4. Williamson JR, Vogler NJ, and Kilo C: Estimation of vascular basement membrane thickness: theoretical and practical considerations. Diabetes 18:567, 1969.

5. Caird FI, Pirie A, and Ramsell TG: Diabetes and the Eye. Oxford, Blackwell, 1968, pp. 37–58.

6. Armitage P: Statistical Methods in Medical Research. Oxford, Blackwell, 1971, pp. 131–135; 207–213.

7. Hjelm M and Tengström B: Enzymatic determinations of blood galactose with galactose oxidase and galactose dehydrogenase. Biochem Med 2:174, 1968.

8. Bloodworth JMB Jr, Engerman RL, Camerini-Dàvalos RA, and Powers KL: Variations in capillary basement membrane width produced by aging and diabetes mellitus. In Advances in Metabolic Disorders, Suppl. 1, Early diabetes. Camerini-Dàvalos RA and Cole ES, editors. New York, Academic Press, 1970, pp. 279–287.

9. Kinoshita JH: Cataracts in galactosemia. Invest Ophthalmol 4:786, 1965.

10. Gabbay KH: The sorbitol pathway and the complications of diabetes. N Engl J Med 288:831, 1973.

11. Spiro RG and Spiro MJ: Studies on the biosynthesis of the hydroxylysine-linked disaccharide unit of basement membranes and collagens. I. Kidney glucosyltransferase. J Biol Chem 246:4899, 1971.

12. Spiro MJ and Spiro RG: Studies on the biosynthesis of the hydroxy-lysine-linked disaccharide unit of basement membranes and collagens. II. Kidney galactosyltransferase. J Biol Chem 246:4910, 1971.

13. Bunn HF, Gabbay KH, and Gallop PM: The glycosylation of hemoglobin: relevance to diabetes mellitus. Science 200:21, 1978.

14. McFarland KF, Catalano EW, Day JF, Thorpe SR, and Baynes JW: Nonenzymatic glucosylation of serum proteins in diabetes mellitus. Diabetes 28:1011, 1979.

15. Schnider SL and Kohn RR: Glucosylation of human collagen in aging and diabetes mellitus. J Clin Invest 66:1179, 1980.

16. Urbanowski JC, Cohenford MA, Levy HL, Crawford JD, and Dain JA: Nonenzymatically galactosylated serum albumin in a galactosemic infant. N Engl J Med 306:84, 1982.

Flicker Threshold and Pattern VEP Latency in Ocular Hypertension and Glaucoma

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Latency of the pattern visual-evoked potential (PVEP) was measured in 24 ocular hypertensive (OHT) patients, eight open-angle glaucoma (OAG) patients, and 37 control subjects. The PVEP stimulus was a 2.3 cycle/degree sinusoidal grating, counterphase-modulated at 1 Hz. Field size was 9 degrees and mean luminance 1.7 log ft-lamberts. For 22 of the 32 patients, a psychophysical measure of dynamic contrast sensitivity at 8 Hz (DRC) was obtained with a 4 degrees diameter stimulus, by determining the mean value for the contrast sensitivities to a homogeneous flickering field and to a 1.2 cycle/degree counterphase-flickering grating. Patient DRC values were compared with previously published control data from 21 subjects. Mean PVEP latencies of both the OHT and the OAG patients were greater than normal ($P < 0.001$), with the OAG value larger than the OHT value ($P < 0.001$). Mean DRCs were lower than normal ($P < 0.002$) for both patient groups, with the OAG value lower than the OHT value ($P < 0.025$). DRC correlated with PVEP latency for these patients (r = −0.66, $P < 0.001$). Invest Ophthalmol Vis Sci 24:1524–1528, 1983

Open-angle glaucoma (OAG) patients, as well as some ocular hypertensive (OHT) patients with normal visual fields, have shown abnormalities in a measure of the contrast required to detect flicker and flickering patterns at 8 Hz ("dynamic response coefficient" or DRC[1]). Further, optic nerve damage in glaucomatous eyes has been reported prior to definite field loss[2]; and increased latencies of visually evoked potentials (VEPs)

have been reported in glaucoma patients and some OHT patients.[3,4] Discerning such early abnormalities may eventually permit the systematic detection of glaucomatous damage prior to the development of frank scotomata.

