Principles and Practice of Clinical Electrophysiology of Vision

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Pattern Electroretinography in the Evaluation of Glaucoma and in Optic Nerve Function

Graham E. Holder

The damage to the nerve fibers and retinal ganglion cells that is caused by raised intraocular pressure and the presumed ganglion cell contribution to the pattern electroretinogram (PERG) have led many investigators to examine the PERG in glaucoma since the early reports of PERG abnormalities.[2, 17, 35] More recent research has begun to address the important question of whether the PERG can be used to differentiate those patients with ocular hypertension who will develop glaucomatous visual loss from those who will not. This has implications for the initiation of treatment.

To some extent the findings in glaucoma must be considered in the light of the registration and analysis techniques. Wanger and Persson[63] found a significantly reduced P50 component in 10 of 11 eyes with unilateral glaucoma by using high-contrast, 24-minute checks and additionally reported a positive correlation between the magnitude of the PERG and the extent of the visual field defect. Subsequent reports of transient PERG changes[23, 27, 36, 39, 64] have differed in their observations. Some authors who included both the P50 and N95 components in their analysis described an abnormal reduction in P50,[23, 27] whereas others found N95 reductions.[36, 64] Howe and Mitchell[27] observed latency changes in N95 but not P50. PERG P50 component abnormalities can be present in conjunction with a normal pattern visual evoked potential (PVEP),[39] the same authors reporting abnormal PERGs in all (28 of 28) eyes with disc change and field loss.

The steady-state PERG amplitude is dominated by that of the N95 component,[11] and a reduction in steady-state PERG amplitude could then reflect either a primary reduction in N95 or a reduction secondary to a reduced P50 component. Bobak and colleagues[12] found an absence of the second harmonic component of the response to a sinusoidal grating modulated at 7.5 Hz in three of four glaucomatous eyes. The effects of spatial frequency (square wave gratings, 8.3 Hz) were studied by Porciatti and colleagues,[44] who found that the maximum abnormality occurred with medium spatial frequencies and peaked in the region of 1.5 cycles per degree. This confirmed a previous case report.[45] A more recent study[4] using checkerboard stimulation describes the maximum abnormality with 0.8-degree checks, but unfortunately this was the smallest check size used. Trick[56] investigated temporal frequency and concluded that a high temporal frequency (i.e., steady-state PERGs) gave maximum abnormality detection. In retrospect this is particularly interesting because the P50 of the transient PERG was also analyzed in these patients, and the greater abnormality with the steady-state PERG suggests a greater degree of N95 involvement. A recent study[46] using three temporal frequencies and three check sizes in 51 glaucoma patients found that *no* individual glaucoma patient (early disc and field changes, normal acuity) was abnormal at 2.5 SD from the normal mean, which suggests that patient selection criteria may be an important factor.

The value of the PERG in ocular hypertension has yet to be established. The requirement is an *accurate* predictor of those patients with raised pressure who are likely to develop visual loss so that treatment can be considered prior to the development of visual field defects, most of the field loss in glaucoma be-

ing irreversible. Indeed, a loss of some 40% of optic nerve fibers can occur without a demonstrable visual field defect.[47] However, many patients with ocular hypertension do not develop glaucoma, and these patients should not be treated. Unfortunately, many of the results so far published suggest that the PERG in ocular hypertension may not reflect the chance of glaucomatous visual loss. Various prospective studies have reported a conversion rate of between 0.4% and 17.4% from ocular hypertension to glaucoma.[3, 18, 28, 33, 41, 61] Despite this, the incidence of abnormal PERG in ocular hypertension has been reported as 4 of 7,[62] 11 of 12,[44] 12 of 16,[1] and 14 of 22,[64] the latter study finding N95 component abnormalities with sparing of P50. Typical PERG findings are shown in Figure 69–1. The observation[40] that 6 eyes with ocular hypertension had initially abnormal PERGs that normalized following a reduction of intraocular pressure is of great interest, but it is impossible to tell which of these eyes (if any) would actually have developed field loss if left untreated.

