The Nature and Extent of Retinal Dysfunction Associated with Diabetic Macular Edema

Vivienne C. Greenstein,1 Karen Holopigian,1 Donald C. Hood,2 William Seiple,1 and Ronald E. Carr1

PURPOSE. To evaluate the nature and extent of retinal dysfunction in the macular and surrounding areas that occurs in patients with diabetes with clinically significant macular edema (CSME).

METHODS. Eleven patients were evaluated before focal laser treatment. Multifocal electroretinogram (ERG) and full-field ERG techniques were used to assess the effects of diabetic retinopathy and CSME on macular, paramacular, and peripheral retinal function. A modified visual field technique was used to obtain local threshold fields. The relationship between local sensitivity changes and local ERG changes was determined.

RESULTS. Local ERG responses were significantly delayed and decreased in amplitude, and timing changes were observed in a larger area of the retina than amplitude changes. Visual field deficits were similarly widespread with marked sensitivity losses occurring in retinal areas with normal ERG amplitudes and in areas that appeared to be free of fundus abnormalities. Despite this similarity and the finding that retinal areas with elevated thresholds have timing delays, timing delays were not good predictors of the degree of threshold elevation.

CONCLUSIONS. The results demonstrate the widespread nature of timing deficits and visual field deficits that are associated with CSME. (Invest Ophthalmol Vis Sci. 2000;41:3643–3654)

Diabetic macular edema results in loss of visual acuity. The risk of further loss of acuity can be reduced with focal laser surgery.1 Focal laser surgery consists of either focal laser treatment to individual leaking microaneurysms, grid laser treatment to areas of diffuse leakage and capillary nonperfusion, or a combination of the two. In this study our objectives were first to evaluate the nature and extent of retinal dysfunction in the macular and surrounding areas that occurs with clinically significant macular edema (CSME), and second to assess the effects of focal and grid laser treatment on retinal function using electroretinographic (ERG) and psychophysical techniques. Full-field ERG techniques have been used in previous studies to examine retinal function in patients with diabetic retinopathy and there are reports of abnormalities in various components of the full-field ERG. These abnormalities, which include reductions in the amplitudes of the components and delays in implicit times, appear to be related to the severity of the retinopathy (e.g., see References 2 through 6). The problem with full-field ERG techniques is that they are of little value for assessing the effects of CSME on central retinal function. The development of focal ERG techniques has allowed the examiner to study local retinal areas. Focal ERG results obtained from patients with diabetes who have retinopathy and from patients with diabetes who have CSME show reductions in amplitudes, delays in implicit times and reductions in oscillatory potential (OP) amplitudes.7–12 Visual field techniques have also been used to study retinal function in patients with diabetes, and there are reports of visual field deficits that increase with increasing retinopathy level.13,14 However, the relationship between local sensitivity changes and focal ERG changes associated with CSME remains to be determined.

Because one of our objectives was to evaluate the extent of retinal dysfunction associated with CSME, both full-field and multifocal ERG techniques were used. The full-field ERG was used to provide a measure of retinal function of the entire retina, and the multifocal ERG technique was used to obtain local ERG responses from the central retinal area.15 In this study, the effects of CSME on the components of ERG responses were evaluated. In addition, the relationship between multifocal ERG changes and local sensitivity changes was determined by comparing the multifocal ERG responses to local threshold fields obtained with a modified visual field technique (Humphrey, San Leandro, CA). In the second study,16 the effects of focal and grid laser treatment on local ERG responses and on local sensitivity were assessed.

METHODS

Subjects

Eleven patients with CSME were recruited from the Diabetic Retina Clinic at Bellevue Hospital, New York City. The age range was 33–67 years (mean, 56.5 ± 9 years). The level of

From the 1Department of Ophthalmology, New York University School of Medicine; and the 2Department of Psychology, Columbia University, New York, New York.

Supported by National Eye Institute grant R01-EY-02115, an unrestricted grant to the Department of Ophthalmology from Research to Prevent Blindness, and grants from the Helen Hoffritz Foundation and the Allene Reuss Memorial Trust.

Submitted for publication March 17, 1999; accepted April 13, 2000.

Commercial relationships policy: N.

