Articles

Transient-like function and associated retinal capillary anomalies

Analysis of a patient with early retinopathy secondary to juvenile-onset diabetes mellitus

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A juvenile diabetes patient exhibiting limited early microvascular changes in the retina has been studied intensively. Like some others showing early signs of diabetic retinopathy, he manifests anomalies in a retinally based transient-like function. At all points tested in this case the sustained-like function was found to be normal. Because his functional and anatomic anomalies are stable and cover a reasonably extensive area of visual field and retina, it is possible to attempt correlative studies with other visual response functions. The transient-like function proves to be a more sensitive indicator of anomaly in this patient than static perimetry or critical flicker frequency.

Key words: retina, diabetic retinopathy, microvascular anomalies of the retina, kinetic and static perimetry, transient-like function, sustained-like function, desensitization-sensitization function of Westheimer, critical flicker-fusion frequency, quantitative layer-by-layer perimetry, vision testing

Neuropsychophysics tests seek to provide point-by-point and layer-by-layer analysis of retinal function. A sustained-like function has been defined which is apparently sensitive to events occurring in the inner and outer retinal plexiform layers. A transient-like function has been developed which has been (most probably) localized in the inner plexiform layer. Other tests are specific to the receptors and the optic nerve beyond the nerve head.

Diabetic retinopathy, a disease which affects the microvasculature of the inner retina, has proved to be of special interest because one group of patients with early diabetic retinopathy (commonly exhibiting hard exudates) shows changes in the sustained-like function only and a second group which exhibits microvasculature anomalies shows only transient-like function changes. If capillary nonperfusion is observed or more advanced changes are noted, both sustained-like and transient-like functions exhibit altered response.
A functional remission in a patient with relatively early changes associated with diabetic retinopathy was recently reported. In the present report, a juvenile diabetes patient with circumscribed retinal vascular changes is studied in depth. He shows characteristic changes in his transient-like function in this circumscribed area and also at least one microaneurysm outside of that area. An extensive area of the visual field exhibits loss of the transient-like function, which allows a comparison with a number of other psychophysical tests of vision, including kinetic perimetry, static perimetry (stimulus continuously exposed and pulsed), and critical flicker-fusion frequency (CFF).

The working hypothesis which has evolved in the analysis of an extensive series of patients is presented below. Of particular value in the long view is that detailed histories and chemistries on these patients are available and should yield important correlations, given the fact that subcategories of functional involvement can be defined.

Working hypothesis — early diabetic retinopathy

1. In regions of hard exudates where an active pathological process is evident, the sustained-like function is most probably affected, and measured functional changes exceed the bounds of the observed exudates. The outer plexiform layer is the most likely site of exudates and anomaly.

2. In regions exhibiting anomalies of the microvasculature per se (dilated, tortuous, irregular capillaries, microaneurysms), alterations in the transient-like functions are evident. Because the latter function apparently is organized there, the inner plexiform layer seems the most likely site of the functional anomalies. The patient considered in this paper falls in this category.

3. A given response alteration tends to dominate in a specific visual field (retinal) area.

4. Isolated microaneurysms may or may not result in an alteration of function. Probably at issue is whether there is an associated effective breakdown in the blood-retinal barrier.

5. In areas of more advanced retinopathy and/or areas of capillary nonperfusion, both the sustained-like and transient-like functions are found to be anomalous at the same retinal locus.

6. At early stages of the pathological process, anatomically observed changes may improve, and functional remissions (improvements) may be noted. Such changes have not been recorded in the patient considered here; rather, his fundus appearance and responses were remarkably stable.

Methods and procedure

Sustained-like and transient-like functions. The apparatus used in the present set of experiments has been previously reported in detail. Three luminous fields are needed for these tests. A modified Kodak carousel projector with an appropriately sized aperture and cam-activated shutter provided a small flashing test spot, field I. The projector presented a flash of 2.7 min diameter and 180 msec duration every second. Luminance of this flashing test light, field I, is varied in 0.1 log unit steps by inserting Kodak Series VI Wratten neutral-density filters into the light path of the carousel projector.

A background field, field II, was generated by a modified Leitz Prado projector fitted with appropriately sized photographically reproduced apertures positioned in the slide plane. Luminance of this background field, field II, is varied by a balanced pair of neutral-density wedges variable over a 4 log unit density range. For the sustained-like function tests, a series of different diameter (area) fields are used for field II. For the transient-like function, a four-veded windmill configuration is employed. The rotation of the windmill used to generate the transient-like function was achieved optically by rotation of a Dove prism at a rate of 1 cy/sec. This resulted in 8 on and off transitions per second of the projected target array at any given point in the visual field.

