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Psychophysical Evidence for Post-Receptoral Sensitivity Loss in Diabetics

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Although numerous reports show that the sensitivity of the S cone system is decreased in diabetic patients, few studies have been directed toward identifying the possible sites of the sensitivity loss. In this study, a psychophysical technique was used to test hypotheses about sites of S cone system sensitivity loss in a group of patients with early diabetic retinopathy. A model of the S cone system was assumed and the experimental conditions were chosen to distinguish between explanations for S cone sensitivity loss at the receptor level from explanations for loss at a post-receptoral level. Within the context of the model, the data were consistent with S cone system sensitivity loss occurring at a post-receptoral level. Invest Ophthalmol Vis Sci 33:2781–2790, 1992

Diabetes is known to affect the sensitivity of the short wavelength sensitive (S) cone system. There are reports of tritan-type defects using hue discrimination techniques and reports of reduced S cone pathway sensitivity using spectral sensitivity techniques. These defects are evident even in the early stages of diabetic retinopathy.[1-5] These measurements, however, reflect the sensitivity of the S cone system as a whole and thus do not provide sufficient information for identifying the anatomical sites or physiologic mechanisms of S cone sensitivity loss. The anatomic sites may be at the level of the inner retina, reflecting a disturbance of retinal circulation. Evidence for inner retinal dysfunction comes from reports of reductions in the scotopic threshold response amplitude[6] and in oscillatory potential amplitudes[7-9] in patients with mild degrees of retinopathy. It is possible, however, that inner retinal disease may compromise outer retinal function, because of a shift in oxygen tension.[10]

In a recent psychophysical study, S cone system sensitivity losses in five diabetics were interpreted as reflecting functional abnormalities at the receptor level and at a second stage opponent site.[11] Support for the primary site being at the receptor level comes from studies whose results have been interpreted as evidence that the S cone photoreceptors are more "fragile" than the L and M cone photoreceptors. For example, S cones appear to be more susceptible to light damage.[12] Therefore, S cone receptors may be more vulnerable to changes in retinal metabolism that occur in diabetes. S cone sensitivity loss in some diabetics may even reflect a pre-retinal locus rather than any underlying retinal pathology as the lenses of type 1 diabetic patients age or yellow at an accelerated rate.[13,14]

The purpose of the present study was to assess S cone system sensitivity in patients with early diabetic retinopathy and test hypotheses about the sites and mechanisms of S cone sensitivity loss. The diabetics we studied were selected from a group of 24 patients whom we had recently tested for S (pi 1) cone sensitivity loss using a Stiles two-color increment threshold technique.[5] An important requirement for inclusion in the present study was that the patients showed no middle-wavelength sensitive (M, pi 4) or long-wavelength sensitive (L, pi 5) cone sensitivity loss using the two-color increment threshold technique.

To test hypotheses about possible sites of sensitivity loss, a model of the initial stages of the S cone system was assumed.[15] A skeletal version of this two-stage model is shown in Figure 1. Within the context of the model, the term "S cone pathway" (bold line in Fig. 1) refers to the pathway from the S cone receptor through the opponent site. The first stage is made up of the three cone types—the S, M, and L cones—and the S and LM cone pathway up to the opponent site. Light is absorbed at the first stage by the S, M, and L cones, which act as linear transducers. The spectral sensitivities of these cones are assumed to correspond to the Smith and Pokorny fundamentals.[16] The signals from the L and M cones are summed into a LM

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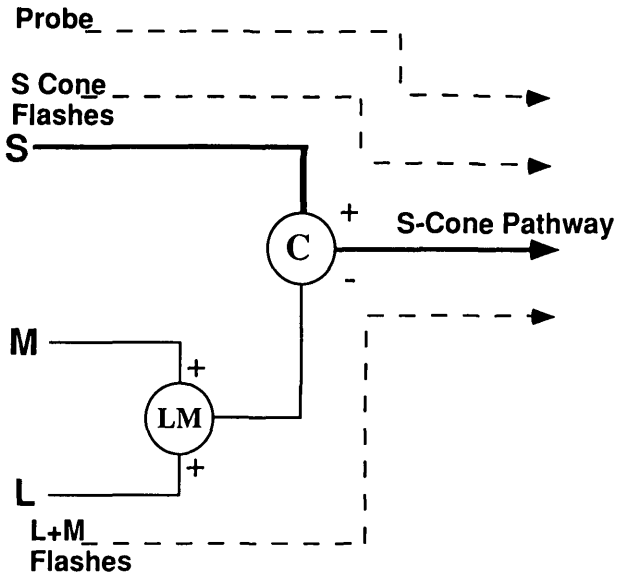

Fig. 1. The skeletal model of the initial stages of the S cone system. The S, M, and L cones act as linear transducers. The signals from the L and M cones are summed to make the LM signal. The difference between the S cone and LM signals constitutes an opponent chromatic signal (C).

signal. The difference between the S cone and LM signals constitutes an opponent chromatic signal (C) at the second stage. To distinguish S cone sensitivity loss at the receptor level from loss at post-receptor levels, experimental conditions in this study were designed to produce changes in the S cone pathway or only at the opponent site.

The stimuli or lights chosen to stimulate the S cone pathway or the opponent site via the LM pathway were displayed on a color television monitor and generated using the technique described by Zaidi et al.[15] The lights were varied along theoretically defined lines and were restricted to one plane of a three-dimensional color space. The color plane defined by the S and L + M color axes is shown in Figure 2. Lights are represented in the figure by (L, M, S) cone excitations. These were obtained by transforming the CIE(1931) co-ordinates for each light to Smith-Pokorny fundamentals.[16] The light at W is metameric to equal energy white with a luminance defined to be 1 U, where one unit of luminance is specified as being equal to 50 cd/m^2. The heights of the cone fundamentals were set so that L + M was equal to V_λ(CIE spectral luminosity function) and that S and L + M were equal to 1 at W. Cone excitations vary in a linear fashion along every straight line in the plane.