Materials and Methods. This is a retrospective study: patient and control data (Table 1) were selected from test results obtained previously, either for diagnostic purposes or to set diagnostic standards of normality, and also from control data of a previous study.[1]

Thirty-two patients with open angles and intraocular pressures (IOPs) above 21 mmHg in at least one eye were compared with two control groups. About half the patients were using antiglaucomatous medication; however, no eye receiving pilocarpine was included. The patients were subdivided into an ocular hypertension (OHT) group of 24 patients with no evidence of visual field defects, and an open-angle glaucoma (OAG) group of eight patients who did show typical glaucomatous visual field defects. One OHT patient had pigmentary dispersion syndrome, and one had exfoliation syndrome. The OAG group comprised three patients diagnosed as primary open-angle glaucoma, one patient with pigmentary glaucoma, one with Sturge-Weber, and two with exfoliation syndrome. The OAG and OHT groups did not differ with respect to mean values of IOP, or of known duration of IOP elevation. However, compared with the OHT patients,

Table 1. Patient population characteristics

Group	Number of patients	Mean ± SD			
		Age (years)	Decimal Snellen visual acuity	Current IOP (mmHg)	Optic disc (c/d)
Control$_{PVEP}$*	37	30.8 ± 14.0	0.92 ± .20	—	—
Control$_{DRC}$†	21	51 ± 22.0	0.99 ± .24	—	—
OHT	24	41.0 ± 18.4‡	0.99 ± .19§	24.7 ± 5.6‖	0.36 ± .21‖
OAG	8	52.2 ± 15.9‡	0.80 ± .25§	21.5 ± 9.6‖	0.66 ± .26‖

* PVEP Control data (obtained in collaboration with Dr. J. Camisa).
† DRC Control data from reference 1.
‡ Mean age of the PVEP Control group differed from that of the OHT group ($P < 0.002$) and also from that of the OAG group ($P < 0.001$). Mean age of the DRC control group differed from that of the OHT group ($P < .025$), but not from that of the OAG group. The difference between OHT and OAG group means was also significant ($P < 0.005$; t-tests, two-tailed).

§ Mean Snellen visual acuity of the PVEP Control group differed significantly from that of the OHT group ($P < 0.05$), but not from that of the OAG group. Mean Snellen visual acuity of the DRC Control group differed significantly from that of the OAG group ($P < 0.02$), but not from that of the OHT group. The difference between OHT and OAG group means was significant ($P < 0.005$; t-tests, two-tailed).

‖ Differences between OHT and OAG means were not significant for Current IOP level, but were significant for Optic disc C/D ratio ($P < 0.001$).

on the average the OAG patients were older, had larger optic nervehead cup to disc (C/D) ratios, and had poorer Snellen visual acuities.

These two patient groups were compared with two different control groups (Table 1), who had been tested previously in the same laboratories. PVEP control data had been obtained from a group of 37 subjects (unpublished data: Camisa et al), and DRC control data from another group of 21 subjects.[1] The control subjects had no known visual, ocular, or neurologic disorders. The mean Snellen visual acuities of each group was 20/25 (0.80) or better (Table 1). The mean age of the PVEP control group was lower than that of the patient groups, while the mean age of the DRC control group was similar or higher.

The testing methods have been described previously. All patients had PVEP measurements.[5] A patterned stimulus was used because latencies to patterned stimuli seem more sensitive to optic nerve damage than latencies to unpatterned stimuli, first at the retinal level, in electroretinography,[6] and then at the cortical level, in evoked potentials.[7] The PVEP stimulus was a 2.3 cycle/degree sinusoidal grating, presented at 55% contrast, and counterphase modulated at 1 Hz. Field size was 9 degrees and mean luminance 1.7 log foot-lamberts. A scalp electrode 2.5 cm above inion was referenced to another over the temporal bone.[5] The latency of the P100 peak was measured.

