Principles and Practice of Clinical Electrophysiology of Vision

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81

Diabetic Retinopathy

George H. Bresnick

Diabetic retinopathy is a disease of the retinal blood vessels that develops in the complex metabolic milieu of systemic diabetes mellitus. The primary pathophysiological process affecting[4] the retinal blood vessels in diabetes is probably a metabolic derangement that leads to vessel closure altered permeability. Retinal arterioles and capillaries close, and this leads to retinal ischemia and ultimately cell death. Secondary changes include retinal edema as well as fibrovascular proliferation, the latter thought to be due to ischemia. In this so-called proliferative phase there is the risk of developing visual loss from vitreous hemorrhage and tractional retinal complications. An important feature of the retinal vascular disease is its focal nature; at any given time, small areas of retina may be affected by retinal ischemia or edema, while adjacent areas may show no obvious signs of retinal vascular pathology. Retinal vascular disease typically occurs a number of years after the onset of diabetes and progresses at different rates in different individuals: some patients may maintain mild retinopathy or progress only slowly over many years, while others may deteriorate to severe changes rather rapidly. Because of these multiple factors, electrophysiological abnormalities are complex and often difficult to interpret.

To approach the interpretation of the electrophysiological measurements in a given diabetic patient intelligently, one must consider (1) the extent of retinal vessel closure and increased permeability, best determined by fluorescein angiography; (2) the severity of secondary lesions resulting from retinal ischemia and abnormal permeability (e.g., retinal hemorrhage, ischemic infarcts [cotton-wool spots], lipoprotein [hard] exudates, venous beading, and retinal neovascularization), best assessed by color fundus photographs; (3) the rapidity with which retinopathy is developing; and (4) systemic factors (e.g., hyperglycemia, electrolyte imbalance, acidosis), the effects of which on retinal electrophysiology may be difficult or impossible to predict.

The conventional electroretinogram (ERG) has been most used to study patients with diabetic retinopathy,[15, 22] but the pattern ERG (PERG), visual evoked cortical potential (VECP), and electro-oculogram (EOG) have also been evaluated. Abnormal ERG b-wave amplitudes were described only in eyes with fairly advanced retinopathy. In subsequent studies the oscillatory potentials (OPs) were found to be reduced in amplitude[37] and delayed in timing[39] at earlier stages of the disease. More recently, PERG abnormalities have been described in moderately severe diabetic retinopathy,[3] and VECP latency delays have been reported.[28]

The practical applications of electrophysiological testing in the management of diabetic retinopathy have not been widespread, although considerable investigative effort has been expended and theoretical interest engendered. To date investigations would suggest the following:

1. ERG abnormalities have been demonstrated before the onset of clinically visible vascular retinopathy; this suggests possible effects on the neurosen-

sory retina of the metabolic derangement caused by systemic diabetes.[5]

2. The extent of ERG abnormality increases with the severity of retinopathy (graded by fundus photographs and angiography).[1, 7, 9, 16]

3. Finally, the likelihood of progression from nonproliferative diabetic retinopathy (NPDR) to proliferative retinopathy (PDR)[6, 8, 33] or from mild proliferative to severe proliferative retinopathy is predicted by OP amplitude reduction independent of other predictive factors such as the duration of diabetes and capillary nonperfusion and leakage.[6, 8] The value of ERG testing in predicting progression along less severe levels of retinopathy has not yet been demonstrated.

ELECTRORETINOGRAPHY—OSCILLATORY POTENTIALS

Oscillatory Potential Amplitudes and Retinopathy Severity

Abnormalities of the ERG OPs appear to be the most sensitive indicator of early retinal dysfunction in diabetes. The OPs are higher-frequency oscillations (100 to 160 Hz) superimposed on the ascending limb of the slower b-wave and originate in the middle and possibly inner layers of the retina (Fig 81–1). The wavelets are believed to arise from inhibitory feedback circuits from amacrine to bipolar cells or from ganglion cells to amacrine cells, although an origin within the bipolar cells themselves has been postulated.[18, 34, 35] The OPs are probably of both cone and rod system origin[23, 27] and appear to arise independently of the b-wave. The clinical method used most frequently to elicit the OPs in studying diabetes has been to use a conditioning flash followed in 15 to 30 seconds by a second flash and to record the responses from the second flash.[2, 6, 31] It is thought that this "conditioning flash" technique, usually employing a bright flash (photographic strobe light) stimulus, enhances the OP amplitudes by adapting rods and thus favoring cones; with only a single flash the rod and cone responses tend to partially cancel each other because of phase differences in the responses driven by the two photoreceptor types.[27]

The amplitude of the OPs in studies of diabetes has usually been expressed as the sum of the individual wavelets (OP sum), although some authors claim that individual wavelets arise at different depths within the retina and that selective involvement of one or another wavelet may be a more sensitive indicator to detect disease and may help localize the site of pathology within the retina.[13, 24] The OP sum decreases as a function of retinopathy severity, with the most profound and consistent reduction occurring in proliferative retinopathy. The OP sum reduction is usually more profound when new vessels are present on the optic disc (NVD) and less so when new vessels are present elsewhere (NVE) only[7] (Fig 81–2). The Diabetic Retinopathy Study (DRS) showed conclusively that eyes with NVD occupying an area equal to or greater than one third of the disc area carry a poor prognosis for vision if the eye is not treated with panretinal photocoagulation.[14] The presence of vitreous or preretinal hemorrhage increases the risk of severe visual loss, whereas NVE without vitreous hemorrhage is associated with a relatively lower risk. For this reason, eyes with NVD (with or without vitreous hemorrhage) and eyes with NVE with vitreous hemor-

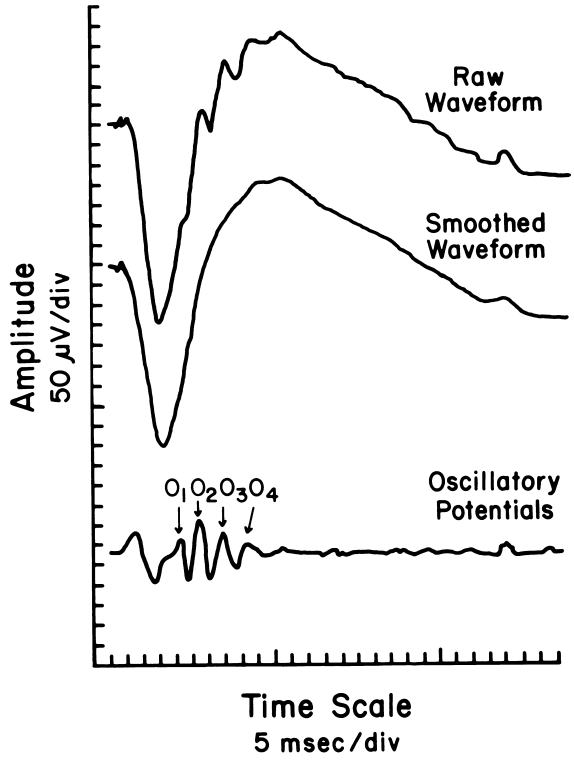

FIG 81–1.
Digital subtraction of a digitally smoothed waveform *(center tracing)* from a raw waveform *(top tracing)* to yield a waveform with faster potentials *(bottom tracing).* Data are from a nondiabetic control subject aged 34 years. The stimulus was a bright flash unit attentuated with a 2.0-log-unit neutral-density filter. O_1 indicates the first oscillatory potential; O_2, the second oscillatory potential; O_3, the third oscillatory potential; and O_4, the fourth oscillatory potential. (From Bresnick GH, Palta M: *Arch Ophthalmol* 1987; 105:660–664. Used by permission.)