Three types of lights were used: ΔS cone lights, ΔL + M lights, and achromatic lights. ΔS cone lights, lights along the horizontal or S cone axis in Figure 2, produced changes in S cone quantal absorption but not in L and M cone quantal absorption. Therefore, S cone lights produced changes in sensitivity only in the S cone pathway indicated by the bold line in Figure 1. ΔL + M lights produced changes in L and M cone excitations, whereas the excitation of the S cones remained constant. They affected the L + M pathway shown in Figure 1 and thus affected the opponent stage of the S cone pathway. The third type of light—steady achromatic lights varying in luminance along the diagonal axis in Figure 2—resulted in a proportional increase or decrease in excitation of all three cone types. These steady lights changed sensitivity only at the first stage.[15]

The lights were presented to the patients using a probe-flash technique. The technique consisted of the presentation of brief test lights (probes) on a series of flashed backgrounds (flashes). The probe lights to be discriminated from the flashes were decrements to the S cone system. The S cone lights were in the "yellow" direction on the S cone axis. The use of two kinds of flashes in the probe-flash technique, S cone and L + M flashes, enabled us to vary the sensitivity of the S cone system. For example, to produce changes in both the S cone receptor and at the opponent stage, S cone flashes were used. They were either S cone increments or decrements from the steady "white" adapting field. To produce changes only at the opponent stage, L + M flashes were used. They were L + M increments or decrements from the steady "white"

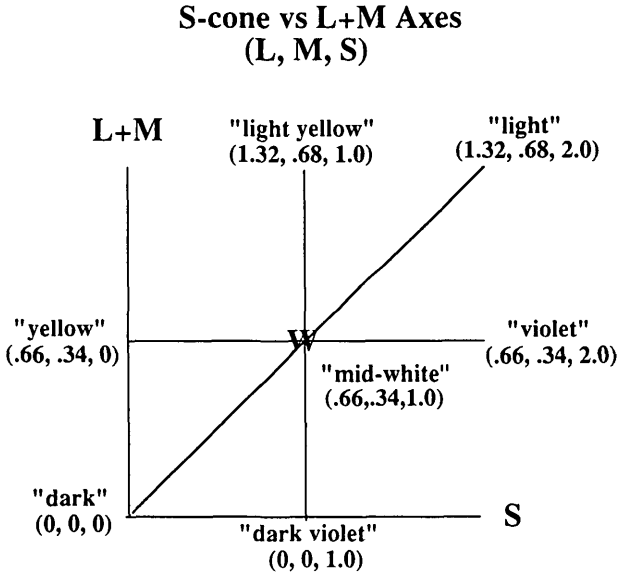

Fig. 2. Schematic of the color plane defined by the S and L + M color axes. The ordered triplets (L, M, S), were obtained by transforming the CIE (1931) coordinates for each light to Smith-Pokorny (1975) fundamentals. The light at W is metameric to equal-energy white with a luminance defined to be one unit (50 cd/m^2). The heights of the cone fundamentals at W were adjusted so that L + M = V_λ (the CIE spectral luminosity function) and S = L + M = 1.

adapting field, and S cone excitation was kept constant.

Methods

Subjects

Eight patients with Type 1 diabetes participated in the study. Their results were compared to those of six age-similar normal observers. All patients had Snellen acuities of 20/20 or better in the tested eye. The age range of the patients was 26–67 yr. Their length of time on insulin ranged from 10–40 yr. The level of diabetic retinopathy and presence of macular edema were determined on the basis of clinical contact lens examination, color fundus photography, and fluorescein angiography. All eight patients had early diabetic retinopathy (microaneurysms only). Questionable macular edema (not involving the center of the macula) was recorded for three patients. None of the patients had a history of hypertension or other metabolic disorders, and none showed evidence of significant lens opacities or glaucoma. One of the requirements for inclusion in this study was that M (pi 4) and L (pi 5) cone sensitivities be within the normal range. As mentioned, the patients were selected from a previous study by Greenstein et al[5] that was designed to measure S (pi 1) and M (pi 4) cone sensitivity in diabetics using a two-color increment threshold technique. To assess M cone sensitivity, foveal increment thresholds were obtained for a 480 nm test light (1.2°, 200 msec) superimposed on 14°, 600 nm steady adapting fields. To assess L cone pathway sensitivity, the wavelength of the test light was changed to 660 nm and the duration was changed to 10 msec.

Informed consent was obtained from all subjects prior to testing.

Apparatus

Stimuli were displayed on a Tektronix 690 SR color television monitor (Tektronix Inc., Beaverton, OR). The monitor provided an interlaced display of 480 × 512 pixels at 120 Hz. The mean luminance was 50 cd/m^2. The CIE chromaticities (xy coordinates) of the television phosphors were: red (.63, .34), green (.31, .595), and blue (.155, .070). Images were generated using an Adage 3000 raster-based frame buffer generator (Adage, Inc., Billerica, MA). The Adage allowed for 10 bit specification of the output of each television gun, leading to a palette of 2^{30} possible colors, of which 256 could be displayed on any frame. All stimulus generation and data collection were done automatically under computer control. For a detailed description of the calibration and color specification procedures, see Zaidi et al.[15]

Procedure

The sensitivity of the S cone system was assessed using two techniques: a steady-state threshold technique and a probe-flash technique. The spatial and temporal paradigm is shown in Figure 3. In a pilot study, some of the flashes gave rise to a transient Maxwell's spot. This interfered with discrimination tasks that used a circular probe. Therefore, a butterfly-shaped probe was used. For the steady-state threshold technique, foveal difference thresholds were obtained for a test light, 50 msec in duration, superimposed on a series of 10° steady "white" adapting fields of increasing luminance. These backgrounds result in different levels of S, M, and L cone excitation. The test light was a pure S cone decrement from the "white" adapting light. After adapting for 2 min to each steady adapting field, thresholds for the test light were obtained using a random double staircase technique.