Eighteen OHT patients and four OAG patients had DRC measurements[1] in addition to PVEP testing. This psychophysical measurement used two types of stimuli, a homogeneous flickering field, and a counterphase-flickering grating of low spatial frequency (1.2 cycles/degree), both presented at a flicker rate of 8 Hz and a mean luminance of 1.6 log ft-lamberts on a screen subtending 4 degrees of visual angle. The average of the contrast sensitivities to these two stimuli was defined as the DRC,[1] an estimate of the level of the low spatial frequency end of the 8 Hz spatio-temporal con-

trast sensitivity curve. Although the two components of this derived measure are highly correlated, they nevertheless, as we pointed out in a previous study,[1] appear to tap partially independent components of glaucomatous vision changes.

Results. Comparisons of patients using topical antiglaucomatous medication (after exclusion of eyes medicated with pilocarpine) with those not using medication revealed no significant mean differences (t-tests, two-tailed), and therefore the results are presented without reference to medication.

The mean PVEP latencies of both the OHT and the OAG group were significantly different ($P < 0.001$) from the PVEP control group mean (Table 2). Similarly, the mean DRCs of both the OHT and the OAG group were significantly different ($P < 0.002$) from the

Table 2. Pattern VEP latency and DRC: mean values, differences between means, and 95% confidence limits for differences between means

A:	Mean ± SD (number of eyes)			
	PVEP latency (msec)		DRC	
Group	(msec)	(n)	(value)	(n)
Control	107 ± 5.7*	(74)	35.4 ± 3.7†	(37)
OHT	114 ± 9.2	(46)	32.4 ± 4.7	(35)
OAG	129 ± 12.2	(15)	27.7 ± 5.5	(8)

B:	Differences between means (95% confidence limits)	
Difference	PVEP latency (msec)	DRC
OHT–control	7.8‡ (4.8 to 10.8)	−2.9§ (−5.0 to −0.9)
OAG–control	22.4‡ (15.9 to 28.8)	−7.7§ (−11.8 to −3.6)
OAG–OHT	14.6‡ (7.7 to 21.5)	−4.7‖ (−9.0 to −0.5)

* PVEP control data (obtained in collaboration with Dr. J. Camisa).
† DRC control data from reference 1.
‡ Limits of 95% confidence interval for difference between means.
‡$P < 0.001$; §$P < 0.002$; ‖$P < 0.025$ (t-tests, one-tailed).

Table 3. Pattern VEP latency and DRC: abnormal patients

		Number (%) of patients						
	PVEP latency				DRC			
		Abnormal*				Abnormal†		
Group	Number of patients	One eye	Both eyes	One or both	Number of patients	One eye	Both eyes	One or both
Control	37‡	1 (3%)	0 (0%)	1 (3%)	21§	1 (5%)	0 (0%)	1 (5%)
OHT	24	5 (21%)	5 (21%)	10 (42%)	18	4 (22%)	3 (17%)	7 (39%)
OAG	8	1 (12%)	5 (62%)	6 (75%)	4	0 (0%)	3 (75%)	3 (75%)

* Using 119 msec as the upper limit of normal, which is 2 SD above the mean PVEP latency for the normal subjects, the result was counted as abnormal if the latency was greater than 119 msec.

† Using 30 as the lower limit of normal DRC,[1] the result was counted as abormal if the DRC value was 30 or less.

‡ PVEP control data (obtained in collaboration with Dr. J. Camisa).

§ DRC control data from reference 1.

DRC control group mean. The two patient groups differed from each other: statistically significant differences between the OHT and OAG group means were at the level of $P < 0.001$ for PVEP, and $P < 0.025$ for DRC.

DRC and PVEP latency were correlated ($r = -0.66$, $P < 0.001$) over the patient group as a whole (OHT + OAG), and at a lower level within the OHT group ($r = -0.47$, $P < 0.005$), but were uncorrelated within the OAG group, which was of much smaller size.