A large flat general surround field, field III, of 10 cd/m² luminance (31.5 apostilbs) was projected onto a screen 129 cm from the eye of the observer. A Gunkel illuminator (Foringer, Inc., Baltimore, Md.) with adjustable luminance device added served as the source. The luminance of field III is comparable to the established setting of lumi-
nance of the cupola of the Goldmann Haag-Streit perimeter. It serves to control general adaptation and to minimize spurious interactions when small background fields are used.

Observations were monocular, with an opaque eyepatch occluding the nontested eye. The nose-insert/headrest attachment of the Gunkel illuminator secured the subject's head.

A typical test session was as follows:

1. Appropriate test points were selected for examination of the sustained-like and transient-like functions. These were based on analysis of fundus photos, fluorescein angiograms, and kinetic and static field studies. The flashing test field (field I) luminance was adjusted to a "criterion" setting of 1.0 log unit above the measured static (increment) threshold on the surround field (field III) alone.

2. An optimal refractive correction as determined by prior examination was placed before the subject. An added spherical correction was determined for the specific test point in the visual field considered. The endpoint considered was approached from the over-plus side by the maximum-plus, minimum-minus technique in order to control accommodation, and then classic stigmatoscopy was applied as a check on these techniques.

3. After blur was minimized, the static perimetric threshold was determined at the particular visual field point of interest.

4. The sustained-like function (desensitization-sensitization function of Westheimer) was determined by presenting circular background fields (field II) of varying size, upon which the small flashing field (field I) was centered carefully. Background field sizes were presented in a largest-to-smallest order, and luminance of the background field was adjusted in both an ascending and descending series. The background field luminance needed to make the criterion test field just visible and just disappear was determined for each background size.

5. The transient-like response is defined as the difference in background field (field II) luminance between stationary and moving windmill background field conditions needed to bring the flashing test field (field I) to threshold. Unless otherwise specified, a fixed light/dark ratio (50/50), number of vanes (4), and an optimal windmill size and rotation rate (8 on-off transitions/sec) were employed.

Static and kinetic perimetry. Static and kinetic perimetry were performed with a Goldmann Haag-Streit perimeter to which a light chopper had been added and which presented a 150 msec test flash every second. As stated above, observations were monocular, with the eye optimally corrected for the specific test conditions by subjective techniques including classic stigmatoscopy.

Cupola luminance was set at 10 cd/m² (31.5 apostilbs).

Since a question might arise as to whether a static threshold measured with a pulsed stimulus exceeding the critical duration may influence the response of a transient mechanism, static perimetric determinations were repeated with the test spot continuously presented, and the results were compared.

Kinetic perimetry was conducted by careful tracking a continuously presented target both from nonvisible to visible and from visible to nonvisible.

Visual sensitivity (further evaluation of static or increment thresholds). The same tangent screen apparatus used to measure the sustained-like and transient-like functions described above was used to assess visual sensitivity at 3° and 4° eccentricity on the 45°, 135°, 225°, and 315° half-meridians. Field I (the flashing test light) and field III (the large area general surround) were used; field II was not used for this test.

The location of the test stimulus on the screen was not moved; rather, four fixation targets were
Fig. 2. Modified display of points tested in the visual field. The schema used on the Haag-Streit or Oculus perimeters was used. The meridian designations have been transformed to correspond to that distribution of points as observed on the retina by the clinician by direct ophthalmoscopy. The visual field as defined in the Haag-Streit system has 0° located to the right of the patient (as seen by the patient) with meridians proceeding counterclockwise. On this projection, 0° appears to the right on the retina as seen by the clinician with meridians proceeding clockwise. Thus 90° in the superior field is seen inferiorly on the retina. Certain symbols were introduced in ref. 1. The solid black disc corresponds to the sustained-like function (lower left-hand corner of figure), and the large asterisk to the transient-like function. If either of these were anomalous, they were crossed out or cancelled. Thus partial loss of the transient-like function is characterized by the large asterisk covered with halftone dots, and near total loss of the transient-like function is symbolized by the asterisk covered by a series of vertical lines (grating). Because so many points were tested, secondary symbols were used here (small asterisk, open and filled squares). These correspond to the larger symbols as indicated. To aid in locating points tested in Fig. 3, added numbers were placed on this figure at specific points of reference. Clearly there is a zone of normal response to the sustained- and transient-like functions (small asterisks), a zone of partial loss of transient-like function (open squares), and a zone of near total loss of transient-like function (filled squares).

simultaneously presented on the screen. The observer was instructed to fixate one of the four fixation crosses. Thus the observer shifted his gaze so that the unmoved test flash stimulated the retinal locus of interest; hence the physical characteristics of the distal stimulus were invariant. At each test locus 10 ascending and 10 descending series of test flash luminances were run to determine threshold. For a specific trial, the retinal locus tested and whether an ascending or descending series was presented were randomly determined. Each session consisted of a minimum of 80 individual threshold measures; in one session all the data at 4° eccentricity were measured; in another session all the data at 3° eccentricity were determined.

