

Foveal cone photopigment bleaching in central serous retinopathy

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Color-matching techniques were used to follow the course of central serous retinopathy in thirteen patients. During periods of neurosensory detachments, cone optical densities were low. In some patients optical densities remained low following clinical resolution of the disease. In addition, abnormalities of bleaching were observed for one patient in one eye that appeared clinically unaffected during a period of detachment of the fellow eye. Analysis of the data indicates that for longitudinal measurements of optical density, standard Nagel anomaloscope matches can provide an accurate estimate of changes in foveal optical density, although they cannot provide a measure of the absolute optical density.

I. Introduction

Central serous retinopathy (CSR) is a disease that presents a serous elevation of the neurosensory retina, although it may also be associated with a pigment epithelial detachment.¹ During the active phase of the disease, fluorescein angiography reveals areas of dye leakage into the subretinal space. During the period of neurosensory detachment CSR causes a misorientation of the cone photoreceptors,² presumably due to the mechanical deformation of the retina. In addition, CSR causes an abnormality of color vision with blue cone pathways showing large deficits.^{3,4} Since CSR is characterized by a separation of the sensory retina from the retinal pigment epithelium, one of the best ways to evaluate the status of a patient is to measure the concentration of photopigment near the elevation as well as the kinetics of photopigment bleaching and regeneration.^{5,6} Van Meel *et al.*⁵ reported that cone photopigment kinetics, as measured by retinal densitometry, are slowed during periods of active leakage. Measurements with an imaging densitometer⁷ indicate that rod photopigment concentration is abnormally low, even when the elevated portion

of the retina has flattened, indicating continued abnormalities in the retinal pigment epithelium/photoreceptor complex.⁸ To evaluate adequately the effects of the natural history of the disease as well as to evaluate the benefits of treatment modalities,⁹ it is important to develop better methods of assessment of visual function.

To better assess the health of the retinal pigment epithelium complex, we have developed two noninvasive techniques that examine (a) the effective concentration of photopigment in functioning cones and (b) photopigment bleaching and regeneration. We have used these techniques, based on color matching, to measure photoreceptor function in diseases such as diabetes and retinitis pigmentosa.¹⁰⁻¹³ In the steady-state color matching technique, the patient matches a standard light with mixtures of two primary lights, one longer and one shorter in wavelength than the standard light. The main difference between steady-state color matching and Nagel anomaloscope color matches is that a series of retinal illuminances is tested, ranging from a relatively low illuminance to retinal illuminances that bleach most of the cone photopigments. The difference between the moderate and high illuminance color matches reflects changes in photopigment concentrations. This technique is based on the fact that the absorption spectrum of a pigment depends on the concentration of the pigment.¹⁴ When the concentration of photopigment is decreased by bleaching, the photoreceptors undergo changes in their spectral sensitivities. These changes in spectral sensitivities cause a predictable change in the color match.^{10,11} As previously described,¹¹ we obtain estimates of (a) the baseline (or moderate illuminance) color match, (b) the optical density (from the difference between the

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baseline and high illuminance color matches), and (c) the retinal illuminance required to bleach half of the photopigment (the half-bleach illuminance or I_0).

In the second technique, dynamic color matching, the patient continuously adjusts the variable hemifield to make color matches as the retinal illuminance is changed from dim to bright, then back to dim. Dynamic color matching provides information concerning the rate of bleaching and regeneration of the photopigment as well as estimates of photopigment optical density at a few retinal illuminances. Dynamic color matching is more similar to most retinal densitometry techniques than is steady-state color matching because measurements of photopigment concentration can be made following exposure of the eye to a light bright enough to bleach substantial portions of photopigment. However, in dynamic color matching, density estimates are typically made before the eye is exposed to bright light. Thus this technique can be used to discriminate between slow regeneration and abnormally low optical densities in affected eyes.

