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Assessment of the Eye at Risk of Neovascularisation

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The causal linkage between retinal ischaemia and ocular neovascularisation has been recognised and widely accepted by the ophthalmic community since the early pioneering work of Michaelson,[1] Ashton,[2] Patz,[3] Wise,[4] and many others. In the initial stages of this research, the presence of retinal vascular occlusion in eyes with neovascular retinopathies was surmised primarily on the basis of histological specimens of the retinal vessels obtained from autopsy eyes of patients with diabetic retinopathy. Trypsin digestion preparation of the retinal vasculature showed focal areas of capillary acellularity, which were interpreted as being nonperfused capillaries in life.[5,6] Subsequently, the development of fluorescein angiography of the retinal vessels allowed assessment of their perfusion status in the living eye. In the case of diabetic retinopathy, focal nonperfusion of the retinal capillary bed, as well as of arterioles in the more advanced stages of the disease, was demonstrated angiographically. In a few cases in which both *in vivo* fluorescein angiography and *post mortem* trypsin digestion preparations were available, clinicopathological correlation studies showed a topographical correlation between capillary acellularity and angiographic nonperfusion.[7,8,9]

Numerous clinical studies over the years support the notion that retinal ischaemia provokes ocular neovascularisation. Both cross-sectional and longitudinal studies have demonstrated the following:

(1) retinal vascular growth in diabetic retinopathy and in sickle cell retinopathy preferentially occur at the border between perfused and nonperfused retinal zones,[10,11]
(2) disc neovascularisation in diabetic retinopathy occurs mainly in eyes with extensive mid-peripheral or generalised capillary nonperfusion,[12]
(3) iris neovascularisation in central retinal vein occlusion (CRVO) is found primarily in eyes with widespread retinal vascular nonperfusion.[13,14,15,16]

In a recent large-scale longitudinal study of eyes with nonproliferative diabetic retinopathy (NPDR), the extent of capillary nonperfusion, arteriolar abnormalities, and fluorescein leakage present at the baseline visit, (as measured by a standardised angiographic grading system) were significant risk factors for the subsequent development of proliferative retinopathy (PDR).[17] The difference in rates of developing new vessels within one year between eyes with and without these abnormalities ranged from two to threefold, depending upon the subgroup of NPDR severity considered. On the basis of this study, it is clear that fluorescein angiography is a useful tool in assessing the risk for neovascularisation in eyes with NPDR.

Besides determining the anatomic extent of nonperfusion in eyes with vascular retinopathy, evaluating the effects of ischaemia on various functions of the eye can also be useful. The major test, in this respect, has been electroretinography, although other measures such as perimetry[18] and pupillary light response[18] have been used. Conventional electroretinography (ERG) is a non-invasive test that reflects the light-induced electrical activity of the outer and middle layers of the retina throughout its entire extent; therefore, it can relatively easily detect extensive or generalised ischaemia. As example, ampli-

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tude reductions in the oscillatory potentials of the ERG have been shown to have prognostic value in predicting the onset and severity of PDR development, especially new vessels on the disc.[19,20,21,22]

On the other hand, the conventional ERG is relatively insensitive to focal abnormalities in the retinal vascular bed. The same can be said for the relative afferent pupillary defect (RAPD), which has been claimed to be a good predictor of the development of neovascularisation of the iris (NVI) in eyes with widespread retinal vascular nonperfusion due to CRVO.[18] Perimetry has the theoretical advantage of being able to identify localised zones of decreased retinal sensitivity due to focal ischaemia[23,24], as well as a more generalised decrease in sensitivity from widespread ischaemia and perhaps also metabolic abnormalities. While perimetry has not yet been shown to be a useful clinical tool to predict focal neovascularisation in conditions such as diabetic or sickle retinopathies, it does have predictive value for NVI in eyes with CRVO.[18]

The typical findings on fluorescein angiography and ERG testing, the interpretation of the results of these tests, and the usefulness of the tests in identifying eyes at risk for neovascularisation, vary with different disease entities. Three disorders that are representative of the spectrum of findings in retinal vascular disease are:

(1) diabetic retinopathy, which exhibits focal retinal ischaemia but can show as well more widespread retinal abnormality due to retinal vascular leakage and metabolic derangement;
(2) central retinal vein occlusion, which manifests diffuse involvement of the retinal vascular system, and a spectrum of degrees of ischaemia;
(3) sickle retinopathy, which characteristically shows focal ischaemia of the peripheral retina due to small arteriolar obstruction, with presumed mostly normal retina elsewhere.

In the ensuing discussion the differences in angiographic and electrophysiological findings for each entity, will be related to the distribution of neovascularisation, and the prognostic values of these tests (Table I).

A. Diabetic retinopathy

In diabetic retinopathy, focal retinal ischaemia is manifested ophthalmoscopically by cotton-wool spots and retinal haemorrhage and microaneurysms, and angiographically by focal areas of nonperfusion.[10] More extensive ischaemia can develop with larger arteriolar obstruction.[25,26] Studies using wide-angle fluorescein angiography, including sweeps of the mid-periphery and far-periphery, have clearly shown that the topographical distribution and extent of nonperfusion can vary considerably from eye to eye.[27] Several patterns have been demonstrated: (1) predominately posterior ischaemia; (2) predominately peripheral ischaemia; (3) diffuse posterior and peripheral ischaemia. Shimizu and his colleagues have demonstrated convincingly that the extent of nonperfusion can easily be underestimated in some eyes if only conventional 30 degree photography of the posterior pole is used.[27]

Previous correlative cross-sectional studies have shown a definite positive association between the presence and extent of retinal new vessels, and the location and extent of retinal vascular nonperfusion. It is important to note, although it is not widely appreciated, that new vessels on the disc (NVD) in diabetes are found primarily in eyes with extensive ischaemia.[27] It has also been shown that the presence of NVD carries a poor prognosis for retaining vision, if the eye is not treated with laser photocoagulation. In fact, the presence of NVD was found to be one of the major risk factors for severe visual loss in the Diabetic Retinopathy Study.[28] The poor prognosis undoubtedly relates to the association of NVD with severe ischaemia; that is, the presence of NVD, in most but not all cases, is an indicator of an eye with poor retinal perfusion.