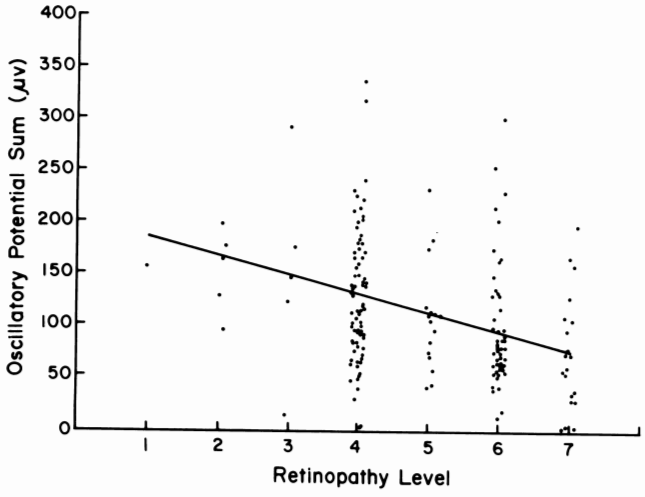

FIG 81–2.
Scatterplot of the summed amplitude of OPs as a function of retinopathy severity graded in color fundus photographs. The fitted regression line is shown as a *solid line.* (From Bresnick GH, Palta M: *Arch Ophthalmol* 1987; 105:929–933. Used by permission.)

rhage have been designated by the DRS as having high-risk characteristics (DRS-HRC), and prompt panretinal photocoagulation is almost always recommended.[14] It is thus of practical import that OP amplitudes are more severely and consistently reduced in eyes with DRS-HRC than in eyes with NPDR or PDR without DRS-HRC.[7] The finding of more severe reduction of OP amplitudes in eyes with NVD thus points to a widespread retinal abnormality associated with new vessel growth in that location (see Figs 81–9 and 81–10). This concept is borne out by wide-angle fluorescein angiography studies of diabetic retinopathy that show that eyes with large areas of peripheral as well as posterior capillary nonperfusion are the ones most likely to develop NVD[30] (see Figs 81–9 and 81–10). Thus OP amplitudes can clinically be very useful to detect eyes that have widespread retinal ischemia but in which angiography is difficult (see Fig 81–11), and if the OP amplitude is well maintained, this suggests that any new vessels result from a more localized retinal ischemia than is true with NVD.[7]

This suggests, although it has not been proved, that eyes with NVE and a better preserved ERG might be treated with more localized laser photocoagulation (e.g., "scatter" laser treatment restricted to the quadrant or region with NVE) whereas eyes with NVE or NVD associated with more severe ERG abnormality require panretinal photocoagulation. In addition, an occasional patient with NVD may have a relatively well preserved ERG, thus suggesting mechanisms other than widespread retinal ischemia as a stimulus for new vessel growth on the optic disc (see Fig 81–12).

Oscillatory Potential Amplitudes as a Predictor of Retinopathy Progression

Not only are the OP amplitudes generally more reduced in eyes with PDR (especially DRS-HRC) than in eyes with NPDR, but OP amplitude reduction can also help predict which eyes with NPDR are at high risk to progress to PDR and DRS-HRC. In a study by Simenson,[32] the OP amplitudes were measured in a group of diabetic patients with NPDR, and the incidence of PDR over a 5- to 9-year follow-up period was determined. Among 129 eyes with normal OP amplitudes at the start of the study, only 5 developed PDR; in contrast, 38 of 51 eyes with reduced OP amplitudes developed PDR over the follow-up period.[32] Subsequent follow-up after 13 to 15 years showed persistent differences in PDR development between the two groups: with normal initial OPs, 30 of 149 (20%) developed PDR; with abnormal initial OPs, 36 of 58 (62%) developed PDR.[33]

In a study from our laboratory,[6, 8] the amplitude of the OPs predicted the progression of eyes with nonproliferative retinopathy or mild PDR to severe PDR. The end point chosen was the development of DRS-HRC. In our study, eyes entering with abnormal OPs amplitudes had a 28% rate of progression to DRS-HRC after 1 year and a 52% cumulative rate after 2 years; eyes with normal OP amplitudes had a

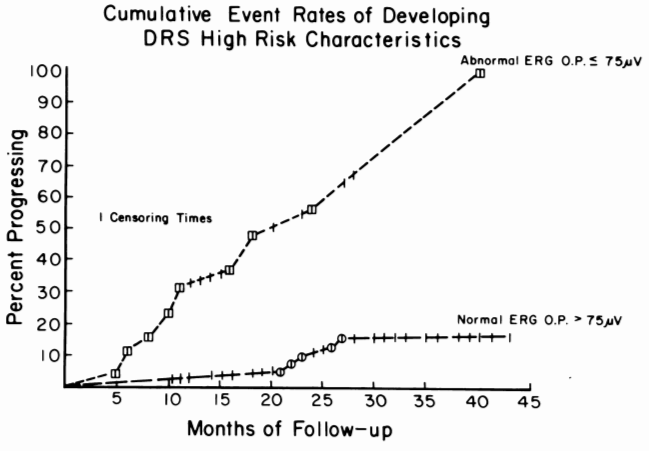

FIG 81–3.
Cumulative percentage of eyes progressing to DRS-HRC. Eyes with abnormal and normal OP amplitudes are compared. (From Bresnick GH, Korth K, Groo A, Palta M: *Arch Ophthalmol* 1984; 102:1307–1311. Used by permission.)

TABLE 81–1.

Probability of Progression to Diabetic Retinopathy Study High-Risk Characteristics*

Patient	Age (yr)	DRS-HRCs†	Months of Observation‡	Retinopathy Level§	Fluorescein Leakage	Summed Oscillatory Potential Amplitude (μV)	Risk Score¶
1	23	Yes	9	6	70	59	2.69
2	50	Yes	55	5	25	88	1.23
3	42	Yes	21	6	2	134	0.66
4	21	No	52	4	0	115	0.05
5	35	No	57	4	3	320	−1.20

*From Bresnick GH, Palta M: *Arch Ophthalmol* 1987; 105:810–814. Used by permission.
†DRS-HRCs = Diabetic Retinopathy Study high-risk characteristics.
‡Months of follow-up or months until DRS-HRCs developed.
§Retinopathy levels are summary gradings of fundus photographs ranging from no retinopathy (level 1) to nonproliferative retinopathy (levels 2 to 5) to proliferative retinopathy (levels 6 and 7).
¶Risk scores were computed from the Weibull regression equation (see the text), with increasing risk for increasing positive value.

cumulative rate of 0% and 7% after 1 and 2 years, respectively (Fig 81–3). Although the level of retinopathy severity at study entry was an important factor in the rate of subsequent progression, the amplitudes of the OPs remained a significant risk factor even after correcting for the initial retinopathy level.

By using combined quantitative information regarding overall retinopathy severity (graded in color fundus photographs), the extent of fluorescein nonperfusion and leakage, and OP amplitudes, one can construct theoretical probability curves (derived from statistical regression equations) for the development of DRS-HRC[8] (Table 81–1 and Fig 81–4). While such data and the rather sophisticated statistical analyses used are not essential to routine patient management, they are useful for basing more rational decisions regarding frequency of follow-up and timing of the application of panretinal photocoagulation; the OP results provide a measure of overall retinal dysfunction that has predictive power regarding retinopathy progression (see Figs 81–7, 81–8, and 81–10).

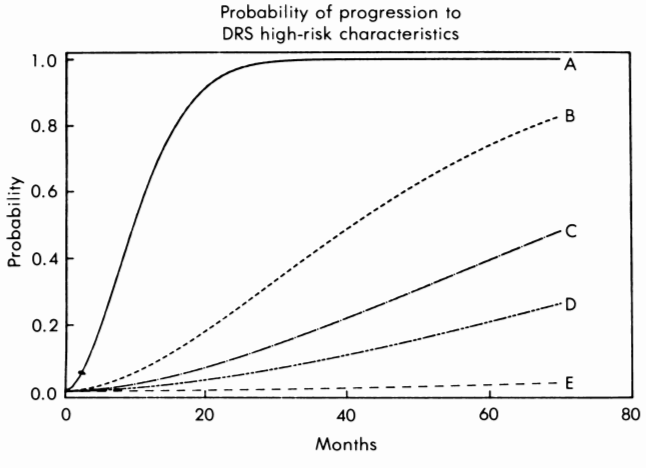

FIG 81–4.

Probability of progression to DRS-HRC for five patients chosen to represent the range from high risk to low risk of progression. Curves are theoretical and based on the Weibull regression model. (From Bresnick GH, Palta M: *Arch Ophthalmol* 1987; 105:810–814. Used by permission.)

CONVENTIONAL ELECTRORETINOGRAPHY IN DIABETIC RETINOPATHY

Aside from the OPs, the amplitude of the b-wave of the scotopic ERG as well as the implicit time of the response to a 30-Hz flickering light has received attention in diabetic retinopathy.

Scotopic b-Wave

In very late stages the ERG may be small or absent and corresponds to considerable retinal degeneration.[15, 22, 29]

The measurement of the voltage sensitivity function (Rushton-Naka relationship) has proved more fruitful. In CRVO, for example, log K has distinguished between ischemic and nonischemic types. Considerations such as those detailed in other sections suggest that elevated log K is more closely associated with retinal or disc neovascularization in diabetes and is a more sensitive indicator of early functional retinal abnormality than is a reduced

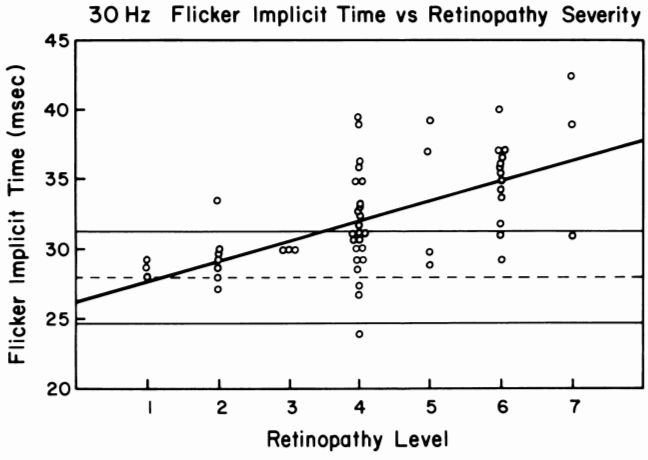

FIG 81–5.
Relation of flicker implicit time without background light to retinopathy severity. Retinopathy levels are summary gradings of fundus photographs ranging from no retinopathy (level 1) to nonproliferative retinopathy (levels 2 to 5) to proliferative retinopathy (levels 6 and 7). The *heavy solid line* is a regression line fit by the least-squares method. The *dashed line* is the mean value for flicker implicit times without background light along with 95% confidence limits *(solid lines)* for controls. (From Bresnick GH, Palta M: *Arch Ophthalmol* 1987; 105:660–664. Used by permission.)

