Color matches in diseased eyes with good acuity: detection of deficits in cone optical density and in chromatic discrimination

William H. Swanson

Retina Foundation of the Southwest, 9900 North Central Expressway, Suite 400, Dallas, Texas 75231, and Department of Ophthalmology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235

Gary E. Fish

Texas Retina Associates, 7150 Greenville Avenue, Suite 400, Dallas, Texas 75231, and Department of Ophthalmology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235

Received January 17, 1995; revised manuscript received March 30, 1995; accepted April 24, 1995

Reduced foveal cone optical density in diseased eyes with normal acuity can affect color matches. Using field diameters of 1°, 2°, 4°, and 8°, we measured mean color-match midpoints and match widths in patients who had good acuity and who exhibited three categories of eye disease: hereditary macular degeneration ($n = 12$), retinitis pigmentosa ($n = 19$), and glaucoma ($n = 18$). Results were compared with those for normal observers of comparable ages. Mean color-match midpoints were abnormal only for the population with hereditary macular degeneration, indicating a reduction in cone optical density in the central 4°. Mean color-match widths were enlarged for both hereditary macular degeneration and retinitis pigmentosa, a result consistent with a reduction in the number of foveal cones.

Key words: photopigment, optical density, chromatic discrimination, macular degeneration, retinitis pigmentosa, glaucoma.

1. INTRODUCTION

The normal human macula contains a foveal depression approximately 1.5 mm in diameter (corresponding to the central 5° of visual angle), inside of which is a 0.26-mm (1°) rod-free foveola.[1] The fovea is surrounded by a 2.5-mm- (8°-) diameter parafovea and a 5.5-mm- (18°-) diameter perifovea. Cone density and visual resolution both decrease rapidly from foveola to perifovea, so damage to foveal cones can dramatically impair visual function.

Visual acuity is a common clinical index of the severity of damage to foveal cones and is often used to follow the natural history of diseases and to evaluate the success of proposed treatments. However, visual acuity can remain normal despite extensive foveal cone damage: hereditary macular degeneration can reduce the number of foveal cones by 90% without causing abnormal acuity.[2,3] Optical density of cone photopigments can be a more sensitive index of foveal cone damage.[4–7]

The optical density of cone photopigments is a function of the length and the alignment of cone outer segments, the number of photopigment molecules per disk, and the packing density of the disks within the outer segments. Cone photopigment optical density is therefore a sensitive index of changes in cone outer segments. For instance, the length of cone outer segments decreases with increased distance from the foveola, resulting in a measurable variation in cone photopigment optical density across the macula.[8]

Color matching is a simple clinical method that can detect reduced cone photopigment optical density: profound reductions in cone photopigment optical density can result in pseudoprotanomaly, or color matches that require an abnormally high fraction of the long-wavelength primary because of reduced optical density rather than because of a protanomalous pigment.[9] However, color matches are also affected by variations in density of prereceptoral filters and by photopigment polymorphisms, so for individual patients moderate reductions in photopigment optical density may not produce pseudoprotanomaly.

The current study combines two approaches that have been used previously to improve the sensitivity of color matches to reduced cone photopigment optical density in diseased eyes. The first approach is to compare color matches of populations.[10] The average effects of prereceptoral filters and photopigment polymorphisms should be quite similar for patient and normal populations of comparable ages, so the mean difference in color-match midpoints of the two populations should reflect the mean difference in photopigment optical density. The second approach is to have each observer make matches for two or more field sizes: prereceptoral filters and photopigment polymorphisms will have similar effects for all field sizes, so the variation in color match with field size will reflect the variation in cone optical density across the macula.[4] These two approaches have previously been combined in studying patients with age-related maculopathy.[6] The current study focuses on three additional diseases for which earlier studies suggest that there

0740-3232/95/102230-07$06.00

may be three different effects on foveal cone outer segments: hereditary macular degeneration, retinitis pigmentosa, and glaucoma.

Hereditary macular degeneration is a family of rare genetic eye diseases that produce progressive degeneration in the macula while leaving the rest of the retina unaffected.[11] Hereditary macular degeneration often affects acuity by the second decade of life and can lead to a complete absence of foveal cones.[3]

Retinitis pigmentosa is a family of genetic eye diseases that produce progressive degeneration of the rods, and eventually the cones, throughout the retina.[12] Visual acuity may remain normal even when visual fields are quite restricted.[13]

Glaucoma is a family of eye diseases that cause progressive damage to the optic nerve that can be slowed or halted by reduction in intraocular pressure (IOP).[14] The primary site of damage is the optic nerve, but there is also evidence of cone damage in some patients.[15,16]

For both hereditary macular degeneration and retinitis pigmentosa, reduction in cone optical density can precede loss of acuity.[5,7,17,18] For patients with retinitis pigmentosa, cone degeneration is often greater in the parafovea than in the fovea,[19] whereas in hereditary macular degeneration cone damage is often greatest in the fovea.[3] Therefore the pattern of optical-density reduction across the macula may be different in these two diseases, with hereditary macular degeneration causing greater losses in the fovea and retinitis pigmentosa causing greater losses in the parafovea. For glaucoma, effects of disease on photopigment optical density should be secondary, probably small, and uniform across the macula.

