Specific deficits of flicker sensitivity in glaucoma and ocular hypertension

Christopher W. Tyler

Temporal modulation sensitivity for a 5° flickering field was measured in central and peripheral retina for 46 eyes with glaucoma and ocular hypertension. Prior to showing any visual field loss by conventional perimetry, 90% of patients exhibited significant losses in sensitivity around a specific frequency of about 30 to 40 Hz. Low-frequency sensitivity and critical flicker frequency were often unaffected by such losses. The central field showed almost as pronounced a loss as 20° in the periphery.

Key words: flicker, temporal frequency, visual sensitivity, glaucoma, ocular hypertension, perimetry

The technique of measuring the temporal frequency characteristics of the human eye by varying modulation depth of sinusoidal flicker was introduced by de Lange.[5, 6] He appreciated the clinical value of this increased information over the conventional measure of critical flicker frequency (CFF) and suggested the use of such measurements before and after medical treatment.

This approach was taken up by Breukink,[4] who examined the diagnostic value of de Lange curves in 100 patients with various retinal diseases, using a 2° field with a large equiluminant surround. He analyzed the data in terms of the qualitative similarity of effects to three manipulations for normal eyes: luminance reduction, eccentric viewing, and elimination of the equiluminant surround. Luminance reduction results mainly in a loss of modulation sensitivity in the high-frequency region. Eccentric fixation produces a general loss in sensitivity, whereas elimination of the equiluminant surround produces a loss in the low- and medium-frequency regions. These effects provided a framework for the discussion of his abnormal results. Five of Breukink's patients had simple glaucoma. For these patients the main loss was in the high-frequency region, although one patient showed middle-frequency (4 to 30 Hz) losses only and hence did not fit into his classification scheme.

This paper describes an experimental study which uses the de Lange technique in a population of patients with ocular hypertension and glaucoma, using a temporal version of the visuogram analysis of functional loss[3] to assess the temporal characteristics of sensitivity loss in these conditions. Many of the patients showed losses specific to limited ranges of temporal frequency, which are of a different form from those described by Breukink.[4] The results are considered both in terms of their experimental significance and their potential clinical application.

From the Smith-Kettlewell Institute of Visual Sciences, San Francisco, Calif.

Supported by NIH grants EY 02124 and EY 01186 and the Smith-Kettlewell Eye Research Foundation.
Submitted for publication Oct. 31, 1979.

Reprint requests: Christopher W. Tyler Ph.D., Smith-Kettlewell Institute of Visual Sciences, 2232 Webster St., San Francisco, Calif. 94115.

0146-0404/81/020204+09$00.90/0

Methods

The flicker sensitivity functions were measured by varying the modulation depth of a sinusoidally flickering light to perceptual threshold for various frequencies of flicker. The frequency range chosen was from 5 Hz upwards, both because pilot data below 5 Hz showed greater variability than above this frequency and because it is above the range at which pupil responses are elicited.[9]

The flicker apparatus consisted of a square array of 25 high-luminance light-emitting diodes. These light sources have an extremely linear current/luminance function. A steady DC signal controlled the mean luminance at 40 cd/m^2 and a two-decade 10-turn logarithmic potentiometer controlled the added amplitude of sinusoidal modulation. An additional one-decade range switch permitted control of the modulation from 0.1% to 100%, which is important because good observers can give readings in the range of 0.3% to 0.5% under optimal conditions.

The field of 25 light-emitting diodes was set behind a circular diffusing sheet in a tube with a white inner surface, so as to give the appearance of a uniform field 2.5 cm in diameter. This field was placed in a large (40 cm) equiluminant steady field made by projection of 4 incandescent bulbs onto a diffusing surface. There was a 1 mm dark border around the flickering field. The apparatus was viewed from a forehead and chin rest at a distance of 28.5 cm, so that the flickering field subtended 5°. Black fixation spots were placed 45° down to the right and left of the flickering field at a distance of 10 cm (20° from the fovea). For peripheal observation the patient was instructed to fixate on the appropriate one of these points to present the field to the nasal retina 14° below the blind spot (Fig. 1). The aims of the peripheral positioning were to test an area of retina which is affected early in the course of the disease (as in Bjerrum's scotoma, which extends in an arc above and below the blind spot) and at the same time to avoid the possibility of stimulating in the blind spot itself.