**CFF determinations.** The Goldmann perimeter has been fitted with a chopper that interrupted the light beam in a near square-wave fashion.

The patient was optically corrected with stigmatoscopy for the specific test conditions for the specific retinal locus of interest as described above. The threshold of the target to be used was measured, flashing once every second. Flicker thresholds were then measured with the test stimulus set at a superthreshold level of 1 log unit above threshold with background luminance set at 10 cd/m². Thus the stimuli were equated for visual effectiveness rather than physically. These near square-wave flicker thresholds have been measured in eight retinal locations; at 4° eccentricity and at 7° eccentricity on the 135°, 45°, 225°, and 315° half-meridians. A Goldmann target IV (area 3.32 log min arc²) was used for determinations made at 4° eccentricity, and a Goldmann target V (area 4.52 log min arc²) was used for the measures at 7° eccentricity. These size targets are chosen because they match most closely the limited area of spatial interaction of the sustained-and transient-like functions at these eccentricities.

**Case history**

L. B. is a 25-year-old male who was first seen in the Ophthalmology Clinic on July 14, 1978. He has had diabetes for 8 years, requiring 50 U of N.P.H. insulin. He was without ocular complaint but presented for a routine check for diabetic retinopathy. There was no history of hypertension. Family history was positive for glaucoma only.

Visual acuity uncorrected was 20/20 OU. He had several ocular examinations during the course of the psychophysical testing which were entirely normal, with ophthalmoscopy showing no evidence of dot and blot hemorrhages, exudates, or
Fig. 3. Magnified duplicate of Fig. 1 with numbered reference points 1 through 6 superimposed. Location of points in the central 10° of field was achieved by carefully plotting the center of the blind spot with reference to the point of fixation. For this range of eccentricities the tangent error was considered negligible. Note the relationship of point 4 to one of the isolated microaneurysms and the location of points 2, 3, and 5 to the bound of the anomalous capillary bed. Point 1 corresponded to 4° eccentricity on the 135° half-meridian. This valuable reference point will be used often below.

visible microaneurysms. Two fluorescein angiograms were performed. There was no evidence of a progression or change in his ocular status during the year.

In the right eye, in the early venous phase of the fluorescein angiogram, two microaneurysms were noted, one at approximately 5° to 6° from the fovea on the 315° half-meridian and a second one at 7° to 8° on the 60° half-meridian (Figs. 1 and 2). In the inferotemporal quadrant (reference the foveal avascular zone) there are microvascular irregularities, microaneurysms, and multiple alterations in the vascular width causing the appearance of irregularities. This is comparable with the appearance of an old branch vein occlusion with collateral circulation. The far peripheral venous system inferotemporally appeared to be filling at a much slower rate than any of the other venous branches. There is a possibility that this venous branch is showing some vascular occlusive change, with collateral circulation going superiorly and possibly also to a vessel which enters the large vein at a position more proximal to the disc than the apparently partially occluded vein. No late fluorescence was noted in the region of the capillary abnormalities or in the region of the two isolated microaneurysms. The left eye revealed no abnormalities.

Systemically he had no symptoms suggestive of neurological, gastrointestinal, or renal disease. On physical examination there were no signs indicating pathological involvement of any system.

Laboratory evaluation included the following: fasting blood sugar 210 mg/dl (normal 65 to 110); serum cholesterol 180 mg/dl (normal 120 to 240); serum triglyceride 130 mg/dl (normal 10 to 140); blood urea nitrogen 12 mg/dl (normal 10 to 20); and creatinine 0.9 mg/ml (normal 0.7 to 1.4).

Results

Sustained-like and transient-like functions. The sustained-like and transient-like functions were measured in many parts of the
Fig. 4. Normal sustained-like function (left) and transient-like function (right). The 4° eccentricity point in the visual field projects inferiorly onto the retina (Fig. 3). The abscissa of the left function is area subtended by circular background field II. Both ordinates are luminance of background field II needed to just bring the small flashing test field (field I) to threshold. Separate measures are taken for just appearance and just disappearance of field I. Range bars are included. A minimum of four determinations were made for each plotted point. For explanation of disc and asterisk see legend to Fig. 2.

