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Rod and cone psychophysics and electroretinography: Methods for comparison in retinal degenerations

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Abstract. Methods have been developed to compare full field rod and cone electroretinograms with results of rod and cone static perimetric measurements across the visual field. In a limited number of patients with retinal degeneration, including two subtypes of retinitis pigmentosa, there were close relationships between electroretinographic and psychophysical parameters. Maximum b-wave amplitude and visual field area were highly correlated, as were electroretinographic and perimetric measures of sensitivity loss. Future application of the methods to large numbers of patients with typical retinitis pigmentosa may help elucidate different mechanisms of retinal degeneration.

Introduction

The traditional clinical method to assess rod and cone function in retinal degenerations is the suprathreshold rod and cone electroretinogram (ERG). When rod and cone sensitivity is measured it is usually with a psychophysical method, such as dark adaptometry performed at one retinal locus. In recent years other ERG and psychophysical techniques and analyses have been developed with the goal of determining more about the underlying pathophysiology of retinal degeneration. ERG methods to determine response sensitivity as well as magnitude have been used [1, 2]. Psychophysical measures of photoreceptor sensitivity at many loci across the visual field also have been applied [3, 4, 5].

Comparison of such ERG measurements with those from psychophysics not only is of fundamental interest [6] but also may provide a further means of investigating retinal degeneration [1, 7]. For the rod system, there have been two attempts to relate ERG measures of dysfunction to those determined psychophysically with dark-adapted static perimetry [7, 8]. To our knowledge no similar attempts have been made for cone function.

In the present study we describe methods to relate both rod and cone ERG data with rod and cone static perimetric measurements. These methods are applied to the test results from a number of patients with retinal degenerative diseases, including typical retinitis pigmentosa (RP).

Methods

Testing techniques

ERGs. Full field ERGs were elicited and recorded with techniques previously described [9]. In brief, rod ERGs were elicited with flashes of blue light (Wratten 47B) at different intensities in the dark-adapted state. To reduce the contribution of cone ERG to the measured voltages at higher stimulus intensities of blue light, an intensity range comparable to that proven by Birch et al. [8] to be eliciting only rod ERGs was used. For cone ERGs, 29-Hz flashes of white light at different intensities on a white background of 6.8 cd/m^2 were used. Other methods for eliciting cone ERGs (e.g. single flash, chromatic flicker) also were investigated but found to be less suitable for the Naka-Rushton analysis (see below) than the 29-Hz white flicker.

Perimetry. Descriptions of the automated perimeter, testing procedures, and methods of data analysis for two-color dark-adapted static perimetry have been published [5, 10]. Briefly, for "rod perimetry", absolute thresholds were measured for monochromatic blue-green (500 nm) and red (650 nm) stimuli (target diameter, 103′) at 76 loci throughout the visual field. For "cone perimetry", increment thresholds were measured at the same loci with a monochromatic orange (600 nm) stimulus on a white background of 10.0 cd/m^2 (31.5 asb).

Data analysis

Parameters for both rod and cone systems that represent ERG magnitude, ERG sensitivity loss, visual field area, and psychophysical sensitivity loss were derived from the many measurements made in each subject. ERG b-wave amplitude was compared with visual field area and ERG sensitivity loss with psychophysical sensitivity loss. In making these comparisons it is assumed that the ERG b-wave amplitude generated from each small retinal area depends only on the number of functioning photoreceptors therein, and that the 76 measures of psychophysical sensitivity adequately sample the variation of sensitivity across the entire visual field.

ERG parameters

The Naka-Rushton equation [11]

$$V = Vmax \cdot I^n/(I^n + K^n)$$

was applied to both rod and cone ERG intensity-response functions. V is rod b-wave amplitude or cone flicker peak-to-peak amplitude; Vmax is the amplitude at which the response saturates; I, the stimulus intensity; K, the stimulus intensity at which the ERG reaches one-half Vmax; and n, the exponent responsible for the slope of the function.

