Visual Function and the Subsequent Development of Exudative Age-Related Macular Degeneration

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The eyes of 47 subjects with exudative age-related macular degeneration in the fellow eye were tested with a battery of visual function tests at baseline and followed for at least 18 mo. Fundus photographs also were obtained at baseline. These photographs were used to verify the absence of exudative lesions in the 47 eyes tested. Functional and funduscopic baseline data each were compared against outcome data obtained typically at 18 mo. The baseline data were analyzed for their ability to distinguish eyes that had developed detectable exudative age-related macular degeneration from eyes that had not. Eyes with relatively slow foveal dark adaptation rates in the presence of fundus photographs that lacked exudative lesions were especially likely to develop subretinal neovascularization. The resulting sensitivity/specificity and odds ratios were comparable to those of the most effective funduscopic risk indicators. Low S (blue) cone-mediated sensitivity also was associated with an exudative outcome. Invest Ophthalmol Vis Sci 33:3091-3102, 1992

Exudative age-related macular degeneration (AMD) is a leading cause of legal blindness. Fortunately, laser treatment for the most prevalent type of exudative AMD, subretinal neovascularization (SRN),1 has been shown to help preserve central vision for many eyes.2-5 Because the effectiveness of such treatment is appreciably less for subfoveal than for extrafoveal neovascular membranes,3,4,6,7 and because neovascular membranes tend to grow rapidly toward the fovea,8,9 early detection of SRN becomes very important. This is why the establishment of risk indicators for neovascularization is important.

Most risk indicators that have been shown to be effective are funduscopic risk indicators. Focal hyperpigmentation, along with drusen size, confluence, and type (eg, soft versus hard), all have been shown to have prognostic value.10-13 Funduscopic risk indicators are anatomic, however, and therefore may not always reflect physiologic change that has prognostic significance. In contrast to indices of fundus appearance, measurements of visual function have the advantage of depending directly on physiology as well as on anatomy. In addition, visual function can be measured locally and can be quantified relatively easily. Of course, functional assessment and funduscopic assessment are not mutually exclusive.

The only visual function shown to have prognostic utility is absolute sensitivity. Specifically, it has been reported by Sunness et al14 that low absolute sensitivity can predict the development of advanced AMD with a high degree of specificity. However, only one of the subjects who developed advanced AMD developed SRN; the others developed pigment epithelial detachments or geographic atrophy.

Recently, in a cross-sectional study relating visual function to fundus appearance,15 we showed that several types of functional deficit are related systematically to the presence of known funduscopic risk indicators. The existence of significant and meaningful relations suggested that certain visual functions could have prognostic value.

In particular, the success with which dark adaptation and color matching could together discriminate eyes with “low-risk” from “high-risk” fundus appearance was especially striking, suggesting that a combination of these two functions should be evaluated against longitudinal outcome data for prognostic purposes. It is likely that the dark adaptation and color matching data complemented each other because the color matching data helped identify those “high-risk” eyes that had spuriously normal dark adaptation rates resulting from reduced quantum catching capability.

More specifically, because the bleaching stimulus
used for dark adaptation may have been effectively
dim for these eyes, their dark adaptation rates may
not have been slow.15

In the present report, we again evaluated the ability
dark adaptation and color matching to comple-
ment each other, this time regarding their ability to
predict the development of SRN within follow-up pe-
riods that typically were 18 mo. We also evaluated the
utility of several other visual functions, and we com-
pared functional data against funduscopic data.

Subjects and Methods

Subjects

The ostensibly nonexudative eyes (ie, “study eyes”) of 47 subjects with SRN in their fellow eye were tested at baseline and followed for at least 18 months. All subjects had 20/25 or better best corrected acuity at baseline. No subjects had congenitally defective color vision, diabetes, myopia greater than 5 diopters, history of ocular hypertension, or eye disease other than age-related macular degeneration. In addition, no subjects claimed to have used drugs known to be de-

erived from chloroquine. For all 47 subjects, clinical examination plus stereo color fundus photographs taken at baseline (subsequently screened by MLK) provided no evidence for SRN or pigment epithelial detachments in any study eye.

