THE DETECTION OF AUTOMATED PERIMETRIC STIMULI IN OCULAR DISEASE

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SUMMARY

Automated perimetry has made viable a rapid threshold examination of the visual field and has reinforced the role of perimetry in the diagnostic procedure. The aim of this study was twofold: to isolate the influence of certain extraneous factors on the sensitivity gradient, since these might limit the early detection and accurate monitoring of visual field loss, and to investigate the efficacy of certain novel combinations of stimulus parameters in the detection of early visual field loss. The work was carried out with particular reference to glaucoma and to ocular hypertension.

The effects of media opacities on the visual field were assessed by forward intraocular light scatter (n=15) and were found to mask diffuse glaucomatous visual field loss and underestimate focal loss. Correction of the visual field indices for the effects of forward intraocular light scatter (n=26) showed the focal losses to be, in reality, unaffected. Measurement of back scatter underestimated forward intraocular light scatter (n=60) and the resultant depression of the visual field. Perimetric sensitivity improved with patient learning (n=25) and exhibited eccentricity- and depth-dependency effects whereby improvements in sensitivity were greatest for peripheral areas of the field and for those areas which initially demonstrated the lowest sensitivity. The effects of practice were retained over several months (n=16). Perimetric sensitivity decreased during prolonged examination due to fatigue effects (n=19); these demonstrated a similar eccentricity-dependency, being greatest for eccentricities beyond 30°. Mean sensitivities over the range of adaptation levels employed obeyed the Weber-Fechner law (n=10) and, as would be expected, were independent of pupil size. No relationship was found between short-term fluctuation and adaptation level. Detection of diffuse glaucomatous visual field loss was facilitated using a size III stimulus of duration 200msec at an adaptation level of 31.5asb, compared with a size III stimulus of duration 100msec at an adaptation level of 4asb (n=20). In a pilot study (n=10), temporal summation was found to be higher in glaucomatous patients compared with age-matched controls, although the difference was not statistically significant.

Key words: Glaucoma
Intraocular light scatter
Learning and fatigue effects
Adaptation level
Temporal summation

To W.S. and H.K.P.

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CHAPTER 1

AUTOMATED PERIMETRY

1.1. INTRODUCTION

The visual field is a topographical representation of the functional integrity of the visual system. It is classically defined as:

> "That portion of space in which objects are visible at the same moment during steady fixation of the gaze in one direction" (Traquair 1927).

The visual field has been likened to an island of vision in a sea of blindness, with a central peak corresponding to high foveal sensitivity and a gradual decline of sensitivity with increase in eccentricity. Disturbances at any stage of visual processing are characteristically reflected as changes in the height or the extent of this island.

1.2. FUNDAMENTALS OF PERIMETRY

Visual field examination (perimetry) measures the sensitivity of the visual system to light. When assessing the function of the visual system the minimum or threshold stimulation necessary to produce a response is measured. This minimum light stimulation may be carried out in darkness (absolute threshold) or against a background of given luminance. In the latter case, the minimum (or threshold) contrast between stimulus and background is measured. This is known as the increment threshold or the differential light threshold, the reciprocal of which is the differential light sensitivity. The variation in differential light sensitivity with eccentricity is known as the sensitivity gradient.

The method of presentation of the light stimulus may be either kinetic or static. In kinetic perimetry the luminance of the stimulus is constant and the threshold is approached in spatial steps. In static perimetry the position of the stimulus is constant and the luminance is variable.

The examination strategy is the course of decisions and actions that takes place in order to detect or assess a defect of sensitivity within the visual field. The examination strategy may be either threshold or suprathreshold. A suprathreshold strategy involves exposure of a stimulus at a luminance level slightly above the expected normal threshold at each test

location, the point being accepted as normal if the stimulus is seen. The threshold strategy measures the true increment threshold at each location tested. Threshold determinations map the actual contour of the sensitivity gradient and will detect subtle defects more easily than a suprathreshold strategy, but at the expense of increased examination time.

Computer-assisted perimetry is a form of visual field examination in which all or part of the examination is performed by a microcomputer or microprocessor instead of a human examiner. The term automated perimetry is applied when the decisions involved in the examination strategy are exclusively controlled by computer (Greve 1982) and no operator interaction is required. Semi-automated perimetry implies operator control of the examination strategy.

For optimum perimeter design the dynamic range should be maximised to permit an adequate range of sensitivity over which visual loss may be detected, assessed and followed-up. The dynamic range is defined as the measurement range over which the neuro-visual system can be examined using a specific instrument with a given set of experimental variables. Both dynamic range and sensitivity are expressed in decibels (dB). A decibel is one tenth of a log unit of the threshold stimulus luminance, 0dB representing the maximum stimulus luminance.

1.3. HISTORICAL PERSPECTIVE

Reviews of the development of visual field examination may be found in Atchison (1979a), Griffin (1980) and Drance (1985). The first investigation of visual field defects is generally accredited to Hippocrates in the 5th century B.C. who recognised hemianopic defects associated with brain disease in perceptive patients complaining of "half-blindness". Galen (138-210 A.D.) described scotomata and peripheral contractions. It was not, however, until the 19th century that visual field examination became part of the clinical routine (Von Graefe 1856). Two contemporaries of Von Graefe, Aubert & Foerster (1857), found that the extent of the field depended on the angular subtense of the target at the eye and subsequently developed the first commercial semi-circular arc perimeter which allowed the testing of each meridian out to 90°. In the latter half of the 19th century, little attention was paid to the relativ

merits of examination of the central and peripheral field. Generally, a single large target was used; if the field limits were normal, the entire field was assumed to be normal. Bjerrum (1889) emphasised the need for different sized targets and in his investigations of glaucomatous defects showed that little importance should be attributed to small, concentric narrowings of the field, but rather to scotomata, sector defects and partial restrictions. His compatriot Roenne also noted the significance of the nasal step feature. The work of Traquair (1927) supported that of Bjerrum (1889) and described the necessity of investigating a defect with a larger stimulus in order to elicit fully the characteristics of depth and uniformity.

During the latter half of the 19th century and the early 20th century clinical perimetry became an essential part of ophthalmology. The examination conditions were, however, poorly controlled and factors such as the background illumination level and the reflectance and colour of targets were rarely standardised. Perimetry emerged as a clinical science through the work of Ferree & Rand during the 1920s and 1930s. These workers investigated the factors which influenced the size and shape of the visual field using white and coloured stimuli. Two further developments revolutionised perimetry and led to its refinement as a clinical science. Firstly, Sloan (1939) measured the contrast sensitivity at given locations in the field with a stationary target, thus pioneering the technique of static perimetry. Secondly, Goldmann (1945a,b,1946) designed a hemi-spherical projection perimeter which provided controlled and uniform background luminance, stimulus luminance and stimulus size with a means to monitor patient fixation. Examination conditions were thus standardised, facilitating reproducible quantitative kinetic perimetry.

The method of static perimetry was introduced by Sloan (1939) using an arc perimeter but it was not until the development of the hemi-spheric Tubinger perimeter in the early 1960's through the work of Aulhorn & Harms that static perimetry became a viable technique. The Tubinger provided the advantages of Goldmann standardisation without the problems associated with kinetic perimetry, discussed in Section 1.4.

In recent years, work has been directed towards the automation of perimetry and elimination

of examiner variability (Heijl & Krakau 1975a), although early attempts at automation were not without problems, with little control over adaptation level or stimulus luminance (Harrington & Flocks 1954; Bedwell 1967). A summary of the development of computerised perimetry may be found in Fankhauser et al. (1977) and Fankhauser (1985). The first serious attempts at automation are ascribed to Dubois-Poulsen & Magis in the 1960's who used electromotors to move the stimulus and to change the filter setting in the Goldmann perimeter. Lynn & Tate (1975) were the first to suggest the use of a microcomputer to control the stimulus presentation. Greve et al. (1976) demonstrated that the automation of perimetry was feasible and Fankhauser et al. (1972) claimed that a computer controlled method was able to extract the necessary clinical data even in the presence of large sensitivity fluctuations and patient inattention. Research dealing with the theoretical aspects of the automation of perimetry (Fankhauser et al. 1972; Koch et al. 1972; Spahr 1973; Spahr 1975) led to the development of the first commercially available automated perimeter, the "Octopus", which was displayed at the International Perimetric Society meeting in Tubingen in 1976. Various other instrument prototypes were subsequently developed with a view to optimisation of the test strategy and examination of the patient-instrument interaction (Heijl & Krakau 1975a,b; Greve et al. 1976). These prototypes have been extensively modified, in the light of clinical experience, to the instruments of today.

1.4. KINETIC AND STATIC PERIMETRY

The principles of the two perimetric techniques are illustrated in Figure 1.1. in relation to the island or hill of vision.

Kinetic perimetry involves a horizontal approach to the hill of vision using a moving stimulus. Several approaches may be made to the hill to determine its gradient, using stimuli of a different size or luminance, usually moving the stimulus from non-seeing to seeing. Until 1940, perimetry was almost exclusively based on the kinetic technique. Stimuli of constant size and luminance are moved to determine the limits of the visual field i.e. where a "seen" response is elicited from the patient. The area contained within these limits is known as the isopter for that stimulus; typically, several isopters for stimuli of different sizes will be plotted during one examination. The amount of visual field information obtained is proportional to the

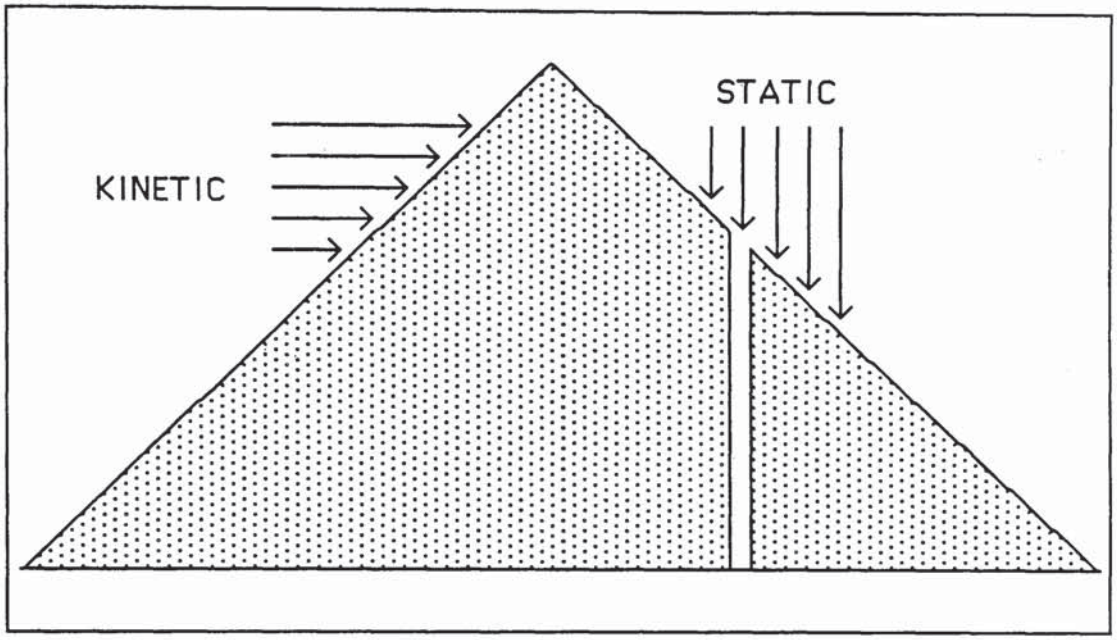


Figure 1.1. Illustrating the principles of kinetic and static perimetry in relation to the hill of vision.

number of isopters plotted. Kinetic perimetry suffers from variations in patient reaction time and speed of target movement which produces unreliable results particularly when the slope of the hill of vision is flat (Aulhorn 1969; Fankhauser 1969). Greve (1973) reports that Goldmann and others have recommended a stimulus velocity of 5°/sec for kinetic evaluation of the peripheral field and 2°/sec for examination of the central field. Johnson & Keltner (1987) have recommended a stimulus velocity of 4°/sec for examination of the central or the peripheral field with any stimulus size. In kinetic perimetry, the stimulus is moved over neighbouring locations between which spatial interactions may occur. When a moving stimulus is just below threshold it will excite a series of receptors infraliminally; in the periphery where spatial summation is high, summation of these successive infraliminal stimuli (successive lateral summation) can occur to produce a response, so shallow depressions in sensitivity may be missed (Greve & Verriest 1971; Greve 1973).

The ability to detect visual field defects using kinetic perimetry depends on the speed of movement of the stimulus, the slower the movement is, the smaller the defects that can be detected. The optimum speed for the detection of defects is thus zero i.e. static perimetry. Static perimetry adopts a vertical approach to the hill with a stationary stimulus of variable strength (luminance and/or size) which is exposed for a specified duration. The approach may be from non-seeing to seeing or vice versa. Static perimetry thus involves the measurement of the differential light threshold ($\Delta L/L$) where L is the background luminance and ΔL the increment threshold for a stationary stimulus exposed for a specified duration. Stimulus luminance is increased in discrete steps of a given magnitude rather than continuously. The size of these luminance steps is determined by the intra-individual variation of threshold and the significance ascribed to slight depressions in sensitivity (Greve 1973). The duration of the stimulus is discussed in Section 1.6.3. Static perimetry is not influenced by the reaction time of the patient and as the stimulus is stationary, Greve (1975) has suggested that it is more suitable for the detection of defects, particularly those which are small, shallow, centrally situated and progress slowly. Indeed, static perimetry has been shown to be more sensitive than kinetic perimetry for the detection of small isolated scotomata, that are often the first and only sign of glaucomatous damage (Harms 1952; Drance et al. 1967b; Aulhorn & Harms 1967, 1972; Armaly 1971; Greve & Verduin 1977).

Static perimetry is however more time consuming than kinetic perimetry (Greve 1975). The step-wise change of stimulus luminance and the patient reaction time after each change take longer than the continual centripetal movement of a stimulus until it is seen. Use of a suprathreshold strategy or presentation of multiple stimuli are time-saving techniques that may be employed with static perimetry (Greve 1982).

Several workers have advocated the combination of kinetic and static techniques as the most effective means of examination both in the detection and assessment of defects (Harms 1957; Schmidt 1965; Armaly 1969,1971,1972; Aulhorn & Harms 1972; Greve 1973; Rock et al. 1973). The detection phase determines whether there is a defect present; the assessment phase provides information about the size and intensity of the defect (Greve 1973). Kinetic perimetry is used to examine the blindspot and periphery in the detection phase and static perimetry to qualitatively and quantitatively examine the central field in both phases. In the normal eye, kinetic thresholds are lower (higher sensitivity) than static thresholds in the periphery, whereas for the central field, the reverse is true (Fankhauser & Schmidt 1960).

1.5. THE AUTOMATION OF PERIMETRY

The automation of perimetry offers many advantages over traditional manual methods namely,

1) The examination strategy is exactly defined and reproducible. Inter and intra-examiner variations in technique, which are a fundamental source of error are minimised (Berry et al. 1966; Heijl 1984; Ross et al. 1984).

2) Instruments may be operated by unskilled technical assistants.

3) The computer system allows for flexibility of the testing routine through software modification.

4) A large number of programs, strategies and stimulus parameters are available, thus testing may be optimised to the suspect pathology, thereby increasing sensitivity and specificity (Aulhorn & Durst 1977; Heijl 1977c; Greve 1982).

5) An excess of computer capacity can be used for novel types of graphical output (Greve 1982), and to monitor variables such as screen intensity and eye position.

6) The capacity for storage and handling of large quantities of data allows for statistical analysis of numerical data obtained at consecutive examinations (Fankhauser et al. 1972; Krakau 1978; Greve 1982; Heijl 1984).

7) Random stimulus presentation minimises the influence of expectancy and improves fixation, thus revealing the full extent of any defect (Heijl & Krakau 1977; Krakau 1978; Aulhorn et al. 1979; Keltner & Johnson 1981).

8) Automated perimetry is less labour intensive and time consuming than manual methods and therefore is more cost-effective (Johnson & Keltner 1980; Heijl 1984).

9) The quality of precise mapping of the extent and depth of defects is equal to or superior to that obtained by conventional methods (Koerner et al. 1977; Keltner et al. 1979; Mogil et al. 1985).

Automated perimetry is however considered to be unsuitable for the assessment of functional visual field loss (Smith & Baker 1987).

1.6. STIMULUS PARAMETERS

For optimum perimeter design the dynamic range should be maximised to permit an adequate range of sensitivity over which visual field loss may be detected, assessed and followed-up.

The dynamic range corresponds to the range between the maximum possible stimulus luminance ΔL_m and the threshold stimulus luminances L_o for an eye possessing normal sensitivity (Fankhauser 1979). The dynamic range is the effective range of measurement which is a function of the perimeter-patient interaction. It should not be confused with the entire operational range of the neuro-visual system, nor with the the entire range of stimulus luminances of the instrument. The detection, assessment and follow-up of defects may be compromised where sensitivity has fallen below the limits imposed by the dynamic range (Fankhauser 1979). Since ΔL_o rises with increasing background luminance L, a large dynamic range is obtained by maximising ΔL_m and minimising L. ΔL_m is determined by constraints related to the design of the perimetric apparatus, although in recent years these have become less stringent. The useful dynamic range in perimetry is limited at one end by photon noise and noise in the neurovisual system and at the other by stray light interference.

Stray light may arise from light scattered within the media but may also be produced in the perimetric apparatus itself. As a result, light is scattered beyond the geometrical boundaries of the stimulus (Fankhauser & Haeberlin 1980).

The choice of stimulus parameters incorporated in automated perimeters has its basis in research aimed at extending the dynamic range in manual perimetry. It has also been influenced by engineering considerations and compatibility with previous instruments.

1.6.1. Stimulus generation

The first perimeter of Tate & Lynn (1977) as well as that of Chaplin et al. (1973) utilised stimuli presented on a television screen however this method suffered from the difficulty of ensuring reproducibility of spot size and brightness. In addition, the use of phosphor screens, found on most cathode ray tubes, does not give independent control of stimulus size and intensity; the brighter the spot, the larger it is due to "blooming" of the phosphor.

The use of lasers as a stimulus light source has been proposed by Favella et al. (1974a,b) and Luizzi & Bartoli (1973). The incandescent lamp of a Goldmann perimeter was replaced by a He-Ne laser, although little is known about the efficiency and suitability of this source.

Several automated perimeters employ light emitting diode (LED) stimuli, embedded in a screen. These are driven by a high frequency pulse current thereby permitting variable stimulus intensity. The maximum intensity of early LEDs was limited, however these stimuli are now capable of operating at high luminance levels (Fankhauser 1979) and have the advantage of being silent in operation, mechanically robust and relatively cheap (Taylor et al. 1984; Lieberman & Drake 1987). LEDs however suffer several disadvantages as a perimetric stimulus. The main disadvantage is that the stimuli locations are fixed, although this may be overcome by altering the patient's fixation or rotating the perimeter bowl (Heijl 1984). Indeed, Phelps (1985) does not consider fixed stimuli locations to be a limitation provided the LED density is sufficient and the stimuli are optimally located for detection and description of visual field defects. The LED light output is highly directional, thus accurate mounting of LEDs in the perimeter bowl is essential and small individual variations in light output

necessitate individual calibration (Heijl 1985a). The stimulus size is fixed, and the spectral output limited to a narrow band; red, yellow and green LEDs have been available for some time however a blue LED, capable of operating at high luminance, has only been accessible since around 1983. The chromatic nature of LED output may not be considered as a disadvantage, however the results may not be directly compared with those of white-light perimetry (Fankhauser 1979).

If the LEDs are recessed in the perimeter bowl this can give rise to an impression of "black holes" on the perimeter surface (e.g. the Dicon instrument). A true differential light threshold is not measured since the stimulus intensity is not added to an even background; the black hole effect may produce changes in local retinal adaptation (Heijl 1985a; Mills 1985). Indeed, it may be found that the LED luminance is less than the background luminance at threshold thus giving a negative differential threshold particularly within the sensitive central 20° of the field, the so-called "dark-hole" phenomenon (Desjardins & Anderson 1988), although this is considered to be of little clinical significance (Britt & Mills 1987). The Competer and Perimat systems use LEDs mounted behind a diffusing film which provides a homogeneous surface to the perimeter bowl and makes the mounting less critical (Heijl 1984). A higher variance in the threshold response has been demonstrated with uncovered LED stimuli than when the stimuli are covered with a diffusing film (Britt & Mills 1987; Desjardins & Anderson 1988). Flanagan et al. (1988) have illustrated the differences in shape of the sensitivity profile determined by black hole LEDs, isoluminant LEDs and the geometrically equivalent projected polychromatic stimulus of the Humphrey Field Analyser. Centrally, the profile of the Dicon black hole stimulus followed that of the Humphrey projected stimulus size Goldmann II (0.216°) and beyond 5° that of stimulus size Goldmann I (0.108°). The Topcon isoluminant profile followed that of the Humphrey stimulus size II over the whole field, despite being closer in size to the Goldmann III (0.431°) stimulus.

Fibre-optic systems, employed in the early Fieldmaster and more recently the Tubingen automatic perimeter, use a central stimulus source from which light is guided along fibre-optic cables which insert into the perimeter. The technique offers a consistent luminance level and facility to alter stimulus colour (Mills 1984) but again the stimuli locations and size are fixed

and the technique is relatively expensive. It is important that the spectral response curve of both LED and fibre-optic stimuli matches that of the retina, however the spectral response of a fibre optic source (frequently a Tungsten light is used) is less linear with varying intensity than an LED source. Thus, a "white" stimulus may appear red-orange at low intensities. This is usually overcome by applying a constant voltage to the Tungsten source and using filters to alter the intensity (Taylor et al. 1984). Although the stimuli may be presented individually, their intensities cannot easily be altered individually, unlike LEDs, and thus fibre-optic instruments are more suited for one-level suprathreshold screening than for threshold measurements (Phelps 1985).

Projection systems using an integrating hemisphere are considered the best form of stimulus generation (Tate & Lynn 1977). The luminance of the stimulus is determined by the luminous intensity of the light source and the aperture of the projection system. The luminance of the projected spot is added to that of an evenly illuminated background and a true differential threshold is measured. Projection offers the advantages of an easily calibrated light source, independent control of stimulus size and intensity, the alternative of coloured stimuli and the ability to position the stimulus at any location, thus allowing both static and kinetic perimetry and a high spatial resolution. Indeed, the spatial resolution on the Octopus 201 perimeter is 0.1°. An alternative method of providing high spatial resolution may be to move the fixation target (Fankhauser 1979), employed in the recently introduced Dicon TKS4000 instrument.

The main disadvantages of a projection system are its cost, complicated and vulnerable mechanical construction and slow speed of presentation compared with LED systems (Heijl 1984). The incandescent light source is subject to changes in calibration with aging and the positioning of the movable mirror, which governs stimulus position, must be frequently checked (Heijl 1985a). The quick and accurate movement of a projected stimulus requires a very precise and rapid system of servomotors, and these stepping motors may be audible. As a result the patient may become conditioned to respond to the noise; the checking of false positive responses (see Section 1.13.) and use of background "white noise" may overcome this tendency. With a single light source, the luminance may be easily monitored

and its intensity adjusted by neutral density filters. The measurement of the stimulus intensity is not however at the testing plane, and the exact level of light as calculated at the source may not be projected into the perimeter bowl (Taylor et al. 1984).

For a projection system, the maximum stimulus luminance (ΔL) is limited by stray light scattered beyond the geometric boundaries of the stimulus image. This results in an increase in the apparent size of a perimetric stimulus which may reduce the apparent depth and area of scotomata (Wilson 1968; Weale & Wheeler 1977) and led Fankhauser (1979) to propose a maximum stimulus luminance of 1,000asb. If a higher ΔL is used, the amount of stray light may become a problem (Fankhauser & Haeberlin 1980; Haeberlin et al. 1980).

1.6.2. Stimulus size

Larger stimuli e.g. Goldmann size III (0.431°) are used in automated perimetry than are traditionally utilised in kinetic perimetry, since these enhance the dynamic range and offer better resistance against the effects of uncorrected refractive error (Fankhauser 1979; Heijl 1985; Atchison 1987) and media opacities (Radius 1978; Fankhauser 1979; Greve 1979; Van Den Berg 1987) on sensitivity. Larger stimuli are thus considered to act as a filter, separating pre-receptor from receptor and post-receptor disturbances (Fankhauser 1979). Although the majority of automated projection perimeters offer a choice of stimulus size, Goldmann size III is designated the default value (Heijl 1985a) and all normative data is available for a size III stimulus, although normative data for a size V stimulus has recently been incorporated in the Humphrey Field Analyser Statpac Plus software.

The use of a size III stimulus, instead of size I, increases the dynamic range by 3-4dB at fixation and by approximately 12dB at 50° eccentricity on a background of luminance 4asb by virtue of spatial summation (Fankhauser 1979). Indeed, the use of Goldmann size V stimulus has been advocated in cases of glaucoma where absolute field loss has been recorded with a size III stimulus i.e. the limits of the dynamic range with this target had been reached (Wilensky et al. 1986) and also in Retinitis Pigmentosa (Wood et al. 1986b).

The increase in dynamic range with larger stimuli occurs due to spatial summation: impulses

from many adjacent receptor cells converge on a single ganglion cell i.e. a small stimulus of given threshold luminance has less stimulating power than a larger stimulus of the same luminance (Hallett 1963; Owen 1972) and thus ΔL is smaller with a larger target. Spatial summation is described by the formula:

$$\Delta L \times A^k = \text{constant}$$

where ΔL is the incremental threshold, A is the stimulus area and k is the summation coefficient. When summation is complete i.e. k=1, this is known as Ricco's law (1877).

It is well established that spatial summation increases with peripheral angle and is greater at lower adaptation levels, for shorter stimulus durations and for smaller stimulus sizes (Barlow 1958; Gougnard 1961; Fankhauser & Schmidt 1960; Sloan 1961). Some authors consider spatial summation to be independent of age (Dannheim & Drance 1971a; Brown et al. 1989) whereas Aspinall (1967) found the value of k to increase with age. The variation in k under different conditions has led to the formulation of several other laws to describe partial summation, the best known of which are Piper's law (1903) where k=0.5 and Pieron's law (1929) where k=0.33. A choice must be made between the increased chance of detecting a defect with a larger stimulus and the decreased chance of detection because the stimulus diameter exceeds the area of spatial summation although the accuracy of measurement of a defect increases as stimulus size decreases (Greve 1973). Greve (1973) has summarised the literature showing that spatial summation may be enhanced in areas of visual field defects i.e. the differential light sensitivity is relatively higher for larger stimuli. The sensitivity to a smaller stimulus will not however be affected to such an extent hence the intensity of a defect measured with a smaller stimulus will be greater than when it is measured with a larger stimulus.

Since automated projection perimetry allows accurate positioning of the stimulus at any location, this has resulted in the availability of high resolution programs (see Section 1.13.) for which Bek & Lund-Anderson (1989) recommend use of the smallest possible stimuli. The minimum stimulus size is however limited by the contrast transfer function of the eye, which is approximately 6 minutes at the fovea (Campbell & Green 1965) and by the ability to project such a size.

Smaller target sizes have also been recommended for investigating the central field, since it is felt that size III may saturate this area and thus is an insensitive target for the earliest detection and sensitive monitoring of visual field loss (Wood et al. 1986a; Wild et al. 1987). Indeed, Dubois-Poulsen (1952) believed that, in some forms of ocular pathology, a reduction in stimulus size was more efficient in detecting early field changes than an equivalent reduction in luminance. The results of Gramer et al. (1981) indicate that glaucomatous field defects are indeed more apparent with small targets, however this finding is not in agreement with an earlier study using manual perimetry which showed normal spatial summation in glaucoma (Dannheim & Drance 1974). Interestingly, the use of an increasing stimulus size with eccentricity to achieve equal cortical representation and thus produce an isosensitive profile has been proposed (Wild et al. 1986a,b; Wood et al. 1986a).

The default to a Goldmann size III stimulus was also based on the finding that, for manual static perimetry out to an eccentricity of 30°, this and larger stimuli were unaffected by up to 3 Dioptres of spherical defocus (Sloan 1961). Atchison (1987) however found a Goldmann size III stimulus to be affected by up to 5 Dioptres of defocus within the central 30° of the visual field. The effects of defocus on manual static thresholds have been investigated by numerous workers (e.g. Fankhauser & Enoch 1962; Sloan & Brown 1962). The more recent studies of the effects of defocus on automated perimetry are discussed in Section 1.13.1. and show that even small amounts of defocus may produce a generalised depression of sensitivity using stimulus size III (Weinreb & Perlman 1986; Goldstick & Weinreb 1987; Heuer et al. 1987a; House et al. 1990). LED stimuli generally subtend smaller angles than that of Goldmann size III and therefore would be expected to be more susceptible to the effects of defocus.

Interestingly, Crick & Crick (1981) have proposed the use of "sine-bell" stimuli which contain a minimum of high spatial frequency components and thus are unaffected by visual acuity and obviate the need for refractive correction. The Sine Bell Screening Perimeter was intended to be a simple and cheap instrument for use in glaucoma detection throughout the world. Such stimuli however have not been utilised in the design of commercially available perimeters.

Conversely, high-pass spatial frequency filtered stimuli (low spatial frequencies are filtered out) have also been proposed as a method of visual field investigation (Frisen 1986, 1987a,b; 1989). The advantage of such stimuli is that detection and resolution thresholds are similar. The normal discrepancy between detection and resolution thresholds can be viewed as an index of the visual system's contrast sensitivity function for patterns. Complex patterns such as letters contain a wide range of spatial frequencies. When viewed from a distance, letters are first detected by channels with high contrast sensitivity tuned to low spatial frequencies. As the viewing distance is reduced the contrast of the pattern increases as channels tuned to increasingly higher spatial frequencies provide more detail. Recognition becomes possible when critical detail can be resolved. According to this reasoning, it should be possible to increase the detection threshold by filtering out low spatial frequency components. Such high-pass resolution targets are therefore either resolvable or invisible, and thus are advantageous as perimetric stimuli since the test task is simple, thresholding is quicker, there is a narrower threshold zone and a reduction in locations tested is possible as the stimuli probe visual function over a larger area (Douglas et al. 1989; Frisen 1989). Peripheral acuity (minimum angle of resolution) is considered to be proportional to local retinal ganglion cell separations and thus acuity measurements can be used to estimate the separation between functional retinal ganglion cells by virtue of this proportionality factor (Frisen 1987a). The major limitation of such a technique is in the definition of small circumscribed defects (Frisen 1987a). Feedback is also incorporated in the test (Frisen 1987b). A correct response is confirmed by the presentation of a black square at the tested location and fixation is encouraged by changing the size of the fixation point when a stimulus is about to appear; the fixation point is also occasionally replaced by a "look here" message.

1.6.3. Stimulus duration

Stimulus duration is considered to be less significant than both background luminance and stimulus size in increasing dynamic range. Temporal summation describes the transmission delays along the visual pathway such that additional photons, in striking a given receptor, cause an increase in that receptor's potential if they arrive before the effects of the preceding photons have worn off completely. Temporal summation is described by the formula:

$$\Delta L \times T^k = \text{constant}$$

where ΔL is the incremental threshold, T is the stimulus duration and k is the summation coefficient. When k=1, the product of luminance and stimulus duration is constant. This constancy is known as Bloch's law (1885). It applies to stimuli of short exposure, less than the critical time, t_c. When $T<t_c$, threshold is determined by the luminous flux of the stimulus only. As the neural mechanism is saturated, summation becomes partial and then ceases. When $T>t_c$, threshold luminance is independent of stimulus duration. Most investigators find the critical time is of the order of 60-100msec (Barlow 1958; Greve 1973). Temporal summation increases with increase in peripheral angle and with dark adaptation and is greater for small stimuli (Barlow 1958; Saunders 1975). For large stimuli (0.75°) temporal summation is greater at shorter wavelengths (Sperling & Joliffe 1963). Temporal summation is independent of age (Dannheim & Drance 1971b) and also depends on the type of cognitive task to be performed, which implicates cortical factors (Blackwell 1963; Adler 1970). The influence of higher centres in the process of temporal summation is underlined by the fact that stimuli to the fellow eye (Matin 1962; Battersby & Defabaugh 1969) and even auditory stimuli (Treisman 1964; Bernstein et al. 1973) may have some effect on performance.

Using manual perimetry Harms (1952) obtained a critical time of 100msec although Dannheim & Drance (1971b) found that some summation occurred within the central 30° after 100msec for a Goldmann size IV stimulus at adaptation levels of 10asb and 0.1asb. Aulhorn & Harms (1972) found no further increase in differential light sensitivity beyond a stimulus duration of 500msec. Therefore, if exposure times are greater than or equal to 500msec, the effects of temporal summation are overcome; however, such long stimulus durations can cause fixation to wander. Greve (1973) observed that the interindividual variation in temporal summation was small and considered that short stimulus durations were suitable for the examination of patients with poor fixation. Other arguments for short stimulus presentations include (Greve 1973) decreased examination time, decreased spatial summation, better patient acceptance and the prevention of saccadic eye movements towards the stimulus. The latency for a saccadic movement to an eccentricity of 30° varies from 50 to 250msec, however a saccade may only be made towards a "seen" stimulus and this is the principle of eye movement perimetry (Jernigan 1979; Trope et al. 1989), in which the patients' eye movements are

analysed with respect to the position of the stimulus, which indicates whether the stimulus was seen. Eye movement perimetry has been adapted for use with the Octopus Automated Perimeter but is limited by the ability to accurately monitor small eye movements within the central 6° of the visual field (Trope et al. 1989). A further argument against the use of long stimulus durations in diseased eyes is that temporal summation may be increased (Wilson 1970) and this may compensate for the decrease in differential light sensitivity. Contrary to this Holmin et al. (1987) found a reduction in general sensitivity and apparent enlargement and deepening of existing defects in a sample of glaucoma patients using a stimulus duration of 250msec compared with the normal 500msec of the Competer perimeter although normal areas of the same field appeared to be unaffected at the shorter stimulus duration. Holmin & Krakau (1979) also reported greater threshold fluctuation in defective field areas with a shorter stimulus duration. Krakau (1989) explained the reduction of relative defects with prolonged stimulus durations by means of a hypothetical model based on rarefaction of optic nerve fibres.

The maximum stimulus duration is limited by local adaptation i.e. under steady fixation or with a stabilised retinal image visual objects presented continuously in the same place disappear after a time. This is known as the Troxler (1804) phenomenon. The local adaptation time decreases with peripheral angle and increases as the size and luminance of the stimulus increase (Verriest & Lavallee 1966).

The majority of commercially available perimeters employ relatively short stimulus presentations. The inter-stimulus duration may vary according to patient reaction time or be of a specific duration e.g. 200msec, 400msec, 800msec, 1.2s or 3.2s.

1.6.4. Stimulus location

The probability of detection of small defects by static perimetry depends essentially on the number of locations examined. The positioning of a given number of stimuli is also very important (Greve 1975; Bebie et al. 1976b; Fankhauser & Bebie 1979); for specific purposes some particular arrangement of examination points may be more suitable than others. For small scotomata (radius<1°) the probability of detection is very low and is independent of the

choice of stimulus grid; for larger defects a regular rectangular grid of resolution 6° has twice the detection probability than examination of two meridians with a radial resolution of 1.5° (Fankhauser & Bebie 1979). Improvements in detection are possible through the use of a more dense stimulus grid (Greve 1975) at the expense of increased examination time (Fankhauser & Bebie 1979). Indeed, Greve (1973,1975) has calculated that examination of 452 locations within the central 30° would be required to detect a 3° circular defect with a probability of 95%.

Thus it is evident that a compromise must be reached between defect detection and length of examination. Gutteridge (1984) summarises three possible options: 1) systematic sampling, 2) higher density sampling of areas where field defects occur more frequently or 3) a combination of systematic sampling and higher density sampling. By systematic sampling, the probability of detection of a 4.2° scotoma using a 6° square grid has been calculated to be 100% (Fankhauser & Bebie 1979) however King et al. (1986) demonstrated that this grid is not adequate for identification of a scotoma the size and depth of the blind spot, a finding supported by Wild et al. (1986c) who considered that stray light effects masked the blind spot (Fankhauser & Haeberlin 1980). A 6° separation is deemed sufficent for the detection of field loss secondary to chiasmal and supragenículate lesions (Weber 1987).

In the second option the areas which are usually sampled with a higher density are the macula (fixation) region, arcuate region, horizontal and vertical midlines and around the blind spot. In other areas where defects occur with lower frequency, the separation between stimuli is greater. Weber & Dobek (1986) demonstrated that the most effective method for detecting glaucomatous losses using the square stimulus configuration of the Humphrey Field Analyser would be to develop a program with a 3° grid within 10° eccentricity, a 4.2° grid between 10° and 20° and a 6° grid between 20° and 30° eccentricity. This recommendation coincided with the availability of the Octopus G1 program in which resolution reaches a maximal value of 2.8° in the macula area (Flammer et al. 1987). This program was considered to improve both the detection and the assessment of defects compared with a 6° square grid configuration (Gloor & Gloor 1986; Dannheim 1987) although the description of focal losses using the visual field indices loss variance and corrected loss variance (see Section 1.12.)

was found to be similar for both programs (Gloor & Gloor 1986).

The third option involving systematic searching of the central field and sampling of selected parts of the peripheral field has been advocated for the detection of glaucomatous defects in the Armaly-Drance method of combined static and kinetic perimetry (Rock et al. 1971; 1973; Armaly et al. 1972). The Armaly-Drance method has been applied in spatially adaptive programs such as the Octopus SAPRO (Haeberlin et al. 1983; Funkhauser & Fankhauser 1985) in which the software modifies the spatial resolution within an examination as a result of the patient's responses; a coarse grid is used in areas of normal sensitivity and an increasingly finer grid in areas where field loss is encountered. Asman et al. (1988) however found that spatial enhancement did not improve sensitivity or specificity when used with a threshold-related eccentricity-compensated suprathreshold screening program on the Humphrey Field Analyser.

1.7. ADAPTATION LEVEL

A low background luminance of the perimeter bowl can be used to produce an increased dynamic range (Fankhauser 1979). Early automated perimeters utilised a low background luminance (Spahr 1973; Heijl & Krakau 1975a) to overcome the limitations imposed on dynamic range by the relatively low output of the stimulus projection bulb, which limited ΔL_m, the maximum stimulus luminance (Heijl 1985a). Fankhauser (1979) reported that a 4asb background luminance increased the dynamic range by about 5dB compared with the standard Goldmann background of 31.5asb and the additional use of a Goldmann size III (0.431°) stimulus compared with size I (0.108°) amounted to a gain of 19dB in dynamic range at 50° eccentricity (i.e. a gain of about 50 times). Stimulus light output is however no longer a constraint in instrument design and other factors such as the optimum adaptation level for the early detection of visual field defects should be considered. Use of a 31.5asb background luminance requires less pre-adaptation and is less sensitive to stray light from ambient room lights than a lower background (Heijl 1985a).

Decreasing the background luminance from photopic to mesopic and scotopic ranges alters the basic operating curve of the retina (Aulhorn & Harms 1972). A sharp distinction between

function of the rod and cone systems does not appear to exist; there is a gradual transition from dominant cone to dominant rod function.

In the photopic range the Weber-Fechner law holds:

$$\Delta L/_L = \text{constant}$$

where ΔL is the incremental threshold and L is the background luminance i.e. contrast sensitivity is constant. At the lower end of the scotopic range ΔL becomes a constant for threshold excitation which is independent of L i.e. ΔL = constant. Various equations have been suggested which describe the transition over the mesopic to high scotopic ranges. According to Barlow (1972) the relationship is:

$$\Delta L/_L + ID = \text{constant}$$

where ID is the photon and neuron noise of the eye. It is frequently stated that the Rose-de-Vries law is appropriate in the low photopic or mesopic ranges where:

$$\Delta L/_{\sqrt{L}} = \text{constant}$$

although Barlow (1972) suggests the Weber-Fechner law may hold well into the scotopic regions and that the Rose-de-Vries law may be applicable in the photopic region. Fankhauser (1979) suggests that the Rose-de-Vries law is applicable for the adaptation levels of the currently available perimeters; this statement has not however been substantiated and many workers consider the levels to conform to the Weber-Fechner law (Aulhorn & Harms 1972; Greve 1973; Klewin & Radius 1986).