2. METHODS

A. Observers

All the patients were required to be free of ocular disease other than their primary diagnosis, free of systemic disease that could affect visual function (i.e., endocrine disorders, neurological or neuromuscular disorders, past or present cancer), free of congenital color defect, and have acuity of 20/32 or better [the log minimum angle of resolution, or logMAR, was 0.20 or less.

Patients with hereditary macular degeneration were diagnosed and were recruited by one of the authors (GF), an ophthalmologist specializing in retinal disease. Historically, classification of patients with hereditary macular degeneration has been based on clinical appearance (e.g., presence of flecks and/or atrophic lesions), symmetry, and age of onset.[11] It is now clear that a number of different genes can cause similar fundus changes and that there can be considerable variability of fundus appearance in patients with the same genetic defect.[20] We restricted our sample to patients who we believed would historically be considered to have fundus flavimaculatus or Stargardt's disease,[11] specifically excluding patients with Best's disease, fenestrated sheen macular dystrophy, central areolar choroidal dystrophy, hemorrhagic macular dystrophy, or hereditary macular degeneration without fundus abnormalities. Age and acuity data for these patients are listed in Table 1.

Patients with retinitis pigmentosa had previously been diagnosed by ophthalmologists specializing in retina disease and were recruited from the patient files of the Retina Foundation of the Southwest. Patients were selected to match in age distribution the patients with hereditary macular degeneration. Patients with retinitis pigmentosa were excluded if there was any clinical evidence of macular lesions or macular edema or if full-field cone electroretinogram (ERG) 30-Hz flicker amplitudes were less than 0.2 μV. A 0.2-μV criterion was used because it is 4 times the lowest measurable signal,[21] and patients with signals smaller than this would be expected to have few remaining functioning cones; the mean normal for this age range is 63 μV, with a lower limit of 42 μV.[22] Age data and clinical information for these patients are listed in Table 2.

Patients with glaucoma were referred by a group of ophthalmologists specializing in glaucoma (Glaucoma Associates of Texas); these patients were considered to be clinically stable by the referring physician (with well-controlled IOP and no progression evident in the visual field or the optic nerve), to have no sign of macular edema or macular lesions, and to have field defects that did not extend into the central 8°. Patients with diagnoses other than primary-open-angle glaucoma were excluded. Age data and clinical information are given in Table 3.

Normal volunteers were recruited by advertisement. They were required to have normal acuity and contrast sensitivity as measured with the Regan Contrast Sensitivity Charts and normal color vision as measured with a battery of tests: the Ishihara plates, the Farnsworth–Munsell 100-hue test, the Farnsworth–Munsell D-15 test, the Adams desaturated D-15 test, and anomaloscopy. They were required to be free of prior eye disease, prior intraocular surgery, family history of genetic eye disease, and systemic disease that could affect visual function (i.e., endocrine disorders, neurological or neuromuscular disorders, past or present cancer). All the normal observers age 40 and over were required to have fundus exams within normal limits for their age; all but three of these normal observers were seen by one of the authors, and these three had recently been examined by their own ophthalmologists.

Table 1. Age and Acuity for Patients with Hereditary Macular Degeneration

Observer ID No.	Age (years)	Acuity (log MAR)
520	28.5	0.00
748	29.2	0.00
461	30.1	0.18
499	32.5	0.00
185	36.7	0.07
482	37.5	0.00
439	38.2	0.10
473	38.6	0.18
246	40.2	0.10
417	43.6	0.00
715	48.0	0.00
488	50.1	0.20
Mean ±1 SD[a]	37.8 ± 7.0	0.07 ± 0.08
Normal observers	38.0 ± 6.7	

[a]SD, standard deviation.