Of the 47 subjects, 31 were male and 16 were female. The age range was 55–86 yr. No other subjects meeting eligibility criteria for entry into the study had been enrolled for 18 mo. Two additional subjects were tested at baseline but died prior to 18 mo. An additional subject who had been tested at baseline subsequently was determined to already have SRN in his study eye. All subjects who enrolled in the study gave written informed consent.

Outcome Assignments

All outcome assignments (SRN, acuity loss of two or more lines due to other [nonexudative] causes, or minimal acuity loss) were made without knowledge of subjects’ baseline functional data. Diagnoses of SRN or confirmation of SRN from clinical diagnoses were based on evaluation of fundus photographs by the two authors (MLK and JDZ), who are retina specialists. For two subjects who developed SRN, outcome records did not exist at 18 mo. For these two subjects, the next available records were used. They were from 22 and 27 mo. The 22 mo subject received laser treat-
ment at that time. He had reported being symptomatic for the previous 2–3 mo. The 27 mo subject was known to have developed a four-line acuity loss and an area of possible occult SRN on fluorescein angiog-
Fundus Appearance Scores and Ratings

Fundus appearance was evaluated using scores assigned to the baseline fundus photographs by the University of Wisconsin at Madison Fundus Photograph Reading Center. Categorical scores for drusen area, confluent drusen area, and atrophic area for each of the separate subregions of the macula were converted to quantitative ratio scores for larger regions (e.g., the entire macula or for the central subregion of 3000 µm diameter) as described previously. Scores for hyperpigmentation, predominant drusen type, and largest drusen size were not converted to ratio scores. Instead, these scores were converted to categorical scores for larger regions by taking the maximal score from the smaller component subregions. Atrophic areas were determined from scores regarding retinal pigment epithelial degeneration and geographic atrophy.

For the four eyes with acuity-loss outcomes but without exudative AMD, an attempt was made to ascribe the cause of the acuity loss. For those three eyes that had both baseline and 18 mo fundus photographs, sets of photographs were evaluated subjectively in a masked fashion with additional sets of photographs from eyes whose baseline fundus appearances were matched as closely as possible to those three eyes. For the fourth acuity-loss eye, 18 mo fundus photographs did not exist. For this eye, 8 mo photographs were compared separately against baseline photographs. For all seven sets of photographs (from four acuity-loss eyes plus three matched controls), categorical judgments were made (by JDZ) regarding the likelihood that different types of change (e.g., progressive cataract or macular degenerative change) could have caused the acuity loss. The four allowable categories were “no change detected,” “probably not,” “possibly,” and “probably.”

Statistical Analyses

Statistical analyses and graphs were done using the commercial package SYSTAT (SYSTAT Inc., Evanston, Illinois). All significance values are for one-sided tests unless noted otherwise. Significance values for Spearman’s rank order correlation coefficients were interpolated from a look-up table. In the text, the term “sensitivity/specificity ratio” refers to the percentage of exudative outcomes forecast correctly divided by the percentage of minimal-acuity-loss outcomes forecast incorrectly.

Results

Color Matching and Dark Adaptation

Figure 1 plots the dark adaptation time constant versus the color-match-area effect at baseline. Filled symbols represent eyes that developed SRN within “18 mo” of baseline (“exudative-outcome” eyes), hatched symbols represent eyes that lost two lines of acuity because of nonexudative causes (“non-exudative-acuity-loss” eyes), and open symbols represent eyes with zero or one line of acuity loss (“minimal-acuity-loss” eyes). The horizontal dashed line corresponds to an upper limit of normal for the dark adaptation time constant, and the vertical dashed line corresponds to a lower limit of normal for the color-match-area effect. Thus, the lower right quadrant is the only quadrant for which the dark adaptation time constant and color-match-area effect are each within their own normal limits. These limits had been derived independently of each other from a population of nondiseased elderly eyes. To facilitate comparison with a known funduscopic risk indicator, eyes with macular focal hyperpigmentation are represented by squares and eyes without macular focal hyperpigmentation are represented by circles.