Distributions of abnormal values of PVEP latency and DRC are shown in Table 3. For latencies, the upper limit of normal was taken as 119 milliseconds (2 SD above the normal mean). Seventy-five percent of OAG patients had abnormal latencies, nearly all in both eyes. Of the OHT patients, however, less than half had abnormal latencies, and half of these in one eye only. There was one instance (3%) of an abnormality in the normal control group, occurring in one eye of the oldest subject of the group.[1] The patient distributions of DRC abnormality were roughly similar to those of latency abnormality. The proportion of patients with an abnormal value either of PVEP latency or of DRC, or of both, was greater than the proportions of abnormality for either variable alone (Table 4).

Within the OAG group, the optic nervehead C/D ratio was significantly correlated both with PVEP la-

Table 4. Discrimination of Abnormality by PVEP Latency, by DRC, or by Both Combined

| | | Number (%) of Patients | | |
Group	Number of patients	Abnormal PVEP latency	Abnormal DRC	Abnormal PVEP latency and/or DRC
OHT	18	6 (33%)	7 (37%)	9 (50%)
OAG	4	3 (75%)	3 (75%)	4 (100%)

Includes only those patients for whom both variables had been measured. Patient is counted abnormal if latency > 119 msec for one or both eyes. Patient is counted abnormal if DRC is 30 or less for one or both eyes.

tency ($r = 0.55$, $P < 0.05$) and with DRC ($r = -0.68$, $P < 0.05$), but in the OHT group C/D ratios did not correlate either with PVEP latency or with DRC. Current intraocular pressures (measured either on the day of experimental measurements or on another occasion within 1–2 months) and Snellen visual acuity were uncorrelated with PVEP latency or DRC within each patient group.

Several age effects were noted: An age effect on DRC had been found previously in normal subjects (DRC Control group).[1] In the patients, both DRC and optic nervehead C/D ratio correlated with age within the OAG group ($r = -0.91$, $P < 0.001$; and $r = 0.62$, $P < 0.01$, respectively), but neither was correlated with age within the OHT group. In contrast, PVEP latency and Snellen visual acuity were uncorrelated with age within the control and OAG groups, but both were correlated with age within the OHT group ($r = 0.43$, $P < 0.005$; and $r = -0.33$, $P < 0.025$, respectively). Current IOP showed no correlation with age within either of the two patient groups.

Discussion. Glaucoma-associated abnormalities of visual latency, or of flicker-sensitivity, have been found in separate studies.[4] Latencies of PVEPs were prolonged in glaucoma,[3] as were those of the pupil light reflex.[4] Diminished critical flicker fusion frequencies have been described in the early stages of glaucoma, sometimes in parts of the visual field that had seemed normal by kinetic perimetry.[8] Sinusoidal flicker stimulation at variable modulation depths has been used with ocular hypertensive and glaucoma patients to demonstrate reduced central sensitivity to both slow[1] and rapid[9] flicker.

Our data strengthen the contention that these tests, which tap responses mainly from the central few degrees of the visual field,[1,10] reveal aspects of foveal vision that are not measured by Snellen acuity testing.[1,5] Although Snellen visual acuity was subnormal in many patients of the glaucoma group (and variability of acu-

ity was increased), both PVEP latency and DRC were uncorrelated to acuity in this group.

Like Snellen visual acuity, age appears not to have been a major determinant of the observed DRC and PVEP abnormalities. DRC normally declines with age,[1] but the mean age of the DRC control group was about the same as that of the OAG group, and greater than that of the OAG group (Table 1). While the PVEP control group was lower in mean age than either the OHT or OAG groups, control group data showed that the peak (P100) PVEP latency to a 2.3 cycles/degree sinusoidal grating (in contrast with latency to a checkerboard stimulus) is uncorrelated with age. Furthermore, when subsets of the PVEP control group were matched for age to the OHT and OAG groups by deleting the youngest control subjects, the significance of the control-patient differences in PVEP mean latencies was maintained at the $P < 0.001$ level. (A similar lack of relationship of PVEP latency to Snellen visual acuity, to intraocular pressure level, or to age has been reported recently by Towle et al.[3])

Other age effects were observed. Several variables were age-related within the patient groups, but differently in the OHT and the OAG group. Among the OHT patients, PVEP latency and Snellen visual acuity were correlated with age, while DRC and nervehead C/D ratio were not. Among the OAG patients, in contrast, DRC and nervehead C/D ratio were correlated with age while PVEP latency and Snellen visual acuity were not. These differences in patterns of age correlation between PVEP latency and DRC may have arisen in part from differences in stimulus conditions: both the diameter and the spatial frequency of the PVEP stimulus were approximately double those of the DRC stimulus, while the former's temporal modulation was slower. Thus, in our conditions, PVEP may have been affected by visual changes further from the fovea than was DRC.