Table 2. Age, Acuity, Inheritance, and Peak-to-Peak Amplitude for the 30-Hz Full-Field ERG for Patients with Retinitis Pigmentosa

Observer ID No.	Age (years)	Acuity (log MAR)	Inheritance	30-Hz ERG (μV)
682	45.5	0.00	dominant	9.5
119	34.0	0.10	dominant	14.6
911	44.0	−0.02	dominant	16.5
70	43.8	0.20	dominant	17.9
908	33.3	−0.08	dominant	21.1
455	39.4	0.20	isolate	1.0
904	28.1	0.06	isolate	1.4
673	50.2	0.00	isolate	4.4
903	42.7	0.00	isolate	9.2
906	46.6	0.07	isolate	14.0
910	40.9	0.01	isolate	20.1
741	37.9	0.01	isolate	20.6
676	29.2	0.10	isolate	24.7
669	32.7	0.1	multiplex	0.2
408	30.3	0.00	recessive	0.2
672	35.7	0.00	recessive	0.5
909	34.3	0.02	recessive	1.2
902	46.5	−0.06	recessive	6.8
668	43.6	0.10	unilateral	2.8
Mean ±1 SD	38.9 ± 6.6	0.04 ± 0.08		
Normal observers	38.0 ± 6.7			

Table 3. Age, Acuity, Primary Treatment, IOP for Patients with Glaucoma

Observer ID No.	Age (years)	Acuity (log MAR)	Treatment	IOP (mm Hg)
694	41.4	0.00	Medications only	18
681	63.7	0.01	Medications only	19
942	65.8	−0.04	Medications only	17
693	75.4	0.11	Medications only	16
825	76.3	−0.04	Medications only	10
735	77.3	0.13	Medications only	19
708	62.0	0.03	Argon-laser trabeculoplasty	19
814	76.7	0.01	Argon-laser trabeculoplasty	18
920	78.1	0.05	Argon-laser trabeculoplasty	18
938	80.3	0.02	Argon-laser trabeculoplasty	15
734	33.3	−0.20	Trabeculectomy	12
922	47.2	0.00	Trabeculectomy	11
648	54.7	0.11	Trabeculectomy	10
679	61.2	0.01	Trabeculectomy	12
674	70.6	0.00	Trabeculectomy	8
692	72.9	0.10	Trabeculectomy	11
270	76.1	0.00	Trabeculectomy	12
283	78.1	0.05	Trabeculectomy	10
Mean ±1 SD	66.2 ± 13.9	0.02 ± 0.07		
Normal observers	65.4 ± 11.2			

Because the magnitude of the color-match-area effect is affected by age,[23,24] two groups of normal observers were used for comparisons with patients. One group of normal observers (age range, 27–49; mean ±1 SD, 38 ± 7 years) was used for comparison with the patients with hereditary macular degeneration (age range, 28–50; mean ±1 SD, 38 ± 7 years) and for comparison with the patients with retinitis pigmentosa (age range, 28–50; mean ±1 SD, 39 ± 7 years). A second group of normal observers (age range, 34–80; mean ±1 SD, 65 ± 11 years) was used for comparison with the patients with glaucoma (age range, 33–81; mean ±1 SD, 68 ± 14 years). The two groups of normal observers had only two members in common.

B. Apparatus and Procedures

Rayleigh matches were gathered with a computerized anomaloscope (protocol is described in detail elsewhere[25,26]). Briefly, the anomaloscope uses a combination of light-emitting diodes and interference filters to yield narrow-band primaries of 667, 588, and 551 nm. These primaries are combined in a three-channel Maxwellian-view optical system with a 2-mm artificial pupil.

The observer views a circle divided in half; the left-hand semicircle is filled with a red–green mixture (667 and 551 nm, respectively), and the right-hand semicircle is filled with a 588-nm yellow standard. The mean retinal illuminance of the yellow standard is set to 57 Td, and the computer presents a series of red–green-mixture fields. Each time a red–green-mixture field is presented the observer is required first to decide whether the two sides are the same color and, if not, then to decide which side is redder. The protocol estimates the end points of the matching range by means of two interleaved staircases (average of 40–80 trials in all) that determine when the mixture field is just detectably redder or greener than the standard field.

Matches were made for the different field sizes in the following order: 2°, 4°, 1°, 8°. For 77% of the observers a retest was conducted with the 2° field; in these cases the 2° match midpoint and width were set equal to the average for test and retest values.

C. Data Analysis

There are several methods used in the literature for reporting color matches. We used a traditional method[27]: the retinal illuminances for the red and the green lights are expressed in units of R and G, respectively. The sum R + G is held constant, and color mixtures are expressed as R/(R + G), ranging from 0.0 (only the green primary) to 1.0 (only the red primary). The units for R and G are such that the quantal catch of the long-wavelength-sensitive (L) cones remains constant as R/(R + G) varies from 0.0 to 1.0, whereas the quantal catch of the middle-wavelength-sensitive (M) cones varies linearly with R/(R + G). The midpoint of the matching range is reported in units of log(G/R), and the width of the matching range is expressed in the Nagel units conventionally used in anomaloscopes [this calculation is accomplished by multiplication of the R/(R + G) value by 73].