Corresponding author: Vivienne C. Greenstein, Department of Ophthalmology, NYU Medical Center, 550 First Avenue, New York, NY 10016. vcg1@is3.nyu.edu

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retinopathy and degree of macular edema were determined for each patient on the basis of results of slit lamp biomicroscopy, color fundus photographs, and fluorescein angiography. A summary of the clinical characteristics of the patients is shown in Table 1. None of the eyes studied had significant lens opacities or ocular disease unrelated to diabetes. All subjects had central fixation. The right eye was tested in eight patients. The multifocal records and visual fields for the three other patients were reversed to provide easier comparisons.

Nine control subjects ranging in age from 40 to 62 years (mean, 51.6 ± 8 years) with no known abnormalities of the visual system also participated in the study. All had normal full-field ERGs and normal findings in ophthalmic examinations. Informed consent was obtained from all subjects before their participation. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the committee of the Institutional Board of Research Associates of New York University Medical Center and Bellevue Hospital.

**Multifocal ERG Technique**

Multifocal ERGs were recorded using the Veris technique (EDI, San Mateo, CA). The visual stimulus consisted of 103 hexagonal areas scaled with eccentricity. The stimulus array was displayed on a high-resolution black and white monitor driven at a frame rate of 75 Hz. Each hexagonal area was modulated from black to white independently according to a binary m-sequence ($L_{\text{max}} = 400$ candelas [$\text{cd/m}^2$] and $L_{\text{min}} = 9$ cd/m$^2$). The surround luminance was 200 cd/m$^2$.

Because we were interested in evaluating the changes in retinal activity associated with specific sites of structural abnormalities within the macular area, the stimulus conditions that are typically used for the multifocal ERG were modified. To optimize the identification of localized changes, we tested the patients (P)1 through P5 with the monitor positioned at a viewing distance of 64 cm. At this viewing distance, the 103 hexagons fell within a smaller field of approximately 28° by 22°. In addition, because it has been reported that in CSME macular OPs can be selectively reduced, the m-sequence

![Graphical representation of multifocal ERG recordings](image)

**TABLE 1. Clinical Characteristics of Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Visual Acuity</th>
<th>Level DR*</th>
<th>Classification of CSME †</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>20/200 (.10)</td>
<td>4</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>20/80 (.25)</td>
<td>3</td>
<td>I</td>
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<tr>
<td>4</td>
<td>52</td>
<td>20/50 (.40)</td>
<td>3</td>
<td>I</td>
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<td>I</td>
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<tr>
<td>11</td>
<td>57</td>
<td>20/30 (.67)</td>
<td>3</td>
<td>I</td>
</tr>
</tbody>
</table>

Values in parentheses represent visual acuity expressed as a decimal.

* Classification of level of diabetic retinopathy (DR): level 3: microaneurysms with one or more nonproliferative lesions present of mild to moderate degree; level 4: microaneurysms with one or more other nonproliferative lesions present of severe degree; level 5: severe overall nonproliferative retinopathy; level 6: proliferative retinopathy without diabetic retinopathy high-risk characteristics.

† Classification of CSME (based on fluorescein angiograms): I, Intermediate with approximately equal leakage from microaneurysms and dilated capillaries; D, Diffuse with leakage mainly from dilated capillaries.

![Graphical representation of multifocal recordings superimposed on the fluorescein angiogram of a control subject](image)

**FIGURE 1.** Top: The two displays used in the multifocal recordings superimposed on the fluorescein angiogram of a control subject. Bottom: Multifocal records for two control subjects obtained with the two displays.
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Table 2. Amplitudes and Implicit Times

<table>
<thead>
<tr>
<th>Patient</th>
<th>30-Hz* Amplitude</th>
<th>30-Hz† Implicit Time</th>
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<tbody>
<tr>
<td>1</td>
<td>125</td>
<td>32.2‡</td>
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<tr>
<td>2</td>
<td>92.2</td>
<td>32‡</td>
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<tr>
<td>3</td>
<td>71.4</td>
<td>35.6‡</td>
</tr>
<tr>
<td>4</td>
<td>119</td>
<td>32.2‡</td>
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<tr>
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<td>139</td>
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<td>6</td>
<td>84.2</td>
<td>33.2‡</td>
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<tr>
<td>7</td>
<td>134.5</td>
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<tr>
<td>11</td>
<td>138.1</td>
<td>31.3</td>
</tr>
</tbody>
</table>