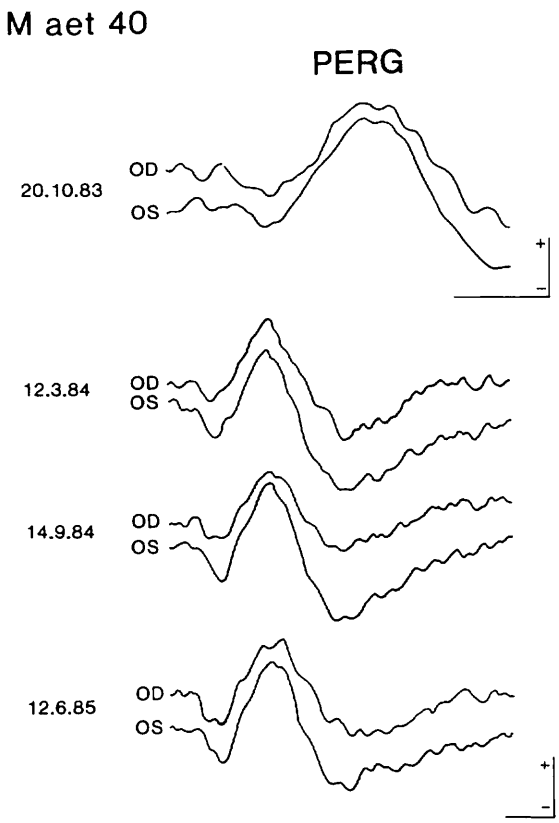

FIG 69–1.
Serial PERGs in a patient initially diagnosed as having unilateral ocular hypertension. The first recordings used a limited analysis time, but no interocular asymmetry is evident. Follow-up recordings initially show no abnormality but later reveal the development of a P50 component reduction at a time when perimetry showed no visual field defect. A field defect was noted some 2 months later. Treatment was commenced, and the pressure normalized; P50 returns to normal, but suspicious changes in N95 remain (Calibration, 25 ms, 5 μV).

The selection and assessment of patients may be a critical factor in these results. Trick[55] examined 12 "high-risk" and 12 "low-risk" ocular hypertensives. The optimum stimulus for PERG abnormality detection was 30-minute checks (steady-state PERGs), with 50% of the "high-risk" group showing abnormalities but only 8.3% of the "low-risk" group doing so. A subsequent study[57] reported abnormal PERGs in 15 of 130 unselected ocular hypertensives, a similar percentage to those who may be expected to develop glaucoma. There was a poor correlation between the electrophysiological findings and acquired dyschromatopsia.[58] It was suggested that color vision defects represented X–ganglion cell dysfunction, the PERG findings reflecting Y–ganglion cell dysfunction. Another recent study[46] examined the PERGs in 52 ocular hypertensives by using three temporal frequencies and three check sizes. There was a significant difference between the mean value for the ocular hypertensives and a normal control group only with 30-minute checks reversing at 11 per second. No individual patient had findings that were abnormal when compared with the normal controls.

A long-term prospective study examining both P50 and N95 components in a large number of patients is necessary before definite conclusions can be drawn that enable the PERG to reasonably affect the management of the patient with ocular hypertension. Although some results look promising, more evidence is needed before treatment should be initiated purely on the basis of the PERG findings.

PATTERN ELECTRORETINOGRAPHY IN OPTIC NERVE DYSFUNCTION

A study of the PERG in optic nerve disease is of both theoretical and practical interest. The early animal studies of Maffei, Fiorentini, and coworkers implicated the retinal ganglion cells in the generation of the PERG (see Berninger and Arden[7] for a review) by demonstrating PERG reduction following optic nerve section; this was paralleled by a histologically confirmed loss of ganglion cells. Optic nerve lesions in humans can eventually be expected to result in retrograde retinal ganglion cell degeneration, and PERG abnormalities are therefore anticipated in optic nerve dysfunction if the human PERG has a gan-

glion cell origin. From a clinical viewpoint, the PERG gives valuable information regarding the pathways mediating central vision distal to the optic nerve, thus enabling improved interpretation of abnormal PVEPs.

The transient PERG consists of two main components: a positive component, P50, at approximately 50 ms and a larger negative component, N95, at some 95 ms. The exact timing and amplitude relationships of these components depend upon stimulus and recording parameters. Recent work[7] shows that P50 and N95 have different characteristics and that at least 50% of the PERG is contrast related for check sizes less than 120 minutes.[60] Berninger and Schuurmans[11, 52] demonstrated spatial tuning for the N95 component, not for P50, and suggested that N95 is contrast dependent and probably arises in the ganglion cells but that there is a significant luminance contribution to P50.

Drasdo and colleagues[16] extracted the "pattern-specific response" (PSR[54]) from the PERG and correlated the amplitude of the negative PSR (N95) with the volume of the ganglion cell layer. The observation that P50 and N95 can be selectively affected in disease processes[23, 48] also suggests that they may have different origins. Most PERG studies so far have confined their analyses to P50 and do not examine N95; this is probably due to the superficial similarity between the PERG P50 component and the b-wave of the ERG, but it may also reflect the greater technical difficulties in recording an N95 component of sufficiently low variability to be clinically useful (see below).