R_{max}.[10] Preliminary studies show that the extent of log K elevation in diabetic retinopathy is not as great as that associated with "ischemic" central retinal vein occlusion (CRVO), and the predictive power of the analysis has not yet been demonstrated. In diabetic retinopathy it is more likely that different focal areas of retina go through a cycle of hypoxia and ischemic infarct at different times; the sum total effect on the electrophysiological function of the retina would be less than in a condition such as CRVO in which the entire retinal venous system is compromised at once.

Temporal Aspects of the Electroretinogram

Delays in the implicit time of the response to a 30-Hz flickering light correlate with the severity of diabetic retinopathy[9] from NPDR to PDR (Fig 81–5) and with the results of angiography in the absence of stimulus attenuation by media clouding or a reduction in pupillary aperture. This may be due to a reduction in retinal sensitivity, for in CRVO there is a strong correlation between log K elevation and delayed implicit times.[21] Delays in the timing of scotopic a-wave and b-wave in diabetic retinopathy[9, 15] are less closely correlated with retinopathy severity.[9]

In addition, the implicit time of the photopic b-wave recorded to a single flash is often prolonged in eyes with diabetic retinopathy (as is the scotopic response). Since both the 30-Hz flicker responses (Fig 81–6) and the photopic single-flash response are measures of cone function, these results indicate a reduction in cone system sensitivity in patients with diabetic retinopathy (in addition to the scotopic system involvement that classically has been described). The ability of timing delays in the ERG to predict progression of retinopathy has not yet been shown.

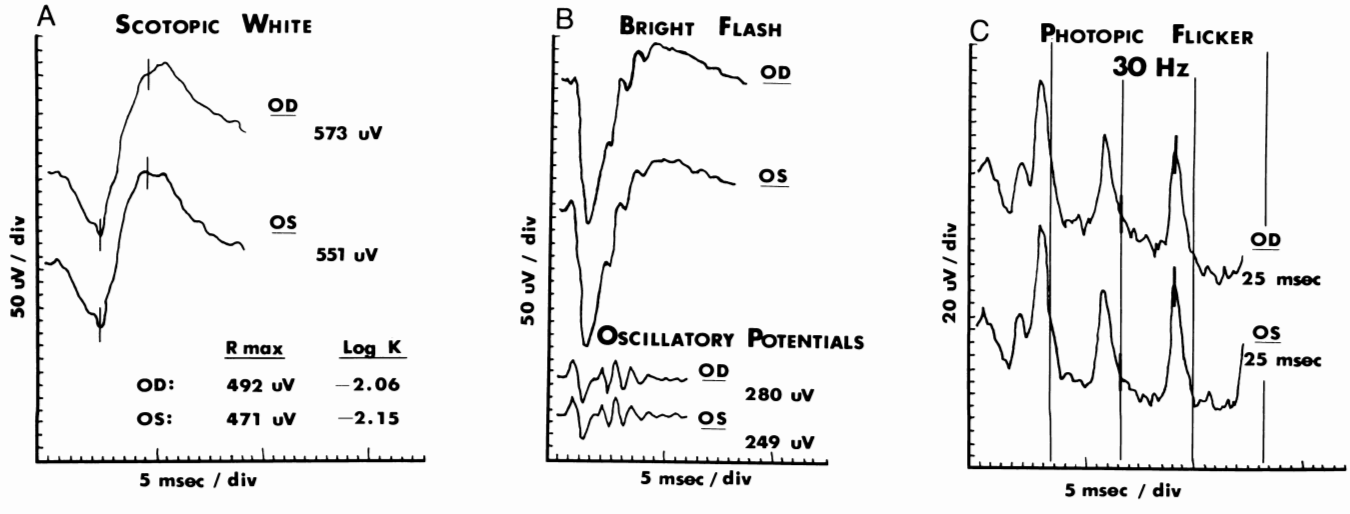

FIG 81–6.
ERG from a normal 31-year-old nondiabetic subject.

ELECTRORETINOGRAPHY TO DETECT EARLY FUNCTIONAL ABNORMALITY IN PATIENTS WITH DIABETES MELLITUS

The detection of early functional abnormalities in patients with diabetes mellitus could indicate that the basic condition is out of control, and electrophysiological measurement may provide a method for assessing the effects of different systemic treatments.[25, 26] From a theoretical point of view, if retinal electrophysiological abnormalities occur before any retinal vascular abnormalities, the abnormal systemic and/or local effects of diabetes must cause a neuropathy that is not just a disorder *secondary* to retinal vascular disease.[5] None of the published studies purporting to show electrophysiological or psychophysical abnormalities preceding retinal vascular ones have ruled out capillary nonperfusion and permeability abnormalities by fluorescein angiography and vitreous fluorophotometry or other hemodynamic abnormalities by a technique such as laser Doppler velocimetry. However, with no clinically detected vascular changes, OP timing delays or OP amplitude reductions have been documented as indicators of early retinopathy. Interestingly, other studies have claimed that some diabetic patients without retinopathy have *greater* than normal OP amplitudes, a so-called hyperresponsive state; these might reflect milder degrees of retinal hypoxia[31, 32] and are sometimes associated with OP timing delays. Simonsen believes that the hyperresponsive state indicates a low risk for subsequent new vessel development.[31] Another study examined the OPs as well as the PERG[12]: OP amplitudes were found to distinguish diabetic patients with no retinopathy from normal nondiabetic controls, while the PERG amplitude and the OP and PERG timing were unable to make this distinction.

However, although the magnitude of mean values in diabetic patients with no retinopathy may be slightly but statistically significantly changed from nondiabetic controls, many diabetic individuals will fall within the normal range. It remains to be determined whether those eyes with these rather subtle ERG abnormalities are more likely to develop clinically visible retinopathy than are those with normal ERGs. It is also difficult to compare results among different studies because the nature of patient selection is likely to affect the proportion of patients with abnormal ERG results (as is a variation in ERG techniques and measurements). Factors such as type of diabetes (insulin dependent vs. non–insulin dependent), history of the level of diabetes control, age of the patient, and duration of diabetes (as well as other possibly unrecognized factors) must be well matched or carefully considered if meaningful comparisons between studies are to be made.

AUTHOR'S ELECTRORETINOGRAPHIC PROTOCOL FOR DIABETIC RETINOPATHY

An ERG protocol to evaluate the degree of functional abnormality in diabetic retinopathy should include the following as a minimum: (1) OP amplitude (and timing), (2) 30-Hz flicker timing, and (3) scotopic b-wave amplitude (and timing).

The protocol used in our clinical laboratory for following patients with diabetic retinopathy is as follows:

1. Dark adapted b-wave amplitude (30-minute dark adaptation). An intensity-response series spanning relative log intensities from a 4.0-log-unit up to a 0.0-log-unit neutral-density filter in 0.2-log-unit steps is used to generate an intensity response curve based on the Naka-Rushton equation. The usefulness of the Naka-Rushton parameters (R_{max} log K, n) for clinical practice in diabetic retinopathy has not yet been shown.
2. OPs elicited by a bright flash stimulus (photographic strobe light).
3. Thirty-hertz flicker timing. We perform the 30-Hz flicker after 2 minutes of light adaptation, although a minimum 10-minute period of light adaptation is recommended in the International ERG Standard Protocol.[20] We also elicit a photopic single flash, although the value of amplitude and/or timing delays for the photopic single flash has not yet been demonstrated in diabetic retinopathy.

Patients with no retinopathy or mild NPDR are unlikely to have important ERG abnormalities. The significance of minor abnormalities in OP amplitude or timing for future progression of retinopathy has not been determined.