Fig. 5. Data of point 1 on Figs. 2 and 3. Data were obtained over an extended period of time. Comparable data sets were obtained on at least ten other occasions spanning well over 1 year.
Fig. 6. Sustained-like and transient-like data from samples at several eccentric test points (from fixation) along the 135° half-meridian. Data obtained at 4° eccentricity correspond to point 1 on Figs. 2, 3, and 5.

are near the bound of the anomalous capillary bed.

Fig. 4 shows a normal sustained-like and transient-like function obtained from this observer at 4° eccentricity along the 90° half-meridian. On the left side of the figure the typical U- or V-shaped sustained-like function is seen; background luminance of field II needed to bring the small flashing field I to threshold was measured for different areas of field II.

The transient-like function is shown on the right of Fig. 4. The upper points correspond to background luminance of field II needed to bring the small flashing test target to threshold for the four-vaned windmill not rotating, and the lower points, pointed to by the arrowheads, correspond to data obtained when the windmill target was rotating. The difference in setting, nonrotating and rotating, is the magnitude of the transient-like effect (for specified conditions) at the test point.

The magnitudes of both the sustained-like and transient-like functions increased with eccentricity from the point of fixation.10–12

In Fig. 5, data obtained at 4° eccentricity on the 135° half-meridian are presented. This corresponds to point 1 in Figs. 2 and 3 which lies within the anomalous capillary bed. Data obtained on three of several trials (August and December 1978 and February 1979) are presented. Not included in this figure are data obtained in April 1979, which are identical and are depicted in Fig. 11. The data showed Patient L. B. to be very consistent, the sustained-like function to be normal at all times tested, and the transient-like function to be essentially absent.

The sustained-like and transient-like func-
Fig. 7. Sustained-like and transient-like functions data from samples along several meridians at 4° eccentricity from fixation. The heavy lines cutting across the distribution approximately match the boundary of the anomalous zone defined in Fig. 2. The data obtained at 135° correspond to point 1 on Figs. 2, 3, 5, and 6.

Tensions measured at several eccentricities along the 135° half-meridian are shown in Fig. 6. At 1° eccentricity, the data were normal or near normal. At 2° eccentricity on the 135° half-meridian, the magnitude of the transient-like function was smaller than found at 1°. At 4°, 6°, and 8° eccentricities on this half-meridian, the transient-like function was either absent or greatly reduced. Since the magnitude of the transient-like function normally increases with eccentricity from fixation, the data obtained at 2° eccentricity also must be regarded as at least partially anomalous.

Similar measures were made at several locations 4° from fixation (Fig. 7). On the 90° and the 180° half-meridians, the transient-like functions were approximately normal for this eccentricity (Fig. 4). At the 105°, 120°, 135°, 150°, and 165° half-meridians, all at 4° eccentricity, the transient-like functions were clearly reduced or essentially absent.

Transient-like function data are summarized in Fig. 8. Data in the upper row were all within the range expected from the normal retina at this eccentricity; the middle row exhibited transient-like functions that were somewhat reduced; the lower row of functions exhibited transient-like functions that were absent or essentially absent. The lower row had all been measured in the quadrant of the visual field that corresponds to the abnormal vascular bed.

Referring to the middle row of Fig. 8, the reduced transient-like functions were measured at 330° and 340° half-meridians. The fluorescein angiogram (Figs. 1 and 3) shows a microaneurysm near these retinal locations.
These psychophysical functions were all measured during the course of 1 year. They were apparently stable over that time and showed no significant nor systematic differences. These data cumulatively establish a stable reduced transient-like function in the area subtended by the vascular bed.

**Static (increment thresholds) and kinetic visual fields.** Static and kinetic visual fields were measured in an effort to relate the observed anomalous psychophysical functions with other measures of visual function. The kinetic field of the right eye is shown in the main part of Fig. 9, with the data points left out for clarity. The inset on the lower left shows two isopters and the blind spot with the associated data points, to provide some indication as to the nature of the raw data. Each isopter was based on extensive testing, and multiple measures (several repetitions) were taken at all critical points. A spectacle correction of +3.00 D optimized refraction for the perimeter for central isopters.

There was a consistent constriction of isopters in the more central areas of the 90° to 180° quadrant in this visual field.

The inset on the lower right shows two partial isopters which map the kinetic field when the stimulus started from the center of the visual field and proceeded to the periphery i.e., from seeing to nonseeing. These isopters indicate the disappearance of the stimulus. The later examination with these small and dim stimuli proved to be extremely difficult.

There was clearly a kinetic perimetric deficit in the area of the anomalous vascular bed. It was difficult to assess the degree of correlation between these results and the alterations on the transient-like function; that is, it was hard to assess co-variance of a dynamic stimulus with one which had a fixed locus.