Optic Nerve Demyelination

The first studies of the transient PERG in optic nerve demyelination reported a variable incidence of P50 component abnormality,[2, 13, 14, 42, 45, 50] some authors[30, 37] expressing the view that the PERG was of little value in the detection of optic nerve disease. Serra et al.[50] generally found PERG reduction only after repeated attacks of optic neuritis. These early studies omitted analysis of the N95 component, but Porciatti and von Berger[45] did note that the negative after-potential (N95) may be more affected. None of these studies described extinction of the transient PERG. This has been reported in some more severely affected eyes,[14, 15, 29, 49] and it was suggested[15] that a normal PERG (N95 was not examined) indicated demyelination and an extinguished PERG indicated axonal loss. It may be relevant that the studies that found extinction usually used monocular stimulation and recording; this has the associated difficulty of control of fixation in an eye with reduced visual acuity. In one study[14] the authors state in discussion that the findings with monocular stimulation were confirmed with binocular stimulation but do not present a full analysis. Binocular stimulation and recording have the great advantage that fixation is maintained by the good eye in a patient with monocular visual loss. There is no significant contamination from the cortically generated PVEP, providing an ipsilateral outer canthus or temple reference is used.[6, 53] The use of mastoid or ear reference electrodes cannot be recommended under any circumstances.

Abnormalities of steady-state PERGs in optic nerve demyelination have also been reported.[12, 17, 43] The merging of P50 and N95 in the steady-state PERG precludes individual component assessment. Although the steady-state PERG amplitude is dominated by that of N95,[60] a reduction could be either a primary N95 component abnormality or secondary to a reduced P50 component. The steady-state PERG may provide invaluable research data, but the transient PERG is more appropriate for routine clinical purposes.

The observation that the N95 component is usually selectively affected if the PERG is abnormal in optic nerve disease[20, 23, 48] further emphasizes the advantages of component separation. An analysis of the incidence and nature of abnormal PERGs in a series from the authors' laboratory of 141 patients with optic nerve demyelination is shown in Table 69–1.[24] Illustrative findings are shown in Figure 69–2. There were 199 eyes with a delayed PVEP P100 component, of which some 40% had abnormal PERGs; 85%

TABLE 69–1.

PERG Findings in 199 Eyes With Optic Nerve Demyelination (141 Patients)*

Finding	Symptomatic	Symptom Free	All
Normal PERG	50	71	121
N95 only	48	18	66
P50	2	2	4
P50 + N95†	7	1	8
Totals	107	92	199

*From Holder GE: *Electroencephalogr Clin Neurophysiol* 1990, in press. Used by permission.

†The term P50 + N95 has been used when both components were reduced, but N95 was proportionally more involved than P50 when compared with the fellow eye.

Two additional eyes had normal PVEPs but a reduced PERG N95 component. Many patients in this series were referred with signs or symptoms of multiple sclerosis, which may or may not have included a history of symptoms of optic nerve disease. Other patients were referred with presumed optic neuritis. "Symptom-free" eyes had never experienced any symptoms of optic nerve dysfunction; all "symptomatic" eyes had a history of optic nerve involvement.