Patients with retinopathy severity ranging from moderate NPDR to mild PDR can benefit from ERG testing; a reduced OP amplitude is a significant risk factor for predicting progression to a more advanced proliferative stage (DRS-HRC).[6, 8]

Patients with PDR as severe as DRS-HRC can benefit from ERG testing prior to panretinal photocoagulation. Although it has not been proved, it seems reasonable that patients with very poor ERG responses might require more extensive panretinal photocoagulation than those with less abnormal

ERGs. Again, although not proved, patients with NVE alone (i.e., no NVD present) might be considered for more limited scatter photocoagulation (as opposed to full panretinal treatment) if a less abnormal ERG were present. On the other hand, eyes with severe NPDR or NVE alone and a very poor ERG are at high risk to develop DRS-HRC and should probably be considered for full panretinal treatment even in the absence of these high-risk characteristics (see Fig 81–10).

The value of ERG testing following panretinal photocoagulation is questionable since the treatment itself causes such a profound decrease in all ERG responses.

We generally recommend repeat ERG testing on an annual basis; if an eye has normal or near-normal OP amplitudes, then it is very unlikely to develop DRS-HRC within the 12-month period between ERG testing. If routine ophthalmoscopy and/or fundus photography in between annual ERG test visits suggests significant retinopathy progression, then repeat ERG testing earlier than 12 months might help determine the extent of deterioration in the retinal status.

There are very few studies in which changes in the ERG over time have been reported or related to future retinopathy progression.[11, 31] It would make sense that longitudinal evaluation of the ERG would be a more reliable predictor of retinopathy progression than a single ERG performed at only one point in time. This important clinical question has not yet been adequately addressed in reports in the literature.

VISUAL EVOKED CORTICAL POTENTIALS

Another measure of electrophysiological dysfunction of the visual system tested in diabetes is the VECP. Delays in the latencies of the major components of the VECPs that are elicited in response to a checkerboard pattern-reversal stimulus have been observed in some diabetic patients without retinopathy or visual complaints.[28] Although one would expect some prolonged VECP latencies simply on the basis of the already described intraretinal delays, the VECPs may also denote conduction abnormalities in the optic nerve or more centrally in the visual system.

ELECTRO-OCULOGRAPHY

The EOG is a measure of the standing potential of the eye. It is expressed as the ratio of the highest potential in the light to the lowest potential in the dark (the light peak/dark trough ratio of Arden). A normal EOG ratio requires the normal participation of both the retinal pigment epithelium (RPE) and the photoreceptors (outermost retinal layers). Abnormal ratios have been described in diabetic patients, even in the absence of ophthalmoscopically visible retinopathy.[17] More recent EOG studies suggest that the RPE itself is electrophysiologically abnormal in diabetes.[38] This encourages us to look more closely at experimental evidence and clinical pathological evidence that the choriocapillaris-RPE-photoreceptor complex may be abnormal in diabetes.[19]

CASE EXAMPLES

The following seven case examples demonstrate a number of the features of ERG abnormality in eyes with diabetic retinopathy along with illustrations of how the ERG can be practically applied in managing the retinal complications in patients with diabetes mellitus.

Reference Nondiabetic

For reference purposes to the ERG results in the diabetic patients, a normal ERG in a 31-year-old nondiabetic volunteer is presented first (see Fig 81–6).

Nondiabetic ERG Values

Eye R_{max} (μV) (Normal, >303)*	log K (Normal, <−1.63)*	OP sum (μV) (Normal, >113)*	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)*
OD 492	−2.06	280	25
OS 471	−2.15	249	25

*The normal listed in this and subsequent ERG data tables represent the limit of normal for our laboratory expressed as the mean ± 2 SD from the mean.

CASE 1

Moderate NPDR with ERG changes indicating a need for close follow-up is indicated in this 36-year-old woman who has had insulin-dependent diabetes for 24 years.

February 1988
Fundi (OU)

- Moderate NPDR (Fig 81–7,A)
- Scattered microaneurysms and few retinal hemorrhages
- One cotton-wool spot

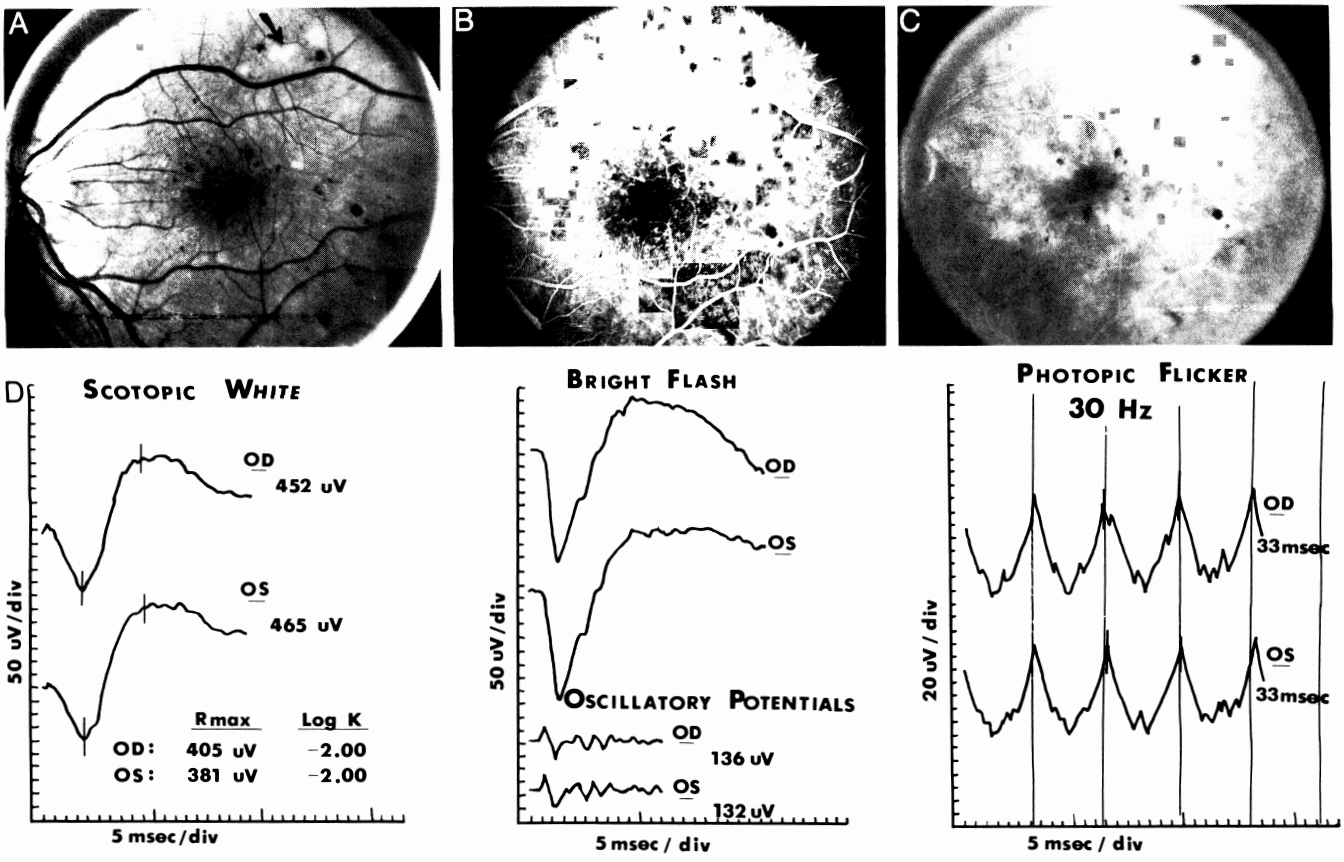

FIG 81–7.
Case 1: 36-year-old woman who has had insulin-dependent diabetes for 24 years. **A,** fundus photograph, left eye, February 1988. *Moderate NPDR* with several retinal hemorrhages and one cotton-wool spot *(arrow)* above the superior temporal vein is present. **B,** fluorescein angiogram, left eye (early arteriovenous phase), February 1988. Numerous microaneurysms are present as well as small areas of capillary nonperfusion corresponding to the zone of the cotton-wool spot (see **A**). **C,** fluorescein angiogram, left eye (late phase), February 1988, late intraretinal leakage throughout the posterior pole. **D,** ERG, both eyes, February 1988.

Fluorescein Angiogram (OU)

- Numerous microaneurysms (Fig 81–7,B and C)
- Mild capillary nonperfusion
- Moderate intraretinal leakage

Case 1 ERG Values

Eye R_{max} (μV) (Normal, >303)	log K (Normal, <−1.63)	OP Sum (μV) (Normal, >113)	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)
OD 405	−2.00	136†	33*
OS 381	−2.00	132†	33*

*Abnormal values (Fig 81–7,D)
†Borderline values.

January 1989

Over the next year both eyes developed more severe NPDR, and the left eye developed NVE in the inferonasal quadrant.

Summary

Reduced ERG OPs and delayed 30-Hz flicker timing alerted to the need for closer follow-up in a patient presenting with moderate NPDR and progressing to more severe NPDR and early NVE over a 1-year period.

CASE 2

Moderately severe NPDR with ERG changes indicating a high risk for developing proliferative retinopathy is depicted in this 64-year-old woman who has had insulin-dependent diabetes for 25 years.