The average effects of photopigment polymorphisms and prereceptoral filters should be comparable for populations of comparable ages, so differences in mean color-match midpoints should reflect differences in mean cone photopigment optical density for the two populations. Match midpoints for each patient were converted to deficit scores by subtraction of the mean values for the corresponding normal group. Match widths for each patient were converted to deficit scores by subtraction of the logarithm of the patient's match width from the logarithm of the mean normal match width. Analyses of variance (ANOVA's) were performed on the deficit scores so that we could look for the main effects of disease and of field diameter and for an interaction between them. The Box[28] index for sphericity was used to correct the probability values for differences in SD's of the populations. When a main effect was significant ($P < 0.05$), pairwise comparisons were made by means of *post hoc* Newman–Keuls tests.

3. RESULTS

Figure 1 shows match midpoint as a function of diameter for the three patient groups and their age-matched normal groups. At all the diameters the mean midpoints for the patients with hereditary macular degeneration fell well below mean normal, whereas those for patients with retinitis pigmentosa or glaucoma did not. As shown in Table 4, an ANOVA on the deficit scores (difference from mean normal) for match midpoint showed a significant main effect of disease and a significant interaction between disease and stimulus diameter. *Post hoc* pairwise comparisons showed that the patients with hereditary macular degeneration had greater deficits than either the patients with retinitis pigmentosa or the patients with glaucoma ($P < 0.05$) and that there was no difference between the patients with retinitis pigmentosa and the patients with glaucoma.

For each patient group the mean deficit score for match midpoint was converted to an optical-density defect. Over our range of values for log(G/R), the relationship between optical density and log(G/R) can be considered linear.[29] Therefore the mean optical-density defect is a constant times the mean deficit score for the match midpoint. Figure 2 shows the optical-density defects computed from the color matches shown in Fig. 1 by comparing each patient's midpoint with the mean for their age-matched group. The shaded region shows ±1 SEM. For patients with hereditary macular degeneration the mean optical-density defect worsened by a factor of 2 as the field diameter decreased from 8° to 1°, whereas for the patients with retinitis pigmentosa or glaucoma there was no optical-density defect for any field size ($t > 0.79$, $P > 0.43$).

Mean values for match widths are shown in Fig. 3. The patients with hereditary macular degeneration and retinitis pigmentosa had increased match widths at all the field diameters, whereas the patients with glaucoma had

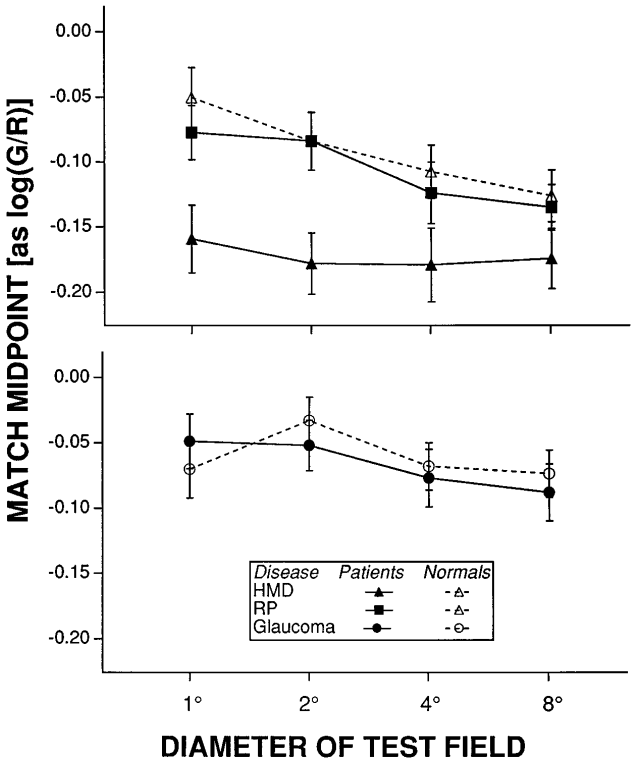

Fig. 1. Mean color-match midpoints as a function of field diameter for three patient groups (solid symbols), along with means for the age-matched normal observers (open symbols). The error bars show ±1 standard error of the mean (SEM). HMD, hereditary macular degeneration; RP, retinitis pigmentosa.

Table 4. Results of ANOVA of Match-Midpoint-Deficit Scores for the Three Patient Groups[a]

Source	df	SS	MS	F	P	ε	P^*
Disease	2	0.2217	0.11084	3.940	0.026		
Error	46	1.294	0.02813				
Diameter	3	0.0056	0.00185	1.278	0.284	0.864	0.284
Disease × diameter	6	0.0468	0.00780	5.382	<0.0005	0.864	<0.0005
Error	138	0.2001	0.00145				
Total	195	1.7349					

[a]df, Degrees of freedom; SS, sum of squares; MS, mean square; F, ratio; P, probability; ε, sphericity index; P^*, the P value corrected for violation of the assumption of sphericity.