Vmax was used for comparison with visual field area. Since K and Vmax both influence ERG sensitivity, the difference between log (Vmax/K) in the patient and that in normals was considered the measure of ERG sensitivity loss to be used to compare with psychophysical sensitivity loss (see below). The parameter n was within the normal range (rods: mean = 0.86, s.d. = 0.12; cones: mean = 0.94, s.d. = 0.18; 30 subjects) in the patients studied.

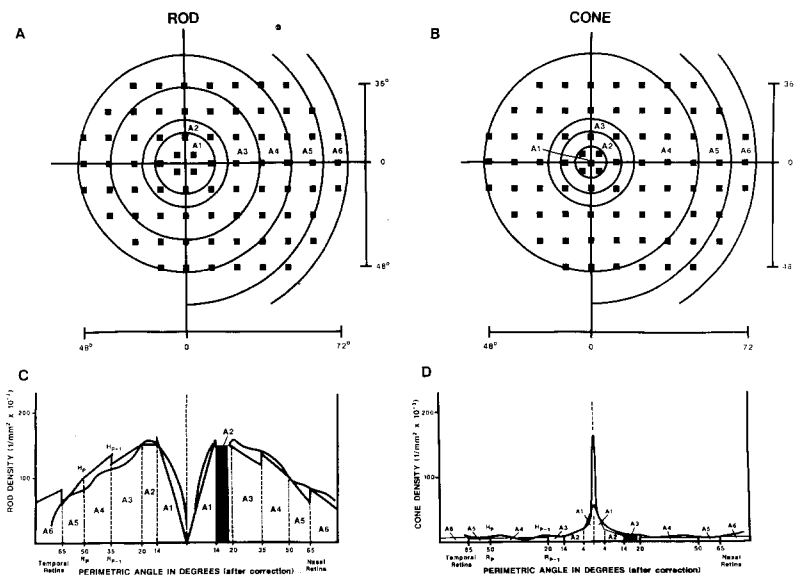

Fig. 1. Methods used to model the psychophysical sensitivity loss for comparison with ERG sensitivity loss. Upper row: The annular subdivisions of the grid of test points for rod (A) and cone (B) analyses. Lower row: Horizontal profiles of the annuli in relation to Osterberg's [12] rod (C) and cone (D) photoreceptor counts. Trapezoidal regions were defined along the horizontal axis (perimetric angle corrected according to Drasdo and Fowler [13]). The volume of the solid of revolution described by each trapezoid gives the total number of photoreceptors in each annulus. The number of photoreceptors within each annulus relative to the whole retina was used to weight the mean sensitivity loss in each annulus. See Appendix for explanation of abbreviations.

Table 1. Rod and cone perimetric and ERG data.

Pt	Age (yrs)	Rod				Cone			
		Perimetry		ERG		Perimetry		ERG	
		L	FA	K	Vmax	L	FA	K	Vmax
1	39	0.28	−0.05	−2.15	2.41	0.19	−0.11	−1.18	2.09
2	71	1.23	−0.20	−1.90	2.25	0.69	−0.25	−0.83	1.95
3	49	1.95	−0.15	−1.32	2.17	0.68	−0.21	−1.15	1.85
4	65	2.20	−0.46	−2.25	1.93	0.92	−0.47	−0.63	1.82
5	12	2.07	−0.60	−2.15	1.98	0.76	−0.54	−1.14	1.87
6	14	2.35	−0.62	−1.99	2.02	0.80	−0.68	−0.92	1.93
7	43	–	–	–	–	1.08	−0.98	−1.21	1.17
Normal mean				−2.35	2.59			−1.19	2.24
s.d.				0.14	0.07			0.25	0.14
no. of subjects				30				30	

L: sensitivity loss; FA: field area; Note: all test data are in log units.