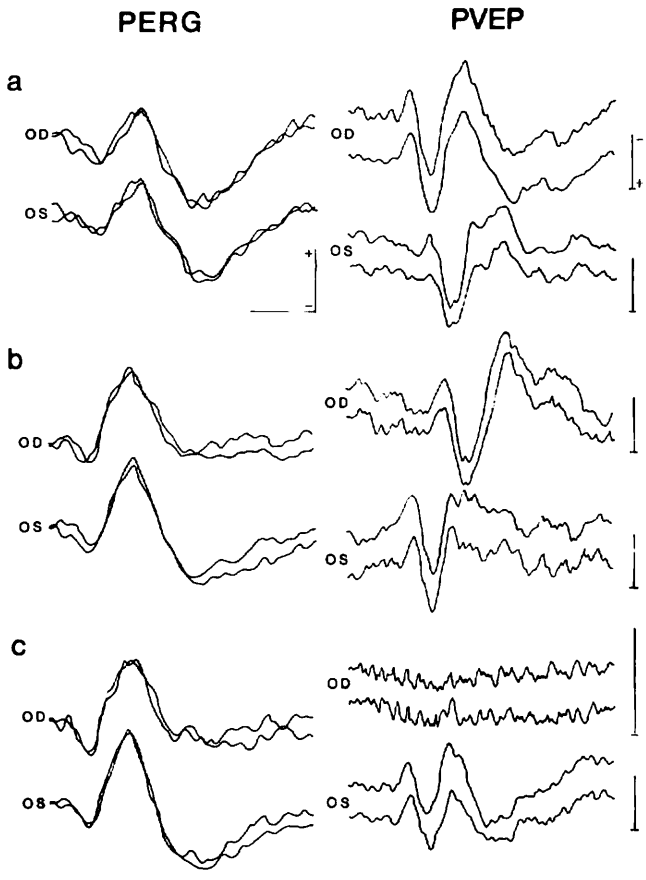

FIG 69–2.
PERG findings in three patients with multiple sclerosis and unilateral optic nerve demyelination. PERGs were recorded binocularly; PVEPs were recorded monocularly. The first patient shows a delayed PVEP from the affected eye but normal PERGs. The second patient shows a delayed PVEP, symmetrical PERG P50 components, and a reduction in the N95 component of the PERG from the affected eye. The PVEP is abolished in the affected eye of the third patient; the PERG shows an N95 component reduction with no P50 involvement. (From Holder GE: *Br J Ophthalmol* 1987; 71:166–171. Used by permission.)

of these abnormalities were confined to the N95 component. There was a much higher incidence of abnormal PERG in those eyes with symptoms of optic nerve disease than in those with a subclinical PVEP abnormality. Two eyes had abnormal PERGs (N95 reduction) but normal PVEPs. The magnitude of the P50 reduction, when seen, was usually much less than that regularly seen with more distal anterior visual pathway dysfunction, but examination during the acute phase of optic neuritis may show a more pronounced P50 reduction.[9] An example of this is shown in Figure 69–3. No patient had an extinguished PERG, and delays were also not a feature of the PERG abnormalities, which is in keeping with previous reports.[30, 32, 43, 50] Many of the patients had PVEP delays well in excess of 15 ms. However, in a study of 67 patients with delayed PVEPs in 84 eyes due to more distal anterior visual pathway dysfunction, all involved eyes showed P50 reductions, and no patient with a PVEP delay greater than 15 ms had a mild PERG abnormality when the PERG abnormalities were classified as mild, moderate, or severe.[21]

Other Optic Nerve Diseases

There are insufficient studies of other conditions affecting the optic nerve to draw definite conclusions as to the nature of the PERG abnormalities. Most reports that have appeared cite small numbers of patients without full clinical details. Not all authors examined the N95 component. Celesia and Kaufmann[14] observed P50 loss in some cases of optic atrophy due to meningitis (one case), retrobulbar neuritis (three cases), optic nerve compression (one case), and ischemic optic neuropathy (ION) (one case), but give no further details. Idiopathic and heredofamilial optic atrophy have both been reported to show a loss of N95 with a normal P50.[8, 10, 20] A recent study[29] found a normal P50 in acute sequential bilateral Leber's optic atrophy (N95 was not examined), but a P50 reduction at follow-up. Another report describes a mean P50 amplitude reduction in a group of patients including four with juvenile optic atrophy.[59]

Optic nerve compression and ION may also give PERG abnormalities. In this author's experience N95 abnormalities commonly occur in compressive lesions if the PERG is abnormal, but there may be a greater proportion of P50 abnormalities in ION.[20] Other authors have reported normal P50 components in acute ION.[29] Another study that only examined P50 found reductions in both ION and compression[49] upon monocular stimulation. It has been suggested that the PERG may be a useful prognostic indicator for final visual outcome in the preoperative assessment of optic nerve compression.[29] Results from this author's laboratory (Holder, unpublished observations) confirm the usefulness of the PERG, an abnormal PERG suggesting a lack of significant postoperative improvement presumably by demonstrating retrograde degeneration to the retinal ganglion cells. Two interesting papers have documented the evolution of PERG changes following optic nerve