December 1986
Fundi (OU)

- Moderately severe NPDR (Fig 81–8,A and B)
- Moderate retinal hemorrhages

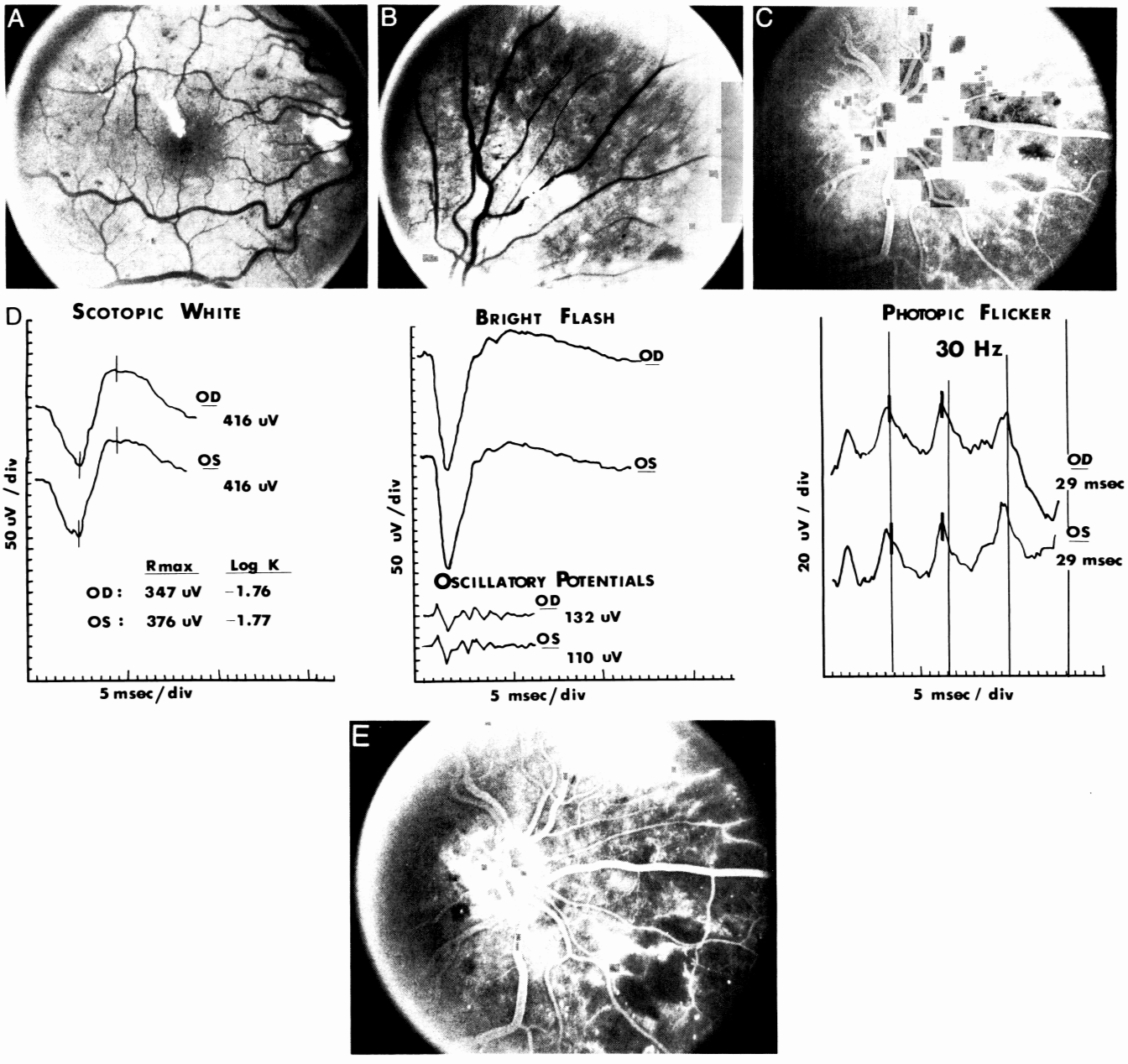

FIG 81–8.

Case 2: 64-year-old woman who has had insulin-dependent diabetes for 25 years. **A,** fundus photograph, right eye, December 1986. Moderately severe NPDR with scattered retinal hemorrhages and hard exudates is present. **B,** fundus photograph, right eye, December 1986 (superior nasal quadrant). Cotton-wool spots, a sheathed retinal vein, and irregularly dilated veins can be seen. **C,** fluorescein angiogram, right eye, December 1986 (nasal to the disc). Multiple areas of capillary nonperfusion are apparent, some surrounded by microaneurysms. **D,** ERG, both eyes, December 1986. **E,** fluorescein angiogram, right eye, November 1988. Capillary nonperfusion is more extensive, and there is leakage from NVE in the upper part of the photograph (compare with **C**).

- Hard exudate formation
- Cotton-wool spots
- Dilated, beaded veins

Fluorescein Angiogram (OU)

- Severe capillary nonperfusion (Fig 81–8,C)
- Severe leakage

Case 2 ERG Values

Eye R_{max} (μV) (Normal, >303)	log K (Normal, <−1.63)	OP Sum (μV) (Normal, >113)	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)
OD 347	−1.76	132†	29*
OS 376	−1.77	110*	29*

*Abnormal values (Fig 81–8,D).
†Borderline values.

November 1988

Over the next 2½ years, both eyes developed NVE.

Fundi (OU)

- Retinal hemorrhages, cotton-wool spots, venous beading worse
- New vessels (NVE) in the superior nasal quadrants

Fluorescein Angiogram (OU)

- Increased capillary nonperfusion (Fig 81–8,E)
- New vessel leakage in the superior nasal quadrants

April 1989

Six months later the left eye developed NVD. Panretinal photocoagulation was performed in the left eye, with regression of new vessels.

Summary

Severely reduced ERG OPs and delayed 30-Hz flicker timing along with severe fluorescein angiographic nonperfusion and leakage indicated a high risk for developing PDR. New vessels elsewhere developed in both eyes within 2 years and NVD in the left eye in 2½ years.

CASE 3

Proliferative diabetic retinopathy with NVD, vitreous hemorrhage (DRS-HRC), and severe ERG abnormalities is exemplified by this 35-year-old woman who has had insulin-dependent diabetes for 23 years.

February 1988

Fundi (OU)

- PDR (DRS-HRC) with vitreous hemorrhage (Fig 81–9,A)
- NVD
- NVE in multiple quadrants

Fluorescein Angiogram (OU)

- New vessel leakage (Fig 81–9,B and C)
- Severe midperipheral capillary nonperfusion
- Severe intraretinal leakage

Case 3 ERG Values

Eye R_{max} (μV) (Normal, >303)	log K (Normal, <−1.63)	OP Sum (μV) (Normal, >113)	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)
OD 269*	−2.09	61*	34*
OS 233*	−2.34	52*	34*

*Abnormal values (Fig 81–9,D).

The patient underwent panretinal photocoagulation in both eyes and showed good regression of new vessels and later clearing of the vitreous hemorrhage.

Summary

Severely reduced OPs, very delayed flicker, and reduced scotopic b-wave (reduced R_{max}) are present in this patient with severe PDR (DRS-HRC) and severe midperipheral nonperfusion. The reduced R_{max} is consistent with midperipheral retina infarction secondary to retinal ischemia. The normal log K values imply normal sensitivity of the remaining functional retina; however, the prolonged 30-Hz flicker implicit times suggest reduced retinal sensitivity.

CASE 4

Asymmetrical diabetic retinopathy (PDR, one eye; NPDR, fellow eye) with ERG changes indicating a high risk for developing proliferative retinopathy in the fellow eye is present in this 66-year-old man who has had insulin-dependent diabetes for 12 years.