With the Haag-Streit Goldmann perimeter, static thresholds were measured in the right eye along the 135° to 315° and 45° to 225° meridians, and these are shown in Fig. 10. These are increment sensitivity (background luminance 10 cd/m²) plots of response to the test spot as a function of retinal eccentricity. There was a marked decrease in sensitivity on the 135° half-meridian as compared with any of the other three half-meridians. However, the decrease in sensitivity apparently did not correspond well with the boundary of the transient-like functional anomaly (Fig. 6 and below). A meaningful difference only appeared beyond 5° on the 135° half-meridian. From fixation to about 4° eccentricity there seemed to be poor correspondence between sensitivity changes and the loss of the transient-like function discussed earlier. Beyond 5° with increasing ec-
Fig. 9. Kinetic visual field. Cupola luminance 10 cd/m² or 31.5 apostilbs. Central isopters were determined with a +3.00 DS correction using a maximum-plus, minimum-minus criterion. **Left inset**, Points tested in two individuals' isopters. These data were all taken nonseeing to seeing. **Right inset**, Limited data obtained with stimulus seen to nonseen.

centricity, there was an increasing loss in sensitivity on the 135° half-meridian vs. the other three half-meridians tested. By 10°, the difference in sensitivity was of the order of a log unit. In the area of the microaneurysm (315° half-meridian), no orderly sensitivity alteration was noted where partial loss of the transient-like function was recorded. Similarly, no changes were noted in measures of kinetic perimetry in this zone.

Results of static perimetry obtained with the nonflashing test spot were very similar to those obtained with the flashing test spot with flash exposure longer than the critical duration. Minor differences existed, but we regard these as manifestations of experimental variability.

**Sensitivity measures and the transient-like function.** Two different approaches were used in order to establish the relationship between alterations in the transient-like function and alterations in static perimetric sensitivity.

**Approach 1.** Thresholds for the test flash at 3° and 4° eccentricity on the 45°, 135°, 225°, and 315° half-meridians (measured as described above) are shown in the left half of Fig. 11.

Sensitivity measured at 4° eccentricity on the 135° half-meridian was reliably reduced as compared to the sensitivities measured at 45°, 225°, and 315° half-meridians. This reduction, although reliable, was only of the order of 0.05 log units and might easily be overlooked on routine clinical testing, particularly if limited replications had been made. Note that Goldmann settings 2a and 2b differ by 0.1 log unit. The data obtained at 3° eccentricity showed essentially no measurable difference in sensitivity at any of the four tested loci. It will be remembered that along the 135° half-meridian, the capillary bed was
Transient-like function and capillary anomalies

Fig. 10. Static sensitivity (increment threshold) cuts through visual field with Goldmann target size 0. Blur was minimized at the point of fixation. The test target was flashed for 150 msec every second in the upper two curves and left continuously on (until the patient responded) in the lower two curves. Test point 1 (Figs. 2, 3, and 5 to 8) is indicated. Symbols showing the results of testing the transient-like function at points 4° eccentricity from fixation are shown. Test range variation is shown in the upper left-hand figure. On the lower left-hand figure, data for 0° to 10° eccentricity, 315° half-meridian, have been folded over (mirror reflection on the 135° half meridian for ease of comparison and have been displaced upward by the distance (A'-A). Luminance of the test flash appears on the ordinate; 1.0 log units corresponds to Goldmann 2e, 0.5 log units to Goldmann 3e, and 0.0 log units to Goldmann 4e. The reader is reminded that on the 315° half-meridian, the transient-like function is reduced in amplitude between 4° and about 6°. It is also reduced in amplitude at 2° on the 135° half-meridian and essentially absent at more eccentric points (including 4° eccentricity). See Figs. 2 and 6.

Fig. 11. Magnitudes of the transient-like functions measured at 3° and 4° eccentricity are plotted in the right half of Fig. 11. On the 135° half-meridians at both 3° and 4° eccentricity, the transient-like functions were essentially absent. These were changes of up to 0.5 log unit. Although there was no reduction in sensitivity at 3° on the 135° half-meridian, the transient-like function at this location was absent. The transient-like function obtained at 4° eccentricity on the 135° half-meridian (obtained on 4/10/79) can be compared with similar data exhibited in Fig. 5. Similarly, measures taken near the microaneurysm (over a somewhat more restricted time course) also proved stable. These data support the contention that the retinal anomalies have been stable since the start of data collection approximately 1 year ago.