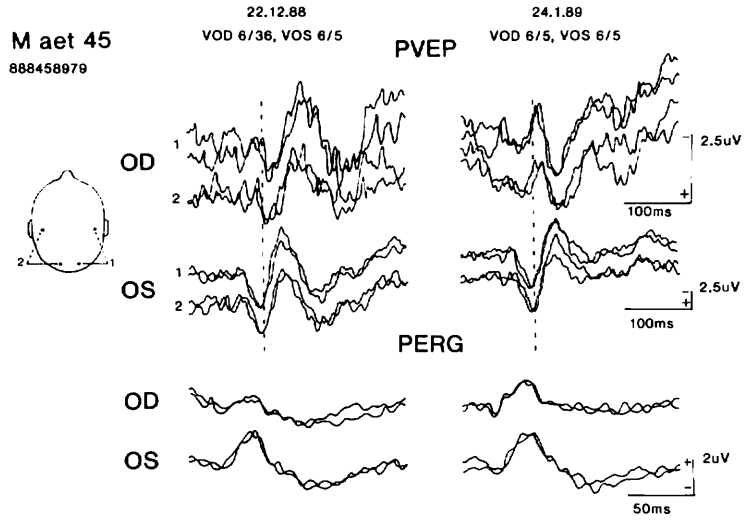

FIG 69–3.
PERG and PVEP findings during the development of and 4 weeks following an acute retrobulbar neuritis in the right eye. The initial recordings were taken 5 days after the first symptoms were noted. Three days following electrophysiological examination, vision in the right eye had deteriorated to no perception of light but subsequently recovered. Left eye findings were normal throughout. Note the P50 component reduction in the right eye PERG when first seen but restoration of P50 accompanied by an N95 component abnormality when the examination was repeated 1 month later. The PVEP P100 latency increased from 120 to 140 ms but improved in definition, and the visual acuity improved to 6/5. The *dotted vertical line* indicates the upper limit of normal PVEP P100 component latency (mean + 3 SD). (From Holder GE: *Electroencephalogr Clin Neurophysiol* 1990, in press. Used by permission.)

trauma.[19, 34] Despite the development of severe optic atrophy and significant reduction, extinction of the PERG did not occur. Sherman reported similar observations in a patient 4½ years following optic nerve trauma resulting in unilateral blindness.[51] Extinction of the PERG following traumatic optic neuropathy has, however, been reported when using monocular stimulation.[29]

CONCLUDING REMARKS

The discussion of optic nerve demyelination clearly suggests that the PERG is indeed of little value in the absolute diagnosis of optic nerve disease, where the cortically generated PVEP remains the investigation of choice. However, knowledge of the PERG allows improved interpretation of abnormal PVEPs. The PERG is often normal in optic nerve disease, but when abnormal, it is usually the N95 component that is involved; in more distal dysfunction the P50 component is affected.[21, 23, 48] This specificity enables the distinction between abnormal PVEPs due to optic nerve disease and those not due to optic nerve disease. Macular dysfunction, media opacities, refractive error, etc., can all give rise to a delayed PVEP,[5, 14, 21, 25, 31, 38] and PERG recording will usually establish that the delay is not due to optic nerve dysfunction. However, technical considerations are of paramount importance; in this author's experience a high-contrast stimulus is necessary to maximize the detection of an N95 component abnormality (see Fig 69–4). It should be emphasized that other stimulus and recording parameters may give different results.

Recording of the PERG in patients with abnormal PVEPs has been routine in our laboratory for some years; there are many cases where the misdiagnosis of optic nerve disease was avoided by recording the PERG. It was recently demonstrated[26] in a series of patients with severe hypothyroidism that the only patient to show a PVEP delay also had a delayed, reduced PERG. The normalization of both investigations following treatment suggested that the PVEP delay in this patient was secondary to reversible central retinal dysfunction and not due to optic nerve dysfunction. However, it must again be stressed that application of the highest technical standards is essential to obtain clinically satisfactory recordings,[22] particularly with regard to the reduction of N95 component variability.