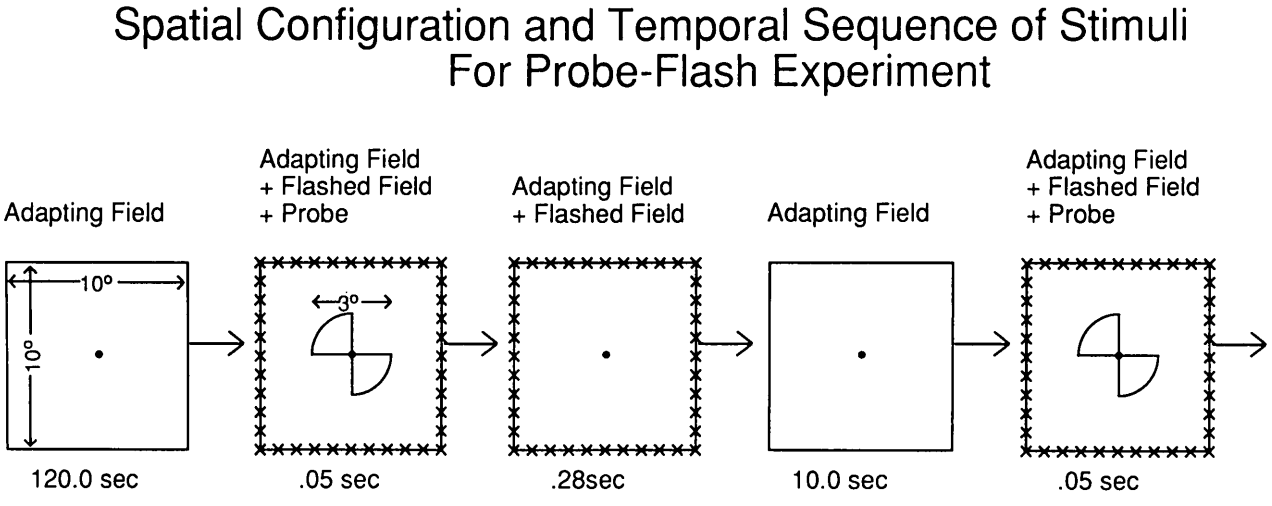

Fig. 3. The spatial and temporal paradigm. The adapting (solid line) and flashed (crosses) fields were spatially identical 10° squares. The probe consisted of two quadrants of a 3° disc.

Thresholds were defined as the minimum excursion in the "yellow" direction from white that could be detected 66% of the time. For the probe-flash technique, after adapting for 2 min to a 10° steady "white" adapting field, the steady field was changed to a flashed field for 330 msec. The 3°, 50 msec probe light was presented simultaneously with the onset of the flash. The observer's task was to indicate the presence or absence of the probe light. Probe thresholds were obtained on a steady "mid-white" adapting field with no flash, on a series of S cone flashes and then on a series of L + M flashes. The probes were always equiluminant tritan pairs with the flashes and were decrements to the S cone pathway.

Results

Figure 4A shows foveal difference thresholds for S cone decrements on steady "white" adapting backgrounds. The mean thresholds for six normal observers (filled triangles, solid lines) are compared to thresholds for the eight diabetic patients. To make comparing these results to those for S cone flashes easier, the steady adapting lights that change S, L, and M cone excitation proportionately are plotted on the horizontal axis in S cone units. Probe thresholds are plotted in negative ΔS cone units on the vertical axis. For normal observers, probe thresholds increase approximately linearly with an increase in S + L + M excitation. Compared to the data for normals, probe thresholds for seven diabetic patients are raised for all adapting levels. A comparison of the mean threshold data (±2 SEMs) for the normal observers to the mean data (±2 SEMs) for diabetics is shown in Figure 4B. The slope of the function is 0.092 for normals and 0.169 for patients. The value for normals is very similar to Weber's fraction for $\pi 1$, which is 0.087.[17]

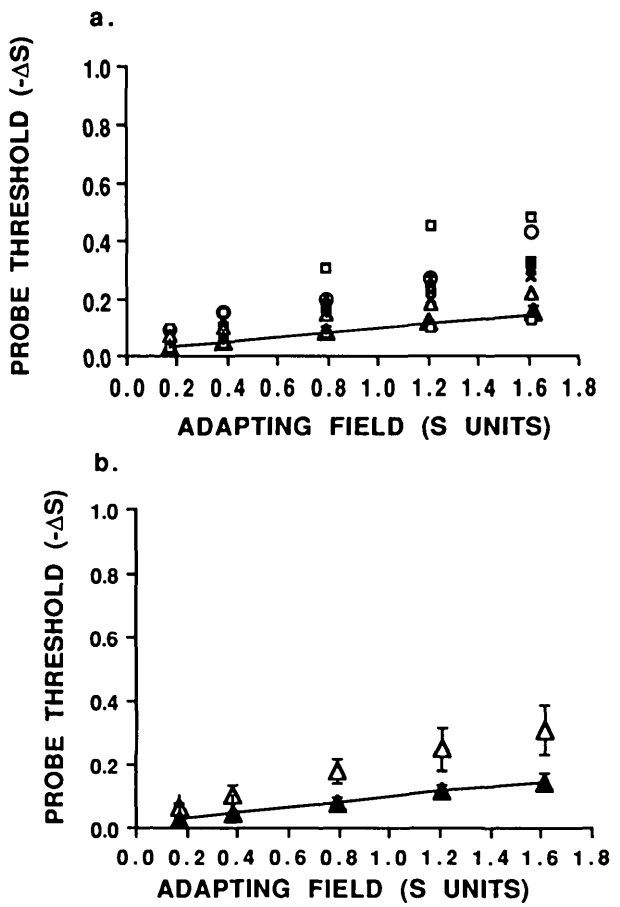

Fig. 4. Difference thresholds for the steady-state (no flash) condition versus the adapting light in S units. The steady adapting lights, which change S, L, and M cone excitation proportionately, are plotted on the horizontal axis in S cone units to make it easier to compare these results to those for S cone flashes in Figure 5. (a) Mean thresholds for six normal observers (filled triangles) are compared to thresholds for eight diabetic patients. (b) Mean thresholds for normal observers are compared to the mean thresholds for the diabetic patients. The error bars indicate ±2 SEMs.

Mean probe-flash data for normal observers (filled triangles, solid lines) and individual data for the eight diabetics are shown in Figures 5A and B. Probe thresholds are plotted as a function of the difference between the color of the flash and the "white" adapting background. For S cone flashes (Figure 5A), flash values are in S−(L + M) units to allow for comparison to L + M flash data. As the excitation of L + M cones is held constant along the S axis, these units reflect S cone increments or decrements. Probe thresholds are plotted in negative ΔS cone units. For L + M flashes (Fig. 5B), flashes (L + M increments or decrements from the steady W adapting background) and probe thresholds also are plotted in S cone units. The zero points on the x axes in Figures 5A and B represent the "no flash" or steady state condition, ie, probe thresholds obtained on a steady "white" background.