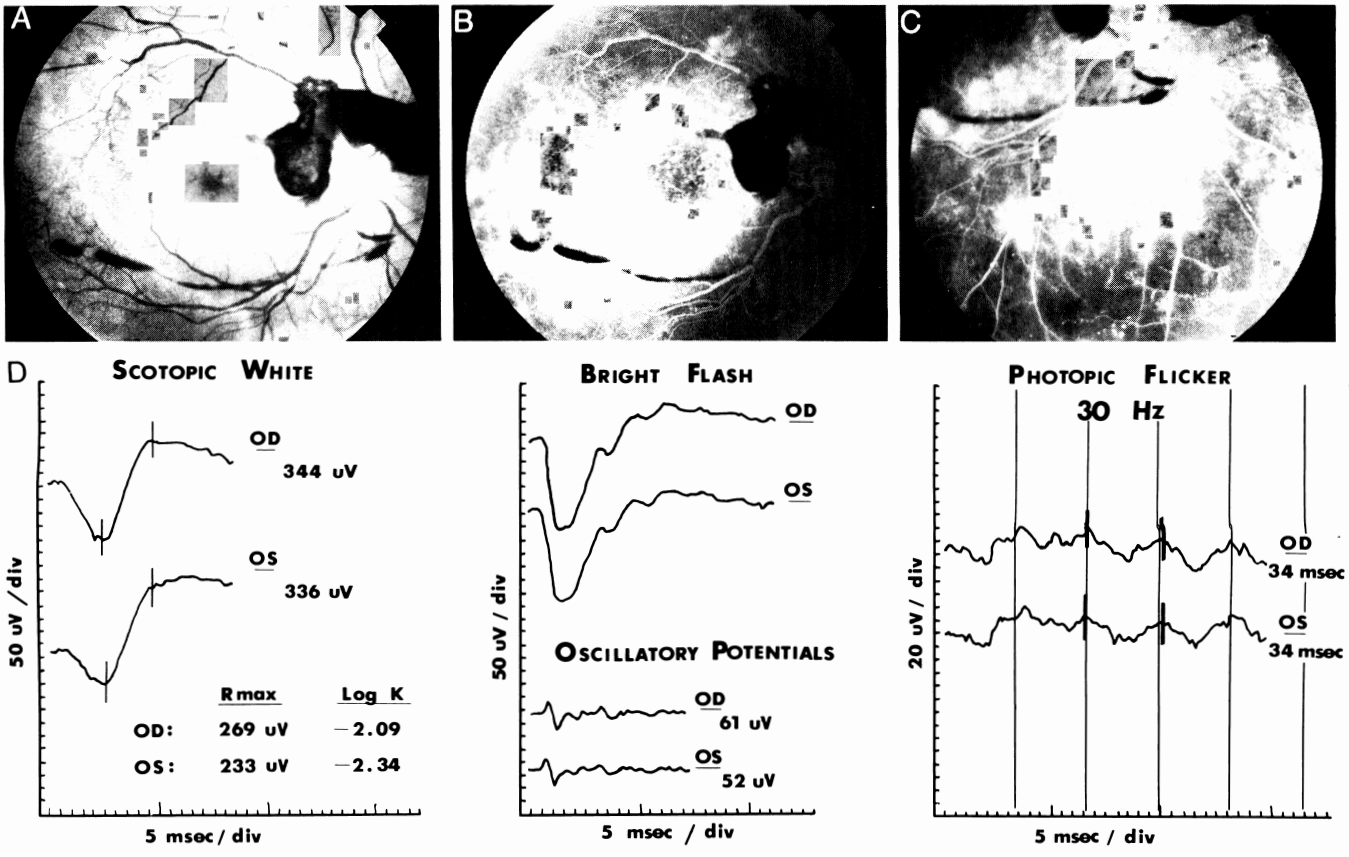

FIG 81–9.

Case 3: 35-year-old woman who has had insulin-dependent diabetes for 23 years. **A,** fundus photograph, right eye, February 1988. Severe PDR with new vessels is present in the far temporal portion of this wide-angle (50 degrees) photograph. Preretinal hemorrhage is seen around the optic disc and layered along the inferior temporal vascular arcade. **B,** fluorescein angiogram, right eye (arteriovenous phase), February 1988. There is leakage from new vessels temporally and above the disc (wide-angle [50 degrees] angiogram). **C,** fluorescein angiogram (late phase, below the disc), February 1988. Severe capillary nonperfusion is present in the midperiphery, with new vessel leakage at the border between perfused and nonperfused retina. **D,** ERG, both eyes, February 1988.

January 1986

Fundi

OD (Fig 81–10,A)

- PDR with NVD and vitreous hemorrhage (DRS-HRC)

OS (Fig 81–10,B and C)

- Moderately severe NPDR
- Moderately severe retinal hemorrhages
- Hard exudates
- Dilated veins

Fluorescein Angiogram.—Adequate-quality angiography could not be obtained because of nuclear sclerotic lens changes, OS > OD.

Case 4 ERG Values

Eye R_{max} (μV) (Normal, >303)	log K (Normal, <−1.63)	OP Sum (μV) (Normal, >113)	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)
OD 296*	−1.69†	56*	32*
OS 364	−1.59*	83*	32*

*Abnormal values (Fig 81–10,D).
†Borderline values.

Prompt panretinal photocoagulation was performed in the right eye; the left eye was followed without treatment.

July 1987

After an 18-month period, the left eye also developed NVD as well as rubeosis iridis involving the angle (8 months following extracapsular cataract

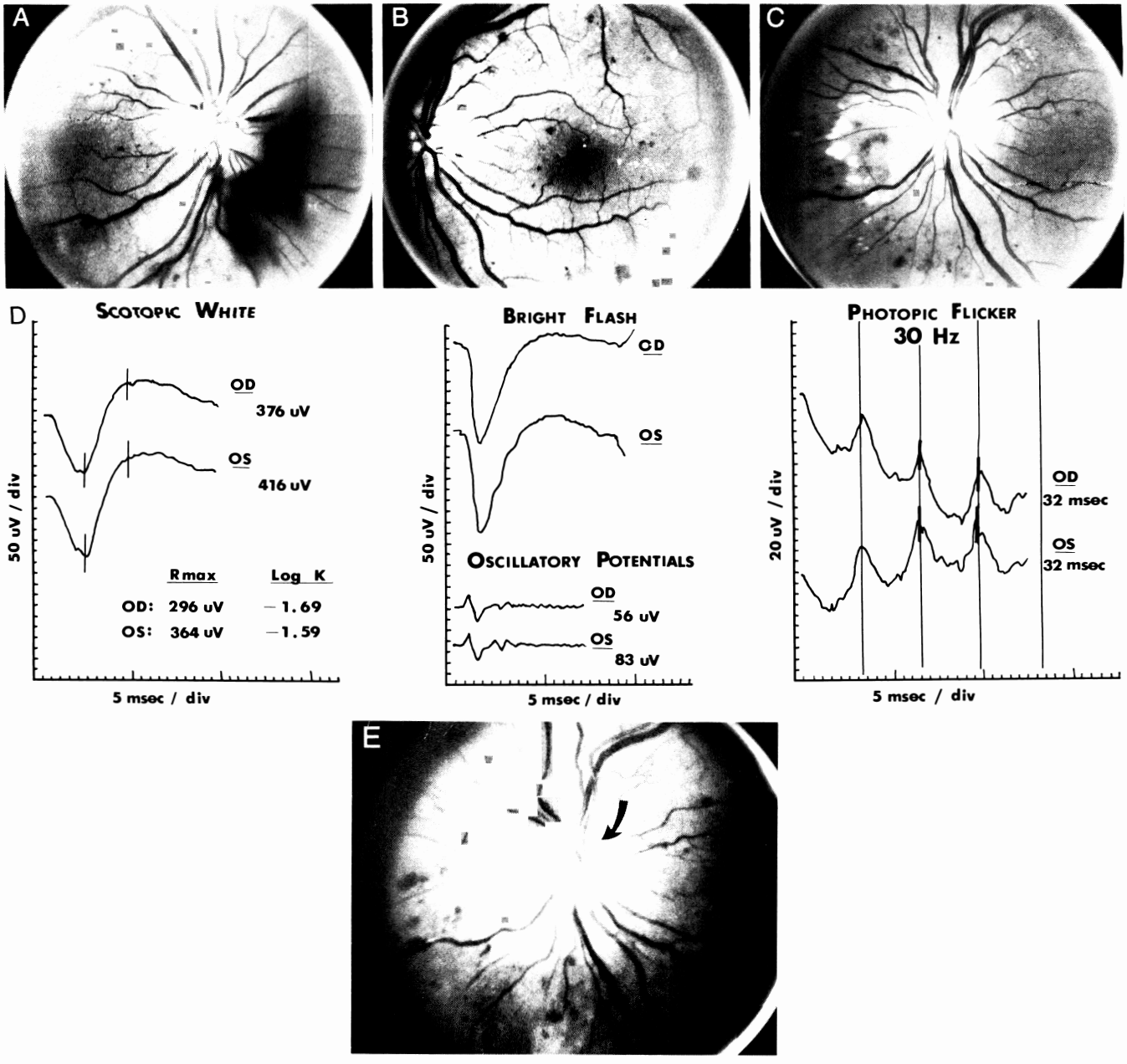

FIG 81–10.

Case 4: 66-year-old man who has had insulin-dependent diabetes for 12 years. **A,** fundus photograph, right eye, January 1986. PDR with NVD and vitreous hemorrhage (DRS-HRC) is present. **B,** fundus photograph, left eye, January 1986. Moderately severe NPDR with retinal hemorrhages, microaneurysms, and some hard exudates can be seen. **C,** fundus photograph, left eye, January 1986. Hemorrhages and exudates are present nasal to the disc; no NVD is present. **D,** ERG, both eyes, January 1986. **E,** fundus photograph, left eye, July 1987. New vessels are now present on the superior temporal aspect of the disc *(arrow).* Note the beading and dilation of the inferior temporal vein (compare with **C**).

surgery and posterior chamber lens implantation). Panretinal photocoagulation was performed with resultant partial regression of the NVD and full regression of the rubeosis. The intraocular pressure remained normal throughout the period of observation.