The patient was seated in the apparatus and informed of procedure. At each frequency tested the experimenter adjusted the log potentiometer until the patient was satisfied that flicker had just disappeared. Usually each point was measured twice, but at some intermediate frequencies only one reading was taken. (CFF for 100% modulation was measured by varying the test frequency while modulation remained at 100%.) Almost all patients showed extremely good reliability under this method of experimenter admustment, with a

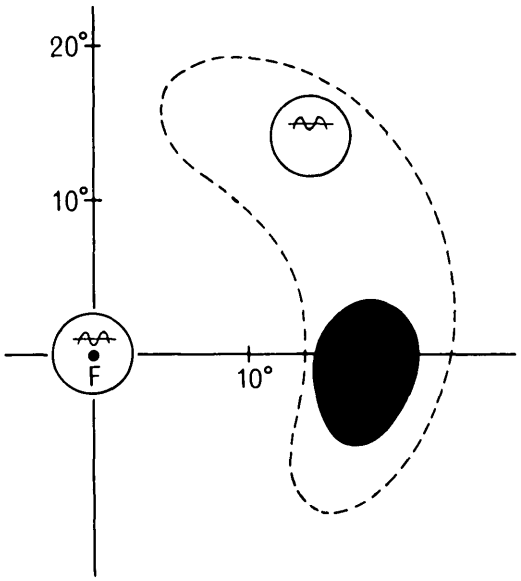

Fig. 1. Stimulus configuration as seen by a patient viewing with the right eye. Full circles represent the area of the flickering stimulus in its two alternative positions. *F*, Point of fixation. Also shown is the projection of the blind spot (black region) and an example of the form of Bjerrum's scotoma (dashed line).

mean standard deviation of only 1.2 db (15%) of the mean threshold at any frequency. Thus the criterion for abnormality (described in Results) lies at 5 S.D. from the normal mean in terms of the experimental variability of patients' responses. This means that less than one normal response in a million will appear abnormal on the basis of experimental variability alone (as opposed to variability across observers, which is discussed in Results).

The population was drawn from the normal glaucoma population of Moorfields Glaucoma Clinic, London. Patients were selected solely on the basis of exhibiting mild or no field losses on the Goldmann perimeter in the eye to be tested. Forty-one patients were tested, of whom 75% showed marked field losses in the untested eye. The age range of the patients was 29 to 78 years (mean 59). Twelve normal observers from roughly the same geographic population were tested to provide a response baseline. (Individuals with a high consumption of alcohol or tobacco were eliminated from the sample.) The age range of normals spanned 30 to 67 years and was similar to that of the patients but with a somewhat lower mean age (44).