Creation of an exponential cutoff to separate outcomes: An exponential curve has been fit empirically through the data to optimally separate exudative outcomes from minimal-acuity-loss outcomes. The shape and position of the exponential curve took into account the following three factors. First, a strong positive correlation existed between dark adaptation time constant and color-match-area effect for the minimal-acuity-loss eyes (Spearman’s r = .53, P = .002), espe-
cially for those eyes with color-match-area-effects less than .06 (Spearman's r = .81, P = .0005). A positive correlation is expected when the dark adaptation rate depends inversely on the cones' ability to absorb quanta from the bleaching stimulus. Second, when a smooth-curve-fitting paradigm ("Lowess") was used to fit the minimal-acuity-loss data, the curve that was generated increased progressively with values of the color-match-area-effect up to about .05. The exponential curve drawn closely parallels the smooth curve generated by the curve-fitting paradigm between values of about .01 and .04. (For reasons of clarity, that smooth curve is not shown.) Third, because the dashed lines representing normal limits were derived independently for the two functional indices, any single cutoff that uses both functional indices simultaneously would be expected to intrude appreciably into the first and third quadrants and only minimally into the fourth (ie, lower right) quadrant. The second (ie, upper left) quadrant would be completely circumscribed.

Four eyes had nonexudative acuity-loss outcomes, two on each side of the exponential curve. Although data from the four nonexudative acuity-loss eyes are represented graphically, they will not be used for statistical purposes in the text because of their small number and the uncertainty regarding their appropriate classifications (see Note 1). Because the data from the only eye whose acuity loss was "probably" a result of the other acuity-loss eye whose data lie to the upper left of that curve had several independent, high-risk fundus features at baseline, omission of these four eyes probably does not constitute an unduly favorable bias. Nevertheless, statistics that include data from nonexudative acuity-loss eyes classified as: (1) advanced AMD; or (2) favorable outcomes, respectively, are reported in Table 1. Regardless of how the non-exudative-acuity-loss eyes are classified or which endpoints are chosen, most comparisons and conclusions in the text remain essentially unaltered. Two possible exceptions will be specified in the text's second and third notes.

Statistical comparisons with focal hyperpigmentation: Among the 37 eyes that had measurable color-match-area-effects and exudative outcomes or minimal-acuity-loss outcomes, the given exponential cutoff served as a risk indicator having a sensitivity/specificity ratio of 9.3 and an odds ratio of 26. The kappa statistic regarding the agreement between outcome and risk indicator was 0.62. Thus, the exponential cutoff can be considered a good risk indicator. If the constraints on the exponential curve's shape and position are weakened appreciably, allowing the two eyes at about (.05, 348) to fail, the corresponding values would decrease to 4.7, 12, and 0.51, respectively. These values still are fairly good. For comparison, the presence of hyperpigmentation for the same 37 eyes yielded a sensitivity/specificity ratio of 3.9, an odds ratio of 7.5, and a kappa of 0.41. For all 43 eyes with exudative outcomes or minimal-acuity-loss outcomes, the corresponding values were 3.5, 6.5, and 0.39, respectively.

Additional evidence for the exponential cutoff: Because two exudative-outcome eyes (and four minimal-acuity-loss eyes) did not accept any R/G ratio for a small-field Rayleigh match at baseline, and consequently did not have any measurable color-match-

<table>
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<th>Table 1. Statistics for risk indicators</th>
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<td><strong>Nonexudative-acuity-loss eyes omitted</strong></td>
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<td>Sensitivity/specificity ratio</td>
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| **Nonexudative-acuity-loss eyes considered advanced AMD** |
| Sensitivity/specificity ratio | 8.6 | 3.0 | 2.5 | 1.8 | 5.2 | 4.3 |
| Odds ratio | 21 | 4.7 | 3.8 | 12 | 6.5 | 8.0 |
| Kappa | 0.58 | 0.33 | 0.29 | 0.31 | 0.41 | 0.43 |

| **Nonexudative-acuity-loss eyes considered favorable outcomes** |
| Sensitivity/specificity ratio | 5.3 | 3.3 | 2.0 | 1.6 | 3.7 | 4.6 |
| Odds ratio | 14 | 6.0 | 2.9 | 7.1 | 11 | 11 |
| Kappa | 0.52 | 0.37 | 0.22 | 0.20 | 0.47 | 0.48 |