Previous color matching results from CSR patients show that for color matches at low retinal illuminances, there is a pseudoprotanomalous shift.² That is, more long-wavelength primary is required to match a standard light. Unlike retinal densitometry, color matching is insensitive to either the number of cones or media changes causing blur,¹¹ as long as vision is good enough to perform the task. Thus a gradual loss of photoreceptors will not change color matches. In contrast, a decrease in concentration of photopigment will cause a shift in the moderate illuminance color matches; more long-wavelength primary would be required to match the standard. As described in a previous paper,¹¹ a change in the moderate illuminance color matches together with more light required to obtain bleaching is consistent with disorientation of the cone photoreceptors.¹¹

II. Method

The patient makes color matches using the high illuminance, Maxwellian view, color matching apparatus described previously.¹⁰ The stimulus is a 4° bipartite field. Following instructions and obtaining an informed consent, the patient is aligned to the optical axis of the optical system using infrared LEDs, a video monitor, and an XYZ bite bar positioner. The patient matches the variable hemifield, a mixture of a 546-nm green and a 650-nm red primary, to the standard 589.6-nm orange. By turning one knob (the color knob), the patient adjusts the ratio of the red and green primaries (R/G ratio) without appreciably affecting the luminance. By turning a second or brightness knob, the patient adjusts the luminance without appreciably changing the R/G ratio. In steady-state color matching, the patient makes ten matches at eight retinal illuminances, in increasing order beginning with 260 trolands (Td) and ending at 130,000 Td. The average match is computed at each illuminance. In dynamic color matching, the patient makes a practice match, then dark adapts for 15 min. Next, the patient is

instructed to adjust continuously a control potentiometer so that the variable hemifield is first too red, then too green, then too red. As the patient continuously makes the adjustments, the computer samples the position of the potentiometer at 2 Hz, and the data are saved. The patient makes adjustments for 3 min at either 260 or 5500 Td, then adjusts for 6 min at 89,000 Td, and finally adjusts for 6 min at the initial retinal illuminance. To minimize biasing of the data due to previous exposure to bright lights, a patient participates no more often than once every two weeks with a given eye. Although this does not eliminate the possibility that our experiment is affecting the results, it does help to minimize the possibility in a patient group known to have abnormal photopigment kinetics.^{5,6} Thus we cannot obtain both steady-state and dynamic color matching data on the same eye of one patient in a short time period. Many patients recover at least partially from the acute phase of CSR between tests.

III. Patients

Twelve otherwise healthy patients (31–61 yr, ten males, and two females) were chosen by one of us (L.A.L.) based on retinal exams and visual acuity of 20/50 or better. These patients had no other complicating ocular conditions. A thirteenth subject, on systemic thyroid medication, was also tested. Since the serous elevation of the retina during CSR can induce hyperopic refractive changes, the visual acuities of patients were corrected with trial lenses whenever possible. One male required laser photocoagulation during the study. Another had had photocoagulation at another institution prior to our study. All were tested during the neurosensory detachment phase of the disease: (a) the patient reported symptoms in at least one eye; (b) the clinical appearance of that eye indicated a buildup of serous fluid on or prior to the day of the test; or (c) one eye had an accompanying pigment epithelial detachment. Those patients available were retested.

IV. Results

A. Steady-State Color Matching: Optical Density

At low retinal illuminances, the color matches of patients with active central serous retinopathy required more long-wavelength primary to match the standard than did either normals or the better eye of the same patient following resolution of the serous detachment (Figs. 1–4). This is the previously described pseudoprotanomalous color match.^{2,15} Note that the high illuminance color matches do not differ between better and worse eyes (Figs. 1–4). There is no significant difference between the mean high illuminance color matches for normal males vs healthy males with CSR, 0.233 and 0.221, respectively, with $t(24) = 0.00769$. This comparison was made for males to avoid the possibility of including heterozygous females (i.e., carriers of red-green color vision defects). Only the better eye or best performance was included, so