Perimetric parameters

Visual field area. The photoreceptor system mediating detection at each of the 75 extrafoveal test loci was first determined from the test results with the blue-green and red targets [10]. Rod visual field area was defined as the proportion of rod-mediated loci with a reduction in sensitivity to the blue-green stimulus of less than 30 dB compared with the mean normal at each locus [8]. Cone visual field area was defined as the proportion of loci, including the fovea, with less than 10 dB reduction in sensitivity compared with the mean normal at each locus.

Sensitivity loss. Details of the method for computing psychophysical sensitivity loss are in Fig. 1 and the Appendix. The goal was to produce a parameter that in some sense may be proportional to the retinal capacity for generating an ERG. Briefly, the visual field was divided into six annuli, and the mean sensitivity loss for all test loci within each annulus was determined. Each mean sensitivity loss was weighted by the relative number of photoreceptors in the annulus (derived from photoreceptor counts [12] and the unevenness of the retinal image [13]). The final index of rod psychophysical sensitivity loss is the sum of these weighted sensitivity losses.

Results

The rod and cone ERG and perimetric data used for comparison of ERG and psychophysical parameters are given in Table 1. Among the patients in

this study, four had atypical retinal degenerations (Patients 1–4; 3 female and 1 male) and three had typical RP (Patients 5–7; 2 female and 1 male). Some clinical details and test results from four of these patients are given below.

Patient 1 is a 39-year-old woman who complained of some night vision disturbances and "losing her place" when reading. Visual acuity was 6/6 in each eye, and the anterior segments were normal. Fundus examination revealed pigmentary disturbances limited to the central retina. The optic nerve and retinal vessels appeared normal.

Fig. 2 shows the perimetric (upper) and ERG (lower) results for Patient 1. Psychophysical sensitivity losses are displayed in gray scale with darker tones indicating greater loss. The greatest rod and cone sensitivity losses are distributed in an annular fashion within the central 40–50°, sparing the fovea and more peripheral regions. The intensity-response data for rod and cone ERGs of the patient (squares) are shown with the curves that were fitted to these data. Mean normal functions (curves without data points) are also displayed. The most significant ERG abnormality in this patient is the reduction in Vmax for the rods.

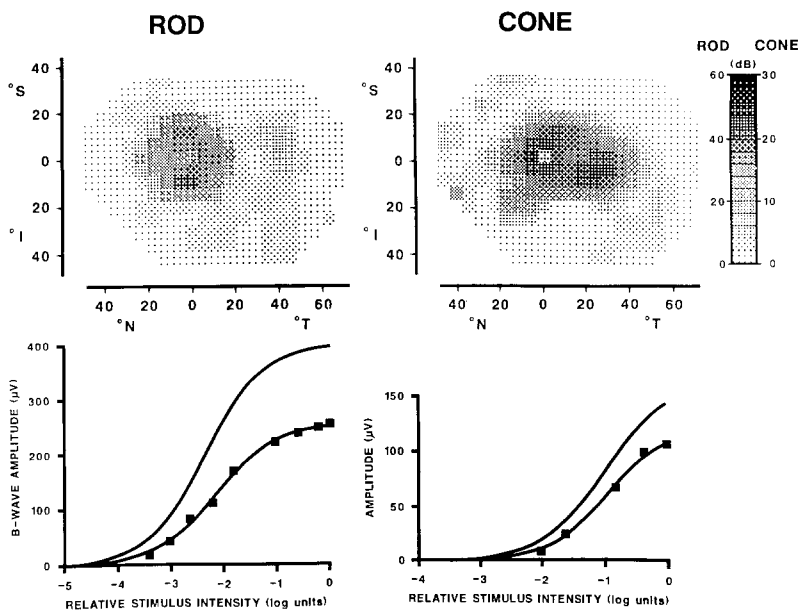

Fig. 2. Perimetric (upper row) and ERG (lower row) data for the right eye of Patient 1. Perimetric sensitivity losses for rods (left) and cones (right) are shown in gray scale. Key is at far right (rods: left scale, 0–60 dB; cones: right scale, 0–30 dB). Intensity-response functions for rod ERGs (left) and cone ERGs (right) of the patient (squares with fitted curve) are shown in relation to the mean normal function (curves without symbols).

