Principles and Practice of Clinical Electrophysiology of Vision

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Retinitis Pigmentosa: Cone-Rod Degenerations: A Comparison of Clinical Findings to Electrophysiological Parameters

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Retinitis pigmentosa (RP) for many years was regarded to be a rod-cone dystrophy, and this concept was reinforced by the fact that many patients with RP reported night blindness as one of their earliest symptoms; furthermore, a majority of RP patients with recordable but abnormal electroretinograms (ERG) demonstrated cone (photopic) tracings that were more recordable than the rod-isolated ERG tracings.[7, 15] In the last decade, ERG and psychophysical studies in patients with RP have demonstrated that large numbers of patients who meet standard definitions of RP[32] have good residual rod function.[1, 35, 44] In examining which RP patients have reasonable rod function it was found on ERG testing that many have a cone-rod pattern of retinal dysfunction.[20] That is, the rod-isolated ERG b-wave amplitudes are greater than the cone-isolated ones. At UCLA, of patients with identifiable inheritance patterns who had recordable ERGs and fields large enough for measuring final rod thresholds, 114 of 278 (41%) had cone-rod function, and 164 of 278 (59%) had rod-cone patterns.[25] The group had an inheritance pattern without distinctive fundus patterns or syndromes, and patients with advance disease and nonrecordable ERGs were excluded. Thus, the number of RP patients with residual rod function is greater than might have been thought. Further studies will be needed to see whether these ERG designations are helpful in determining specific genetic types of RP.

The fact that many patients with RP show measurable rod function correlates with the symptoms reported by RP patients; a survey of 500 consecutive patients in the UCLA RP Registry showed 14% reporting no symptoms of night blindness and 18% saying they saw better at dusk.[25] RP patients with cone-rod degeneration who have progressive visual field loss, pigment epithelial atrophy, and pigment deposits typical of RP usually do not complain of night blindness until their visual fields are less than 12 degrees.[20]

The terms *cone-rod* and *rod-cone* have been used in referring to various retinal diseases and are derived from changes noted on the ERG when recorded under conditions that allow cone- and rod-evoked responses to be clearly separated and identified. When a cone-rod or rod-cone pattern of dysfunction is identified, both the cone and rod ERG tracings must be abnormal; the b-wave amplitude of the photopic ERG (cone response) is compared with that of the scotopic ERG (rod-mediated response). If the photopic b-wave amplitude is reduced more than the scotopic rod b-wave amplitude, a cone-rod pattern of dysfunction is present; conversely, if the rods are more severely affected, a rod-cone dysfunction pattern is present (Fig 64–1).

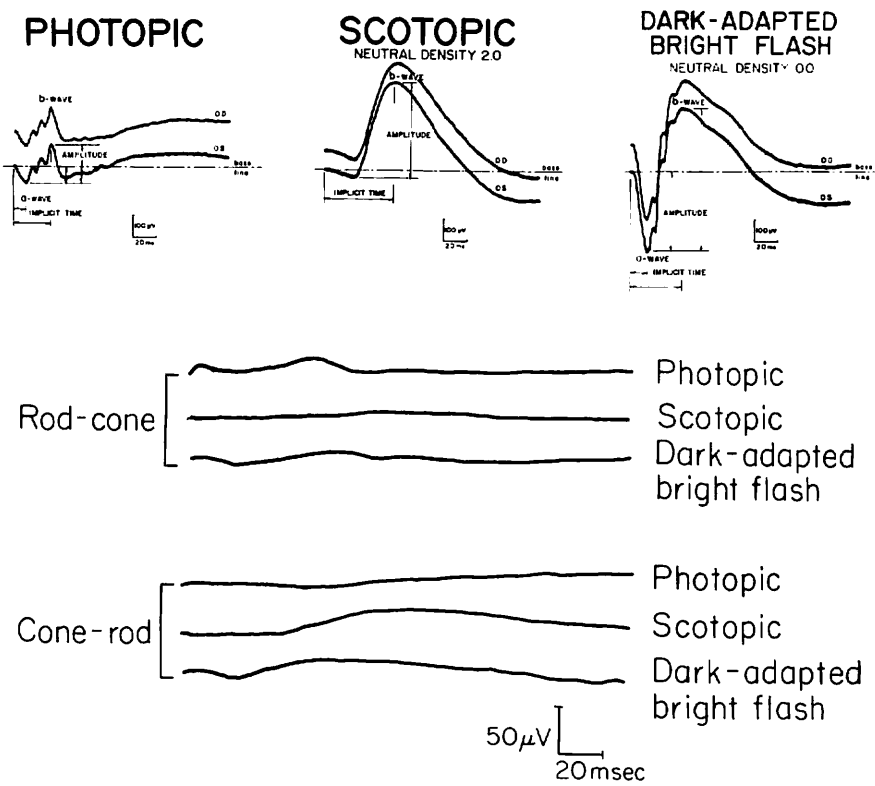

FIG 64–1.
Normal electrographic tracings of cone (photopic), rod-mediated (scotopic), and mixed cone and rod (dark-adapted bright-flash) responses *(top)*. Measurements for amplitudes and implicit times are shown graphically. A-wave amplitudes are measured vertically from the baseline to the negative peak, and the b-wave amplitudes are measured from the bottom of the a-wave to the peak of the positive b-wave; a-wave and b-wave implicit times are measured from 0 (stimulus onset) to the waveform peaks. Examples of tracings from RP patients with advanced rod-cone and cone-rod degeneration are shown *(bottom)*; the more affected receptor system is named first in the descriptive term. (From Heckenlively JR: *Trans Am Ophthalmol Soc* 1987; 85:439. Used by permission.)

Various hereditary retinal degenerations were designated by these ERG eponyms for several decades. Just as RP patients have been thought to selectively have rod-cone patterns of degeneration, bull's-eye macular dystrophies typically have been regarded as having cone-rod ERG patterns.[12] While cone-rod patterns of loss are commonly seen in patients who have bull's-eye maculopathies, these macular lesions are not pathognomonic for cone-rod ERG changes, and bull's-eye patterns of atrophy are seen in patients with toxic retinopathies, RP with rod-cone patterns (including Bardet-Biedl syndrome), and other retinal dystrophies.[17, 26, 38, 45]

HISTORICAL BACKGROUND

Donders is generally credited with first describing "retinitis pigmentosa" in 1855 and 1857,[8] although there were early observations of familial complicated night blindness by Ovelgün in 1744[39] as well as reports of poor vision and pigmented lesions in the retina by Schon in 1828[41] and von Ammon in 1838[43]; subsequently various authors have attempted to suggest, without great success, other names for the disease. Leber introduced *tapetoretinal degeneration* in 1916,[29] a term that also was inaccurate since humans do not have a tapetum. The term *retinitis* may be a misnomer because there is little evidence of inflammation on histopathology in RP.[33]

In 1945 Karpe demonstrated that there was an abnormal to nonrecordable ERG response in patients with pigmentary retinopathy and that this electrophysiological response occurred in many patients before the appearance of clinical or ophthalmoscopic changes.[27] With the advent of ERG testing that allowed the rod and cone system to be tested separately, Gouras and Carr found that in early cases of dominant RP patients had a marked reduction of the scotopic (rod) ERG while the photopic (cone) ERG

could be relatively normal.[15] Because of investigations by Carr, Gouras, Berson, and Krill showing that preferential rod damage was occurring more than cone damage in early cases, the term *rod-cone dystrophy* came to be used interchangeably with RP, in fact to the point where for some clinicians only a nonrecordable or an abnormal ERG in the rod-cone pattern was considered as being consistent with the diagnosis of RP. With the advent of indirect ophthalmoscopy, however, earlier cases of RP were more commonly seen, and earlier ERG changes were recognized.

In 1968 Berson and associates published an article on progressive cone-rod dystrophy; while their report of this ERG pattern was not regarded as being related to RP, they noted that the cone ERG was more affected than the rod tracing. This article appears to be first usage of the term *cone-rod* in ERG testing.[4]

DISTINGUISHING CONE-ROD RETINITIS PIGMENTOSA FROM OTHER DYSTROPHIES WITH CONE-ROD PATTERNS

The finding that some patients with RP had cone-rod patterns of degeneration created some confusion since other hereditary and acquired retinal diseases have also been reported to have cone-rod ERG patterns and because terms such as *cone-rod dystrophy*,[12] *cone dysfunction syndromes*,[14] and *progressive cone dystrophy*[2] have been employed in patients with cone-rod patterns, whether RP or non-RP. Some authors have reported RP patients with what appear to be cone-rod patterns under different classifications, such as delimited RP[31] or sector RP.[11]

A careful clinical and family history, serial visual field examinations, and visual physiological testing are frequently needed to determine whether a given patient with a cone-rod pattern of dysfunction has a form of RP or some other dystrophic or degenerative process. Cone-rod patients with an RP process will demonstrate progressive visual field loss and diminution of the ERG, whereas patients with a cone-rod dystrophy in the general class of cone dystrophy or dysfunction have *relatively stable peripheral visual fields*, although some cases will demonstrate central scotomas. Serial *kinetic* (not automated static) visual field testing is often the best way to classify the disorder in a patient with a particular cone-rod dysfunction; progressive peripheral visual loss with a ring scotoma is likely to be RP, while stable peripheral fields with possible central scotomas are more typical of patients in the general class of cone degeneration. A few patients will have central scotomas that undergo progressive expansion to 30 or more degrees, and they should be regarded as having a process different from typical cone degeneration; the term *RP inversa* has been employed in cases of this type (again a class of disorder, not a disease).