Consider the results for normals. Probe thresholds are lowest at the zero points and increase with increasing flash amplitude (distance) from these steady state adapting points. For example, in Figure 5A, probe thresholds increase when the flashes are S cone increments or S cone decrements. Thresholds, however, are highest when flashes are S cone increments. A similar "V" shaped pattern can be seen for L + M flashes. Sensitivity decreases with increasing distance from the adapting field for L + M increments and decrements. The data for the diabetic patients in Figures 5A and B show a similar trend, with thresholds at their lowest at the zero points, then increasing on either side of these adaptation points. Compared to the normal, however, probe thresholds for seven diabetics are increased. These are the seven diabetics who show increased thresholds for the steady state condition. The probe threshold increases for these patients are very similar for the S cone and L + M flash conditions. The similarity of the data is illustrated further in

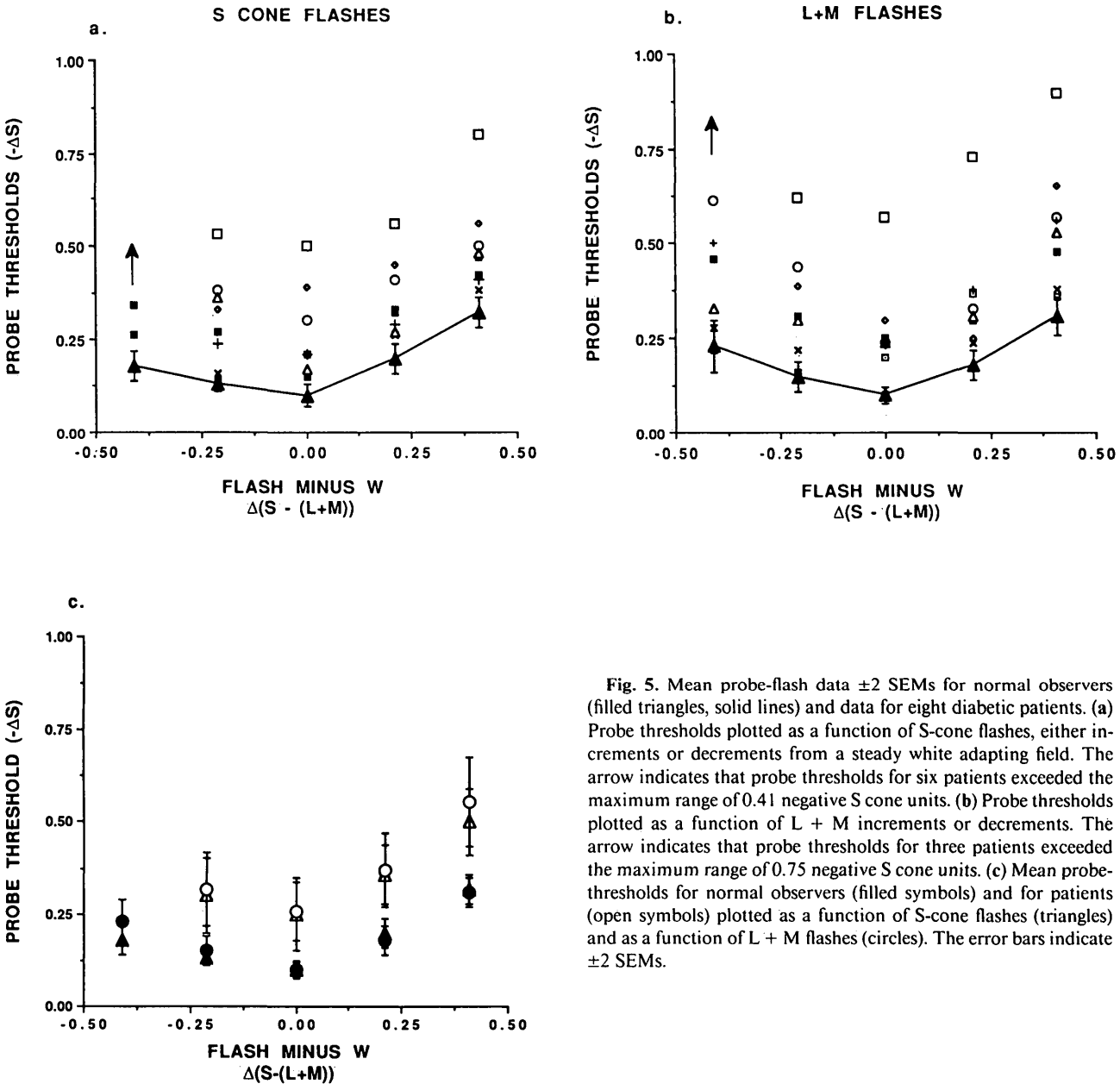

Fig. 5. Mean probe-flash data ±2 SEMs for normal observers (filled triangles, solid lines) and data for eight diabetic patients. (a) Probe thresholds plotted as a function of S-cone flashes, either increments or decrements from a steady white adapting field. The arrow indicates that probe thresholds for six patients exceeded the maximum range of 0.41 negative S cone units. (b) Probe thresholds plotted as a function of L + M increments or decrements. The arrow indicates that probe thresholds for three patients exceeded the maximum range of 0.75 negative S cone units. (c) Mean probe-thresholds for normal observers (filled symbols) and for patients (open symbols) plotted as a function of S-cone flashes (triangles) and as a function of L + M flashes (circles). The error bars indicate ±2 SEMs.

Figure 5C, which compares the mean probe-flash data for normal (filled symbols) and diabetic (open symbols) observers (±2 SEMs) for the S cone flash (triangles) and L + M flash (circles) conditions.

Discussion

Using steady state and probe-threshold techniques, we found that S cone system sensitivity was decreased in seven diabetic patients with early background retinopathy. In a previous study, using Stiles two-color increment threshold technique and a Maxwellian view system, these seven patients showed selective S cone pathway sensitivity losses. M and L cone pathway sensitivities were within the normal range.