All funduscopic data were determined using the central 3000 μm of the macula only. Cut-offs are identical to those used in text. Functional data are from all subjects with measurable color-match-area-effects. Funduscopic data are from all subjects.
area effect, the number of exudative-outcome eyes to the upper left of the exponential curve may be considered unsatisfactorily small. In addition, creation of the exponential curve in Figure 1 may be considered post-hoc. To address these concerns, Figure 2 plots data from the five eyes (x's) known to have developed clinical or funduscopy evidence of SRN after “18 mo” and from the one eye (+) that initially had been enrolled in the study but was later dropped from enrollment because baseline fundus photographs revealed a small area of SRN temporal to the foveal avascular zone. For four of the five eyes that developed SRN after “18 mo,” the data in Figure 2 are from the 18 mo testing session, rather than from the baseline testing session. Additional information regarding all six eyes is provided in the figure legend. Except for the eye dropped from the study, the data in Figure 2 were not analyzed until after creation of the exponential curve in Figure 1. These data, therefore, provide additional independent evidence that the given exponential curve (or perhaps a similar curve with a descending tail for progressively negative color-match-area effects) does serve as a cutoff for a good risk indicator. Although the impressive sensitivity/specificity and odds ratios still may be regarded as inflated because of the optimization process, it is clear that the efficacy of the exponential-type curve did not result merely from chance.

**Possibility of age-confounds:** To evaluate the possibility that the success of dark adaptation combined with color matching resulted from a confounding effect of age, Spearman’s rank order correlation coefficients were computed for each function separately with age. Among minimal-acuity-loss eyes only, the correlations with age for the dark adaptation time constant and color-match-area effect were weak (Spearman’s r = .12 and Spearman’s r = .08, respectively). Thus, although eyes with exudative outcomes tended to be (nonsignificantly) older than eyes with minimal-acuity-loss outcomes (median age = 74 yr versus 71 yr, P = .074, all eyes; and median age = 74 yr versus 71.5 yr, P = .156, eyes with measurable color-match-area effects only; Mann-Whitney U tests), direct effects of age on visual function appeared to be small.

**S Cone-Mediated Sensitivity and Absolute Sensitivity**

Figures 3 and 4 plot S cone-mediated sensitivity and absolute sensitivity, respectively, versus age. The solid curves, describing the change of sensitivity with age, provide robust locally-weighted regression of the data from minimal-acuity-loss eyes only. Symbols are as in Figure 1.
Fig. 4. Absolute sensitivity versus age. Smooth curve and symbols are as in Figure 3.

age for minimal-acuity-loss eyes, were generated by the smooth-curve-fitting paradigm, “Lowess.” To generate these curves, the “tension” parameter was set at the SYSTAT default setting, 0.5. “Lowess” is a robust, locally weighted regression paradigm.26

Of the two types of sensitivity, S cone-mediated sensitivity appeared better able to help distinguish between outcome groups. Specifically, for six exudative-outcome eyes, S cone-mediated sensitivities were about 0.5 log U or more below the smooth curve that described the age changes among minimal-acuity-loss eyes (Spearman’s $r = -0.44, P = .002$). The data from the oldest subject tested also were quite low. However, the correction for age-related change among minimal-acuity-loss eyes cannot yet be made with accuracy sufficient to warrant creation of a precise cutoff for a risk indicator, especially given the possibility of gender-dependent effects.1517’27 When age corrections were made separately for men and women, the same exudative-outcome eyes remained differentiated.

Unlike S cone-mediated sensitivity, the cross-sectional absolute sensitivities did not appear to help predict outcomes after effects of age (Spearman’s $r = -0.46, P = .001$) were removed. However, evidence from an incomplete dataset suggested that longitudinal 18 mo sensitivity reductions of roughly 0.5 log U or more could signify development of subretinal neovascularization within the succeeding 18 mo. That is, three of the four eyes that lost 0.5 log U or more of absolute sensitivity during any 18 mo period appeared to develop SRN within the succeeding 18 mo. (For S cone-mediated sensitivity, the corresponding number was four of six eyes.)