The degree of dark or light adaptation depends not only upon the background luminance but also upon the pupil size and the extent of media absorbtion. A given level of background intensity may be in the photopic range for a normal sized pupil, but may come to be in the mesopic range for a constricted pupil in the presence of media opacities. If the bowl luminance is reduced to increase the dynamic range, the perimeter may no longer be operating on a linear portion of the Weber-Fechner curve, and a small change in L, resulting from light output alterations or lowering of retinal adaptation due to a constricted pupil, or the presence of media opacities, will have different effects on L and ΔL respectively resulting in the production of a pseudo-defect. On the linear portion of the Weber-Fechner curve, these changes would affect the background L and threshold ΔL equally and thus the ratio between

them would remain constant.

The rationale for examination at a different adaptation level is that one of the receptor systems may be selectively affected in certain ocular diseases. This hypothesis is discussed fully in Section 6.1. Early authors, not concerned with enlargement of the dynamic range, proposed that low adaptation levels facilitated the detection and differential diagnosis of disturbed visual function (Jayle & Aubert 1958; Hara 1979). Indeed, it has been recently suggested that perimetry at low adaptation levels permits early detection of both diffuse and focal glaucomatous visual field defects (Fellman & Lynn 1985; Drum et al. 1986; Starita et al. 1987).

Examination under more than one adaptation level has also been proposed to aid differential diagnosis. Greve et al. (1977) demonstrated with the Friedmann Visual Field Analyser that examination under both mesopic and photopic conditions could discriminate between maculopathies and central neuropathies. Indeed, dark and light-adapted static perimetry permits assessment of visual disability and classification of sub-types of Retinitis Pigmentosa (Marmor et al. 1983) and a Humphrey Field Analyser has been modified for this purpose (Jacobson et al. 1986).

There have also been claims of enhanced detection of defects at higher adaptation levels. Wilson (1968) demonstrated, at an adaptation level of 674asb, abnormalities of both spatial and temporal summation in lesions of the post-geniculate pathways and abnormalities of spatial summation, only, in pre-geniculate lesions. Shiga (1968) reported depression of isopters in the early stages of retinal (including glaucoma) and third neuron disease at adaptation levels of 220asb and 700asb, whereas the isopters of normal eyes enlarged under such conditions. Paige (1985) also found enhanced detection of subtle visual field defects at an adaptation level of 315asb compared with 31.5asb in a mixed sample of glaucoma suspects, glaucoma patients and neuro-ophthalmological patients using a modified Humphrey Field Analyser. Similarly, Elenius & Leinonen (1986) reported enhanced detection of progressive cone dysfunction at an adaptation level of 628asb.

Heijl (1985) considered that perimetry at lower background levels than the standard Goldmann 31.5asb did not offer any diagnostic advantages and this has been substantiated by Asman & Heijl (1988) who found no tendency to a greater defect at adaptation levels of either 3asb or 315asb compared with 31.5asb. Studies of the influence of background luminance on threshold fluctuations have also yielded equivocal results. Using manual static perimetry, Aulhorn & Harms (1967) found an increase in the intraindividual variation with decreased background luminance and Crosswell et al. (1990), using automated perimetry, also found both short and long-term fluctuations to increase with decrease in adaptation level. Jayle et al. (1965) noted a decrease in fluctuations with decreased background luminance whereas Fankhauser & Schmidt (1960) and Greve (1973) reported no significant difference in threshold fluctuations with change in background luminance.

The comparison of sensitivity data between automated perimeters is confounded by the fact that the differential light sensitivity expressed in decibels (dB) is a logarithmic representation of projected stimulus luminance (ΔL) referenced to a maximum value (ΔL_m), which is instrument specific. The background luminance (adaptation level) also varies between instruments. Thus, for the Octopus automated perimeter, 0dB represents a 1000asb stimulus on a 4asb background, and for the Humphrey Field Analyser 0dB represents a 10,000asb stimulus on a 31.5asb background.

1.8. STRATEGIES

The strategy is the course of decisions and actions which occur in order to detect or assess a visual field defect. The purpose of the detection phase is to determine the presence or absence of a defect. Since threshold perimetry is time consuming, many perimeters employ suprathreshold (supraliminal) strategies for the detection procedure.

1.8.1. Suprathreshold

In this strategy, the stimulus is exposed slightly above the expected normal threshold at each tested point, and the point is accepted as normal if the stimulus is seen. According to the choice of stimulus luminance, suprathreshold screening may be performed in three different ways (Heijl 1985b) namely, one-level screening, eccentricity compensated screening and

threshold related eccentricity compensated screening.

In one-level screening targets of the same intensity are used throughout the field, regardless of location (Keltner et al. 1979). This is a rapid, simple method of perimetric screening compared with manual Goldmann procedures (Bebie et al. 1976a; Fankhauser 1979) at the expense of specificity (Hong et al. 1981; Gramer & Kreiglstein 1981). Despite this, high sensitivity figures have been quoted in studies using this type of test (Johnson & Keltner 1980; Bobrow & Drews 1982). Keltner et al. (1979) demonstrated that the detecton of shallow defects was improved if the suprathreshold screening test was repeated using at least two different stimulus luminances i.e. using a two-level strategy.

With eccentricity compensated screening the stimulus intensity increases with increase in eccentricity i.e. it is adapted to the normal shape of the hill of vision and is therefore similarly supraliminal at all locations. Estimates of the interindividual variations in the normal shape of the hill vary from 2dB (Verriest & Israel 1965; Greve & Wijnans 1972) to 10dB (Heijl 1985b) resulting from age, media opacities, miosis and patient alertness.

Threshold related screening overcomes the problem of intraindividual variation by measuring the actual threshold at one or more test points, correcting for the normal decay of sensitivity with eccentricity and increasing the stimulus luminance to make the stimulus supraliminal (often 5-8dB above threshold, although Greve (1981) advocated that a stimulus which was suprathreshold by 4dB was acceptable, and Chauhan & Henson (1987) suggested that the maximum information was obtained by using a stimulus that was 6dB suprathresold. Such a threshold related eccentricity compensated test will have better sensitivity and specificity than a one level test, however if the initial threshold determinations are faulty or performed in areas with pathologically increased thresholds the choice of screening intensities may be erroneous. Most automated perimeters attempt to eliminate this risk by performing threshold determinations at 2-4 points and taking the most sensitive point(s) as the reference level. The accuracy of the initial threshold determination may also be improved by using a test logic with more than one reversal, where the probability of seeing changes from 0 to 1 (Heijl 1977c) or by repeating threshold determinations (Heijl 1985a). Threshold related eccentricity

compensated screening procedures have been shown to detect defects earlier than routine manual kinetic perimetry with or without sparse static testing (Heijl 1976; Dyster-Aas 1980). It is possible to extend the test further by using a maximum intensity stimulus at all missed points, which allows a classification of tested points into three categories: normal points, points in relative defects and points in absolute defects. A further refinement is to measure the depth of all defects identified by the supraliminal test.

1.8.2. Threshold

Visual field examination may also be conducted by determining a true increment threshold at each location tested. Threshold determinations map the actual contour of the hill of vision and will detect subtle defects more easily than a supraliminal test, but at the expense of increased examination time which limits the number of points examined.

The methods of threshold determination in general use in static clinical perimetry are variations on the "method of limits" (Guilford 1954) or the "staircase method" (Stiles & Crawford 1934) which is considered superior (Spahr 1975), although can only be usefully employed when fully automated with a computer (Fankhauser et al. 1972; Koch et al. 1972).

The "method of limits" consists of a series of stimuli, originating at an infraliminal level, presented in steps of ascending luminance until the stimulus is seen. The first stimulus is chosen about 2-4dB below the mean threshold for the corresponding age group for that eccentricity and increased in constant steps of e.g. 2 or 4dB (Bebie 1976a).

The "repetitive up and down method" or bracketing technique is considered to approximate to the optimal strategy from considerations of information gain per response (Spahr 1975). The mean threshold for a given age group at a given location is selected as the first stimulus. If this meets with no response, the next stimulus is increased by 4dB, otherwise it is reduced by 4dB. This process is repeated with the luminance increment / decrement being halved until the threshold has been crossed twice, designated 4-2-1 where the final 1dB resolution is achieved by interpolation, taking the mean of the last seen and last unseen stimuli as threshold, as in the Octopus, or where the threshold is crossed three times, as in the early

Topcon perimeter and the final 1dB increment is actually measured (also designated 4-2-1).

The number of stimuli which must be presented in order to achieve the end point is approximately 4 or 5 (Spahr 1975). Most automated perimeters employ a version of the bracketing technique with varying luminance increment levels.

The average number of stimuli needed for the bracketing method is greater than that for the method of limits, however the bracketing method yields the true threshold with greater accuracy, independent of whether the first stimulus was infra- or supraliminal (Bebie et al. 1976a). The precision of automated threshold determinations can be increased by allowing the process to continue through several reversals at each tested point, requiring more stimulus presentations and thus increased examination time (Bebie et al. 1976a). Most algorithms have a tolerance for patient errors, particularly in complex programs where the threshold is crossed several times during its determination (Bebie et al. 1976a; Heijl 1977c). Interestingly, Gandolfo et al. (1985) using the computerised Goldmann perimeter (Perikon-Optikon) demonstrated that the mean sensitivity and short-term fluctuation were not significantly different when measured by the method of limits, the bracketing technique or a double resolution method of limits.

Full threshold determination has been shown to be more sensitive in the detection of shallow defects than a strategy which only quantifies abnormal areas (Stewart 1989). Interestingly, Kosoko et al. (1986a) have shown that the time required for a full threshold strategy is unaffected by the age or ocular status of the patient whereas a threshold related suprathreshold screening test was quicker to run in young, normal subjects than in elderly or glaucomatous patients.

1.9. FLUCTUATIONS

The measurement of perimetric sensitivity is a psychophysical test in which the patient can only respond with a yes (seen) or no (not seen) answer. Very dim stimuli will never be seen, and very intense stimuli will always be seen. Between these extremes lie a range of stimulus luminances over which the patient response will vary. The visual threshold is defined as the

stimulus luminance that has a 50% probability of being detected. To measure this accurately would require the presentation of many stimuli at each location. Indeed, in order to increase the probability of a "seen" response from 16% to 84%, the stimulus luminance must be increased by a factor of approximately two to four (Fankhauser & Bebie 1979). Thus when the visual threshold is measured only several times at one location, as is routine during standard static examination procedures, the result is not always identical. The variability of the threshold value obtained has been termed "fluctuation" and is divided into a short-term and a smaller long-term component (Flammer 1985).

Short-term fluctuation is the variability of repeated measurements at one location that arises during a single examination (Bebie et al. 1976b; Flammer et al. 1984c). It depends mainly on the zone of uncertain responses for stimuli near threshold, which is described by the frequency-of-seeing curve. The variability of sensitivity values obtained when the examination is performed on another occasion (separated by a period of hours to years), once the variation due to repeated measurements at a given time (i.e. the short-term fluctuation) has been removed, is called the long-term fluctuation (Bebie et al. 1976b; Flammer et al. 1984a). Long-term fluctuation is further divided into a homogeneous component which affects all locations within the visual field similarly (i.e. the entire hill of vision rises or falls) and a smaller heterogeneous component which affects locations within the visual field differently (Flammer et al. 1984a) and is in part a consequence of short-term fluctuations (Flammer et al. 1983). The components of short and long-term fluctuations are significantly positively correlated, although it is not possible to accurately predict long-term fluctuation from measurement of short-term fluctuation in an individual (Flammer et al. 1984a).

1.9.1. Short-term fluctuation

A number of factors influence the magnitude of the short-term fluctuation, primarily the level of the differential light sensitivity itself (Flammer et al. 1984c). The level of the differential light sensitivity is related to the pathological state of the eye; indeed, greater short and long-term fluctuations have been shown in glaucoma patients than in glaucoma suspects, which are in turn higher than in normal eyes for both automated static (Flammer et al. 1984b) and

automated kinetic (Capris et al. 1987) perimetry. An increased level of short-term fluctuations has also been shown to precede a decreased sensitivity for both manual (Werner & Drance 1977; Koerner et al. 1977; Werner et al. 1982) and automated perimetry (Koerner et al. 1977; Holmin & Krakau 1981; Heijl & Drance 1983; Flammer et al. 1984b,c; Flammer et al. 1985; Zingirian et al. 1988), particularly in patients with raised intraocular pressure (Werner & Drance 1977; Flammer et al. 1984b; Gloor et al. 1984; Rabineau et al. 1985; Sturmer et al. 1985). The strategy for threshold measurement also affects the level of short-term fluctuation (Bebie et al. 1976a; Flammer et al. 1984b; Parrish et al. 1984; Lewis et al. 1986; Brenton & Argus 1987; Henson & Anderson 1989), although Zingirian et al. (1985) found the strategy to exert no influence on threshold fluctuations in automated perimetry. Koerner et al. (1977) reported no difference between the fluctuations obtained with manual and automated perimetry, however Sucs & Verriest (1987) found a greater value using automated perimetry.

Another important factor in determining the short-term fluctuation is the location within the visual field. Some authors have reported short-term fluctuation to be independent of eccentricity within the central 30° for manual (Werner et al. 1982) and automated (Flammer et al. 1984c; Flammer & Zulauf 1985) perimetry although most studies are in agreement that short-term fluctuation increases with increase in peripheral angle for both manual (Aulhorn & Harms 1967; Greve & Wijnans 1972; Werner & Drance 1977; Donovan et al. 1978) and automated perimetry (Van den Berg et al. 1985; Brenton & Phelps 1986; Lewis et al. 1986; Heijl et al. 1987a,b; Langerhorst 1988; Rutihauser et al. 1989). Conversely, Rabineau et al. (1985) found the short-term fluctuation to be greatest in the central field, although their protocol involved examination periods of an hour or more. Patient cooperation and reliability has also been shown to be a factor in determining the magnitude of the short-term fluctuation (Flammer & Niesel 1984; Flammer et al. 1984c). Some authors report little change in the level of short-term fluctuation with increase in the age of the patient (Flammer et al. 1984c; Flammer & Niesel 1984; Brenton & Phelps 1986; Rabineau et al. 1985; Langerhorst 1988), others finding it to increase slightly with increase in age (Katz & Sommer 1986; Katz & Sommer 1987). Pupil size has a negligible effect on short-term fluctuation in normals but in glaucoma patients, decrease in pupil size is associated with increased fluctuations (Flammer

et al. 1984c), particularly for those patients receiving miotic therapy. Reaction time is not a significant factor in determining the level of the short-term fluctuation (Flammer et al. 1984c). Short-term fluctuation decreases with experience of both manual (see Section 4.3.1.) and automated perimetry (see Section 4.3.2.), and increases with patient fatigue for both manual (Haidor & Dixon 1961; Ronchi & Salvi 1973) and automated perimetry (Heijl 1977; Flammer & Niesel 1984; Flammer et al. 1984a; Mills et al. 1987) as reviewed in Chapter 5. Short-term fluctuation has also been shown to be related to general health (Langerhorst et al. 1989) and to be independent of stimulus size (Gilpin et al. 1989). The effect of background luminance on the level of short-term fluctuations is somewhat equivocal (see Section 7.9.3.).

1.9.2. Long-term fluctuation

It can be difficult to differentiate a true change in the visual field from the background noise of the long-term fluctuation (Gloor & Vokt 1985). Covariates of the long-term fluctuation are the short-term fluctuation, variations in patient reaction time between examinations and variations in intraocular pressure (Flammer et al. 1984a). The long-term fluctuation is also related to the absolute level of the differential light sensitivity (Ross et al. 1984; Piltz et al. 1986; Magee et al. 1987; Werner et al. 1987; Heijl et al. 1989b). Long-term fluctuations have been reported to increase with increase in peripheral angle (Magee et al. 1987; Heijl et al. 1989b; Werner et al. 1990a) and to be greater in the superior than the inferior field (Werner et al. 1990a). Conversely, Rutihauser et al. (1989) found no relationship between long-term fluctuation and eccentricity. Long-term fluctuation has been noted to increase with increase in age (Katz & Sommer 1987) and to be related to general health (Langerhorst et al. 1989). The heterogeneous component of the long-term fluctuation has been reported to increase with decreasing background luminance and with smaller stimuli, although the homogeneous component is unaffected by these factors (Gilpin et al. 1989; Crosswell et al. 1990).

Fluctuations limit the accuracy of threshold determination and the interpretation of change within the visual field. Scotomata may be undetectable in the presence of threshold fluctuations which represent background noise. This background noise may be attenuated by computer averaging methods, but Fankhauser & Bebie (1979) consider the detrimental effect of fluctuations on the detection of sensitivity loss to be grossly underestimated.

1.10. RELIABILITY PARAMETERS

Fluctuation is one of the important factors in assessing the reliability of results obtained by automated perimetry. The level of fluctuation is not only influenced by the factors summarised in Section 1.9. but also by the co-operation of the patient. This latter factor is assessed by the reliability parameters or "catch trials". The number of catch trials presented during an examination is approximately 10% of the total number of stimuli presented. The inclination of the patient to press the response button of the instrument without having perceived a stimulus is examined by the false positive catch trials; the perimeter produces the same sound as when displaying a stimulus, although no stimulus is actually presented, and records whether the patient responds or not. The opposite is tested by false negative catch trials in which a strong supraliminal stimulus is exposed at a location where the threshold has already been measured, thus checking the patient's concentration. The fixation ability is tested by exposing stimuli in the blind spot of the tested eye at random intervals (Heijl & Krakau 1975a). The number of erroneous responses to the catch trials influences the sensitivity and specificity of the test (Enger & Sommer 1987). Indeed, Katz & Sommer (1990) found high rates of false positive responses and fixation losses to be associated with an apparent reduction in the extent of both diffuse and focal glaucomatous visual field loss.

The rate of false negative responses has been noted to increase with decreasing mean sensitivity and thus is higher in glaucoma patients than in normal subjects (Heijl et al. 1987c; Jenni & Flammer 1987; Katz & Sommer 1988; Nelson-Quigg et al. 1989; Reynolds et al. 1990). No such trend however has been found between the rate of false positive responses and mean sensitivity (Heijl et al. 1987c; Jenni & Flammer 1987; Katz & Sommer 1988; Nelson-Quigg et al. 1989) or number of fixation losses (Heijl et al. 1987c; Katz & Sommer 1988) although Reynolds et al. (1990) found the rate of false positive responses to be positively correlated with fixation losses. Most authors are in agreement that patient reliability is unrelated to age (Heijl et al. 1987c; Jenni & Flammer 1987; Katz & Sommer 1988; Bickler-Bluth et al. 1989), pupil diameter or visual acuity (Katz & Sommer 1988). It has been suggested that reliability may be improved with increasing patient experience of automated perimetry (Kosoko et al. 1986b; Bickler-Bluth et al. 1989) although Niles & Trope (1988)

found no evidence of a decrease in any of the measured reliability factors in a sample of glaucoma patients over 3 examinations despite a concomitant decrease in mean defect. Reynolds et al. (1990) found the rate of all catch trials to increase with increasing test time although the rate of catch trials was not reduced by using a screening strategy compared with a full-threshold strategy on the Humphrey Field Analyser.

The Humphrey Field Analyser "Statpac" software normal database has been compiled from fields with certain minimum reliability criteria, namely false positive and negative responses ≤33% and fixation losses ≤20%. It has been suggested that these criteria are too stringent for patients with no previous experience of automated perimetry, since a high percentage of first fields are deemed unreliable (Enger & Sommer 1987; Katz & Sommer 1988). Indeed, Bickler-Bluth et al. (1989) have suggested that increasing the fixation loss criteria to 33% would substantially increase the percentage of fields graded as reliable and would have minimal effect on the sensitivity or specificity of the test.

Interestingly, Olsson et al. (1988) have reported the use of a statistical method ("maximum likelihood estimation") to estimate the rate of false positive and negative reponses. This method uses all the data obtained from the threshold strategy as well as the results of catch trials. It is claimed that this reduces the number of catch trials required to estimate reliability in abnormal fields by 50% compared with the conventional method.

1.11. DATA REPRESENTATION

Traditionally, perimetric data has been represented graphically. The results of manual kinetic perimetry are represented by isopters and computer analysis of the area contained within an isopter is available (Kosaki & Nakatani 1983). The numerical printout of threshold values, together with the computer capacity of automated perimeters permits many possible mathematical and statistical manipulations of the data.

The numerical (decibel) printout of automated perimetry although accurate is difficult to read and interpret (Greve 1982). To overcome this problem the grey scale plot is frequently used whereby measured sensitivities are transformed into graphic symbols, each symbol

corresponding to a specific sensitivity range in steps of 5dB. Lighter symbols are employed for areas of greater sensitivity although there is consequent loss of information. Graphical displays, however, are considered to be poor in representing diffuse glaucomatous damage (Flammer 1986). Areas of the visual field not examined i.e. those areas between stimuli are represented by symbols corresponding to interpolated sensitivities which are derived from measured sensitivities of the neighbouring points using coordinate differences as weight factors (Fankhauser & Bebie 1979). The interpolation is thus carried out on a rectangular grid (Weber & Spahr 1976) although linear interpolation from an irregular grid has also been described (Charlier et al. 1987). Weber & Geiger (1989) compared the relative merits of three different interpolation procedures on rectangular grids, concluding that interpolation from four points gives the smoothest appearance, and linear interpolation (from one point to the next) gives realistic borders in the cardinal orientations although not along the diagonals. A combination of the two methods (mixed interpolation) is recommended for scientific studies. The grey scale is more easily visualised with defocus or from a distance (Fankhauser et al. 1977; Jay & Yavitz 1981) although the interpolation procedure may lead to erroneous interpretation. It has however been demonstrated that interpolated sensitivities are only slightly less accurate than direct measurements provided the interstimulus grid does not exceed a 6° separation (Fankhauser & Bebie 1979). The latter authors as well as Flammer (1986) advocate this representation for the detection of visual field change despite the loss of information (Fankhauser et al. 1977; Fankhauser 1979). Additionally, there is no standardisation between grey scales from different perimeters due to the variations in dB scales and use of different symbols.

Weber & Kreiglstein (1989) described a new display, the Graphical Analysis of Topographic Trends (GATT). GATT superimposes greyscale maps of two fields, producing the following patterns: stable unchanged areas are displayed normally, whereas areas of the visual field showing change are represented by a mixed greyscale composed of alternating stripes from the previous and present fields. The contrast between stripes indicates the amount of change and the orientation of the stripes depends on the direction of change, a deterioration being represented by horizontal stripes whereas an improvement is indicated by vertical stripes. GATT may also compare two groups of two fields, but is limited by the

informational content of interpolated greyscales.

The sensitivity gradient may also be represented by a two (Fankhauser et al. 1977) or three-dimensional plot. Three-dimensional graphs have been used to represent data derived by both manual and automated perimetry (Flammer et al. 1981; Hart & Hartz 1982; Hart & Burde 1983; Accornero et al. 1984; Haas et al. 1986; Jaffe et al. 1986; Swann & Bloesch 1986) however care must be taken to control all variables in three dimensional dispalys. Visual fields to be compared with one another must be derived from the same test point locations and sensitivity axis scaling must be identical (Hart & Hartz 1982) as well as resolution and orientation of the plot (Wild et al. 1987b).

Bebie et al. (1989) have recently described a new method of analysis, the cumulative defect curve, which consists of the cumulative distribution of the local defect values and allows for easy recognition of both local and diffuse damage (Kaufmann & Flammer 1989). Another novel display mode are perimetric probability maps which depict measured pointwise sensitivities in terms of the frequency with which the measured findings are seen in a normal population, each frequency being associated with a particular symbol. The clinical usefulness of these maps has been shown to depend on the choice of the normal visual field model, whether assumed Gaussian or empirically determined, although again they differentiate between generalised and local field loss (Heijl & Asman 1989; Heijl et al. 1989c). Indeed, Zalta (1990) has noted cases where an arcuate scotoma is present on the probability display despite an apparently normal greyscale, attributing this to the presence of shallow defects which do not overlap two grey-scale densities.

1.12. VISUAL FIELD INDICES

The numerical printout of threshold values, together with the computer capacity of automated perimeters permits many possible mathematical and statistical manipulations of the data. The visual field indices (Flammer et al. 1985, 1986) are data reduction statistics which summarise particular features of the island of vision with a single value.

The mean sensitivity (MS) represents the arithmetic mean of the differential light sensitivity at

all tested locations within the visual field. It is defined as (Flammer 1986):

$$MS = 1/_m \cdot \sum_{i=1}^{m} X_i$$

where $X_i = 1/_n \cdot \sum_{k=1}^{n} x_{ik}$;

x_{ik} is the sensitivity at test location i, replication k; X_i is the average local sensitivity at test location i; n is the number of replications (independent measurements within the same session) and m is the number of test locations. Calculation of MS does not involve the use of any age-corrected normal values. MS is independent of the short-term fluctuation and the heterogeneous component of the long-term fluctuation if the number of stimulus locations is sufficiently large (Flammer et al. 1983). It is sensitive to diffuse damage, although defects involving small areas have little influence on MS.

The mean defect (MD) is the arithmetic mean of the difference between measured values and normal values at each of the tested locations. It is defined as (Flammer 1986):

$$MD = 1/_m \cdot \sum_{i=1}^{m} (z_i - X_i)$$

where z_i is the age-corrected normal value at test location i, and the remaining factors are as those for MS. A value of zero indicates a normal field and a positive value expresses directly the amount of diffuse damage (Augustiny & Flammer 1985; Flammer et al. 1985). MD is elevated by diffuse depression of the differential light threshold, and is relatively unaffected by local defects and the short-term fluctuation. It is analogous to the Humphrey Field Analyser Statpac index mean deviation (Heijl 1987b). The formula used by Heijl et al. (1987b) for the calculation of mean deviation in Statpac analysis involves the subtraction of the normal reference threshold from the measured threshold and therefore a depression of the visual field is indicated by a negative value. It also includes a weighting function representing the variance of normal threshold measurements at location i.

The defect volume (DV) represents the visual field in a three-dimensional form. DV is defined as the decrease in volume (i.e. depth or area) of this three-dimensional form due to

depression of the differential light sensitivity (Van den Berg et al. 1985). It is calculated from the normal volume of the visual field (estimated from the areas of normal sensitivity within a given field) minus the sum of the measured threshold values (Langerhorst et al. 1985). The volume of the three-dimensional field has also been investigated as a method of analysis using the Monte-Carlo technique, which derives the integral of sensitivity over the three-dimensional surface of the visual field by a statistical sampling process (Wild et al. 1987a). The volume of the derived visual field is linearly related to mean defect, and the technique has been applied in the study of the effects of perimetric experience on the sensitivity gradient (Wood et al. 1987c).

The short-term fluctuation (SF) described in Section 1.9. is the average of the local scatter over the total visual field. It is the square root of the average square of local standard deviations over the whole field. In some standard programs of the Octopus automated perimeter it is expressed as the root mean square (RMS) fluctuation. It is calculated as follows (Flammer 1986):

$$SF = \sqrt{1/m \sum_{i=1}^{m} (SD_i)^2}$$

where SD_i are the standard deviations of x_{ik} (sensitivity at test location i, replication k). A reasonable estimate of SF requires many test locations to be measured twice. The use of ten double determinations to calculate SF (e.g. as in the Humphrey Field Analyser program 30-2 with Statpac analysis) gives the value to an accuracy of +/-25% (Bebie et al. 1976b). The precision of the RMS fluctuation as an estimate of SF depends on n(k-1) where n is the number of points replicated and k the number of replications at each point (Bebie et al. 1976b). Estimation of the SF by the RMS assumes that SF is independent of eccentricity whereas the variance differs among regions of the field, as reviewed in Section 1.9.1. Chauhan et al. (1990) have shown however that the number of double determinations has little effect on the RMS fluctuation although increasing the number of determinations at each test location from two to three resulted in an increase in the local fluctuation with no further increase occurring above three determinations. A weighting function for the normal intra-test variance at location i is introduced in the formula of Heijl et al. (1987b) for the calculation of SF

which minimises SF in normals.

Mills et al. (1987) have investigated several statistical techniques for estimating the SF from single threshold determinations. Indeed, Schultzer et al. (1990) have described a method for estimation of SF from a single determination of the field, by examination of the residuals following the fitting of a polynomial surface to the sensitivity values obtained. Although the use of a higher degree polynomial surface provided an increasingly improved fit to the data, it ultimately modelled more of the random variation in the data rather than the shape of the sensitivity gradient itself. The lowest order of polynomial which provided a significant fit at $p<0.05$ was therefore selected. The precision of estimation of the RMS vale by this method was of the order of +/-6.5% with a confidence limit of 95%.

The loss variance (LV) index represents the local non-uniformity of a visual field defect. It is small if visual field damage is even and diffuse, but is increased in the presence of large scotomata. It is calculated as follows (Flammer 1986):

$$LV = 1/_{(m-1)} \sum_{i=1}^{m} (z_i - MD - X_i)^2$$

LV may be helpful in the detection of early defects, as it increases with small defects as well as with increased scatter (SF). Double threshold determinations are not required for the calculation of LV, thus saving examination time (Flammer 1986). It is analogous to the Humphrey Field Analyser Statpac softwarevisual field index pattern standard deviation (PSD), described by Heijl et al. (1987b). PSD includes a weighting function for the variance of normal threshold measurements at location i which minimises the PSD in normals.

LV may be increased by real defects or by increased scatter. An additional index, corrected loss variance (CLV) was therefore introduced (Flammer et al. 1985) which helps to separate real deviations from those due to scatter (Augustiny & Flammer 1985). The scatter (SF) is estimated from double threshold determinations; it is then possible to calculate how much of the loss variance is due to SF and how much is due to an additional component expressing real local deviations. It is calculated as follows (Flammer 1986):

$$CLV = LV - 1/_{n} (SF)^2$$

It is analogous to the Humphrey Field Analyser Statpac software index corrected pattern standard deviation (CPSD) described by Heijl et al. (1987b).

CLV has been shown to be more sensitive than the RMS in discriminating between glaucoma suspect patients with no sensitivity loss and normal observers (Liao et al. 1988). The relationship between MD and CLV has also been investigated in glaucoma patients and a combination of the indices MD and CLV proposed to define the various stages of glaucoma (Gollamudi et al. 1988; Pearson et al. 1990).

The third central moment (M3) of the distribution of the deviation of measured values from expected values is sensitive to deviations restricted to a very low number of test locations. It may therefore be helpful in the detection of very early visual field defects (Brechner & Whalen 1984). It is calculated as follows (Flammer 1986):

$$M3 = 1/m \sum_{i=1}^{m} (z_i - MD - X_i)^3$$

Skewness (Q) yields principally the same information as M3. By raising the difference between the observed threshold and normal value to the third power, a small subset of depressed values will have a large impact on the final global Q statistic. It is calculated as follows (Flammer 1986):

$$Q = M3 / \sqrt{(LV)^3}$$

Both M3 and Q indices are considered to be more sensitive to localised defects and less affected by diffuse defects than are the indices MD, LV and CLV (Brechner & Whalen 1984; Bebie 1985) although Pearson et al. (1989) found no correlation between Q and either MD or PSD in glaucoma and in ocular hypertension.

The visual field indices described previously do not account for the location of the defect. The location of the defect can be described by the index spatial correlation (SC) which is low if the defects are randomly distributed throughout the field, and increases if they are clustered. The mathematical formula for this measure of the density of correlated defects is

given by (Bebie 1985):

$$SC = 1/p \sum_{(ij)} (z_j - MD - X_j).(z_j - MD - X_j)$$

where p is the number of pairs involved in the summation; ij indicates a summation over pairs of adjacent test locations and z_j and X_j are the age-corrected normal value and the average local sensitivity at test location j respectively.

The analysis of localised loss that is spatially sensitive based on a geographical type of cluster analysis has been developed for results of suprathreshold (Chauhan et al. 1988) and threshold (Chauhan et al. 1989) perimetry, in which the cluster indices SIZ (total number of clustered points depressed more than 5dB below age-corrected normal values), CLUS (mean depth of the clustered points) and PCLUS (the percentage of mean defect that is clustered) are computed as well as the total number of clusters, total cluster size and total cluster depth. The cluster indices SIZ, CLUS and PCLUS as well as MD and CLV when regressed against time have however been shown to have poor sensitivity for the detection of change, the most sensitive index PCLUS having a sensitivity of less than 65% (Chauhan et al. 1990).

1.13. ANALYTICAL SOFTWARE

The numerical output of automated perimetric data has necessitated the development of software for data handling and statistical analysis.

JO and STATJO was a package designed for the Octopus 201 (Flammer et al. 1983b) which consisted of an examination program JO and an analysis program STATJO. Sensitivity was determined twice at each of 49 stimulus locations and the visual field indices mean sensitivity and short-term fluctuation were calculated for the entire field, upper and lower hemifields and at various eccentricities. It also measured the influence of examination time, reaction time and the number of false positive and negative responses.

Program DELTA performs data reduction on the Octopus, calculating mean sensitivity, mean defect and short- and long-term fluctuations (Bebie & Fankhauser 1981; Gloor et al. 1980a,

1981). It also performs a statistical t-test on visual field data selected from two or two groups of examinations to determine whether change has occurred in mean sensitivity (Fankhauser & Jenni 1981). Use of the t-test in determination of visual field change has been criticised by Hills & Johnson (1988) since the distributions of sensitivity values under comparison are frequently non-normal and have varying standard deviations (short-term fluctuation).

Program SAPRO is a spatially adaptive routine written for the Octopus. Defective areas are identified and then explored with finer stimulus grids at two or three levels of resolution, each grid possessing twice the resolution of the former (Fankhauser et al. 1981). SAPRO classifies the differential sensitivity of a particular location into one of three ranges rather than determining the actual sensitivity values.

The F-program was developed for the Octopus to provide high resolution programs (maximum 0.2°) of linearly arranged stimuli which may be orientated at any meridian in the (Fankhauser et al. 1981). The strategy employed is the normal or shortened repetitive bracketing procedure described by Spahr (1975) and Bebie et al. (1976a). The program permits calculation of mean sensitivity, overall fluctuations and normative local age-matched data is printed out for comparative purposes.

Program DELTA performs data reduction on the Octopus, calculating mean sensitivity, mean defect and short- and long-term fluctuations (Bebie & Fankhauser 1981; Gloor et al. 1980a, 1981). It also performs a statistical t-test on visual field data selected from two or two groups of examinations to determine whether change has occurred in mean sensitivity (Fankhauser & Jenni 1981). Use of the t-test in determination of visual field change has been criticised by Hills & Johnson (1988) since the distributions of sensitivity values under comparison are frequently non-normal and have varying standard deviations (short-term fluctuation).

Program G1 has been recently introduced for the Octopus, which measures 60 stimulus locations out to an eccentricity of 26° either once or twice (Flammer et al. 1987). If only one measurement has been performed at each location, then the indices mean sensitivity, mean defect, loss variance, third central moment and skewness are printed out; corrected loss

variance and short-term fluctuation are calculated from double threshold determinations. The program also uses a two-level screening procedure for more peripherally situated stimuli. An equivalent program N1 for use in neuro-ophthalmological cases allows assessment of the horizontal and vertical meridional area, macula, temporal crescent and blind spot area (Safran & Mermoud 1989). The program consists of three phases, each of which may be checked separately or successively thus potentially shortening the examination time.

The OCTOSOFT program was written to allow a personal computer to receive, store, analyse and dispay data from the Octopus 500 Automated Perimeter, which has no data storage facility of its own.

Bebie (1990) has described an accessory program OCTOSMART intended as a training aid in the critical evaluation of visual fields and evaluated by Hirsbrunner et al. (1990). Based on raw measurement data from the Octopus G1 examination, the program provides statements on the printout regarding the degree of disturbance and reliability of the examination as well as the cumulative defect curve. The interpretative statements produced by the program are merely the statistical comparison of the result of a given test with stored data and are not intended to be diagnostic of any particular disease condition. The program should not be confused with perimetric expert systems which attempt to give a diagnosis based on defect patterns (Sturmer et al. 1889; Hirsbrunner et al. 1990)

The STATPAC program is a package for the statistical analysis of standard central visual fields performed on the Humphrey Field Analyser (Heijl et al. 1987b). It is based on a new mathematical model of the normal visual field (Heijl et al. 1987a,b) and facilitates interpretation of single fields and illustrates change over time in consecutive fields. The program prints out reliability indices, test time and the number of stimuli presented; it also calculates four global visual field indices: mean deviation, pattern standard deviation, short-term fluctuation and corrected pattern standard deviation and prints out perimetric probability maps (Heijl & Asman 1989; Heijl et al. 1989c). For follow-up, the program contains several different options. These range from an overview format where the threshold printouts and probability maps from several tests are printed in reduced size without data reduction to a box and whiskers

plot illustrating the distribution of individual sensitivity values over time. If 5 or more tests are available, a linear regression of MD, PSD, CPSD and SF is performed over time to determine whether the resulting slope is significant. Statpac 2 is an extension of the Statpac analysis and is based on empirical data obtained by repeated measurements on stable glaucoma patients. It contains a glaucoma change probability analysis, which uses symbols to indicate change on a pointwise basis, a modified linear regression analysis of MD intended to minimize learning effects by discarding the results of the first test and a glaucoma hemifield test which evaluates the MS of five zones in the superior field and compares these zones with their mirror image zones in the inferior field.

1.14. EXTRANEOUS FACTORS AFFECTING VISUAL FIELD ASSESSMENT

1.14.1. Optical defocus

The effects of defocus on perimetric thresholds have been investigated by several workers. Harms (1952) using static manual perimetry demonstrated that uncorrected refractive errors increased the differential light threshold out to an eccentricity of 10°. Sloan (1961) noted a change in threshold over the central 30° for Goldmann stimuli sizes I and II, although larger stimuli (sizes III, IV and V) were not affected. Similarly, Fankhauser & Enoch (1962) demonstrated that increment thresholds over the central 30° for a Goldmann size I stimulus were markedly affected by blur. Serra (1983) found that spherical defocus of 2.50DS reduced the extent of the Goldmann II2e isopter by 50%. The effects of blur on perimetric thresholds are minimal beyond 35° to 40° for any size of stimulus since spatial summation is greater peripherally (Tate 1985). Atchison (1987), using the Goldmann perimeter, found moderate defocus of up to 5.00DS caused an increase in threshold within the central 30° for stimuli equal to or smaller than Goldmann size III.

The effect of defocus on the central visual field has also been examined using automated static perimetry. Benedetto & Cyrlin (1985) investigated the effects of defocus on stimulus size Goldmann III of the Octopus automated perimeter, finding the loss of sensitivity to be greater at fixation than at 30°. Indeed, Weinreb & Perlman (1986) found sensitivity over the central 6° to decrease with positive spherical defocus of 1.00 and 2.00 Dioptres, although

the slope of the hill of vision remained independent of refractive error. Similarly, Heuer et al. (1987a) found small amounts of spherical defocus produced a depression of the differential light threshold that was of the same magnitude at all eccentricities within the central 25°. Goldstick & Weinreb (1987) examined the effect of spherical defocus on the Octopus automated perimeter global analysis program G1 (stimulus size Goldmann III). They found that mean defect increased significantly with spherical defocus of 1.00DS and 2.00DS increasing the mean defect by 3.6dB and 5.3dB respectively although no change in the visual field indices corrected loss variance, skewness, short-term fluctuation and reliability were found. Wild et al. (1988) examined the effects of the peripheral refractive correction, measured using the Canon Autoref R1 infra-red automated refractor, at eccentricities of 20° and 40°. Differential light sensitivity was measured at these eccentricities on the Octopus Automated Perimeter using Goldmann stimuli sizes 0 and III with and without the peripheral correction. They found that the peripheral refractive correction did not influence perimetric sensitivity at either eccentricity for either stimulus size.

House et al. (1990) examined the effect of defocus on the visual field measured using high resolution perimetry. Defocus of +1.00DS and +2.00DS resulted in a significant decrease in mean sensitivity within the central 30° of 1.04dB and 2.37dB respectively.

Refractive effects may also occur due to accommodative spasm or fatigue, which are common in young uncorrected hyperopes and undercorrected presbyopes respectively, and lead to a depression of central sensitivity (Tate 1985). The corrective lens may also induce artifacts in the field due to magnification or minification of the image and to prismatic effects for peripherally located stimuli. Greve (1973) has calculated that, at 12° eccentricity, a +15.00DS lens would cause an alteration in stimulus position of 2.5°; this would mean that the edge of the blind spot is displaced from 12° to 9.5°. It is therefore recommended that aphakics are examined with contact lenses. Atchison (1979b) calculated the alteration in static perimetric sensitivity caused by spectacle lens prismatic effects. For lens powers between -6.00DS and +10.00DS the maximum sensitivity alteration for a Goldmann size I stimulus was 3dB for a 14mm vertex distance. Atchison (1979b) therefore considered that the prismatic effects of corrective ophthalmic lenses up to powers of +/-10.00DS could be

ignored within the central 30°. Such lens rim artefacts have been examined by Zalta (1989) in relation to automated perimetry.