Approach 2. It was necessary to consider whether the changes in static sensitivity parallel alterations in the transient-like function. Fig. 12, A, is a plot of the magnitude of the transient-like function against retinal eccentricity. The closed circles are the amplitudes of the transient-like function for observer L. B. along the 45° half-meridian, and
Fig. 11. Data taken at 3° and 4° eccentricity. Left, Static perimetric sensitivities. Dashed line, Mean ± 1 S.D. of the descending series of threshold measures; solid line, ascending threshold measures. Right, Magnitudes of the transient-like function. Each curve was generated on the same instrument in random order during one session. Test point 1 (Figs. 2, 3, and 5 to 8) is indicated.

the open circles are previously published normative population data. The 45° half-meridian was chosen as a normal half-meridian, on the basis of the fluorescein angiogram. These two sets of data were in good agreement. This implies that such data (45°) can be used as a normal control and further indicate that L. B., now a well-trained observer, was functioning reliably. Also indicated on Fig. 12, A, are transient-like function magnitudes obtained along the 135° half-meridian, i.e., within the area of increasing vascular anomaly. With increasing eccentricity, the magnitude of the transient-like function approached zero. Fig. 12, C, is a plot of the difference (α) between the magnitudes (taken on the logarithmic scale of Fig. 12, A) of the transient-like functions obtained on the 45° half-meridian and the 135° half-meridian. Zero difference is at the top of Fig. 12, C.

In Fig. 12, B, are plotted the log relative sensitivity (static perimetric sensitivity) for flashing test light measured along the 45° half-meridian and the log sensitivity measured along the 135° half-meridian. These two functions are smoothed versions of the static perimetric measures shown in Fig. 10. Fig. 12, D, plots the log difference between these two functions (β). The differences β (Fig. 12, D) may be compared to the differences α in the transient-like function (Fig. 12, C). Again, zero difference is at the top of Fig. 12, D.

Clearly, α and β were not varying in a parallel manner; the difference in transient-like functions was monotonically increasing, with an asymptotic value reached between 2° and 3°, whereas the rate of fall off in sensitivity was not meaningful before 5° to 6° eccentricity. Thus, although the changes in sensitivity may be somewhat related to the change in the transient-like function, the relationship is not simple and the two factors (α and β) need not be closely linked. An alternative is that more than one mechanism has been altered, each following a different spatial course. In this particular case, the data suggest that the transient-like function was a more sensitive measure of this form of retinal involvement than static perimetry. That is, proportionately, its magnitude was far more substantially affected than that of static sensitivity over the range of eccentricities considered. The argument is further supported by the clear lack of sensitivity changes in the area of the isolated microaneurysm.

CFF. As described in Methods and procedure, CFF was measured at eight retinal locations. The data obtained at 4° eccentricity are shown in Fig. 13, A, and the data from 7° eccentricity are in Fig. 13, B.

At 4° eccentricity a Goldmann IV target was used (51.72 min arc diameter), whereas at 7° eccentricity a Goldmann V target was used (102.40 min arc diameter). It is well established that increasing retinal eccentricity increases the diameter of the minimum and asymptotic diameters of the sustained-like function. In turn, these dimensions apparently define the areal bound of interaction for the transient-like function. The two different size fields were used here to compensate for the change in asymptotic diameter of field II. Note, this contributed to the CFF being higher for the 7° eccentric target than the 4° eccentric target.
Transient-like function and capillary anomalies

Fig. 12. A, Log magnitude of the transient-like function as a function of retinal eccentricity. Data from test point 1 (Figs. 2, 3, and 5) are indicated. C, Log magnitude of the transient-like function measured on the 45° half-meridian minus the log magnitude of the transient-like function measured on the 135° half-meridian. This difference is \( \alpha \). B, Static perimetric sensitivities measured on the perimeter. D, Differences in sensitivity between the 45° half-meridian and the 135° half-meridian sensitivities (\( \beta \)).

The flicker thresholds measured at the two eccentricities along the 135° half-meridian were not distinguishable from the thresholds measured along any of the other half-meridians. Thus there was no orderly relationship found between the CFF thresholds and the alterations in the amplitude of the transient-like function. Many replications of these tests were conducted. Note that the optimum rate of 8 on and off transitions per second, used when testing this transient-like function, differed from the measured CFF frequencies (30 to 50 Hz).

Discussion

This data set is consistent with findings previously described in that class of early diabetic retinopathy patients exhibiting modest microvascular changes in the retina. To date, among roughly 50 patients studied in some depth, no case has been found which essentially deviates from the working hypotheses defined in the Introduction. It should be emphasized that microvascular anomalies per se are not unique to diabetic retinopathy nor are the alterations in function reported here. Three things make this patient special. (1) He has a relatively large area in his retina with uniform loss of the transient-like function only. (2) His functional alterations in both that area and in the area of the single aneurysm are remarkably stable in time, which allows comparisons to be made with other functions. (3) He is now a highly trained and reliable observer and is readily available to the investigators.