Color Matching Ranges, D-15 Test, and Flicker Sensitivity

There was some evidence that a reduced small-field matching range might signify the development of SRN within an 18 mo follow-up period. In particular, there may have been some tendency for eyes with exudative outcomes to have narrower small-field matching ranges than eyes with minimal-acuity-loss outcomes ($P = .107$, two-sided Mann-Whitney U test). Small-field matching ranges are plotted versus age in Figure 5. No corresponding effect for large-field matching ranges was evident ($P = .879$, two-sided Mann-Whitney U test). Of the three eyes that accepted a large-field match but rejected all potential small-field matches, two had exudative outcomes.

Although the matching range results may be considered implausible, they are consistent with separate evidence that the small-field matching range can shrink19 or vanish152128 because of macular degeneration, possibly at certain stages of the disease.19

Failure of the D-15 test was a fairly sensitive indicator of an exudative outcome. Of the 11 subjects with exudative outcomes, eight failed the D-15 test at baseline. However, the D-15 test was neither a specific indicator nor independent of age. Of the 32 subjects with minimal-acuity-loss outcomes, 12 failed the D-15 test at baseline. Of these 12 subjects, only one was younger than 70 yr.

Fig. 5. Small-field matching range versus age. Smooth curve and symbols are as in Figure 3.
For the single test of flicker sensitivity measured for all eyes, there was no evidence of systematic relation to outcome ($P = .802$, two-sided Mann-Whitney U test).

**Funduscopic Risk Indicators**

To help compare the utility of different indices of fundus appearance, three additional graphs are plotted.

**Drusen type and drusen size**: Figure 6 plots outcome results as a function of the largest drusen size within the central 3000 $\mu$m of the macula versus outcome results as a function of the maximal-ranking drusen type for any of the five subregions that make up that 3000 $\mu$m diameter region. (Consistent with a prior report, funduscopic risk indicators from the central 3000 $\mu$m of the macula tended to be as or more effective than the corresponding indices from the central 6000 $\mu$m.) The scores—which are those used by the Fundus Photograph Reading Center at the University of Wisconsin at Madison—are defined in the figure legend. For distinguishing outcomes, the optimal cutoff for drusen size was 250 $\mu$m (inclusive), while the optimal cutoff for drusen type was soft-distinct (inclusive; see Note 2). The resulting sensitivity/specificity ratio, odds ratio, and kappa for drusen size were 2.4, 3.6, and 0.27, respectively. For drusen type, the corresponding values were 1.7, 8.8, and 0.26.

**Drusen area, confluent drusen area, and atrophic area**: Just as dark adaptation and color matching were found to be complementary, drusen area and atrophic area appeared to be complementary. In particular, the summed drusen/atrophic area within the central 3000 $\mu$m could be used to effectively distinguish eyes with exudative outcomes from eyes with minimal-acuity-loss outcomes. For the optimal cutoff of precisely 10%, eight of 11 eyes with exudative outcomes failed, as did six of 32 eyes with minimal-acuity loss outcomes. The sensitivity/specificity ratio, odds ratio, and kappa values for distinguishing exudative outcomes were 3.9, 12, and 0.50, respectively. (Shifting the cutoff by as little as 1% in either direction would have reduced these values considerably, however.) When confluent drusen area was used in place of drusen area, the corresponding optimal values improved marginally, to 5.1 (see Note 3), 12, and 0.51, respectively. The optimal cutoff for the summed confluent drusen/atrophic area was 8.5%. Figure 7 plots the summed confluent drusen/atrophic area within the central 3000 $\mu$m versus age.

Confluent drusen area alone was not nearly as effective as the summed confluent drusen/atrophic area. When the confluent drusen area was compared for exudative-outcome eyes versus minimal-acuity-loss eyes, the significance value ($P = .102$, Mann-Whitney U test).
Whitney U test) was much poorer than the corresponding significance value \( (P = .005) \) obtained when the atrophic area was added. Six eyes had measurable atrophic areas within the central 3000 \( \mu \text{m} \).