It is possible that S cone system sensitivity loss in diabetic patients reflects a pre-retinal locus. Lutze and Bresnick reported that the lenses of diabetics yellow at an accelerated rate.[14] An increase in density or a yellowing of the lens compared to the normal population would be reflected in decreased sensitivity to S cone lights. The seven patients in our study who showed sensitivity losses had normal M cone pathway sensitivity but decreased S cone pathway sensitivity when the same test light (480 nm) was used to assess M and S cone pathway sensitivity in a two-color increment threshold procedure.[5] Therefore, for these patients, we can reject an explanation for S cone sensitivity loss based on a pre-retinal filter effect. A pre-retinal filter

would result in an increase in thresholds to a 480 nm test light for all adapting levels.

A decrease in sensitivity to S cone lights also could reflect a defect at the level of the S cones. For example, there could be a decrease in S cone responsiveness because of a decrease in quantal catch. This could result from a decrease in photopigment density. Alternatively, decreased sensitivity could be a result of changes in post-receptoral mechanisms. To test these hypotheses, we have used a model of the normal S cone system proposed by Zaidi et al.[15] The model, which provides a good description of psychophysically elicited responses of the S cone system of normal observers under different adaptation conditions, is outlined in the following section.

Model

A schematic representation of the model is shown in Figure 6. It is a detailed version of the skeletal model described in the introduction. Zaidi et al[15] have assumed that sensitivity is affected by pre-opponent S and L + M adaptation processes at the first stage, and by a compressive response function (R) at the second or opponent stage. The pre-opponent S and L + M adaptation processes are time-dependent gain mechanisms and are affected only by changes in steady adapting lights. Flashed lights do not affect these gain mechanisms. The gain mechanisms are assumed to sluggishly depend on the history of light exposure. The probe light is on for too brief a period to significantly alter the subject's adaptation state. The post-opponent response, R, is a sigmoidal function of the instantaneous opponent signal C:

$$\text{If } C > 0 \qquad R = p_{ø}[1 - e^{-øc}] \tag{1}$$

$$\text{If } C \leq 0 \qquad R = p_{v}[1 - e^{-vc}] \tag{2}$$

where pø, pv, ø, and v in equations 1 and 2 are free parameters estimated from the probe-flash data for normal observers.

The gain of the two pre-opponent branches is altered by changes in the steady adapting field. The gain of the S and LM pre-opponent branches is given by K_S and K_{LM}. K_S and K_{LM} have values equal to 1.0 in the dark-adapted state and take on values of <1.0 with light adaptation, according to the following equations:

$$k_s = \frac{k}{k + S_a} \tag{3}$$

$$k_{LM} = \frac{k}{k + LM_a} \tag{4}$$

where Sa is the response of the S cones to the steady adapting light a, LMa is the response of the L and M cones to the steady adapting light a, and k is a constant. It is assumed that k is identical for the S and LM pre-opponent branches, and the value of k is estimated from the steady-state adaptation data shown in Figure 4A. The curves through the data for normals (filled triangles) in Figures 7A, B, and C show the fits of the model to the mean steady state threshold and probe-flash data for normal observers.

The effects of diabetes on these functions can now be predicted, provided that hypotheses about sites and mechanisms of disease action are specified. Within the context of the model, S cone sensitivity loss could

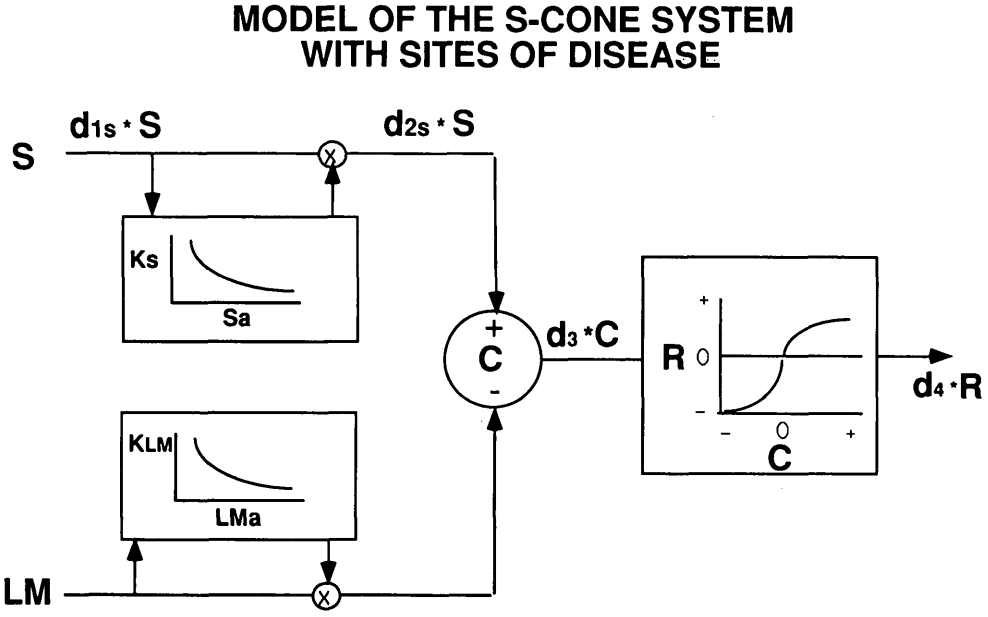

Fig. 6. A model of the S cone system with adaptive and static mechanisms. As in Figure 1, the opponent signal is the difference between the S signal and the sum of the L and M signals. Multiplicative gain controls have been added to the S and LM branches before the opponent site, and a compressive nonlinearity has been added following the opponent site. D1s, d2s, d3, and d4 are multiplicative constants that represent the possible effects of diabetes on S cone system sensitivity at four sites.