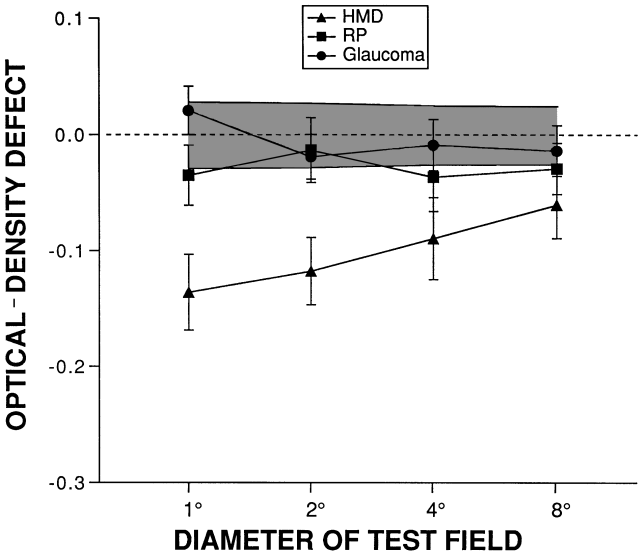

Fig. 2. Mean optical-density defect (computed from data shown in Fig. 1) as a function of field diameter for the three patient groups. A negative value indicates an optical density below the mean normal. The error bars show ±1 SEM for each patient group, and the shaded region shows ±1 SEM for normal observers.

normal match widths. As shown in Table 5, an ANOVA on the deficit scores for match width showed a significant main effect of disease and no significant interaction between disease and stimulus diameter; *post hoc* pairwise comparisons showed that each group was significantly different from the other two ($P < 0.01$).

For each patient group the mean deficit score was converted to a chromatic discrimination defect. Because the quantal catch of the L cones does not vary as the red–green mixture varies, only the M cones detect a difference between the red–green mixture and the yellow standards. The M-cone modulation is a linear function of the width in Nagel units,[27] so the ratio of M-cone modulations is therefore equal to the ratio of match widths in Nagel units. For normal observers the ratio of chromatic discrimination thresholds is a constant times the ratio of Nagel widths. For patients with reduced cone optical density the amount of M-cone modulation for a fixed change in R/(R + G) will be greater than for normal observers, and the L-cone quantal catch will not be constant with R/(R + G). Therefore, for some patients, the computed chromatic defect will be a slight underestimation of the magnitude of the actual defect.

Mean chromatic discrimination defects are shown in Fig. 4. For patients with hereditary macular degeneration the mean chromatic discrimination defect was relatively constant (between −0.8 and −0.9 log unit) with field diameter. For patients with retinitis pigmentosa the defect more than doubled as field diameter decreased from 8° to 1°, yet even at 1° it was not as severe as for the patients with hereditary macular degeneration.

4. DISCUSSION

The color matches for the three patient groups reveal three distinct patterns. The patients with hereditary macular degeneration have mean match midpoints that require more long-wavelength light in the mixture than do those of normal observers, with greater defects in the foveola than in the parafovea, and they have enlarged match widths at all the field diameters. The patients with retinitis pigmentosa have normal match midpoints and enlarged match widths, with greater match-width defects for smaller fields. The patients with glaucoma have normal match midpoints and match widths.

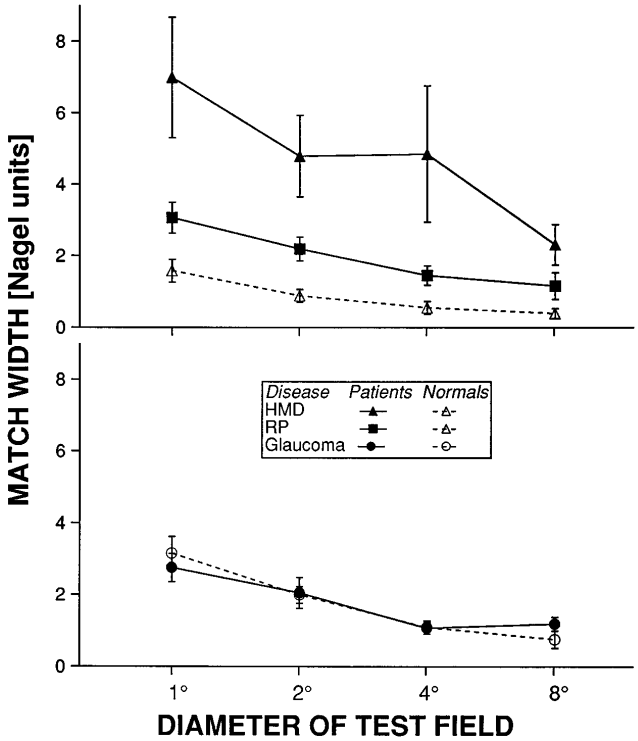

Fig. 3. Mean color-match widths as a function of field diameter for the three patient groups (solid symbols), along with means for the age-matched normals (open symbols). The error bars show ±1 SEM.