Comparison with functional data: Because the summed confluent drusen/atrophic area within the central 3000 \( \mu \text{m} \) appears to be highly effective, it is worthwhile to compare this area against the combination of the dark adaptation time constant and color-match-area effect. This is done in Figure 8. Figure 8 is identical to Figure 1, except that the diameter of each data “point” is proportional to the summed confluent drusen/atrophic area within the central 3000 \( \mu \text{m} \). The same eyes that had focal hyperpigmentation within the central 6000 \( \mu \text{m} \) had focal hyperpigmentation within the central 3000 \( \mu \text{m} \).

Clearly, the summed confluent drusen/atrophic area is related systematically to the dark adaptation time constant and color-match-area effect. Many of the most affected central fundi are represented in or near the high-risk region defined by the exponential curve. In addition, the majority of eyes with relatively unaffected central fundi are represented in the only quadrant for which the dark adaptation time constant and color-match-area effect were simultaneously normal. The eye with the largest summed confluent drusen/atrophic area, represented in the lower left quadrant, is from the youngest person (55 yr) enrolled in the study. Quite possibly, this eye had maintained good acuity mainly because of the subject’s young age.

**History of exudative disease in the fellow eye:** Effects of at least one additional variable may be important. That variable is the duration elapsed between the diagnosis of exudative disease in the fellow eye (ie, the first eye to develop exudative disease) and the subsequent assignment to an exudative outcome for the study eye. Among study eyes that developed exudative disease within “18 mo” of baseline, the five eyes without focal hyperpigmentation appeared to develop exudative disease appreciably sooner \( (P = .006, \text{ two-sided Mann-Whitney U test}) \) than did the six eyes with focal hyperpigmentation. The median elapsed durations were 19 mo and 37.5 mo, respectively; there was no overlap between the two groups. The drusen risk characteristics for the eyes without focal hyperpigmentation did not appear to be more severe than for the eyes with focal hyperpigmentation. Therefore, the apparent duration effect, which needs to be replicated, is consistent with the following possibility. Eyes without focal hyperpigmentation that develop exudative disease may do so because of factors that affect both eyes together rather than because of intraocular factors only.

**Discussion**

Before proceeding with the discussion, it is important to note the possibility that functional tests may have served, in some cases, to detect a stage of SRN that subsequently developed to a degree detectable clinically or fundus photographically. This possibility is especially relevant because the absence of SRN at baseline was not verified using fluorescein angiograms, but rather using fundus photographs. In particular, although a recent study of Macular Photocoagulation Study fellow eyes across a 5 yr follow-up period showed that fundus photographs identified SRN in the same eyes as did fluorescein angiograms, the SRN may have been detectable earlier on angiograms in some cases.

**Dark adaptation time constant combined with color-match-area effect:** Of the several visual functions tested, the combination of dark adaptation and color matching was the most effective for distinguishing those eyes found to develop SRN from those that retained good visual acuity. The effectiveness of that combination was comparable to that of the most effective funduscopic risk indicator, the summed confluent drusen/atrophy area within the central 3000 \( \mu \text{m} \) of the macula.

The combination of dark adaptation and color matching was effective probably because those eyes that had relatively slow foveal dark adaptation rates despite having reduced quantal absorption (as inferred from color matching) already had been severely...
compromised or had suffered multiple compromise. Neither dark adaptation nor color matching appeared to be an effective risk indicator by itself, perhaps because neither by itself could reliably provide evidence of enough compromise. The dark adaptation time constant by itself could not distinguish those eyes whose retinas functioned normally from those eyes for which reduced cone quantum absorption caused the dark adaptation bleaching stimulus to be effectively dim.