What ocular factors can be used to identify those eyes with NPDR that are at highest risk to develop new vessels, and particularly PDR with 'DRS high-risk characteristics?' The Early Treatment Diabetic Retinopathy Study (ETDRS) has shown that the severity of retinal haemorrhages and microaneurysms, intraretinal microvascular abnormalities (IRMA) and venous beading (graded in standard stereoscopic fundus photographs) are

Table I *Angiographic and ERG changes by degree of retinal ischemia*

Disease Entity	*Fluorescein Angiography*	*ERG*			
		Scotopic Rmax	*B-Wave log k*	*Oscillatory Potentials*	*Implicit Times*
DIABETIC RETINOPATHY					
(a) mild ischaemia	focal nonperfusion; focal leakage	nl	nl	nl or sl ↓	nl or sl ↑
(b) moderate ischaemia	multifocal nonperfusion; focal or generalised leakage	nl or ↓	nl or sl ↑	↓ ↓	↑
(c) severe ischaemia	extensive nonperfusion; focal and severe generalised leakage	↓ ↓	↑	↓ ↓ ↓	↑ ↑
CRVO					
(a) mild to moderate ischaemia	focal nonperfusion; generalised leakage	nl, ↑ or ↓	nl or ↑	↓ ↓	↑ ↑
(b) severe ischaemia	severe nonperfusion; generalised leakage	↓ ↓	↑ ↑ ↑	↓ ↓ ↓	↑ ↑ ↑
SICKLE CELL RETINOPATHY					
(a) mild ischaemia	focal peripheral nonperfusion; little or no leakage	nl	nl	nl	nl
(b) severe ischaemia	focal peripheral nonperfusion; little or no leakage	nl or sl ↓	nl or sl ↑	nl or sl ↓	nl

significant risk factors for developing PDR; cotton-wool spots, surprisingly, are a less significant predictor of PDR than these other factors.[17]

The ETDRS has developed a standardised grading system for fluorescein angiograms.[29] This study and another one have found that the significant angiographic predictors of PDR are the extent of capillary nonperfusion as well as the severity of fluorescein leakage.[17,21,22] Leakage may be a predictor of new vessels perhaps because the increased permeability of the retinal vessels allows passage of neovascular growth factors from the blood into the retina and vitreous, or simply because vascular leakage often accompanies capillary non-perfusion. From the practical viewpoint, leakage is a useful predictor of PDR, because it is often easier to diagnose than nonperfusion, and because it tends to be more generalised than nonperfusion. Thus diffuse leakage in the posterior retina is often part of a generalised retinal vascular permeability defect, whereas ischaemia is often more focal

more peripheral and more difficult to demonstrate in the face of a small pupil, media opacities, or light fundus pigmentation.[21,22]

The ERG provides an additional clinical measure of the risk of neovascularisation in eyes with diabetic retinopathy. The most useful component in this respect is the oscillatory potentials (OPs), high frequency wavelets on the ascending limb of the b-wave. The OPs are thought to arise in the inner retinal layers, possibly reflecting feedback signals flowing in a radial direction (inner retina toward outer retina)[30,31] and perhaps arising in the bipolar cells.[32] This component of the ERG is especially sensitive to retinal ischaemia, and the OP amplitude may be abnormal in diabetes in the presence of normal a- and b-wave amplitudes.

Reduction in the OP amplitudes correlates with the presence and severity of diabetic retinopathy.[20,33] There is a close correlation with both capillary non-perfusion and leakage in fluorescein angiograms.[33,34] Two longitudinal studies have shown that reduced OP amplitudes predict the development of neovascularisation;[19.20,21,22] one of these studies[21,22] showed that reduced OP amplitudes predict the development of DRS-high risk characteristics, a useful finding since eyes with these characteristics should generally receive prompt panretinal photocoagulation treatment.

Other ERG measures that correlate with retinopathy severity in diabetes are the temporal aspects of the response (implicit times of the 30 Hz flicker and OPs),[35] and the 'sensitivity' of the retina as measured in the scotopic b-wave intensity-response function.[36] Neither of these ERG measures has yet been shown to predict progression to new vessels.

It is particularly instructive, from the pathophysiological viewpoint, to examine the b-wave intensity response function in diabetic retinopathy, and to compare the function in CRVO and sickle cell retinopathy. When the scotopic b-wave amplitude is measured at a series of increasing stimulus intensities, the resulting data points can be fitted to an exponential equation, known as the Naka-Rushton function.[37] The following parameters can be derived from the curve: Rmax (the theoretical maximum b-wave response); log k (the half-saturation constant, i.e. the stimulus intensity at which one-half the Rmax is reached); n (the slope of the linear portion of the function). It has been proposed by Massof *et al.*[38] that a reduction in Rmax may indicate a loss of responding retinal units, as with infarction of the retina, while an elevation of log k may represent a reduction in the retinal sensitivity, as can occur with retinal hypoxia or a metabolic abnormality in the retina. If it is true that hypoxic retina, but not infarcted retina, is the source of the presumed neovasculogenesis factor in the vascular retinopathies, then one would expect log k to be a better predictor of new vessel formation than Rmax.