Patient 2 is a 71-year-old man who noted loss of peripheral vision and night vision only over the past several years. No other family members were affected. Visual acuity was 6/15 in each eye, and there was minimal nuclear sclerosis in both lenses. Optic nerves appeared normal; retinal vessels were only minimally attenuated; and bone spicule-like pigmentation was present 360° around the mid- and far-peripheral retina. Serological testing was negative.

Fig. 3 shows that the greatest rod and cone perimetric sensitivity losses in Patient 2 are in the peripheral visual field; the central field is far less affected. Vmax for rod and cone ERGs are both significantly reduced and K for the rods is abnormal.

Among the three patients with typical RP, there were two (Patients 5 and 6) with regional differences in retinal function and comparable loss of rod and cone function within the affected regions. These patients exemplify Type 2 or 'R' RP, a psychophysical subcategory of RP defined by dark-adapted perimetric measurements [3, 4, 5].

Patient 5, a 12-year-old girl, has been aware of increasing night and side vision disturbances for many years. She is the only one with RP in her family. Visual acuity was 6/7.5 in each eye and there are no cataracts. There was sparse bone spicule-like pigment in the nasal retina and a granular

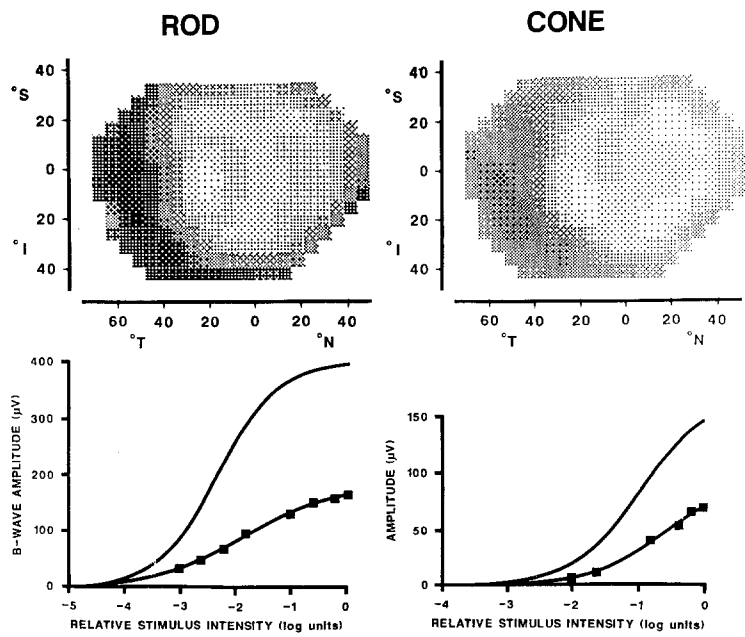

Fig. 3. Rod and cone perimetric and ERG data for the left eye of Patient 2.