* Mean normal amplitude: 126 ± 45 μV (SD).
† Mean normal implicit time: 28 ± 2 msec (SD).
‡ Significant delay in implicit time compared with control subjects.

stimulation rate was slowed to allow for the assessment of macular OPs. This was achieved by inserting four frames between consecutive stimulus frames. For patients P6 through P11, more conventional stimulus conditions were used. The monitor was positioned at a viewing distance of 32 cm, the hexagons fell within a field of approximately 47° (width) by 39° (height), and the m-sequence stimulation rate was the same as the subject’s frame rate. To illustrate the retinal areas stimulated by the two displays, the hexagonal arrays are superimposed on the fluorescein angiogram of a control subject in Figure 1 (top).

Recording Technique

The pupil of the eye to be tested was dilated with 1% tropicamide and 2.5% phenylephrine hydrochloride and the cornea anesthetized with proparacaine hydrochloride. The diameter of the dilated pupil ranged from 8 to 9 mm across subjects. ERGs were recorded monocularly with a bipolar contact lens electrode (Burian-Allen; Hansen Ophthalmic, Iowa City, IO). The fellow eye was occluded, and the subject’s vision was corrected for best acuity for the viewing distance after insertion of the contact lens.

To obtain multifocal ERGs, the continuous ERG record was amplified with the low- and high-frequency cutoffs set at 10 and 30 Hz (preamplifier P511J; Grass Instruments, Quincy, MA), and it was sampled every 0.83 msec (1200 Hz) with an analog-to-digital board. A recent study showed that using a high-pass filter set at 10 Hz can distort the waveform of the multifocal ERG, and a filter setting of 1 Hz was recommended. The waveform distortion is associated only with sustained negative ERGs and can make the waveforms appear biphasic. Although in the present study some changes in waveform shape were observed at different retinal locations for the slower m-sequence condition, none of the patients with diabetes showed deep negative waveforms. The effects of using a 1-Hz filter setting rather than a 10-Hz setting would therefore be relatively minor in our study.

The m-sequence had 214 – 1 elements for P1 through P5. The recording time was approximately 9 minutes. To improve the subject’s ability to maintain fixation, the test was broken up into 16 overlapping segments, each lasting approximately 34 seconds. For P6 through P11, the m-sequence had 214 – 1 elements and required 3.6 minutes for a single test. Again, to improve the subject’s ability to maintain fixation, the 3.6-minute test was broken up into eight overlapping segments each of 25 seconds’ duration. A session included two 3.6-minute tests. Stimulus control and data collection were performed with the software that accompanies the system (VERIS Scientific software; EDI). The quality of the recordings was controlled by real-time display, and contaminated segments were discarded and repeated. Local retinal response components were extracted using the fast m-transform algorithm. The first-order component was used in this study for analysis.

Analysis of Multifocal Responses

The amplitudes and implicit times of the individual responses were calculated using a software program written in MATLAB (MATLAB; The MathWorks, Natick, MA). The technique used in this study for measuring individual responses is described in detail by Hood and Li. Because there are regional differences in the waveform of the multifocal responses, a template was obtained for each of the 103 areas tested by averaging the records from the control subjects. The template for each area was fitted to the respective areas in the records of each of the patients by varying three parameters. One parameter shifted the template vertically to account for small changes in baseline, one scaled the amplitude, and the third scaled the time vector by a single value. The templates were multiplicatively scaled in both time and amplitude and fitted to the first 100 msec of the response, by using a least-squares fitting procedure to find the best fitting parameters. The amplitude and implicit time of each local response was derived from the scale factor for each parameter. Amplitude was calculated as the voltage difference between the first trough and the first peak of the scaled template. Implicit time was measured to the first prominent response peak of the scaled template. A multiplicative scaling of time, as opposed to a shift, provided a superior fit. This was previously demonstrated in records obtained from patients with retinitis pigmentosa and more recently in patients with early diabetic retinopathy. The program also provides a goodness-of-fit parameter or statfit. In this study responses with a statfit worse than 0.75 were not reported in the figures. Hood and Li found that a statfit of 0.75 provides a conservative definition of a true signal and that a criterion of 0.75 corresponds to a false alarm rate of less than 3%. The template method used in this study for determining response amplitude and implicit time has not only been shown to provide reasonable fits to the slowed responses of patients with retinitis pigmentosa but has also recently been shown to provide good fits to the slowed responses of patients with early diabetic retinopathy. The advantage of using a template is that a goodness-of-fit criterion can be set to allow for comparison across responses and across subjects.