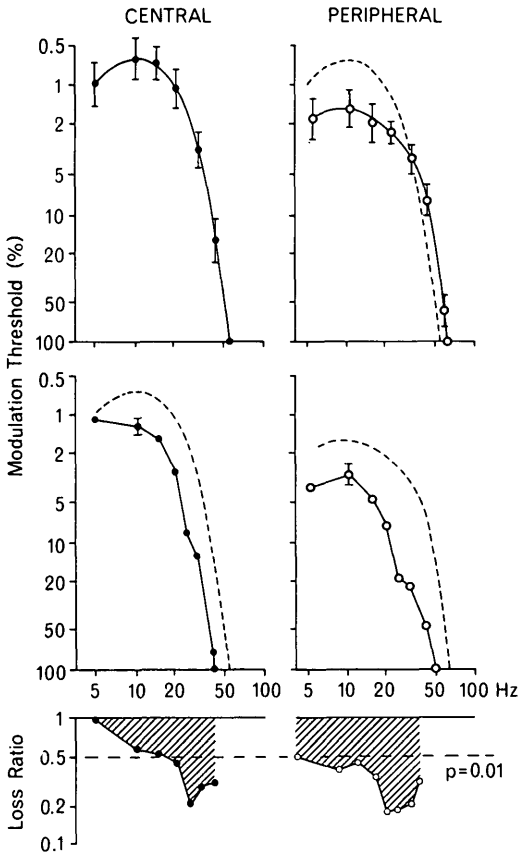

Fig. 2. Upper panel, Flicker sensitivity for 5° field shown in terms of modulation threshold as a function of temporal frequency in double logarithmic coordinates for the normal observers in this study. Sensitivity for central vision is shown on the left, and sensitivity for the 20° peripheral condition is given on the right, with central sensitivity replotted as dashed line for comparison. Error bars represent 1 S.D. of the mean response across observers. **Center panel,** Flicker sensitivity for a typical ocular hypertensive patient, with central *(left)* and 20° peripheral *(right)* viewing. Note reduction in sensitivity compared with normal (dashed lines). Error bars represent 1 S.D. of each setting averaged across temporal frequency. **Lower panel,** Loss ratio for this patient in comparison to normals. A value of 1 represents equality with the normals, and regions of loss are shown hatched. Values below dashed line are significantly different from normal at a probability level of p = 0.01.

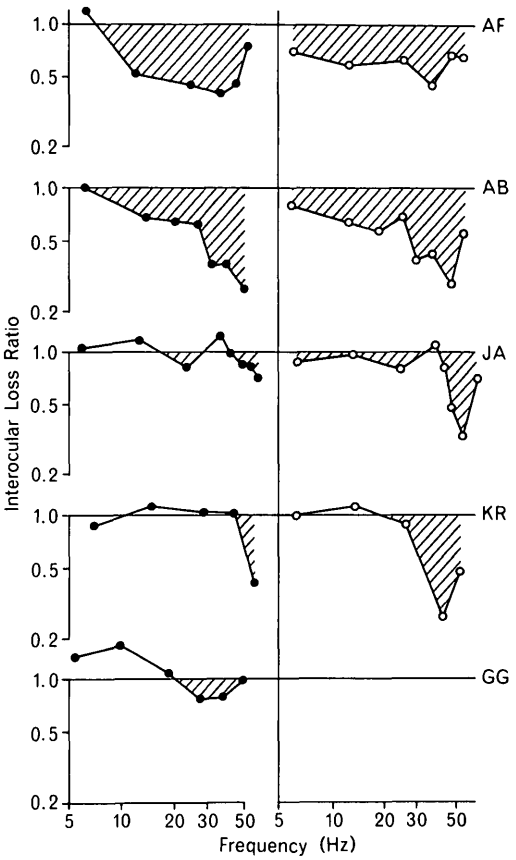

Fig. 3. Interocular temporal visuograms of the loss in the eye with the highest known intraocular pressure relative to the other eye for five patients. Central test fields are shown at left, and 20° peripheral condition at right.

This mean age difference might be embarrassing if sensitivity tended to decline with age, but in this population of normals, for example, there is actually a nonsignificant positive correlation (0.04) of age with sensitivity at 40 Hz. Given the lack of correlation with age in the patient population reported below, there seems to be little ground for concern over the mismatch of mean age in the normal and patient populations.

Results

The format in which the data were obtained is shown in Fig. 2 for a typical patient, 54 years old. His right eye showed completely normal Goldmann perimetric fields with the I_4 target (which was the size in routine use at the Moorfields clinic). Snellen acuity was 6/5. Fundus examination revealed no cupping of the disc. The intraocular pressure had been 38 mm Hg 2 years before but was brought down to 14 mm by the use of pilocarpine and adrenaline drops. The left eye had shown less elevation of pressure (22

Table I. Clinical data for five patients of Fig. 3

Patient (age)	*Tested pressure (mm Hg)*	*Highest known pressure (mm Hg)*	*Field losses*	*Acuity*	*Fundus*	*Treatment when tested*
A. F. (59):						
OD	33	37	Enlarged papilla	20/15	Normal	Guanethidine, adrenaline
OS	40	47	Spotty losses	20/15	Normal	
A. B. (54):						
OS	16	22	None	20/20	Normal	Pilocarpine
OD	14	38	None	20/15	Normal	
J. A. (50):						
OS	22	30	None (except 2° lower macular scotoma)	20/15	Normal	None (OD dilated)
OD	22	22	None (except 2° lower macular scotoma)	20/15	Normal	
K. R. (47):						
OD	19	19	None	20/30	Normal	None
OS	41	41	Peripheral restriction (due to aphakia?)	20/80 (Aphakic)	Normal	
T. G. (41):						
OS	20	26	Enlarged papilla	20/200 (Cataract)	Slight cupping of disc	Diamox
OD	28	44	None	20/15	Slight cupping of disc	Pilocarpine, adrenaline

mm) and was clinically normal. The right eye was regarded as having a condition of ocular hypertension (since the fields were normal).