The visual field defects associated with strabismic and anisometropic amblyopes have been reported by Philipp & Mayer (1989) using program G1 on the Octopus automated perimeter. They found central scotomata of the order of 6.5-7.0dB mean maximal depth in a sample of strabismic and anisometropic amblyopic patients, although the visual field indices mean defect and corrected loss variance were significantly higher in the anisometropic group compared with the strabismic patients. This was predominantly due to additional flat defects occurring in the paracentral and peripheral areas.

1.14.2. Variation with age

Studies with manual kinetic perimetry report a general contraction of the visual field with increasing age (Ferree et al. 1929; Goldmann 1945a; Weekers & Roussel 1945; Drance et al. 1967a; Egge 1984) with greater sensitivity reduction occurring in the peripheral than in the central areas of the field (Verriest & Israel 1965; Aspinall 1967). In comparing the data of Verriest & Israel (1965) with that of Zehnder-Albrecht (1950), Greve (1973) concluded that the reduction of sensitivity was greater for kinetic than for static perimetry.

The depression of sensitivity with increasing age has recently been quantified by Williams (1983), who showed a linear relationship between the central I2 isopter area and age in a population of normal subjects from 10-80 years of age, and Suzumura et al. (1985) who calculated the volume of the 3-dimensional visual field representation and found the sensitivity loss with aging to be greatest for the central isopter and to spread gradually to the periphery.

Studies with manual static perimetry show the average differential light sensitivity to decrease with age (Goldmann 1945a; Jayle 1960) although the shape and slope of the hill of vision remains constant. This constancy is assumed in the Octopus age-corrected normal threshold values (Bebie 1985). Recent studies using automated perimetry showed age to have a heterogenous effect on the visual field (Jacobs & Patterson 1985). Indeed, Katz & Sommer

(1986), using the Humphrey Field Analyser showed the greatest decrease of sensitivity to occur in the periphery, with the most depression occurring in the superior quadrant. This is in agreement with the study of Haas et al. (1986) who used the Octopus Automated Perimeter and reported that age reduced the upper hemi-field to a greater extent than the lower hemi-field. The peripheral area was affected most, with the pericentral area being affected less than the central field. Jaffe et al. (1986) also demonstrated that the age-related decline in sensitivity increased with eccentricity and was twice as rapid at 30° than at fixation, resulting in a steepening of the sensitivity profile. Interestingly, Katz & Sommer (1987) showed greater long and short-term fluctuations in older eyes. The model of the normal field constructed by Heijl et al. (1987a,b) incorporated in the Statpac software considers the normal reference field to change in both height and shape with age. Contrary to the above studies, Iwase et al. (1988) found a constant value of differential light sensitivity for all locations within the central 30° which did not decline until the age of 37 years. They showed no correlation between the rate of decline and eccentricity. Collin et al. (1988) noted a decrease in mean sensitivity of 0.101dB/year between the ages of 20 and 40 years and of 0.172dB/year between the ages of 40 and 60 years, although then found similar rates of loss for the superior and inferior hemi-fields. Jaffe et al. (1986) attributed age-related changes in sensitivity to a functional or anatomic loss of photoreceptors, ganglion cells and higher structures. Johnson et al. (1989a) also attributed such changes to neural losses as opposed to pre-retinal factors.

1.14.3. Pupil size

Variations in pupil size have several implications in perimetry. The pupil may enhance or degrade the image quality and it also controls the amount of light reaching the eye. The effects of pupil size on perimetric thresholds are considered in Chapter 6.

1.14.4. Training and fatigue

Training effects in perimetry result in greater sensitivity and an improved quality of response; conversely, fatigue effects result in a decrease in sensitivity. Both factors appear to be of greater importance in defective than in normal visual fields and are reviewed fully in Chapters 4 and 5.

1.14.5. Media opacities

Media opacities may significantly affect the normal and abnormal perimetric profile through light scattering, absorbtion and image distortion. These effects are discussed in Chapter 3.

1.14.6. Interocular differences

In the detection of visual field loss comparisons may be made between threshold data and either normal age-matched values, prior data, values of other locations in the same field e.g. opposite hemi-field or the patient's fellow eye. Comparison of the suspicious field with that of the fellow eye assumes that in normal individuals the two fields are indeed symmetrical. Brenton & Phelps (1986) predicted that asymmetry exceeding 6dB should occur in fewer than 1% of locations and that an asymmetry in mean sensitivity exceeding 1.4dB should occur in fewer than 1% of normal subjects. This has been substantiated by Rutihauser et al. (1989) who found the RMS component of variance attributable to right-left eye differences to lie between 0 and 3.3dB, depending on location. Indeed, Feuer & Anderson (1989) have proposed that a 2.0dB difference between eyes may be meaningful on a single occasion, and a difference as small as 1.0dB may be relevant if shown consistently in a series of 4 examinations. They reported several cases in which a 1.0dB depression in mean sensitivity was the only recognisable abnormality in the visual field of eyes with early glaucoma.

1.14.7. Other factors

A blood alcohol level of 0.05% has been shown to have little effect on both static and kinetic manual perimetry in young healthy individuals. The ingestion of alcohol resulted in increased central sensitivity under photopic and mesopic adaptation levels, enlargement of the blind spot and constriction of the central and intermediate isopters (Gandolfo 1983). The effect of alcohol on the outcome of automated perimetry has also been studied. Riedel et al. (1985), using Octopus program 51 to examine the temporal field (60-90°), reported statistically significant reductions in differential light sensitivity with concentric constriction at a blood alcohol level of 100mg/l. Significant increases were also noted in the short-term fluctuation and in the number of false positive and negative responses. Zulauf et al. (1986) however found a blood alcohol level of 0.08% to barely influence the results of automated perimetry using Octopus program JO out to an eccentricity of 25°. The number of false negative

responses, number of stimuli presented and short-term fluctuation increased although the only statistically significant finding was the increase in the number of false positive responses. Learning and fatigue effects estimated from the double threshold determination at each location in program JO were unaffected by alcohol. Wild et al. (1989) found a blood alcohol level of 50-70mg% produced a decreased mean sensitivity ($p<0.01$) and increased pattern and corrected pattern standard deviations ($p<0.01$) with an increase in the number of stimulus presentations required ($p<0.05$) as assessed with program 30-2 and Statpac analysis on the Humphrey Field Analyser. Greater depressions of sensitivity due to alcohol were also noted with increasing eccentricity.

The effects of drugs on the automated perimetric profile have also been examined. Haas & Flammer (1985) found short-term doses of 5mg and 10mg Diazepam in young healthy individuals to produce an insignificant diffuse depression of sensitivity measured with Octopus program JO. Short-term fluctuation and fatigue and learning effects were unaltered. Topical Guttae Timolol 0.5% used on normal subjects produced no measurable effect on the visual field indices measured with Octopus program G1 (Martin & Rabineau 1987). Mann et al. (1987) found no correlation between the visual field indices mean sensitivity, mean defect, short-term fluctuation and corrected loss variance measured with Octopus program JO and the drug type, average daily dose or cumulative dose for either of the anti-malarial drugs Chloroquine and Hydroxychloroquine. Both centrally and non-centrally acting anti-histamine drugs were found by Wild et al. (1989) to produce a statistically insignificant decrease in mean sensitivity assessed with the Humphrey Field Analyser program 30-2 and Statpac analysis. Short-term fluctuation was increased with anti-histamine therapy although surprisingly this only reached significance for the non-centrally acting drug.

Mizutani & Suzumura (1985) examined the diurnal variability of the visual field using Octopus program 31 in normals, ocular hypertensives and glaucoma patients. A small diurnal variation was observed in normals, but some ocular hypertensives demonstrated large variations in mean sensitivity corresponding to diurnal variations in intraocular pressure. The authors suggested that these patients who exhibited greater diurnal variation in mean sensitivity were more likely to develop glaucoma.

Koskela et al. (1990) found mean sensitivity to increase on average by 0.45dB in a single subject following an 8 kilometre jog, and considered that physical exercise could influence the factors underlying the long-term fluctuation.

CHAPTER 2

RATIONALE FOR THE RESEARCH

This study is a continuation of previous work on automated perimetry in the Department of Vision Sciences at Aston University carried out in collaboration with the Birmingham and Midland Eye Hospital. In early studies, visual fields derived by conventional kinetic and semi-automated static techniques were compared with a pioneering automated perimeter, the Octopus 201 (Flanagan et al. 1984a,b; Wild et al. 1984). This work hypothesised that different combinations of stimulus parameters presented by a given instrument could, in certain ocular and / or neurological disorders, be manipulated to provide diagnostic information additional to that obtained from the conventional perimetric examination. It was however recognised that patient-specific extraneous factors, such as intraocular light scatter arising from cataract, could influence the outcome of perimetric examination and confound the interpretation of results (Barnes et al. 1985; Wild et al. 1986c).

Further work in the Department concentrated on the effects of certain of these extraneous factors, namely media opacities, learning effects, pupil size, accommodative microfluctuations and peripheral refractive error on the automated perimetric profile of the normal eye (Wood et al. 1987a,b,c; 1988a,b; 1989). The format of the normal sensitivity gradient was also investigated in relation to the underlying anatomy and physiology of the retina and to its cortical representation (Wild et al. 1986a,b; Wood et al. 1986a). Retinitis pigmentosa patients were also noted to show abnormal behaviour over the dynamic range (Wood et al. 1986b), a finding which subtantiated earlier work (Flanagan et al. 1984b), in exhibiting enhanced spatial and temporal summation and stato-kinetic dissociation.

The aims of the current study were twofold. Firstly, to extend the study of the effects of extraneous factors and potential artefacts on the sensitivity gradient of the abnormal eye, in primary open-angle glaucoma and ocular hypertension, since these factors limit the early detection and accurate monitoring of visual field loss. In particular, the influence of the extraneous factors of media opacities and learning effects were to be considered. The study of Wood et al. (1988a) on the effects of pupil size on the sensitivity gradient of the normal

eye using LED stimuli was also to be extended to projection perimetry in a normal sample. Secondly, to determine the optimum stimulus conditions for the earliest detection of visual field loss by investigating the parameters of adaptation level, stimulus configuration, stimulus size and stimulus duration. The latter study was also carried out with particular reference to glaucoma and to ocular hypertension.

The research was carried out at the Department of Vision Sciences, Aston University and the Birmingham and Midland Eye Hospital. Patients with abnormal ocular conditions were recruited from the Birmingham and Midland Eye Hospital and the ophthalmology clinics of the Birmingham General and East Birmingham Hospitals. All patients were selected with the knowledge and co-operation of the consulting ophthalmologist. Patients who satisfied the specified inclusion and exclusion criteria for each study were recruited by the ophthalmologist from out-patient clinics. Each patient was given a short explanation of the particular study and was reassured that participating would not have any adverse effect on their sight or affect their overall care and management. Names and addresses of those patients who were interested in participating were passed to the Department and initial contact made by letter. Patients were requested to return a form stating whether they would be willing to take part in the particular study. Appointments were then made by telephone and a confirmatory letter sent. Patients were unpaid volunteers although any travelling expenses incurred in attending the Birmingham and Midland Eye Hospital or Department of Vision Sciences were refunded in full. In addition, a copy of the automated visual field data for each patient was made available for their hospital notes. Normal subjects for control purposes were recruited from the University optometry clinics and the undergraduate and academic populations of the University.

The study involved the use of three different automated perimeters, namely the Octopus 201 at the Birmingham and Midland Eye Hospital and the Humphrey Field Analyser 630 and Dicon AP3000 at Aston University. The former two employ projected stimuli while the latter has LED stimuli. The Octopus 201 and Dicon AP3000 were utilised for the study on the effects of media opacities on the automated perimetric profile since the previous work of Wood et al. (1987a,b; 1989) showed the effects of intraocular light scatter to be markedly

different for projected and LED stimuli. Due to certain limitations and disadvantages of LED stimuli, projection perimetry is now accepted as the preferred method; indeed, the Humphrey Field Analyser is probably regarded as the "standard" instrument of today. The study therefore concentrated on the use of projection perimetry.

The initial part of the study examined the effect of media opacities on the perimetric profile in glaucoma. The aim was to separate perimetric attenuation due to optical degradation (arising from media opacities) from that due to neural dysfunction in glaucoma. It was recognised that the main cause of visual disability in the presence of media opacities results from an increase in forward intraocular light scatter. A light scattering simulation was therefore made, as used by Wood et al. (1987a,b; 1989) and applied to a sample of 15 glaucoma patients with clear media. Modification of the concentration of light scattering suspension was required to produce suitable amounts of light scatter in an elderly patient sample. Perimetric assessment was carried out using the Octopus 201 and the Dicon AP3000. Induced intraocular light scatter was shown to cause diffuse depression of the visual field and decrease scotomata, thus masking the earliest visual field changes associated with glaucoma. It was acknowledged that the decrease in focal loss caused by the light scattering simulation could result from a reduction in the depth or area of the scotomata. To further investigate the effects of light scatter nomograms relating perimetric attenuation to light scatter, which were derived by Wood et al. (1989) from patients with lenticular opacities, were applied to the data obtained without the simulation thus correcting for the effects of light scatter. Re-evaluation of the visual fields in an increased sample of 26 glaucomatous patients showed that intraocular light scatter caused a diffuse depression of the field. The apparent decrease in focal losses caused by the light scattering simulation was found to be artefactual; it was attributed to the use of inappropriate age-matched normative data in the software package for calculation of the visual field indices by the perimeter.

The experimental design had assessed intraocular light scatter employing the subjective technique of glare disability which measures forward light scatter i.e. light which is scattered from the crystalline lens to the retina. There are, however, several reports in the literature regarding the relationship between perimetric attenuation and light back scattered from the

lens which seemed to conflict with the findings on forward intraocular light scatter. The degree of back scatter had been measured with a commercially available device, the Opacity Lensmeter, but the exact *in vivo* relationship between forward and back scatterd light remained obscure. The relationship between forward scatter, determined using glare disability, and back scatter measured with the Opacity Lensmeter was therefore determined in a sample of 60 patients of all ages. Patients had varying degrees of media opacification but were otherwise normal. These patients were recruited from a local optometric practice. Measurement of back light scatter was found to underestimate forward light scatter. It was concluded that measurement of back light scatter would therefore not predict the visual disability experienced by the patient or the extent of the visual field alteration in the presence of media opacities.

Another major extraneous factor affecting perimetric assessment and the early detection of visual field loss, namely the learning effect, was also examined in a sample of 25 newly referred glaucoma patients. The influence of repeated examinations, undertaken on consecutive days to maximise the learning effect, was studied using a custom full-field program designed for the Humphrey Field Analyser. Both eyes were tested to evaluate any inter-ocular transfer of the learning effect. Statistically significant improvements were found in the visual field parameters, although there was evidence of a "fatigue" effect counteracting this improvement. It was found that fatigue manifested both during one visit i.e. there was a transfer of the fatigue effect from the first to the second eye tested as well as from one daily visit to the next. The amount of learning was found to be related to the sensitivity of the field at the first examination; patients in whom the sensitivity was initially low appeared to improve the most, whereas those who showed high sensitivity initially displayed a minimal improvement. It was decided to follow the patients up at a later date, after an interval as would normally be encountered between hospital out-patient visits to see if the learning effect was retained, or if there was a "forgetting" of the skills required of the patient in automated perimetric assessment. Patients who took part in the first part of the study were contacted by letter; sixteen of these were willing to return for further examination. It was acknowledged that glaucoma patients would also show change in the visual field over this time period related to progression of the disease process or the long-term effects of therapy. A protocol

was therefore designed which separated these latter factors from the learning effects and it was found that the previous improvement in sensitivity with learning appeared to be retained. There was a slight regression evident at the outset of the first examination, but peak performance was reattained during this examination.

The findings in the learning study of an inter-test fatigue effect, both between eyes tested and between consecutive daily examinations, and the eccentricity and depth-dependence of the learning effect prompted further investigation into perimetric fatigue effects. A study was designed to evaluate fatigue effects in 19 glaucomatous patients who were fully trained, highly motivated and experienced in automated perimetry. This study would have implications in the perimetric follow-up and monitoring of the efficacy of therapy in glaucoma patients. Like the learning effect, the effects of fatigue showed an eccentricity-dependency i.e. the deterioration of perimetric sensitivity due to fatigue increased with increase in peripheral angle. It was found that the data did not support a depth-dependency of the fatigue effect. The second study on fatigue used a similar protocol to the learning study and was designed to evaluate the interaction of learning and fatigue effects in glaucoma suspect patients who were naive to automated perimetry. Such a study would have implications for the earliest detection of glaucomatous visual field loss. Results showed that learning and fatigue effects counterbalanced during the first examination although in subsequent examinations, once patients were fully trained, fatigue effects were more prominent.

There have been claims in the literature that the detection of visual field defects may be enhanced and additional diagnostic information attained by performing perimetric examination at higher or lower than standard adaptation levels, although the optimum adaptation level for the earliest detection of glaucomatous visual field loss has not been determined. In many of these studies, the concurrent effect of pupil size change on sensitivity at a different adaptation level has not been considered. It has recently been suggested that the detection of diffuse glaucomatous loss is enhanced at low adaptation levels (Drum et al. 1986). Diffuse loss, however, is non-specific for glaucoma and studies have suggested that focal losses may be more evident at higher adaptation levels (Shiga 1968; Paige 1985; Drum et al. 1986; Mills et al. 1986; Lustgarten et al. 1990). The current

study was carried out to investigate the normal perimetric response at higher than standard levels, with pharmacological control of pupil size, in a sample of 10 young normal subjects. The accuracy of sensitivity determination at each adaptation level was also considered, since greater accuracy in perimetric assessment would facilitate the early detection and sensitive monitoring of visual field loss. In addition, the validity of the Weber-Fechner and Rose-de-Vries laws for the adaptation levels used was examined. Over the range of higher adaptation levels employed, the differential light threshold was found to be a constant proportion of the adapting luminance level and was also independent of pupil size change, both of these latter factors indicated validity of the Weber-Fechner law. No relationship between short-term fluctuation or the reliability parameters and adaptation level was found.

The optimum stimulus configuration i.e. stimulus grid, stimulus size and stimulus duration for the detection of early glaucomatous visual field loss has yet to be established. An evaluation was made of the efficacy of certain novel combinations of stimulus parameters offered by current automated perimeters for the detection of early glaucomatous visual field loss. The efficacy of the "G1" glaucoma program, which contains a higher density of stimuli in the central field area was compared with the regular stimulus grid of the 30-2 standard program. Indeed, Weber & Dobek (1986) have suggested that the detection of scotomata may be enhanced by the use of a more dense stimulus grid within the central 10° of the visual field. The effect of stimulus size was also examined since it has been proposed that large stimuli may saturate the central visual field and smaller stimuli may be more appropriate for the early detection of change in this area (Wood et al. 1986a). This study employed 20 trained ocular hypertensives and glaucoma patients with minimal visual loss. The selection of stimulus parameters was made from those offered by two automated projection perimeters, namely the Octopus Automated Perimeter and Humphrey Field Analyser. Use of the centrally weighted grid of the Octopus G1 program did not enhance the detection of diffuse or focal glaucomatous visual field loss compared with the regular simulus grid of program 32. Similarly, the detection of diffuse and focal loss was not improved by use of a size I compared with a size III stimulus. It was however acknowledged that the sample comprised patients with relatively pure early diffuse loss. The detection of diffuse glaucomatous loss was, however, facilitated using a size III stimulus of duration 200msec at an adaptation level of 31.5asb

compared with a size III stimulus of duration 100msec at an adaptation level of 4asb.

The finding of Wood et al. (1986b), using manual static perimetry, that retinitis pigmentosa patients exhibited enhanced sensitivity to stimuli of short duration and other claims in the literature, again using manual static perimetry, that temporal summation is enhanced in glaucoma patients prompted a study into the temporal processing of perimetric spot stimuli using automated techniques. This pilot study employed the Humphrey Field Analyser with a custom ROM chip set to vary the stimulus duration and compared the temporal summative properties of 10 glaucomatous patients with an age-matched control group. The parametric adjustment at which any abnormal response was maximal was to be determined; such anomalous behaviour could then be evaluated as a potential diagnostic indicator of early glaucomatous damage. Temporal summation was found to be more complete in the glaucomatous sample than the normal controls although, within the limits of the small sample, the difference was not statistically significant. The pilot study did not support the hypothesis that changes in temporal summative properties preceded glaucomatous visual field loss.

Work continued throughout the study relatively unimpeded although some difficulties were encountered in the recruitment of suitable volunteer patients. This resulted since the study protocols frequently involved attendance on more than one occasion and, in the learning study, attendance on consecutive days was required. Some difficulties were also encountered in the recruitment of patients in the following groups: those naive to automated perimetry and those with relatively pure morphological cataract types. The response rate, to a request to participate in a study, varied from 60-70%. The recruiting ophthalmologists took great care in selecting suitable patients for each study and explained the nature of the work to each potential patient during their busy clinic schedules.

CHAPTER 3

THE EFFECT OF MEDIA OPACITIES ON THE VISUAL FIELD IN GLAUCOMA

3.0. GENERAL INTRODUCTION

The prevalance of primary open-angle glaucoma increases with age; indeed, studies indicate that 6-11% of the population over the age of 75 years may be affected (Kini et al. 1978; Gibson et al. 1985; Whitmore 1989). Estimates of the prevalence of senile lens opacities in this age group vary from 46-91% (Kini et al. 1978; Sperduto & Siegel 1980; Whitmore 1989). Glaucoma and cataract therefore frequently coexist, an important consideration in the light of an increasingly elderly population. Perimetric attenuation arising from optical degradation due to cataract must be differentiated from that due to neural dysfunction in glaucoma.

Media opacities lead to optical degradation through light scattering, absorbtion and image distortion; it is generally accepted that the main cause of visual disability experienced by patients with media opacities is due to the increase in intraocular light scattering (Zuckerman et al. 1973; Bettelheim & Ali 1985). Indeed, Stiehl et al. (1983) emphasised the importance of correcting for intraocular light scatter in quantitative determinations of retinal illuminance and Hemenger (1984) proposed that the measurable depression in the contrast sensitivity function with age was accounted for by the age-related increase in intraocular light scatter. Furthermore, from studies on the point spread function of the eye, Van den Berg (1987) predicted considerable changes in the visual field resulting from relatively mildly disturbed media, due to increased scatter over large and / or small angles.

CHAPTER 3.1

THE EFFECT OF INDUCED INTRAOCULAR LIGHT SCATTER ON THE VISUAL FIELD IN GLAUCOMA

3.1.1. LIGHT SCATTERING THEORIES

Light scattering theories have been extensively reviewed by Kerker (1969) and their application to ocular tissues by Miller & Benedek (1973). The light wave is an electromagnetic field, and the physically observable properties of light (refraction, reflection, scattering and absorbtion) result from the interaction between the electromagnetic field and any matter placed in that field. The processes involved in the scattering of light can be described by considering the analogy of a beam of light passing through a dusty room. The observer sees a shaft of light piercing the room, the brightness of the beam decreasing with distance from the light source. These observations may be explained in the following way: dust particles in the atmosphere consist of many atoms and molecules, composed of positively charged heavy nuclei and negatively charged light electrons. When light interacts with a dust particle the electric field of the light beam exerts an oscillatory force on the nuclei and electrons of the dust particle. The nuclei, being heavy, are unmoved by the action of this force; however, the lighter electrons are displaced from their normal orbits. The particle in the electric field is thus subjected to polarisation i.e. the nuclei and electrons move in opposite directions, inducing a dipole moment in the particle. This induced dipole oscillates at 10^{14} cycles/sec in synchrony with the electromagnetic field and subsequently radiates electromagnetic fields (light) in all directions. Thus, energy in the light wave is used to accelerate electrons and this energy then reappears as light travelling in all directions from the dust particle. The incident beam loses power as it excites electrons in its path. The observer sees the shaft of light because the eye detects light scattered sideways from the dust particles; in the absence of scattering particles, the light beam would be invisible to the observer.

The simplest quantitative description of the scattering power of a medium is its "turbidity". Media appear turbid because they attenuate the light passing through. The turbidity would be expected to be proportional to the density of scattering particles, assuming that each particle is independent i.e. there is no correlation between the relative positions of the

scattering particles. In fact, Maurice (1957) showed that as the density of scattering particles increases, the turbidity does not remain proportional to the density because the assumption of independent scattering fails to hold true. Maurice's computation of the turbidity of the normal cornea gave such a large value that the cornea would be expected to be opaque unless, at the very close collagen packings found in the corneal stroma, each fibre did not scatter light independently.

The dependence of light scattering on particle separation occurs because the scattered light waves from each particle interact, and the total electric field at any observation point is the sum of the individual fields. Each of the scattered waves will be at a different point, or phase, of their oscillation cycle at the observation point. The resultant electric field occurs from the superposition of these constituent waves, which interfere with one another either constructively or destructively, depending on the relative phases of the waves. The difference in phase between waves depends on the spacing of the scattering particles compared with the wavelength of light. If two particles are separated by distances comparable with the wavelength of light, the two scattered waves will be 180° out of phase and will cancel each other out giving no scattered electric field at the observation point. Conversely, if two particles are separated by distances which are small compared with the wavelength of light, the phases of the two scattered waves will be similar and the resultant field will have an amplitude twice as large as the amplitude of each individual wave. As light intensity is proportional to the square of the electric field, the intensity of the scattered light would be four times that scattered from each particle. Thus, both transparency and turbidity result from the superposition of the phases of the scattered waves. Water is transparent because the waves scattered from each water molecule interfere destructively in all directions except the forward one. Light is completely transmitted and none appears to be scattered.

The concept of correlation between the positions of neighbouring particles may be understood by noting that the degree of correlation ranges continuously from zero e.g. in a gas, to complete correlation e.g. in a perfect crystalline lattice of atoms. The particle positions are completely random in a gas, and perfectly ordered in a crystalline lattice. The degree of light scattering is not only dependent upon the inter-particle distance compared with the

wavelength of light but also upon the correlations between these particles.

The assumption of independent scattering, where there is no correlation between the particles and thus no correlation in the phase of the scattered waves, may be applied to the scattering of light by gas particles at atmospheric pressure. In the case of a dilute gas, the refractive index varies throughout the medium due to local concentration fluctuations. If the concentration of the gas is increased, such that the spacing between gas molecules becomes comparable to the size of the molecules, correlations between the positions of the gas molecules will be present and the scattering will not be proportional to the number of illuminated particles.

In contrast to the random positions of gas molecules, the atoms in a crystal are rigidly fixed in a geometric array (lattice). Since the wavelength of light is much larger than the individual atoms, there will always be a pair of atoms which scatter out of phase at any particular scattering angle. There is complete destructive interference of the scattered waves and no scattering is observed.

Scattering from pure liquids is intermediate between that of crystals and gases. Einstein (1910) considered that scattering in a liquid was due to local thermal fluctuations in the density of the liquid which rendered it optically inhomogeneous. In the case of a solution local variations in concentration must also be considered (Debye 1944) but this only applies when the particles are small compared with the wavelength of light. When the size of particles becomes equal to or greater than the wavelength of light, these particles in dilute solution may be treated by the Mie theory (1908) which is a general expression for scattering by a sphere. If the size of a particle is comparable to the wavelength of light the scattered wavelets will be out of phase; more light is then scattered in the forward direction and the scattered intensity is no longer proportional to the reciprocal of the fourth power of the wavelength (Debye 1944). The total volume of a liquid may be considered as comprising many small volume elements, which are smaller than the wavelength of light. Pairs of these elements are independent scatterers, thus scattered wavelets are out of phase, destructive interference occurs and no scattering is observed. However, liquids are not orderly and the

packing of particles in each member of the pair of volume elements may not be the same i.e. the refractive index varies between elements. Consequently, destructive interference is not complete and some scattering will occur. Based on the theories of Einstein (1910) and Debye & Beuche (1949) the liquid state is considered as a fluctuation in concentration, corresponding to refractive index fluctuations.

Rayleigh (1871) first derived an equation to calculate the intensity of light scattered by a small sphere where the sphere radius does not exceed one twentieth the wavelength of light. This equation predicts that the intensity of scattered light is inversely proportional to the fourth power of the wavelength scattered. It is this dependence on wavelength that causes the blue end of the visible spectrum to be more strongly scattered, giving the sky its characteristic colour. The scattered intensity is also directly proportional to the volume of individual particles; the larger this is, the more intense the scattering. Rayleigh's equation also includes a term for polarisability i.e. how much dipole moment is induced in the medium by a unit electric field. Polarisability is related to the refractive index of the medium.

Rayleigh's equation for a liquid would predict that the intensity of scattered light increases with concentration and molecular weight; indeed, for a dilute solution the intensity of scattered light is directly proportional to the molecular weight (Debye 1947). The scattering of light by dilute solutions can therefore be used to evaluate molecular parameters.

Debye & Beuche (1949) developed a general treatment for the scattering of light by an inhomogeneous material, the so-called "random-fluctuation" theory. They showed that the intensity and angular distribution of scattered light was dependent on fluctuations in refractive index and the size of regions over which these fluctuations occurred, characterised by the correlation function. Turbidity was due to fluctuations in the refractive index over spatial domains comparable to the wavelength of light. Fluctuations in refractive index may arise from fluctuations in density and fluctuations in optical anisotropy (i.e. the refractive index in a medium is a function of orientation). Debye & Beuche's (1949) calculations also showed that the size of particles as well as the inter-particle separation was important in predicting turbidity.

Non-polarized light scattering from concentrated solutions, gels and inhomogeneous solids may also be treated by the random fluctuation theory of Debye & Beuche (1949). This theory has been applied to crystalline polymers by Stein et al. (1959) who measured the fraction of incident light that was scattered as a function of scattering angle, polarisation, wavelength of light and sample orientation to determine parameters useful in characterising the organisation of crystallites in polymer films and changes in organisation that occurred on processing the polymer.

Bettelheim & Siew (1983) considered the random fluctuation theory to be compatible with the observed behaviour of dilute and concentrated solutions as well as gels and to be applicable over the important concentration range of biological tissues. The random fluctuation theory also predicts an increase in turbidity on dilution of a cytoplasmic gel whereas the dilute solution approximation predicts a decrease of turbidity with dilution.

3.1.2. INTRAOCULAR LIGHT SCATTERING

3.1.2.1. Corneal transparency and turbidity

Light scattering theory would predict that the normal cornea is transparent since the diameter of the fibres is small compared with the wavelength of light and their refractive index is close to that of the ground substance, thus rendering them inefficient scatterers. The large number of fibres however compensates for this inefficiency, and Maurice (1957) calculated that 90% of incident light would be scattered i.e. the cornea would appear turbid, if the fibres were arranged randomly such that they acted as independent scatterers. He therefore concluded that the fibres did not scatter light independently of one another and suggested a "lattice theory" of transparency in which the scattered light was supressed by mutual interference. A crystalline lattice was the only distribution that would ensure transparency on a purely theoretical basis. Although electron microscopy revealed the cornea to have a non-crystalline quasi-regular structure, this was regarded at the time as an artefact resulting from the fixation procedure (Jakus 1964).

Attempts to confirm the lattice structure proposed by Maurice (1957) have failed. Goldmann & Benedek (1967) concluded that a lattice arrangement of collagen fibres was not a

necessary condition for corneal transparency. They observed a structural organisation of collagen fibres in shark stroma which was incompatible with the lattice theory, finding the collagen fibres to be separated by small distances compared with the wavelength of light. Hart & Farrell (1969) suggested that the quasi-regular quasi-random structure revealed by the electronmicroscope was not in conflict with corneal transparency. They evaluated a "radial distribution function" from electronmicrographs of rabbit cornea. This function describes the likelihood of finding two scattering centres separated by a specified distance which, in turn, determines the optical path difference for scattered light from the two particles and thus whether the scattered wavelets interfere constructively or destructively. This distribution function showed that the position of collagen fibres remained correlated over two neighbouring fibres at the most and, by a mathematical summation of the phases of waves scattered by such a partially ordered array, they calculated a magnitude and wavelength dependence of scattered light that was in good agreement with that found experimentally.

Other modern theories of corneal transparency also suggest that perfect lattice periodicity is neither required theoretically nor found experimentally, providing the collagen fibre diameter remains small compared with the wavelength of light (Feuk 1970; Cox et al. 1970; Benedek 1971; Twersky 1975). Feuk (1970) observed that the arrangement of stromal fibres was consistent with random displacements of the fibres around perfect lattice positions. The root mean square displacement, found to be qualitatively consistent with electronmicrographs, was about one tenth of the average inter-fibre spacing. Using the Debye-Waller theory of thermal diffuse x-ray scattering, Feuk (1970) found the calculated scattering from this arrangement to be in agreement with the observed value. Cox et al. (1970), using radial distribution function calculations, predicted the presence of a local order of collagen fibres extending to at least 200nm from individual fibres. Benedek (1971) treated the human cornea as a dilute solution in terms of its light scattering properties. He presented proof that light is scattered only by those fluctuations in refractive index whose Fourier componants have a wavelength equal to or larger than one half the wavelength of light in the medium. In applying this principle to collagen fibres, he demonstrated physically and quantitatively that a limited correlation in the position of collagen fibres led to corneal transparency. Interestingly, Twersky (1975) considered the normal cornea to be modelled by a densely packed

two-dimensional gas, with the gas particle (mechanical) radius being 60% greater than the fibre (optical) radius. Using this model he obtained a theoretical transmittance of 90% for the normal cornea.

Corneal turbidity as a result of swelling is attributed to marked heterogeneity in the spatial distribution of collagen fibres leading to fluctuations in refractive index over distances comparable to or larger than the wavelength of light (Goldmann et al. 1968; Cox et al. 1970; Benedek 1971; Farrell et al. 1973). This heterogeneity results from "lakes" which, when observed with the electronmicroscope, appear as irregular areas within the lamellae where no mature collagen fibres are apparent. As corneal swelling increases, the lakes increase in size and cluster together. This concept of corneal turbidity was supported by studies of the wavelength dependence of light transmission through cold swollen corneas, which indicated that the increased scattering was caused by large inhomogeneities in the ultrastructure (Farrell et al. 1973). Indeed, Farrell & McCally (1977) considered that any theoretical attempt to model and understand corneal transparency and its loss during swelling, in terms of ultrastructure, must account for a short-ranged ordering of fibrils in normal corneas and for the formation of regions devoid of fibrils in swollen corneas.

There has been much research into the use of light scattering measurements to determine corneal ultrastructure (Gallagher & Maurice 1977; McCally & Farrell 1977; Andreo & Farrell 1982; McCally & Farrell 1982). The use of scattering measurements to examine stromal ultrastructure is based upon the assumption that most corneal scattering occurs within the stroma and not from the limiting cellular layers. Indeed, McCally & Farrell (1976) showed that the stroma accounted for more than 60% of the total light scattered between angles of 20° and 145°; this contribution rose to more than 75% for scattering in backward directions (angles $\geq$ 90°). Contrary to this Lindstrom et al. (1973), who measured the intensity of back scattered light as a function of depth in the rabbit cornea during intraocular pressure changes, found the main contribution in scattered intensity to emanate from regions close to the limiting membranes i.e. the epithelium and endothelium. McCally & Farrell (1976) suggested that this difference was due to distortions introduced by the spatial response function of the measuring apparatus. Freund et al. (1982) proved that the collagen fibrils of

rabbit stroma are indeed the primary source of light scattering in the cornea, discounting the epithelium, endothelium, Bowman's layer and the stromal keratocytes as possible sources.

Olsen (1982) described a clinical method for *in vivo* measurement of corneal back scatter using a slit-lamp photometer system. He found a significant correlation between increase in back scatter and age ($p<0.001$) although there was a poor correlation with corneal thickness, suggesting that the normal interindividual variation in corneal thickess results from variations in mass content as opposed to water content. The increase in scatter with age suggested that age-related changes occurred in the fibril ultrastructure.

3.1.2.2. Lenticular transparency and turbidity

It is generally accepted that an increase in forward light scatter as distinct from the absorbtion process produces the retinal image degradation in cataractous eyes (Bettelheim & Ali 1985). Indeed, Zuckerman (1973) demonstrated that if a cataract were composed primarily of randomly distributed light absorbing regions rather than light scattering centres, far less light would reach the retina than is the case. Furthermore, image contrast and resolution would be higher than observed.

From the principles of light scattering it emerges that turbidity is due to fluctuations in refractive index over spatial domains comparable with the wavelength of light. There are two contributions to refractive index fluctuations: fluctuations in density and fluctuations in optical anisotropy. In its normal state the lens is transparent despite the presence of a high concentration of protein in the lens fibre cell cytoplasm which would be expected to scatter light. An explanation of lens transparency was therefore sought in the spatial correlations of the individual scatterers. The physical basis for transparency of the normal lens was first studied by Trokel (1962), who showed that, if lens protein crystallins were individual scatterers, the scattering intensity would be proportional to the protein concentration and 70% of visible light would be scattered. Trokel (1962) concluded that the high transmittance of the lens resulted from a paracrystalline state of the lens proteins. This view was endorsed by Philipson (1969), who did not show peaks in the visible absorption spectra of human lenses. The transparency of the normal lens was also explained by the size of the spatial

Fourier components of refractive index fluctuation and the amplitude of optical anisotropy fluctuations which were both smaller than the wavelength of light (Benedek 1971; Bettelheim & Paunovic 1979).

Despite improved understanding of the molecular structure of lens crystallins, their exact spatial order remains unkown. The work of Delaye & Tardieu (1983) showed that the paracrystalline state suggested by Trokel (1962) does not exist in the normal lens. Delaye & Tardieu (1983) studied calf lens cytoplasm using small angle x-ray scattering and demonstrated that paracrystalline order was unnecessary to account for lens transparency; a limited short-range order of the lens proteins was sufficient, as is found in dense liquids or glasses. A structure with short-range order would reduce the scattered intensity to 2.5% of that which would occur if the crystallins were independent scatterers. The study of Latina et al. (1987) supported the concept of a longer range ordering of lens proteins, than was proposed by Delaye & Tardieu (1983), in a gel-like structure.

Interestingly, Hemenger (1982) proposed a new form for the optical density of the crystalline lens, which evaluated the individual contributions from light scattering and absorption but which only allowed an approximate separation of the scattering portion into that from the nucleus and that from the lens cortex. Utilising previous data (Ludvigh & McCarthy 1938; Weale 1954; Said & Weale 1959; Boettner & Wolter 1962; Zigman et al. 1976; Bettelheim & Paunovic 1979) he further suggested that light scattering in the crystalline lens was not of the Rayleigh type (proportional to 1/wavelength^4) but instead was inversely proportional to the square of the wavelength. He further proposed (Hemenger 1984) that the relatively large cortical fibres were responsible for light forward scattered by the lens, while the smaller protein aggregates in the lens nucleus were the cause of backscattered light. Hemenger (1988) later substantiated his proposal that the lens fibre architecture was indeed responsible for small angle scattering (at angles less than 8°) in the lens.

In the absence of electronmicrographs of the lens ultrastructure, biochemical evidence provided the early theories of cataract formation. Biochemical analyses showed cataractous lenses to contain an elevated percentage of insoluble high molecular weight (HMW) protein

called the albuminoid fraction in addition to the normal soluble crystalline lens proteins (Spector 1965). This finding was compatible with Trokel's prediction (1962) that the presence of substantial numbers of large protein aggregates, randomly distributed within the background of the crystalline protein content, would have an important effect on transparency. Philipson (1969) also noted a pronounced variation in protein concentration in the nuclear region of human cataractous lenses such that light interacting with the central opaque region was almost totally scattered.