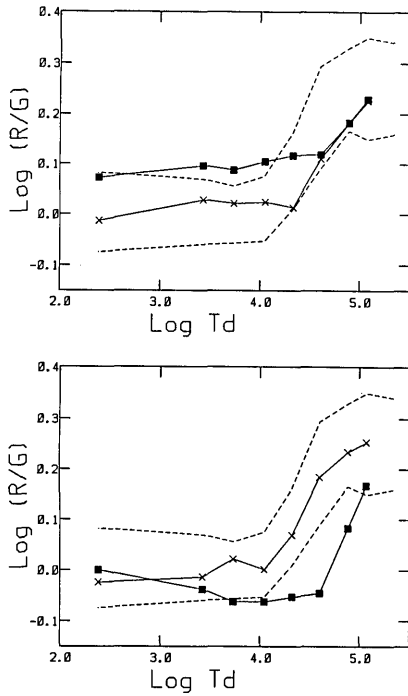


Fig. 1. Top: Clinically affected eye of a 37-yr old male during the neurosensory detachment phase, ■, and two months later following resolution of the fluid and return to 20/20 visual acuity, ×. Bottom: Clinically unaffected eye of the same observer during the detachment phase of the fellow eye, ■, and following resolution, ×. Dashed lines are the 95% confidence limits for the normal population.

that if a difference were present, it would not be masked by high variability. The moderate illuminance color matches were altered, having higher $\log(R/G)$ values, while the high illuminance color matches did not differ; i.e., the effective optical density of the cone photopigments was abnormally low.¹¹

For five patients with 20/20 visual acuity at the final retest, the effective optical densities were significantly less than that for normal observers, 0.27, with measurements ranging from 0.1832 to 0.1031. For another patient with 20/20 visual acuity during the active phase, the optical density, 0.1073, was significantly lower than that for normal observers.

B. Steady-State Color Matching: Half-Bleach Illuminance

In most patients, in addition to the abnormal low illuminance color matches, there is a translation of the entire color-match vs illuminance curve to higher retinal illuminances (Figs. 1–3). This indicates that more light is required to bleach the photopigment of this eye than that of a normal or less affected eye; this is consistent with the Stiles-Crawford effects reported previously.² The parameter that quantifies this shift is the half-bleach illuminance (I_0 , the retinal illuminance that bleaches one-half of the photopigment). I_0 was higher than the 99% confidence limits of normal observers^{11–13} for eleven of thirteen patients during the active phase. In one patient this high I_0 occurred both

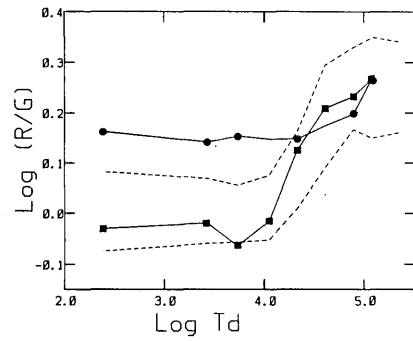


Fig. 2. Affected eye of a 31-yr old male, comparing data from the affected eye, ●, and the unaffected eye, ■. Dashed lines are the 95% confidence limits for the normal population.

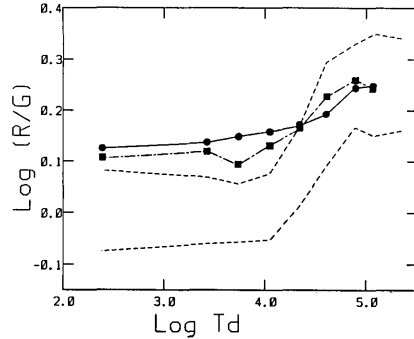


Fig. 3. Data from the affected eye of a 33-yr old female. During the period of maximal detachment, ●, there was a minimal color-match illuminance effect. Data gathered two months later, ■, when acuity had returned to 20/20 were still abnormal but had a higher optical density. Dashed lines are the 95% confidence limits for the normal population.