Our preliminary results on the Naka-Rushton parameters in diabetic retinopathy indicate that both Rmax reduction and log k elevation occur in the same eye, although the highest correlation with retinopathy severity appears to be for log k.* It is also noteworthy, however, that the extent of log k elevation is much less in the typical eye with PDR than it is in eyes with ischaemic CRVO.[39] This probably relates to diabetic retinopathy being a more slowly evolving disease, and one with focal ischaemic involvement: at any given point in time in diabetic retinopathy, there are areas of retinal atrophy due to prior ischaemic infarction, areas of hypoxia due to more recent focal ischaemia, and areas with relatively normal vascular perfusion. This heterogeneous picture should result in some response compression (reduction in Rmax) from the infarcted areas, reduced retinal sensitivity (elevated log k) from the hypoxic areas, and some relatively normally responding units. The net effect would be a relatively modest change in Rmax or log k at any given point in time, unless there is extensive infarction, or florid widespread active ischaemia. One would not expect the Naka-Rushton parameters to be particularly good predictors of neovascularisation in diabetic retinopathy except, perhaps, in the florid cases. As we shall see below, the retinal sensitivity as measured by log k may be the best ERG predictor for the development of iris new vessels

*Roecker E, Pulos E, Severns M. Bresnick GH: unpublished observations.

in CRVO, because of the more acute and generalised nature of the vascular involvement in that condition. In contrast, the retinal sensitivity is probably a poor predictor of retinal neovcascularisation in sickle cell retinopathy, because of the focal nature of vascular obstruction in that condition.[40]

Additional factors that may well affect the ERG response in diabetes besides capillary nonperfusion are (1) metabolic derangement from the diabetes itself, (2) associated electrolyte abnormalities due to insulin/blood sugar effects and renal disease, and (3) retinal vascular permeability changes affecting the extracellular ionic environment of the neurons. It is very difficult to know how much each of these contribute to ERG abnormalities in a given case.

The following case† is an example of a patient with moderately severe NPDR with fluorescein angiographic and ERG changes indicating high risk for developing PDR. For reference purposes to the ERG results, a normal ERG in a 31 year old nondiabetic volunteer is presented first. (Fig. 1.) (Table II.)

Case 1

- Sixty-four year old woman with insulin-dependent diabetes for 25 years.

December 1986.

- Fundi—moderately severe NPDR OU (Fig. 2a, 2b)
  —moderate retinal haemorrhages
  —hard exudate formation
  —cotton wool spots
  —dilated, beaded veins
- Fluorescein angiogram OU (Fig. 2c)
  —severe capillary nonperfusion
  —severe leakage

ERG Results (Table III.) (Fig 2d)

November 1988

Over next two and one-half years, both eyes developed new vessels elsewhere (NVE).

- Fundi OU
  —retinal haemorrhages, cotton wool spots, venous beading worse.
  —new vessels (NVE) in superior nasal quadrants OU
- Fluorescein angiogram OU (Fig. 2e).
  —increased capillary nonperfusion
  —new vessel leakage superior nasal quadrants OU

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 oscillatory potentials 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 two years, and NVD in the left eye in 2½ years.

The next case shows asymmetric diabetic retinopathy (PDR one eye, NPDR fellow eye) with ERG changes in the fellow eye indicating a high risk for developing PDR. Fluorescein angiography could not be obtained because of nuclear sclerotic lens changes.

Case 2

- Sixty-six year old man with insulin-dependent diabetes for 12 years.

January 1986

- Fundi (Fig. 3a, 3b, 3c)
  OD—PDR with NVD and vitreous haemorrhage (DRS-HRC)
  OS—moderately severe NPDR
  —moderately severe retinal haemorrhages
  —hard exudates
  —dilated veins
- Fluorescein angiogram—adequate quality angiography could not be obtained because of nuclear sclerotic lens changes, OS<OD.

ERG results (Table IV.) (Fig 3d)

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

† This and the next two case examples are reprinted from: Bresnick GH, Diabetic Retinopathy in Heckenlively JP, Arden GB: Handbook of clinical electrophysiology of vision testing. Mosby-Year Book Publishers, Chicago. In press.

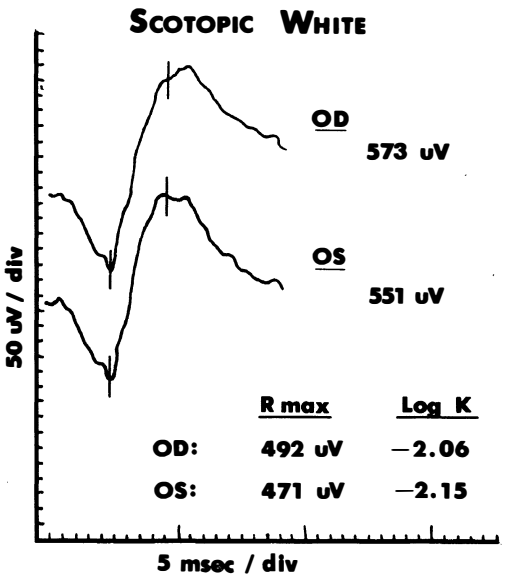


Fig 1(1).

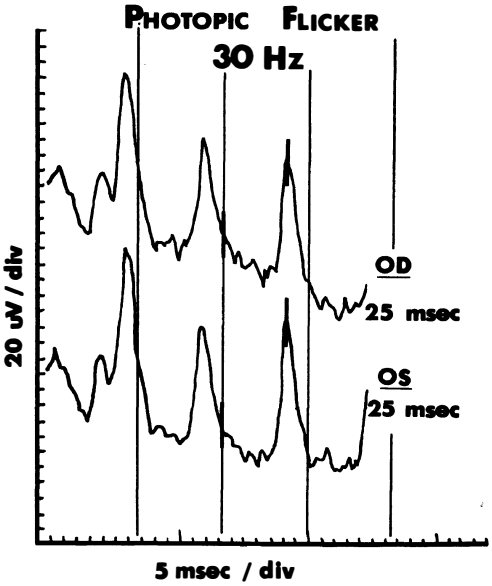


Fig 1(2).