At the meetings of the International Perimetric Society in Tokyo in 1978, the request was made by many speakers that the relative sensitivity/effectiveness of the several new available test methods be compared. This is one such effort.

The fluorescein angiogram of the right eye of this juvenile diabetes patient revealed a relatively circumscribed retinal area containing an anomalous capillary bed plus rare scat-
tered microaneurysms. This retinal area is shown to be at least approximately congruent with an area that gave evidence of little or no transient-like response (as defined herein).

Within this area several visual functions were measured and compared to each other and to responses measured in still normal areas of the visual field. The functions systematically tested and which proved to be normal at all points evaluated are the sustained-like function and CFF. Careful measures of sensitivity showed alterations within the anomalous vascular field, but their progression or rate of change did not closely match that of the reduced transient-like function (Fig. 12). The reduced sensitivity was also apparent in measures of kinetic visual field. Correlations with kinetic perimetry were difficult to make in such circumscribed areas with such modest loss in sensitivity.

Fig. 13. CFF (in Hz) plotted as a function of half-meridian. Data points are average ±1 S.D. 1. Measures made at point 1.

Careful measures of the alterations in the transient-like function and the distribution of static sensitivities showed that they may not be closely related; that is, the distribution of anomalous sensitivity is different from that of anomalous transient-like functions. In this case, these data indicate that the transient-like function is a sensitive measure of retinal involvement; there were areas of normal or near normal sensitivity with markedly reduced transient-like function.

The rate of change of the transient-like function associated with the retinal distribu-
tion of the vascular anomaly is more rapid than the rate of change in sensitivity. Although the alterations in sensitivity and the alteration in the transient-like function are both related to the vascular anomaly, there is not a simple relationship between the transient-like function and sensitivity per se. In addition, the two may have separate loci of effect.

As mentioned above, there were a few scattered microaneurysms in this retina. An isolated microaneurysm can be identified in the fluorescein angiogram near the area marked with the number 4 in Fig. 3. The kinetic visual fields, static perimetric measures of sensitivity, and the sustained-like functions measured near this retinal location are normal. However, the middle row of Fig. 8 shows that in the neighborhood of this microaneurysm the amplitude of the transient-like function is reduced. Not only is the amplitude of the transient-like function altered here without effect on the other measured visual functions, including sensitivity, but also the visual effect exceeds the anatomically defined locus of the microaneurysm. Similar observations have been reported relative to alterations in the sustained-like function; major changes in the sustained-like function have been reported in patients with early diabetic retinopathy exhibiting hard yellow exudates.

The present data have been collected in conjunction with ongoing projects to study psychophysically visual anomalies as well as to develop psychophysical procedures that promise clinical usefulness. Two such procedures that we have been studying in depth we have called a sustained-like function and a transient-like function. The names were chosen to emphasize the procedures followed to generate these psychophysical functions and are operationally defined. The use of these names is not meant to relate these (sustained-like and transient-like) psychophysical paradigms to other psychophysical phenomena currently being analyzed in other laboratories where similar terminology has evolved (e.g. refs. 18 and 19). It is not yet possible to draw the desired close parallels between classification systems.

For example, attention is drawn to the CFF data presented in Fig. 13. There were essentially no differences found in CFF thresholds measured in the normal portion of the visual field and in areas of field that evidenced extinguished transient-like functions (as defined herein). Time-varying stimuli were used in both experiments. Clearly, the two different paradigms measure different visual functions and therefore, by inference, have apparently different primary sites of action. In other forms of pathology a degree of linkage may be found.

The apparent independence between the transient-like function and the other psychophysical functions measured in this report suggests that the transient-like function reflects a unitary system, just as the sustained-like function does in other instances. Simply, specific retinal pathology alters one or the other of these responses.

The paradigm that yields the transient-like function yields a rather complicated group of perceptual phenomena summarized by Enoch et al. Among these phenomena are motion aftereffects, momentary disappearance of part or parts of the rotating windmill vanes, etc. Also reported is the difference between the threshold of the test flash based upon a "flashing" response criteria and a "brightness" threshold. Attempts to establish
electrophysiological correlates to the transient-like function herein described should differentiate correlates of this measured function from correlates of other, and for our current purposes, secondary perceptual phenomena. The relationships between the transient-like function and other transient phenomena defined either psychophysically or electrophysiologically is far from clear at this point and must await further study.

It is apparent that the transient-like function is a reliable, sensitive, localized response and is of great value in visual analysis and diagnosis.