Table 5. Results of ANOVA of Match-Width-Deficit Scores for the Three Patient Groups[a]

Source	df	SS	MS	F	P	ε	P^*
Disease	2	14.3344	7.16722	19.971	<0.0005		
Error	46	16.5083	0.35888				
Diameter	3	0.1430	0.04768	0.333	0.801	0.670	0.718
Disease × diameter	6	1.0529	0.17549	1.227	0.296	0.670	0.305
Error	138	19.7328	0.14299				
Total	195	50.5719					

[a]df, Degrees of freedom; SS, sum of squares; MS, mean square; F, ratio; P, probability; ε, sphericity index; P^*, the P value corrected for violation of the assumption of sphericity.

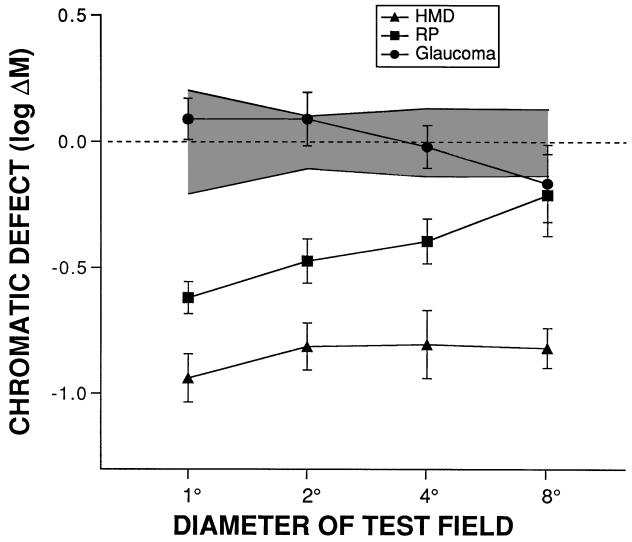

Fig. 4. Mean chromatic discrimination defect (ΔM) as a function of field diameter for the three patient groups. Defects were computed from data shown in Fig. 3 and were expressed in terms of modulation of the M cones. A negative value indicates subnormal chromatic sensitivity. The error bars show ±1 SEM for each patient group, and the shaded region shows ±1 SEM for normal observers.

The abnormal mean match midpoint for patients with hereditary macular degeneration indicates reduced cone optical density in this population. Because normal cone optical density is approximately 0.33 for a 2° field,[29] for our patients with hereditary macular degeneration the mean cone optical density for a 2° field is only approximately 60% of the normal value. This estimate is in the range found by means of a densitometric study[7] in which seven eyes of four patients with hereditary macular degeneration and acuity 20/32 or better had optical densities ranging from 3% to 75% of the normal value.

The mean match midpoints for our patients with retinitis pigmentosa were not statistically different from those of normal observers. Three studies found that patients with retinitis pigmentosa and good acuity tend to have reduced foveal cone optical density.[5,18,30] Pooling data from these three studies, we find that for the 34 patients with retinitis pigmentosa and good acuity the mean ±1 SD for optical density is 57% ± 28% of the normal value. For our sample size, with these estimates for mean and SD, the power to detect a difference between patients and normals would be 0.98 (with $P < 0.01$). It is therefore surprising that we did not find abnormal mean match midpoints for our patients with retinitis pigmentosa. These three studies indicate that there is considerable variability in amount of optical-density defect in patients with retinitis pigmentosa, so it is possible that our population of patients with retinitis pigmentosa happened to have higher average optical densities than did the populations in the other studies. It is also possible that mean effects of prereceptoral filters and photopigment polymorphisms were different for our retinitis pigmentosa and normal populations, obscuring the effects of a small mean optical-density defect.

Cone degeneration is generally considered to begin in the fovea in patients with hereditary macular degeneration and in the midperiphery in patients with retinitis pigmentosa. Our data support this hypothesis. For patients with hereditary macular degeneration the cone optical-density defect is on average twice as large in the foveola than in the parafovea, indicating greater damage to foveolar cones. For patients with retinitis pigmentosa color matches were normal, despite extensive loss of cones throughout much of the retina (indicated by full-field ERG flicker amplitudes reduced more than a log unit below normal[22]).