Full-field ERG

Full-field cone ERGs were measured using a photostimulator (Grass Instruments, Quincy, MA) in a Ganzfeld. After 5 minutes of light adaptation to a white Ganzfeld of 40 cd/m², full-field cone ERGs were obtained to 30-Hz flicker. The signal was amplified (1 K; preamplifier P511J; Grass) and filtered (1–10,000 Hz). In addition, OPs were recorded under cone-
dominated conditions. They were measured as a function of increasing stimulus intensity (0.5–5.6 cd-sec per meter squared) for P1 through P5. The signal was amplified (5 K) and filtered (100–1000 Hz).

Visual Fields
To compare multifocal data with visual field data, two custom displays were designed for the Humphrey perimeter (Humphrey, San Leandro, CA). Thresholds were measured either at 103 locations, which corresponded to the centers of the 103 hexagonal areas in the multifocal display viewed at 32 cm, or at 58 locations, which corresponded to the centers of 58 of the 103 hexagonal areas viewed at 64 cm. (We were limited to 58 locations, because the minimum separation between the \(x\) and \(y\) coordinates on the perimeter is 2\(^\circ\)). The background luminance was 10 cd/m\(^2\).

RESULTS
Full-field ERG
None of the patients showed significant decreases in amplitude for 30-Hz full-field flicker; however, 7 of the 11 patients showed significant increases in implicit times (Table 2). Cone-dominated OPs obtained from P1 through P5 were reduced in amplitude and delayed in all patients except P1.
Multifocal ERGs

Figure 1 (bottom left) shows the 103 responses obtained from a control subject when the display subtended 28° by 22° and the m-sequence was slowed. Bottom right shows the 103 responses obtained from another control subject when the display subtended 47° by 39° and the fast m-sequence was used. The responses obtained with the fast m-sequence had a single peak; however, when the slower m-sequence was used, early positive peaks became apparent, and regional differences in timing and waveform could be seen.20,21 Figure 2 (top) shows multifocal records obtained from two of the patients (P1 and P5) using the slowed m-sequence and the smaller stimulus display. For P1, the greatest reductions in amplitude and increases in implicit time appeared to be in the central area. For P5, the marked reductions in amplitude and delays in implicit time extended into the inferior field. The records for P1 and P5 also showed differences in waveform shape compared with the control subjects. The early positive peaks seen mainly in the central area for control subjects were either absent or reduced in amplitude. These differences in waveform shape were only apparent when the slowed m-sequence was used. The multifocal ERG records obtained from two of the patients using the fast m-sequence are shown in Figure 2 (bottom). The responses for P8 and P9 were decreased in amplitude particularly in the central 10°, and implicit times were delayed.

The amplitudes and implicit times of the individual responses for all subjects were analyzed as described. The mean and median implicit times and response amplitudes were compared for the nine control subjects for the slowed and for the fast m-sequence conditions. The mean and median implicit time values for each of the 103 areas were very similar (Spearman rank order correlations were \( R = 0.97 \) for the slowed m-sequence and \( R = 0.96 \) for the fast m-sequence). Local mean implicit times for the slowed m-sequence (calculated for each of the 103 locations) ranged from 29.8 to 35.8 msec, and local median values ranged from 29.2 to 35.8 msec. As previously reported,21 the responses for the central locations were slower. The variability was very low; the range of local SDs (calculated for each of the 103 locations) was from 0.4 to 1.5 msec. Local mean and median implicit times for the fast m-sequence for each of the 103 locations ranged from 25.8 to 29.2 msec. Again, the variability was very low: The range of local SDs was from 0.6 to 1.3 msec. The mean and median response amplitudes for each of the 103 areas were also very similar (Spearman rank order correlations were \( R = 0.95 \) for the slowed m-sequence and \( R = 0.9 \) for the fast m-sequence).
For the slowed m-sequence condition, the local mean amplitude values ranged from 0.1 to 0.4 μV, and the median values ranged from 0.1 to 0.4 μV. The range of local SDs was 0.02 to 0.11 μV. For the fast m-sequence, the range of local mean amplitude values was 0.3 to 0.4 μV, and the range of median values was 0.3 to 0.4 μV. Local SDs for response amplitudes ranged from 0.1 to 0.2 μV.