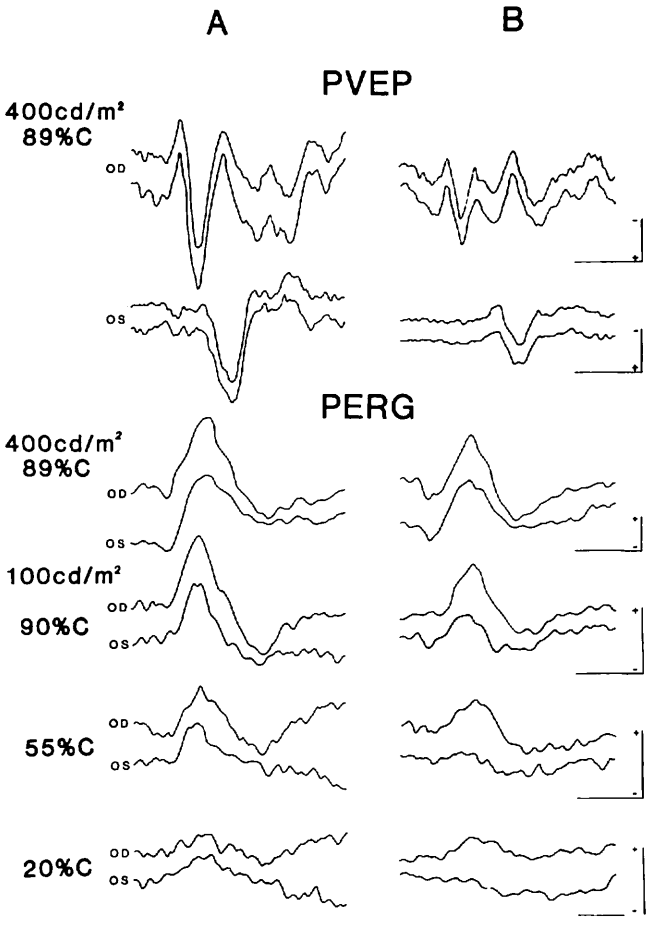

FIG 69–4.
The effects of variations in stimulus luminance and contrast in recordings from two patients with unilateral retrobulbar neuritis that, with our usual stimulus parameters, show unilateral PERG N95 reductions. It is notable that the recordings from patient B with 55% contrast show a significant P50 component reduction in the affected eye where the PERG is now almost extinguished. This suggests that a maximum contrast stimulus should be used routinely to maximize the detection of N95 abnormalities. As contrast is decreased, there is the expected loss of PERG definition from both the normal eyes and the abnormal eyes. At 20% contrast there is no longer a significant interocular PERG asymmetry. The quality of recordings taken at such low contrast levels is usually poor. (From Holder GE: *Electroencephalogr Clin Neurophysiol* 1990, in press. Used by permission.)

REFERENCES

1. Ambrosio G, Arienzo G, Aurilia A, et al: Pattern electroretinograms in ocular hypertension. *Doc Ophthalmol* 1988; 69:161–166.
2. Arden GB, Vaegan, Hogg CR: Clinical and experimental evidence that the pattern electroretinogram (PERG) is generated in more proximal retinal layers than the focal electroretinogram (FERG). *Ann N Y Acad Sci* 1982; 388:580–601.
3. Armaly MF: Ocular pressure and visual fields: A ten year follow up study. *Arch Ophthalmol* 1969; 81: 25–40.
4. Bach M, Hiss P, Rover J: Check-size specific changes of pattern electroretinogram in patients with early open angle glaucoma. *Doc Ophthalmol* 1988; 69:315–322.
5. Bass SJ, Sherman J, Bodis-Wollner I, et al: Visual evoked potentials in macular disease. *Invest Ophthalmol Vis Sci* 1985; 26:1071–1074.
6. Berninger TA: The pattern electroretinogram and its contamination. *Clin Vis Sci* 1986; 1:185–190.
7. Berninger TA, Arden GB: The pattern electroretinogram. *Eye* 1988; 2(suppl):257–283.
8. Berninger TA, Arden GB, Bird AC: Leber's optic atrophy. *Ophthalmic Paediatr Genet* 1989; 10:211–227.
9. Berninger TA, Heider W, Dodt E: Follow-up study of patients with acute optic neuritis (abstract). *Invest Ophthalmol Vis Sci* 1985; 26(suppl):218.
10. Berninger TA, Jaeger W, Krastel H: Electrophysiology and perimetry in autosomal dominant optic atrophy. Presented at the 24th International Society for Clinical Electrophysiology of Vision Symposium, Palermo, Italy, 1985.
11. Berninger TA, Schuurmanns RP: Spatial tuning of the PERG across temporal frequency. *Doc Ophthalmol* 1985; 61:17–25.
12. Bobak P, Bodis-Wollner I, Harnois C, et al: Pattern electroretinograms and visual-evoked potentials in glaucoma and multiple sclerosis. *Am J Ophthalmol* 1983; 96:72–83.
13. Boschi MC, Frosini A, Scaioli V: Correlations among clinical data, pattern electroretinogram, visual evoked potential and retinal fiber layer findings in multiple sclerosis. *Doc Ophthalmol Proc Ser* 1984; 40:133–141.
14. Celesia GG, Kaufman D: Pattern ERGs and visual evoked potentials in maculopathies and optic nerve diseases. *Invest Ophthalmol Vis Sci* 1985; 26:726–735.
15. Celesia GG, Kaufman D, Cone SB: Simultaneous recording of pattern electroretinography and visual evoked potentials in multiple sclerosis. *Arch Neurol* 1986; 43:1247–1252.
16. Drasdo N, Thompson DA, Arden GB: A comparison of pattern ERG amplitudes and nuclear layer thickness in different zones of the retina.*Clin Vis Sci* 1990; 5:415–420.
17. Fiorentini A, Maffei L, Pirchio M, et al: The ERG in response to alternating gratings in patients with diseases of the peripheral visual pathway. *Invest Ophthalmol Vis Sci* 1981; 21:490–493.
18. Graham PA: The definition of pre-glaucoma: A prospective study. *Trans Ophthalmol Soc U K* 1968; 88:153–165.
19. Harrison JM, O'Connor PS, Young RSL, et al: The pattern ERG in man following surgical resection of the optic nerve. *Invest Ophthalmol Vis Sci* 1987; 28:492–499.
20. Holder GE: Abnormalities of the pattern ERG in optic nerve lesions: Changes specific for proximal retinal dysfunction, in Barber C, Blum T (eds): *Evoked Potentials III*. London, Butterworths, 1987, pp 221–224.
21. Holder GE: Pattern electroretinography in patients