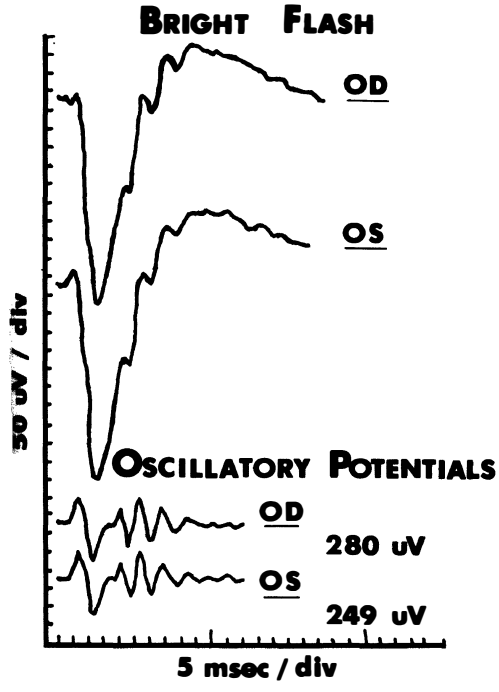


Fig 1(3).

Fig. 1. *Electroretinogram from a normal 31 year old nondiabetic volunteer subject.*

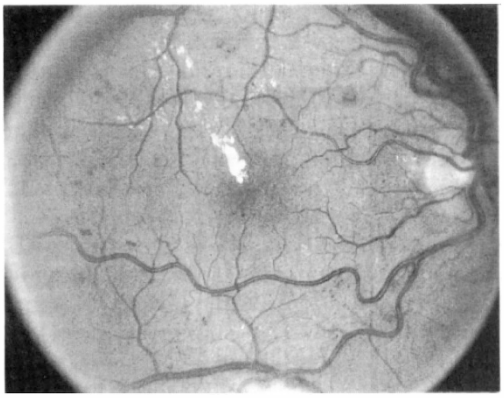


Fig. 2a

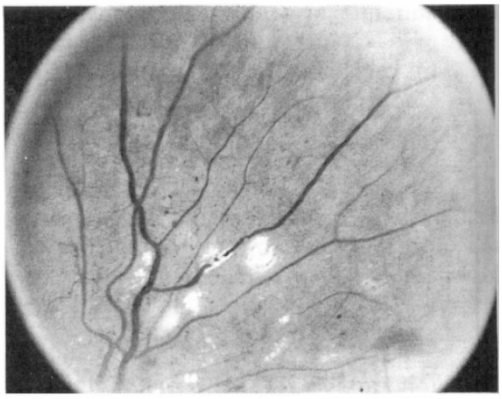


Fig 2b

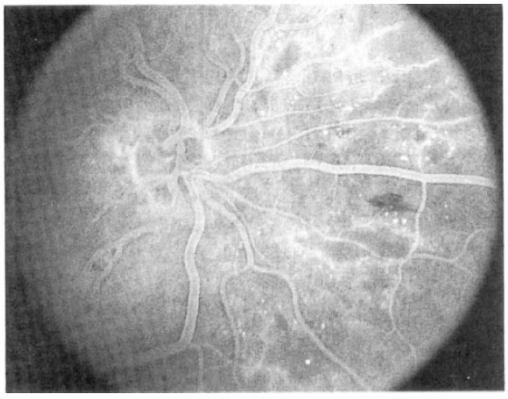


Fig 2c

Fig. 2 Case 1. *Sixty-four year old woman with insulin-dependent diabetes for 25 years; (a) Fundus photograph, right eye, December 1986. Moderately severe NPDR with scattered retinal haemorrhages and hard exudates; (b) Fundus photograph, right eye, December 1986 (superior nasal quadrant). Cotton-wool spots, sheathed retinal vein, and irregularly dilated veins; (c) Fluorescein angiogram, right eye, December 1986, (nasal to the disc). Multiple areas of capillary nonperfusion, some surrounded by microaneurysms; (d) Electroretinogram, both eyes, December 1986. e. Fluorescein angiogram, right eye, November 1988. Capillary nonperfusion is more extensive; leakage from NVE in upper part of the photograph. (Compare Fig. 2c).*

Table II *Normal volunteer*

Rmax (*nl >303 μV)**	*log k* (*nl <−1.63)**	*OP sum* (*nl >113μV)**	*30 Hz flicker implicit time* (*nl ≤28 msec)**
OD 492 μV	−2.06	280 μV	26 msec
OS 471 μV	−2.15	249 μV	27 msec

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

Table III *Case 1*

Rmax (*nl >303 μV*)	*log k* (*nl <−1.63*)	*OP sum* (*nl >113 μV*)	*30 Hz flicker implicit time* (*nl ≤28 msec*)
OD 347 μV	−1.76	132 μV**	29 msec*
OS 376 μV	−1.77	110 μV*	29 msec*

ERG (abnormal values have asterisk*; borderline values have double asterisk**). (Fig. 2d.)