Benedek (1971) first applied light scattering principles to the cataractous lens and presented a calculation which provided a quantitative relationship between lens turbidity and the molecular weight, refractive index, size and density of protein aggregates. Benedek's calculations showed that, if protein aggregation were indeed the correct mechanism of cataract formation, the aggregates would have a molecular weight greater than 50×10^6 g/mole. If these aggregated clumps were uncorrelated in position they would scatter light independently of one another. If, however, the size of the aggregate were large enough, these individual scatterers could produce the observed turbidity of the cataractous lens. Further biochemical evidence for this theory exists in the finding that cataractous lenses contained 2-3 times more HMW protein aggregates than were present in normal lenses (Jedziniak et al. 1973). Indeed, HMW protein aggregates of molecular weight greater than 150×10^6 g/mole were found to represent 10-15% of the total soluble protein of both normal human lenses over 72 years of age and cataractous lenses (Jedziniak et al. 1973). This increased concentration of HMW protein has been found mainly in the nuclear region of sclerotic cataractous lenses (Jedziniak et al. 1975). Indeed, Fu et al. (1984) also showed higher molecular weight proteins to be present in the nucleus than the cortex of both normal and cataractous lenses, although there was a greater proportion of HMW protein in cataractous lenses.

The theory that cataract formation is an aggregation process, passing from soluble HMW proteins to insoluble proteins, which form microphases of a size comparable with the wavelength of light, has been found attractive by a large number of researchers. There is a vast literature concerning the transition of soluble lens proteins to aggregates and insoluble

lens protein as a function of aging and cataractogenesis, as reviewed by Harding & Dilley (1976) and Benedek (1984). The search for the biochemical mechanisms responsible for the formation of such aggregates remains one of the central themes in cataract research, although the aggregates are thought to be stabilised by covalent disulfide bonds (Spector 1984).

Spector et al. (1974) found a gradual increase in the proportion of soluble HMW protein which commenced in the second decade of life and occurred almost entirely in the nuclear region. Quantitative analysis of light back-scattered from the lens indicated that in the nuclear region the increase in back-scatter paralleled the increase in HMW protein, while in the cortex back-scatter appeared to be independent of HMW protein. It was therefore proposed that cortical back-scatter was due to normal morphologic irregularities between the cortical fibres. This substantiated the earlier study of Philipson (1973), who showed a different mechanism for the formation of nuclear and cortical cataracts. The formation of human cortical cataracts was shown to commence with enlargement of intercellular spaces, followed by a breakage of lens fibre cell membranes, loss of protein matrix and the creation of large refractive interfaces between zones with different protein concentration. The only change detected, however, in nuclear cataracts was an aggregation of protein molecules. The age-dependent changes that occur in nuclear cataract formation have also been shown to involve a low molecular weight (LMW) polypeptide, present only in lenses which are at least 20 years old (Spector et al. 1975; Kramps et al. 1976). It has been further suggested that LMW protein interacts with other polypeptides to form HMW or water-insoluble protein (Jedziniak et al. 1978).

Extension of the Debye-Beuche theory (1949) to gels or concentrated solutions shows that not only the size of particles, but also the interparticle separation is important in predicting turbidity (Bettelheim & Siew 1980; 1983). Lens turbidity may result from an increase in the size and number of the HMW protein aggregates, and may also result from dilution if the interparticle distances reach the order of the wavelength of light (Bettelheim & Siew 1983).

Bettelheim & Paunovic (1979) proved the Debye-Beuche (1949) random fluctuation theory to be applicable to protein in thin sections of normal lenses. They analysed the angular

distribution of scattering intensity to obtain parameters that would describe the scattering units within the lens fibres. Their model predicted that particles of size 200-900nm were dispersed and separated from each other by distances of 480-1400nm. A mean diameter of 300nm for the scattering structures in both the nucleus and the cortex was found although the particles were larger in the nucleus. This is consistent with data determined electronmicroscopically for the size of HMW protein aggregates in the bovine lens nucleus, found to be 500nm in diameter (Kramps et al. 1975), and also with the hypothesis that cortical scattering results from the loose structure of lens fibre cells, whose invaginating processes are about 300nm in diameter (Hogan et al. 1971). Aggregates in the cataractous lens were however found to be of similar size; Delaye et al. (1982) reported a value of 300-500nm in calf lenses. Similar values to these were reported by Bettelheim et al. (1981) who found the diameter of aggregates to be between 270 and 550nm and other authors who noted aggregates of the order of 300-500nm in rabbit (Liem-The et al. 1975), human (Ringens et al. 1978) and rat (Beyer-Mears et al. 1978) cataractous lenses. The size of the protein aggregates is therefore similar in normal and cataractous lenses, the important difference is that the protein aggregates are more dense and closely packed in cataractous lenses (Bettelheim et al. 1981).

A major interest in the study of nuclear cataracts is the relationship between the optical parameters obtained from light scattering and the clinical description and classification. Siew et al. (1981a) classified eight nuclear cataractous lenses by stereoscopic photography immediately prior to intracapsular extraction. Following surgery, thin sections of the lenses were cut perpendicularly to the posterior-anterior axis and their light scattering properties examined. They found the random-density and orientation fluctuation theory of light scattering to be applicable to the thin sections and identified protein aggregates as the scattering centres that caused density fluctuations. Within the lens, both the size of the scattering units and the spacing between them were found to decrease towards the centre of the lens. Thus, scattering was accounted for by the relatively large size and close packing of scattering units in the centre of the lens. These nuclear changes were also suggestive of syneresis, the chemical process in which a gel contracts on standing and exudes liquid, which is the most important process in cataractogenesis due to ageing (Siew et al. 1981b).

Thus, a good qualitative correspondence was found between the clinical description and structural parameters of the cataractous lens with respect to the spatial distribution of the elements causing turbidity.

Bettelheim et al. (1981) summarised three processes that contributed to nuclear cataractogenesis and accounted for the changes in refractive index and particle density: a syneretic process (Bettelheim 1979), an increase in the concentration but not in the size of protein aggregates and an association between aggregates and optically anisotropic membrane components that leads to a decrease in structural birefringence.

3.1.3. ASSESSMENT OF FUNCTIONAL INTEGRITY IN THE PRESENCE OF MEDIA OPACITIES

Numerous clinical tests exist for the assessment of visual function in the presence of media opacities (Fuller & Hutton 1982; Brodie 1987; Guyton 1987; Charman 1987). The traditional measure of high contrast high spatial resolution, Snellen acuity, has been shown to provide an inadequate description of the visual performance of the patient with media disturbances, since intraocular light scattering canot be modelled by defocus (Hess & Garner 1977; Hess & Woo 1978). Contrast sensitivity testing (assessment of the intra-resolution limit) is therefore advocated in addition to traditional acuity measures (Hess & Woo 1978); indeed, contrast sensitivity testing has been shown to predict visual performance for targets typical of everyday life (Owsley & Sloane 1987).

Le Grand (1935) first described a method for quantitative assessment of macular function independent of lenticular opacities by the production of interference fringes on the retina. The method was re-evaluated in the 1970s using interferometers with He-Ne lasers as the monochromatic light source (Goldmann & Lotmar 1969, 1970; Green 1970; Green & Cohen 1971) and led to the development of the commercially available Rodenstock Retinometer (Rassow & Wolf 1977). Two laser beams (emanating from a common source so the wavefronts are coherant) are passed through "windows" in the cataract and focused at two adjacent points close to the nodal point of the eye; the overlapping beams produce an interference pattern on the retina whose spatial frequency depends only on the distance

between the point sources and the wavelength of light; it is independent of axial length. Since the grating is imaged directly on the retina it is resistant to optical aberrations. Two clear pinhole areas in the opacity with maximum separation of 1.1mm are required. Green & Cohen (1971) hypothesised that the laser light may penetrate a cataract by three mechanisms. Firstly, the patterns are not imaged on the retina but are formed by the interference of two pinpoint sources of light focused onto the lens; thus, enough light could enter the eye through microscopic holes even when the whole lens appears opaque. Secondly, the interference technique by-passes the effects of optical aberrations (the image is not formed by the cornea and lens) and therefore any remaining clear areas of the lens may be fully used. Thirdly, red light from the He-Ne laser is scattered less than light of shorter wavelengths.

Lotmar (1972,1980) later developed an achromatic interferometer which uses an incandescent light source to illuminate a pinhole which is imaged on the subject's pupil. Two identical diffraction gratings (100 lines/mm) in contact with one another are placed in the light path. As one of the identical gratings is rotated with respect to the other, Moire fringes are produced whose spatial frequency varies with grating position. The Moire fringes are split into two coherent light beams that interfere to form a grating image on the retina. The advantages of this method are the low cost of an incandescent light source, an absence of ghost fringes and a simple means of continuously varying the spatial frequency of the fringes. The method was adapted for clinical use by Goldmann et al. (1980) and led to the development of the commercially available Haag-Streit Lotmar visometer. Results obtained with this technique were shown to be comparable with those obtained using laser interferometers (Lotmar 1980).

The grating image should theoretically be unaffected by the refractive state of the eye. Indeed, interferometric acuity is independent of refractive error of up to +/-10 dioptres (Halliday & Ross 1983) although in the presence of large refractive errors the interfering beams may form fields that barely overlap at the retina and refractive correction is required (Enoch et al. 1979; Goldmann et al. 1980). Furthermore, since the production of the grating image is a function of the amplitude of the electromagnetic wave, partial obstruction of one of

the beams should not adversely affect the grating image. The pupil is routinely dilated for measurement of interferometric acuity, although Bosse (1989) has suggested that this may not be necessary in cases of mild to moderate cataract.

Early work reported a good correlation between pre-operatively determined interferometric acuity and post-operative Snellen letter acuity in patients with lenticular opacities (Green 1970; Green & Cohen 1971; Cohen 1976; Rassow & Ratzke 1977; Kolling 1978; Enoch et al. 1979; Goldmann et al. 1980; Spurny et al 1986; Hanna et al. 1989) and corneal opacification (Gstalder & Green 1972; Enoch et al. 1979). Other studies however have disputed these findings, showing pre-operative interferometric acuity to overestimate post-operative Snellen letter acuity (Bernth-Petersen & Naeser 1982; Bloom et al. 1983; Halliday & Ross 1983; Faulkner 1983; Fish et al. 1986; Miller et al. 1988). There have also been reports of pre-operative interferometric acuity underestimating post-operative Snellen acuity (Miller et al. 1988; Hanna et al. 1989). These discrepancies may result due to the severity of opacification within the sample; in cases of mature opacity where effective windows in the opacity do not exist, interference may be compromised to the extent that readings cannot be obtained (Goldmann et al. 1980; Faulkner 1983; Halliday & Ross 1983; Minkowski & Guyton 1984; Steinert et al. 1984; Klein et al. 1986; Datiles et al. 1987). The presence of maculopathy also affects the predictive ability of the test (Bloom et al. 1983; Faulkner 1983; Fish et al. 1986); indeed, in cases of maculopathy and amblyopia it has been shown that grating acuity falls off more slowly than letter recognition with eccentricity from the fovea (LeGrand 1968; Gstalder & Green 1971). Interferometric acuity reflects foveal function; however, if the grating pattern subtends a large area (e.g. a 5° field) and the stimulus is bright visual performance in parafoveal areas is enhanced (Enoch & Hope 1973). Thus, apparently good acuity may result even if the fovea is non-functional. It has been suggested that smaller fields more accurately centred on the fovea may be more selective in patients where macular disease is suspected (Lotmar 1972; Goldmann et al. 1980) however patient recognition of grating fields smaller than 3.5° is poor and it is difficult to aim the field at the fovea (Halliday & Ross 1983). Faulkner (1983) has hypothesised that photoreceptor orientation accounts for the disparities between pre- and post-operative acuity measurements whereas Fuller & Hutton (1982) have speculated that extrafoveal fixation is more likely to occur when

information is projected into the eye itself. Minkowski & Guyton (1984) consider the cause of the discrepancy to depend on whether the retinal disorder is reversible or non-reversible.

The Potential Acuity Meter (PAM) was developed by Minkowski et al. (1983) and is attached to a slit-lamp. This instrument uses a condensing lens system to project a miniaturised Snellen chart (6/120-6/6) through a 0.1mm aperture in the opacity to focus on the retina. The PAM has a field of 6° and uses a low cost incandescent lamp to illuminate the chart. Despite the large depth-of-focus conferred by using point source optics, the PAM requires gross spherical correction for optimal performance and pupil dilation. There have been reports that the PAM may both underestimate (Minkowski et al. 1983; Steinert et al. 1984; Miller et al. 1988) and overestimate (Fish et al. 1986) post-operative Snellen acuity compared with pre-operative PAM measurements. As with interferometric techniques predicative ability of the PAM is less accurate with more dense cataracts (Minkowski & Guyton 1984; Klein et al. 1986; Datiles et al. 1987a) and corneal opacification (Steinert et al. 1984), however the PAM does not overestimate acuity in amblyopia (Minkowski et al. 1983). Similar hypotheses have been advanced for these discrepancies as for interferometers. Studies have shown interferometry to be more accurate than PAM measurement in predicting post-operative acuity (Steinert et al. 1984; Spurny et al. 1986).

Other tests of visual function with the capability of penetrating ocular opacities have similar drawbacks. Flash and flicker visual evoked potential (VEP) and electroretinogram techniques require bright stimuli to penetrate the cataract and elicit a measurable response. Even a small-field stimulus would be scattered by the opacity and stimulate relatively large retinal areas. Under such conditions, foveal function may not be discriminated from the peripheral retinal response (Burian & Burns 1966; Goldmann & Lotmar 1970; Fricker 1971; Spillman & Roberge 1972; Armington 1974). Despite these drawbacks, Thomson & Harding (1978), using the flash VEP, found that if the affected eye showed no reduction in the amplitude of the second positive (P2) component, then the post-operative acuity was usually ≥6/12. When there was a 50% reduction or greater in the P2 amplitude this was found to give a post-operative acuity of ≤6/24. Indeed, the VEP is considered to be a better predictor of visual function in cases of dense opacification than the use of laser interferometry or the

PAM (Galloway 1988; Odom et al. 1988).

Hyperacuity tests (Westheimer 1975) are thought to reflect central visual processing since thresholds are dimensionally far smaller than the limit of resolution imposed by the retinal receptor mosaic. It is thought that neighbouring receptors pool information to achieve accurate localisation of features in the retinal image (Whitaker & Walker 1988). Hyperacuity tests are resistant to stimulus alterations in contrast, luminance and blur which lead to loss of high spatial frequencies in the stimulus and thus affect visual acuity (Enoch & Williams 1983; Enoch et al. 1984, 1985; Essock et al. 1984, 1985; Williams et al. 1984; Whitaker & Buckingham 1987a,b; Whitaker & Elliott 1989). The relative localisation of features required in a hyperacuity task is dependent on the whole range of spatial frequencies in the stimulus (Westheimer & McKee 1980). Indeed, optimum vernier acuity is impaired at a slower rate than Snellen acuity in cases of retinal image degradation caused by cataract (Enoch et al. 1984). Hyperacuity tests overcome the disadvantages of interference acuity, and flash VEP and electroretinogram tests since firstly, a window in the cataract is not necessary to evoke a meaningful response; secondly, hyperacuity falls off rapidly with retinal eccentricity (Westheimer 1982) and thirdly, unlike resolution acuity, hyperacuity in the presence of blur is not improved by an increase in intensity and contrast above critical values (Westheimer & McKee 1980). In addition, stimuli confined to small retinal areas (less than 30 minutes of arc) produce the lowest thresholds (Westheimer & McKee 1977). Hyperacuity has been shown to yield characteristic changes in response dependent on the severity of the media opacity and to discriminate neural from optical losses (Enoch et al. 1984, 1985; Essock et al. 1984, 1985; Whitaker & Deady 1989; Whitaker & Elliott 1989).

Williams et al. (1984) suggested that a vernier acuity test configuration consisting of two small points of light separated by a gap ranging from approximately 2' to 2° was resistant to image degradation and thus was suitable for clinical application in the case of media opacities. This test was extended to examine relative functioning over the central 16° of the visual field in the presence of media opacities which was termed "hyperacuity perimetry".

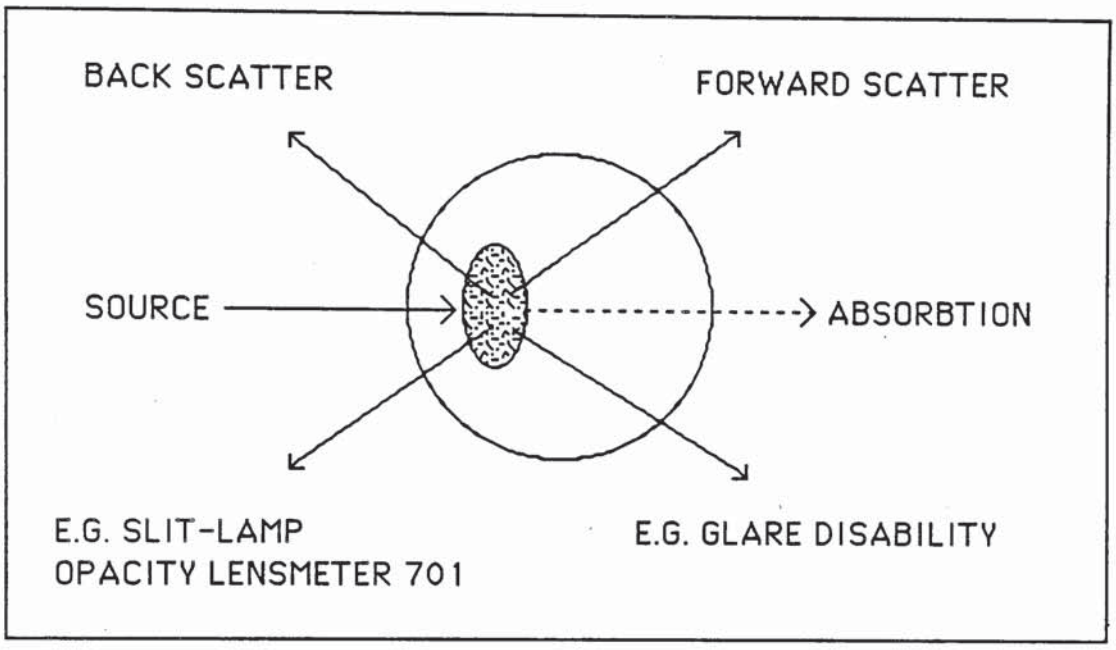


Figure 3.1. Illustrating the relationship between forward and backward intraocular light scatter

3.1.4. ASSESSMENT OF INTRAOCULAR LIGHT SCATTER

3.1.4.1. Objective techniques

Objective methods, reviewed by Brown et al. (1988), only assess the extent of backward light scatter i.e. light that is scattered at an angle of more than 90° to the incident source. The slit-lamp appearance of the cornea and lens results since these structures scatter light at an angle of more than 90° to the incident source (back towards the observer). Visual degradation due to media opacities however results from an increase in forward light scattering, i.e. light that is scattered at an angle of less than 90° to the incident source. The difference between forward and backward light scatter may be understood by considering Figure 3.1.

Many investigators have assumed that light back-scattered from the lens is representative of forward light scatter and image degradation (Allen & Vos 1967; Sigelman et al. 1974), but Allen & Vos (1967) showed the relationship between Landolt C variable contrast visual acuity and backward light scatter, determined by microdensitometric analysis of negatives from slit-lamp photography of the cornea and lens, to be coincidental in nature. Similarly, Sigelman et al. (1974), using scanning microdensitometry, found the eye to tolerate high levels of cortical back-scatter without appreciable loss of visual acuity.

The image degrading effect of cataract can be directly assessed objectively with a target projection ophthalmoscope, first described by Cotlier (1981). A resolution test chart is projected through the dilated pupil and observed on the patient's retina. The Cotlier principle has been developed to the commercially available Keeler "Acuityscope" (Brown et al. 1987).

Photographic methods of lens measurement have been shown to compare well with clinical observation for the measurement of the lens and estimation of the amount of cataract (West et al. 1985). Slit-image and retro-illumination photography each have their own advantages and limitations, and ideally, the two systems should be used in combination. The images produced by photographic techniques are translated into numerical scores by the image analysis techniques of scanning densitometry (Hockwin et al. 1982, 1984) and computerised area density analysis (Maclean & Taylor 1981; Gilchrist 1987). The possibility exists of

dispensing with the film by imaging the eye on video camera (Hockwin et al. 1986).

Precision slit-lamp photography of the anterior eye is capable of providing information about the dimensions and densities (light scattering properties) of the refractive structures of the eye. By multiple adjustments of the viewing angle, a three dimensional image may be represented photographically (Brown 1969). The major difficulty encountered with this method is the lack of a uniform focus over the entire lens due to the narrow depth of field of the slit-lamp camera. Brown (1969, 1972) corrected this problem by applying Scheimpflug principle (1906) optics to the slit-lamp camera. By tilting the objective plane, film plane or a combination of both, the entire plane of the slit-beam can be maintained in focus at the full aperture of the objective. The relative advantages of each of these methods is discussed by Brown (1969). Good reproducibility of the camera adjustment relative to the patient's eye is also a pre-requisite for accurate documentation and follow-up. Dragomirescu et al. (1978, 1980) proposed an adaptation to the camera consisting of a flashing green fixation target and two phototransistors, which were stimulated by reflection from the patient's cornea and triggered an acoustic signal when the slit beam was in perpendicular alignment. This device allowed reproducible adjustment of the slit-beam in the optical axis of the eye at any meridian and the technique was found to give highly reproducible results in the assessment of cataract (Datiles et al. 1987b). The slit-image is effective in measuring nuclear cataract (West et al. 1985; 1988), but is inefficient in cases of cortical cataract which may be missed if the opacity does not lie on the axis of the slit beam.

Retro-illumination photography of media opacities was first described by Fincham (1955). Hockwin et al. (1975) used a fundus camera to monitor the progress of senile lens opacities by retro-illumination, and Hendrickson et al. (1977) suggested an improvement to this method using a 9-grade colour standard with which to compare the fundus reflex. Direct measurement of the luminance of back-scattered light was made by Ben-Sira et al. (1980), who utilised a reference light patch within the microscope field of view adjacent to the area to be measured. This patch was calibrated in terms of an "opacity value" on a scale of 1-10, such that each increment corresponded to an optical density increment of 0.15. Kawara & Obazawa (1980) improved on the system of Fincham (1955) by using cross polarisers to

eliminate the corneal reflection, giving rise to the commercially available Neitz camera. The retro-illumination camera design has been developed further with the addition of fixation lights and a standard density in the commercially available "Oxford" camera. The disadvantage of retro-illumination photography is an inadequate depth of field, such that two separately focused exposures are required to measure cataract in a lens that has both anterior and posterior opacities. The method is also unsatisfactory with nuclear cataract, which is best assessed with the slit-image.

Several comprehensive classification systems for the visual grading of cataract have been proposed, as reviewed by Brown et al. (1988). The Oxford clinical cataract classification and grading system (Sparrow et al. 1986; Brown et al. 1987) is a slit-lamp based system in which individual features are graded on a scale of 0 (feature absent) to 5, by visual comparison with standard diagrams. The method may also be used in conjunction with photographic and image analysing techniques.

In order to clinically evaluate the optical performance of the crystalline lens and intraocular lenses, Hendrickson & Robert (1986) measured the relative brightness of the optic disc and macula using the photopapillometer (Hendrickson et al. 1984; Robert & Hendrickson 1984) which enabled calculation of a contrast transfer ratio (pap/mac). This ratio provides an evaluation of the efficiency of the ocular media and was found to be highly correlated with the visual acuity of patients with developing cataract.

Scattered light may also be measured directly by photometric means (Blumenthal et al. 1977). Weale (1986a,b), using polarised light and the method of Koeppe (1920), showed that some of the light returned from a cataract appeared to have been reflected rather than scattered, since it was interrupted by a polarizing filter. Weale (1988) further proposed the use of blue-free light in cataract photography to reduce the fogging resulting from lenticular fluorescence.

Other methods reviewed by Brown et al. (1988) for the objective assessment of cataract include ultrasound to measure lens dimensions (Delmarcelle & Luyckx-Bacus 1971), laser

quasielastic light scattering to estimate the size of lens protein molecules and measurement of the fluorescence (fluorimetry) which is enhanced in cataractous lens nuclei. The method of laser quasielastic light scattering is based on fluctuations in scattered laser light intensity caused by translational Brownian motion of the lens proteins. Indeed, Bursell et al. (1989) have demonstrated changes in human diabetic lenses prior to visible opacification using this technique.

3.1.4.2. Subjective techniques

Increased forward light scattering due to media opacities results in a greater than normal depression of visual function in the presence of glare light. It is this sensitivity to glare that is the basis of the clinical tests used to evaluate the subjective effects of media disturbances. Indeed, Wolf & Gardiner (1965) found a linear relationship between glare sensitivity and lens opacification, as assessed by slit lamp photometry. Assessment of glare sensitivity (e.g. measurement of visual acuity acuity against the bright background of a window) has been advocated in the evaluation of cataract patients to aid the decision for surgical removal (Junker 1976; Cinotti 1979; Maltzman et al. 1988) and several commercially available glare testers have been described and clinically evaluated (Neumann et al. 1988; Terry & Brown 1989).

Miller et al. (1972) developed a clinical instrument, the Miller-Nadler glare tester, to quantify glare sensitivity. It consisted of a circular bright glare source surrounding a series of randomly orientated black Landolt rings of Snellen equivalent 3/60. The luminance of the ring target was varied by means of neutral density filters. A circular fluorescent glare source was recommended as the patients found it less fatiguing than a point source and it encouraged patient fixation on the target located at the centre of the glare source. A simpler, less expensive version of this glare tester was subsequently developed by Le Claire et al. (1982) which consisted of an audioviewer table-top projector with specially made slides, each of which supplied a constant glare source and a variable contrast central target. This instrument was validated in further studies (Hirsch et al. 1984) and is currently used. One major drawback was the critical positioning of the patient with respect to the screen, since misalignment of the patient's position 10cm off axis caused a 50% decrease in glare intensity. Van der Heijde

et al. (1985) therefore suggested a spectacle mounted device, which allowed measurement of visual acuity through a central aperture of 6mm diameter surrounded by a circular array of 24 yellow LEDs as a glare source, the intensity of which was variable. They found a linear relationship between glare luminance and visual acuity.

Paulsson & Sjostrand (1980) developed a method for the assessment of the glare effect of light scattered by the ocular media. They recognised that the contrast sensitivity function was a more representative description of visual performance than measurement of visual acuity, and developed a system which measured the depression of contrast sensitivity when a bright light source was introduced into the visual field. A direct measure of intraocular light scattering, the light scattering factor (LSF) was calculated from this method using the derived equation:

$$LSF = L/E\ (M_2/M_1 - 1)$$

where L is the luminance of the contrast sensitivity monitor, E is the direct illumination onto the eye from the glare source and M_2 and M_1 are the detection contrast thresholds in the presence and absence of glare light respectively. Although contrast sensitivity is depressed in the presence of glare, the peak of the contrast sensitivity function (around 4 c/deg) remains unaltered (Finlay & Wilkinson 1984).

Subsequent studies have measured the LSF, employing circular glare sources, to evaluate corneal and lenticular changes (Griffiths et al. 1984, 1986), patients with radial keratotomy (Atkin et al. 1986) and lenticular opacities (Abrahamsson & Sjostrand 1986; Ginsburg et al. 1987). Griffiths et al. (1984) reported that wide angle glare sources were more appropriate for the evaluation of lenticular opacities, since they did not produce corneal epithelial haloes in the viewing field. Atkin et al. (1986) found glare scores obtained in their study to correlate poorly with the Miller-Nadler glare score or a questionaire index of glare complaints. Abrahamsson & Sjostrand (1986) noted that an increasing glare score was related to greater media turbidity whereas visual acuity was weakly correlated with the glare score. Harper & Halliday (1989) have also utilised the measurement of contrast sensitivity depression under glare conditions to compare the relative merits of contact lenses, epikeratophakia and intraocular implants in the correction of aphakia.

An alternative method of quantifying glare effects (the "direct compensation technique"), in which the annular glare source flickers at 8 Hz, has been proposed by Van den Berg (1986). The angular subtense of the flickering glare source may be varied from 3.75°-30°. As a result of light scattering within the eye, flicker is also perceived in the centre of the annulus. This flicker is compensated for by adjusting a central flickering light in counterphase with the glare source; the patient's task is to minimise or abolish the central flicker perception. A poor correlation was found between visual acuity and scatter assessed by this method. Van den Berg & Spekreijse (1987) subsequently validated this method in a sample of 100 patients with cataract and other media disturbances such as corneal grafts, and Witmer et al. (1989) applied it to pseudophakic eyes. They found the intraocular light scatter in pseudophakic eyes to be twice that in normal eyes and considered this to be due to the combination of the posterior capsule and implant lens. Van den Berg et al. (1990) also adapted the method to assess light transmission through the ocular coats

Interestingly, Sample et al. (1987, 1988) have described a method to assess light absorption by the human crystalline lens by measurement of scotopic thresholds at wavelengths of 410 nm and 560nm. Age related changes in absorption would be expected to reduce sensitivity more to the 410nm stimulus than to the 560nm stimulus, reflecting an increase in lens density. The difference between the thresholds at each wavelength is used as an index of lens absorption. Sample et al. (1989) subsequently modified a Humphrey Field Analyser to provide a more practical method of measurement with the ability to change the retinal location of the test spot and so avoid scotomata.

3.1.5. SIMULATED MEDIA OPACITIES

In psychophysical assessment of patients with media disturbances, the integrity of the visual system behind the opacity cannot be determined with certainty. As a consequence, a variety of opacity simulations have been developed.

3.1.5.1. Corneal opacity simulation

Lancon & Miller (1973) used bovine corneal buttons hydrated to various thicknesses. Light scattering and turbidity of the button were assessed and correlated with visual acuity and

glare sensitivity measured through the button. They found low degrees of oedema increased glare sensitivity but had little effect on visual acuity.

Miller et al. (1972), in their description of the design principles and construction of a glare tester, made measurements on a sample of subjects who looked through optical cells containing various concentrations of 6-14μm diameter latex particles. This diameter was selected as it is similar to the size of basal corneal epithelial cells, thus the cells mimicked various degrees of epithelial oedema. The transmission of a He-Ne laser beam through the cells was measured and the test repeated with an equivalent neutral density filter to distinguish the scattering and glare effects from those due to decreased retinal illumination. Their conclusion was later substantiated by Lancon & Miller (1973), namely that mild turbidity affected glare sensitivity before visual acuity. Miller et al. (1976) simulated the effects of corneal oedema on visual acuity using flat sided cell culture flasks containing a suspension of latex particles of diameter 4-8μm, considering this to be close to the size of basal epithelial cells; similarly, Hess & Garner (1977) positioned diffusing lenses close to the cornea containing spherical particles of 19μm diameter with an average inter-particle separation of 30μm. This particle size was selected as it mimics the diffraction effects from an oedematous cornea (Finkelstein 1952). Hess & Garner (1977) measured contrast sensitivity and Snellen and Landolt visual acuities; they concluded that small degrees of corneal oedema only affected high spatial frequencies and could be represented by equivalent defocus whilst larger degrees of scattering affected all spatial frequencies and were better simulated with a diffusing lens.

3.1.5.2. Lenticular opacity simulation

Zuckerman et al. (1973) assumed that a cataract consists of a random distribution of scattering centres of different refractive index to that of the surrounding matrix and simulated cataracts with a glass lens covered in petroleum jelly spots. The transfer ratio and resolution were measured photographically as a function of the percentage of cataract, determined by the surface area of the glass lens covered in jelly spots. The study confirmed that image degradation in a human cortical cataract results from phase aberrations introduced in the optical wavefront due to fluctuations in refractive index. The study showed that, if a cataract

were composed of randomly distributed light absorbing regions as opposed to light scattering centres, far less light would reach the retina than is actually the case.

Miller et al. (1976) considered their corneal oedema simulation (see Section 3.1.5.1.) of latex particles of 4-8μm diameter to also simulate cortical cataract, as the lens fibre is 8-10μm diameter. Diffusing lenses containing a suspension of 5μm particles in liquid media were also used to simulate cataract by Hess & Woo (1978). Hess & Woo (1978) photographed a complex visual scene through such a diffusing lens and also through equivalent defocus, both of which equally degraded the high spatial frequencies in the picture. In addition, the diffuser was found to affect low spatial frequencies and produce more severe visual degradation than equivalent defocus. The results obtained were similar to those in patients with uniocular cataract, where contrast sensitivity and visual acuity were compared with those of the normal fellow eye. No correlation was present between the spatial domain of contrast sensitivity loss and the type of opacity (cortical or nuclear). They considered that, as a cataract develops, optical aberrations and narrow-angle scattering are the main causes of visual loss but when scattering becomes isotropic all spatial frequencies become affected.

The simulation of Miller et al. (1972) was subsequently applied to calibrate a clinical glare tester for use on cataractous and aphakic patients, using 12mm thick flat bottles containing various concentrations of 10μm spheres in distilled water (Le Claire et al. 1982).

Willams et al. (1984) investigated the effect of optical degradation, produced by viewing a target displayed on a CRT screen through ground glass, on various hyperacuity tasks. The amount of degradation was varied by altering the distance between the ground glass and CRT screen. Ground glass acts as a low-pass spatial filter, which attenuates high spatial frequencies thus mimicking a uniform opacity. As the distance between the ground glass and CRT screen increased the attenuation extended to lower spatial frequencies. In contrast to resolution acuity, it was found that the hyperacuity threshold at the optimum feature separation was resistant to this form of image degradation, and thus the visual processes involved in hyperacuity were not dependent on high spatial frequencies.

The effects of media opacities on the perimetric profile have also been simulated using selective occluders and diascleral illumination to produce stray light comparable to that resulting from lens opacities (Niesel et al. 1978: Niesel & Wiher 1982). Recently, the absorbing, scattering and blurring effects of media opacities on the automated perimetric profile have been investigated with neutral density filters (Klewin & Radius 1986; Baldwin & Smith 1987; Eichenberger et al. 1987; Heuer et al. 1987b,1988), orthoptic occluders (Eichenberger et al. 1987; Heuer et al. 1987b, 1988; Urner-Bloch 1987) and spherical blur (Heuer et al. 1987b) respectively. Wood et al. (1987a,b) used varying concentrations of latex beads suspended in distilled water to simulate intraocular light scatter. A bead diameter of 500nm was selected since this is similar to the diameter of protein aggregates in human (Bettelheim & Siew 1983) and calf (Delaye et al. 1982) cataractous lenses. Varying concentrations of beads were used since it has also been demonstrated that interparticle separation is another important parameter in intraocular light scattering. The influences of these opacity simulations on the perimetric profile are discussed in Section 3.1.6.

3.1.6. INFLUENCE OF MEDIA OPACITIES ON PERIMETRIC THRESHOLDS

3.1.6.1. Manual kinetic perimetry

In kinetic perimetry media opacities cause a flattening of the sensitivity gradient resulting in a concentric constriction of the peripheral isopters (Aulhorn & Harms 1967; Drance 1975; Kolker & Hetherington 1976; Niesel et al. 1976; Greve 1979; Harrington 1981) and loss of the inner isopters (Niesel et al. 1978), the effects being greatest for small stimuli (Radius 1978; Greve 1979). The stimulus moves through a larger area of uncertainty as the sensitivity curve flattens; therefore, in determining the threshold there is an increased variation in response (Aulhorn & Harms 1967; Greve 1979) and pseudo-glaucomatous defects are easily produced. Conversely, early glaucomatous defects less than 5° in size and less than 1.0 log unit in intensity may be masked (Greve 1979). Bigger & Becker (1971) reported that a specific glaucomatous field defect disappeared or was reduced following uneventful cataract extraction in 41% of eyes studied (n=64). However, they hypothesised that this may have been due to a decrease in intraocular pressure following surgery. Niesel & Wiher (1982) simulated opacities using orthoptic occluders in 10 cases of chronic glaucoma. Goldmann kinetic perimetry revealed a resultant isopter constriction and pericentral relative field defects

smaller than 4°-6° were obscured, however the detection of absolute scotomata was unaffected. The peripheral field constriction and apparent diminuation of field defects could be compensated for by increasing the intensity of the test target by 3 dB, if the visual acuity was reduced by no more than 50%.

Local depressions in sensitivity can also occur when the opacity is localised and irregular; the effect is greater for more posteriorally located opacities (Greve 1979). Indeed, Gayer-Morgan (1958) noted a considerable loss of upper field in a patient in whom opacification of the lens was denser inferiorally; the field defect disappeared following lens extraction. Asymmetrical opacities situated in the posterior layers of the lens cause a visual field defect on the opposite side, whereas corneal opacities result in a defect on the same side as the opacity (Lyne & Phillips 1969). Such localised paraxial media opacities may resemble hemianopic or quadrantic defects.

3.1.6.2. Manual static perimetry

Static perimetry is recommended as a more sensitive method for the visual field assessment of patients with media disturbances; the technique gives better separation of general and local reductions in sensitivity since the flattened hill of vision is approached vertically (Aulhorn & Harms 1967; Greve 1979). Indeed, Calabria et al. (1985) have suggested that static perimetry may be used to monitor the progression of lens opacities. As the sensitivity gradient is flattened (Drance 1975) and the image is defocused the differential light sensitivity is preferentially reduced in the central field (Greve 1973,1979; Niesel et al. 1978). A large stimulus is required as smaller stimuli may not be seen in cases with poor acuity (Greve 1979), the effects of scatter are less (Van den Berg 1987) and there is an increased dynamic range (Fankhauser 1979; Greve 1979). In this way, Greve (1979) proposed that visual field examination was possible even when the disc could not be visualised by ophthalmoscopy.

3.1.6.3. Automated static perimetry

The effects of media disturbances on the automated perimetric profile have been investigated in a variety of ways, by comparing visual fields of patients before and after

cataract extraction and also by applying simulations to both normal and glaucomatous eyes. By computer simulation it has been suggested that cataract gives rise to an increased mean defect without alteration of the corrected loss variance (Augustiny & Flammer 1985).

Using the Octopus G1 program, an improvement in mean sensitivity and decrease in short-term fluctuation was demonstrated after cataract extraction and intraocular lens implantation (Guthauser et al. 1986, 1987). The improvement in mean sensitivity was highly correlated with pre-operative lens density as quantified by the Zeiss-Scheimpflug slit-lamp camera with computerised densitometry. As would be expected, from a measurement of back scattered light, the improvement in visual acuity was less well correlated with lens density. The post-operative change in focal losses was equivocal in two case reports: in a glaucoma patient the corrected loss variance increased, whereas in a patient with cataract only, it decreased slightly (Guthauser et al. 1986). The depressing effect of cataract was reported to be greater in the central area of the field examined. These results were substantiated in a further study on a sample of 36 normals, ocular hypertensives and early glaucoma patients (Guthauser & Flammer 1988). The decrease in mean defect following surgery correlated well with the lens density value, determined over the central 3mm of the lens. The central region of the field was affected to a greater extent than the midperiphery, and the decrease in sensitivity caused by the cataract correlated moderately with eccentricity of test location. A lower correlation was found between lens density and visual acuity, as would be expected, since the technique measured back scatter from the lens. The corrected loss variance decreased after surgery i.e. focal losses decreased, but this change was unrelated to lens density. The decrease in post-operative corrected loss variance was considered to occur because the effect of opacities on the perimetric profile was non-uniform pre-operatively. It should be noted that patients with a marked pre-operative corrected loss variance were excluded from the study.

Hendrickson et al. (1987) demonstrated a post-surgical improvement in mean sensitivity, using Octopus program G1, in a sample of cataract patients with no other ocular pathology and suggested that the effects of cataract and glaucoma on the visual field may be differentiated since the "central" sensitivity was depressed less by cataract than by

glaucoma. They also showed a correlation between the contrast transfer ratio of the ocular media and the attenuation of perimetric sensitivity. Similarly, Urner-Bloch (1987) demonstrated a decrease in mean defect following cataract surgery. Interestingly, an increase in corrected loss variance was found in seven out of nine cases studied i.e. the presence of cataract had masked the focal losses which became more apparent post surgically, although again this was in patients who were otherwise normal.

Contrary to the previously mentioned studies which showed media opacities to have a significantly deleterious effect on the automated perimetric profile, Faschinger (1987) reported that the automated perimetric profile was only slightly depressed in the presence of corneal dystrophies.

Klewin et al. (1988) studied the effect of pseudophakic correction of the aphakic eye using Octopus program 24 automated visual fields. The sample consisted of 90 aphakic patients, who were otherwise normal, 52 of whom were pseudophakics and 38 contact lens corrected aphakics. They found a mean defect of between 1 and 20 dB in the pseudophakics and a similar mean defect of between 0.4 and 19.7 dB in the contact lens corrected group.