Retinal degeneration/dystrophy patients with cone-rod patterns of dysfunction on the ERG are uniquely different from typical rod-cone RP patients in that on initial presentation they usually are not night-blind, although they may note problems in dark or light adaptation. As the ERG pattern would suggest (the rod b-wave amplitudes are larger than the cone b-wave amplitudes), on psychophysical testing after 40 minutes of dark adaptation the final rod threshold is usually less than 2.0 log units of elevation above normal and typically no worse than 1.1 log units if the visual field is greater than 12 degrees. Further studies on these issues are presented later in this section.

Spectral sensitivity testing has been used to better define the relative contributions of rods and cones to vision under dark-adapted conditions. In 1956, Zeavin and Wald reported the use of a modified perimeter in which threshold profiles were measured along vertical and horizontal meridians in dark-adapted RP patients with orange and blue stimulus spots.[46] These colors were chosen because in the normal dark-adapted eye, cones are more sensitive to orange than to blue and rods are more sensitive to blue than to orange. Using different colors therefore allows for more selective measurement of retinal function of rods and cones across the retina. These authors correlated their results with the visual field in three patients with dominant rod-cone degeneration, but no classification of disease was performed.

Massof and Finkelstein in 1981 pursued this technique further and reported detailed studies in various types of RP patients; they found that two basic degenerative mechanisms were present that were consistent within pedigrees, which they could separate on the basis of sensitivity profiles.[35, 36] Those RP patients characterized by a diffuse loss of rod sensitivity, which they called type 1, report night blindness from infancy or childhood. Patients characterized by regional combined loss or rod and cone sensitivity, called type 2, reported adulthood-onset of night blindness. These two patterns were found in autosomal dominant, autosomal recessive, X-linked recessive, and simplex RP.[37] Further studies performed at the Moorfields Eye Hospital in Lon-

don validated the concept of classifying RP types by the presence of residual rod function.[10, 30]

In 1981 Heckenlively and colleagues reported the clinical features of 20 patients with RP from all three mendelian inheritance patterns where the patient or another affected family member had a cone-rod ERG pattern.[23, 28, 32] These RP patients, all with progressive disease by history and serial visual fields, typically had temporal disc atrophy, disc telangiectasia, optic disc pseudoedema, and none to few retinal pigmentary deposits. Visual field changes at times were distinctive, with ring scotomas closer to fixation than in patients with rod-cone degeneration, occasional pseudoaltitudinal defects, and tight concentric (onion skin–like) fields with decreasing isopter size and intensity, often coinciding with a demarcation line between normal and abnormal functioning retina seen on fundus examination.[19] Conversely, patients with rod-cone degeneration frequently demonstrate larger jumps in sensitivity on Goldmann kinetic perimetry between large and small isopters.

Reported in this chapter is a study that was devised to further investigate patients with cone-rod degeneration who satisfy all the standard definitions of RP but who do not have ERG rod-cone patterns of loss as in typical RP.[16] In particular, an attempt was made to study the natural history and clinical characteristics of cone-rod RP patients by taking a cross section of early to advanced cases and correlate electrophysiological phenomena to clinical findings and family history. This preliminary attempt to correlate ERG with clinical findings was hindered by the heterogeneity of the study group, and as genetic types emerge in the future, this approach may correlate significantly more often.

PATIENTS AND METHODS

Seventy-three patients with RP and cone-rod ERG patterns of loss or evidence of rod function on psychophysical testing were studied. All patients had progressive visual field loss from a hereditary pigmentary retinal degeneration. All ERGs that were recordable were abnormal. Patients were placed in groups defined by the following criteria: group I patients had cone-rod patterns of loss on the ERG, with the scotopic rod ERG b-wave amplitude at least 30% larger than the photopic b-wave amplitude. Group II consisted of patients who had recordable ERGs in which the cone and rod b-wave amplitudes were nearly equal and the final rod thresholds (DAs) were better than 2.0 log units of elevation after 40 minutes of dark adaptation with a 2-degree target 12 to 30 degrees above fixation. Group III patients also had recordable and nearly equal cone and rod b-wave amplitudes, but the final rod threshold was worse than 2.0 log units of elevation. Group IV comprised patients with nonrecordable ERGs by single-flash techniques but who had DAs better than 2.0; thus these patients had residual rod function. Group V patients had nonrecordable ERGs and DAs worse than 2.0 but had at least three of the features noted on past studies to be associated with cone-rod degeneration[20, 28]; these characteristics include no retinal pigment deposition, temporal optic atrophy, bull's-eye macular lesion, and fields less than 8 degrees but a history of recent night blindness. It should be noted that groups IV and V played a minor role in the overall analysis of data since much of the analysis centered on a correlation of patients with recordable ERGs to clinical findings.

All patients had an ophthalmologic examination that included best visual acuity, intraocular pressures, biomicroscopy, indirect ophthalmoscopy, fundus photography, fluorescein angiography, and Goldmann visual fields.

Fundus photographs were reviewed for optic nerve head and macular status and the amount of pigmentation present. The optic nerve was evaluated for diffuse, temporal, or no atrophy and whether the margins were blurred. The macula was judged as to normalcy and whether it had a bull's-eye lesion or central or diffuse atrophy. Late frames of the fluorescein angiogram were reviewed to establish whether edema was present or absent.

The amount of pigmentary deposits as subjectively recorded as none (sine pigmento), mild, moderate, or severe. Optic nerve head temporal atrophy (missing disc tissue) was noted as none, mild, or severe, while pallor was noted as none, temporal in location, or diffuse. Best corrected visual acuity was noted for analysis on a linear scale where 20/20 = 1, 20/25 = 2, 20/30 = 3, 20/40 = 4, 20/50 = 5, 20/60 = 6, 20/70 = 7, 20/80 = 8, 20/100 = 9, 20/200 = 10, 20/400 = 11, count fingers = 12, hand motion vision = 13, light perception = 14, and no light perception = 15.

ERG was performed with a full-field (Ganzfeld) combination single-flash averager unit. Our laboratory normal values and analysis of data of age and gender effects are published elsewhere.[32, 34] Amplitudes and implicit times are measured in a standard fashion. The signal was recorded with a bipolar Burian-Allen corneal contact lens with a reference electrode to the earlobe. All eyes were dilated maxi-

mally. After 30 minutes of dark adaptation a drop of 1% proparacaine was placed in each eye, and the contact lens electrodes were placed under dim red illumination. A rod-mediated waveform was generated by means of a 2.0 neutral-density filter in front of a Grass xenon photostimulator set in the Ganzfeld unit with the I-8 intensity setting (−2.11 log ft-lambert-sec). A mixed cone and rod response was obtained by removing the neutral-density filter and stimulating with the I-8 white flash (−0.075 log ft-lambert-sec). Photopic flicker was performed at 30 Hz with the I-8 stimulus and the amplitude measured. The Ganzfeld background light (8.0 ft-lambert) was then turned on for 5 minutes, and the photopic ERG was performed with the I-16 flash (+0.32 log ft-lambert-sec).

The final rod threshold was measured in each eye after the patient was dark-adapted for 40 minutes; this was performed with a 2-degree target at 12, 20, and 30 degrees above fixation to ensure a representative reading in case the target fell within a scotomatous area.

Goldmann visual fields were performed with the IV-4-e and I-4-e isopters, and other sizes were used to define the field as necessary. Targets were moved from nonseeing to seeing areas. When present, scotomas and enlarged blind spots were documented. If a ring scotoma was present, its extent was noted and in particular whether it was between 30 to 50 degrees or 10 to 30 degrees from fixation. Altitudinal-like defects, arcuate scotomas, enlarged blind spots, and central scotomas were noted.

Visual field size was estimated by using the value where the IV-4-e isopter crossed the 0-, 90-, 180-, and 270-degree marks on the visual field chart, adding the values, and dividing by 4. Peripheral islands were added by degrees occupied to the value in the quadrant in which the island was located before the division by 4.

The following parameters were investigated among groups: visual acuity, amount of retinal pigmentary deposits, presence or absence of macular lesions, temporal optic nerve head atrophy, inheritance patterns in relation to other parameters, age of onset of night blindness, and visual field size and shape in relation to the degree of night blindness and other parameters. ERG values were correlated with other clinical features.

Inheritance pattern was determined by taking a careful family history and often by obtaining records from relatives' ophthalmologists or examining other family members. Isolated cases were not assumed to be autosomal recessive but were termed "simplex" if they were the only known occurrence or "multiplex" if only siblings in one generation were affected.

All statistical analyses used patients as the unit of observation in order to meet the assumption of uncorrelated observations required for the statistical procedures used. One eye was chosen by using a uniform random number generator for each of the 67 bilateral patients.