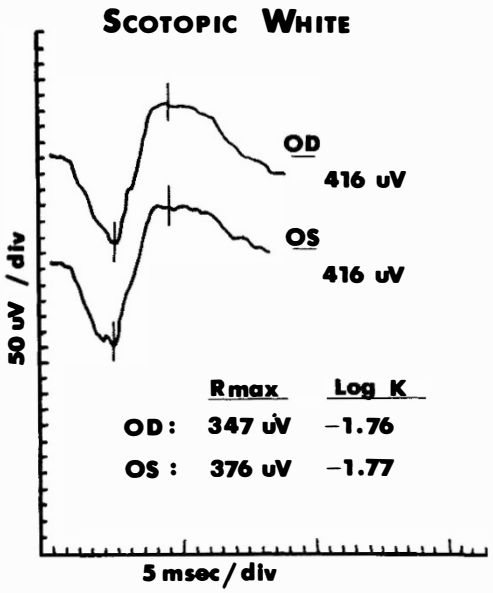
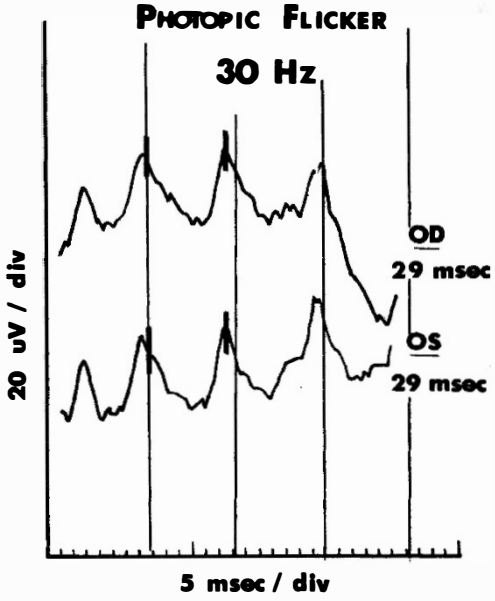


Fig 2d(1).



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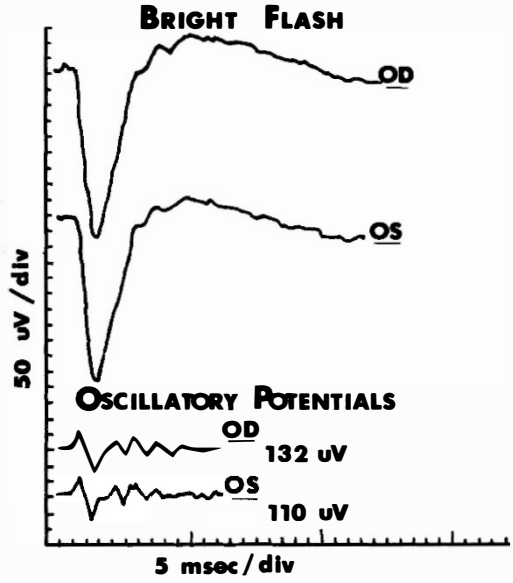


Fig 2d(3).

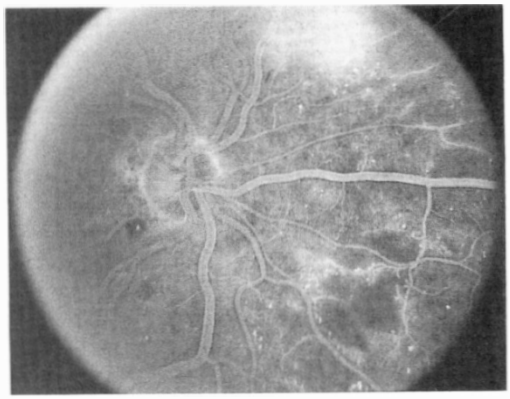


Fig 2e.

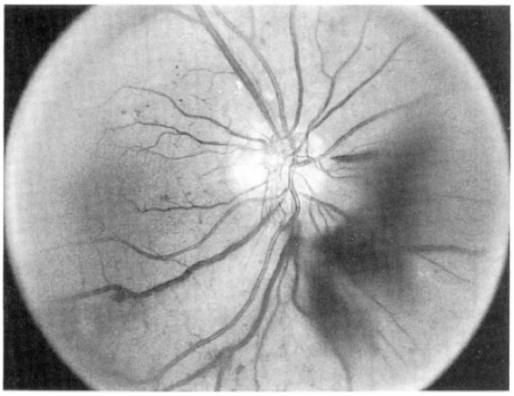


Fig. 3a

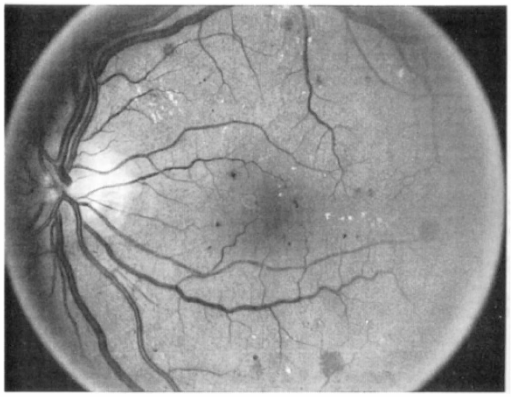


Fig 3b

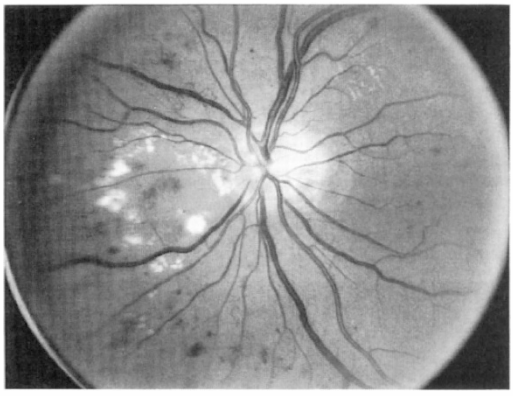


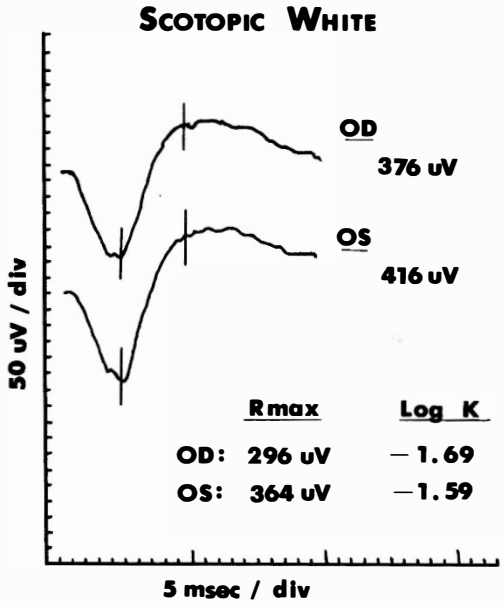
Fig 3c

Fig. 3 Case 2. *Sixty-six year old man with insulin-dependent diabetes for 12 years; (a) Fundus photograph, right eye, January 1986 PDR with NVD and vitreous haemorrhage (DRS-High Risk Characteristics); (b) Fundus photograph, left eye, January 1986. Moderately severe NPDR with retinal haemorrhages, microaneurysms and some hare exudates; (c) Fundus photograph, left eye, January 1986. Haemorrhages and exudates nasal to the disc; no NVD present.*