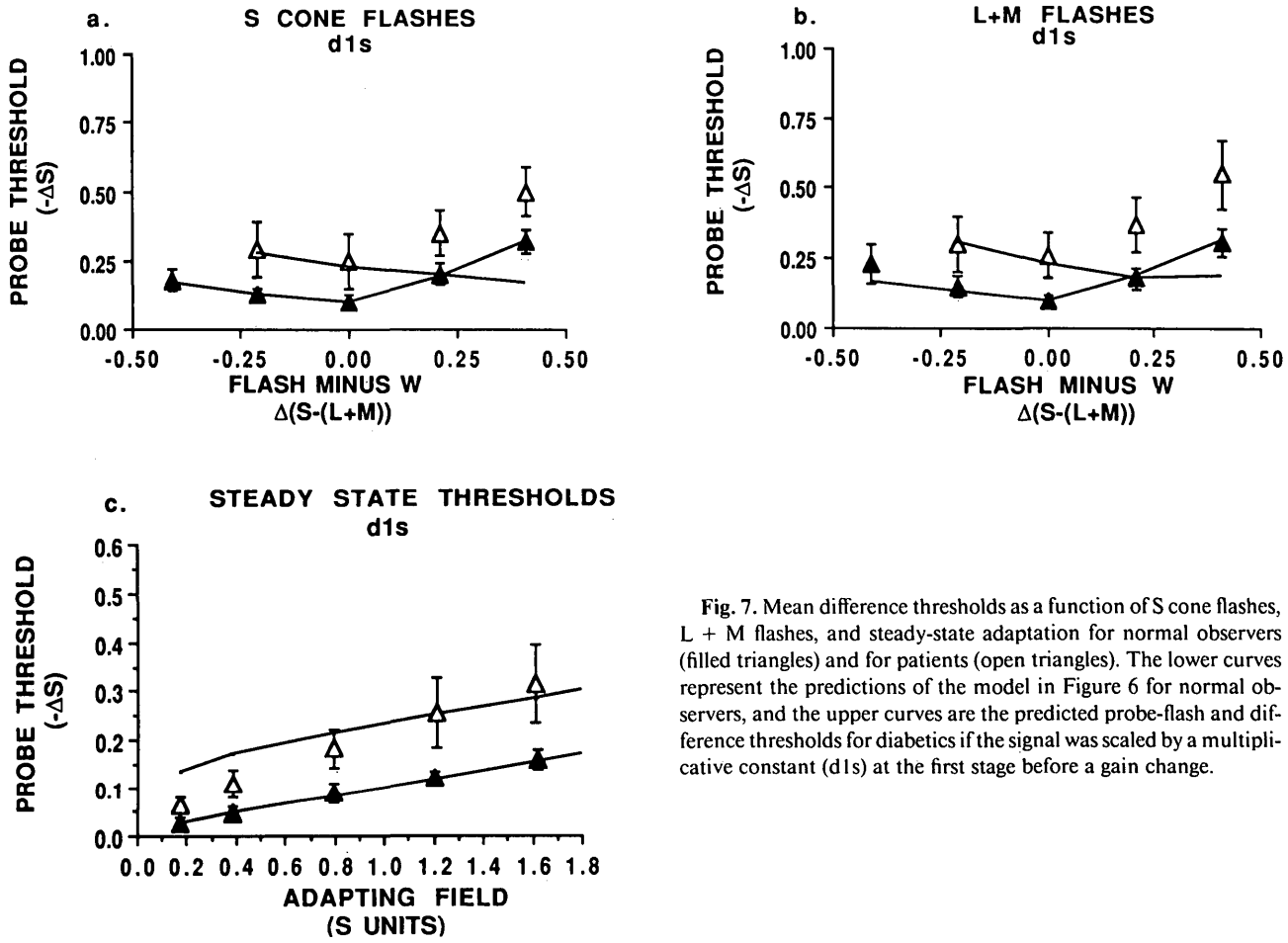

Fig. 7. Mean difference thresholds as a function of S cone flashes, L + M flashes, and steady-state adaptation for normal observers (filled triangles) and for patients (open triangles). The lower curves represent the predictions of the model in Figure 6 for normal observers, and the upper curves are the predicted probe-flash and difference thresholds for diabetics if the signal was scaled by a multiplicative constant (d1s) at the first stage before a gain change.

occur at the first stage, before or after the time-dependent gain mechanism in the pre-opponent S branch, at the second or opponent stage or after the response (R) of the opponent stage. These possibilities are represented at different sites in the model by scaling of the signal by multiplicative constants d1s, d2s, d3, and d4 (Fig. 6). In the model, the constants d1s, d2s, d3, and d4 are assumed to be equal to 1.0 in the normal S cone system. They take on values between zero and 1.0 when the system is affected by diabetes. As mentioned, the primary site of sensitivity loss may be at the S cone receptor level. Indirect support for this hypothesis is provided by the vulnerability of the S cone receptors to light damage.[12] There could be a decrease in photopigment density or a tilting or misalignment of the photoreceptors, resulting in a decrease in quantal catch. This hypothesis can be tested by assuming that diabetes affects sensitivity by scaling the signal at the level of the S receptors by the multiplicative constant d1s. The signal is scaled before the time-dependent gain change. Alternatively, the site of sensitivity loss could be in the pre-opponent S branch after the time-dependent gain change. This possibility is represented by scaling the signal by a multiplicative constant d2s. The site also could be at the stage of opponent combination of cone signals after the gain change. A class of such changes is represented in the model by scaling the signal by a multiplicative constant d3. Finally, the site could be after the response, R, of the opponent stage. Again, a possible class of changes is represented by the response being scaled by a constant d4.

The predictions of the model for changes in d1s, d2s, d3, and d4 are shown by the upper curves in Figures 7–10A, B and C, respectively. The curves were derived by allowing the value of the multiplicative constant (d1s, d2s, d3, or d4) to equal the amount necessary to predict the probe threshold for the "no flash" condition. The fits to the diabetic data are poor for a scaling of the signal at the level of the S cone receptor before a gain change or for a scaling of the signal in the pre-opponent S branch after a gain change (this is equivalent to scaling the constant in the time-dependent gain mechanism). Therefore, within the context of the model, the hypothesis that diabetes is only affecting sensitivity at the S receptor