with delayed pattern visual evoked potentials due to distal anterior visual pathway dysfunction. *J Neurol Neurosurg Psychiatry* 1989; 52:1364–1368.
22. Holder GE: Recording the pattern electroretinogram with the Arden gold foil electrode. *J Electrophysiol Technol* 1988; 14:183–190.
23. Holder GE: Significance of abnormal pattern electroretinography in anterior visual pathway dysfunction. *Br J Ophthalmol* 1987; 71:166–171.
24. Holder GE: The incidence of abnormal pattern electroretinography in optic nerve demyelination. *Electroencephalogr Clin Neurophysiol* 1991; 78:18–26.
25. Holder GE, Chesterton JR: The visual evoked potential in Harada's disease. *Neuroophthalmology* 1984; 4:43–45.
26. Holder GE, Condon JR: Pattern VEPs and pattern ERGs in hypothyroidism. *Doc Ophthalmol* 1989; 73:127–131.
27. Howe JW, Mitchell KW: Simultaneous recording of pattern electroretinogram and visual evoked cortical potential in a group of patients with chronic glaucoma. *Doc Ophthalmol Proc Ser* 1984; 40:101–107.
28. Jensen JE: Glaucoma screening: A 16-year follow up of ocular hypertensives. *Acta Ophthalmol* 1984; 62:203–209.
29. Kaufman DI, Lorance RW, Woods M, et al: The pattern electroretinogram: A long-term study in acute optic neuropathy. *Neurology* 1988; 38:1767–1774.
30. Kirkham TH, Coupland SG: The pattern electroretinogram in optic nerve demyelination. *Can J Neurol Sci* 1983; 10:256–260.
31. Lennerstrand G: Delayed visual evoked cortical potentials in retinal disease. *Acta Ophthalmol* 1982; 60:497–504.
32. Lorenz R, Dodt E, Heider W: Pattern electroretinogram peak times as a clinical means of discriminating retinal from optic nerve disease. *Doc Ophthalmol* 1989; 71:307–320.
33. Lundberg L, Wetrell K, Linear E: Ocular hypertension: A prospective twenty-year follow up study. *Acta Ophthalmol* 1987; 65:705–708.
34. Mashima Y, Oguchi Y: Clinical study of the pattern electroretinogram in patients with optic nerve damage. *Doc Ophthalmol* 1985; 61:91–96.
35. May JG, Ralston JV, Reed JL, et al: Loss in pattern-elicited electroretinograms in optic nerve dysfunction. *Am J Ophthalmol* 1982; 93:418–422.
36. Ohta H, Tamura T, Kawasaki K, et al: Negative wave in human pattern ERG and its suppression in glaucoma. *Acta Soc Ophthalmol Jpn* 1986; 90:108–113.
37. Ota I, Miyake Y: The pattern electroretinogram in patients with optic nerve disease. *Doc Ophthalmol* 1986; 62:53–60.
38. Papakostopoulos D, Dean Hart C, Cooper R, et al: Combined electrophysiological assessment of the visual system in central serous retinopathy. *Electroencephalogr Clin Neurophysiol* 1984; 59:77–80.
39. Papst N, Bopp M, Schaudigel OE: Pattern electroretinogram and visually evoked cortical potentials in glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1984; 222:29–33.
40. Papst N, Bopp M, Schaudigel OE: The pattern evoked electroretinogram associated with elevated intraocular pressure. *Graefes Arch Clin Exp Ophthalmol* 1984; 222:34–37.
41. Perkins ES: The Bedford glaucoma survey. Long term follow up of borderline cases. *Br J Ophthalmol* 1973; 57:179–185.
42. Persson HE, Wanger P: Pattern reversal electroretinograms and visual evoked cortical potentials in multiple sclerosis. *Br J Ophthalmol* 1984; 68:760–764.