Table IV *Case 2*

Rmax (*nl* >303 μV)	*log k* (*nl* <−1.63)	*OP sum* (*nl* >113 μV)	*30 Hz flicker implicit time* (*nl* ≤28 *msec*)
OD 296 μV*	−1.69**	56 μV*	32 msec*
OS 364 μV	−1.59*	83 μV*	32 msec*

ERG (abnormal values have asterisk*; borderline values have double asterisk**). (Fig. 3d.)



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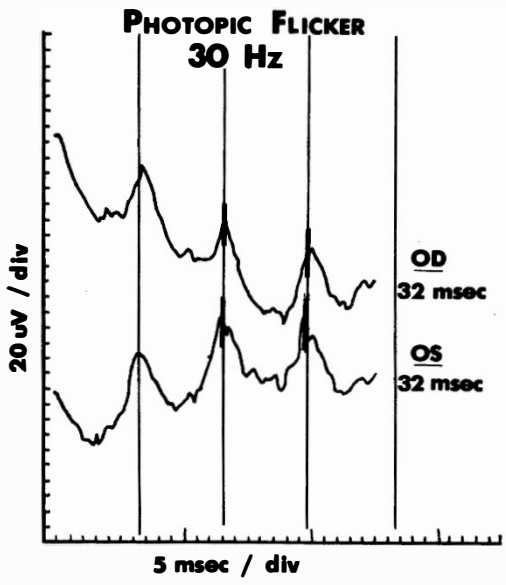

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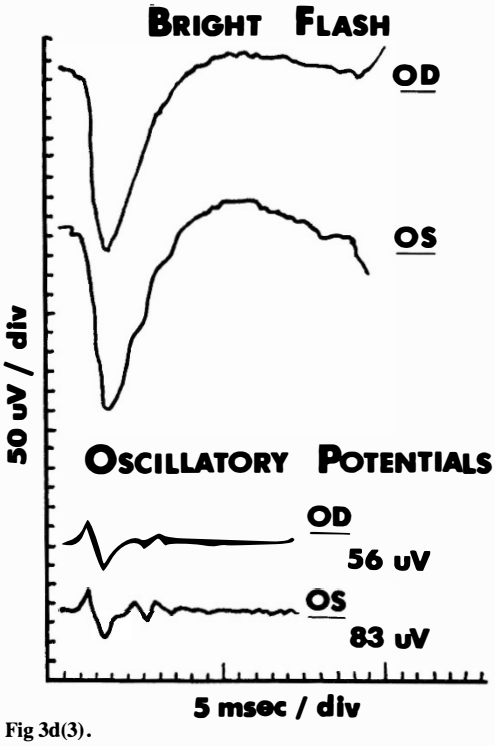

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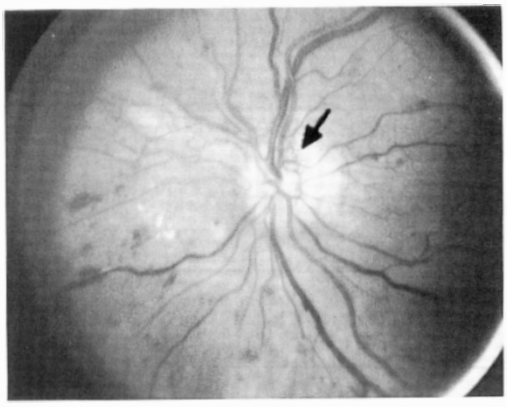

Fig 3e.

Fig 3. *(d) Electroretinogram, both eyes, January 1986; (e) Fundus photograph, left eye, July 1987. New vessels now present on superior temporal aspect of the disc (arrow). Note beading and dilation of inferior temporal vein. (Compare Fig. 3c).*