Urner-Bloch (1987) applied an opacity simulation (orthoptic occluders) to a group of normal patients and to a sample of patients with visual field loss (mainly glaucomatous). In the normal group the occluders produced a homogeneous increase in mean defect i.e. a diffuse depression of the visual field, with no alteration in the corrected loss variance and short-term fluctuation indices. In those with field loss an increase in the mean defect was found but corrected loss variance was decreased i.e. there was a diffuse depression of the visual field and decrease in focal losses. These latter findings were in agreement with her work on cataract patients, namely that the presence of media opacities results in a diffuse depression of the visual field and masks focal losses.

Orthoptic occluders and neutral density filters were used by Eichenberger et al. (1987) to simulate the effects of opacities in a group of young normals. Using Octopus program G1, they found that both mean and "central" sensitivities were degraded more by the neutral

density filters than the occluders. Loss variance however increased in a linear manner with increase in neutral density filter and exponentially with the occluders i.e. the opacity simulation caused an increase in focal losses. Eichenberger et al. (1987) considered the behaviour of the visual field parameters with orthoptic occluders to be more similar to that observed with cataract.

Heuer et al. (1987b) simulated the absorbing, scattering and blurring effects of media opacities with neutral density filters, orthoptic occluders and positive spherical lenses respectively in 5 normal patients. Profile fields were measured with both the Humphrey Field Analyser and the Octopus Automated Perimeter and glare disability, induced by the occluder, assessed with the Miller-Nadler glare test. Sensitivity measured with the Octopus perimeter was affected more by the absorbing effects of the filters whereas sensitivity measured with the Humphery perimeter was affected more by the occluders due to the greater scattering at the higher background luminance (31.5 asb compared with 4 asb in the Octopus perimeter). Heuer et al. (1988) subsequently utilised ground glass lenses (diffusers) to induce light scattering. The threshold depressions caused by the diffusers were statistically significant and similar at all eccentricities. The observed depression in the differential light sensitivity was predicted almost entirely by the degree of reduction in perimetric stimulus intensity, measured on an optical bench, although the diffuser did not attenuate the intensity of the background. Glare disability also correlated well with the attenuation of stimulus intensity by the diffuser. The effect of an equivalent neutral density filter on visual sensitivity was less than the diffuser since a filter reduces the intensity of both the stimulus and background and thus the contrast remains constant.

Wood et al. (1987a,b) quantified the perimetric attenuation in young normal patients resulting from light scatter simulated with cells containing various concentrations of latex beads suspended in distilled water. A good correlation was found between the amount of induced forward light scatter and the perimetric attenuation, which varied with the stimulus type, eccentricity and bowl luminance. Attenuation was found to be greater peripherally for the stimulus parameters of the Octopus 201 automated perimeter i.e. a steepening of the sensitivity gradient resulted, and greater centrally for the smaller LED stimulus of the Dicon

AP3000 leading to a flattening of the sensitivity gradient. Attenuation was also greater for the 10asb background luminance of the Dicon compared with the 45asb background. Nomograms were drawn from the data which related perimetric attenuation to forward light scattering factor as a function of eccentricity for both instruments employed in the study. The simulation of Wood et al. (1987a,b) was subsequently shown to be an accurate representation of forward intraocular light scatter in a study of patients with uniocular opacities (Wood et al. 1989). The inter-ocular difference in perimetric response was compared with the inter-ocular difference in light scattering factor, and a similar quantitative relationship to the previous study established. Similar nomograms were drawn from the data which would allow the correction of the perimetric profile for the effects of intraocular light scatter caused by media opacities (Wood et al. 1989).

3.1.7. AIM OF THE STUDY

The aim of the study was to investigate the attenuation in perimetric response arising from induced forward light scatter in glaucoma patients, using the light scatter simulation and technique of Wood et al. (1987a,b). This would allow perimetric attenuation arising from media opacities to be differentiated from that due to neural dysfunction in glaucoma. Such an investigation would aid the accurate perimetric assessment and follow-up of glaucoma patients with concomitant development of media disturbances.

3.1.8. MATERIALS AND METHODS

The sample of 15 patients (mean age 69.1 years, SD 6.8 years) comprised 13 primary open angle glaucoma patients and 2 low tension glaucomas with known moderate field loss determined by previous manual Goldmann or Octopus automated perimetry. The depth and type of field loss in the sample is illustrated in Figure 3.2. using the classification system based on that of Caprioli & Sears (1987), and comprised patients with a combination of diffuse and focal loss. All patients had clear media, visual acuities ≥6/9 and were receiving topical ß-blocker therapy only. Exclusion criteria comprised patients on miotic therapy, those with abnormal angles or irides, aphakia or pseudophakia, retinal degenerative conditions, secondary glaucomas and diabetes or other systemic conditions with marked ocular complications.

Light scatter was induced using cells containing a suspension of varying concentrations (0.10%-0.75%) of 0.5μm diameter latex beads in distilled water placed before the eye. The cells were composed of pairs of plano CR39 uncut lenses, mounted each side of a plastic ring, which separated the lenses by approximately 5mm. Two holes were drilled into the ring for injection of the bead suspension. The concentrations of beads were greater than those used previously (Wood et al. 1987a,b). This was necessary due to greater absorbtion of induced forward light scatter by the ocular media in an elderly sample, the depression of contrast sensitivity with age (Wright & Drasdo 1985) and changes in calibration of the Nicolet CS2000.

The right eye of each patient was examined with the Octopus 201 using both phases of program G1 (59 stimuli; stimulus Goldmann size III; 0.431°; stimulus duration 100msec; bowl luminance 4asb) with and without a given cell. At another session patients were examined with the Dicon AP3000 using the macula threshold and the 45° meridional threshold program at eccentricities of 2.5°, 5°, 10°, 17.5° and 27.5° (stimulus size 0.28°; Goldmann size II equivalent; stimulus duration 400msec; bowl luminance 10asb) with and without the same cell. These eccentricities were chosen as they are similar to those in program G1 for the same meridian. The threshold at each eccentricity for the Dicon AP3000 was taken as the mean of four measurements. The appropriate near refractive correction was used, patients were adapted to the bowl luminance for 10 minutes before each test and encouraged to rest at intervals.

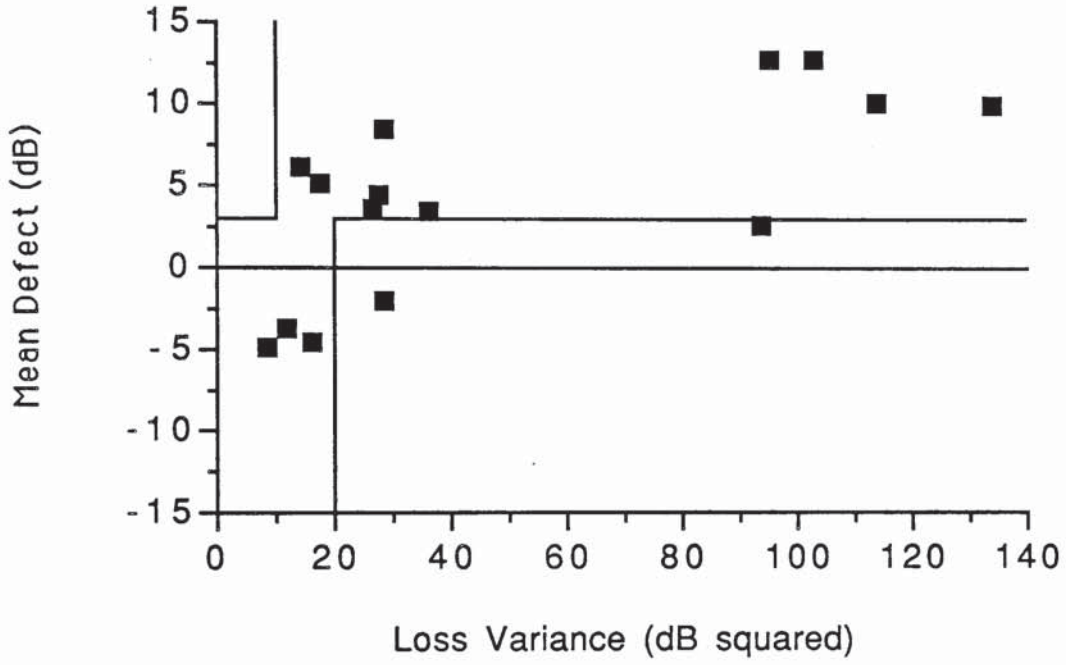


Figure 3.2. The type and depth of field loss within the sample based on the classification of Caprioli & Sears (1987) showing mean defect (diffuse loss) as as function of loss variance (focal loss). Solid lines represent criteria for relatively pure diffuse depression (enclosed area parallel to the ordinate) and relatively pure focal loss (enclosed area parallel to the abscissa).

The effects of induced forward light scatter were assessed by measuring the depression of contrast sensitivity under glare conditions, using the method developed by Griffiths et al. (1986) and used by Wood et al. (1987a,b; 1989) in relation to automated perimetry. Contrast sensitivity was measured both with and without a given cell in the presence and absence of wide (30°) and narrow-angle (3.5°) ring glare sources. Vertical sine wave gratings of spatial frequency 1c/deg, counterphased at 2Hz, were generated on the monitor. A low spatial frequency was chosen for several reasons: optical attenuation due to blur is avoided (Campbell & Green 1965), threshold determinations are less variable (Vaegan & Halliday 1982), low spatial frequencies are relatively unaffected by cataract (Jankelovits et al. 1988; Elliott et al. 1989) and are more susceptible to glare compared with high and intermediate frequencies (Paulsson & Sjostrand 1980; Elliott 1987). A low temporal frequency was chosen since phase alternating stimuli produce more reliable responses in the elderly (Vaegan & Halliday) and to avoid the production of after images. Contrast sensitivity was measured using the method of increasing contrast, since this latter method is considered to be more reliable and produce the most consistant results compared with the von Bekesy tracking method and the method of adjustment (Ginsburg & Cannon 1983), and an average of 6 contrast determinations taken. Patients wore their distance optical correction for threshold determinations. A recovery time of 5 minutes was allowed between exposure to each of the glare sources (Collins 1989).

The monitor was 3m from the observer; the screen luminance was 101.25cd/m^2 and was calibrated at the beginning of each session. The monitor was surrounded by a circular rear-illuminated diffusing screen. The illuminance of the narrow and wide-angle glare sources at the eye were 63.6 and 1272.4 lux respectively. A light scattering factor (LSF) was calculated for each patient, with and without the cell, using the equation of Paulsson & Sjostrand (1980), described in Section 3.1.4.2., namely:

$$LSF = L/E\ (M_2/M_1 - 1)$$

where L is the luminance of the contrast sensitivity monitor, E is the direct illumination onto the eye from the glare source and M_2 and M_1 are the detection contrast thresholds in the presence and absence of glare light respectively.

Octopus examinations were performed at one session, and the Dicon examinations and scatter assessment at another. All examinations were carried out within a maximum period of 2 weeks. The order of sessions and order of examinations within each session were randomised. All patients received training in the various psychophysical procedures.

Natural pupils were used throughout since the procedure was intended for clinical application. Mean pupil size measured on the monitor of the Octopus perimeter was 6.2mm (SD 1.4mm). No allowance was made for the effect of the glare source on pupil size. Variation in pupil size has been shown to have little effect on contrast sensitivity at all spatial frequencies (Campbell & Green 1965), and the pupil has been shown to assume a diameter that optimises resolution over a wide range of ambient luminances (Campbell & Gregory 1960) and contrast levels (Woodhouse 1975). Indeed, Abrahamsson & Sjostrand (1986) used a correction factor of only 1.2 to account for a reduction in pupil size of 3-4mm in the presence of a glare source of luminance 21,000 cd/m^2 (65,973.5 lux). In addition, Vos (1983) showed that pupil size did not significantly alter the results of his glare experiments.

The Octopus G1 fields were analysed in terms of the proportionate differences between each of the two global visual field indices mean sensitivity and loss variance, obtained in the presence and in the absence of the various cells as a function of the induced scattering factor (light scattering factor with cell - that without cell). Indices were used from phase 2 only of the program to minimise the effects of training in glaucoma patients, described in Chapter 4 and corroborated by Werner et al. (1988, 1990b) and Heijl et al. (1989a). The Dicon results were similarly analysed in terms of mean sensitivity; the loss variance index could not be calculated for the Dicon data due to the lack of published and substantiated age-matched normative data. Perimetric attenuation (dB) due to light scatter was considered in terms of proportionate change in the decibel scale as opposed to the transformed absolute ΔL in apostilbs, or the ratio $\Delta L/L$, in order to account for the differing amounts of glaucomatous field loss within the sample. Although it is a relative logarithmic scale, the decibel scale is used in a linear context and as such the calculation is permissible. Indeed, proportionate change in visual field indices has been utilised previously (Mikelberg et al. 1987). In addition, induced scatter produces an unknown decrease of retinal illumination for both stimulus and

background, the exact magnitudes of which are unknown although the ratio between ΔL and L is known.

3.1.9. RESULTS

With increase in both narrow and wide angle induced forward light scatter Octopus G1 mean sensitivity and loss variance decreased. The proportionate change in Octopus G1 phase 2 mean sensitivity as a function of induced narrow and wide angle induced light scattering factor is shown in Figure 3.3. and is seen to be of a linear form. Mean sensitivity decreased with increase in induced forward light scatter. The proportionate change in Octopus G1 phase 2 loss variance as a function of both narrow and wide angle induced light scattering factor is shown in Figure 3.4. Loss variance initially decreased rapidly with increase in induced forward light scatter and then reached a plateau, when no further decrease was noted in loss variance with increasing induced forward light scatter.

Dicon mean sensitivity also decreased monotonically with increase in both narrow and wide angle induced forward light scattering factor. The relationship between proportionate change in mean sensitivity and induced light scattering factor, shown in Figure 3.5. is of a predominantly linear form.

Wide angle scattering factors could not be obtained in 2 of the 15 patients for induced light scatter, due to the high illuminance of the glare source at the eye, which obscured the view of the gratings on the monitor.

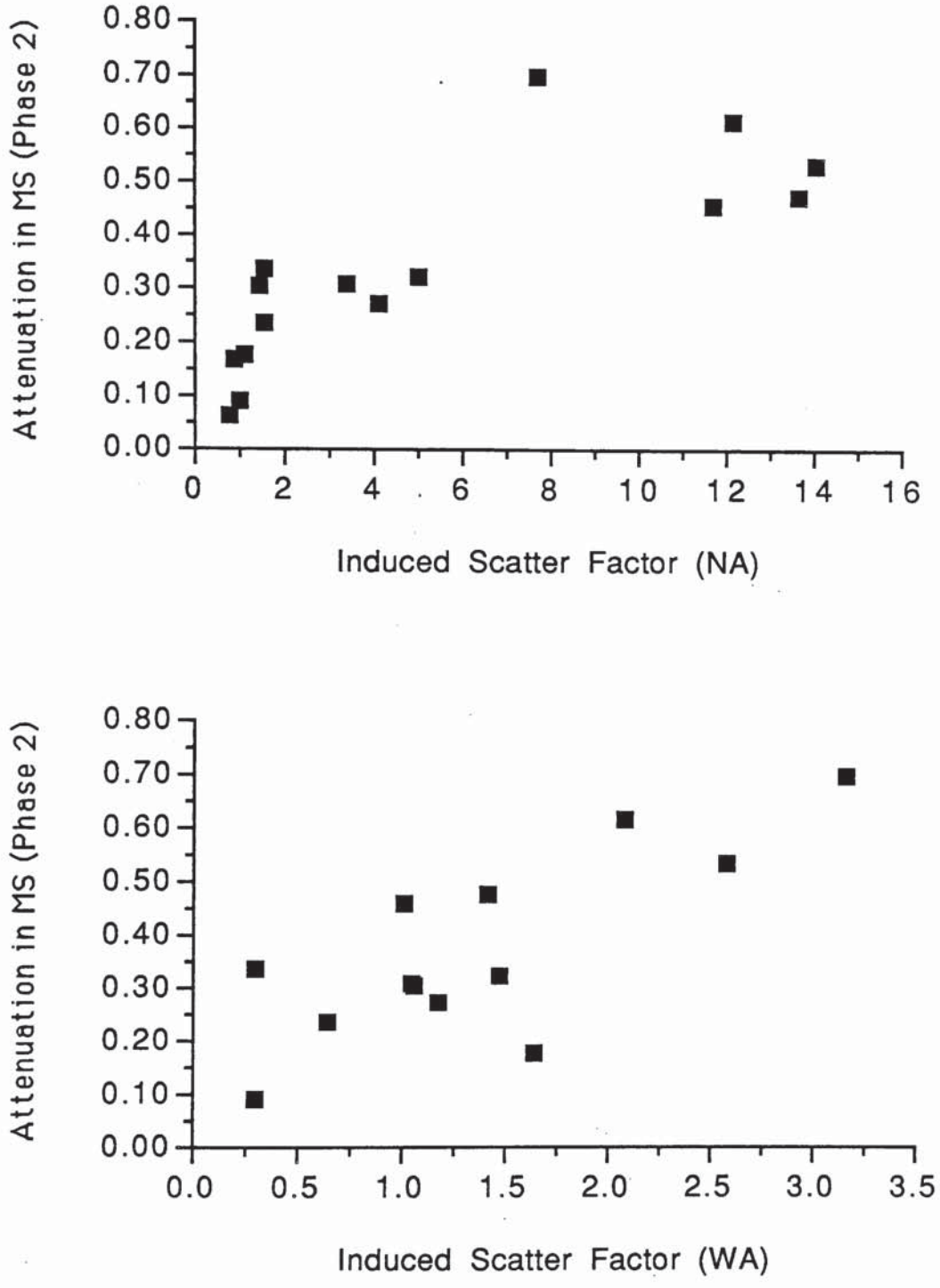


Figure 3.3. Showing the relationship between proportionate change in Octopus G1 mean sensitivity as a function of induced forward light scatter. Top: narrow-angle glare, bottom: wide angle glare.

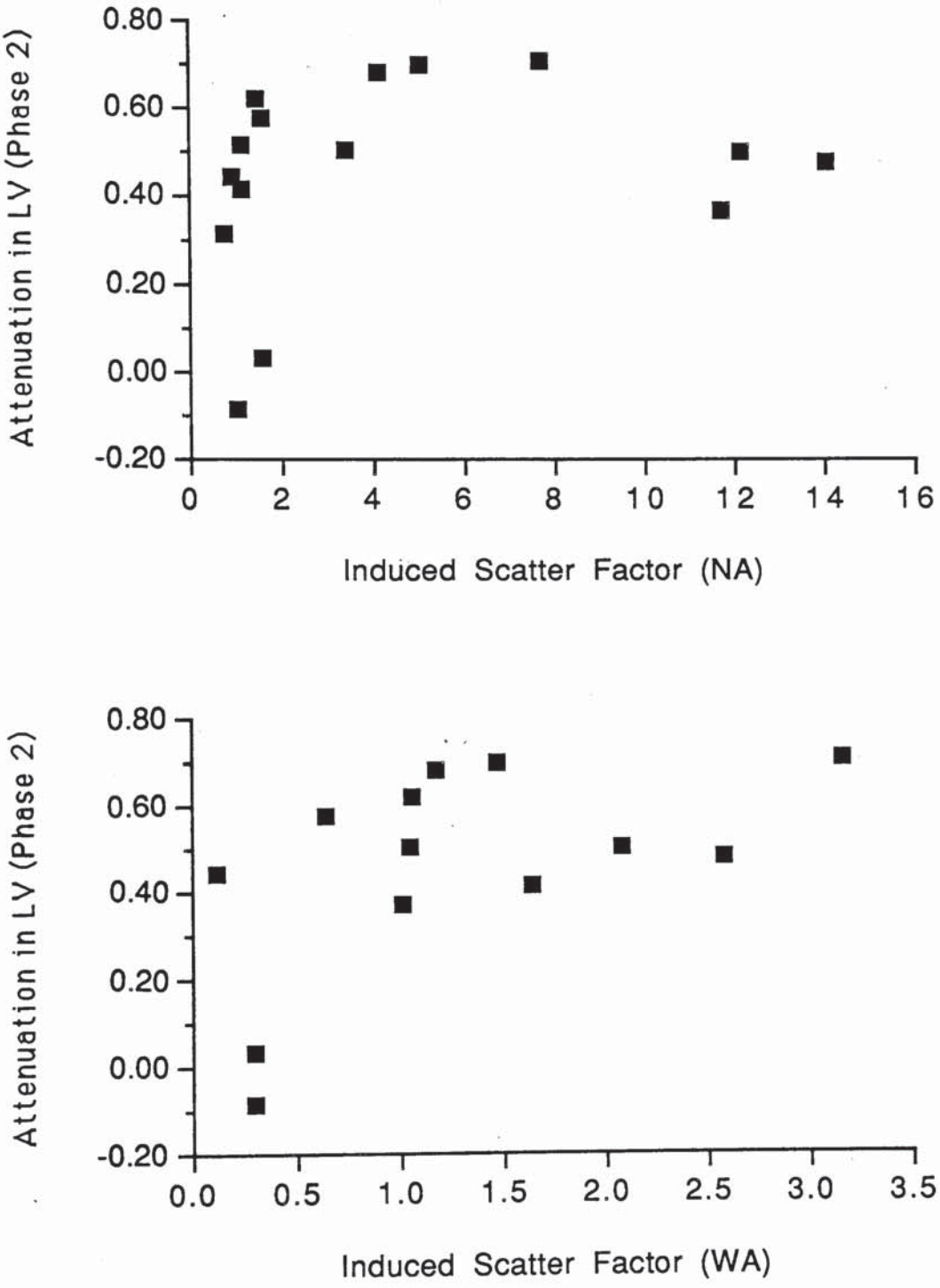


Figure 3.4. Showing the relationship between proportionate change in Octopus G1 loss variance as a function of induced forward light scatter. Top: narrow-angle glare, bottom: wide angle glare.

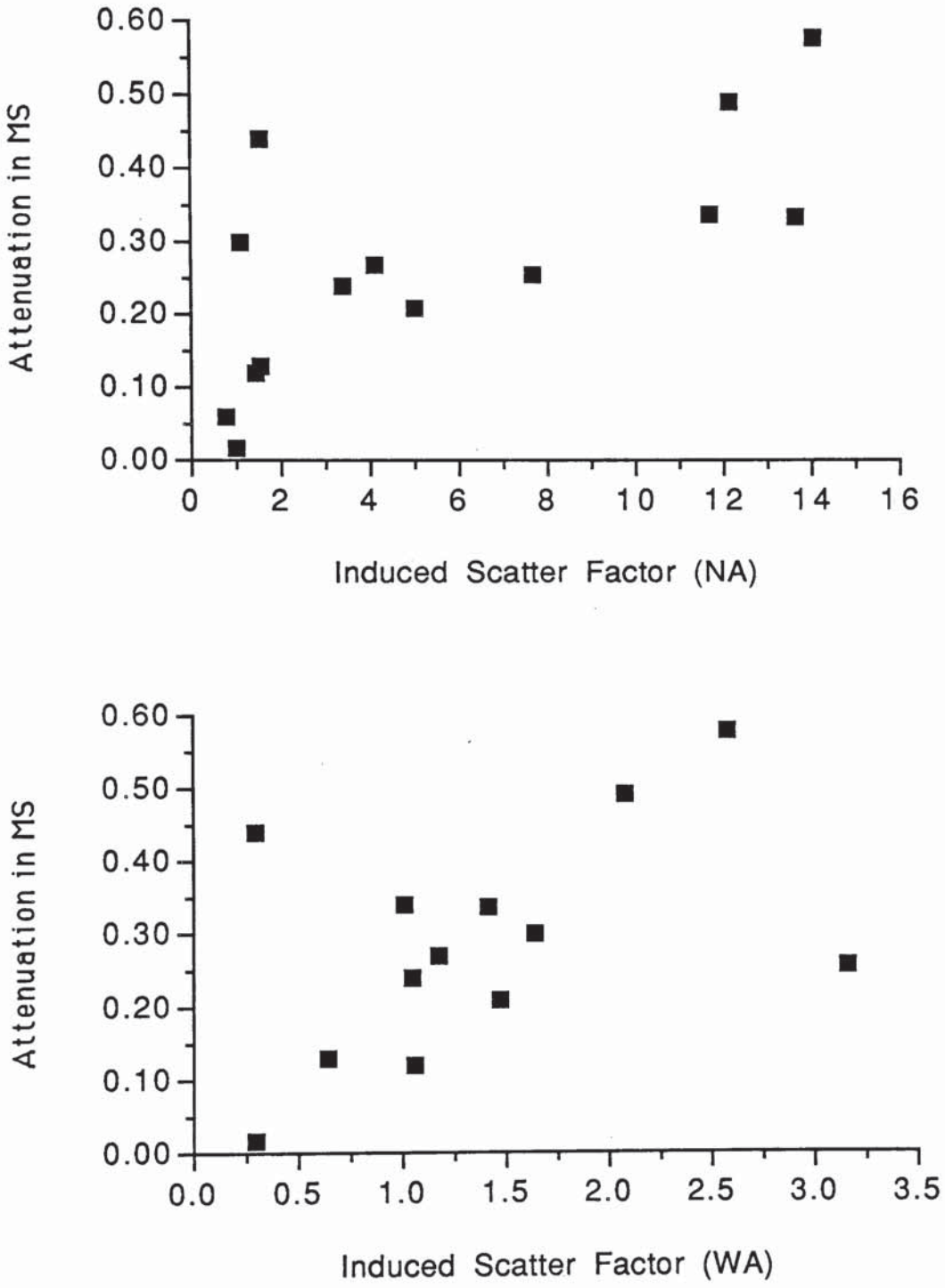


Figure 3.5. Showing the relationship between proportionate change in Dicon mean sensitivity as a function of induced forward light scatter. Top: narrow-angle glare, bottom: wide angle glare.

3.1.10. DISCUSSION

The results indicate that induced forward light scatter falsifies the sensitivity gradient of the glaucomatous field in two ways. Firstly, sensitivity is globally depressed. Secondly, an apparent decrease in loss variance indicates that the depth and / or area of scotomata are reduced. This may be due to the detection of scattered light from perimetric stimuli by adjacent retinal areas of greater sensitivity. Alternatively, the general depression of the hill of vision may be more pronounced in normal than in scotomatous areas producing a localised flattening of the focal loss. The findings are in agreement with other studies (Guthauser et al. 1986; Urner-Bloch 1987) and imply that diffuse glaucomatous defects are more difficult to recognise in the presence of forward light scatter and that the full extent of the focal loss may be underestimated.

Media opacities have their greatest influence on the threshold by virtue of their lack of homogeneity which causes light scattering. It has been suggested that cataract may affect the visual field before any change in central acuity is evident (Klewin & Radius 1986). From studies on the point spread function of the human eye, Van den Berg (1987) predicted considerable changes in the visual field resulting from relatively mildly disturbed media due to increased light scatter over large and / or small angles. It would seem that the results from the current study support this view. Indeed, visual acuity is accepted to be a poor indicator of the disability produced by cataract (Hess & Garner 1977; Hess & Woo 1978; Van den Berg 1986). It correlates poorly with back-scattered light (Allen & Vos 1967) and is depressed less than contrast sensitivity by intraocular light scatter (Van den Berg 1986; Hess & Garner 1977).

The contrast sensitivity response of the elderly glaucomatous sample could be expected to influence the magnitude of the calculated light scattering factors, although it is used as a relative measure in the computation. The contrast sensitivity profile decreases as a function of age, with the greatest attenuation occurring at the highest spatial and temporal frequencies (Owsley et al. 1983; Ross et al. 1985; Wright & Drasdo 1985). Above the age of 50 however, the depression is independent of age (Ross et al. 1985). The contrast sensitivity profile is also affected by glaucoma (Arden & Jacobson 1978) although no

particular depression has been reported for either low spatial (Vaegan & Halliday 1982) or low temporal frequencies viewed centrally (Atkin et al. 1978). Sensitivity losses have been found at all spatial frequencies for gratings modulated at 2 Hz presented eccentrically 10° from fixation, although for central viewing reduced sensitivity was found only at medium spatial frequencies of 2-4 c/deg (Lundh 1985). Losses have been found for centrally viewed gratings of low spatial frequency modulated at a higher temporal frequency of 8 Hz (Atkin et al. 1978, 1979; Bodis-Wollner 1981; Ross et al. 1984).

In addition to light scatter, media absorption leads to an equivalent reduction at retinal level of the perceived stimulus intensity and background illumination. For conditions under which the Weber-Fechner law applies ($\Delta L/L$ = constant), a stimulus previously at threshold will remain so. At low levels of retinal adaptation, such as are encountered in the Octopus automated perimeter (4asb), the ratio $\Delta L/L$ increases and the intensity of the projected stimulus must increase to evoke a response. It would therefore seem appropriate to separate the perimetric attenuation arising due to scatter from that due to absorption.

The differences in perimetric attenuation with eccentricity reported by Wood et al. (1987a,b, 1989) whereby light scatter steepened the hill of vision for the large projected Goldmann III stimulus (0.431°) of the Octopus, and flattened the hill of vision for the smaller 0.28° LED stimulus of the Dicon was not found. This may be due to a greater attenuation of sensitivity in normal areas compared with scotomatous areas resulting in a flattening of the hill. The increased short and long-term fluctuations in the perimetric response of glaucoma patients may be a further factor (Flammer et al. 1984).

3.1.11. CONCLUSIONS

Care should be exercised when interpreting or monitoring perimetric changes based on inspection of the visual field indices. Significant alterations in the indices may result in patients with relatively clear media. If the effects of forward light scatter on the differential light threshold are not considered, the concomitant development of media changes may mask both increasing diffuse and focal glaucomatous loss.

CHAPTER 3.2

CORRECTION OF THE PERIMETRIC PROFILE FOR FORWARD INTRAOCULAR LIGHT SCATTER

3.2.1. INTRODUCTION

The previous experiment showed the effect of induced forward light scatter on the glaucomatous perimetric profile, namely an apparent increase in diffuse loss and a decrease in focal loss. The conclusion of a reduction in focal loss was in agreement with the work of both Guthauser et al. (1986) and Urner-Bloch (1987), who studied the automated visual fields of glaucoma patients pre- and post-cataract extraction. It disagreed, however, with the work of Eichenberger et al. (1987), who employed an opacity simulation and Guthauser & Flammer (1988), who also studied the automated visual field of glaucoma patients pre- and post cataract extraction. It was accepted that the reduction in the index describing focal loss, the loss variance, could result from a decrease in either the area or the depth of one or more scotomata, since both these factors are considered in the calculation of the index. Normative age-matched data is also required for the computation of the loss variance. It was hypothesised that the reduction in focal loss was a computational artefact resulting from failure to account for the effects of light scatter on the format of the normal reference age-matched hill of vision.

The induced forward light scatter simulation employed in the experiment was previously shown to be an accurate representation of forward intraocular light scatter in a sample of patients with non-nuclear uniocular opacities by Wood et al. (1989). They derived nomograms which related perimetric attenuation to the light scattering factor as a function of eccentricity, employing the fellow eye with clear media as a control. These nomograms are reproduced in Figure 3.6. and show that the attenuation in perimetric sensitivity is less at fixation than in the periphery for subjects with non-nuclear opacities. The reverse was found for patients with nuclear opacities, which was in agreement with previous reports that the visual performance of subjects with nuclear cataracts is dissimilar to other types of cataract in terms of the light scattering factor (Abrahamsson & Sjostrand 1986) and perimetric profiles (Lyne & Phillips 1969).

3.2.2. AIM OF THE STUDY

The aim of the study was to correct the glaucomatous perimetric profile for the effects of naturally occurring forward intraocular light scatter, in order to investigate the hypothesis that the reduction in focal losses caused by induced forward light scatter was artefactual. It was hypothesised that this artefact resulted from the use of inappropriate age-matched normative data, in the presence of forward intraocular light scatter, for the computation of the visual field indices.

3.2.3. MATERIALS AND METHODS

The sample comprised 26 patients, 15 of whom took part in the previous experiment and an additional 11 patients (4 with primary open angle glaucoma and 7 ocular hypertensives) who conformed to the same inclusion criteria. The grand mean age of the combined sample was 65.0 years (SD 8.0 years). The depth and type of field loss in the sample is illustrated in Figure 3.7. based on the classification of Caprioli & Sears (1987). The right eye of the 11 additional patients was also examined with both phases of program G1 on the Octopus Automated Perimeter. At another session, forward intraocular light scatter was assessed by measuring the depression of contrast sensitivity due to narrow-angle glare light, as described in Section 3.1.8. Grand mean pupil size measured under the adaptation level of the Octopus bowl perimeter was 5.9mm (SD 1.6mm).

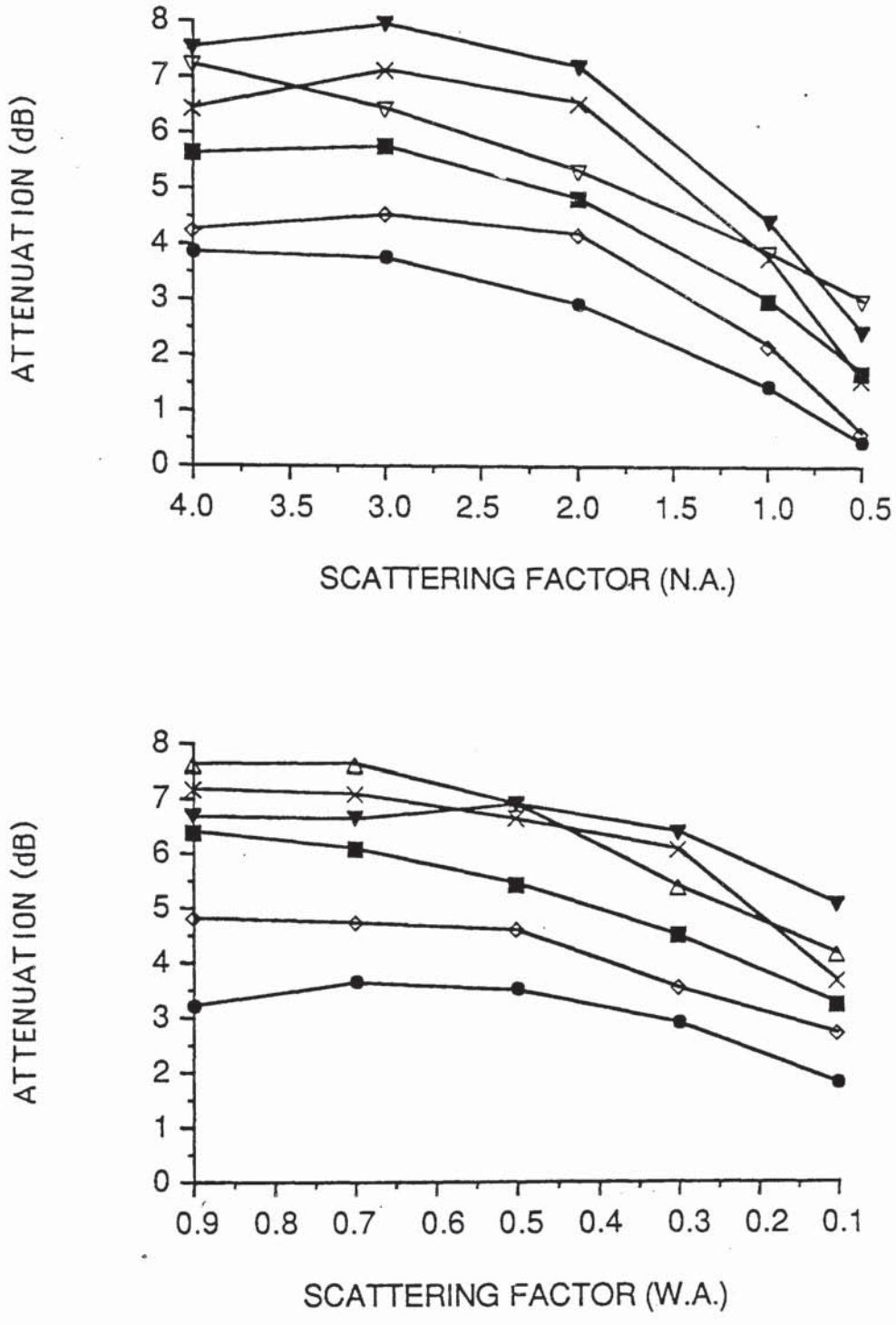


Figure 3.6. Nomograms (after Wood et al. 1989) illustrating the attenuation in perimetric sensitivity (dB) for the projected stimulus of the Octopus 201 automated perimeter against narrow (top) and wide-angle (bottom) intraocular light scatter as a function of eccentricity: 0° filled circles, 6° open diamonds, 12° filled squares, 18° crosses, 24° open triangles and 30° filled inverted triangles, for subjects with non-nuclear opacities.

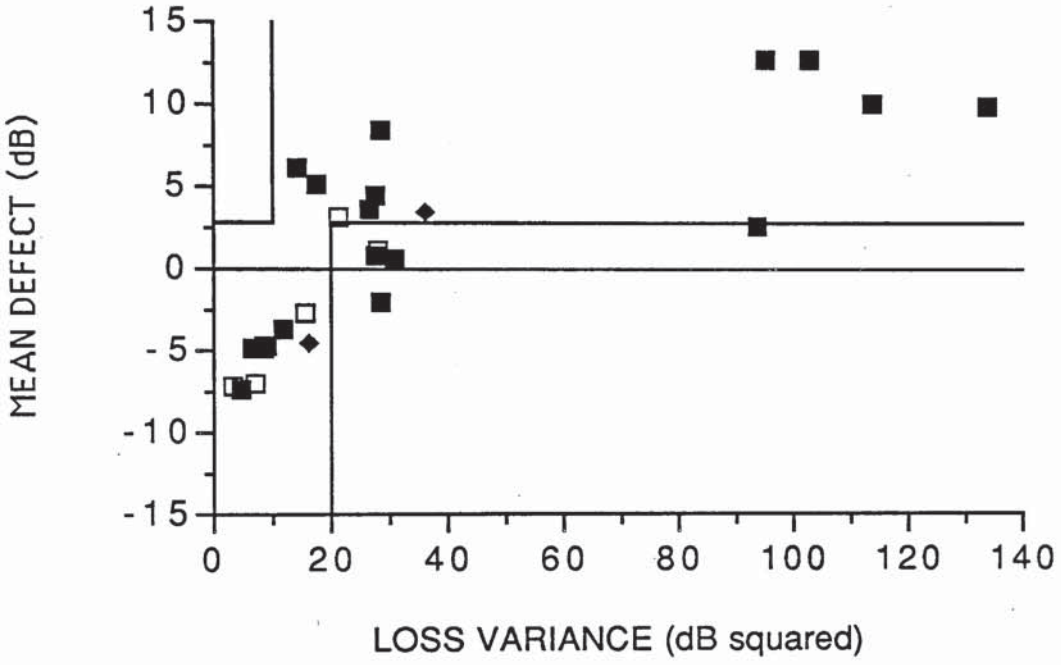


Figure 3.7. The depth and type of field loss within the sample after the classification of Caprioli & Sears (1987) showing mean defect (diffuse loss) as a function of loss variance (focal loss). Solid lines represent criteria for relatively pure diffuse depression (enclosed area parallel to the ordinate) and relatively pure focal loss (enclosed area parallel to the abscissa). The diagnoses are indicated (primary open-angle glaucoma: filled squares; low-tension glaucoma: filled diamonds and ocular hypertension: open squares).

The pointwise decibel values of sensitivity and the age-matched normative value of sensitivity from the Octopus G1 printout (phase 2) were each corrected for the effects of forward intraocular light scatter, as a function of eccentricity. The light scattering factor was read along the abscissa and the corresponding perimetric attenuation for each eccentricity was read from the ordinate of the nomogram and added to the decibel printout values. The visual field indices mean sensitivity, mean defect and loss variance were then recalculated for the transformed fields using the formulae of Flammer (1986). An equivalent correction for wide-angle intraocular light scatter was not considered feasible due to the curtailed range of scattering factors. Although the nomogram was based on perimetric sensitivity measured with program 31 of the Octopus automated perimeter, which has a 6° regular square stimulus grid, it was considered acceptable to apply this to sensitivity values determined with the irregular stimulus grid of program G1 since the differences in perimetric attenuation between the two programs at similar eccentricities were likely to be clinically insignificant.

3.2.4. RESULTS

Narrow-angle light scattering factors ranged from 0.23-4.82 (mean 1.6; SD 1.0) representing patients with media defined as "clear" by the recruiting ophthalmologist. This compared with values of 1.2-14.5 (mean 4.4; SD 4.0) in the sample of patients with diagnosed uniocular non-nuclear lenticular opacities used to derive the nomograms of Wood et al. (1989).