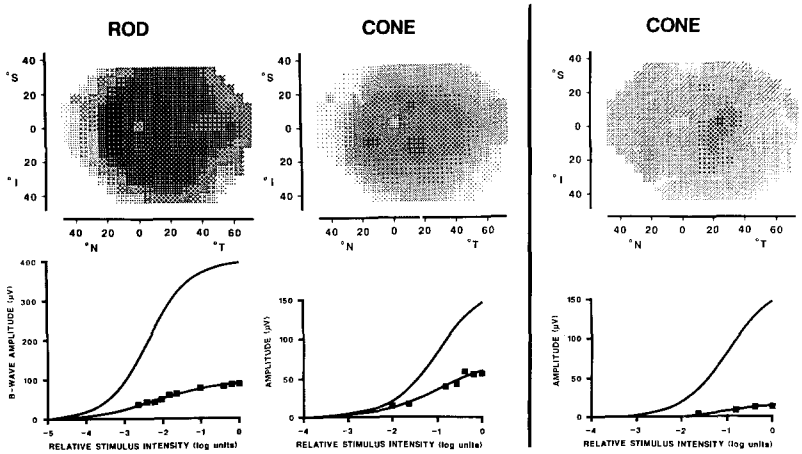

Fig. 4. Data for the right eyes of two patients with typical RP. Left two columns: Rod and cone perimetric and ERG data for Patient 5. Right column: Cone perimetric and ERG data for Patient 7.

appearance to the rest of the midperipheral retina. Fig. 4 (left two columns) shows that Patient 5 has pericentral and midperipheral rod and cone perimetric sensitivity losses with less abnormality farther in the peripheral field. Rod and cone ERG Vmax are both reduced without a significant change in K.

Patient 7 exemplifies the Type 1 or 'D' psychophysical subcategory of RP. In this subtype there is severely reduced rod sensitivity diffusely across the visual field from early in life and later loss of cone function in a more regionalized pattern [3, 4, 5]. Patient 7 is a 43-year-old woman with long-standing complaints of nyctalopia. Three generations of her family were known to have RP. Visual acuity was 6/9 in each eye and there were no cataracts. There were a waxy appearance to the optic nerves, minimal attenuation of the retinal vessels, and sparse bone spicule-like pigment throughout the midperipheral retina. The diagnosis was autosomal dominantly-inherited RP.

There was no detectable rod ERG, and the dark-adapted perimetric testing revealed cone mediation of almost all loci. Fig. 4 (right column) shows only the cone test results. There is more cone sensitivity loss in the midperipheral than in the farther peripheral field. Vmax for the cones is significantly reduced but K is normal.

In Fig. 5 are graphs comparing the ERG and psychophysical parameters for all patients. Rod field area is strongly correlated with rod Vmax (Fig. 5A; $r = 0.89$; $P = 0.007$; slope of regression line $= 0.84$). A high correlation is also found for cone field area and cone Vmax (Fig. 5B; $r = 0.86$;

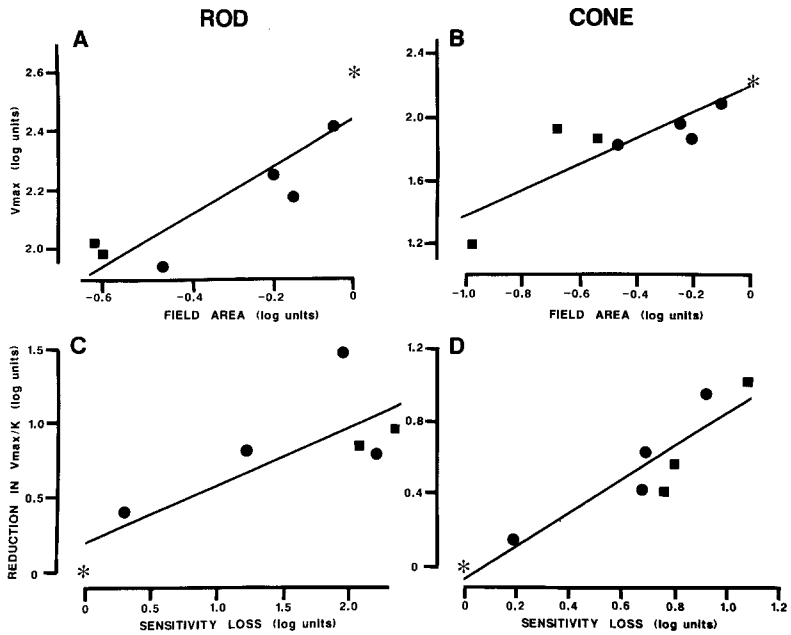

Fig. 5. Relationship of perimetric to ERG parameters in patients with atypical retinal degenerations (circles), patients with typical RP (squares), and normal subjects (*). ERG Vmax is plotted against visual field area for rods (A) and cones (B). ERG sensitivity loss (reduction in Vmax/K) is plotted against psychophysical sensitivity loss for rods (C) and cones (D). Regression lines are drawn through the data points in each graph.