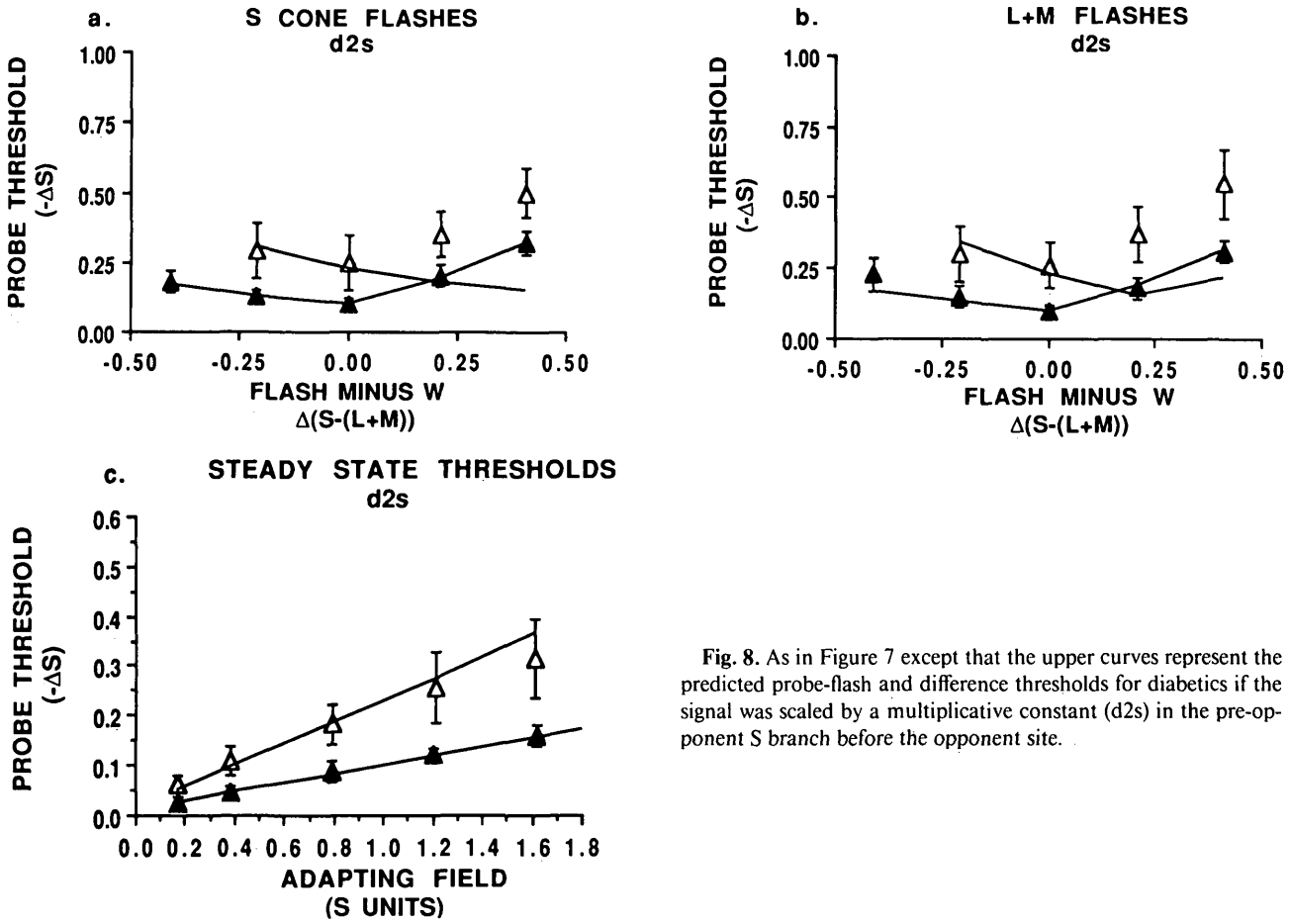

Fig. 8. As in Figure 7 except that the upper curves represent the predicted probe-flash and difference thresholds for diabetics if the signal was scaled by a multiplicative constant (d2s) in the pre-opponent S branch before the opponent site.