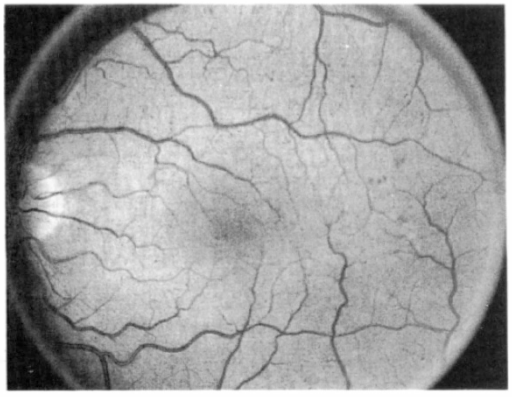

Fig. 4a

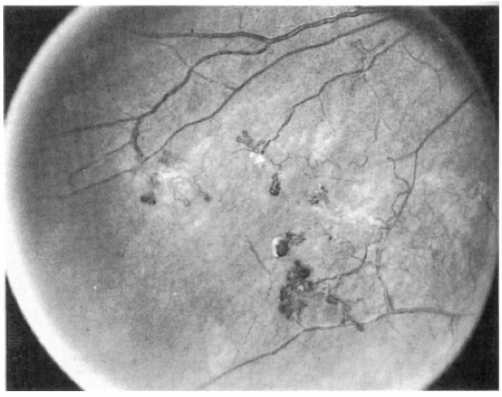

Fig 4b

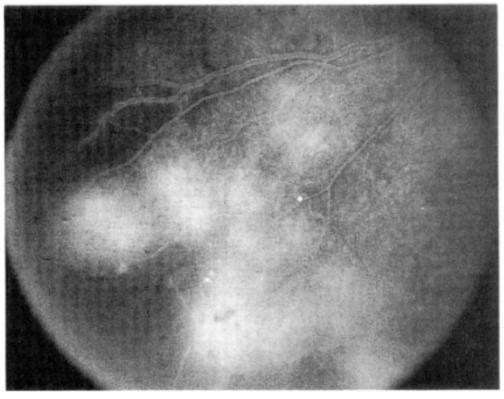

Fig 4c

Fig. 4 Case 3. *Forty-nine year old man with diabetes for 22 years; (a) Fundus photograph, left eye, April 1987. Relatively mild intraretinal changes present, consisting of a few microaneurysms and retinal haemorrhages; (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. Severe capillary midperipheral nonperfusion (left portion of photograph) with new vessel leakage at border between perfused and nonperfused retina; (d) Electroretinogram, both eyes, April 1987.*

Table V

Rmax (*nl >303 μV*)*	*log k* (*nl <−1.63*)	*OP sum* (*nl >113 μV*)	*30 Hz flicker implicit time* (*nl ≤28 msec*)
OD 280 μV*	−1.75	47 μV*	34 msec*
OS 241 μV*	−1.50*	43 μV*	36 msec*

ERG (abnormal values have asterisk*) (Fig. 4d.)

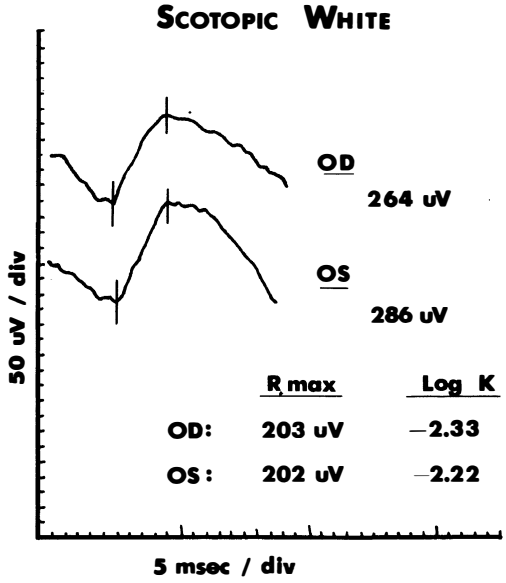

Fig 4d(1).

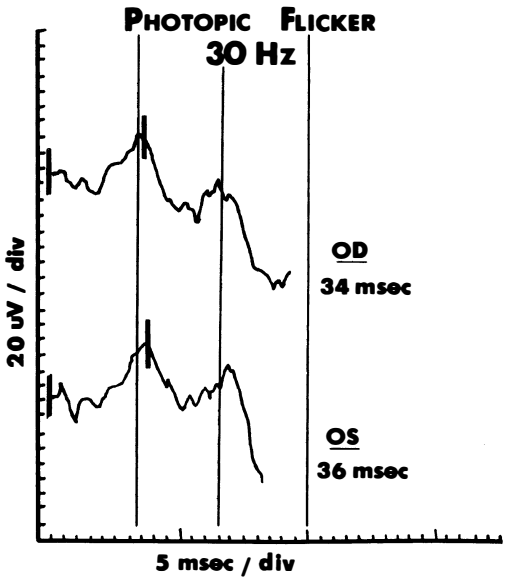

Fig 4d(2).

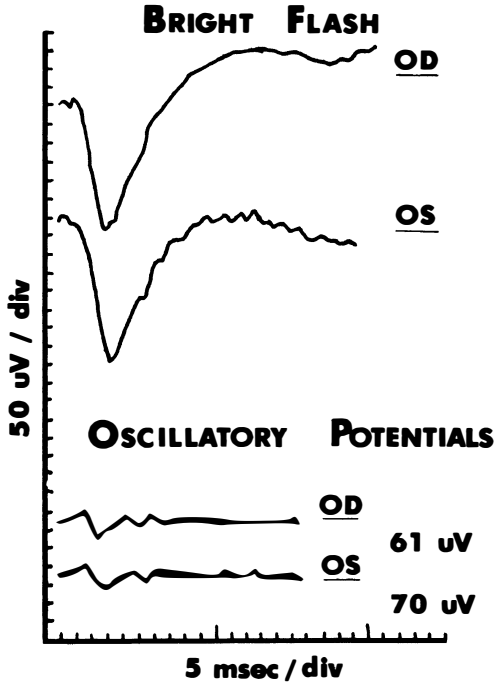

Fig 4d(3).

developed NVD, as well as rubeosis iridis involving the angle (8 months following extracapsular cataract surgery and posterior chamber lens implant). 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 (Fig. 3e)
  —NVD
  —Ischaemic retinal swelling nasal to disc.

Summary:
Severely reduced ERG oscillatory potentials, 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. Response to subsequent panretinal photocoagulation was satisfactory. (The cataract surgery probably contributed to the development of rubeosis iridis in an eye with ischaemic retinal changes).

In the following case, new vessels and capillary nonperfusion were located preferentially in the midperipheral fundus; ERG abnormalities alerted the clinician to the need for careful midperipheral fundus examination and angiography.

Case 3
- Forty-nine year old man with insulin-dependent diabetes for 22 years.