Correction of both the sensitivity data and the age-matched normative data, on a pointwise basis for narrow-angle forward intraocular light scatter, resulted in a linear increase in mean sensitivity and corresponding linear decrease in mean defect with increase in forward intraocular light scatter (Figure 3.8.). The loss variance, however remained essentially unchanged (Figure 3.9.)

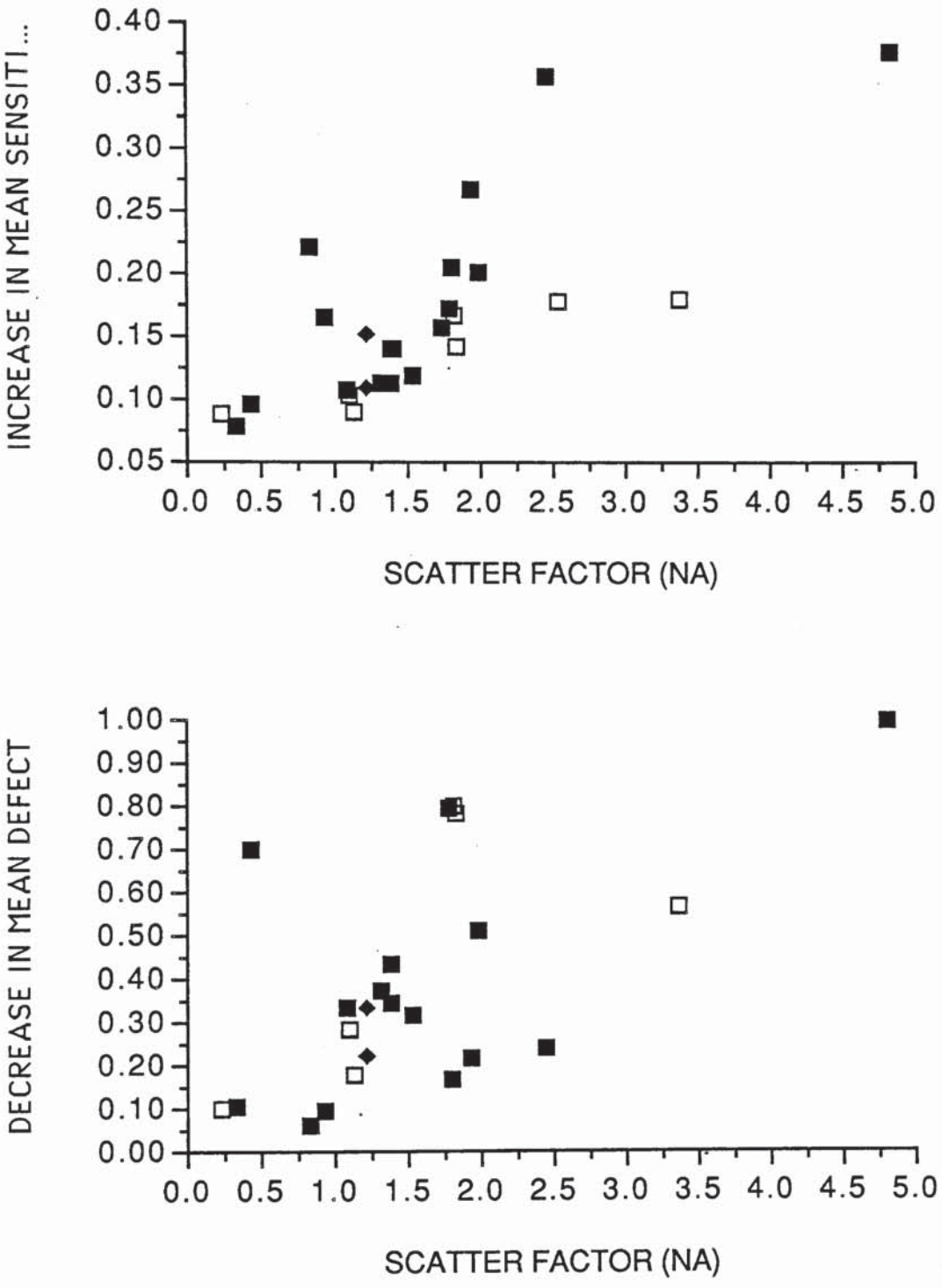


Figure 3.8. Proportionate increase in Octopus phase 2 mean sensitivity (top) and decrease in mean defect (bottom), calculated from the pointwise distribution of sensitivity following correction for the effects of naturally occurring narrow-angle forward intraocular light scatter, as a function of narrow-angle scatter factor for 26 glaucomatous patients. The diagnoses are indicated (primary open-angle glaucoma: filled squares, low-tension glaucoma: filled diamonds and ocular hypertension: open squares).

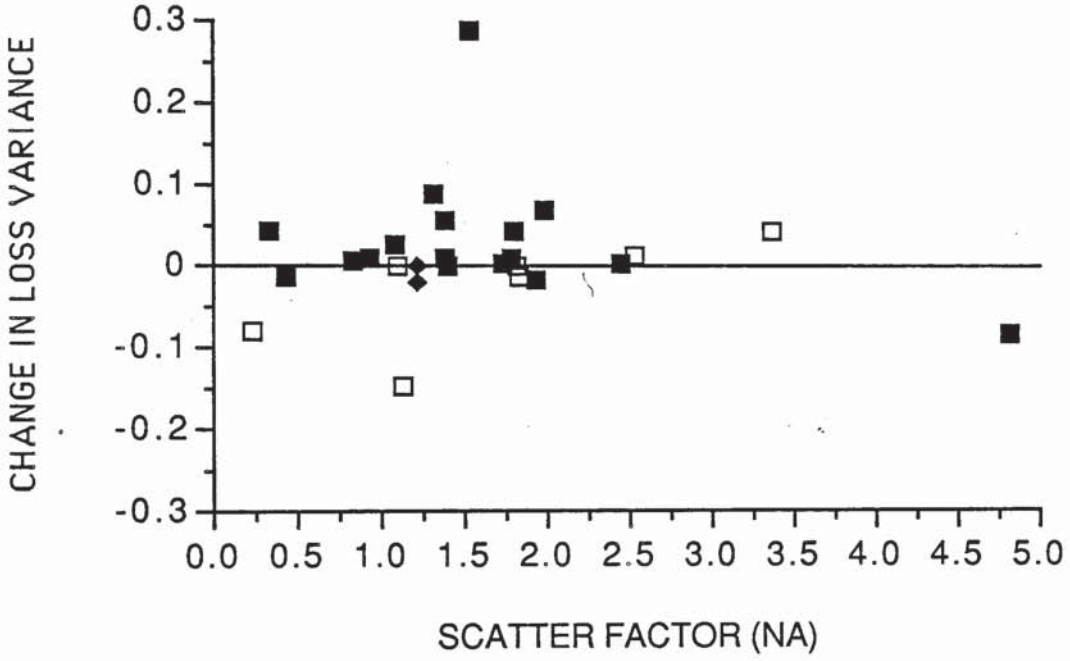


Figure 3.9. Proportionate change in Octopus phase 2 loss variance calculated from the pointwise distribution of sensitivity following correction for the effects of naturally occurring narrow-angle forward intraocular light scatter as a function of narrow-angle scatter factor for 26 glaucomatous patients. The diagnoses are indicated (primary open-angle glaucoma: filled squares, low-tension glaucoma: filled diamonds and ocular hypertension: open squares).

3.2.5. DISCUSSION

The results indicate that induced forward light scatter falsifies the sensitivity gradient through an apparent global depression and lessening of the depth and / or area of scotomata. Recalculation of the visual field indices after correction for naturally occurring forward intraocular light scatter implies, however, that a general depression of sensitivity occurs without change of focal loss. This is in agreement with the computer simulation of Augustiny & Flammer (1985) who suggested that cataract gives rise to an increase in mean defect without alteration of the corrected loss variance. It would seem therefore that the apparent lessening of focal losses with induced forward light scatter, also reported by Guthauser et al. (1986) and Urner-Bloch (1987), may be a computational artefact resulting from the use of inappropriate age-matched normative data in the calculation i.e. a failure to account for the effects of light scatter on the normal reference age-matched hill of vision, thus an inappropriate mean defect index is used to compute the loss variance index. The age-matched normative data is derived from patients who have "average" media for a person of that age. Use of this data in calculating visual field indices in the case of a cataract patient of similar age may be misleading. Indeed, the use of a patient specific normal reference field has been advocated by several authors (Wild et al. 1986c; Van den Berg & Nooteboom 1987; Van den Berg et al. 1987).

The apparent lessening of the focal losses by induced forward light scatter may also be considered in terms of the relationship between the visual field indices mean defect and corrected loss variance. Pearson et al. (1990) have shown mean defect and corrected loss variance to covary, in glaucoma patients with clear media, up to a mean defect of 18 dB. Interestingly, further increases in mean defect resulted in an apparent lessening of the corrected loss variance index. Gollamudi et al. (1988) have therefore proposed combination of the visual field indices mean defect (MD) and corrected loss variance (CLV) in a "difference index":

$$(\sqrt{CLV} - MD)$$

This index was used to define the various stages of glaucomatous visual field loss, dividing patients into "early" (positive index), "mid-stage" (index around zero) and "advanced" stages of glaucoma (negative index).

3.2.6. CONCLUSIONS

This study provides a method for correcting the glaucomatous perimetric profile for the effects of forward intraocular light scatter. It does not, however, take into account the effects of absorbtion. The conclusion of Section 3.1.11. is substantiated i.e. that care must be exercised when interpreting and monitoring perimetric results in the presence of media opacities. Further studies are required on the statistical covariance of the visual field indices mean defect and corrected loss variance in cases of cataract and glaucoma.

CHAPTER 3.3

THE RELATIONSHIP BETWEEN FORWARD AND BACKWARD INTRAOCULAR LIGHT SCATTER

3.3.1. INTRODUCTION

Forward intraocular light scatter is assessed clinically by subjective methods, reviewed in Section 3.1.4.2., whereas back light scatter is measured objectively as reviewed in Section 3.1.4.1. An assumption is frequently made that light back-scattered by the lens (at an angle of more than 90° to the incident source) can be used as an index of image degradation (Sigelman et al. 1974) and that this is related to the light forward scattered (at an angle of less than 90° to the incident source) towards the retina (Allen & Vos 1967). The precise relationship between back scatter and forward scatter in normal human lenses however remains unknown. It has been shown that the intensity of nuclear back scatter in the normal eye increases by a factor of between 2 and 10 from the ages of 20 to 60 years (Sigelman et al. 1974; Ben-Sira et al. 1980; Zeimer & Noth 1984). Visual impairment from cataract, however, results from an increase in forward intraocular light scatter.

The angular dependence of light scattering has been examined *in vitro* using thin sections of both normal (Bettelheim & Paunovic 1979; Siew et al. 1981b) and cataractous lenses (Philipson 1969; Siew et al. 1981a). Philipson (1969) found the intensity of forward scattered light to be greater than that back scattered in the transparent cortex of lenses with galactose induced nuclear cataract; in the nuclear region, however, scattering was greater in the backward direction. He interpreted this to be due to the presence of structures in the cortical lens fibres that were of the order of the wavelength of light, and to particles in the lens nucleus whose dimensions were several times the wavelength of light.

The angular dependence of light scattering has also been studied in whole excised normal (Bettelheim & Ali 1985) and cataractous lenses (Bettelheim & Chylack 1985) and attempts have been made to relate these light scattering parameters to the clinical description of the cataract, obtained by the technique of stereoscopic photography (Siew et al. 1981a).

Bettelheim & Ali (1985) obtained scattering intensities as a function of scattering angle from 0°-135° in whole excised normal human lenses. They found that relative scattering intensities were not only greater at complementary angles in the forward direction than in the backward direction, but also that aging resulted in a greater increase in scattering intensity in the forward direction than in the backward direction. They also proposed that, if the intensity of back scattered light were known, e.g. from the methods of Dragomirescu et al. (1978, 1980) or Sigelman et al. (1974), then linear regression analysis could be used to predict the intensity of forward scattered light. Calculations using this regression analysis indicated that an average normal human lens of 50 years scatters 1.28 times as much white light in the forward as in the backward direction. The subsequent study of Bettelheim & Chylack (1985) applied these principles to whole excised cataractous human lenses, showing an average 50 year old cataractous lens to scatter 2.17 times as much white light in the forward as in the backward direction. Cataractous lenses were also noted to show increased scattering at angles greater than 30°, and reduced scattering at angles less than this, compared with normal lenses of the same age. The studies of Bettelheim & Ali (1985) and Bettelheim & Chylack (1985) are in agreement with the fact that, as the size of scattering particle increases, the ratio of forward to back scattered light intensity increases (Stacey 1956).

The studies in Sections 3.1. and 3.2. showed the effects of induced and naturally occurring forward intraocular light scatter on the perimetric profile, namely that forward light scatter results in a diffuse depression of the visual field with an apparent artefactual reduction in focal loss. Indeed, other authors have determined the influence of media opacities on the automated perimetric profile by relating perimetric attenuation to measurements of forward intraocular light scatter (Heuer et al. 1987b, 1988; Wood et al. 1987a,b, 1989). Perimetric attenuation has also been related to backward intraocular light scatter (Guthauser et al. 1986, 1987; Guthauser & Flammer 1988; De Natale & Flammer 1989) but the relationship between these two measures of intraocular light scatter remains unknown.

3.3.2. THE OPACITY LENSMETER (OLM)

Flammer & Bebie (1987a) introduced a commercially available device, the Opacity Lensmeter (OLM) for the measurement of back scatter particularly in relation to the visual field. The

instrument measures stray light back scattered from the crystalline lens. Stray light is produced by a cylinidrical beam of 1.5mm diameter of wavelength 700nm which is projected into the eye. Some of the light passes through the eye toward the retina but part of it is scattered in the cornea and crystalline lens. Light back scattered from the lens is detected by a photocell at an angle of 27° to the incident beam, and this signal is processed by computer giving a digital display on a scale of 0-99. The normal lens ranges between 4 and 25, depending on the patient's age, and pathological changes in lens transparency result in readings ranging from 30-99. The measurement is normally repeated five times and the printout includes the mean and standard deviation of these readings.

The format of the instrument is similar to a slit-lamp; the patient's head is placed on a chin-rest and the instrument adjusted with a joy stick. The patient's eye is aligned with the optical system while the patient fixates a central green light surrounded by a dark red circle. The operator focuses on the iris of the patient; a minimum pupil diameter of 4mm is recommended (Bebie & Flammer 1987) and this may be checked against a scale in the eyepiece. The measurement is initiated by pressing a button on the console, and the instrument samples 250 times over a period of 0.5 seconds.

3.3.3. THE RELATIONSHIP BETWEEN OLM READINGS AND THE VISUAL FIELD

Wegener & Hockwin (1988) found the OLM to detect only diffuse homogeneous increases in back light scattering and thus suggested that the OLM would not aid in differentiating visual loss due to media changes from that due to neural dysfunction. Indeed, De Natale & Flammer found a correlation of 0.88 ($p<0.0001$) between pre-operative OLM reading and the improvement in mean sensitivity for Octopus program F2 (horizontal meridian) following cataract surgery for either nuclear or cortical cataracts ($n=15$), however the coefficient of correlation was only 0.28 ($p<0.1868$) when posterior sub-capsular opacities ($n=24$) were considered in isolation. Messmer et al. (1990) noted a correlation of 0.97 between pre-operative OLM reading and the improvement in Octopus program G1 visual field index mean defect following cataract extraction with posterior chamber implant, although details of the morphological type of opacity were not given.

3.3.4. AIM OF THE STUDY

The aim of the study was to determine the clinical relationship between forward and back intraocular light scatter in a cataractous population, using the techniques which have been applied to the investigation of the effects of cataract on the visual field. It was hypothesised that measurement of back scatter with the OLM would underestimate the degree of disability experienced by the patient and the extent of perimetric attenuation due to media opacities compared with measurement of forward intraocular light scatter since, the OLM only measures along the optic axis, long wavelength light is used (Rayleigh scattering is inversely proportional to the fourth power of the wavelength) and the instrument only detects light back-scattered at one particular angle. Forward intraocular light scatter was assessed with the method described in Section 3.1.8.

3.3.5. MATERIALS AND METHODS

The sample consisted of 60 patients. Exclusion criteria comprised a history of diabetes and other systemic conditions with ocular complications, corneal disorders or contact lens wearers patients, glaucoma or ocular hypertension, previous intraocular surgery, vitreous floaters and retinal disorders.

Each subject underwent measurement of Snellen VA under normal consulting room conditions, a detailed slit-lamp assessment of the anterior segment and crystalline lens together with ophthalmoscopy using both white and red-free light. The media of one eye of each subject were classified on the basis of these examinations. Normal media were defined as those in which the VA was better than or equal to 6/9, retinal nerve fibres could be seen by ophthalmoscopy with red-free light and no lens opacity was visible within the pupillary area by ophthalmoscopy or slit-lamp examination (n=14; mean age 46.5 years, SD 16.2). Cataractous media were divided into those with primarily anterior cortical opacities (n=26; mean age 73.8 years, SD 7.7), those with nuclear sclerosis (n=9; mean age 76.8 years, SD 6.8) and those with posterior sub-capsular opacities (n=11; mean age 60.7 years. SD 17.9). The grand mean age of the sample was 65.5 years (SD 17.0 years).

Back scatter was taken as the mean of five OLM readings. As recommended by Flammer &

Bebie (1987), a pupil size greater than 4mm was used for all readings; where necessary this was achieved by reducing the ambient illumination of the OLM.

Forward intraocular light scatter was assessed as described in Section 3.1.8. and a forward light scattering factor calculated for each patient from the equation of Paulsson & Sjostrand (1980).

3.3.6. RESULTS

Back light scatter was found to increase with increasing age for the 14 subjects with clear media as shown in Figure 3.10. (r_S=0.92).

The relationship between the forward intraocular light scattering factor and age for the 14 subjects with clear media is shown in Figure 3.11. There was little correlation between forward light scatter and age (narrow-angle glare r_S=0.1; wide-angle glare r_S=0.3).

The relationship between the forward light scattering factor and back scatter for anterior cortical opacities, nuclear sclerosis and posterior sub-capsular opacities is shown in Figures 3.12. for narrow and 3.13. for wide-angle glare light respectively. Data for the clear media is included on each graph for comparative purposes. This data could not however be fitted by a linear or curvilinear function.

The relationship between Logmar acuity and back scatter for the three types of opacity is shown in Figure 3.14. The relationship between these factors was not significant.

The relationship between Logmar acuity and forward light scattering factor for the three types of opacity is shown in Figures 3.15. for narrow and 3.16. for wide-angle glare light respectively. A significant correlation was found between Logmar acuity and forward wide-angle light scattering factor for anterior opacities (r_S=0.46; p=0.02) although correlates for all other opacity types were not statistically significant.

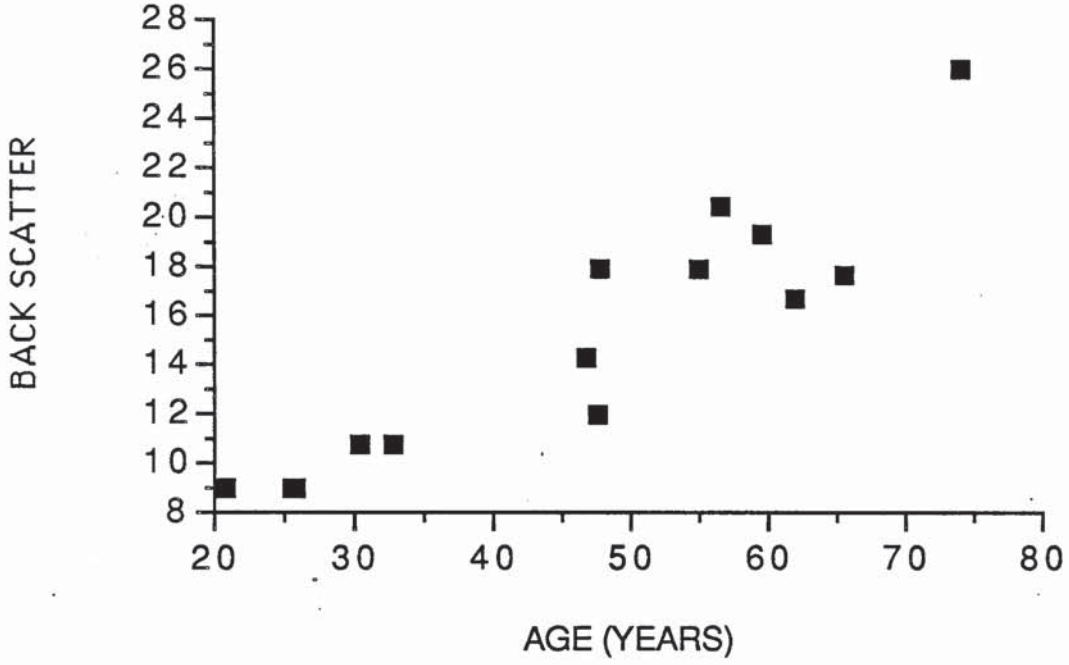


Figure 3.10. Showing the relationship between back scatter, measured with the OLM, and age for 14 subjects with clear media.

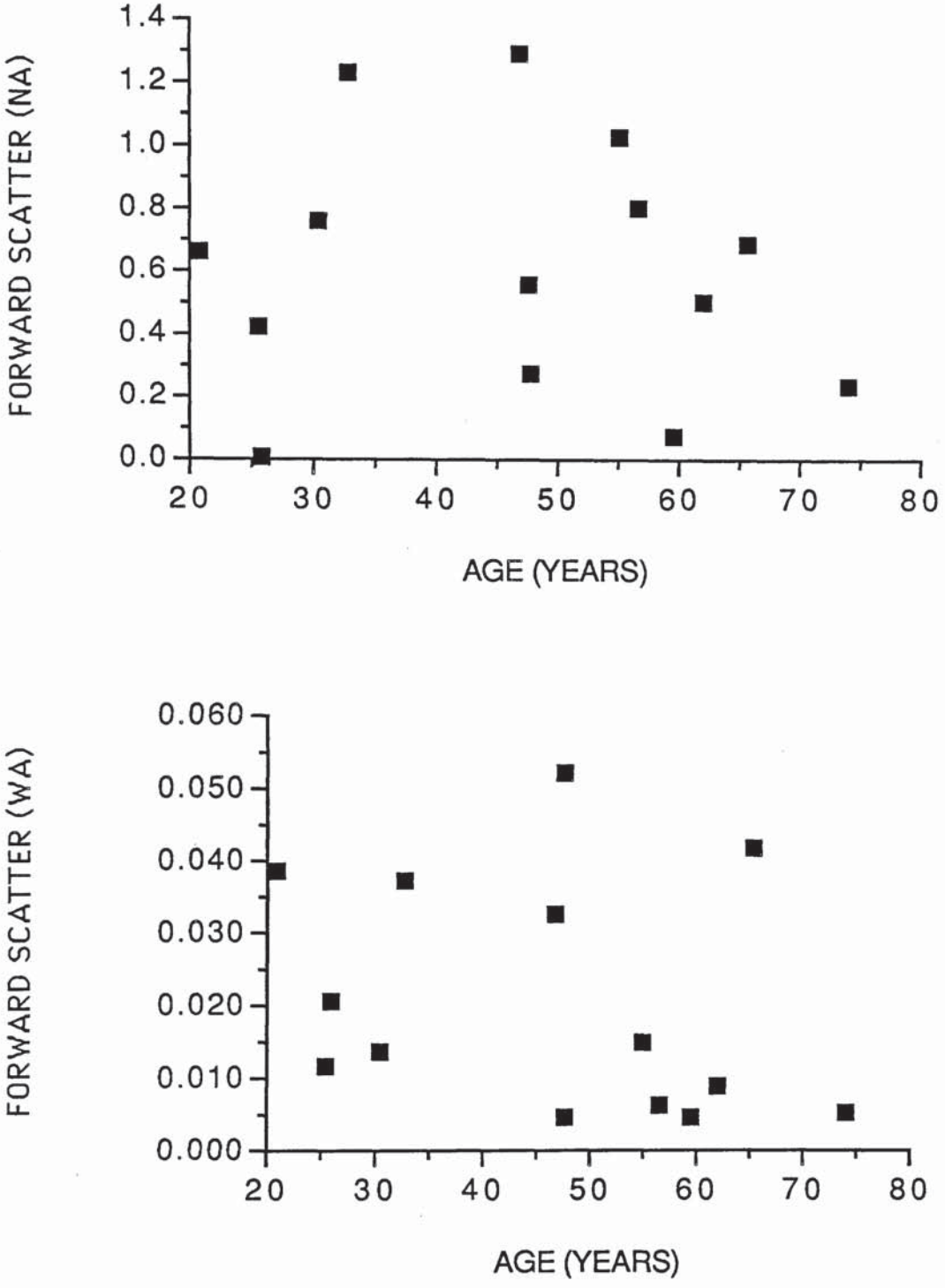


Figure 3.11. Showing the relationship between forward light scatter and age for 14 subjects with clear media (top: narrow-angle glare light, bottom: wide-angle glare light).

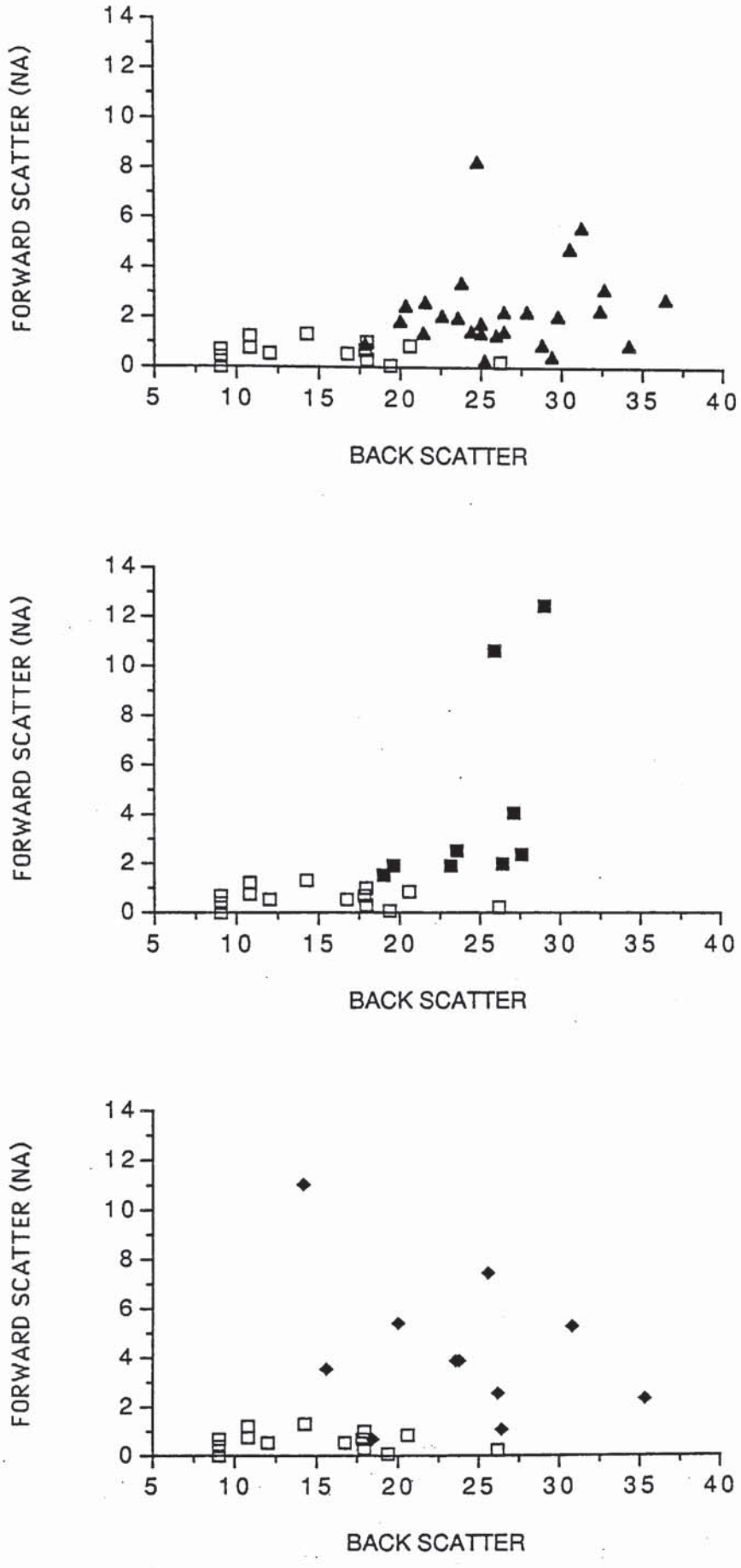


Figure 3.12. Showing the relationship between back and forward scatter (narrow-angle glare light) for anterior cortical opacities (top: filled triangles), nuclear sclerosis (middle: filled squares) and posterior subcapsular opacities (bottom: filled diamonds). Data for clear media (open squares) is included on each graph for comparative purposes.

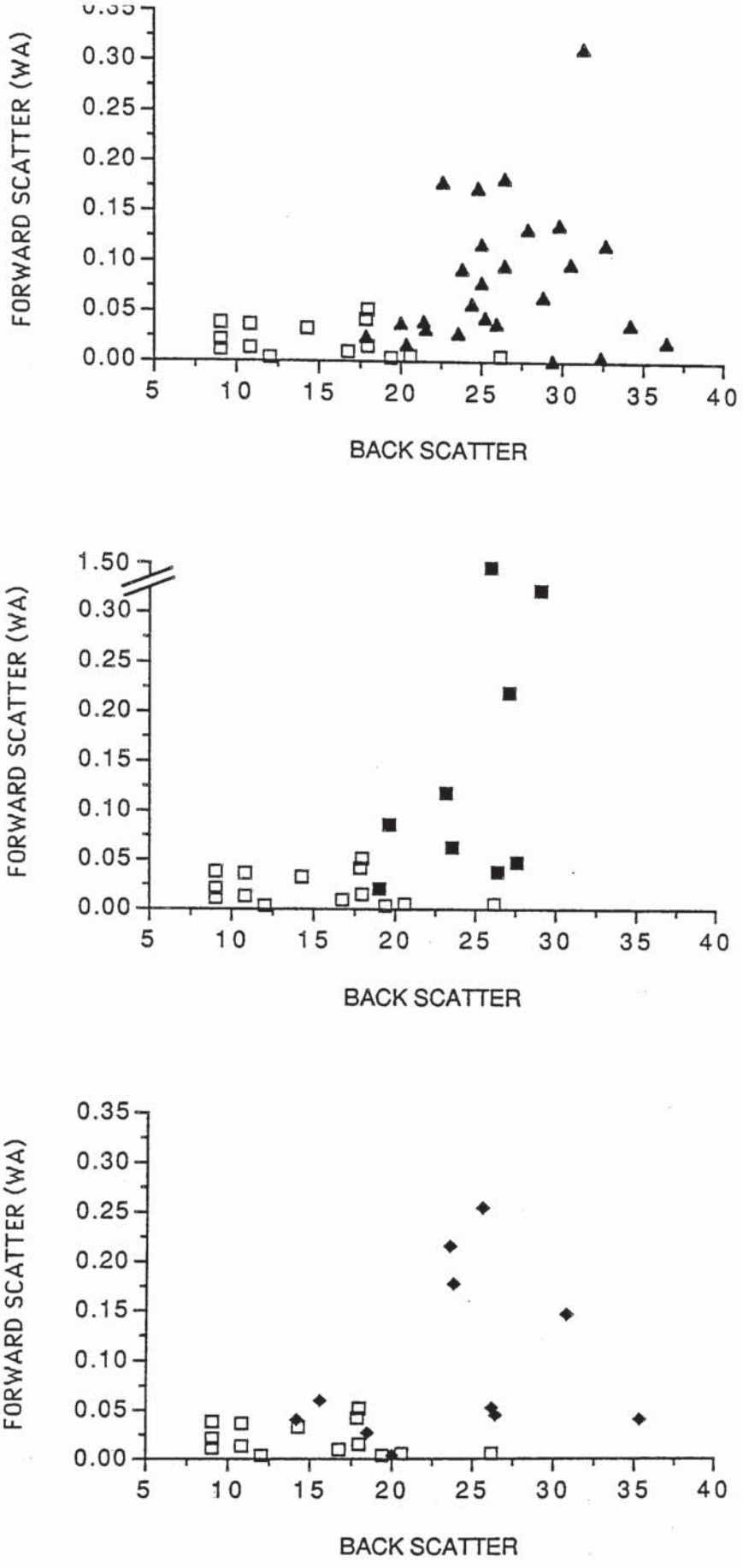


Figure 3.13. Showing the relationship between back and forward scatter (wide-angle glare light) for anterior cortical opacities (top: filled triangles), nuclear sclerosis (middle: filled squares) and posterior subcapsular opacities (bottom: filled diamonds). Data for clear media (open squares) is included on each graph for comparative purposes.

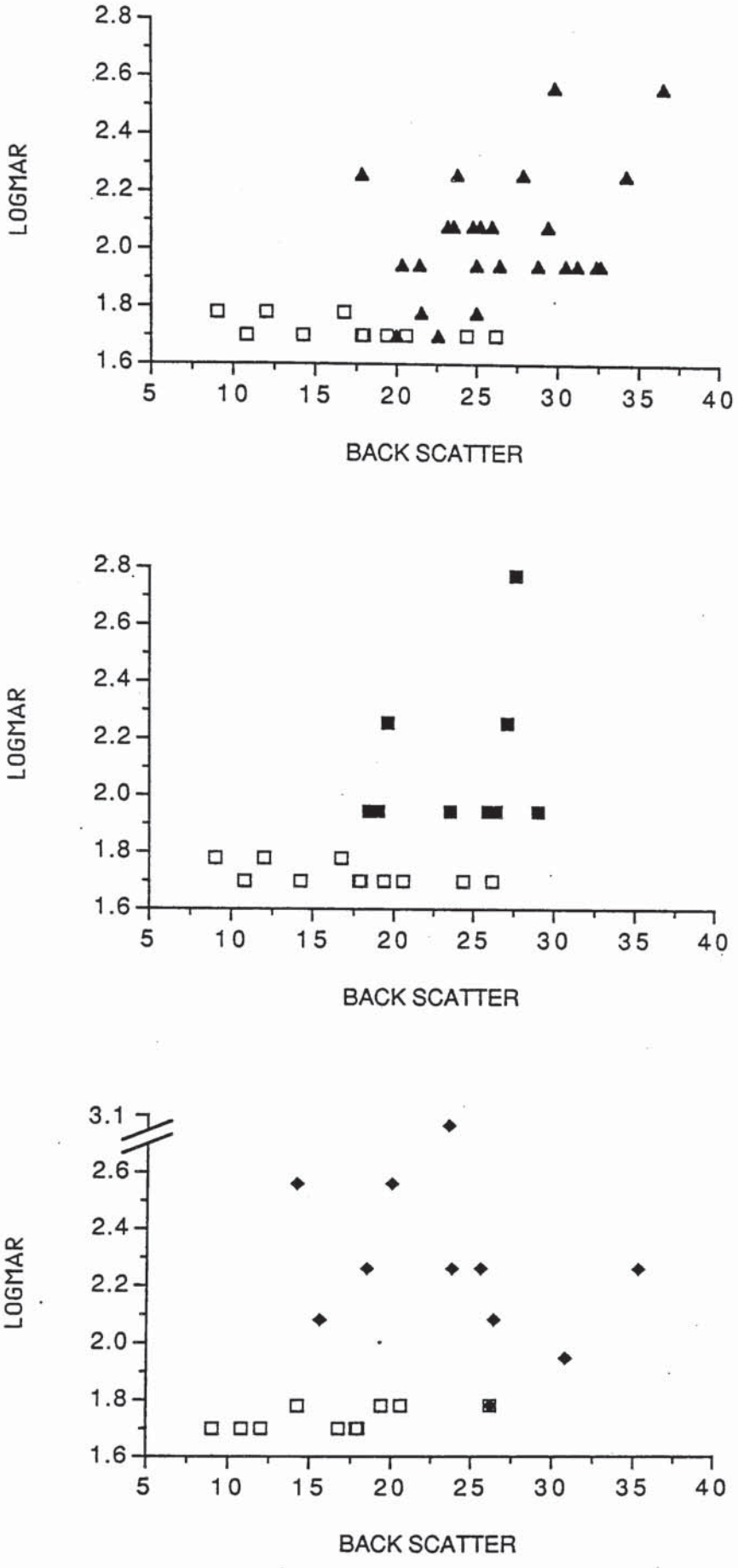


Figure 3.14. Showing the relationship between logmar acuity (log seconds of arc) and back scatter for anterior cortical opacities (top: filled triangles), nuclear sclerosis (middle: filled squares) and posterior subcapsular opacities (bottom: filled diamonds). Data for clear media (open squares) is included on each graph for comparative purposes.

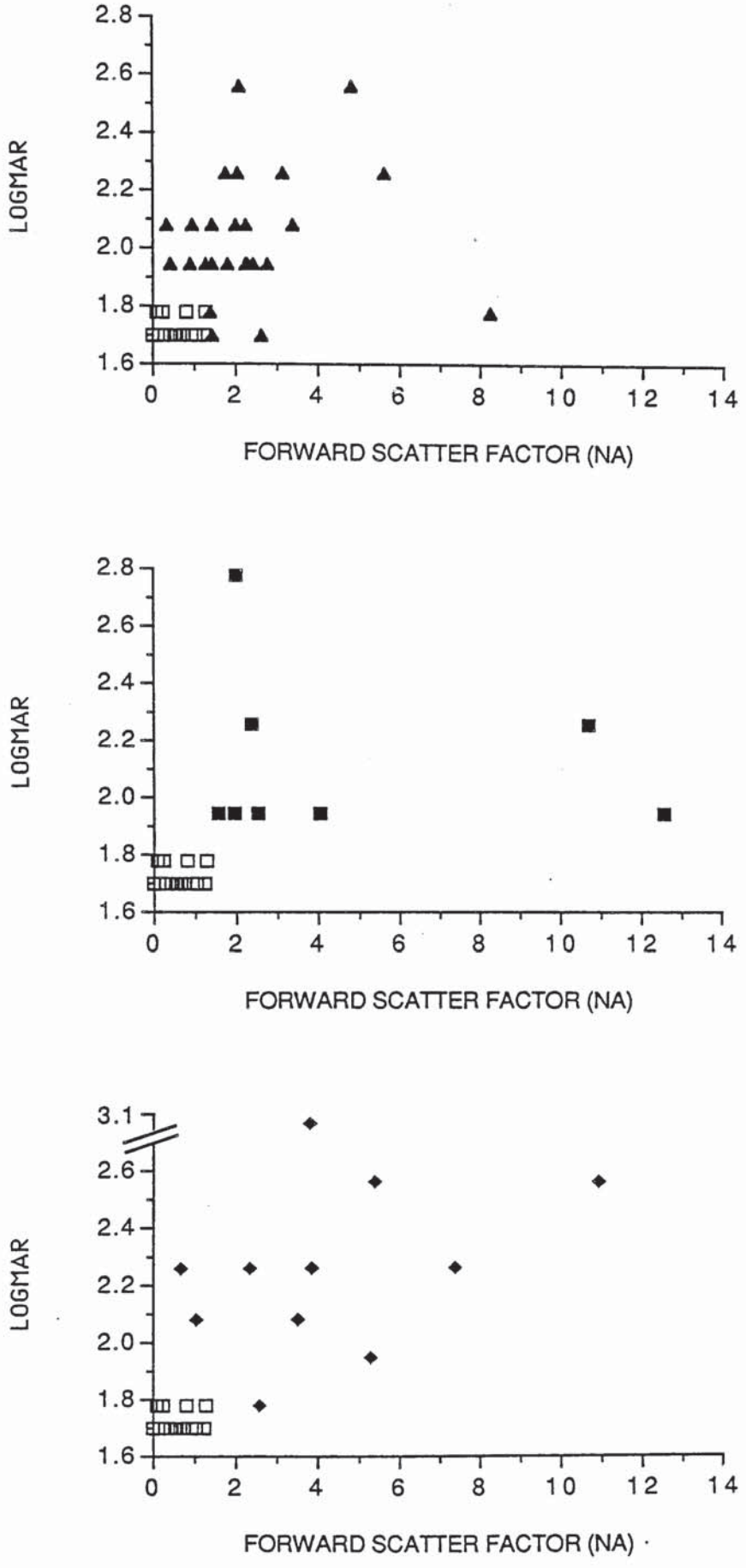


Figure 3.15. Showing the relationship between logmar acuity (log seconds arc) and forward light scatter (narrow-angle glare light) for anterior cortical opacities (top: filled triangles), nuclear sclerosis (middle: filled squares) and posterior subcapsular opacities (bottom: filled diamonds). Data for clear media (open squares) is included on each graph for comparative purposes.