The normal flicker sensitivity profile as a function of temporal frequency is shown in the upper panel of Fig. 2, with the mean response provided by data from 12 normal observers. Error bars represent 1 S.D. of the variability across normal observers, which is approximately constant across temporal frequency. The level at which sensitivity loss regarded as significant will be taken as 2.3 S.D. of the response distribution across normal observers below the normal mean. By this criterion, 1% of normals would spuriously show a significant loss, which is an appropriately low false-positive rate. Central observation is shown in the left graph by filled circles in Fig. 2, and the 20° peripheral condition in the right graph by open circles.

The patient's data are shown in the center panel. It is clear that this patient showed a markedly reduced flicker sensitivity, especially at the high frequencies. Central and peripheral sensitivities were about equally affected. The lower panel shows the degree of loss in the patient's sensitivity relative to the normal observers. These functions are expressed as the ratio of normal to abnormal sensitivity at each temporal frequency and may be called the temporal visuograms of the eye. The dashed line indicates the criterion of 2.3 S.D. of the variance across normals and will be regarded as the level below which the loss is significant. This patient showed a marginally significant loss for both central and peripheral viewing up to 15 Hz, but the loss was dramatic in the region of 20 to 40 Hz. Note that the visuogram plot emphasizes specific aspects of the loss function which are not clearly evident in the sensitivity functions, due to the changing slope of the normal curve.

Interocular comparison. Since there may be substantial variability in many particulars of individual visual systems, it is of value to compare visual losses in the two eyes of patients with a greater glaucomatous involvement of one eye than the other. This type of comparison uses each patient as his or her own control and avoids several potential factors which might add variability to the data,