April 1987
- Fundi OU (Fig. 4a, 4b)
  —midperipheral retinal haemorrhages
  —midperipheral new vessels
  —mild retinal abnormalities in posterior fundus
- Fluorescein angiogram OU (Fig. 4c)
  —midperipheral new vessels
  —midperipheral capillary nonperfusion

ERG results (Table V.) (Fig 4d)

Summary:
Reduced ERG oscillatory potentials 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.

B. **Central Retinal Vein Occlusion (CRVO)**
New vessels on the iris (NVI) and neovascular glaucoma (NVG) have long been recognised as potentially serious complications of CRVO. More recent is the finding that the risk of developing NVI relates to the extent of underlying retinal ischaemia. The extent of capillary nonperfusion in fluorescein angiograms has been shown to relate to the risk of NVI and NVG.[13,14,15,16] In these various collected series, untreated ischaemic CRVO showed a rate of NVI between 40–60%, whereas the rate in non-ischaemic CRVO was substantially less.

There has been no uniform agreement on how to classify CRVO eyes angiographically into ischaemic *vs*. non-ischaemic categories. What has been lacking until recently is a uniform standardised photographic protocol and systematic grading technique for the angiograms.[41] It is generally stated that eyes with 10 or more disc areas of nonperfusion should be classified as ischaemic, and less than 10 disc areas, non-ischaemic.[13,16] However, it is important to specify how much of the fundus is being photographed in such a classification. It now is apparent that the mid-peripheral fundus as well as the posterior fundus must be evaluated for non-perfusion, and it is possible that some eyes developing NVI that were classified angiographically as non-ischaemic would have shown far more peripheral nonperfusion if more completely photographed.

There are several difficulties in relying strictly on fluorescein angiography to classify the degree of ischaemia in CRVO. It has been demonstrated that there can be considerable variation among retina specialists in the interpretation of nonperfusion in a given angiogram from an eye with CRVO.[42] It also can be difficult to detect nonperfusion when an eye with CRVO has extensive retinal haemorrhage. In addition, high quality angiograms are difficult to obtain in eyes with media opac-

ities or small pupils, not an unusual combination in older patients with CRVO. In a series of 140 eyes followed over five years, Hayreh *et al.*[18,43] found the test which best distinguished ischaemic from non-ischaemic CRVO in the early acute phase to be the relative afferent pupillary defect, followed closely by ERG abnormalities (b- and a-wave amplitude and b/a wave amplitude ratios) and visual field constriction and visual acuity reduction; angiographically determined nonperfusion and ophthalmoscopy were considerably less effective than the various functional measures.

Johnson *et al.*[39] have found the ERG to be an excellent predictor of NVI in eyes with CRVO. Of the parameters measured, log k was the most effective, scotopic b-wave and a-wave implicit times somewhat less effective, and Rmax and b/a wave amplitude ratios least effective in distinguishing those eyes with NVI at the time of ERG testing, or those developing NVI during follow-up. Interestingly, oscillatory potential amplitude reduction has been found to be only a moderately good predictor of NVI in CRVO,[44] probably because these potentials are too easily affected by widespread retinal circulatory disturbance. That is, because the OPs are so sensitive to ischaemia, they probably do not allow adequate discrimination between milder and more severe ischaemia in CRVO (Table I). Additional work on the value of various ERG parameters as predictors of NVI development has come from several other laboratories.[45,46,47]

Johnson's initial work also indicated that the ERG was more effective than angiography in predicting NVI.[39] When a group of 'retina experts' were given angiograms from paired eyes of different patients with CRVO (one eye that did and one that did not develop NVI), and were asked to select the one that developed NVI, their results were less accurate than was simply choosing the eye with the more abnormal ERG. A subsequent study from the same group suggested that applying a standardised grading system to the angiograms improved the predictive power of angiography.[48]

The Central Vein Occlusion Study (CVOS) is a prospective collaborative clinical trial that is testing angiography and ERG (both of which are performed and graded in a standard fashion) for their ability to predict the development of NVI.[41] The relatively large number of patients being followed in this study should help clarify the relative value of these two tests (considered separately and combined) in following patients with CRVO.

C. Sickle Cell Retinopathy

Examining sickle cell retinopathy provides a very instructive comparative example to help understand the basis of ERG abnormalities in diabetic retinopathy and CRVO: the ischaemia in sickle cell retinopathy is strictly focal (due to capillary/arteriolar obstruction) and there is no systemic metabolic abnormality to confound the issues. The work of Peachey and colleagues[40,49] in sickle cell retinopathy clearly shows that: (1) focal ischaemia alone causes reduction in ERG amplitudes (a-wave, b-wave, and oscillatory potentials) (2) implicit times are generally normal (presumably because the retina outside ischaemic areas is functioning normally) (3) 'retinal sensitivity' as measured by log k (and reflected in implicit times as well) is generally normal or only mildly abnormal.[40] In their first reported study, Peachey *et al.*[49] showed that the oscillatory potential amplitudes were reduced in eyes with peripheral retinal new vessels compared to eyes without new vessels. Their second report[40] described the relationship between several ERG parameters and peripheral retinal nonperfusion measured angiographically: both a- and b-wave amplitudes were reduced in eyes with peripheral nonperfusion, and decreases in amplitude were correlated with the extent of nonperfusion. Similarly, for eyes with peripheral nonperfusion the scotopic b-wave intensity-response series showed a reduced Rmax, but generally normal log k. Eyes with peripheral new vessels also had reduced Rmax, but only marginally elevated log k. Implicit times were again for the most part normal. As expected, there was a close correlation between the presence and extent of peripheral nonperfusion and the presence of peripheral new vessels (Table I). No longitudinal studies have yet been reported in sickle cell retinopathy to determine the power of the ERG to predict new vessel formation.

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Key words: central retinal vein occlusion; diabetic retinopathy, electroretinography; fluorescein angiography; iris new vessels; oscillatory potentials; retinal ischaemia; retinal new vessels; sickle cell retinopathy

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