P = 0.007; slope = 0.83). There is a definite correlation of rod psychophysical and ERG sensitivity loss parameters (r = 0.80; P = 0.033); the slope of the regression line is 0.38 (Fig. 5C). Cone sensitivity parameters show a higher correlation (r = 0.92; P = 0.001) than the rod data; the slope of this regression line is 0.92 (Fig. 5D).

Discussion

With the two most commonly used visual function tests in patients with retinal degeneration, the full-field ERG and Goldmann kinetic perimetry, it is common to have patients with full kinetic fields to a large target size but nondetectable ERGs. The findings in the present study indicate that when rod and cone function are isolated with ERG and perimetric techniques, results of these tests can be highly correlated, rather than apparently unrelated.

Our methods and results confirm and extend those of previous studies.

Arden et al. [7] studied rod function in patients with autosomal dominantly-inherited RP who were classified as Type 2 or 'R' RP. A model to predict rod ERG parameters from rod perimetric data was devised, and the correspondence of predicted values (of Vmax and K) and actual measurements was examined. Various degrees of correspondence were found in this patient population, leading to the suggestion that different disease mechanisms may be responsible. Birch et al. [8] examined rod function in RP patients with different genetic types. Perimetric data were reduced in a less complex manner and correlations were found between rod field area and Vmax and between rod perimetric threshold and ERG threshold, defined with a 2 μV criterion. Our method of reducing rod perimetric data is akin to that of Arden et al. [7], but the parameters for the rod system that we chose to relate are like those of Birch et al. [8].

Unlike previous studies, we examined patients with atypical retinal degenerations in addition to patients with typical RP. The former were selected because they had relatively large ERG signals and wide expanses of visual field compared with patients with typical RP. This was to test whether the relationships between ERG and perimetric measures held for relatively mild retinal disease as well as more severe dysfunction. Whereas our results confirm those of Birch et al. [8] for rod field area versus Vmax, we found greater rod perimetric sensitivity loss than ERG loss using similar methods of comparison. Either certain assumptions in the testing or analyses are faulty or the Arden group's [7] suggestion of dysfunction at higher levels than the b-wave must be entertained in some patients.

The present study is the first to examine the relationship of the cone ERG and cone perimetric measures across the visual field of patients with retinal degeneration. Analyses of cone function were considered important because this is commonly the only function remaining in patients with RP, even relatively early in the disease. The preliminary investigations reported herein should be extended to large numbers of well-categorized RP patients to determine whether different mechanisms of retinal degeneration can be discovered by these techniques.