The descriptive statistics presented include means and standard deviations for continuous variables such as age and the ERG parameters, as well as the frequencies and percentages for discrete variables such as sex and the presence or absence of various clinical features. A chi-square test (or a Fisher's exact test if the sample size was small) was used to test for association between two discrete variables.

For each continuous variable a two-sample *t*-test was used to test for equal means in two independent groups. If the results of Levene's test for equal variances for the two groups indicated that the dispersion of values was not equal for the two groups (i.e., $p < .05$), the test reported was calculated by using separate variance estimates for the two groups; otherwise, a pooled variance estimate was used to calculate the *t*-test. A one-way analysis of variance (ANOVA) was used to test for equality of means among three or more independent groups. Pairwise t-tests between pairs of groups were performed by using Bonferroni significance levels to adjust for the fact that multiple comparisons were made. If the results of Levene's test for equal variances for three or more groups indicated that the dispersions were not equal for the groups, each pairwise *t*-test reported was calculated by using separate variance estimates for the two groups; otherwise, the pooled variance estimate from the one-way ANOVA was used to calculate the pairwise *t*-test. Some analyses comparing means between groups were also done with a one-way analysis of covariance (ANCOVA) using age and duration of disease as covariates. *T*-tests on adjusted means for each pair of groups were done to assess whether the means differed after adjusting for age or duration of disease.

To assess the relationship between two continuous variables (e.g., age and an ERG variable), scatter plots were prepared and Pearson correlation coefficients calculated.[9] All statistical analyses were done by using the 1988 BMDP Statistical Software on a mainframe IBM computer.

Because of variance and small sample size, a number of comparisons presented in the tables are not statistically significant but are reported because the results often show consistent trends, such as

lower amplitudes or longer implicit times from one group to another.

RESULTS

A total of 73 RP patients were studied: 36 in group I, 5 in group II, 3 in group III, 16 in group IV, and 13 in group V. There were 37 females and 36 males. The mean visual acuity for all groups was 20/30.

There were occasions when the number of values under study did not total 73 since missing values occurred when ERGs were nonrecordable or a characteristic was not available in the chart for inclusion in the study, e.g., if a fluorescein angiogram was not performed on a particular patient. Also, rarely, if a fundus photograph did not adequately show a feature under study, it was excluded from study.

For the overall group, 44 patients stated that they had night blindness, while 30 had no night vision problems. The inheritance pattern of the patients was noted as follows: 16 autosomal dominant, 7 autosomal recessive, 5 X-linked recessive, 37 simplex, and 6 multiplex. Twenty-five of the 72 eyes with data on retinal pigment deposits had no deposits, 27 had mild pigmentary changes, and 20 had moderate to severe pigmentary deposition. The status of the disc could be determined clearly in 70 eyes: 26 of 70 had optic atrophy, 44 of 70 had temporal disc atrophy, and 56 of 70 had no disc pallor, while 5 of 70 had blurred margins. Four of 69 had bull's-eye macular lesions, while 9 of 69 had generalized central or posterior pole atrophy.

Comparison of Groups I to V

A review of the data for Groups I to V suggests that there may be a chronological progression from the phenotype represented by group I to II, to IV, and then to V (Table 64–1). Groups II and III are very similar except for the difference in rod sensitivity. Since there is a mixture of inheritance patterns and thus presumably different causes for the RP, it is best to take a pathophysiological approach when comparing groups I to V to see whether there is a progressively worsening condition. This is suggested by looking at the visual fields where groups I and II with recordable ERGs and good rod function have the largest fields at 45.0 and 47.4 degrees, respectively, and group III with nearly equal cone and rod amplitudes and poor rod function psychophysically has a visual field mean of 25.3 degrees. Group IV with a nonrecordable single-flash ERG but good residual rod function psychophysically has a mean visual field size of 25.2 degrees, and group V with a nonrecordable ERG and poor rod function has a 20.1-degree mean visual field size.

The findings in all groups with recordable ERGs were not greatly different except for the rod-mediated values. The implicit times of groups I to III were not significantly different.

Linear regression analysis demonstrated that there was a significant negative correlation coeffi-

TABLE 64–1.

Comparison of Clinical Characteristics of Groups I to V

	Groups*				
	I	II	III	IV	V
Cases	36	5	3	16	13
Sex (M:F)	17:19	2:3	1:2	8:8	8:5
Age† (mean ± SD.)	37.8 ± 17.3	27.6 ± 5.1	39.3 ± 4.2	36.0 ± 16.6	43.1 ± 16.9
Age of onset‡	25.2 ± 17.9	20.6 ± 3.3	17.0 ± 11.1	20.3 ± 13.6	26.9 ± 12.8
Duration of disease§	12.6 ± 11.5	7.0 ± 3.4	22.3 ± 7.0	15.7 ± 12.9	16.2 ± 10.0
VF size¶	45.0 ± 18.9	47.4 ± 16.7	25.3 ± 17.2	25.2 ± 14.5	20.1 ± 19.1
Visual acuity (median)	20/40	20/40	20/30	20/30	20/40
DA‖ (mean)	1.4 ± 1.4	0.9 ± 0.5**	3.5 ± 1.1**	0.7 ± 0.4**	3.7 ± 0.9**
Pigment††	0.9 ± 1.0	0.6 ± 0.5	2.0 ± 1.0	1.5 ± 1.2	1.0 ± 0.9

*Group I: cone-rod pattern of loss on the ERG; group II: nearly equal cone and rod b-wave amplitudes and DA < 2.0; group III: equivalent cone and rod b-wave amplitudes but DA > 2.0; group IV: nonrecordable ERGs and DA < 2.0; group V: nonrecordable ERGs but DA > 2.0.
†Age in years at initial evaluation.
‡Age in years when the patient first had visual symptoms of either night blindness or visual field loss.
§Number of years at initial evaluation since the patient first had visual symptoms of night blindness or visual field loss.
¶Goldmann visual field size in degrees.
‖Final rod threshold above normal after 40 minutes of dark adaptation. Cases with DA < 2.0 typically had no subjective night blindness.
**Selection criteria.
††Amount of pigmentary deposits in equatorial region where 0 = no pigment, 1 = minimal pigment, 2 = moderate pigment, and 3 = heavy pigment.

cient between visual field size and age of the patients in all groups combined (p = .002) and in groups I (p = .014) and V (p = .039); thus, as patients age, the visual field size becomes smaller.

Influence of Gender

An analysis of the influence of sex on the various ERG parameters (Table 64–2) showed no significant ERG differences. Mean visual field size is larger in males than in females (p = .002) This difference remains significant when analyzed with analyses of covariance using age at examination as a covariate and, separately, using duration of diseases as a covariate (p = .01 and p = .003 respectively). The data also suggest that females with cone-rod degeneration may have a later onset, although the difference in mean age of onset is not significant, but suggests a more severe course in females. This was also seen in female RP patients' postoperative cataract surgery visual recovery time at UCLA.[18]

Inheritance Pattern

A review of ERG parameters by inheritance pattern (Table 64–3) showed few significant differences except for the bright flash dark-adapted b-wave implicit time values; there were significant differences between autosomal dominant and autosomal recessive patients and simplex and autosomal recessive patients. Visual field size was also significantly different in these patients.

Electroretinographic Correlations

Of 70 patients with data on the presence of enlarged blind spots, seven (10%) had enlargement more than twice normal. In a comparison of the ERG parameters to the changes on the visual field, enlarged blind spots, when present, were associated with larger amplitudes (Table 64–4), and there was a significant correlation between larger amplitude and enlarged blind spot in the rod-isolated b-wave, bright-flash dark-adapted b-wave, and flicker ampli-

TABLE 64–2.
Comparison of Test Results by Gender in Those With Recordable ERGs

Parameter* (Mean Normal ± SD)†	Recordable ERGs (Mean ± SD) Female	Male	p Value‡
Photopic A amplitude (58 ± 25 μV)	20.6 ± 9.3 (9)§	27.5 ± 8.9 (8)	.15
Photopic A IT (13 ± 3 ms)	15.4 ± 3.3 (9)	15.1 ± 2.0 (9)	.80
Photopic B amplitude (157 ± 73 μV)	43.3 ± 28.2 (9)	60.0 ± 20.1 (10)	.15
Photopic B IT (33 ± 5 ms)	39.3 ± 5.4 (9)	37.4 ± 5.2 (10)	.44
Scotopic B amplitude (367 ± 170 μV)	89.5 ± 54.3 (19)	109.1 ± 58.2 (17)	.30
Scotopic B IT (68 ± 11 ms)	81.0 ± 14.5 (19)	80.6 ± 13.7 (17)	.94
Bfda A amplitude (269 ± 117 μV)	72.1 ± 50.4 (19)	87.5 ± 45.9 (16)	.36
Bfda A IT (15 ± 4 ms)	19.1 ± 4.4 (19)	17.6 ± 3.9 (15)	.30
Bfda B amplitude (521 ± 219 μV)	121.8 ± 69.5 (19)	163.6 ± 86.1 (15)	.13
Bfda B IT (48 ± 8 ms)	54.3 ± 8.0 (19)	58.1 ± 8.4 (15)	.19
Flicker amplitude (137 ± 40 μV)	28.8 ± 22.2 (12)	31.3 ± 24.2 (15)	.78
Visual field	36.1 ± 21.8 (18)	54.9 ± 7.0 (16)	.002
Age	40.9 ± 17.8 (19)	34.2 ± 16.6 (17)	.25
Age of onset	27.4 ± 18.5 (19)	22.6 ± 17.6 (17)	.43
Duration of disease	13.5 ± 11.1 (19)	11.6 ± 12.2 (17)	.62

*IT = implicit time; Bfda = bright-flash, dark adapted ERG.
†See text for source of normal values.
‡Results of a two-sample t-test (pooled or separate variance t-test P value reported depending on the results of Levene's test of equal variances).
§Values in parentheses indicate sample size.