Summary and conclusions

1. A juvenile diabetes patient with early diabetic retinopathic vascular changes was studied intensively. Consistent with studies of some others with early retinal vascular diabetic changes, alterations in his transient-like function were noted.

2. In the area of the microaneurysm the decrease in the transient-like function far exceeded the bounds of the anatomical anomaly. No other measured function was altered in this portion of the visual field.

3. Throughout the anomalous capillary bed the transient-like function was markedly reduced, with normal sustained-like functions recorded at all test points. There is an unequivocal relationship between the loci of measured anomalous visual functions and these retinal anatomical anomalies.

4. These data provide further evidence for a functional independence between the sustained-like and transient-like functions at the retinal level, either one of which may be altered by pathology and recover independently of the other. This observed independence is taken to define separate channels, particularly since a variety of different pathologies alter response in a comparable manner.

5. Normal or near normal sensitivity, normal sustained-like functions, and normal CFF thresholds were measured at loci where the transient-like function was markedly reduced. These findings suggest that there is only a limited relationship between the transient-like function and these other visual functions.

6. Although a decrease in visual sensitivity was found to approximate the spatial distribution of the tortuous capillary bed, its bound was better defined by the transient-like function.

7. In this patient the reduction or alteration in the transient-like function was a more sensitive index of retinal anomaly than any of the other psychophysical tests sampled.

8. The patient had no presenting symptoms, that is, this well-trained psychophysical observer has no subjective appreciation of any altered visual capability either in the area of the microaneurysm or in the area associated with the irregular retinal vasculature.

9. One must use care in generalizing from one form of time-varying stimulus to other time-varying stimulus conditions and in too closely linking psychophysical paradigms with single-unit electrophysiological experiments.

10. This set of tests holds great promise for the early noninvasive differential diagnosis of diabetic retinopathy and other retinally based anomalies.

Appendix

This brief Appendix complements the more lengthy study presented above. Included here are selected data obtained on a second patient (studied in comparable detail) exhibiting broad field areas of anomalous response to the specific transient-like function developed in this laboratory. In this case etiology is not nearly as well defined, yet the results are generally comparable.

A Caucasian male, now age 60, had well-documented but undefined vascular events, including venous occlusive anomalies apparently affecting his optic nerves and retina at ages 10 and 13, respectively. In recent years he has exhibited anomalous response to glucose tolerance tests, and this is associated to some degree with obesity. Blood chemistry, weight, etc., are now well controlled on a careful diet. His fields are nonsymmetrically constricted from the childhood events and, over a year of testing, show slight overall contraction. In areas showing an otherwise normal fundus, at all points tested in the OS (more than 10 points distributed in the central field) the tran-
sient-like function was abnormal, either reduced or effectively absent whereas at all these tested points the sustained-like function was normal. The magnitudes of sample transient-like data obtained at 2° intervals along the horizontal meridian are shown in Fig. 14, c. Sensitivity (Fig. 14, a, static perimetry) and CFF (Fig. 14, c) OS again show relatively poor correlations with the anomalous transient-like function data. In one set of determinations, there is a parallel in CFF reduction and transient-like function loss (Fig. 14, c and e, at 4° and 6° along the 180° half-meridian), but the change in CFF is only of the order of 2 to 4 Hz, which may not be detectable in routine clinical tests. Similarly, slight differences in sensitivity (0° and 180° half-meridians) are present, but these differences are modest.

Normal transient-like functions were obtained only at the point of fixation in the right eye (Fig. 14, f). Several points were tested in the right central field. The two points of fixation (left and right eyes) exhibit the same static (Fig. 14, b) or increment threshold and CFF (Fig. 14, d) but differ in transient-like function magnitude (Fig. 14, f).

Thus, again there seems to be only modest linkage between the particular response functions considered, and as in the case of patient L. B., the transient-like function was the more sensitive indicator.

The point is that the correlations herein described seem to have a degree of generality and are not linked narrowly to the particulars of the patient L. B. described above. That is, in the case of L. B., unique anatomical-psycho physical correlations can be made, whereas in this individual such close anatomical-psycho physical correlations are not possible. The important point is that what is unique in both patients may have origin in different insults causing a comparable functional result. By inference, those insults, affecting the same functions in the same way, have the same locus but not necessarily the same cause. Mueller’s law of specific nerve energies indicates that the response system can only respond in certain discrete ways regardless of the nature of the exciting process. This same principle is recognized to hold in descriptions of other functions and in pathology (e.g., see Cass).  

We express our profound gratitude to Observer L. B. who has spent endless hours in the development of this data base. Throughout (necessarily) he had little feedback as to that which was being analyzed. We can ask no more of anyone!

REFERENCES