The data are consistent with the existence of certain other qualitative as well as quantitative differences between the visual effects of OHT and those of glaucoma. The visual functions we tested (PVEP latency and DRC) were abnormal in both the OHT and the OAG groups, but tended to be far more abnormal in the OAG than in the OHT patients (Table 2), and were related closely to optic nervehead C/D ratio only among the OAG patients (even though the variability of the C/D ratio was about the same among both groups, Table 1). Thus, the bulk of the OHT population may have characteristics different from those of the OAG population. This is an assumption which, of course, underlies attempts to derive prognostic tests for OHT patients. The observed frequencies of abnormality within both the OHT and the OAG groups (Tables 3, 4) suggest that the search for early detectors

of glaucomatous damage should include prospective studies of PVEP latency and of flicker contrast-sensitivity variables such as DRC.

Little is now understood of the pathophysiology of these visual changes in OHT and OAG. Both the latency and the flicker variables show impairment of temporal characteristics of the visual system at low spatial frequencies, as could occur if glaucomatous optic nerve damage preferentially affected transient visual channels (eg, "Y" ganglion cells).[1,3] Although the role of optic nerve damage in glaucomatous visual defects is well-supported,[2] abnormalities at other more peripheral or central loci also may be involved.[4] Differences between the usual defects of demyelinating disease and glaucoma[4,5,11] imply that the latter may involve a significant retinal component while the former does not. Color vision abnormalities in OHT and OAG, mainly in the blue-yellow region, suggest dysfunction of the outer retinal layers,[4,12] and evidence pointing to a loss of visual sensitivity in glaucoma[4] also casts initial suspicion toward the retinal receptors. The abnormalities of color vision in OHT and OAG correlate with those of pattern VEP.[13] Most recently, however, significant ERG abnormalities were shown in glaucoma using patterned stimuli that apparently evoke corneally recordable signals from the inner retinal layers,[6,14] suggesting a change at the level of the ganglion cell layer, and therefore involving the optic nerve fibers to their terminations in the lateral geniculate nucleus. It might be that effects at the outer retinal level are important for some of the observed changes, while ganglion cell and optic nerve or other CNS effects may underlie other visual deficits. It is not inconceivable, as we have suggested,[4] that some vision changes in glaucoma might involve reduced neurotransmitter availability in the lateral geniculate nucleus, since elevated intraocular pressure can impede rapid anterograde axoplasmic transport, responsible for bringing neurotransmitter components to the axon terminals.