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References

1. Massof RW, Wu L, Finkelstein D, Perry C, Starr SJ, Johnson MA. Properties of electroretinographic intensity-response functions in retinitis pigmentosa. Doc Ophthalmol 1984; 57: 279–96.
2. Arden GB, Carter RM, Hogg CR, Powell DJ, Ernst WJK, Clover GM, Lyness AL, Quinlan MP. A modified ERG technique and the results obtained in X-linked retinitis pigmentosa. Br J Ophthalmol 1983; 67: 419–30.
3. Massof RW, Finkelstein D. Rod sensitivity relative to cone sensitivity in retinitis pigmentosa. Invest Ophthalmol Vis Sci 1979; 18: 263–72.
4. Ernst W, Faulkner DJ, Hogg CR, Powell DJ, Arden GB, Vaegan. An automated static perimeter/adaptometer using light emitting diodes. Br J Ophthalmol 1983; 67: 431–42.
5. Jacobson SG, Voigt WJ, Parel JM, Apáthy PP, Nghiem-Phu L, Myers SW, Patella VM. Automated light- and dark-adapted perimetry for evaluating retinitis pigmentosa. Ophthalmology 93: 1986; 1604–11.
6. Fulton AB, Rushton WA. The human rod ERG: correlation with psychophysical responses in light and dark adaptation. Vision Res 1978; 18: 793–800.
7. Arden GB, Carter RM, Hogg CR, Powell DJ, Ernst WJK, Clover GM, Lyness AL, Quinlan MP. Rod and cone activity in patients with dominantly inherited retinitis pigmentosa: comparisons between psychophysical and electroretinographic measurements. Br J Ophthalmol 1983; 67: 405–18.
8. Birch DG, Herman WK, deFaller JM, Disbrow DT, Birch EE. The relationship between rod perimetric thresholds and full field rod ERGs in retinitis pigmentosa. Invest Ophthalmol Vis Sci 1987; 28: 954–65.
9. Jacobson SG, Borruat FX, Apáthy PP. Rod or cone dysfunction: uniocular presentations. Doc Ophthalmol 1986; 63: 63–71.
10. Apáthy PP, Jacobson SG, Nghiem-Phu L, Knighton RW, Parel JM. Computer-aided analysis in automated dark-adapted static perimetry. In: Greve EL, Heijl A, eds. Seventh international visual field symposium. Dordrecht: Martinus Nijhoff/Dr W Junk, 1987; 277–84.
11. Naka KI, Rushton WAH. S-potentials from colour units in the retina of fish (Cyprinidae). J Physiol 1966; 185: 536–55.
12. Osterberg G. Topography of the layer of the rods and cones in the human retina. Acta Ophthalmol (Kbh) 1935; Suppl VI: 1–102.
13. Drasdo N, Fowler GW. Non-linear projection of the retinal image in a wide-angle schematic eye. Br J Ophthalmol 1974; 58: 709–14.

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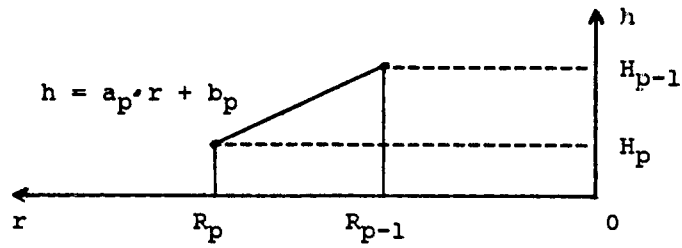
Appendix



The number of photoreceptors N in each annulus p is determined by calculating the volume of the solid of revolution of the photoreceptor density distribution:

$$N_p = \pi \cdot (R_p)^2 \cdot H_p + \pi \cdot \int_{H_p}^{H_{p-1}} [(h - b_p)/a_p]^2 \, dh - \pi \cdot (R_{p-1})^2 \cdot H_{p-1}$$

$$p = 1, 2, \ldots 6$$

where R_p, R_{p-1}, H_p, and H_{p-1} describe the trapezoid shown above and in Figs. 1C and 1D.
The relative number of photoreceptors F within each annulus p is:

$$F_p = N_p \Big/ \sum_{i=1}^{6} N_i \qquad p = 1, 2, \ldots 6$$

The sensitivity loss in dB (l) at each of the 75 test loci is converted from logarithmic to linear units:

$$m = 10^{-l/10}$$

and the mean sensitivity loss M in each annulus p is determined:

$$M_p = \left(\sum_{i=1}^{k} m_i \right) \Big/ k \qquad p = 1, 2, \ldots 6$$

where k is the number of sensitivity measurements in each annulus p.
Each mean sensitivity loss M is weighted by the relative number of photoreceptors in each annulus p:

$$W_p = F_p \cdot M_p \qquad p = 1, 2, \ldots 6$$

and the total sensitivity loss L, represented in logarithmic units, is:

$$L = -\log\left(\sum_{p=1}^{6} W_p\right)$$