TABLE 64–3.

Comparison of ERG, Visual Field, Age, Age of Onset, and Duration of Disease by Inheritance Pattern for All Groups

	Inheritance Pattern (Mean ± SD)				
Parameter*	AD	AR	XL	Simplex	Multiplex
Photopic A ampl	22.5 ± 9.6 (4)†	*‡	*	20.9 ± 9.2 (15)	*
Photopic A IT	14.0 ± 2.8 (4)	*	*	15.8 ± 3.5 (15)	*
Photopic B ampl	46.4 ± 17.0 (7)	*	*	44.0 ± 23.5 (15)	*
Photopic B IT	39.0 ± 5.0 (6)	*	*	39.1 ± 5.3 (14)	*
Scotopic B ampl	72.1 ± 42.4 (7)	82.5 ± 34.0 (4)	60.0 ± 36.5 (4)	94.1 ± 60.9 (23)	77.5 ± 9.0 (4)
Scotopic B IT	80.0 ± 22.6 (7)	86.0 ± 15.5 (4)	80.5 ± 5.3 (4)	79.7 ± 13.2 (23)	78.5 ± 7.7 (4)
Bfda A ampl	55.7 ± 23.7 (7)	49.0 ± 33.2 (5)	102.5 ± 64.0 (4)	72.3 ± 48.2 (26)	50.0 ± 46.9 (4)
Bfda A IT	19.0 ± 3.0 (6)	18.0 ± 5.9 (4)	17.0 ± 1.2 (4)	18.9 ± 4.2 (26)	22.5 ± 5.7 (4)
Bfda B ampl	105.7 ± 47.9 (7)	108.0 ± 54.0 (5)	*	120.0 ± 81.5 (26)	127.5 ± 131.5 (4)
Bfda B IT§	52.0 ± 5.3 (7)	63.2 ± 4.1 (5)	*	54.0 ± 7.9 (26)	54.5 ± 4.4 (4)
Flicker ampl	16.7 ± 19.5 (9)	*	*	34.5 ± 21.6 (20)	30.0 ± 29.2 (4)
Visual field¶	33.7 ± 21.1 (16)	40.6 ± 14.8 (7)	53.0 ± 5.7 (5)	30.4 ± 21.6 (36)	39.8 ± 19.0 (6)
Age‖	35.2 ± 15.0 (16)	26.1 ± 6.2 (7)	25.4 ± 13.5 (5)	41.4 ± 17.5 (37)	44.0 ± 12.8 (6)
Age of onset	20.4 ± 12.2 (16)	12.9 ± 10.5 (7)	14.4 ± 18.4 (5)	26.8 ± 16.1 (37)	30.7 ± 13.5 (6)
Duration of disease	14.8 ± 11.4 (16)	13.3 ± 4.9 (7)	11.0 ± 5.4 (5)	14.6 ± 13.3 (37)	13.3 ± 7.6 (6)

*ampl = amplitude; IT = implicit time; Bfda = bright-flash, dark-adapted ERG; AD = autosomal dominant; AR = autosomal recessive; XL = X-linked recessive
†Sample size in parentheses.
‡Sample size less than 3.
§AD < AR, $p = .002$; simplex < AR, $p = .003$. (p values are the result of Bonferroni pairwise t-tests using the variance estimate from a one-way analysis of variance.)
¶AD < XL, $p = .004$; simplex < XL, $p < .001$.
‖AR < simplex, $p < .001$.

tudes. These data suggest that an enlarged blind spot occurs at an earlier stage of the disease process. The mean implicit times were not significantly different when correlated with the presence or absence of enlarged blind spots.

Ring scotomata nearer to fixation (within 5 to 30 degrees) were often seen in cone-rod dystrophy patients and had no significant correlations to ERG parameters, while scotomas of the type often seen in rod-cone dystrophy patients that occurred in

TABLE 64–4.

Relationship Between an Enlarged Blind Spot on Goldmann Field Testing and ERG, Visual Field, Age, Age of Onset, and Duration of Disease*

	Blind Spot (Mean ± SD)		
Parameter†	Absent	Present	p Value‡
Photopic A amplitude	20.9 ± 7.9 (20)§	27.5 ± 15.0 (4)	.21
Photopic A IT	15.3 ± 3.4 (20)	16.4 ± 2.6 (5)	.51
Photopic B amplitude	45.3 ± 20.0 (20)	63.3 ± 26.6 (6)	.08
Photopic B IT	38.4 ± 4.8 (18)	38.0 ± 3.8 (6)	.84
Scotopic B amplitude	77.6 ± 52.2 (34)	130.0 ± 60.0 (7)	.02
Scotopic B IT	78.9 ± 13.5 (34)	85.4 ± 17.9 (7)	.28
Bfda A amplitude	65.8 ± 45.1 (38)	97.1 ± 42.8 (7)	.10
Bfda A IT	18.5 ± 3.7 (37)	20.0 ± 4.2 (6)	.38
Bfda B amplitude	108.9 ± 68.9 (37)	185.7 ± 94.1 (7)	.01
Bfda B IT	55.7 ± 7.7 (37)	57.7 ± 8.8 (7)	.53
Flicker amplitude	25.5 ± 23.1 (31)	51.7 ± 9.8 (6)	<.001
Visual field	34.6 ± 20.5 (63)	43.9 ± 22.6 (7)	.27
Age	38.3 ± 16.5 (63)	36.6 ± 13.5 (7)	.79
Age of onset	23.7 ± 15.3 (63)	26.4 ± 16.6 (7)	.65
Duration of disease	14.6 ± 11.7 (63)	10.1 ± 7.9 (7)	.33

*Three patients were missing blind spot data.
†IT = implicit time; Bfda = bright-field, dark-adapted ERG.
‡Results of a two-sample t-test (pooled or separate variance t-test P value reported depending on the results of Levene's test of equal variances)
§Sample size in parentheses.

TABLE 64–5.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and Visual Field Ring Scotomas Occurring in 30 to 50 degrees*

	Scotomas (Mean ± SD)		
Parameter†	Absent	Present	*P* Value‡
Photopic A ampl	23.5 ± 9.5 (20)§	14.8 ± 4.1 (4)	.09
Photopic A IT	15.0 ± 2.6 (21)	18.3 ± 5.3 (4)	.31
Photopic B ampl	52.4 ± 22.0 (23)	**¶	—
Photopic B IT	37.9 ± 4.5 (22)	**	—
Scotopic B ampl	88.8 ± 58.9 (34)	75.7 ± 45.0 (7)	.58
Scotopic B IT	80.5 ± 15.4 (34)	78.0 ± 7.2 (7)	.68
Bfda A ampl	75.3 ± 49.2 (36)	52.2 ± 21.1 (9)	.04
Bfda A IT	18.3 ± 3.5 (34)	20.2 ± 4.5 (9)	.18
Bfda B ampl	127.4 ± 79.6 (35)	96.7 ± 67.6 (9)	.29
Bfda B IT	55.3 ± 8.2 (35)	58.9 ± 5.7 (9)	.22
Flicker ampl	29.2 ± 24.0 (33)	33.8 ± 21.4 (4)	.72
Visual field	39.9 ± 19.8 (55)	19.5 ± 15.9 (15)	<.001‖
Age	37.6 ± 16.8 (55)	39.8 ± 14.1 (15)	.65
Age of onset	24.4 ± 16.2 (55)	22.2 ± 11.8 (15)	.63
Duration of disease	13.2 ± 11.3 (55)	17.6 ± 11.4 (15)	.19

*Three patients were missing data on visual field ring scotomas. Note: Visual fields contain central field and large temporal islands more than the 3 o'clock position.
†ampl = amplitude; IT = implicit time; Bfda = bright-flash dark-adapted ERG.
‡Result of a two-sample *t*-test (pooled or separate variance *t*-test *P* value) reported depending on the results of Levene's test of equal variances).
§Sample size in parentheses.
¶Sample size less than 3.
‖Significant.

the 30- to 50-degree portion of the visual field had significant correlation with the bright-flash dark-adapted a-wave amplitude and a trivial significance with smaller visual field size; a review of the data showed that amplitudes were smaller and implicit times longer when correlated with the presence of more anterior equatorial scotomas (Table 64–5). Central scotomas correlated with higher amplitudes and larger field size, which likely was due to patients presenting sooner who had visual acuity loss.