Fundus (OS)

- NVD (Fig 81–10,E)
- Ischemic retinal swelling nasal to the disc

Summary

Severely reduced ERG OPs, delayed flicker timing, and reduced retinal sensitivity (elevated log K) in both eyes, with PDR in the right eye only, indicated a high risk for PDR in the fellow left eye. A strong argument could be made for earlier panretinal photocoagulation of the fellow eye, which did, in fact, develop PDR and rubeosis iridis within an 18-month period. The response to subsequent panretinal photocoagulation was satisfactory. (The cataract surgery probably contributed to the development of rubeosis iridis in this eye with ischemic retinal changes.)

CASE 5

Proliferative retinopathy with new vessels and capillary nonperfusion located preferentially in the midperiphery was present in this 49-year-old man who has had insulin-dependent diabetes for 22 years; ERG abnormalities alerted the clinician to the need for careful midperipheral fundus examination and angiography.

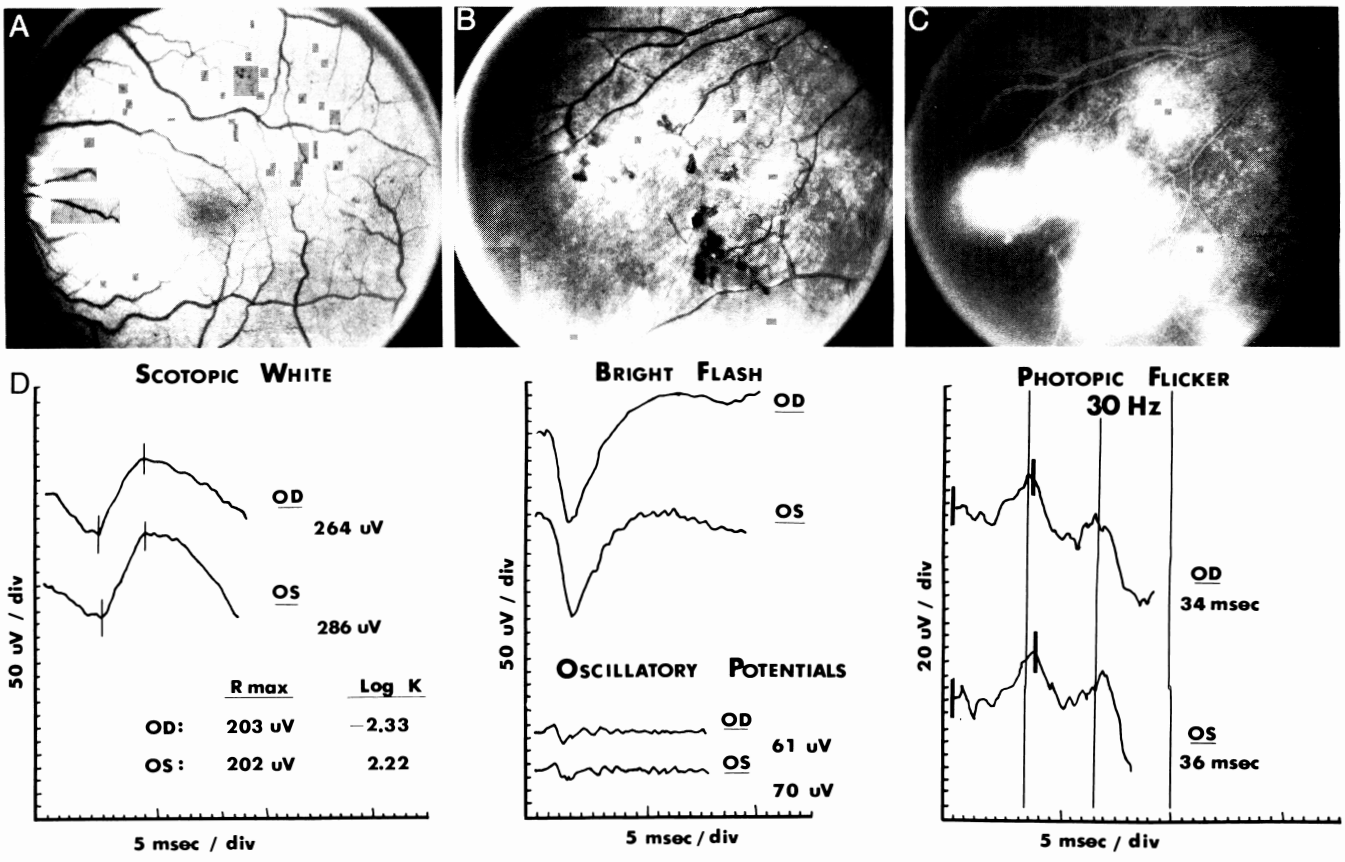

FIG 81–11.

Case 5: 49-year-old man who has had diabetes for 22 years. **A,** fundus photograph, left eye, April 1987. Relatively mild intraretinal changes are present that consist of a few microaneurysms and retinal hemorrhages. **B,** fundus photograph, left eye (inferonasal midperiphery), April 1987. Numerous midperipheral new vessels with dilated tips are present. **C,** fluorescein angiogram, left eye (inferonasal midperiphery), April 1987. There is severe capillary midperipheral nonperfusion (left portion of the photograph) with new vessel leakage at the border between perfused and nonperfused retina. **D,** ERG, both eyes, April 1987.

April 1987
Fundi (OU)

- Midperipheral retinal hemorrhages
- Midperipheral new vessels (Fig 81–11,B)
- Mild retinal abnormalities in the posterior fundus (Fig 81–11,A)

Fluorescein Angiogram (OU)

- Midperipheral new vessels (Fig 81–11,C)
- Midperipheral capillary nonperfusion

Case 5 ERG Values

Eye R_{max} (μV) (Normal, >303)	log K (Normal, <−1.63)	OP Sum (μV) (Normal, >113)	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)
OD 203*	−2.33	61*	34*
OS 202*	−2.22*	70*	36*

*Abnormal values (Fig 81–11,D).

Summary

Reduced ERG OPs and delayed 30-Hz flicker implicit times pointed to midperipheral capillary nonperfusion and proliferative retinopathy in a patient with relatively mild posterior fundus abnormalities. Panretinal photocoagulation was performed in both eyes, with good regression of midperipheral new vessels.

CASE 6

Optic disc swelling with new vessels on the optic discs (NVD) in both eyes was present in this 26-year-old man who has had insulin-dependent diabetes for 23 years; a relatively healthy ERG suggests that the stimulus for NVD was not widespread retinal ischemia.

April 1986
Fundi (OU)

- Disc swelling (OS > OD) (Fig 81–12,A)
- NVD

Case 6 ERG Values

Eye R_{max} (μV) (Normal, >303)	log K (Normal, <−1.63)	OP Sum (μV) (Normal, >113)	30-Hz Flicker Implicit Time (ms) (Normal, ≤28)
OD 747	−1.67†	347	29*
OS 699	−1.83	351	28†

*Abnormal values (Fig 81–12,B).
†Borderline values.

Relatively normal or hypernormal ERG values suggest that widespread retinal ischemia was not present. (Fluorescein angiography was not performed.)

September 1986

Both eyes received panretinal photocoagulation, and the NVD only partially regressed.

Fundi (OU)

- Disc swelling persists (Fig 81–12,C)
- NVD persists

Over the next 2 years, NVD and disc swelling showed only partial regression after additional panretinal photocoagulation treatment.

Summary

Bilateral disc swelling and NVD that are partially responsive to panretinal photocoagulation, in the presence of a nearly normal ERG, suggest that the NVD may have grown more in response to local disc changes than to widespread retinal ischemia.

CASE 7

Severely ischemic retinopathy with so-called involutional diabetic retinopathy and fundus and ERG abnormalities resembling advanced retinal dystrophy[29] are exemplified in a 27-year-old man who has had insulin-dependent diabetes for 23 years. He complained of poor night vision and decreased peripheral vision for 3 years. No family history of retinal dystrophy was given.