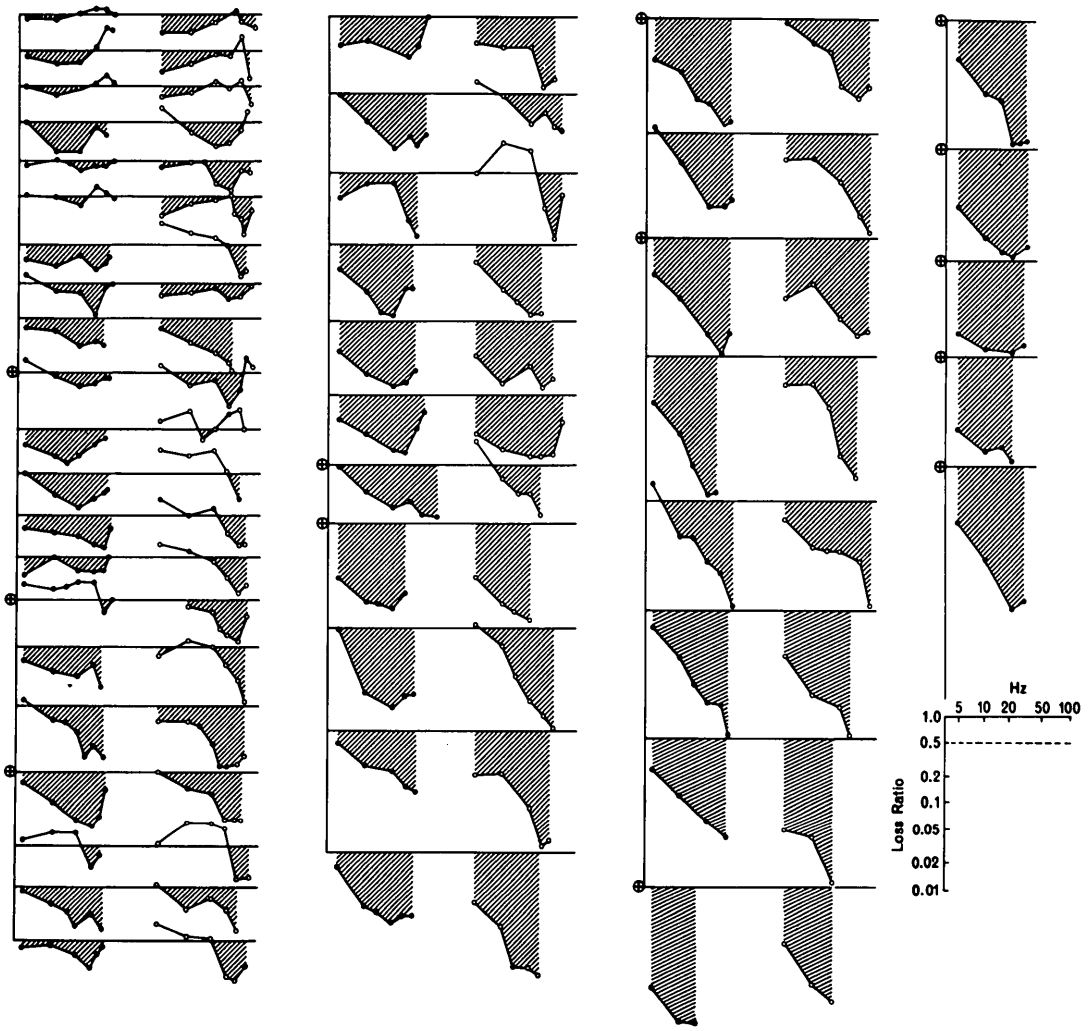

Fig. 4. Temporal visuograms for 46 eyes with ocular hypertension and glaucoma. Visuograms are plotted in terms of loss ratio relative to normal observers as derived in Fig. 2. Data on the left of each column are for central retina *(full circles)*, and on the right for 20° peripheral retina *(open circles)*. Scale is shown at lower right, with dashed line representing level of significant loss at p = 0.01. The average variability of the data is small, and ±1 S.D. is only twice the diameter of the open and filled symbols. Glaucomatous eyes (exhibiting perimetric field losses in addition to ocular hypertension) are indicated by circled crosses.

Table II. Proportion of patients showing significant flicker loss in the temporal visuogram in relation to field losses revealed by Goldmann perimetry (N = 42)

Perimetry	*Normal (ocular hypertension)*		*Loss (glaucoma)*	
Retinal locus	*Central (%)*	*Peripheral (%)*	*Central (%)*	*Peripheral (%)*
Flicker				
Normal	17	14	23	0
Loss	83	86	77	100
Total	100	100	100	100

such as (1) endogenous variations in sensitivity across individuals, (2) retinal differences due to drug treatment of the disease in patients but not in normals, and (3) effects of drugs on pupil size and hence on effective luminance of the display (except where a mydriatic has been used in one eye, as was the case with one patient in this series, J. A.).

It was possible to make interocular comparisons in five patients whose clinical profiles are summarized in Table I. These patients showed a range of clinical conditions. Three were receiving hypotensive drugs when tested, but two were not. One was aphakic in one eye. One had a substantial uniocular cataract. Four had normal fundi in both eyes, whereas one showed slight cupping of the optic disc in both eyes. All had either full Goldmann fields or only slight losses.

Despite this range of conditions, the losses shown by the interocular temporal visuogram were remarkably similar (Fig. 3). The interocular temporal visuogram was obtained by taking the ratio of sensitivity in one eye relative to the other. The baseline was always the eye with the lower of the two intraocular pressures at the maximum recorded level (Table I, column 3). In each case, therefore, the eye with the higher intraocular pressure showed a loss relative to the other eye, particularly at high temporal frequencies (Fig. 3). Although the foveal losses had no very consistent pattern, the peripheral losses were predominant at a particular temporal frequency (30 to 50 Hz) in each of the four cases where they were measurable. In the fifth case (G. G.) it was not possible to measure the peripheral loss due to a cataract in the eye with the lower intraocular pressure (OS), but the foveal loss (which may be slightly elevated due to the cataract) showed the same pattern of maximum loss at a high temporal frequency. These results are illustrative of the pattern of temporal loss in ocular hypertension and glaucoma and of the relative insensitivity of the technique to optical factors, both of which are considered in more detail in the following sections.