To determine whether the patients showed amplitude reductions and increased implicit times localized to particular retinal regions, an amplitude loss and a delay for each response of each patient were calculated. A delay was calculated for each of the patients’ responses by comparing the implicit time with the mean implicit time for the control subjects at the same location. The delay for a response obtained at a particular location was equal to its implicit time minus the mean normal implicit time in milliseconds. The amplitude loss for each of the patients’ responses was calculated in a similar way. The peak-to-trough amplitude for each response was compared with the mean peak-to-trough amplitude for control subjects at the same location. The ERG delay and amplitude loss fields obtained from P6 through P9 using the larger stimulus field and more conventional stimulus sequence rate are shown in Figures 5 and 6. The numbers in the delay fields (Figs. 3 through 6; left) are the delays in milliseconds. Delays within 1 SD of the mean value for that location are represented by white hexagons, delays between 1 and 2 SDs of the mean value by light gray hexagons, and delays greater than 2 SDs of the mean value by dark gray hexagons. Black hexagons represent poor template fits—that is, fits exceeding the statfit criterion of 0.75. For the amplitude loss fields (Figs. 3 through 6; right) the numbers represent the difference in microvolts at each location between the patient’s trough-to-peak amplitude and the mean normal amplitude. Again, amplitude differences within 1 SD of the mean value are represented by white hexagons, amplitude differences between 1 and 2 SDs of the mean by light gray hexagons, and amplitude differences greater than 2 SDs by dark gray hexagons.

As can be seen in Figures 3 and 4, the responses for P1 and P3 through P5 were significantly delayed and decreased in amplitude. However, response amplitudes appeared to be less affected by the disease process than response implicit times. Not only were responses with normal or larger than normal amplitudes significantly delayed, but timing changes affected a
larger area of the field. Similar results were obtained for P2 (not shown). For P1 through P5, the stimulus conditions were chosen not only to optimize the resolution of localized response changes that may occur with CSME but also to allow for assessment of macular OPs. To assess macular OPs, the responses obtained using the slowed m-sequence were summed in four retinal areas, superior nasal, inferior nasal, superior temporal, and inferior temporal (the central 2.5° was omitted). Figure 7 shows the summed responses obtained from two of the control subjects and from two of the patients, P1 and P2. OPs (indicated by arrows) were clearly observable for the control subjects and appeared to be slightly more prominent in the two superior retinal areas. For P1 and P2 the early positive peaks or OPs and a late component at approximately 50 to 55 msec appeared to be absent or nonrecordable; the waveforms were smooth in all four retinal areas. The summed responses obtained from P3 through P5 also showed similar smooth waveforms.

Despite the use of stimulus conditions chosen to optimize the resolution of localized changes, changes in timing appeared to affect almost the entire macular area. The widespread nature of these changes could be seen even more clearly in the delay fields obtained from P6 through P9 in conventional stimulus conditions (see Figs. 5 and 6). For these patients, although decreases in response amplitude were mostly restricted to central retinal areas, delays in response occurred not only in central or macular areas but also in the periphery. In P7 and P9 for example, significant delays could be seen throughout the entire 50° field. Again, locations with normal or even larger than normal amplitudes showed delays in implicit time. Similar results (not shown) were obtained for P11. P10 was the only patient who had responses with normal or better than normal implicit times over a large area of the field. Significant negative correlations between delay in implicit time and loss in amplitude were found in all six patients and in P3 through P4 ($r = 0.3-0.63$).