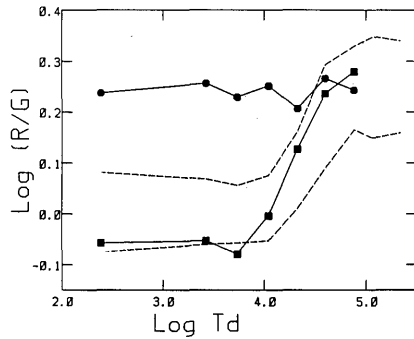


Fig. 4. Data from a 58-yr old female. Data from the affected eye showed no effect of bleaching being essentially dilute at all light levels, ●. Data from the clinically unaffected eye were essentially normal, ■. Dashed lines are the 95% confidence limits for the normal population.

during active leakage in the eye that was clinically affected (Fig. 1, top) as well as in the fellow eye, which was clinically normal and had 20/20 visual acuity (Fig. 1, bottom). Two months later, when the affected eye was resolving, the fellow eye was normal.

C. Dynamic Color Matching

The left panel of Fig. 5 shows data of a patient with chronic CSR, reported in part previously as a comparison for a patient with retinitis pigmentosa.¹³ There

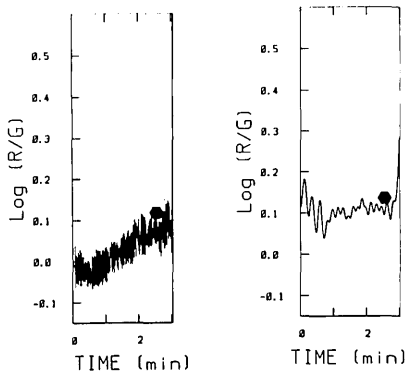


Fig. 5. Comparison of dynamic color-matching data from two different observers during exposure to 2,600-Td light. Both observers were dark adapted for 15 min prior to testing. The first observer (left) showed an effect over time of exposure to this light, undergoing progressive bleaching. The patient's match after 3 min was the same as his 89,000-Td color match, ●. The second observer (right) did not show an increased optical density following dark adaptation.

are three main differences between this patient and normal observers or patients with other diseases tested thus far (including some other patients with CSR; one of whom produced the result shown in Fig. 5, right). First, following dark adaptation, the baseline color match is similar to that of normal observers, indicating normal, or nearly normal, concentration of photopigment. Second, when exposed to 5500 Td, the CSR patient makes color matches requiring increasingly more long-wavelength primary. This indicates that photopigment concentration is continuously decreasing. Third, following exposure to 6 min at 89,000 Td, and then 6 min at 5500 Td, the color matches are similar to or require only slightly more long-wavelength primary (hexagons) than the matches after 3 min at 5500 Td. Normal observers never undergo measurable bleaching during exposure to retinal illuminances of 5500 Td or less. Also, for normal observers recovering from an 89,000-Td light, the color matches have returned to the dark-adapted values by the end of 6 min. Apparently, kinetics are slowed enough in this patient that relatively dim lights can cause appreciable bleaching. This is not the case in all patients with CSR, as shown in the right panel of Fig. 5. This second patient did not have a higher optical density following dark adaptation.

V. Discussion

The simplest explanation of the data gathered during the neurosensory detachment phase is that the serous elevation of the retina is causing two effects. First, the serous elevation causes a distortion of the overlying retina, resulting in a misorientation of the cones.^{2,15} This misorientation causes the cones to be less efficient at capturing the light (resulting in a translation of the data to the right or to higher retinal illuminances) and to act as though they have less photopigment (a decrease of the size of the color match illuminance effect).¹¹ Second, the increased distance between the photoreceptors and the retinal pigment

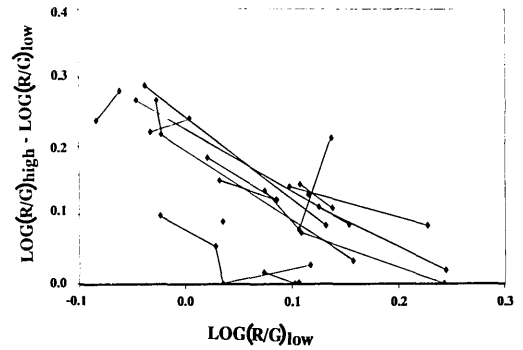


Fig. 6. Difference between the high and low illuminance matches as a function of the low illuminance color match. Multiple data points from single subjects are connected by a single line. In general, matches fall along the diagonal, indicating that changes in the low illuminance color match are reflecting changes in the measured optical density.