We found that small-field match widths for patients with hereditary macular degeneration and patients with retinitis pigmentosa were larger than normal, indicating a loss in red–green color discrimination. For normal observers mean match width increases as stimulus diameter decreases (see Fig. 3), and hence smaller numbers of cones are stimulated. Therefore it is possible that the increased match widths that we find in patients with hereditary macular degeneration or retinitis pigmentosa are due to the stimuli's falling on fewer cones than for normal observers.[2,31,32]

There are reports of abnormalities of cone function in patients with glaucoma,[15,16] and it is known that glaucoma surgery can occasionally lead to macular abnormalities.[33] Both match midpoints and match widths were normal in our population of patients with glaucoma, indicating little or no damage to foveal cones. Because short-wavelength-sensitive cones do not contribute to Rayleigh matches, no conclusions can be drawn from our data concerning the S-cone pathway. A separate study performed on these patients demonstrated macular S-cone pathway deficits.[34]

These results are derived from statistical comparisons of patient populations with age-matched normal populations. In dealing with individual patients, the distinction between normal and abnormal color matches is less clear. The mean data indicate that patients with hereditary macular degeneration have abnormal match midpoints, yet at each field size only 1 or 2 of the 12 patients with hereditary macular degeneration had a match midpoint

more than 2 SD's below normal. The match width was a more sensitive measure of defect: at each field size, between 6 and 8 of the 12 patients with hereditary macular degeneration has match widths more than 2 SD's wider than normal.

5. CONCLUSIONS

Color-match midpoints were abnormal in patients with hereditary macular degeneration and normal in patients with retinitis pigmentosa or glaucoma. For patients with hereditary macular degeneration this result indicates a cone optical-density defect that is greater in the foveola than in the parafovea. Color-match widths were enlarged in patients with hereditary macular degeneration and in patients with retinitis pigmentosa, consistent with reduced numbers of foveal cones. Although these data document effects of disease that are apparent in analyzing population data, for individual patients such effects often may not be detected by clinical anomaloscopy.

ACKNOWLEDGMENTS

This research was supported by National Institutes of Health National Eye Institute grant EY07716 to W. Swanson. We are grateful to Glaucoma Associates of Texas for referring patients with glaucoma and for providing clinical information.