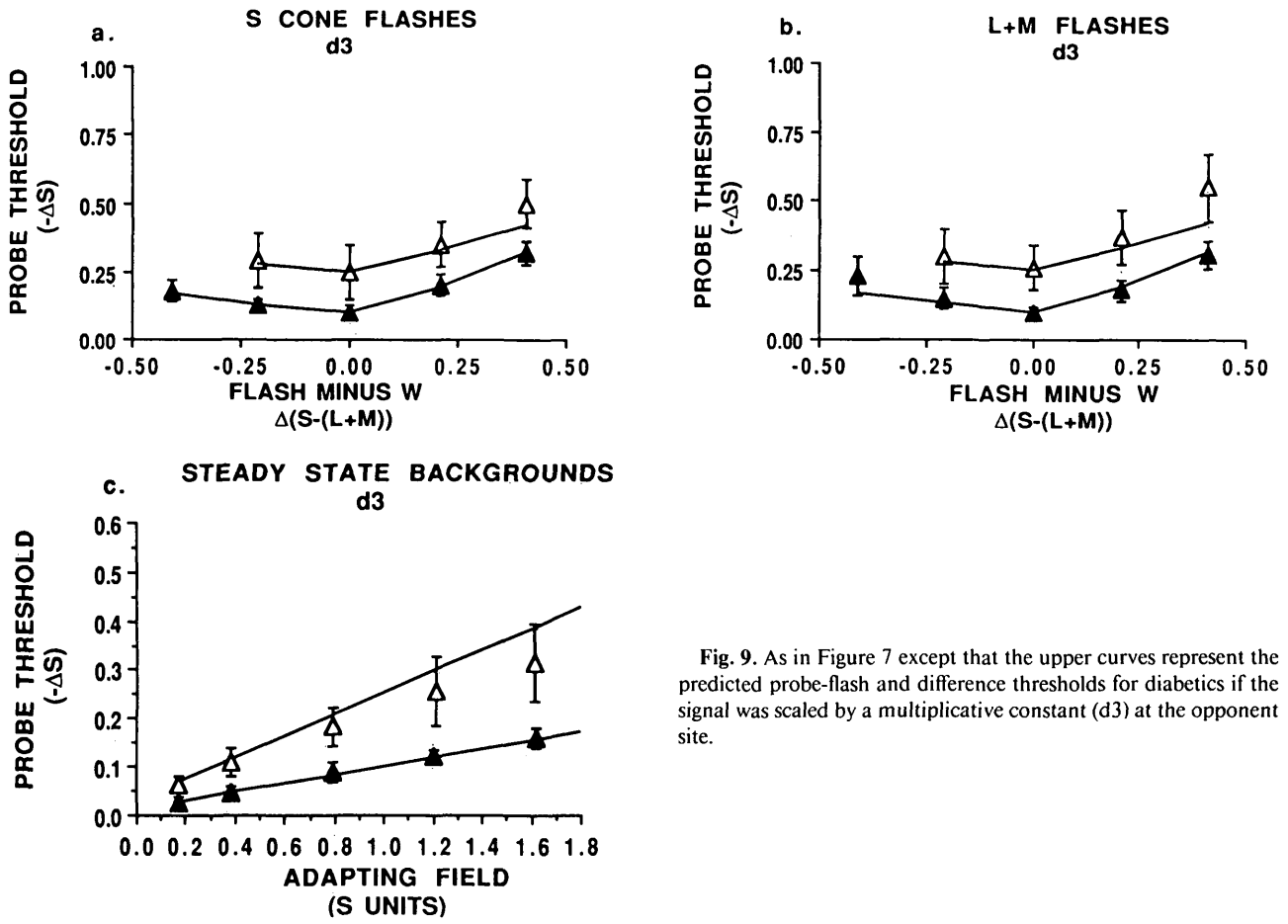

Fig. 9. As in Figure 7 except that the upper curves represent the predicted probe-flash and difference thresholds for diabetics if the signal was scaled by a multiplicative constant (d3) at the opponent site.

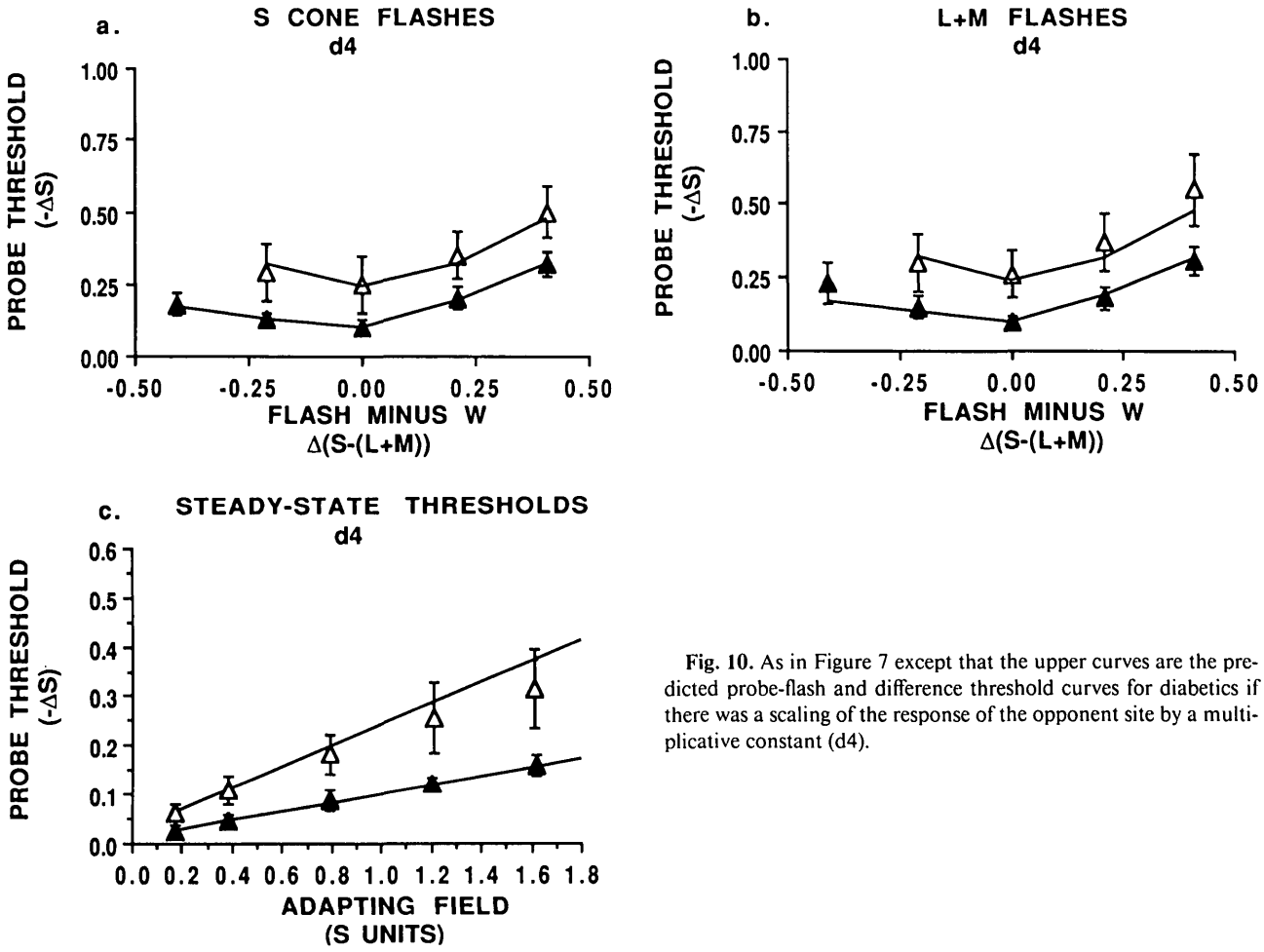

Fig. 10. As in Figure 7 except that the upper curves are the predicted probe-flash and difference threshold curves for diabetics if there was a scaling of the response of the opponent site by a multiplicative constant (d4).

before a gain change or is affecting the pre-opponent S branch can be rejected. The fits to the diabetic data, however, are good for a scaling of the signal at the opponent site (a change in d3) or for a scaling of the response of the opponent site (a change in d4). The change in d3 is equivalent to scaling the pre-opponent signals, S and LM, by the same multiplicative constant or the input to the response stage of the opponent site. The former explanation is less likely, considering that the M (pi 4) and L (pi 5) cone sensitivities for these patients were within the normal range and given recent evidence that sensitivity to changes in luminance for similar stimuli was normal in patients with early diabetic retinopathy.[18] If we consider a d4 change, which provides a slightly better fit to the data, the implication is that the site of sensitivity loss is in the S cone system at or after the opponent site, and that the S and LM pre-opponent branches are unaffected by the disease process.

In conclusion, the S cone system sensitivity losses we have found in patients with early diabetic retinopathy are not consistent with a defect at the level of the S cones before a gain change or with a defect before the opponent site. Rather, the results provide evidence that the sites of sensitivity loss are post-receptoral, at or after the opponent site.

Key words: S cone system, diabetes, probe-flash technique, receptor, opponent site

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