Because the illuminance and duration of the stimulus intended to bleach the eye prior to dark adaptation had been selected to be just sufficient to produce an equilibrium bleach for healthy eyes,29,30 that stimulus may not have produced an equilibrium bleach for many affected eyes. Because photopigment regeneration rates normally are faster for nonequilibrium than for equilibrium bleaches,31 and because much of neural dark adaptation is thought to proceed relatively fast,32 eyes with slow dark adaptation rates for a given quantal absorption could have been compromised in two ways. Either their photopigment regeneration rates were abnormally slow or their neural recovery rates were slow, or both. Direct evidence for altered photopigment regeneration kinetics has not been reported for AMD, but it does exist for other diseases of the pigment epithelium33 and has been reported for normally aging eyes.34,35

Previously,15 we had provided evidence that drusen disease is associated with slowed dark adaptation and that atrophy and local drusen confluence are associated with reduced quantal absorption. Atrophy, in turn, is strongly associated with focal hyperpigmentation.15 On the well-founded assumption that these fundus features are related to or associated with the subsequent development of SRN,13 the successful tradeoff between dark adaptation and color matching (as an index of quantal absorption) might be expected. The strong association that we find between the summed drusen/atrophy area and the subsequent development of SRN is consistent with this expectation.

Our dark adaptation and color matching results are consistent with those from other laboratories. Specifically, other laboratories also have reported eyes with AMD to have slow dark adaptation16 or photostress rates,37 particularly in areas of abnormal choroidal perfusion.38 Several other laboratories have reported abnormally small effects of area21 or illuminance28 on color matching. From these abnormally small effects, it is possible to infer abnormally low quantum absorption capabilities.21,28

**Generality of results:** So far, we have shown that eyes with good acuity that have relatively slow foveal dark adaptation rates despite reduced quantal absorption (as inferred from color matching) appear to be at especially high risk for developing SRN within about 18 mo. It is likely that this result depends on the precise parameters of the stimulus used to bleach the eye prior to the period of dark adaptation. The importance of good acuity among the patient population is unknown. Although poor acuity need not preclude the use of color matching29 to help establish risk, any factor associated with a sufficiently wide matching range could militate against the utility of the color-match-area effect as an index of photopigment absorption. Factors such as reduced ocular transmission also might affect dark adaptation rates. For practical and theoretical reasons, therefore, it is desirable to obtain measures of effective cone photopigment density using alternative methodologies such as retinal densitometry.40-43 In principle, it is possible that the effective photopigment density and photopigment regeneration rate could be measured using a single device, even for eyes with greatly decreased quantum absorption capabilities.

**Discussion of exceptional data:** Of the three eyes that developed SRN but were identified as low-risk based on dark adaptation and color matching, the data of two merit individual mention. The eye whose data were at (.060, 145) in Figure 1 appeared to have the least affected fundus of all 47 eyes. No existing risk indicator (other than the history of exudative disease in the fellow eye) would have identified this eye as high risk. The eye whose data were at (.126, 276) was unusual in two important respects. First, drusen occupied a proportionally much greater area in the parafovea than the fovea. This unusually pronounced extrafoveal degenerative pattern could have caused cone quantum absorption to decrease sufficiently more parafoveally than foveally, causing the color-match-area effect to increase rather than decrease.22 Second, because the small-field matching range for this eye was quite wide, its small-field mid-matchpoint could have shifted in the deutan direction,19 further increasing the color-match-area effect. This exceptional eye illustrates the importance of using all available types of information.

One additional eye that developed SRN also merits individual discussion. For this eye, SRN developed in the nasal peripapillary region. In a strict sense, therefore, this eye did not develop exudative age-related macular degeneration. This eye, which was from the oldest subject tested (Figures 3, 4, and 7), did not have a measurable color-match-area effect at baseline.

**Incidence rate of exudative AMD:** The incidence rate of exudative AMD (16.5% per year) derived from our data (11 of 47 eyes in “18 mo”) would be the highest in the literature,13 comparable only to the 12-15% yearly incidence rate reported by Gregor, Bird,
and Chisholm. They do not know why the incidence rate we found is as high as it is. Because fundus photographs rather than fluorescein angiograms were used to verify the absence of SRN at baseline, it is possible that a systematically disproportionate number of eyes tested in our study already had SRN at baseline. (In such cases, however, our tests can be regarded as detecting SRN at a time that precedes detection via fundus photography.) Because about half the subjects in our study did not present with an active exudative lesion in the fellow eye at the time of recruitment, but instead were recruited from physicians' files, it is also possible that the high incidence rate resulted from the extra time for disease to evolve in many of the eyes that we tested. This is compared to, for instance, the fellow eyes of eyes in the Macular Photocoagulation Study. However, analyses of subject histories did not support this possibility.