Of 70 patients with data on the presence or absence of symmetrical contraction, 39 had symmetrical contraction. For those with ERG values, the group with symmetrical contraction had smaller amplitudes and shorter implicit times.

The size of the visual field correlated closely with the ERG parameters; the smaller the field, the smaller the amplitudes and the more prolonged the implicit times. Data from a similar study where values of the two eyes were averaged prior to analysis are presented in Figure 64–2. When using randomly selected single eyes in those patients with recordable ERGs, the photopic a-wave ($p = .008$) and b-wave

TABLE 64–6.

Pseudoaltitudinal Defects on Goldmann Visual Field Testing by Inheritance*

Pseudoaltitudinal Defects	Inheritance†					
	AD	AR	XR	Simplex	Multiplex	Total
Absent	15	4	4	32	4	59
Present	1	3	1	3	1	9
Total	16	7	5	35	5	68
Percent present	6.2	42.9	20.0	8.6	20.0	13.2

*Three patients were missing data on pseudoaltitudinal defects, and two different patients were missing data on inheritance pattern.
†AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive.

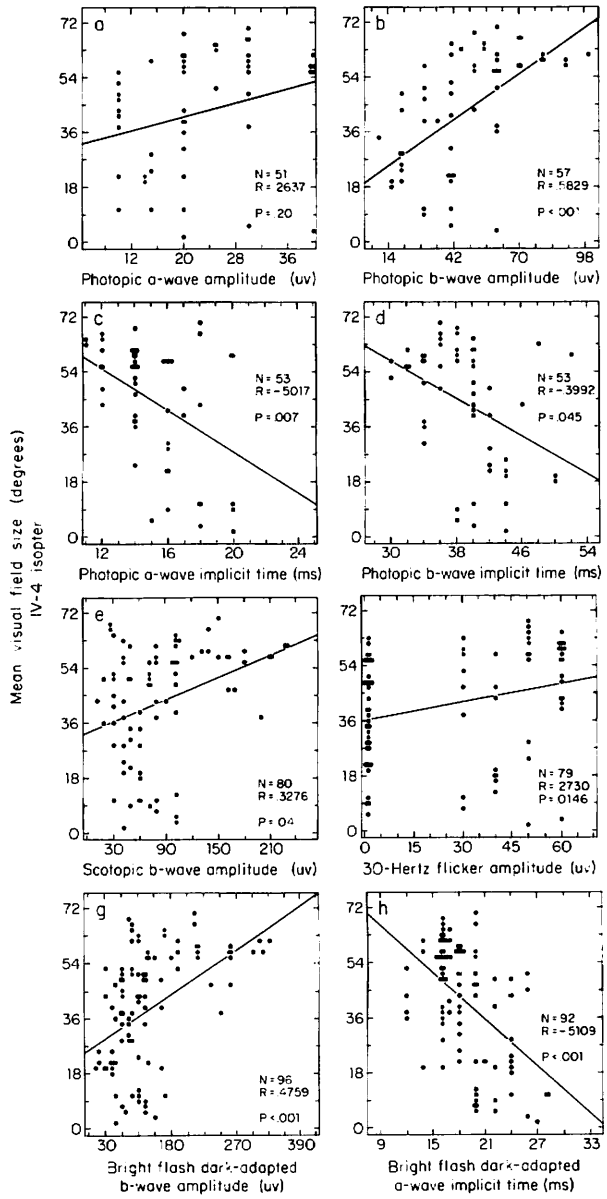

FIG 64–2.
Scatterplots from a similar study using data from both eyes: visual field size (IV-4 isopter) vs. ERG parameters: *P* and *R* values and sample size *(n)* are presented within the graph. Parameters shown are photopic a-wave **(A)** and b-wave **(B)** amplitudes, photopic a-wave **(C)** and b-wave **(D)** implicit times, scotopic b-wave amplitude **(E)**, 30-Hz flicker amplitudes **(F)**, bright flash dark-adapted b-wave amplitude **(G)**, and a-wave implicit time **(H)**. (From Heckenlively JR: *Trans Am Ophthalmol Soc* 1987; 85:454. Used by permission.)

($p < .02$), scotopic a-wave ($p < .05$) and scotopic b-wave ($p < .05$), and bright-flash dark-adapted b-wave ($p < .001$) amplitudes showed longer implicit times associated with smaller visual fields. This may imply that as the visual field shrinks, the retina shows increasing dysfunction in those areas that are still responding to the ERG light stimulus.

Other Visual Field Correlations

Altitudinal-like defects in which either the upper or lower half of the visual field is missing without a pure meridian cutoff correlated significantly ($p < .04$) with visual field size; the mean size of the field was 47.3 degrees if the altitudinal-like pattern was present ($n = 9$), while it was 33.7 degrees if absent ($n = 61$).

Counts of pseudoaltitudinal defects on Goldmann visual field testing suggest that autosomal recessive cases may be more likely to have this visual field pattern while autosomal dominant cases are less likely to have it (Table 64–6). Fisher's exact test comparing just the autosomal dominant and recessive groups shows a borderline significant association ($p = .07$). No noteworthy pattern was seen in the occurrence of altitudinal defects among groups I to V, but sample sizes were small.

Age of Onset and Duration

We found borderline significant negative correlations of the age of onset with photopic a-wave implicit times ($R = -0.37$, $p = .07$) and bright-flash dark-adapted b-wave implicit times ($R = -0.27$, $p = .07$, Fig 64–3). There were significant positive correlations of duration with photopic a-wave implicit times ($R = 0.57$, $p = .003$) and bright-flash dark-adapted a-wave implicit times ($R = 0.40$, $p = .006$). Patients with longer disease durations had prolonged implicit times. As expected, visual field size

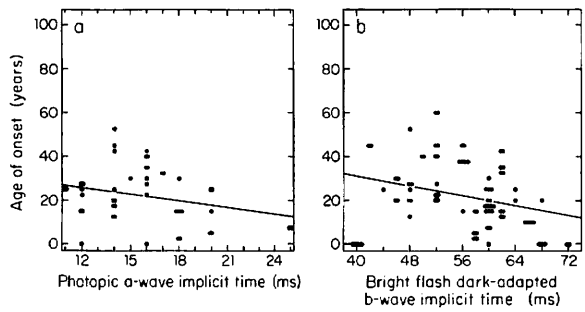

FIG 64–3.
Scatterplots of the age of onset correlated (borderline significance) with **(A)** photopic a-wave implicit time ($p = .07$) and **(B)** bright-flash dark-adapted b-wave implicit time ($p = .07$). The data suggest a longer implicit time in the above two parameters with earlier onset of symptoms. (From Heckenlively JR: *Trans Am Ophthalmol Soc* 1987; 85:455. Used by permission.)

negatively correlated with the duration of disease ($R = -0.30$, $p = .012$).

Visual Acuity

One of the more surprising correlations in the groups with recordable ERGs was that poorer visual acuity correlated with larger ERG amplitudes; for instance, the scotopic b-wave amplitude for patients with visual acuities of 20/50 or better was significantly smaller than the mean for those with worse visual acuity ($p < .03$); the bright-flash dark-adapted a-wave results were borderline ($p < .06$) (Fig 64–4,A–D). This finding was corroborated by an analysis finding higher ERG amplitudes in patients with central scotomas.[16] The likely reason is that patients with poorer visual acuities seek medical care sooner than do those with good central vision.

Since the macula (fovea centralis) contributes at most 15% to the photopic ERG, it is not usually considered to be a significant contributor to the overall waveform, and an association with ERG parameters is not to be expected.[42]

Dark Adaptation

Higher final rod thresholds correlated with longer photopic a- and b-waves ($p = .001$ and $p = 0.025$, respectively) and with bright-flash dark-adapted a-wave implicit times ($p < .001$). The photopic b-wave amplitudes showed a significant negative correlation ($p = .03$) (Fig 64–5,A–F).

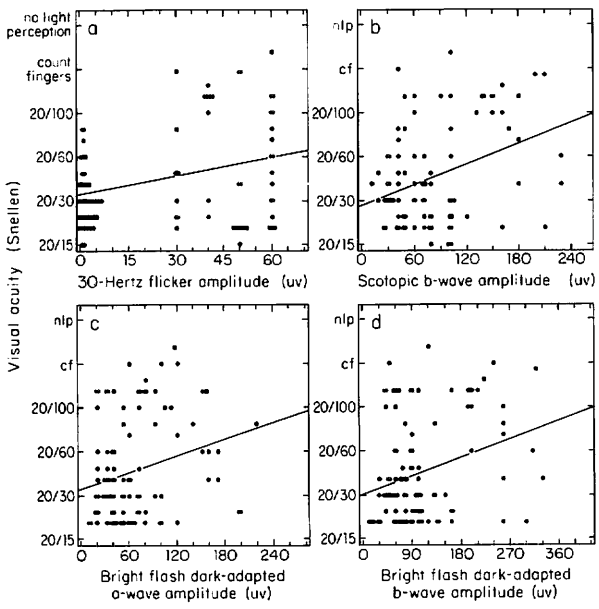

FIG 64–4.
Scatterplots of visual acuity correlated to ERG parameters: **(A)** 30-Hz photopic flicker, **(B)** scotopic b-wave amplitude, **(C)** bright-flash dark-adapted a-wave, and **(D)** b-wave amplitudes. Higher amplitudes often correlate with poorer visual acuity. (From Heckenlively JR: *Trans Am Ophthalmol Soc* 1987; 85:456. Used by permission.)