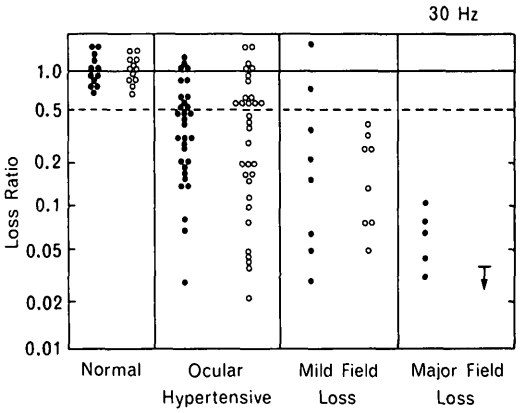

Fig. 5. Sensitivity relative to normal mean at 30 Hz for normals and patients with three categories of field loss. *Filled circles,* Central sensitivity; *open circles,* peripheral sensitivity; *dashed line,* level of significant loss at p = 0.01. For the major field loss category, peripheral sensitivity was absent, and hence loss was greater than the horizontal bar. Note substantial separation of normal and ocular hypertensive groups in terms of degree of loss and progressive increase in loss with increasing field defect.

Temporal visuograms. Temporal visuograms derived as in Fig. 2 for 46 eyes with ocular hypertension and glaucoma are given in Fig. 3. Full lines, filled circles to the left of each column show central foveal losses and dashed lines, open circles to the right of each column show 20° peripheral condition. The data are arranged approximately in order of the severity of loss, with the last five eyes showing no flicker detection at all in the periphery so that only central curves are given. Eyes showing field losses in the tested eye are indicated by a circled cross.

It is immediately obvious that most hypertensive eyes showed marked losses in flicker sensitivity at some point in the visuogram. The significance level is indicated by the dashed line in the scale panel in the lower right corner of Fig. 4 and applied at each measured point, but since the data analysis below will focus attention on just one point, it did not need correction for multiple tests.

An initial analysis of the losses represented

Invest. Ophthalmol. Vis. Sci.
February 1981

Table III. Percentage of cases in which loss has the form of a low-frequency notch (<25 Hz), a high-frequency notch (>25 Hz), or increases up to the maximum frequency testable for central and peripheral vision (N = 45)

Vision	*Low-F loss (%)*	*High-F loss (%)*	*Maximum loss (%)*	*Total*
Central	39	33	27	33
Peripheral	5	46	49	41

in Fig. 4 shows that a very high proportion of ocular hypertensives and all glaucomatous eyes exhibited significant flicker sensitivity losses. These results were partitioned separately for central and peripheral sensitivity in Table II. There are two major observations to be drawn from these figures.

(1) Overall, there was a substantial proportion (about 80%) of significant loss in the central 5° of vision, although none of these patients showed any field losses in this region, and its involvement was usually manifest only late in the course of the disease. (2) For ocular hypertensives, 86% showed significant losses in the periphery, and for losses either in central or peripheral vision (the union of the two sets), the figure rose to 90%. This suggests that the temporal visuograms are highly sensitive to slight disruptions of visual function at an early stage of glaucoma.

Relationship to visual field loss. Although it is difficult to quantify visual field losses because of the range of retinal regions in which they may occur, it is worth considering the relationship of flicker sensitivity losses to a crude breakdown of the extent of visual field loss shown in Fig. 5. For this purpose, in addition to normals, the patients were divided into three categories: (1) ocular hypertensives (no Goldmann field loss), (2) mild field loss (Goldmann field losses that did not include either the central or 20° peripheral region), and (3) extensive field loss (Goldmann field losses that included the 20° peripheral region, so that only the central location could be tested).

The comparison was made for each category of loss and the flicker sensitivity at 30 Hz. (This frequency was chosen rather than 40 Hz because the former gives a greater measurable range of possible loss in the central retina.) If CFF was lower than 30 Hz, as happened occasionally, the sensitivity loss was taken as that for the CFF itself.

The data shown in Fig. 5 for both the central and peripheral locations (except the latter for category 3) show that, in general, the flicker sensitivity loss became worse as the field loss became more extensive. The data also emphasize the separation between normals and most patients, including ocular hypertensives, who showed little overlap in their distributions of flicker sensitivity at 30 Hz.