References

1. Atkin A, Bodis-Wollner I, Wolkstein M, Moss A, and Podos SM: Abnormalities of central contrast sensitivity in glaucoma. Am J Ophthalmol 88:205, 1979.
2. Quigley HA, Addicks EM, Green WR, and Maumenee AE: Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Arch Ophthalmol 99:635, 1981.
3. Towle VL, Moskowitz A, Sokol S, and Schwartz B: The visual evoked potential in glaucoma and ocular hypertension: effects of check size, field size, and stimulation rate. Invest Ophthalmol Vis Sci 24:175, 1983.
4. Atkin A, Podos SM, and Bodis-Wollner I: Abnormalities of the visual system in ocular hypertension and glaucoma: seeing beyond routine perimetry. In Glaucoma Update II, Proceedings of the International Glaucoma Society, Carmel, 1982, Krieglstein GK and Leydhecker W, editors. New York, Springer-Verlag, 1983, pp. 107–116.
5. Bodis-Wollner I, Hendley CD, Mylin LH, and Thornton J: Visual evoked potentials and the visuogram in multiple sclerosis. Ann Neurol 5:40, 1979.
6. Bobak P, Bodis-Wollner I, Harnois C, Maffei L, Mylin L, Podos S, and Thornton J: Pattern electroretinograms and visual-evoked potentials in glaucoma and multiple sclerosis. Am J Ophthalmol 96:72–83, 1983.
7. Halliday AM: Visual evoked potentials in demyelinating disease. In Demyelinating Disease: Basic and Clinical Electrophysiology, Waxman SG and Ritchie JM, editors. New York, Raven Press, 1981, pp. 201–215.
8. Kozousek V: L'importance de la fréquence critique de fusion subjective pour le pronostic de la destruction du champ visuel. Ann d' Oculist (Paris) 201:1126, 1968.
9. Tyler CW: Specific deficits of flicker sensitivity in glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci 20:204, 1981.
10. Celesia GG and Meredith JT: Visual evoked responses and retinal eccentricity. Ann NY Acad Sci 388:648, 1982.
11. Enoch JM, Fitzgerald CR, Campos EC, and Temme LA: Different functional changes recorded in open angle glaucoma and anterior ischemic optic neuropathy. Doc Ophthalmol 50:169, 1980.
12. Drance SM, Lakowski R, Schulzer M, and Douglas GR: Acquired color vision changes in glaucoma. Use of 100-hve test and Pickford anomaloscope as predictors of glaucomatous field change. Arch Ophthalmol 99:829, 1981.
13. Towle VL, Moskowitz A, Sokol S, and Schwartz B: Abnormal color vision and visual evoked potentials in ocular hypertension and glaucoma. ARVO Abstracts. Invest Ophthalmol Vis Sci 22(Suppl):258, 1982.
14. Fiorentini A, Maffei L, Pirchio M, Spinelli D, and Porciatti V: The ERG in response to alternating gratings in patients with diseases of the peripheral visual pathway. Invest Ophthalmol Vis Sci 21:490, 1981.

Time Course and Variability of Dark Focus

Roy Baker, Brian Brown, and Leon Garner

When the eye is deprived suddenly of visual stimulation, the accommodative system drifts from the previous state of accommodation to a state known as the dark focus. This condition also is known as night myopia. We measured the time course of this drift using a continuously recording infra-red optometer. The time course resembles an exponential decay function with a time constant of 1–3 seconds. The recovery of accommodation to the prior level after visual stimulation is restored suddenly has a time constant of 0.2–0.4 seconds. The state of accommodation in the dark depends on the state of accommodation prior to the onset of darkness. Our subjects showed a zone of accommodative inactivity rather than a single resting point of accommodation. Invest Ophthalmol Vis Sci 24:1528–1531, 1983

A century has passed since Lord Rayleigh[1] noted that his visual acuity improved in twilight conditions if he wore −1 diopter (D) lenses. Mellerio[2] reviewed the literature and reported that explanations of night myopia have included parafoveal cupping, choroidal thickness changes, the Purkinje shift, the Stiles-Crawford effect, and optical aberrations following pupil dilation. Ivanoff[3] attributed only 0.4 D of a myopic shift to optical aberrations. The amount of night myopia[4] appears to lie between 0 and 4 D; the above theories fail to explain the major portion of the myopic shift.

Morgan[5] proposed that a "rest" position for accommodation lies between the far and near points. It had been assumed previously that the accommodative rest position was always at the far point, that active accommodation was needed to clearly image near targets on the retina, and that relaxation of accommodation was necessary to form clear images of distant targets. Morgan's theory was confirmed later by evidence for an intermediate rest position of accommodation during total darkness. Campbell[6] and Alpern and David[7] demonstrated that there is a retinal illuminance threshold for accommodation and fixation at about one troland.

Phillips* hypothesized that night myopia can be grouped with other transitory myopias such as empty space, instrument, and sleep myopia; in these conditions there is no visual input to drive accommodation, and the accommodation system drifts toward a "rest" position. Phillips used a pinhole pupil to remove defocus signal feedback ("opening the accommodation

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* Phillips S: Ocular neurological control systems: Accommodation and the near response triad. Unpublished Ph.D. Dissertation, University of California, Berkeley, 1974.