Nyctalopia

ERG parameters also correlated well with the presence or absence of symptomatic nyctalopia (Table 64–7). With the one exception of the bright-flash dark-adapted b-wave implicit time, all other ERG implicit times were longer and amplitudes smaller if the patient was night-blind. Only the bright-flash dark-adapted a-wave implicit time reached signifi-

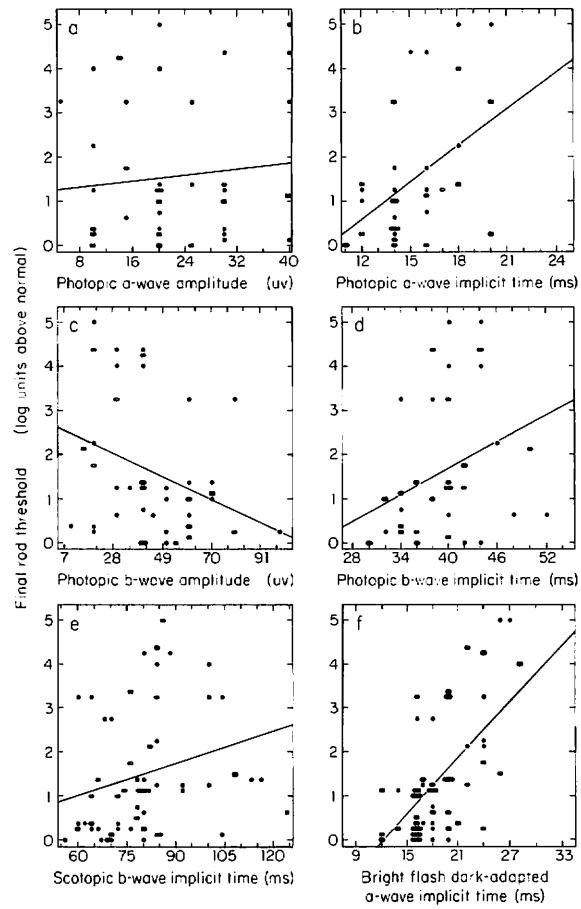

FIG 64–5.
Scatterplots of the dark adaptation final rod threshold at 12 degrees above fixation as correlated to ERG parameters: photopic a-wave amplitude **(A)** and implicit times **(B)**, photopic b-wave amplitude **(C)** and implicit times **(D)**, scotopic b-wave implicit time **(E)**, and bright-flash dark-adapted a-wave implicit time **(F)**. The most significant correlations with elevated final rod threshold were prolongation of photopic (cone) and bright-flash dark-adapted (mixed cone and rod) a-wave implicit times. (From Heckenlively JR: *Trans Am Ophthalmol Soc* 1987; 85:457. Used by permission.)

TABLE 64–7.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and Symptomatic Night Blindness*

	Night Blindness (Mean ± SD)		
Parameter†	Present	Absent	*p* Value‡
Photopic A amplitude	19.9 ± 10.4 (14)§	25.0 ± 7.1 (10)	.20
Photopic A IT	16.0 ± 3.9 (14)	15.0 ± 2.4 (10)	.48
Photopic B amplitude	37.9 ± 17.9 (14)	56.7 ± 22.4 (12)	.03
Photopic B IT	40.0 ± 5.6 (12)	37.7 ± 4.5 (12)	.27
Scotopic B amplitude	77.7 ± 58.5 (22)	92.0 ± 54.3 (20)	.42
Scotopic B IT	79.7 ± 12.7 (22)	78.6 ± 13.5 (20)	.80
Bfda A amplitude	61.0 ± 48.2 (24)	70.9 ± 39.0 (22)	.45
Bfda A IT	20.2 ± 4.0 (23)	17.5 ± 4.1 (21)	.03
Bfda B amplitude	111.5 ± 84.0 (24)	122.1 ± 65.4 (21)	.64
Bfda B IT	55.2 ± 8.2 (24)	56.2 ± 7.2 (21)	.66
Flicker amplitude	30.3 ± 22.2 (18)	26.3 ± 24.7 (19)	.36
Visual field	28.8 ± 19.2 (41)	44.8 ± 19.2 (28)	.001
Age	39.3 ± 16.0 (41)	34.5 ± 16.7 (30)	.22
Age of onset	22.8 ± 14.3 (41)	23.7 ± 16.4 (30)	.81
Duration of disease	16.5 ± 12.2 (41)	10.8 ± 9.3 (30)	.04

*Two patients were missing data on symptomatic night blindness.
†IT = implicit time; Bfda = bright-flash dark-adapted ERG.
‡Result of a 2-sample *t*-test (pooled or separate variance *t*-test *P* value reported depending on the results of Levene's test of equal variances).
§Sample size in parentheses.

cance ($p = .03$). There was a good correlation between visual field size and the presence or absence of night blindness or dark-adaptation problems. Cases with night blindness had significantly smaller visual fields ($p = .001$). There was no relationship between symptomatic nyctalopia and age of onset in this analysis, but the duration of disease was borderline significantly longer in patients with night blindness ($p = .04$).

Pigment Deposition

There was a suggestion of correlation between no (sine), mild, and moderate pigment deposition and ERG parameters (Table 64–8); as the pigment deposition was more marked, the ERG amplitudes decreased, and the implicit times were more delayed. Four pairwise comparisons of the pigmentation groups reached significance.

An oddity in the ERG and pigmentary deposition analysis was that those patients with severe pigmentation were out of step with the other groups (Table 64–8); often their values were between the mild and moderate groups. This finding may reflect the small sample size or an expression of other factors secondarily influencing the amount of pigmentation that accumulates in the degenerative process. A correlation of retinal pigment deposition to skin and iris pigmentation was not performed.

Temporal Optic Atrophy

Temporal optic atrophy, often characterized as a loss of disc tissue temporally or sometimes as pallor of the temporal portion of the disc, has been reported in a number of retinal dystrophies, including congenital stationary night blindness,[21] cone-rod degeneration,[32] and cone degeneration[36]; particularly in cases in which there is tissue missing temporally, the age of onset is usually in infancy or childhood.

A comparison of ERG values with optic nerve status was performed in two ways. Optic nerves were evaluated from fundus photographs as to whether they were pink or pale and, if pallor was present, whether it was diffuse or temporal in nature. No focal nasal pallor was seen.

The second approach for evaluating optic nerve heads was to judge whether there was missing tissue or a flattening on the temporal portion of the disc or whether the disc was normally round. Discs were viewed in stereo to determine whether they were tilted since this hypothesis has often been used to explain why many patients with retinal dystrophy have missing temporal portions of their discs; however, 66 of 69 eyes were found to have no tilt, 3 were definitely tilted, and 4 photographs were not clear enough to categorize the tilt.

The analysis of optic nerve head pallor showed no strongly consistent relationship between the absence

TABLE 64–8.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and Retinal Pigmentation*

	Amount of Pigmentation (Mean ± SD)			
Parameter†	Sine	Mild	Moderate	Severe
Photopic A ampl	25.5 ± 9.6 (11)‡	18.9 ± 6.0 (9)	*§	*
Photopic A IT	14.9 ± 2.9 (12)	15.3 ± 2.6 (9)	*	*
Photopic B ampl	60.5 ± 23.1 (11)	43.0 ± 16.5 (10)	*	*
Photopic B IT	36.5 ± 2.8 (11)	39.1 ± 5.8 (9)	*	*
Scotopic B ampl¶	111.7 ± 65.6 (18)	73.3 ± 46.8 (15)	58.3 ± 18.3 (6)	74.0 ± 59.4 (5)
Scotopic B IT	78.3 ± 14.1 (18)	82.9 ± 17.5 (15)	80.8 ± 4.3 (6)	78.4 ± 8.3 (5)
Bfda A ampl‖	97.6 ± 52.4 (19)	52.8 ± 30.1 (18)	42.5 ± 20.4 (6)	48.0 ± 29.5 (5)
Bfda A IT**	17.3 ± 3.2 (18)	19.6 ± 4.1 (17)	22.7 ± 4.7 (6)	17.6 ± 4.6 (5)
Bfda B ampl	150.3 ± 95.2 (18)	101.3 ± 57.9 (18)	85.0 ± 28.8 (6)	110.0 ± 78.1 (5)
Bfda B IT	53.8 ± 8.1 (18)	56.0 ± 8.7 (18)	55.7 ± 4.5 (6)	60.4 ± 7.4 (5)
Flicker ampl	31.0 ± 25.7 (15)	26.2 ± 22.7 (13)	21.0 ± 22.2 (5)	39.0 ± 23.0 (5)
Visual field	40.3 ± 21.3 (24)	36.1 ± 20.2 (27)	23.8 ± 19.6 (8)	32.4 ± 21.1 (11)
Age	35.7 ± 17.7 (25)	36.5 ± 15.6 (27)	42.3 ± 14.8 (9)	41.3 ± 17.6 (11)
Age of onset	23.6 ± 15.6 (25)	20.6 ± 15.5 (27)	27.2 ± 12.3 (9)	27.8 ± 17.0 (11)
Duration of disease	12.1 ± 11.3 (25)	15.9 ± 11.6 (27)	15.1 ± 10.9 (9)	13.5 ± 11.4 (11)