February 1987
Fundi (OU)

- Pale optic discs (Fig 81–13,A)
- Narrow sclerotic retinal vessels
- Few retinal hemorrhages
- No new vessels

Fluorescein Angiogram

- Diffuse background hyperfluorescence due to RPE atrophy (Fig 81–13,B)
- Poor retinal perfusion (slow filling)
- Focal retinal vascular leakage

ERG

- Flat response to all stimuli (Fig 81–13,C)

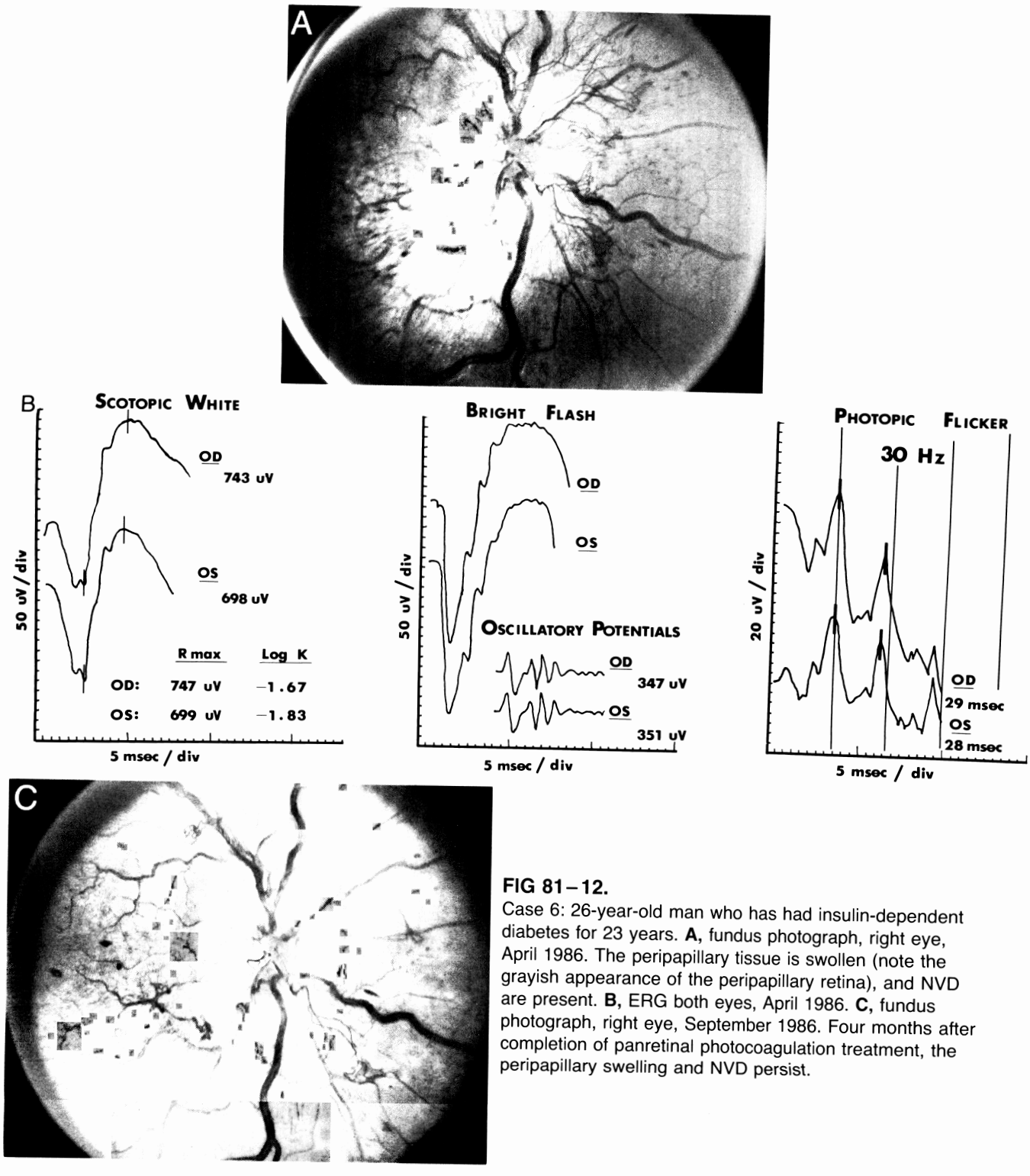

FIG 81–12.
Case 6: 26-year-old man who has had insulin-dependent diabetes for 23 years. **A,** fundus photograph, right eye, April 1986. The peripapillary tissue is swollen (note the grayish appearance of the peripapillary retina), and NVD are present. **B,** ERG both eyes, April 1986. **C,** fundus photograph, right eye, September 1986. Four months after completion of panretinal photocoagulation treatment, the peripapillary swelling and NVD persist.

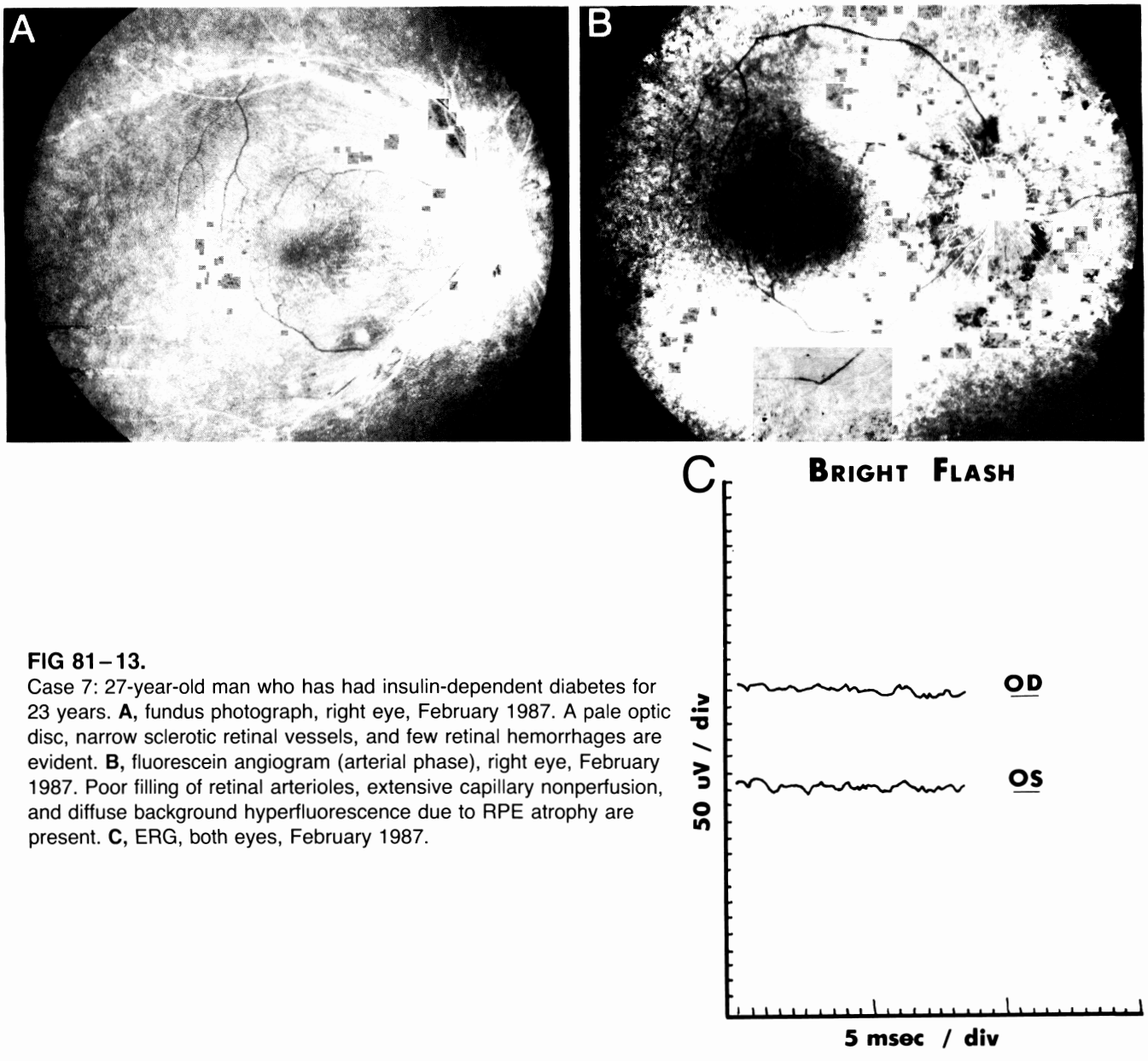

FIG 81–13.
Case 7: 27-year-old man who has had insulin-dependent diabetes for 23 years. **A,** fundus photograph, right eye, February 1987. A pale optic disc, narrow sclerotic retinal vessels, and few retinal hemorrhages are evident. **B,** fluorescein angiogram (arterial phase), right eye, February 1987. Poor filling of retinal arterioles, extensive capillary nonperfusion, and diffuse background hyperfluorescence due to RPE atrophy are present. **C,** ERG, both eyes, February 1987.

Visual fields (OU)

- Constricted to 25 to 30 degrees with a Goldmann III 4e test target

Summary

Absent ERG response in a diabetic patient with severe retinal vessel narrowing and sclerosis, pale optic discs, and diffuse RPE atrophy mimic a primary retinal dystrophy such as retinitis pigmentosa.

Acknowledgment

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