To determine the relationship between local ERG responses and local sensitivity, visual fields were obtained from each patient using a modified Humphrey threshold program (Humphrey). The results were compared with those obtained from the control subjects. The mean and median thresholds were calculated for the nine control subjects for each of the
areas tested (103 locations corresponding to the centers of the hexagonal areas and 58 locations corresponding to the centers of 58 of the 103 hexagonal areas when the multifocal display was viewed at 64 cm). The mean and median threshold values were similar for both visual field tests (Spearman rank order correlations were $R = 0.96$ for the 103 areas and $R = 0.94$ for the 58 areas). For 100 of the 103 locations we tested, the mean and median values ranged from 25 to 36 dB (the values for three locations in the vicinity of the blind spot were excluded). The mean and median values for the 58 locations ranged from 29 to 34 dB. Figures 8 and 9 show the visual fields obtained from P1, P3 through P5, and P6 through P9. The visual fields are expressed as the difference between the mean threshold (in dB/10) of the control group and the patient’s threshold (in dB/10). For example, a value of 0 corresponded to a threshold intensity equal to the value for the control group, a value of 0.3 corresponded to a threshold 0.3 log units above the mean of the control group (3-dB difference), and a value of 1.2 corresponded to a threshold 1.2 log units above the mean (12-dB difference).

In Figure 8 the empty spaces (no values) represent the areas we were unable to test because of programming limitations of the perimeter. In Figure 9 the three hexagons labeled X are hexagons falling on the blind spot of one or more of the control subjects. White hexagons in both figures represent threshold differences within 1 SDs of the mean value, light gray hexagons differences between 1 and 2 SDs of the mean, and dark gray hexagons differences greater than 2 SDs of the mean. All patients except P1 and P9 had regions with normal or near normal sensitivity. These regions did not appear to be restricted to any specific part of the field, nor were the regions of greatest sensitivity loss necessarily associated with the central areas of the field. When comparisons were made between visual fields and the multifocal ERG amplitude loss fields there appeared to be little agreement between the two. There were, however, some similarities between visual fields and the multifocal ERG delay fields. Areas with elevated thresholds tended to show delays in timing. The relationship between implicit time and threshold for all the patients is shown in Figure 10. In Figure 10, the points with significantly delayed timing and elevated thresholds fall above the horizontal line and to the right of the vertical line. For P1, P6, P7, P9, and P11 most of the points fell in this area. Areas with elevated thresholds had timing delays, but timing delays were not good predictors of
the degree of threshold elevation. There were some patients, P3 for example, who had areas with significantly delayed timing and thresholds within the normal range.

**DISCUSSION**

The purpose of this study was to evaluate the nature and extent of retinal dysfunction in the macular and surrounding areas that occurs with CSME. Although there are many studies of the effects of diabetic retinopathy on the full-field cone ERG, it is only recently that focal ERG techniques have been used to assess localized central retinal function. The few studies that have used focal ERG techniques have reported reductions in amplitude and delays in implicit time in eyes with nonproliferative diabetic retinopathy (NPDR) and CSME. For example, in a recent study of patients with NPDR, the mean amplitude to a 4° stimulus was lower in eyes without CSME compared with that in normal eyes and was even lower in eyes with CSME. The mean implicit time was significantly delayed in eyes with CSME. In eyes without CSME, implicit times were the same as in normal eyes. Palmowski et al. used the multifocal ERG technique averaged across all 103 local responses and found that mean implicit times in the first-order component were significantly increased in eyes with NPDR and peak amplitudes were reduced. Because we were interested in comparing local retinal activity to clinically observed fundus abnormalities, we did not average across responses but instead analyzed individual responses for each patient and calculated delay fields and amplitude loss fields. In agreement with the mentioned studies, we also found that implicit times were significantly increased. The delay fields demonstrated not only that implicit times of local ERG responses were increased in retinal areas manifesting edema, they were also significantly increased in areas outside the macular area—areas that appeared to be free of fundus abnormalities on fluorescein angiography. In some cases, significant increases were found throughout the entire stimulus field, an area covering approximately 50°.