*One patient was missing data on retinal pigmentation.
†ampl = amplitude; IT = implicit time; Bfda = bright-flash dark-adapted ERG.
‡Sample size in parentheses.
§Sample size less than 3.
¶Sine < moderate, $P = .005$. (Note: P values reported are the result of Bonferroni pairwise t-tests using the variance estimate from a one-way analysis of variance.)
‖Sine < mild, $P = .003$; sine < moderate, $P = .001$.
**Sine < moderate, $P = .006$.

or presence temporal pallor (Table 64–9). The only significant correlations with temporal diffuse pallor were a shorter bright-flash dark-adapted b-wave mean implicit time ($p = .03$), a later mean age of onset of symptoms ($p = .04$), and an older mean age at examination ($p = .02$). The onset age ranged from 1 year to 55 years in the group with no pallor and from 6 years to 60 years in the group with pallor.

A correlation of those nerve heads with missing temporal tissue to ERG parameters was similar: there was no consistent relationship (Table 64–10). Patients with temporal optic atrophy had significantly smaller photopic a-wave amplitudes ($p = .03$) and marginally larger implicit times ($p = .04$). Eyes

TABLE 64–9.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and Optic Nerve Pallor*

	Optic Nerve Pallor (Mean ± SD)		
Parameter†	No Pallor	Temporal/Diffuse Pallor	p Value‡
Bfda A amplitude	68.9 ± 45.0 (37)§	67.0 ± 51.7 (10)	.91
Bfda A IT	18.9 ± 4.2 (37)	19.5 ± 3.7 (8)	.73
Bfda B amplitude	119.4 ± 76.3 (36)	113.0 ± 84.6 (10)	.82
Bfda B IT	57.0 ± 7.9 (36)	52.0 ± 5.2 (10)	.03
Flicker fusion	29.3 ± 23.6 (27)	28.6 ± 24.5 (11)	.94
Visual field	36.1 ± 21.6 (55)	34.6 ± 17.7 (14)	.79
Age	35.9 ± 15.7 (56)	46.9 ± 16.2	.02
Age of onset	21.6 ± 13.8 (56)	32.9 ± 18.2 (14)	.04
Duration of disease	14.3 ± 11.7 (56)	14.0 ± 10.2 (14)	.92

*Three patients were missing data on optic nerve pallor.
†Bfda = bright-flash dark-adapted ERG; IT = implicit time.
‡Results of a two-sample t-test (pooled or separate variance t-test P value reported depending on the results of Levene's test of equal variance).
§Sample size in parentheses.

TABLE 64–10.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and the Presence of Temporal Optic Atrophy*

	Optic Nerve Status (Mean ± SD)		
Parameter†	No Atrophy	Temporal Atrophy	*p* Value‡
Photopic A amplitude	25.8 ± 9.3 (13)§	17.6 ± 7.6 (11)	.03
Photopic A IT	14.2 ± 2.2 (13)	16.9 ± 3.7 (12)	.04
Photopic B amplitude	52.7 ± 22.8 (13)	43.9 ± 23.3 (14)	.33
Photopic B IT	36.8 ± 3.7 (12)	40.6 ± 5.5 (13)	.06
Scotopic B amplitude	88.6 ± 67.4 (18)	82.2 ± 46.8 (25)	.71
Scotopic B IT	77.3 ± 13.5 (18)	82.3 ± 14.2 (25)	.25
Bfda A amplitude	69.0 ± 51.1 (21)	68.1 ± 42.3 (26)	.94
Bfda A IT	19.1 ± 4.4 (20)	19.0 ± 3.9 (25)	.94
Bfda B amplitude	123.6 ± 90.1 (21)	113.4 ± 66.1 (25)	.66
Bfda B IT	53.8 ± 7.6 (21)	57.7 ± 7.4 (25)	.09
Flicker amplitude	31.1 ± 24.9 (18)	27.2 ± 22.7 (20)	.62
Visual field	39.9 ± 19.8 (25)	33.4 ± 21.2 (44)	.21
Age	38.7 ± 16.3 (26)	37.7 ± 16.5 (44)	.82
Age of onset	25.3 ± 15.3 (26)	23.0 ± 15.4 (44)	.54
Duration of disease	13.4 ± 12.9 (26)	14.8 ± 10.5 (44)	.62

*Three patients were missing data on temporal optic atrophy.
†IT = implicit time; Bfda = bright-flash dark-adapted ERG.
‡Result of a two-sample *t*-test (pooled or separate variance *t*-test *P* value reported depending on the results of Levene's test of equal variances).
§Sample size in parentheses.

TABLE 64–11.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and Macular Lesions*

	Macular Lesion (Mean ± SD)		
Parameter†	Normal Appearing	Bull's eye, Central, Diffuse Atrophy	*p* Value‡
Photopic A amplitude	22.1 ± 9.2 (19)§	22.5 ± 12.6 (4)	.93
Photopic A IT	15.3 ± 3.2 (20)	15.5 ± 3.4 (4)	.91
Photopic B amplitude	49.8 ± 22.3 (21)	35.0 ± 21.8 (5)	.19
Photopic B IT	38.3 ± 4.7 (19)	41.6 ± 5.9 (5)	.20
Scotopic B amplitude	82.6 ± 55.1 (35)	101.3 ± 67.3 (8)	.41
Scotopic B IT	80.4 ± 14.2 (35)	80.5 ± 13.8 (8)	.99
Bfda A amplitude	70.7 ± 47.9 (38)	56.7 ± 34.3 (9)	.41
Bfda A IT	18.6 ± 4.2 (37)	20.2 ± 4.0 (9)	.29
Bfda B amplitude	112.9 ± 69.5 (37)	134.4 ± 103.8 (9)	.57
Bfda B IT	54.4 ± 8.1 (37)	60.2 ± 6.2 (9)	.05
Flicker amplitude	25.0 ± 23.8 (31)	45.0 ± 10.5 (6)	.004
Visual field	36.0 ± 20.5 (54)	35.3 ± 21.5 (13)	.91
Age	38.8 ± 16.3 (56)	35.9 ± 16.9 (13)	.56
Age of onset	25.3 ± 16.1 (56)	18.5 ± 10.6 (13)	.07
Duration of disease	13.6 ± 11.1 (56)	17.5 ± 12.7 (13)	.27

*Four patients were missing data on macular lesions.
†IT = implicit time; Bfda = bright-flash dark-adapted ERG.
‡Results of a two-sample *t*-test (pooled or separate variance *t*-test *P* value reported depending on the results of Levene's test for equal variances).
§Sample size in parentheses.

TABLE 64–12.

Relationship Between ERG, Visual Field, Age, Age of Onset, Duration of Disease, and Macular Edema*

	Macular Edema (Mean ± SD)		
Parameter†	No Edema	Edema	*p* Value‡
Photopic A amplitude	22.2 ± 10.0 (20)§	¶	—
Photopic A IT	15.5 ± 3.4 (21)	¶	—
Photopic B amplitude	52.6 ± 21.9 (21)	18.8 ± 2.5 (4)	<.001
Photopic B IT	38.4 ± 4.4 (20)	¶	—
Scotopic B amplitude	93.7 ± 57.8 (35)	44.0 ± 11.4 (5)	<.001
Scotopic B IT	81.9 ± 14.5 (35)	75.6 ± 8.9 (5)	.35
Bfda A amplitude	76.7 ± 49.1 (36)	35.0 ± 13.8 (6)	<.001
Bfda A IT	18.9 ± 4.0 (35)	21.8 ± 3.9 (5)	.13
Bfda B amplitude	132.3 ± 82.7 (35)	66.7 ± 23.4 (6)	<.001
Bfda B IT	56.7 ± 8.1 (35)	55.3 ± 5.5 (6)	.68
Flicker amplitude	30.3 ± 23.6 (29)	30.0 ± 23.2 (5)	.98
Visual field	39.2 ± 21.0 (50)	20.8 ± 11.3 (10)	<.001
Age	36.5 ± 15.8 (51)	43.3 ± 15.3 (10)	.21
Age of onset	22.8 ± 15.0 (51)	26.7 ± 13.9 (10)	.45
Duration of disease	13.7 ± 10.2 (51)	16.6 ± 12.6 (10)	.43

*Twenty-two patients were missing data on macular edema.
†IT = implicit time; Bfda = bright-flash dark-adapted ERG.
‡Results of a two-sample *t*-test (pooled or separate variance *t*-test results reported depending on the results of Levene's test of equal variances).
§Sample size in parentheses
¶Sample size less than 4.

with temporal atrophy generally appear to have smaller amplitudes and longer implicit times when compared with eyes in which the disc tissue was intact. The one exception to this pattern was the bright-flash dark-adapted a-wave. Patients with temporal atrophy had a slightly smaller visual field than did those with no atrophy.