43. Plant GT, Hess RF, Thomas SJ: The pattern evoked electroretinogram in optic neuritis: A combined psychophysical and electrophysiological study. *Brain* 1986; 109:469–490.
44. Porciatti V, Falsini B, Brunori S, et al: Pattern electroretinogram as a function of spatial frequency in ocular hypertension and early glaucoma. *Doc Ophthalmol* 1987; 65:349–355.
45. Porciatti V, Von Berger GP: Pattern electroretinogram and visual evoked potential in optic nerve disease: Early diagnosis and prognosis. *Doc Ophthalmol Proc Ser* 1984; 40:117–126.
46. Price MJ, Drance SM, Price M, et al: The pattern electroretinogram and visual evoked potential in glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1988; 226:542–547.
47. Quigley HA, Addicks M, Green WR: Optic nerve damage in human glaucoma. *Arch Ophthalmol* 1982; 100:135–146.
48. Ryan S, Arden GB: Electrophysiological discrimination between retinal and optic nerve disorders. *Doc Ophthalmol* 1988; 68:247–255.
49. Seiple WH, Price MJ, Kupersmith M, et al: The pattern electroretinogram in optic nerve disease. *Ophthalmology* 1983; 90:1127–1132.
50. Serra G, Carreras M, Tugnoli V, et al: Pattern electroretinogram in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1984; 47:879–883.
51. Sherman J: Simultaneous pattern reversal electroretinograms and visual evoked potentials in diseases of the macula and optic nerve. *Ann N Y Acad Sci* 1982; 388:214–226.
52. Schuurmans RP, Berninger TA: Luminance and contrast responses recorded in man and cat. *Doc Ophthalmol* 1985; 59:187–197.
53. Tan CB, King PJL, Chiappa KH: Pattern ERG: Effects of reference electrode site, stimulus mode and check size. *Electroencephalogr Clin Neurophysiol* 1989; 74:11–18.
54. Thompson DA, Drasdo N: Computation of the luminance and pattern components of the bar pattern electroretinogram. *Doc Ophthalmol* 1987; 66:233–244.
55. Trick GL: Pattern reversal retinal potentials in ocular hypertensives at low and high risk of developing glaucoma. *Doc Ophthalmol* 1987; 65:79–86.
56. Trick GL: Retinal potentials in patients with primary open angle glaucoma: Physiological evidence for temporal frequency tuning defects. *Invest Ophthalmol Vis Sci* 1985; 26:1750–1758.
57. Trick GL, Bickler-Bluth M, Cooper DG, et al: Pattern reversal electroretinogram (PRERG) abnormalities in ocular hypertension: Correlation with glaucoma risk factors. *Curr Eye Res* 1988; 7:201–206.
58. Trick GL, Nesher R, Cooper DG, et al: Dissociation of visual deficits in ocular hypertension. *Invest Ophthalmol Vis Sci* 1988; 29:1486–1491.

59. Vaegan, Billson FA: The differential effect of optic nerve disease on pattern and focal electroretinograms. *Doc Ophthalmol* 1987; 65:45–56.
60. Van den Berg TJTP, Boltjes B, Spekreijse H: Pattern electroretinogram can be more than the sum of local luminance changes. *Doc Ophthalmol* 1988; 69:307–314.
61. Walker WM: Ocular hypertensives: Follow up of 109 cases from 1963–74. *Trans Ophthalmol Soc U K* 1974; 94:525–533.
62. Wanger P, Persson HE: Pattern-reversal electroretinograms in ocular hypertension. *Doc Ophthalmol* 1985; 61:27–32.
63. Wanger P, Persson HE: Pattern-reversal electroretinograms in unilateral glaucoma. *Invest Ophthalmol Vis Sci* 1983; 24:749–753.
64. Weinstein GW, Arden GB, Hitchings RA, et al: The pattern electroretinogram (PERG) in ocular hypertension and glaucoma. *Arch Ophthalmol* 1988; 106:923–928.