Other factors may have contributed to the high incidence rate. For example, there is a possibility that one or two eyes developed SRN after 18 mo, inflating the 18 mo incidence rate (although not obviating the prognostic significance of our results). Another eye developed SRN in the nasal peripapillary region. Therefore, in a strict sense, the eye did not develop exudative AMD at all. The possibility of a selection bias also exists, because our subjects met a unique set of entry criteria and lived in a relatively limited geographic region. Finally, there is a finite possibility that the difference between the incidence rate that we found and those of other studies is due merely to chance. If the true population incidence rate for subjects that met our eligibility criteria was either 8% or 12% per year—values that correspond to the midpoint and upper end of the range for generally accepted incidence rates—they would be expected to occur 1.8 or 17.9% of the time, respectively. (These values are derived from binomial probabilities that assume cumulative 18 mo incidence rates of 11.7 and 17.3%, respectively.)

Color matching ranges: The finding that narrow small-field color matching ranges might precede the development of SRN may be regarded as paradoxical. However, using 18 mo longitudinal data from eyes that did not appear to develop exudative lesions, we have presented direct evidence elsewhere that small-field matching ranges can shrink over time for eyes with sufficiently affected fundi. Moreover, some subjects with AMD reject all potential small-field matches. The small-field matching ranges of these subjects can be regarded as having shrunk over time. These three sets of results together indicate that a shrinking matching range should be regarded as suspect, whatever its causes. Determining the causes for shrinking matching ranges is of both basic and applied interest.

S cone-mediated sensitivity: Finding that low S cone-mediated sensitivity often appeared to precede the development of SRN is not surprising given the well-documented vulnerability of the S cone system. Unfortunately, because S cone-mediated sensitivity depends so much on preretinal absorptions and is so age dependent, cross-sectional use of S cone-mediated sensitivity to establish risk may be a problem. However, measuring changes of S cone-mediated sensitivity longitudinally may be useful and practical, not only for AMD, but for other diseases as well.

Absolute sensitivity: Finally, the failure to find a relation between absolute sensitivity and the development of exudative AMD may be regarded as conflicting with a prior study on the development of advanced AMD. In that study, however, only one subject developed SRN. Moreover, we did find preliminary evidence that longitudinal reductions of absolute sensitivity are indeed useful for forecasting the subsequent development of SRN.

Notes

Note 1. For the eye whose data were at (.000, 237), the acuity loss was judged "probably" due to macular degenerative changes; there were "no" apparent changes of the optical media. For the eye whose data were at (.033, 178), the acuity loss was judged "probably" due to media changes, but "possibly" due to macular degenerative changes. For the eye whose data were at (.058, 362), the acuity loss was judged "possibly" due to macular degenerative changes and "probably not" due to media changes. Lastly, for the eye whose data were at (.024, 483), 18 mo photographs do not exist. However, the fundus of this eye already had focal hyperpigmentation and predominantly soft-indistinct drusen at baseline. Moreover, on the basis of 8 mo fundus photographs, the acuity loss "possibly" could have been a result of macular degenerative changes. At 8 mo, any acuity loss was "probably not" due to media changes. Of the three sets of baseline and 18 mo photographs chosen for masked matching purposes only, two were rated as "probably not" giving any evidence for macular degenerative or media changes. The third set was rated as "possibly" giving evidence for macular degenerative changes.

Note 2. If nonexudative-acuity-loss outcomes are considered favorable outcomes, the sensitivity/specificity ratio and kappa value each would increase very slightly when the cutoff for drusen type was changed from soft-distinct to soft-indistinct. However, the odds ratio would decrease.

Note 3. If nonexudative-acuity-loss outcomes are
considered advanced AMD outcomes, summing the atrophic area with the confluent drusen area in place of the drusen area would cause the sensitivity/specificity ratio to decrease slightly.

Key words: color matching, dark adaptation, exudative age-related macular degeneration, S cone-mediated sensitivity, subretinal neovascularization

References