Macular Status

The macula was evaluated by whether there were atrophic changes in the macular area by fundus photographs (Table 64–11) and whether macular edema was present on the fluorescein angiogram (Table 64–12).

The presence or absence of macular edema on the fluorescein angiogram was correlated with ERG parameters (Table 64–12); those eyes with edema demonstrated greater evidence of dysfunction than did eyes without edema. In general, amplitudes were significantly smaller (all, $p < .001$), but implicit times were not significantly different. Smaller visual field size correlated ($p < .001$) particularly closely with the presence of macular edema (Table 64–12). These results suggest that patients with macular edema tend to have more advanced disease.

Fishman and colleagues evaluated the blood-retinal barrier with vitreous fluorophotometry in 24 patients with either cone or cone-rod dystrophy.[13] They found that the patients with peripheral pigmentary degeneration and a reduction in scotopic b-wave amplitude had the greatest breakdown of the blood-retinal barrier. Patients with foveal lesions but with normal or only moderately reduced scotopic b-wave amplitudes were found to have normal photometric values. Pruett evaluated fluorescein leakage in 268 eyes from all types of RP and found that 32 of 236 had cystoid edema and 10 of 258 had disc leakage.[40]

Natural History of RP Cone-Rod Degeneration

In the past it has been difficult to judge whether a particular classification scheme for separating the various types of RP pigmentosa was appropriate or had any basis in fact. Because large numbers of patients were found to have rod-cone patterns and night blindness in the 1960s when ERG testing was blossoming as a clinical tool, the term *rod-cone dystrophy* as a term referring to RP was well accepted,[7] and it is still appropriate for certain types of RP.

However, patients with cone-rod ERG patterns who otherwise meet the standard definition of RP

(progressive visual field loss with ring scotomas) have been puzzling to a number of clinicians in the field of RP research, and there has been reluctance to place these patients under the diagnostic umbrella term of RP. This reticence is likely motivated by concerns that these patients may confuse our understanding of RP or that patients with cone-rod RP may be confused with patients who have a cone-rod dystrophy similar to a cone degeneration (stable peripheral visual fields) but do not meet the standard definitions of RP.

The above data suggest, however, that patients with the RP type of cone-rod degeneration have consistent correlations when their ERG parameters are compared with visual field size and shape; the presence of scotomas, symptomatic night blindness, visual acuity, macular and optic nerve status; and the amount of retinal pigment deposits. In light of the multiple interrelationships with significant correlations it is possible to conclude that patients with cone-rod degeneration of the RP type have disease processes that in the long run may be easier to define and understand than patients with rod-cone degeneration. Certainly there is good reason to state that patients with cone-rod degeneration who meet the standard definitions of RP can be said to have a form of RP until more specific biochemical or molecular genetic discriminators better classify RP types.

Although it is difficult and perhaps risky to interpret dynamic processes from static data, the data suggest that patients with cone-rod degeneration probably go through stages where the ERG is abnormal but recordable and the rod tracing shows better values than the cone tracing; the cone and rod amplitudes are both reduced and are more nearly equal in size. As the disease further progresses, the ERG becomes nonrecordable by single-flash techniques, but there is still residual rod function, and the final rod threshold remains fairly good. As the visual field further constricts with time, night blindness finally develops into serious problem for the patient.

The later age of onset of symptoms in patients with cone-rod degeneration suggests that in many patients it may be a milder process than in many of those with rod-cone. This observation was also made by Marmor in an electroretinographic analysis of RP patients. He noted a group of patients who had more recordable ERGs and termed their condition "delimited RP".[31] The data in his paper show that delimited RP patients have more recordable rod-to-cone ERGs and thus likely had cone-rod dysfunction.

An ERG analysis of 215 patients with all types of RP by Heckenlively and Solish showed that patients with cone-rod patterns (or good final rod thresholds) consistently had more recordable ERGs than did patients with rod-cone patterns (or elevated final rod thresholds).[24] Since ERG values of patients with cone-rod degeneration have been shown in the present study to correlate with retinal and optic nerve head status as well as visual field size and shapes, this would imply that RP patients with cone-rod degeneration may have a milder disease than those with rod-cone degeneration. Obviously, generalizations about a number of different genetic diseases will always have exceptions, but as a group comparison it may be a valid assumption.

Correlation of ERG and Visual Field Size

While it may seem logical to find that visual field size correlates with various ERG parameters, this has not been as consistent a finding in patients with rod-cone degeneration in the author's experience. The analysis shows several new pieces of information about visual field changes in cone-rod degeneration; enlarged blind spots are seen earlier in patients who have recordable cone-rod patterns (group I), and pseudoaltitudinal changes are more likely to occur in autosomal recessive patients. The significant correlation of visual field size to patient age is not surprising. This change was studied at UCLA over a period of 8 years in which field size was calculated with planimetry and expressed in percent rates of deterioration per year. Rod-cone degeneration patients (10) averaged −5.5% per year of loss, while a wide range of values was seen for cone-rod degeneration patients (unpublished data).

Issue of Implicit Times Aiding in Diagnosis

Several studies by Berson suggested that some types of RP may have delays in their implicit times; in particular, he illustrated this finding in two patients with autosomal recessive RP whom he compared with three patients with sector RP who had similar rod amplitudes but normal implicit times.[3] His studies in families with dominant RP and reduced penetrance also suggested that affected individuals may have delays in implicit times.[5] This result has not been supported to date in the literature.

Once the various types of RP are better defined, it will be possible to study what happens to ERG parameters as the disease progresses; potentially, it may be possible to use implicit time data to help confirm the type of RP or to pick out groups to be

studied genetically. One possible example is prolonged photopic a- and b-wave implicit times, which have been found in the codon-23 transversion form of autosomal dominant RP.[22]

However, unhealthy retinal tissue is likely to have slower implicit times, it may be difficult to find a clear association with mendelian inheritance types, and it is more likely that there will be a general association of slower implicit times with more advanced disease in many types of RP (but if slower implicit times are present in earlier stages of an RP type, it may provide more important information).

Berson and colleagues also emphasized the important issue that test variables may occur that influence implicit times[6] such as alterations of stimulus intensity, area of light stimulation, and degree of retinal adaptation, all of which must be tightly controlled (see Chapter 48).

It may come as a surprise to learn that a number of patients with RP in the early to middle stages of their disease are not night-blind, but studies as early as 1976 by Weinstein et al. demonstrated that some patients with RP have normal dark adaptation findings.[44] They found that there was a high level of agreement (71% in San Antonio and 90% in Baltimore patients) between the ERG findings and dark adaptometer values, with "normal" ERGs correlating with normal dark adaptation curves, subnormal ERGs with subnormal dark adaptations, and nonrecordable ERGs with abnormal highly elevated final rod thresholds.

The key to classifying the type of retinal degeneration that is present when there is a cone-rod dysfunction pattern on the ERG (RP vs. non-RP) is to employ perimetry, pedigree analysis, and funduscopy. The medical history and psychophysical tests may help to supplement the findings and assist in defining the diagnosis. Serial visual fields will distinguish whether the peripheral visual fields are contracting or whether ring scotomas and enlarged blind spots are developing; likewise, the test will also demonstrate enlarging central scotomas, a sign of progressive cone-rod dystrophy. Pedigree analysis will help establish the inheritance type, a discriminator that has been useful in classifying disease types in numerous disorders.

Differential Diagnosis

The most common non-RP disorders that give cone-rod dysfunction patterns are cone dystrophies or cone dysfunction syndromes, which frequently will show subnormal rod b-wave amplitude values. The visual fields as well as the rod b-wave amplitudes remain relatively stable over time. A second hereditary class of disease that may present with cone-rod patterns is in patients termed to have "cone-rod dystrophy"; they frequently have bull's-eye macular lesions. Many of these patients have stable peripheral visual fields but enlarging central scotomas and in this situation have been termed as having retinitis pigmentosa inversa.

The third main group of non-RP patients who may present with cone-rod dysfunction patterns are individuals without a family history of RP who may or may not have a history of inflammatory disease such as measles, mononucleosis, or nonspecific viritis but who present with atypical pigmentary changes such as macular pigmentation, round unevenly distributed subretinal deposits, or often asymmetrical involvement between eyes. Some of these patients will have a progressive course not unlike RP patients, while others may maintain relatively stable visual fields. Some of these patients later develop premature macular degeneration.

These preliminary studies on patients with cone-rod degeneration of the RP type suggest that it is possible to use specific clinical, psychophysical, and electrophysiological discriminators to identify new subclasses of RP or to separate patients whose degenerations are undergoing similar pathophysiological events. Computerization of these discriminators could potentially help in the diagnosis of various RP types and could be of particular assistance in classifying patients who present with no family history. Computerized detailed knowledge of group natural history by RP type is likely to aid in the evaluation of treatment programs or other forms of intervention for RP.

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