These results are similar to those reported by Fortune et al., who used an approach similar to ours to evaluate local ERG responses of patients with diabetic retinopathy. They reported that implicit times were increased and amplitudes were mildly reduced. Although increased delays of the local ERG responses were associated with increased severity of local retinopathy signs, responses were also delayed in areas without retinopathy. The widespread nature of these timing delays may reflect retinal thickening and/or the effects of retinal hypoxia. Retinal hypoxia may also explain why the majority of our patients had significantly increased full-field ERG implicit times. We found that the effects of CSME and retinopathy on local and full-field ERG response amplitudes were more variable. Although all patients showed decreases in local ERG...
FIGURE 8. Visual fields obtained from P1 and P3 through P5 using a modified threshold program (Humphrey, San Leandro, CA). The number at each point is the difference between the patient’s threshold and the mean threshold of the control group for that point. The empty spaces (no values) represent the areas that were not tested due to programming limitations on the perimeter. White hexagons represent threshold differences within 1 SDs of the mean value; light gray hexagons, differences between 1 and 2 SDs of the mean; and dark gray hexagons, differences greater than 2 SDs of the mean.

FIGURE 9. Visual fields obtained from P6 through P9 using a modified threshold program as in Figure 8. The three hexagons labeled X are those that fell on the blind spot of one or more of the control subjects.
response amplitudes, the affected areas were smaller for the amplitude loss fields than for the delay fields, and in many locations amplitudes were normal or even larger than normal. An analysis of the macular ERG responses in these locations using the scalar-product method\(^\text{15}\) which is dominated by response amplitude did not show any significant decreases in amplitude. This effect was also noted by Fortune et al.\(^\text{9}\) who reported that in their study of patients with early diabetic retinopathy it was common to find ERG responses that were severely delayed, yet these responses were among those with the larger amplitudes.

Because it has been suggested that OPs are sensitive indicators of retinal function and may be useful in estimating the severity of diabetic retinopathy,\(^\text{2,14}\) full-field and macular OPs were also evaluated in P1 through P5. In agreement with previous reports, OP amplitudes recorded with a full-field stimulus were reduced compared with values for control subjects.\(^\text{2,3,5,6}\) We were able to record macular OPs in the control subjects by using a slower m-sequence stimulation rate and in agreement with Miyake\(^\text{10}\) and Wü and Sutter\(^\text{20}\) found OP asymmetry; the OPs were slightly more prominent in the superior retinal areas. We were unable to record macular OPs in the patients with diabetes. Smooth waveforms were evident in all four retinal areas. It is possible that the absence of OPs reflects functional changes in the inner retina. The waveforms resembled those obtained in a recent study designed to investigate the inner retinal contributions to the multifocal ERG.\(^\text{2,5}\) In this study, components resembling OPs in the multifocal responses obtained from monkeys were absent after intravitreal injections of N-methyl-DL aspartate (NMDLA) and tetrodotoxin (TTX). Both NMDLA and TTX affect the activity of inner retinal neurons. Functional changes in the inner retina were also implicated by Palmowski et al.\(^\text{11}\) to explain the differences between waveforms obtained from control subjects and diabetics when second order responses were analyzed.

The first part of this study was designed to evaluate the type and extent of retinal dysfunction associated with CSME. With the multifocal ERG technique, we have shown that local responses were significantly delayed and decreased in amplitude, and that timing changes affected a larger area of the retina than amplitude changes. We found that visual field deficits were similarly widespread with marked sensitivity losses occurring in retinal areas with normal ERG amplitudes and in areas that appeared to be free of fundus abnormalities. Despite the similarities between sensitivity and timing changes, we found that for patients with diabetes with CSME, implicit time was not a good predictor of the degree of sensitivity loss. A possible explanation for this and for the finding of little or no agreement between visual fields and the multifocal ERG amplitude loss fields is that the levels of light adaptation differed for the two methods. In addition, we were comparing a threshold measure to the suprathreshold measures of implicit time and response amplitude.

In Greenstein et al.\(^\text{16}\) the same techniques are used to evaluate any changes in local ERG responses and local sensitivity that may occur in the same group of patients after focal laser treatment.

**References**


