopically matched short- and long-wavelength stimuli are mismatched, the responses to short-wavelength light being much larger in amplitude.\textsuperscript{41,42}

It is likely that negative ERGs in RP patients have been noted earlier than this report. Transitional forms between stationary night blindness and retinitis pigmentosa have been mentioned to occur.\textsuperscript{43} In the era preceding routine use of electroretinography, however, such descriptions were usually given to patients who had complaints of night blindness and no fundus abnormalities but had family members with RP.\textsuperscript{44} Progression of functional loss in one third of CSNB patients with negative ERGs has been described (category 1c\textsuperscript{45}). A reexamination of these patients would be of interest to determine if they eventually developed fundus abnormalities typical of RP. More recently, reduced b/a-wave ratios were reported in some patients with retinal degeneration.\textsuperscript{46}

It remains unclear whether the group of patients we described are a distinct subtype of RP, a stage of RP, or a disease entity best considered apart from typical RP. Future studies to determine if there is intrafamilial consistency of ERG results and how the findings change with time should provide further understand-
Negative ERGs in RP

0.5–500 Hz  

100–300 Hz

NORMAL

RETINITIS PIGMENTOSA

PATIENT 3

PATIENT 2

PATIENT 1

PATIENT 4

FIGURE 5. Cone ERGs in response to a white flash (9 cd • s • m−2) (left) and the result of digitally filtering (100 to 300 Hz) these waveforms for oscillatory potentials (right) in a normal subject and patients 1 to 4. For all subjects, the relationship of display gain between the cone ERG and the 100 to 300 Hz filtered version is constant and is 1:8. Vertical calibrations are in microvolts; horizontal calibrations are in milliseconds.

ing of this expression of disease. Postreceptoral involvement, be it dramatic as in the ERG findings of this study or subtle, may be a more common feature of RP than has been previously acknowledged. It is of interest in this regard that a postreceptoral contribution to the dysfunction in some patients with RP has also been noted in studies using psychophysical techniques.57,48

Key Words
bipolar cell, cone photoreceptor, electroretinogram, retinitis pigmentosa, rod photoreceptor

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References


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