Notch losses in sensitivity. What is the form of the sensitivity loss? When one scans the set of visuograms in Figs. 3 and 4, it becomes clear that sensitivity loss was often greater at some intermediate frequency than at either low or high frequencies. There was a marked tendency for the loss to occur in the form of a notch, as has been reported for losses in spatial frequency sensitivity.[3]

The existence of such notch losses implies that measurement of temporal losses by the conventional CFF technique will show less dysfunction than will the temporal visuogram. In fact, in the present sample there were many cases in which CFF was within normal limits but a significant sensitivity loss occurred at medium frequencies. This situation occurred in 11 cases for central stimulation, nine cases for peripheral stimulation, and nine cases for peripheral stimulation, and nine cases when both central and peripheral positions show normal CFF. Thus some 20% to 25% of this population would appear normal by a CFF test but showed significant losses in their temporal visuogram.

The notch loss can be analyzed in more detail in terms of its peak temporal frequency. In order to quantify this occurrence, I divided the data of Fig. 4 in which a significant loss occurred into three categories: (1) a notch loss peaking below 25 Hz, (2) a notch loss peaking above 25 Hz, and (3) a loss maximal at the highest testable frequency, i.e., no notch. The criterion for a notch loss

was that the loss, both at 5 Hz and at CFF, was less than the peak loss. Note that since the loss tended to increase markedly towards higher frequencies, a sudden shift toward decreasing loss represents a marked change in the slope of the loss function.

The number of each of these cases for the central and peripheral viewing is shown in Table III. The difference in distribution between center and periphery was significant on a χ^2 test at $p = 0.01$ This reflects the preponderance of low-frequency notch losses in central retina and high-frequency losses in the periphery. Thus the two regions of retina seemed to be differently affected by glaucoma.

Note from Table III that, overall, 60% of the losses were in the form of a notch loss; that is, the greatest loss occurred at some temporal frequency other than CFF. Note also that a higher proportion of significant losses occurred in the periphery (98%) than in the central 5° (77%).

Finally, the data may be considered in terms of the test frequency most susceptible to loss. The point of greatest susceptibility overall was in the high-frequency region, since those with a maximum loss at the highest testable frequency also showed substantial losses at slightly lower frequencies. The periphery also showed a greater proportion of notch losses at high frequencies. Thus a single test condition that would maximize the number of cases detected would be a frequency of 40 Hz for the periphery condition. At this point, the range of severity of loss that can be measured is 1.0 log units (or a factor of 10 worse than normal). The 40 Hz test condition would show a loss of 37 of the 42 cases which show any significant loss. An additional test condition at 25 Hz in the periphery would catch three of the remaining cases, adding up to a total of 95% of the cases showing a loss at any frequency in either retinal location.

Effect of age on flicker sensitivity. If flicker sensitivity were affected by the age of the observer, this would tend to lessen the value of the test in older populations. A correlation was therefore performed between age and flicker sensitivity in the periphery at 40 Hz. The correlation was -0.23, which is not significant at $p = 0.05$. The normal sample showed a correlation of 0.04 between age and the same sensitivity measure. Therefore, in the version of the flicker sensitivity test used in this study, age per se did not have a significant effect on flicker sensitivity across the adult population. A flicker sensitivity test is therefore preferable to tests based on visual acuity, which are affected by aging of the optics of the eye.

Discussion

Normal flicker sensitivity. The data from the normal observers are worthy of comment in themselves. It is well known[7] that with a large field size, peripheral CFF can be higher than central CFF. What has not previously been established is whether this is due to a higher sensitivity in the periphery to flicker as such or to a specific increase in the frequency range over which flicker could be detected. The data of Fig. 2 clearly show that the normal peripheral retina has a lower sensitivity than central vision up to 30 Hz and that the increased sensitivity corresponding to a higher CFF is limited to the range above 30 Hz. This result was found for each observer (with some variability in the crossover point) and hence is a reliable aspect of flicker perception.

Thus increased CFF is not due to a general increase in sensitivity in the periphery but represents the sensitivity of a specific high-frequency mechanism.

In terms of receptive field types, this change in the shape of the flicker sensitivity function implies the existence of at least two mechanisms, of which the one with lower temporal-frequency range is more sensitive in central vision, whereas the higher temporal-frequency one predominates in peripheral vision. It is tempting to draw the analogy with the sustained central and transient peripheral mechanisms widely described in neurophysiology and psychophysics, but further evidence would be required before a firm relationship could be established.