epithelium slows the process of photopigment regeneration^{5,6} (presumably due to the increased distance over which diffusion must act). This slowing of regeneration results in a translation of the data to the left or to lower retinal illuminances. These two potential effects of serous elevation can explain most of the data. The exception is the data of the clinically unaffected eye shown in Fig. 1 as well as a similar finding in some patients following recovery. In these cases I_0 is abnormally high, yet the optical density is normal. This combination suggests a separation of the cause of the decreased efficacy of the bleaching lights and the decrease in optical density, although the data do not yet provide sufficient evidence to prove this conjecture.

We also find that two types of abnormality can remain after resolution of visual acuity deficits and the clinical resorption of serous fluid: (a) low effective optical density and (b) higher retinal illuminance required to bleach the photopigment (see preceding discussion). Other studies have found that visual function deficits remain after resolution of the fluid buildup.^{4,8,16} In agreement with our finding that cone photopigment optical density is low following resolution of symptoms, rod photopigment does not necessarily return to normal levels when the serous elevation has flattened.⁸ Thus the retinal pigment epithelium/photoreceptor complex is not yet functioning normally, even though the fluid buildup is substantially reduced. Only long-term follow-up will determine whether the retinal pigment epithelium/photoreceptor complex ever fully recovers in these patients.

It should also be noted that moderate illuminance (baseline) color matches are good predictors of effective optical density for most central serous patients. That is, since the high illuminance (bleached) color matches of a patient with CSR are normal, the changes in optical density are indicated by abnormal low illuminance matches. This can be seen when the effective optical density is plotted as a function of the low illuminance color match for each observer (connected lines, Fig. 6). Most of the data points fall along the diagonal. This, together with the normal high illumi-

nance data of these patients, indicates that the major effect of CSR on color matches is at lower retinal illuminances. Thus, for monitoring of CSR patients in the clinic, the moderate illuminance color match can be useful as an indication of the effective optical density of cone photopigments. Such a match can be made using Nagel or other anomaloscopes, which are available in many clinics. Either the better eye or laboratory normative values could serve as a standard of comparison. The Nagel estimates of optical density, but not the steady-state color matching data described here,¹¹ are sensitive to preretinal filter. Thus the preferred method for Nagel measurements is to follow a single observer over time. For monitoring changes over time, spectral filtering should have little effect in an otherwise healthy eye. Data from patients with congenital color vision defects must be scaled according to the spectral sensitivity of the cones.

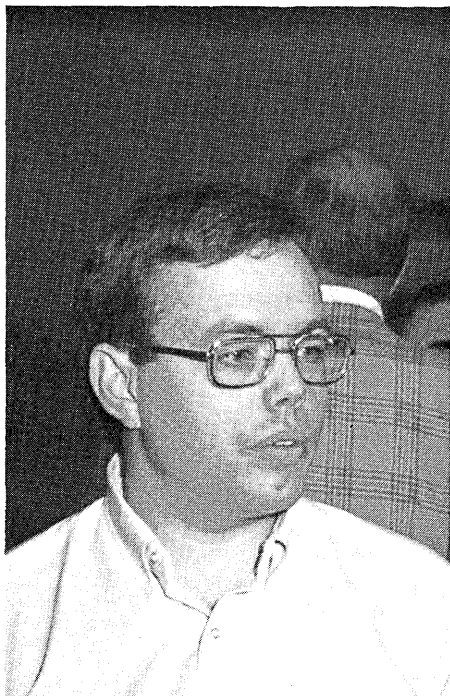
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William H. Swanson of Retina Foundation at the 1987 OSA Annual Meeting in Rochester. Photo: F. S. Harris, Jr.