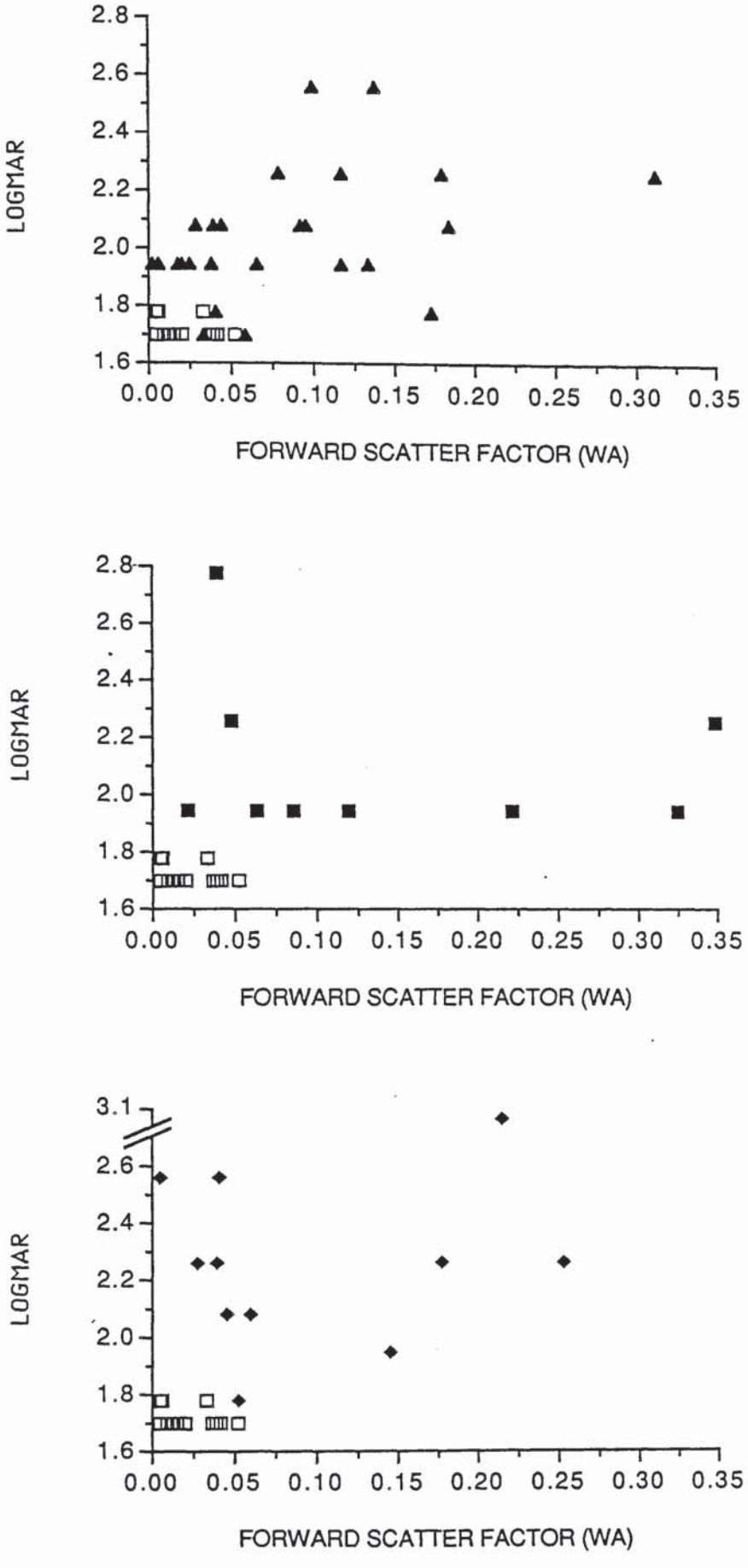


Figure 3.16. Showing the relationship between logmar acuity (log seconds arc) and forward light scatter (wide-angle glare light) for anterior cortical opacities (top: filled triangles), nuclear sclerosis (middle: filled squares) and posterior subcapsular opacities (bottom: filled diamonds). Data for clear media (open squares) is included on each graph for comparative purposes.

	OPACITY TYPE			
	Clear (n=14)	Anterior (n=26)	Nuclear (n=9)	Posterior (n=11)
Back scatter (5 OLM readings)	15.12 0.60	26.44 2.20	24.62 1.40	23.65 1.70
Contrast determinations without glare (6 readings)	-1.72 0.06	-1.56 0.05	-1.51 0.05	-1.38 0.05
Contrast determinations with narrow-angle glare (6 readings)	-1.58 0.06	-1.20 0.07	-1.00 0.07	-0.86 0.06
Contrast determinations with wide-angle glare (6 readings)	-1.63 0.05	-1.30 0.06	-1.14 0.05	-1.11 0.05

Table 3.1. Group mean and group mean standard deviation of 5 back scatter measurements and 6 contrast threshold determinations, with and without narrow and wide angle glare light for the calculation of the forward light scatter factor for each opacity type.

3.3.7. DISCUSSION

A high linear correlation was found between back scattered light measured with the OLM and age for the patients with clear media. Non-linear regression of the data, using a second order polynomial function, did not result in any improvement of the fit. This is in agreement with previous work using the OLM (De Natale et al. 1988; Wegener & Hockwin 1988; Costagliola et al. 1989; Elliott & Hurst 1989; Bonomi et al. 1990; Mizuno et al. 1990). De Natale et al. (1988) investigated lens density in a normal population of 485 eyes of 266 patients aged between 7 and 86 years in which there was no clinical evidence of cataract by slit-lamp examination and the visual acuity was greater than or equal to 6/7.5. In subjects aged up to 65 years they found the relationship between OLM reading and age to be well approximated by a linear regression ($r=0.61$). When subjects over the age of 65 were included, the relationship was best approximated by a quadratic function; inter-individual variation was also larger in older subjects. Wegener & Hockwin (1988) also calculated a linear regression between OLM readings and age (subjects ranged from 25-75 years), although correlation coeffiecients were not stated and cataract patients were included in the sample. Costagliola et al. (1989) reported a linear regression between age and OLM reading ($r=0.85$) for 426 eyes of 213 subjects with clear media and good acuities, aged from 6-77 years. No differences were observed between the OLM readings of males and females of the same age, and a high degree of reproducibility was found when the reading was performed on two separate occasions in a sample of 100 eyes. Elliott & Hurst (1989) also found a high repeatability of OLM measurements; a correlation of 0.97 was calculated from two sets of readings and the coefficient of repeatability was very low ($c=0.55$). They found a high correlation between OLM reading and age in a sample of 83 normal white subjects; the data was fitted with a linear regression ($r=0.89$), but a second order polynomial produced a better correlation ($r=0.92$). Interestingly, dark-skinned subjects showed consistently lower readings than age-matched white subjects; this was attributed to increased absorbtion from more highly pigmented fundi. Tuft et al. (1990) also found a significant linear relationship between the OLM reading and patient age ($p<0.001$) although their sample included patients with lens opacities. The linear relationship between OLM reading and age was substantiated by Mizuno et al. (1990) who found a correlation of 0.71.

Generalisations regarding a cataractous sample are difficult since every cataract is a separate clinical entity (Siew et al. 1981a). From Figures 3.12. and 3.13. it is seen that forward light scatter increases with increasing back light scatter. The data however could not be fitted by linear or curvilinear functions.

For anterior cortical opacities a particular forward light scattering factor is associated with a wide range of OLM readings whilst at higher levels of back scatter there is increased spread of the forward scatter data. The former could be due to the higher resolution of back scatter measurements compared with forward scatter techniques but this explanation is unlikely since an adequate forward scatter resolution is present for other opacity types. Alternatively, the anterior cortical opacities in the sample may not produce marked forward scatter.

The standard deviations of the five back scatter measurements were noted to be higher for anterior opacities than for nuclear or for posterior opacities, although this difference was not statistically significant. The standard deviations of the contrast threshold determinations were similar for all opacity types, with and without glare light as shown in Table 3.1.

In cases of nuclear sclerosis and posterior subcapsular opacities, measurement of back scatter appears to underestimate the glare sensitivity experienced by the patient. This is in agreement with other studies showing different behaviour of the various morphological types of cataract (Baraldi et al. 1986, 1987; Klett et al. 1989). Indeed, Van den Berg (1989) found forward light scatter to be greatest in posterior subcapsular opacities. The underestimation of forward light scatter from measurements of back light scatter could result from the greater absorbtion characteristics of nuclear and posterior subcapsular opacities. Alternatively the data could imply that the OLM is less efficient at detecting light scattered from more posteriorally located opacities and the necessity of pupil dilation for OLM reading, as advocated by Wegener & Hockwin (1988), may be greater for this type of opacity. Posteriorally located opacities scatter light in an irregular fashion (i.e. at all angles) compared with nuclear opacities; since the OLM only detects light scattered from the central lens area at one particular angle this could also lead to an underestimation of backward intraocular light scatter. In addition, a light of wavelength 700nm is used. If intraocular light scattering is of the

Rayleigh type i.e. proportional to the fourth power of the wavelength, this would lead to a lower estimation of back scatter than if white light were used. It is however controversial as to whether intraocular light scattering is of the Rayleigh type, as proposed by Stiles (1929). Some authors consider intraocular light scattering to be wavelength independent (Vos 1963; Wooten & Geri 1987) whereas others consider there is increased scattering of shorter wavelengths, but not to the extent predicted by Rayleigh's equation (Le Grand 1937; Ivanoff 1947; Boettner & Wolter 1962). Indeed, Hemenger (1982) proposed that intraocular light scatter was inversely proportional to the square of the wavelength. The results are in agreement, however, with those of Elliott & Hurst (1989) who found little relationship between glare sensitivity and OLM reading in a small sample of cataract patients.

Wegener & Hockwin (1988) noted some patients with clearly visible cataracts by Scheimpflug photography who did not manifest an abnormal OLM reading. Conversely, Mizuno et al. (1990) found a correlation of 0.72 between the densitometric reading from Scheimpflug photography of the nuclear region and the OLM reading obtained through a dilated pupil, which could account for the discrepancy between their study and that of Wegener & Hockwin (1988). Mizuno et al. (1990) also found a correlation of 0.70 between protein particle size, determined with quasielastic light scattering, in noncataractous eyes and the OLM reading. The OLM reading decreased with increasing proportion of small protein particles of diameter less than 0.1μm.

Pupil size has a considerable effect on the visual capacity of cataract patients, especially those with posterior subcapsular cataracts (Rubin 1972; Elliott et al. 1989). It could be argued that change in pupil size due to the glare source would affect determination of the forward light scattering factor. Indeed, a miotic pupil has been shown to improve contrast sensitivity in elderly patients (Sloane et al. 1988) and thus an underestimation of the light scatter factor would result. Furthermore, Edwards et al. (1989) have also shown an increase in glare sensitivity and a depression of contrast sensitivity following pupil dilation in patients with cortical and nuclear opacities, although there was an improvement in contrast sensitivity following pupil dilation in patients with posterior subcapsular opacities. This latter factor would lead to an overestimation of the forward light scattering factor in cases of posterior

subcapsular opacities compared with other morphological types. The effect of pupil size on contrast sensitivity measurement was not considered significant in this study for the reasons outlined in Section 3.1.8.

Although a pupil diameter of at least 4mm was ensured for measurement of back scatter, the highest OLM reading obtained was 36.4. The readings seem relatively low considering recommended levels of abnormality (Wegener & Hockwin 1988). This could indicate the necessity of pupil dilation for OLM readings, even if the pupil size is greater than 4mm. Indeed, Wegener & Hockwin (1988) found differences of 2-4 units in normals and up to 57 units in cataract patients (average 6.2 units) following pupil dilation although the undilated pupil was greater than 4mm. Elliott & Hurst (1989) also found an average increase in OLM reading after pupil dilation of 3.8 units for pupils smaller than 4mm pre-dilation in normal subjects. For pupils larger than 4mm pre-dilation, no further increase in score occurred. These authors did not mention the effect of pupil dilation on the OLM score in patients with disturbed media. Clarke et al. (1990) found inconsistent results for pupils less than 4mm in diameter, and postulated that this was due to absorbtion of scattered light by the iris. Bonomi et al. (1990) also found pupil dilation to have a significant effect on the OLM reading of patients with opacities although there was little alteration in the reading obtained with clear lenses post-dilation. Natural pupils were used in this current study since perimetry would not normally be carried out with a dilated pupil; in addition, previous studies of the effects of intraocular light scatter, assessed with the OLM, on the visual field have not employed dilation. Since this study was carried out the OLM has been updated and it is now possible to correct the OLM reading to that which would be obtained with a standard pupil of 4mm diameter by means of a nomogram (Messmer et al. 1990).

The relationship between back scatter and the minimum angle of resolution is in agreement with previous studies supporting the concept that visual acuity is not related to back scattered light (Allen & Vos 1967; Sigelman et al. 1974). Elliott & Hurst (1989) however found a high correlation between OLM reading and Logmar visual acuity in 6 patients with pure nuclear sclerosis, although correlates with other types of cataract were poor. Tuft et al. (1990) also showed a significant correlation between OLM reading and decimal Snellen

distance acuity for all opacity types, although the correlation with near acuity was poor. Similarly, Bonomi et al. (1990) found the OLM reading to correlate well with visual acuity in cases of nuclear and mixed opacities but no correlation was found in eyes with cortical or posterior subcapsular opacities. Forward light scatter is not related to visual acuity since the effects of intraocular light scatter cannot be modelled by defocus (Hess & Garner 1977; Hess & Woo 1978).

Although De Natale & Flammer (1989) and Messmer et al. (1990) found good correlations between pre-operative OLM reading and the difference in the visual field index mean defect pre- and post-cataract extraction with intraocular implant, it should be noted that the post-operative mean sensitivity may have been underestimated in their study. Intraocular implants are considered to scatter at least twice as much as the healthy clear lens (Van der Heidje 1985; Witmer et al. 1989) and scatter from the implant could cause a diffuse depression of the field post-operatively, thus leading to an underestimate of the change in mean defect following surgery. This change in mean defect would still correlate well with the pre-operative measurement of back scatter since the back scatter measurement also provided an underestimate of the forward scatter and the resulting depression of the field caused by the cataract.

3.3.8. CONCLUSIONS

The results imply that a direct relationship between forward and backward intraocular light scatter (Allen & Vos 1967; Sigelman et al. 1984) cannot be assumed *in vivo*. Although good agreement has been found between both backward intraocular light scatter and perimetric attenuation (De Natale & Flammer 1989) and forward intraocular light scatter and perimetric attenuation (Wood et al. 1987a,b, 1989) this study indicates that measurement of back scatter would lead to an assumption of forward intraocular light scattering that is an underestimate of the true value, particularly in cases of posterior subcapsular opacities. The visual disability experienced by the patient and the extent of perimetric attenuation due to the media opacities would therefore be underestimated.

CHAPTER 4

THE EFFECT OF PRIOR PERIMETRIC EXPERIENCE ON THE VISUAL FIELD INDICES IN GLAUCOMA

4.1 INTRODUCTION

Various definitions of learning have been proposed by twentieth century theorists. For example:

> "If a response occurs in the presence of a stimulus, an association develops between this stimulus and this response" (Guthrie 1930, 1935)
>
> "If a response occurs in the presence of a stimulus, and this response is followed by some type of reinforcement, an increment in association occurs between that stimulus and that response" (Hull 1943)
>
> "If two events follow one another closely in time, the first event produces an expectation of the occurrence of the second event" (Tolman 1932, 1948)
>
> "A relatively permanent change in behaviour that occurs as a function of practice" (Saltz 1971)

Spence (1956) agreed that learning consists of the development of an association between a stimulus and a response, and he termed this classical conditioning.

The learning effect, when applied to visual psychophysical judgements, describes the improvement in sensitivity which follows repeated trials. For an industrial task (operating a capstan lathe) it has been demonstrated to be perceptual rather than motor in origin (Seymour 1956). There is considerable evidence that perceptual judgements can be improved through practice (for review see Gibson 1953) and perceptual learning has been defined as an increase in the ability to extract information from the environment as a result of experience (Gibson 1969). It has been suggested that most of the practice effects observed with the simple psychophysical judgements involved in differential and absolute threshold measurements are indications of a liberalized standard employed by the subject (McKee & Westheimer 1978) i.e. the observer changes his criterion for discrimination and reponse with practice, but perceptual learning does not occur. In the assessment of the difference between two estimates of the threshold within the same individual or between individuals, this difference can be attributed to a change in sensitivity only if it is assumed that the criterion has remained constant (Aspinall 1974). Only in the forced choice technique of the

method of constant stimuli can it be assumed that the observer chooses without regard to any criterion so that response effects are eliminated (Swets et al. 1961; Swets 1964). Indeed, if criterion-free measures are used thresholds remain remarkably stable (Green & Swets 1966).

4.2. EFFECTS OF PRACTICE ON VISUAL FUNCTION

Training has been found to enhance the performance of various visual tasks. Low (1946) reported an improvement in simple peripheral form acuity (identification of the break in a Landolt circle). Peripheral acuity was trained in 43 subjects through controlled practice, at seven eccentricities extending out to 60°, to a measure that was on average 334% of the starting score; Low estimated that 25 hours were required to develop this function to its optimum. Interestingly, subjects whose fixation was poor during training showed little improvement. Low regarded the peripheral retina as an unpracticed sensory area, and peripheral perception as intermittent and subject to extensive fluctuations in efficiency. Weymouth (1958) showed resolution for 4-position Landolt C's to decline with retinal eccentricity at the rate of 1.77 min/deg for untrained subjects which compared with a rate of 0.37 min/deg for subjects with experience of peripheral acuity measures. Saugstad & Lie (1964) demonstrated similar improvements in peripheral acuity for Landolt rings. They interpreted this to be due to the subject learning to shift his maximum attention from the central visual field to the periphery while maintaining fixation. Interestingly, Webster & Haslerud (1964) examined the effects of competition between tasks at the periphery and centre of attention and showed peripheral perception to be adversely affected by a simple foveal counting task. Subjects were required to respond to peripheral lights situated between 70°-100° eccentricity in the horizontal meridian while counting the number of lights which flashed centrally. The foveal counting task had a significantly detrimental effect on the both the number of responses ($p<0.05$) and the reaction time ($p<0.01$) to peripheral stimuli. Similarly, Abernathy & Leibowitz (1971) noted that when central and peripheral stimuli compete for attention, priority is given initially to the central task although they found practice over 5 sessions to reduce the difference in response to both stimuli.

Wilcox (1936) attributed the improvement in two-bar central acuity he found with practice to

an adoption by the subject of a finer criterion for "doubleness". McKee & Westheimer (1978) also studied the effects of training on a hyperacuity task (vernier offset detection) in which feedback was provided by an error signal to an incorrect response. They found a 40% increase in sensitivity with training which reached a plateau over 2000-2500 responses and considered this improvement to represent a "fine-tuning" of the neural mechanisms involved.

Haider & Dixon (1961) showed training effects during the first session of recording of a visual differential threshold to result in a change in criterion for judgement for the second session. They found training effects to be counterbalanced by fatigue during the first recording resulting in a stable threshold, but in subsequent sessions the threshold increased as a result of fatigue.

Verriest (1963) found no significant diferences in the Farnsworth-Munsell 100-hue colour vision test score between naive and experienced subjects although acknowledged a significant effect of prior experience on test scores for monocular viewing in a later normative study (Verriest et al. 1982). Similarly, Aspinall (1974) found an experienced normal group of subjects to produce a significantly lower mean score with a smaller standard deviation than a naive comparison group. This is in agreement with the recent study of Breton et al. (1988) who found a significant improvement in performance extending over at least four test repetitions for a group of 26 normal naive subjects. Interestingly, those subjects who exhibited the lowest initial test scores showed the greatest improvements with serial practice.

Wittenberg et al. (1969) reported a greater improvement in foveal stereoacuity in a group of subjects who had received training than in an untrained control group but did not describe the changes in threshold which occurred during the training period. Both the method of adjustment and method of constant stimuli were used; the former method involved manipulation of a movable object to make it lie in the same fronto-parallel plane as a reference object. In the method of constant stimuli two or more objects, having a fixed spatial displacement, were compared and one of them judged to be closer or further away than the other. The method of constant stimuli does not involve an associated manipulative task and

thus only this method shows the true improvement of visual performance. Improvement for the method of adjustment could be due to integration of visual and manipulative skills. Peripheral stereoacuity was also found to improve with practice by Fendick & Westheimer (1983) using the method of constant stimuli with feedback; thresholds improved by 60-80% over the first 3000-4000 responses at eccentricities of 2.5° and 5° associated with a concomitant decrease in the standard error of the measurements. Greater improvements were noted for peripheral than for central thresholds.

This greater capacity for improvement in the peripheral compared with central vision was also reported by Johnson & Leibowitz (1974) for peripheral motion thresholds. Subjects attended four consecutive daily sessions, each lasting 1-1.5 hours. Results indicated that practice had little effect on foveal motion thresholds, but greatly improved the detection of movement beyond 20° eccentricity. The major effect of practice was achieved by the third session, beyond which little further improvement occurred; this improvement in performance through training was sustained over three months. The amount of practice required for optimal performance in detection of peripheral motion was less than that required for peripheral acuity (25 sessions according to Low, 1946 and 13 sessions as reported by Saugstad & Lie, 1964). The addition of feedback improved peripheral motion detection in the presence of a peripheral refractive error, however had little effect when the peripheral refraction was corrected, which suggested that feedback served to improve the interpretation of a degraded image.

Mayer (1983) found evidence that the adult pattern of anisotropic contrast sensitivity could be altered through visual experience. By practising the detection of a diagonal grating (10 c/deg) contrast sensitivity could be improved so it became equal to that for horizontal or vertical gratings, although there was no improvement for the cardinal orientations. Practice consisted of 3000 yes/no signal detection trials. This is in agreement with Kelly & Tomlinson (1987) who reported an absence of learning effects over a 5-day training period in the measurement of contrast sensitivity to vertical stationary sinusiodal gratings. However, De Valois (1977) found improvements in contrast sensitivity at all spatial frequencies for three functions measured at 6 month intervals. Improvements were greatest for spatial frequencies

up to 4 c/deg. Additionally, Wildberger & Robert (1988) demonstrated better scores during the second run of the Arden contrast sensitivity test in both normal controls and patients with optic neuropathy, which they attributed to a learning effect.

Interestingly, Schenkein (1987) used auditory biofeedback techniques to make sub-cortical levels of visual processing conscious in the blind field of hemianopic patients. Training, by stimulation of the defective hemi-field with bright flashing lights (400asb; 3-6° in size), improved localization in the "blind" field and this was accompanied by patient reports of an increased visual field which was demonstrable on the Humphrey Field Analyser.

Manny et al. (1988) have investigated the effects of practice on contour interaction. This is a form of lateral masking where the disciminability of a test target is reduced when the target is surrounded by adjacent contours. The task was to correctly identify the orientation of the gap in a Landolt C with a bar positioned at varying angular subtenses from the optotype. Following practice consisting of 200 trials with feedback for each of 6 test stimuli, 6 of the 8 observers failed to demonstrate contour interaction although all observers demonstrated contour interaction prior to practice with feedback.

4.3. LEARNING EFFECTS IN CLINICAL PERIMETRY

The learning effect, when applied to perimetry, is one component of the intra-individual scatter observed in perimetric sensitivity (Aulhorn & Harms 1967; Greve 1973; Flammer et al. 1983a). The learning effect refers to an improvement in the visual field i.e. an increase in sensitivity with repeated testing which is unexplained by external factors e.g. commencement of therapy. This greater consistency of response corresponds to a steepening of the frequency-of-seeing curve (Greve 1973). The learning effect is not considered a component of the long-term fluctuation; the latter is defined as the variation in measurement over time, when the variation due to repeated measurements at a given time (the short-term fluctuation) has been removed (Bebie et al. 1976b; Flammer et al. 1984a). Frisen (1989) has attributed perimetric learning effects to changes in the subject's criterion i.e. the judgement of what defines a meaningful stimulus, and he suggests that criterion differences are a major cause of inter-individual variability. It seems that the willingness of the

patient to give a "seen" reaction to a barely percepible impression is subject to manipulation and can vary from one examination to another.

4.3.1. Manual perimetry

The effects of training in normal subjects have been documented in manual static perimetry (Aulhorn & Harms 1967, 1972). During the course of twenty serial examinations on one day, eccentricity-independent increases of up to one log unit in sensitivity occurred and the variability in threshold decreased; these improvements were maintained over a period of seven days. Dubois-Poulson & Magis (1957) using the Goldmann perimeter and static perimetry found an average spatial summation coefficient of 0.962 for five trained subjects and 0.818 for sixteen untrained subjects but did not mention which retinal regions were studied. Using Goldmann kinetic perimetry, McCluskey et al. (1986) noted an 82% increase in the I2e isopter area in one subject following drug-induced miosis which they attributed to a learning curve.

4.3.2. Automated perimetry in normal subjects

Parrish et al. (1984) reported a high variability in a group of untrained subjects examined with the Perimetron automated perimeter, and Rabineau et al. (1985) observed significantly lower fluctuations in a normal group of subjects who were familiar with the Octopus automated perimeter than in those unused to it, interpreting this as a learning effect. Kosoko et al. (1986a) noted no improvement in sensitivity through repeated testing using the Humphrey field analyser in a normal control group, although in another study (Kosoko et al. 1986b) found a high false positive rate (12%) on the first examination.

The hill of vision has been reported to depress and steepen with advancing age (Jaffe et al. 1986; Heijl et al. 1987a). Heijl (1987) states that the degree of perimetric experience influences these changes, the hill of vision steepening less with age in trained individuals.

In the detection of a pathological field, threshold results are frequently compared with age-matched normative data. In the establishment of a normal model, the empirically determined threshold values will depend on the degree of perimetric experience of the

population used. Brenton & Phelps (1986) used inexperienced novice subjects to construct a normal database with which to compare the results of equally inexperienced patients. In the clinical situation however, fields are repeated, and patients become experienced. Ideally therefore the normal database should be formed from subjects with similar perimetric experience to the patients (Heijl 1987). If the model were based on inexperienced subjects, the limits of normality would be too wide, resulting in a low detection rate of defects. If the model were based on "supernormal" observers, a low specificity would result i.e. a high number of false positives.

An eccentricity dependent learning effect has been quantified in normals by Wood et al. (1987c) using Octopus program 21 to cover the full field. The learning effect, manifested as an increase in sensitivity was greatest in the superior field at eccentricities beyond 30° and in some cases amounted to a 15dB increase at 60°. RMS fluctuations also decreased with seria examination and three types of learning curve were identified: 1) subjects who exhibited an increase in sensitivity from the first to second examination which then reached a plateau over subsequent examinations, 2) subjects in whom the sensitivity gradually increased over each of the five examinations and 3) subjects who exhibited no obvious improvement in sensitivity.

The eccentricity dependency of the learning effect has been confirmed in normals by Heijl (1987) and Heijl et al. (1987b, 1989) who found increases in sensitivity to be greater in mid-peripheral areas than centrally. Untrained fields showed a characteristic concentric contraction, evident on the Humphrey Field Analyser grey-scale printout, which disappeared with repeated testing. Heijl et al. (1989) found a statistically significant average increment of 1.3dB in mean sensitivity ($p<0.001$) for 74 normal subjects examined at two and four months after the initial examination with Humphrey program 30-2. The number of points with sensitivity more than 5dB below the age-corrected normal value also decreased considerably from 12.5% in the first examination to 5.2% at the sixth examination. Training also resulted in smaller variation among subjects; the SD of the average sensitivity deviations decreased from 3.2dB to 1.8dB and the short-term fluctuation lessened. Training influenced threshold values to a greater extent in the outer portion of the central field than paracentrally. The mean

improvement of sensitivity at 21°-27° exceeded that at 3°-9° by 1.1dB, and this was statistically significant ($p<0.001$). The hill of vision also became "smoother" with practice, the corrected pattern standard deviation decreasing by 0.62dB. A smaller group of subjects (n=10) were each tested ten times with an interval of one week between each test, and the improvements in this group were found to occur during the first two or three examinations. The influence of perimetric training was evenly distributed among subjects regardless of age, however those subjects who had the lowest initial sensitivity were found to improve the most through practice.

Martin-Boglind & Wanger (1989) reported a learning effect in high pass resolution perimetry in 10 normal subjects, who had one eye examined on six occasions on days 1, 3, 6, 14, 21 and 44. The mean resolution threshold improved between the first and second examinations by 0.2dB and by 0.6dB between the first and last examinations.

Autzen & Work (1990), using Octopus program 32, quantified the effects of learning on mean sensitivity and short-term fluctuation in 33 normal subjects. Both eyes of each subject were tested twice, and the examinations separated by a period of 3 to 34 days. At each session the right eye was examined first, although data from each eye was considered independently in the analysis. Statistically significant improvements in mean sensitivity were found from the first to the second examination for the whole field, single quadrants and 3 eccentric zones (0-10°, 10-20° and 20-30°) except for the upper temporal zone. The learning effect also showed a positive correlation with age on mean sensitivity of the whole field, the lower quadrants and the eccentric zones out to 20°. The short-term fluctuation also demonstrated a significant learning effect although no correlation with age could be demonstrated.

4.3.3. Automated perimetry in glaucoma patients

Schmied (1980) noted a non-significant improvement in repeated automated examinations on the Octopus automated perimeter, but there were no changes from significant to non-significant field loss.

The learning effect was first quantified in glaucoma patients, using automated static perimetry, by Gloor et al. (1980a,b, 1981). A statistically significant improvement of up to 2dB per point within the central 30° from first to second examinations was observed when the results from the Octopus automated perimeter program 31 were analysed using program Delta, which performs a statistical t-test to compare visual field data from two examinations or two groups of examinations. No further significant improvements were found from second to third examination. They considered therefore that changes of more than 2dB, especially if several adjacent points were affected, represented a significant loss once the learning effect was over (Gloor et al. 1980b). Conversely, Gramer et al. (1986), using the Octopus automated perimeter programs 31 and 33, reported no significant learning effects to be apparent in mean sensitivity, in total loss or in the number of disturbed points when consecutive fields were analysed with program Delta. A learning effect was apparent in the short-term fluctuation which decreased from 3dB to 1dB between the first and second examinations and remained constant thereafter.

Werner et al. (1988) studied the first four automated field examinations (Octopus program 32) of 20 clinically stable glaucoma patients with field loss confirmed from one previous Goldmann examination. Parameters analysed for the presence of a learning effect were mean sensitivity (globally and at 0-10°, 10-20° and 20-30° from fixation), number of disturbed test locations, total loss and short-term fluctuation. The only parameter to show a statistically significant improvement was the short-term fluctuation as measured by the RMS value. However only one eye of each patient, chosen at random, was used in the analysis; it was not stated whether this was the first or second eye examined, and the time interval between examinations was not specified. In a larger sample however, of 60 ocular hypertensive and early glaucoma patients with minimal or no field defect, mean sensitivity between 20° and 30° did show a significant increase from first to second examination (Adelson et al. 1988). In a further retrospective study on the effects of learning in 29 glaucoma suspect patients Werner et al. (1990b) found significant ($p=0.012$) improvements in mean sensitivity due to learning to occur only for test locations outside 20° of fixation using Octopus program 32. They also noted significant ($p<0.01$) reductions in the short-term fluctuation, total loss and number of disturbed points. These significant changes occurred between the first and

second examinations, and were more marked in patients with greater field loss. They concluded that it was not necessary to obtain more than two 'baseline' examinations unless a patient demonstrated unusually high short-term fluctuations, or a visual field inconsistent with their clinical examination.

Katz & Sommer (1988) found the number of false positive and negative responses and fixation losses to be higher in glaucoma patients than in normal subjects, and Niles & Trope (1988) noted that these parameters did not improve with practice in glaucoma patients, despite a concomitant decrease in mean defect from first to third examinations. The recent study of Bickler-Bluth et al. (1989) noted that 35% of ocular hypertensive patients when first examined showed low reliability fields, as defined by the Humphrey field analyser criteria of fixation losses greater than 20% and false positive and false negative responses greater 30% but only 25% of these patients showed low reliability at follow-up after 6 and 12 months. No relationship was observed between reliability and the percentage of statistically significant field defects ($p<0.05$), as defined by the visual field indices mean defect and corrected pattern standard deviation derived from Statpac analysis. A certain reliability of patient response, as defined previously, exists in the normal database contained within the Statpac software. If a patient shows a low reliability of response, the comparison of their results with Statpac normative data may be questionable.

A learning effect has also been demonstrated by Drance et al. (1989) in high pass resolution perimetry in normals (n=15), glaucoma suspects (n=10) and glaucoma patients (n=12). A significant mean improvement of 0.297dB ($p<0.005$) occured mainly between the first and second examinations, which was greatest in the glaucoma group, and greater in patients who showed the lowest initial resolution threshold.

4.4. COMPENSATION FOR LEARNING EFFECTS

Attempts have been made to minimise learning effects in serial automated perimetric studies by allowing patients one (Flammer et al. 1983a; Flammer et al. 1984b; Brenton et al. 1986; Heijl et al.1987a), or two (Wilensky & Joondeph 1984) "practice" sessions, or by using patients who were already experienced in automated perimetry (Gloor et al. 1980b). Katz &

Sommer (1987) considered a learning effect unlikely in a group of normal subjects since these individuals had undergone previous manual perimetry and the interval between manual and automated examinations was over three months. Keltner et al. (1985) employed a latin square design in a comparison study of perimeters to control for any learning, practice or other effects resulting from the presentation order of the various perimeters and Drance et al. (1987) averaged the first two examinations.

Other authors have considered the learning effect to be counterbalanced by fatigue arising from the examination itself (Brenton et al. 1986; Katz & Sommer 1986; Kosoko et al. 1986a) and Jaffe et al. (1986) felt that this was a justifiable assumption in normals. Thresholds and fluctuations are relatively stable in normal subjects over the typical time span of an automated field examination (Rabineau et al. 1985); they increase however during the course of the examination in glaucoma patients, who appear to "fatigue" easily, the greatest changes occurring at the borders of scotomata (Heijl 1977b; Heijl & Drance 1983). It is important therefore to note which eye is tested first. A fatigue effect will be revealed as a decrease in sensitivity and an increase in the number of false negative and positive responses and fixation losses.

Frisen (1989) suggested a method that could be used to compensate for practice effects in serial perimetry by estimating individual visibility criteria. Criteria measurements are currently not possible in ordinary perimetry, however Frisen (1989) also suggested that different visibility criteria may be estimated indirectly using high-pass resolution perimetry. Since the minimum angle of resolution (MAR) is proportional to local ganglion cell separations, and ganglion cell separations are constant in normal eyes, the magnitude of the proportionality factor (the regression coefficient of MAR plotted against ganglion cell separation) is representative of the subjects criterion setting. This method is however limited in its application to abnormal subjects since it cannot differentiate threshold elevations associated with a high criterion from those caused by disease of the visual system; furthermore, ganglion cell separations are frequently altered in disease.

4.5. AIM OF THE STUDY

Previous serial studies on the learning effect in glaucoma patients are retrospective in nature, and results based on data obtained in the clinical situation. Inter-examination periods are not specified and are not common throughout the samples which brings into question conclusions drawn from group summary statistics. Furthermore, such studies do not specify the order of eyes examined, thus masking any inter-ocular transfer of the learning effect, and do not consider the effects of fatigue. The amount of previous exposure to manual perimetry is seldom stated, and the stability of the glaucoma between examinations must always be in doubt. The depth and type of field loss in the sample might also be expected to influence the extent of any learning effect.

Investigation of the learning effect in patients with ocular disease would provide useful clinical information pertaining to the analysis of serial field examinations. It would also indicate the source of the learning effect. It is hypothesised that, if the learning effect were peripheral (retinal) it might not be as apparent in glaucoma patients compared with normal subjects; if the effect were central (cortical), or due to an alteration in the criterion adopted for stimulus detection, similar learning effects might be found in glaucoma patients and normal subjects.

The choice of inter-test periods over which a learning effect can be studied is limitless. A short inter-examination period was chosen in this study for two reasons. Firstly, since it has been suggested that two or three baseline fields performed within a short time period may enhance the recognition of change (Hoskins et al. 1988), the role of learning over such a period should be identified. Secondly, some idea of the potential for improvement over longer inter-test periods may be gained from the relatively optimum conditions of successive daily examinations.

The short-term aim of this study was to quantify the learning effect in serial perimetry of glaucomatous patients, with particular reference to any eccentricity dependency, using a prospective experimental design with control of inter-test interval and sequence of eye tested.

The long-term aim was to examine retention of the learning effect over the typical time-periods as might be encountered between hospital out-patient visits, and thus to investigate the hypothesis of Hoskins et al. (1988) that two or three baseline fields performed within a short time period may enhance the recognition of change. Additionally, the relative contributions of the disease process and regression ("forgetting") of the learned skill to visual field change were to be evaluated.

4.6. MATERIALS AND METHODS

4.6.1. Short-term

The sample comprised 25 patients with suspected glaucoma (13 male and 12 female; mean age 62.8 years, SD 11.3 years) referred by optometrists or general practitioners to the Birmingham and Midland Eye Hospital. Five patients had undergone one previous Goldmann kinetic examination, the remainder were naive to all forms of quantitative perimetry, and no patients had previous experience of automated perimetry. Exclusion criteria comprised intraocular pressures greater than 30mm Hg, congenital or secondary glaucomas, pseudo-exfoliation and pigment dispersion, VA less than 6/12, previous intra-ocular surgery, diabetes or other systemic conditions with marked ocular complications, macula degeneration or other retinal disorders, contact lens wearers, those with abnormal anterior segments and those receiving CNS medication. Patients had no other ocular abnormality, open angles and clear media. Informed consent was obtained from all patients who were unaware as to the purpose of the study.

All patients underwent a full ophthalmological examination prior to automated perimetry consisting of ophthalmoscopic disc assessment, gonioscopy, Goldmann tonometry (average of three measurements), slit-lamp assessment of the anterior chamber and blood pressure measurement. Patients were provisionally entered into a diagnostic category and therapy of 0.5% Guttae Timolol b.d. initiated where the intraocular pressure was greater than or equal to 26mm Hg. The diagnostic categories were as follows:

Diagnostic category	Intra-ocular pressure	Disc appearance
Primary open-angle glaucoma (POAG)	≥ 21 to ≤30	Pathologically cupped
Low tension glaucoma (LTG)	≤21	Pathologically cupped
Ocular hypertension (OH)	≥ 21 to ≤30	Normal

Three weeks after ophthalmological assesssment, patients were examined with the Humphrey Field Analyser 630 and a full-threshold program customised for the study, using stimulus size Goldmann III (0.431°) and duration 200 msec. The program examined 60 points across the field with an inter-stimulus separation of 12°, as shown in Figure 4.1. The program included additional points in the superior periphery of the field, and extended to an eccentricity of 48° nasally and inferiorally, and 54° superiorally and temporally. It comprised points within 30° eccentricity and 36 points between 30° and 50° eccentricity. The time taken to complete the program was in the order of 14 minutes.

Patients were examined on three consecutive days, and to assess retention of the learning effect, after a break of 12 days. All examinations were carried out at the same time of day, and IOP was measured (Goldmann tonometry) after each examination. The right eye was always examined first to evaluate inter-ocular transfer of the learning effect. Patients were pre-adapted to the bowl luminance of 31.5asb for 5 minutes, natural pupils were used with the appropriate near refractive correction and fixation constantly monitored. All patients were given the same instruction, and the examinations controlled by the same perimetrist. After completion of the last custom field, patients were given a rest of 30 minutes and the central fields were examined using the standard 30-2 central thresholding program with Statpac single field analysis. The depth and type of field loss in the sample, derived from program 30-2 is illustrated in Figure 4.2. after the classification of Caprioli & Sears (1987). Corrected pattern standard deviation (CPSD) was used as the index of focal loss instead of loss variance, as the latter is not corrected for the short-term fluctuation.