REFERENCES

1. A. I. Cohen, "The Retina," in *Adler's Physiology of the Eye,* W. M. Hart, ed. (Mosby, St. Louis, Mo., 1992), pp. 579–615.
2. A. M. Geller and P. A. Sieving, "Assessment of foveal cone photoreceptors in Stargardt's macular dystrophy using a small dot detection task," Vision Res. **33,** 1509–1524 (1993).
3. R. C. Eagle, A. C. Lucier, V. B. Bernardino, and M. Yanoff, "Retinal pigment epithelial abnormalities in fundus flavimaculatus," Ophthalmology **87,** 1189–1200 (1980).
4. J. Pokorny, V. C. Smith, and J. T. Ernest, "Macular color vision defects: specialized psychophysical testing in acquired and hereditary chorioretinal diseases," Int. Ophthalmol. Clin. **20,** 53–81 (1980).
5. A. E. Elsner, S. A. Burns, and J. L. A. Lobes, "Foveal cone optical density in retinitis pigmentosa," Appl. Opt. **26,** 1378–1384 (1987).
6. A. Eisner, V. D. Stoumbos, M. L. Klein, and S. A. Fleming, "Relations between fundus appearance and function: eyes whose fellow eye has exudative age-related macular degeneration," Invest. Ophthalmol. Vis. Sci. **32,** 8–20 (1991).
7. G. J. van Meel and D. van Norren, "Foveal densitometry as a diagnostic technique in Stargardt's disease," Am. J. Ophthalmol. **102,** 353–362 (1986).
8. A. E. Elsner, S. A. Burns, and R. H. Webb, "Mapping cone photopigment optical density," J. Opt. Soc. Am. A **10,** 52–58 (1993).
9. J. Pokorny, V. C. Smith, G. Verriest, and A. J. L. G. Pinckers, *Congenital and Acquired Color Vision Defects* (Grune & Stratton, New York, 1979).
10. R. S. L. Young and G. A. Fishman, "Color matches of patients with retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci. **19,** 967–972 (1980).
11. K. G. Noble, "Pathology of the hereditary macular dystrophies," Semin. Ophthalmol. **2,** 110–129 (1987).
12. E. L. Berson, "Retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci. **34,** 1659–1676 (1993).
13. S. A. Madreperla, R. W. Palmer, R. W. Massof, and D. Finkelstein, "Visual acuity loss in retinitis pigmentosa. Relationship to field loss," Arch. Ophthalmol. **108,** 358–361 (1990).
14. H. A. Quigley, "Open-angle glaucoma," N. Engl. J. Med. **328,** 1097–1106 (1993).
15. D. T. Fazio, J. R. Heckenlively, D. A. Martin, and R. E. Christensen, "The electroretinogram in advanced open-angle glaucoma," Doc. Ophthalmol. **63,** 45–54 (1986).
16. K. Holopigian, W. Seiple, C. Mayron, R. Koty, and M. Lorenzo, "Electrophysiological and psychophysical flicker sensitivity in patients with primary open-angle glaucoma and ocular hypertension," Invest. Ophthalmol. Vis. Sci. **31,** 1863–1868 (1990).
17. J. E. E. Keunen, V. C. Smith, J. Pokorny, and M. B. Mets, "Stiles–Crawford effect and color matching in Stargardt's disease," Am. J. Ophthalmol. **112,** 216–217 (1991).
18. G. J. van Meel and D. van Norren, "Foveal densitometry in retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci. **24,** 1123–1130 (1983).
19. M. A. Sandberg and E. L. Berson, "Visual acuity and cone spatial density in retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci. **24,** 1511–1513 (1983).
20. R. G. Weleber, "Stargardt's macular dystrophy," Arch. Ophthalmol. **112,** 752–754 (1994).
21. E. L. Berson, M. A. Sandberg, B. Rosner, D. G. Birch, and A. H. Hanson, "Natural course of retinitis pigmentosa over a three-year interval," Am. J. Ophthalmol. **99,** 240–251 (1985).
22. D. G. Birch and J. L. Anderson, "Standardized full-field electroretinography," Arch. Ophthalmol. **110,** 1571–1576 (1992).
23. W. H. Swanson and G. E. Fish, "Age-related changes in foveal cone architecture," Invest. Ophthalmol. Vis. Sci. Suppl. **35,** 1952 (1994).
24. A. Eisner, S. A. Fleming, M. L. Klein, and W. M. Mouldin, "Sensitivities in older eyes with good acuity: cross-sectional norms," Invest. Ophthalmol. Vis. Sci. **28,** 1824–1831 (1987).
25. J. Pokorny, V. C. Smith, and M. Lutze, "A computer controlled briefcase anomaloscope," in *Colour Vision Deficiencies IX,* Documenta Ophthalmologica Proceedings Series, B. Drum and G. Verriest, eds. (Kluwer, Dordrecht, The Netherlands, 1989), Vol. **52,** pp. 515–522.
26. W. H. Swanson, "Analysis of Rayleigh match data with psychometric functions," J. Opt. Soc. Am. A **10,** 1807–1817 (1993).
27. J. Pokorny and V. C. Smith, "Metameric matches relevant for assessment of color vision," in *Color Vision Deficiencies VII,* Vol. 39 of Documenta Ophthalmologica Proceedings Series (Junk, The Hague, The Netherlands, 1984), pp. 83–94.
28. G. E. P. Box, "Some theorems on quadratic form applied to the study of analysis of variance problems. II. Effects of inequality of variance and the correlation between errors in the two-way classification," Ann. Math. Stat. **25,** 484–498 (1954).
29. S. Burns and A. Elsner, "Color matching at high illuminances: the color-match-area effect and photopigment bleaching," J. Opt. Soc. Am. A **2,** 698–704 (1985).
30. P. E. Kilbride, M. Fishman, G. A. Fishman, and L. P. Hutman, "Foveal cone pigment density difference and reflectance in retinitis pigmentosa," Arch. Ophthalmol. **104,** 220–224 (1986).
31. J. G. Flannery, D. B. Farber, A. C. Bird, and D. Bok, "Degenerative changes in a retina affected with autosomal dominant retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci. **30,** 191–211 (1989).
32. K. R. Alexander, D. J. Derlacki, G. A. Fishman, and N. S. Peachey, "Acuity-luminance and foveal increment threshold functions in retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci. **32,** 1446–1454 (1991).
33. V. P. Costa, M. Smith, G. L. Spaeth, S. Gandham, and B. Markovitz, "Loss of visual acuity after trabeculectomy," Ophthalmology **100,** 599–612 (1993).
34. W. H. Swanson, R. L. Fellman, J. R. Lynn, R. J. Starita, and S. P. Schumann, "What causes tritan color vision defects in glaucoma?" in *Digest of Topical Meeting on Vision Science and Its Applications* (Optical Society of America, Washington, D.C., 1994), pp. 286–289.