Flicker losses in glaucoma. There is only

one previous study of flicker sensitivity in ocular hypertension (10 cases) and glaucoma (11 cases).[2] The authors measured flicker sensitivity at 8 Hz for a uniform field and counterphase grating. At this frequency they found a mean loss of about a factor of 2 for ocular hypertensives and about a factor of 4 for glaucoma. These data are commensurate with the loss obtained in the present group at 5 to 10 Hz. About half the ocular hypertensives fell within the normal criterion in their study, whereas for frequencies in the 30 to 40 Hz range (as above) 90% of ocular hypertensives are classified as abnormal. The higher frequency range is therefore more useful as a diagnostic tool than the 8 Hz commonly used in visual testing.

It is appropriate to consider the temporal visuogram results in relation to other recent psychophysical methods of assessment in glaucoma. One such is the spatial modulation sensitivity method developed originally by Schade[8] and adapted in a clinical form by Arden and Jacobsen.[1] In their study, the greatest losses occurred at the higher range of spatial frequencies tested by them and hence tend to confound age-related optical losses with retinal losses. For all other test conditions, the mean results for ocular hypertensives fell at just greater than the criterion for loss (2 S.D. poorer than normal). This suggests that approximately 40% of their ocular hypertensives would be classified as normal. By contrast, the temporal visuogram method described here shows abnormalities in 90% of ocular hypertensives, so that only 10% would be classified as normal. Thus, on this basis of comparison, the temporal visuogram method appears to be more sensitive to visual loss than a spatial visuogram method. Similarly, only 33% of ocular hypertensives show a central or peripheral flicker sensitivity loss at 5 Hz, which is the closest to a static sensitivity loss measured in this study. Thus the visual loss produced by ocular hypertension is emphasized by the higher temporal frequencies (e.g., 40 Hz), rather than static test patterns.

Conclusion. The results may be summarized by saying that the temporal visuogram provides a highly sensitive measure of visual losses in ocular hypertension and glaucoma. It has the advantage of being relatively immune to aging effects either of the retina or the optics of the eye. It is more sensitive to visual loss than the standard clinical use of Goldmann perimetry. And it is rapid and easy to administer to the patient.

These advantages combine to suggest that the temporal visuogram method could usefully be adopted in clinical practice for the assessment of visual losses in glaucoma. Given the lack of correlation of the visual loss with intraocular pressure, the temporal visuogram would provide a valuable method of assessing the effectiveness of drug therapy in minimizing visual loss and managing the course of the disease.

My thanks are due to Prof. J. Gloster and the staff of the Glaucoma Clinic of Moorfields Eye Hospital, London, for their collaboration and assistance with the testing program and to Profs. R. Weale and G. B. Arden and the Institute of Ophthalmology, London, for the use of facilities.

REFERENCES

1. Arden GB and Jacobsen JJ: Simple grating test for contrast sensitivity: preliminary results indicate value in screening for glaucoma. INVEST OPHTHALMOL VIS SCI 17:23, 1978.
2. Atkin A, Bodis-Wöllner I, Wolkstein M, Moss A, and Podos SM: Abnormalities of central contrast sensitivity in glaucoma. Am J Ophthalmol 88:205, 1979.
3. Bodis-Wöllner I: Visual acuity and contrast sensitivity in patients with cerebral lesions. Science 178:769, 1972.
4. Breukink EW: The attenuation characteristic of the human eye under normal and pathological conditions. Thesis, Rijkuniversiteit te Utrecht, 1962.
5. de Lange H: Experiments on flicker and some calculations on an electrical analogue of the foveal systems. Physica 18:935, 1952.
6. de Lange H: Attenuation characteristics and phase shift characteristics of the human fovea-cortex systems in relation to flicker-fusion phenomena. Thesis, Technische Hogeschool, Delft, 1957.
7. Hylkema BS: Examination of the visual field by determining the fusion frequency. Acta Ophthalmol 20:181, 1942.
8. Schade OH: Optical and photoelectric analog of the eye. J Opt Soc Am 46:721, 1956.
9. van der Tweel LH and Denier van Gon JJ: The light reflex of the normal pupil of man. Acta Physiol Pharmacol Neerl 8:52, 1959.