Ophthalmological examination was repeated one week later and the provisional diagnosis confirmed from the various investigatory techniques and the results of program 30-2. After visual field examination a further diagnostic category, that of glaucoma suspect (GS), was

defined since not all patients fitted the categories described previously. It was defined as having one or more of the following signs: a borderline disc appearance, borderline intraocular pressure and borderline visual field, although this latter factor in isolation did not qualify.

Results were analysed in terms of the visual field indices as described by Flammer et al. (1985) and in the absence of the weighting function for the variation in short-term fluctuation with increase in peripheral angle used by Heijl et al. (1987b) were calculated for the custom program using the formulae of Flammer (1986). Data for the full field was considered in terms of the visual field indices mean sensitivity, short-term fluctuation and also the reliability factors: the percentage of fixation losses, false positive and negative responses and total number of stimuli presented. For the central (out to 30° eccentricity) field the indices mean sensitivity, mean defect and loss variance were calculated. For the peripheral (30°-55° eccentricity) field the index mean sensitivity was calculated for the whole area and the superior and inferior hemi-fields. The homogeneous long-term fluctuation was calculated for each patient from the equation of Bebie et al. (1976b). Age-matched normative data required to calculate the indices mean defect and loss variance was obtained from program 30-1 which has common stimulus locations in the central area. The first field was excluded in calculation of the long-term fluctuation, since the learning effect is not considered one of the components of the long-term fluctuation (Flammer et al. 1983a). Indeed, Bebie et al. (1976b) found values of the long-term fluctuation in untrained glaucoma patients to be surprisingly high. Eight double determinations within 42° eccentricity, four of which were within 30° eccentricity, were used to calculate the short-term fluctuation as recommended in the Octopus Sargon program user's manual (1980). It has been shown that calculation of the short-term fluctuation from ten double determinations gives the result to an accuracy of +/-25% (Bebie et al. 1976).

Statistical analysis for the first three successive daily examinations was undertaken using the Friedmann two-way analysis of variance by ranks and the Wilcoxon signed rank test for matched pairs was used where the Friedmann analysis of variance indicated a significant change. The Wilcoxon test was also used to examine retention effects from the third to

fifteenth day.

4.6.2. Long-term

The 22 patients who had attended for the fourth short-term examination were contacted by letter and requested to attend for another three examinations before their next hospital out-patient visit. The recall period varied between patients as a function of patient compliance and the severity of the condition. Patients were examined with the Humphrey Field Analyser 630 using the same custom program and protocol on two consecutive days. The right eye was again examined first, and visual field indices and reliability parameters calculated for the custom program as described in Section 4.6.1. One week later, patients were examined using the standard 30-2 central thresholding program. Ophthalmological examination was repeated approximately one month later, and the diagnosis reviewed from the various investigatory techniques and the results of program 30-2. Results from the long-term follow-up were evaluated using the Wilcoxon signed-rank test to compare results from the first long-term follow-up examination with those of the last examination several months previously, and to compare the first with the second long-term follow-up examinations.

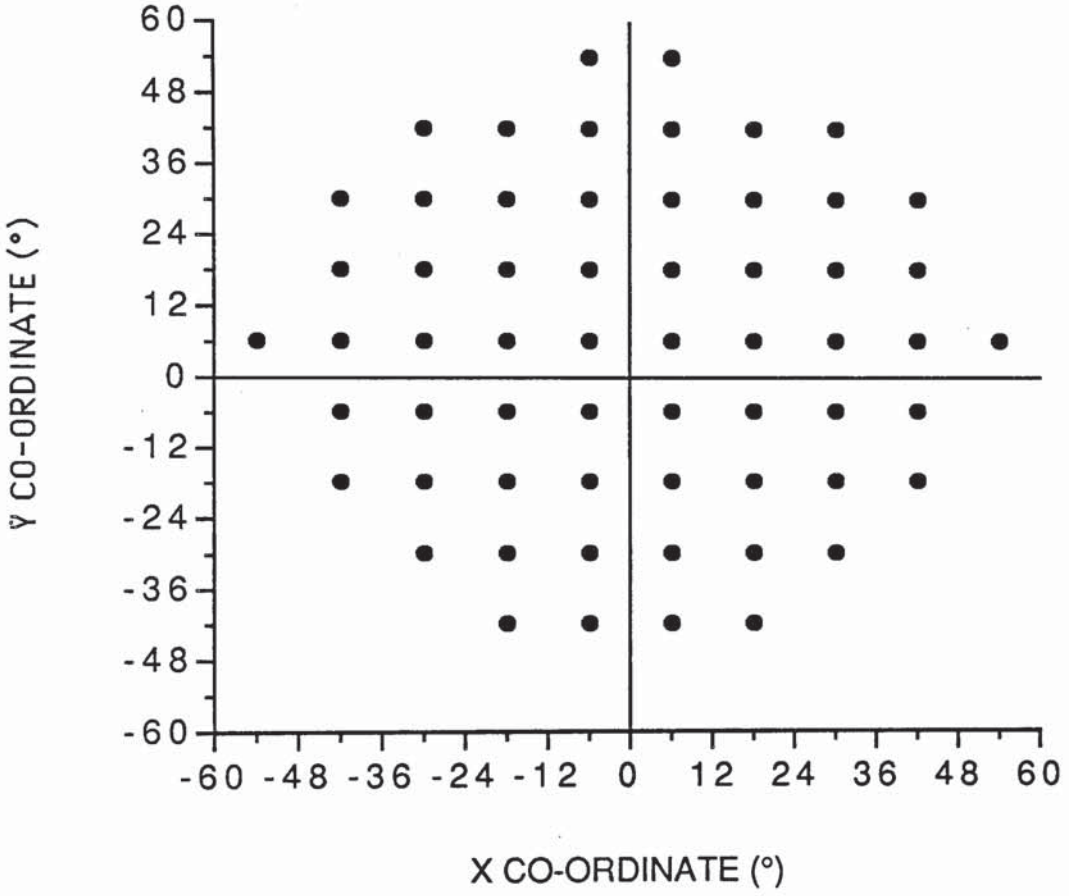


Figure 4.1. Showing stimulus locations of custom program. The program consisted of 60 points with an inter-stimulus separation of 12° and included additional points in the superior periphery, extending to an eccentricity of 48° nasally and inferiorally and 54° superiorally and temporally. It comprised 16 points within 30° eccentricity, and 36 points between 30°-50° eccentricity.

4.7. RESULTS

4.7.1. Short-term

Three patients failed to attend for the final examination on the fifteenth day, however their results are included in the analysis of variance for the first three examinations. The diagnoses of the 22 patients who completed the study comprised 6 ocular hypertensives (2 of whom were receiving therapy of G. Timolol 0.5% bd), 12 glaucoma suspects (2 receiving therapy) and 4 primary open angle glaucoma patients (all on therapy). The type and degree of field loss, illustrated in Figure 4.2. after the classification of Caprioli & Sears (1987), was primarily of the diffuse type. Mean pupil size at the first examination for the 22 patients who completed the study was right 4.5 mm (SD 0.86 mm) and left 4.6 mm (SD 0.84 mm). Pupil size was not significantly different between the treated and untreated groups for either eye.

Significant changes were found in the indices over the course of the first three sucessive daily examinations, as shown in the Tables 4.1.a and 4.1.b. The results of the Wilcoxon signed-rank test for matched pairs are shown in Table 4.2. of median visual field index against examination sequence (days) for 25 glaucomatous suspects. A similar analysis of the reliability parameters is shown in Table 4.3.

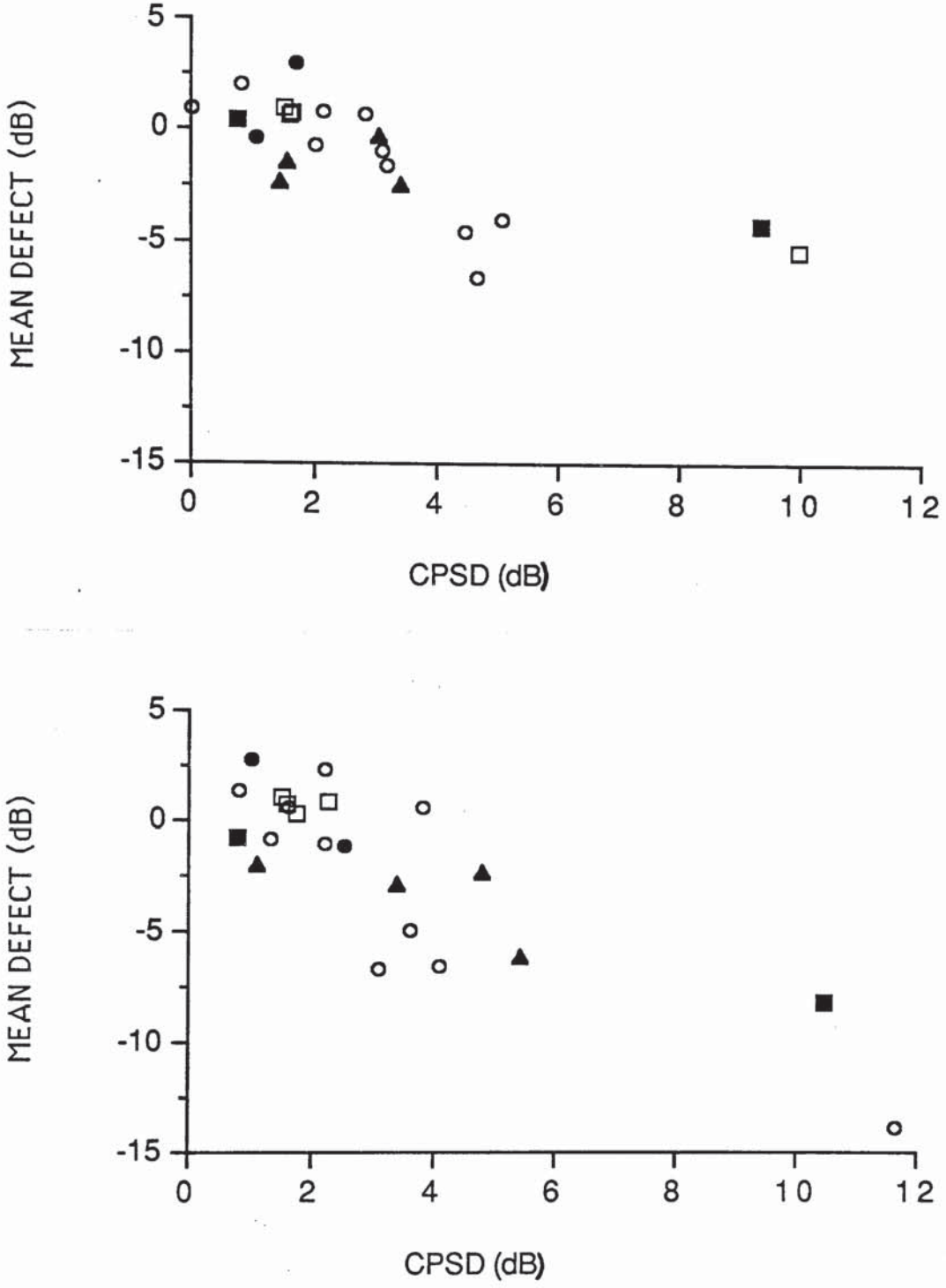


Figure 4.2. Illustrating the depth and type of field loss, derived from Humphrey program 30-2 at the fourth examination, after the classification of Caprioli & Sears (1987) showing mean deviation (diffuse loss) as a function of corrected pattern standard deviation (focal loss). Field loss is seen to be primarily of the diffuse type. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes.

Visual Field Index	Eye	df	Chi-squared	Significance level
Global MS	R	2	15.36	$p < 0.001$
Central MS	R	2	15.92	$p < 0.001$
	L	2	8.14	$p < 0.025$
Peripheral MS	R	2	12.48	$p < 0.01$
Superior peripheral MS	R	2	8.96	$p < 0.025$
Inferior peripheral MS	R	2	13.00	$p < 0.01$

Table 4.1.a. Showing the visual field indices which increased significantly over the first three successive daily examinations (Friedmann two-way analysis of variance by ranks)

Visual Field Index	Eye	df	Chi-squared	Significance level
Global SF	R	2	16.87	$p < 0.001$
	L	2	6.73	$p < 0.05$
Central Mean Defect	R	2	15.92	$p < 0.001$
	L	2	8.14	$p < 0.025$
No. stimuli presented	R	2	16.91	$p < 0.001$
False -ve responses	R	2	7.80	$p < 0.05$

Table 4.1.b. Showing the visual field indices which decreased significantly over the first three successive daily examinations (Friedmann two-way analysis of variance by ranks).

INDEX		DAY			
		1	2	3	15
Global MS (dB)	R	18.02 (18.65;0.81)	21.20*** (20.98;0.75)	21.84 (21.21;0.78)	21.68** (22.1;0.64)
	L	19.94 (19.5;0.70)	20.73 (20.32;0.93)	20.83 (19.96;0.93)	22.87*** (21.18;1.09)
Central MS (dB)	R	26.81 (25.54;0.87)	27.69** (27.57;0.75)	28.44* (28.21;0.62)	28.22 (28.58;0.46)
	L	26.63 (26.46;0.56)	28.19 (26.95;0.83)	27.63 (26.81;0.83)	28.35** (27.65;0.87)
Peripheral MS (dB)	R	16.47 (15.8;0.87)	18.38*** (18.39;0.83)	18.92 (18.21;0.90)	19.54 (18.72;1.03)
	L	17.04 (16.61;0.81)	18.39 (17.38;1.05)	17.78 (17.07;1.00)	20.41*** (18.76;1.14)
Superior peripheral MS MS (dB)	R	13.44 (13.30;0.94)	15.72*** (15.91;0.98)	15.39 (15.67;1.06)	17.04* (17.06;0.92)
	L	14.67 (14.64;0.93)	15.31 (15.32;1.11)	15.22 (14.74;1.01)	18.27** (16.66;1.32)
Inferior peripheral MS (dB)	R	18.25 (18.33;0.93)	22.11*** (20.88;0.82)	21.89 (20.87;0.89)	22.17* (21.97;0.80)
	L	19.33 (18.68;0.87)	19.94 (19.48;1.10)	19.94 (19.31;1.13)	22.22*** (20.88;1.08)
Central MD (dB)	R	3.13 (4.55;0.85)	2.00** (2.53;0.73)	1.50* (1.81;0.60)	1.66 (1.47;0.40)
	L	3.88 (3.64;0.56)	3.00 (3.15;0.82)	2.18 (3.29;0.84)	1.72** (2.43;0.90)
Central LV (dB squared)	R	9.18 (15.65;3.40)	6.16 (11.06;2.52)	5.70 (9.24;2.21)	7.42 (11.01;2.36)
	L	7.20 (13.82;3.89)	6.65 (13.25;3.76)	6.97 (11.80;2.54)	5.87* (10.67;2.83)

Table 4.2. Median visual field index against examination sequence (days) for 25 patients. The significance level for comparison of a given examination with the previous examination are indicated in superscript. *** indicates a probability of $p<0.002$, ** a probability of $p<0.02$ and * a probability of $p<0.05$. The accompanying means and standard errors are given in parentheses. Note that the analysis for day 15 is based on 22 patients.

INDEX		DAY			
		1	2	3	15
Global SF (dB)	R	2.40 (2.54;0.21)	1.80*** (1.83;0.13)	1.58 (1.69;0.14)	1.54 (1.80;0.16)
	L	2.06 (2.21;0.19)	1.66 (2.02;0.21)	1.66 (1.83;0.16)	1.32 (1.65;0.17)
No. of stimuli	R	452.0 (451.9;10.5)	407.0*** (413.6;6.4)	405.0 (409.9;7.9)	401.0 (413.6;10.3)
	L	423.0 (428.8;8.8)	415.0 (410.4;7.7)	408.0 (407.2;7.0)	394.0 (400.1;6.9)
False negative responses (%)	R	16.7 (17.2;3.1)	5.6* (8.6;2.2)	0.0 (8.1;2.8)	0.0 (7.1;2.3)
	L	14.3 (15.6;2.8)	8.3 (12.5;2.9)	10.0 (12.5;3.2)	4.15 (11.9;3.5)
False positive responses (%)	R	0.0 (1.8;0.7)	0.0 (3.8;1.8)	0.0 (1.8;0.9)	0.0* (5.7;1.9)
	L	0.0 (1.4;0.6)	0.0 (3.3;1.7)	0.0 (4.2;1.5)	0.0 (6.2;2.8)
Fixation losses (%)	R	9.1 (14.9;2.9)	9.1 (16.1;3.4)	10.0 (15.2;3.6)	14.0 (17.0;4.3)
	L	8.7 (12.1;2.6)	4.5 (12.6;3.8)	13.6 (16.6;2.6)	11.9 (17.1;3.8)

Table 4.3. Median reliability parameters against examination sequence (days) for 25 patients. The significance level for comparison of a given examination with the previous examination are indicated in superscript. *** indicates a probability of $p<0.002$, ** a probability of $p<0.02$ and * a probability of $p<0.05$. The accompanying means and standard errors are given in parentheses. Note that the analysis for day 15 is based on 22 patients.

Statistically significant changes occurred in the absolute values of the visual field indices and parameters over the course of the four examinations. For the right eyes global, central and peripheral mean sensitivity all increased, and central mean defect, global short-term fluctuation, the number of stimuli presented and the percentage of false negative responses all decreased. These changes occurred mainly from the first to second examinations, although there were further improvements in the global and peripheral mean sensitivity after a break of 12 days. For the left eyes statistically significant increases occurred in global, central and peripheral mean sensitivity and decreases were seen in central mean defect and central loss variance, however these changes were only observed between the third and fourth examinations. No significant changes occurred in the number of fixation losses.

The improvement in global mean sensitivity from first to second examinations was greater than the long-term fluctuation in 11/22 right eyes and 7/22 left eyes. The improvement in global mean sensitivity from third to fourth examinations was greater than the long-term fluctuation in 8/22 right eyes and 8/22 left eyes however these differences were not statistically significant.

Figures 4.3. to 4.6. show the proportionate increases in global, central and peripheral mean sensitivity, and decreases in short-term fluctuation from the first to fourth examinations, as a function of the initial values at the first examination. For the right eyes it is seen that the greatest improvements in global, central and peripheral sensitivity occurred in those patients in whom the sensitivity was lowest at the first examination. The greatest decreases in short-term fluctuation are seen in those patients in whom this value was highest at the first examination. This relationship is however not present for the left eyes. The change in peripheral mean sensitivity for the right eyes ranged from no improvement to an increase of 150.2% (median 21.5%) whereas change in central mean sensitivity ranged from no improvement to an increase of 69.5% (median 6.1%). The relationship between the proportionate increase in peripheral mean sensitivity against the proportionate increase in central mean sensitivity from the first to fourth examinations is shown in Figure 4.7.

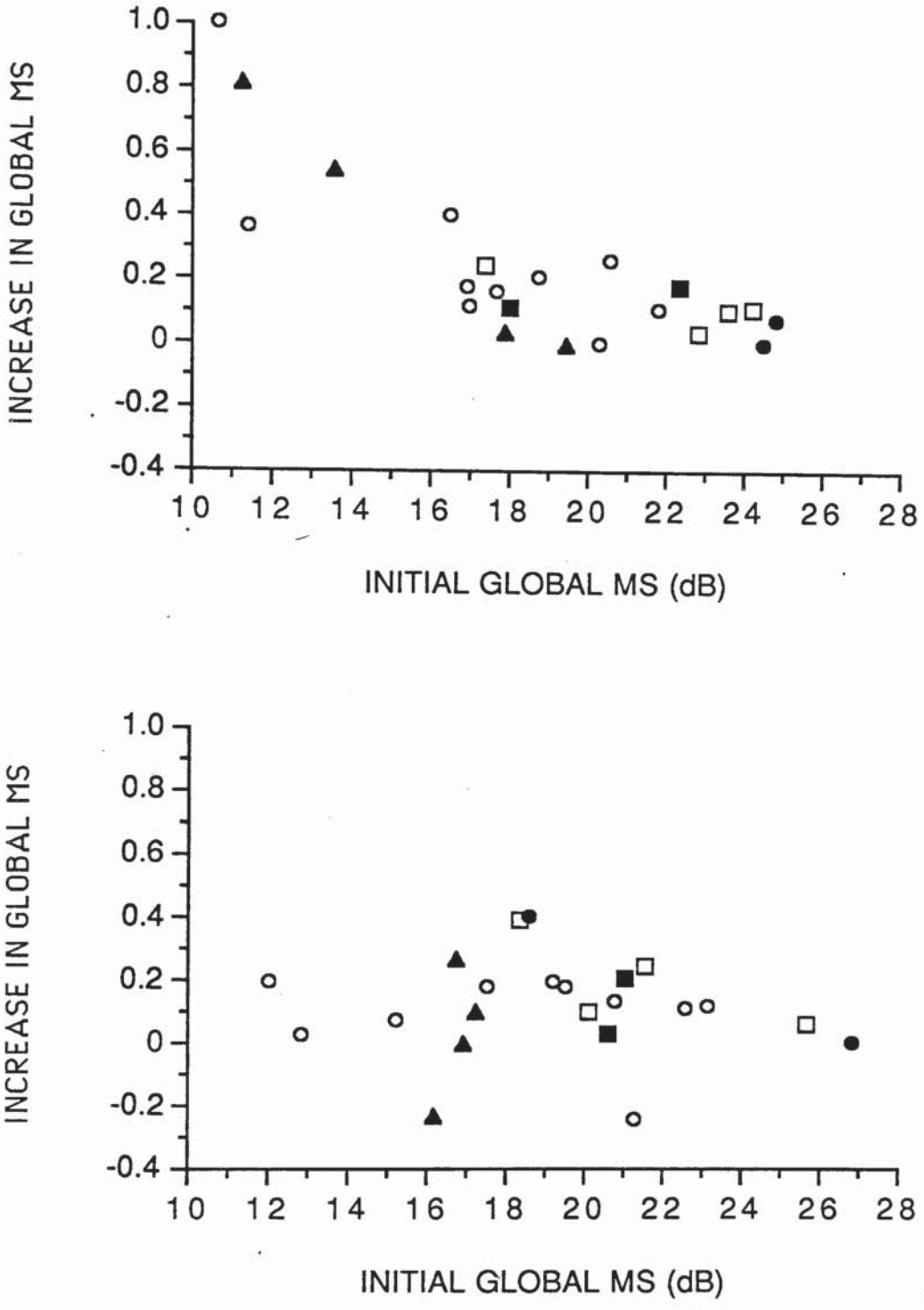


Figure 4.3. Proportionate improvement in global mean sensitivity (MS) from the first to fourth examinations as a function of the initial values at the first examination. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes.

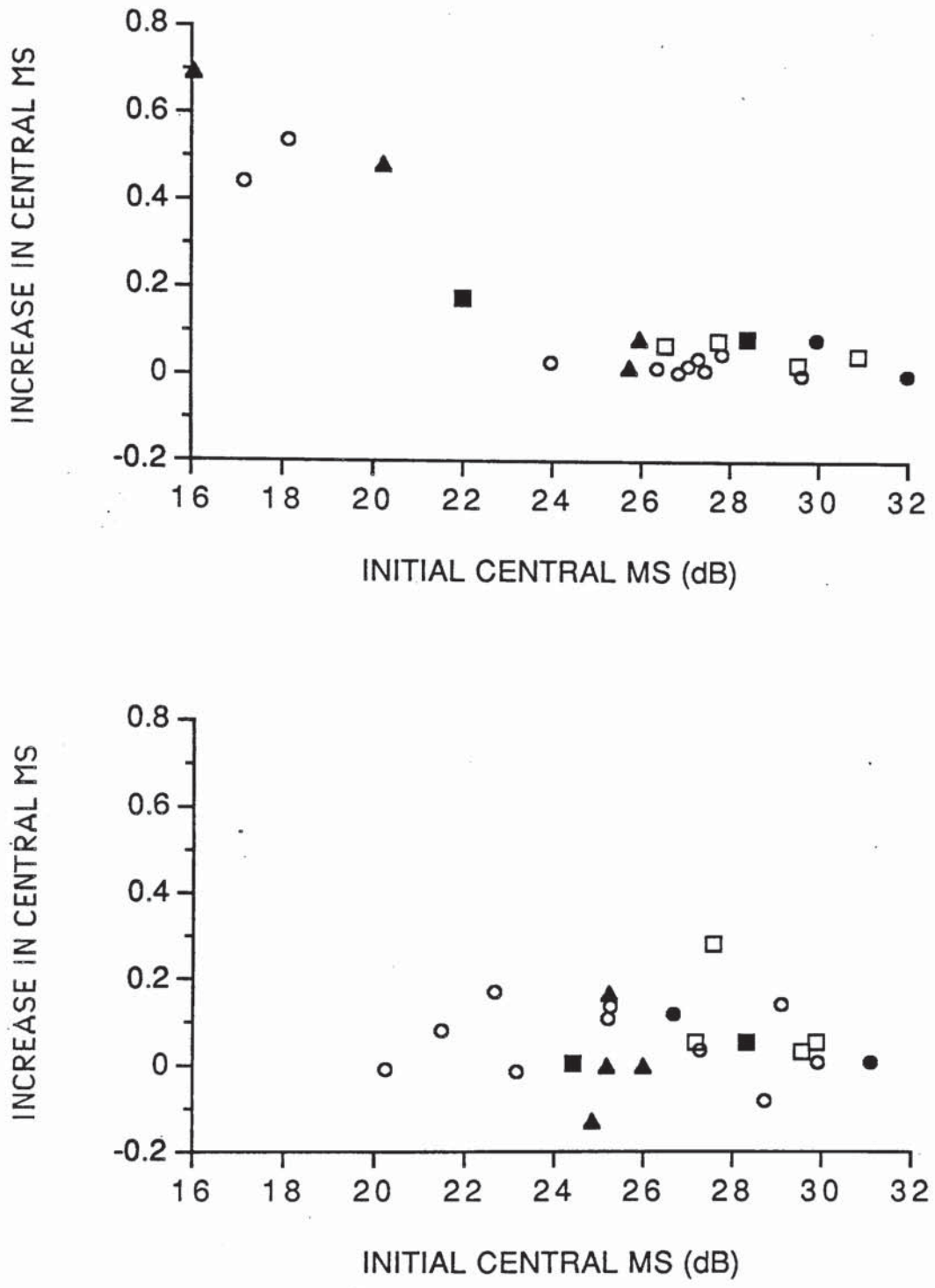


Figure 4.4. Proportionate improvement in central mean sensitivity (MS) from the first to fourth examinations as a function of the initial values at the first examination. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes.

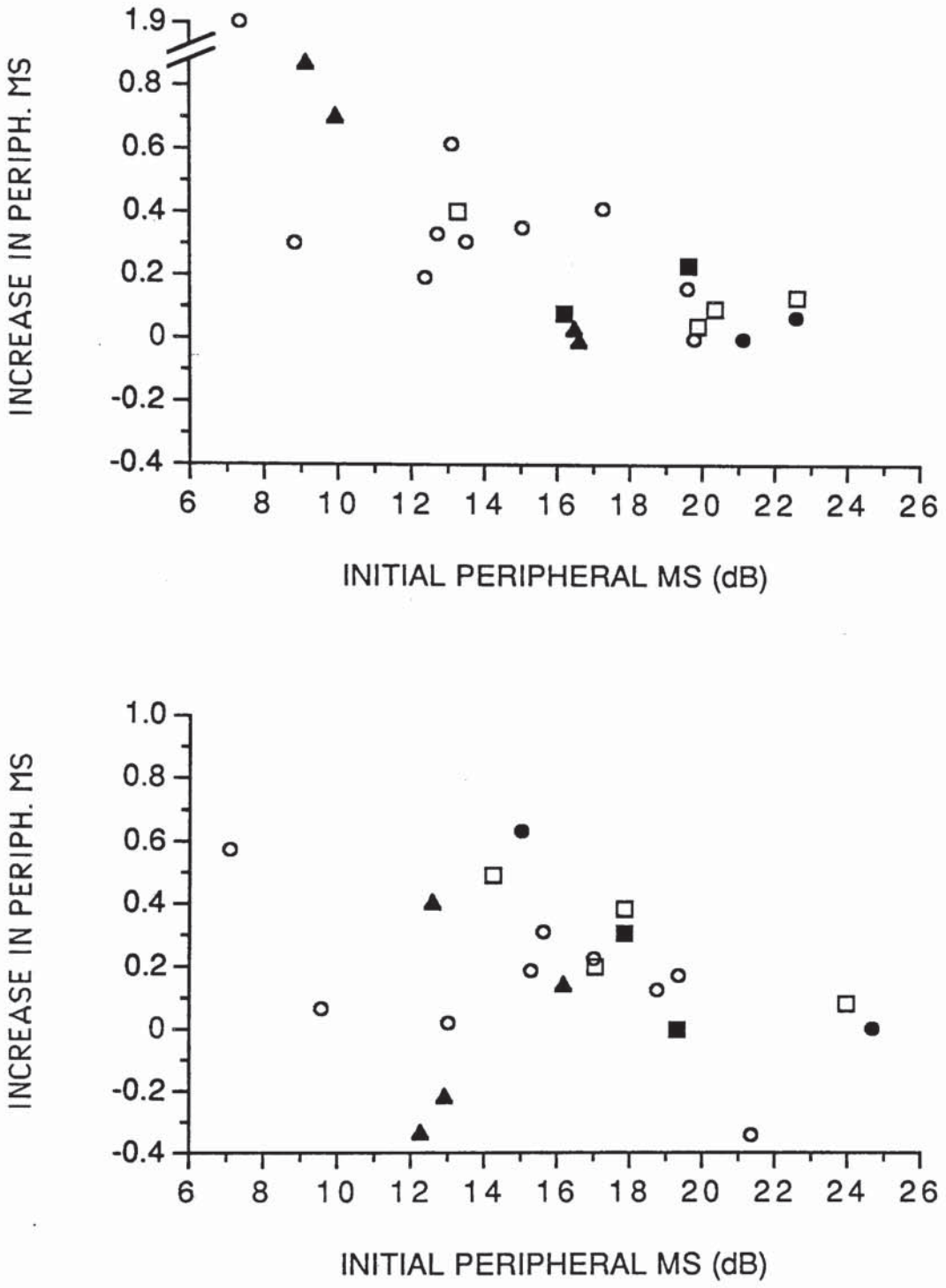


Figure 4.5. Proportionate improvement in peripheral mean sensitivity (MS) from the first to fourth examinations as a function of the initial value at the first examination. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes.

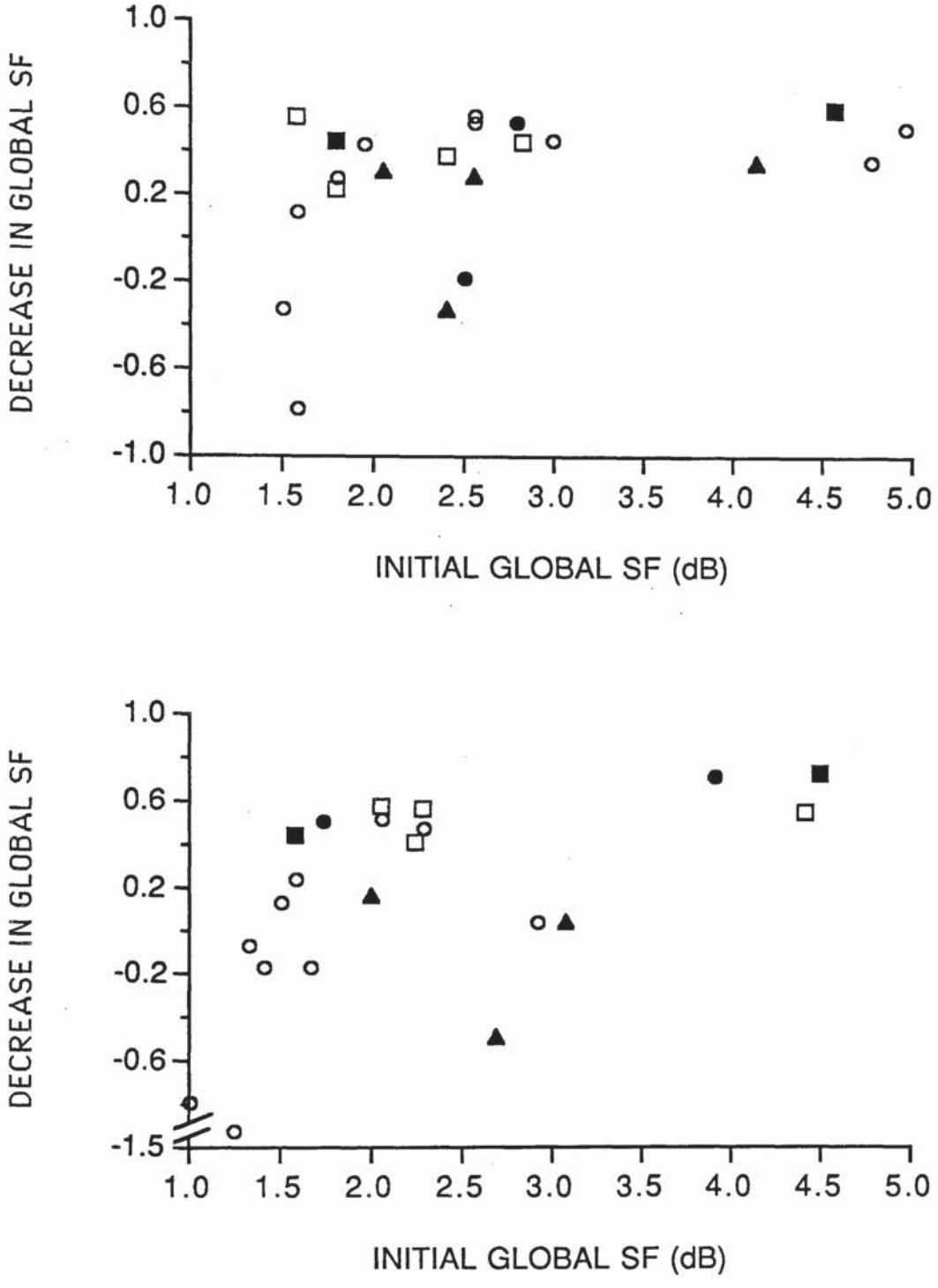


Figure 4.6. Proportionate decrease in global short-term fluctuation (SF) from the first to fourth examinations as a function of the initial value at the first examination. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes.

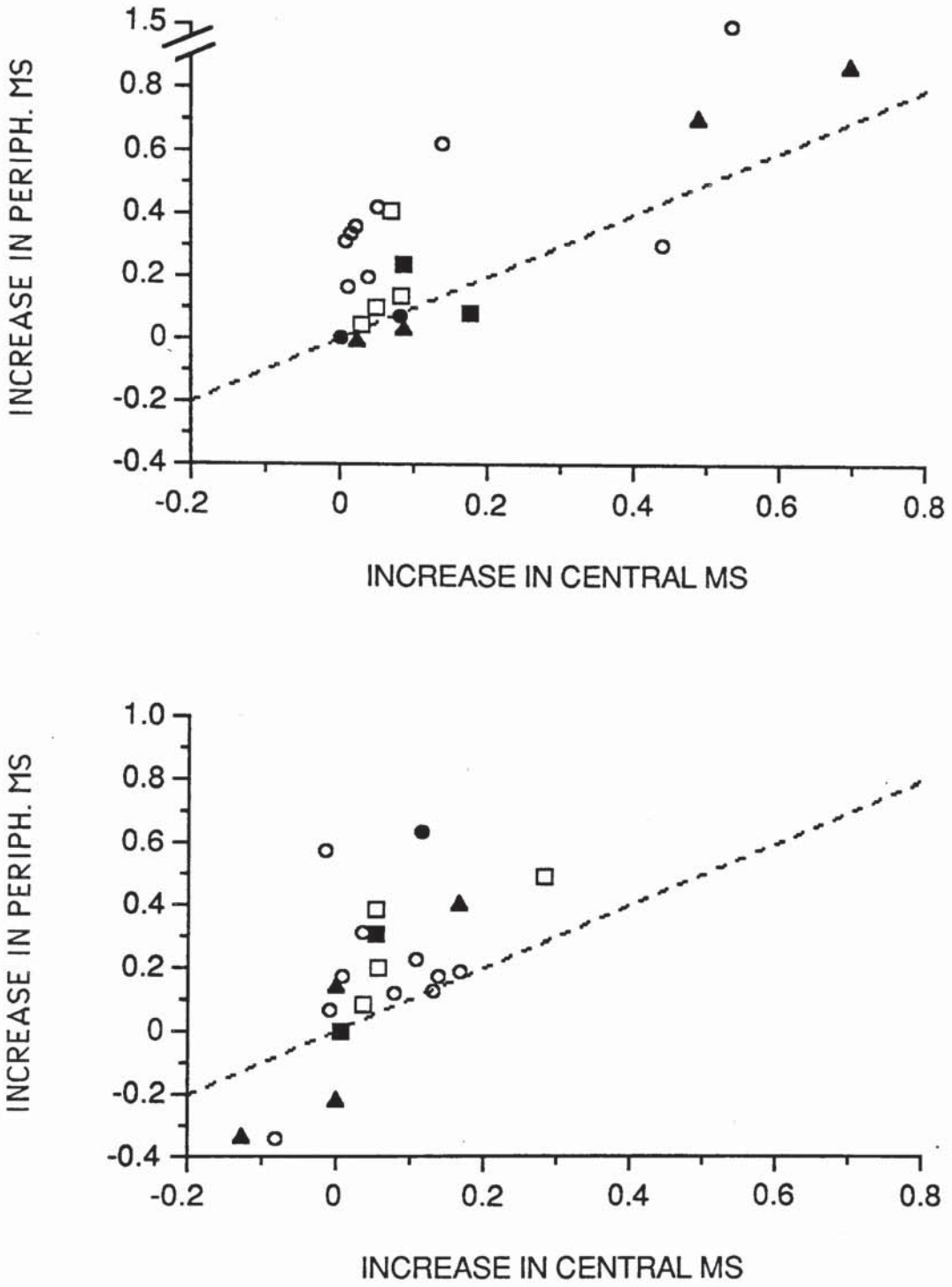


Figure 4.7. The relationship between the proportionate increase in peripheral mean sensitivity (MS) against the proportionate increase in central mean sensitivity (MS) from the first to fourth examinations. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes. Dotted lines represent equal proportionate changes.

4.7.2. Long-term

Sixteen of the original 22 patients who had completed the short-term study attended for the follow-up visits. Two patients were not considered to be clinically stable although their results are included since the protocol of follow-up examination on two consecutive days is designed to differentiate deterioration due to the disease process from that due to "forgetting" of the learned skill. The diagnoses for these 16 patients comprised 6 ocular hypertensives (1 of whom was receiving therapy), 6 glaucoma suspects (1 receiving therapy), 1 low-tension glaucoma and 3 primary open-angle glaucoma patients (all receiving therapy). The type and degree of field loss recorded with program 30-2 is illustrated in Figure 4.8. after the classification of Caprioli & Sears (1987) and shows minimal diffuse loss. The follow-up examinations ranged from 5 to 14.75 months after the fourth examination (mean 8.7; SD 3.1 months).

Small changes, mainly deteriorations, were present in the visual field indices and reliability parameters from the fourth examination to the first follow-up examination. The only statistically significant changes were, for the right eye, a deterioration in central mean sensitivity ($p<0.002$) and increase in mean defect ($p<0.002$). Group average central mean sensitivity for the right eyes deteriorated by 1.6 dB (5.6 %) from the fourth examination to the first long-term follow-up ($p<0.002$). For the left eye statistically significant changes were observed in an increased global short-term fluctuation ($p<0.02$) and increase in the number of stimuli presented ($p<0.05$). The only parameters to show statistically significant changes from first to second follow-up examinations were the right inferior peripheral mean sensitivity ($p<0.02$) and right and left central loss variance ($p<0.02$ for both). Generally, the change in visual field indices recorded from the fourth examination to the first follow-up increased with time to the follow-up examination. Those patients who showed the greatest alteration in visual field indices from the fourth examination to the first follow-up also showed greater changes from the first to the second follow-up examination.

The median visual field indices and reliability parameters against examination sequence for the 16 remaining patients are shown in Tables 4.3. and 4.4. respectively. The data from the fourth examination at Day 15 has been re-analysed for these 16 patients.

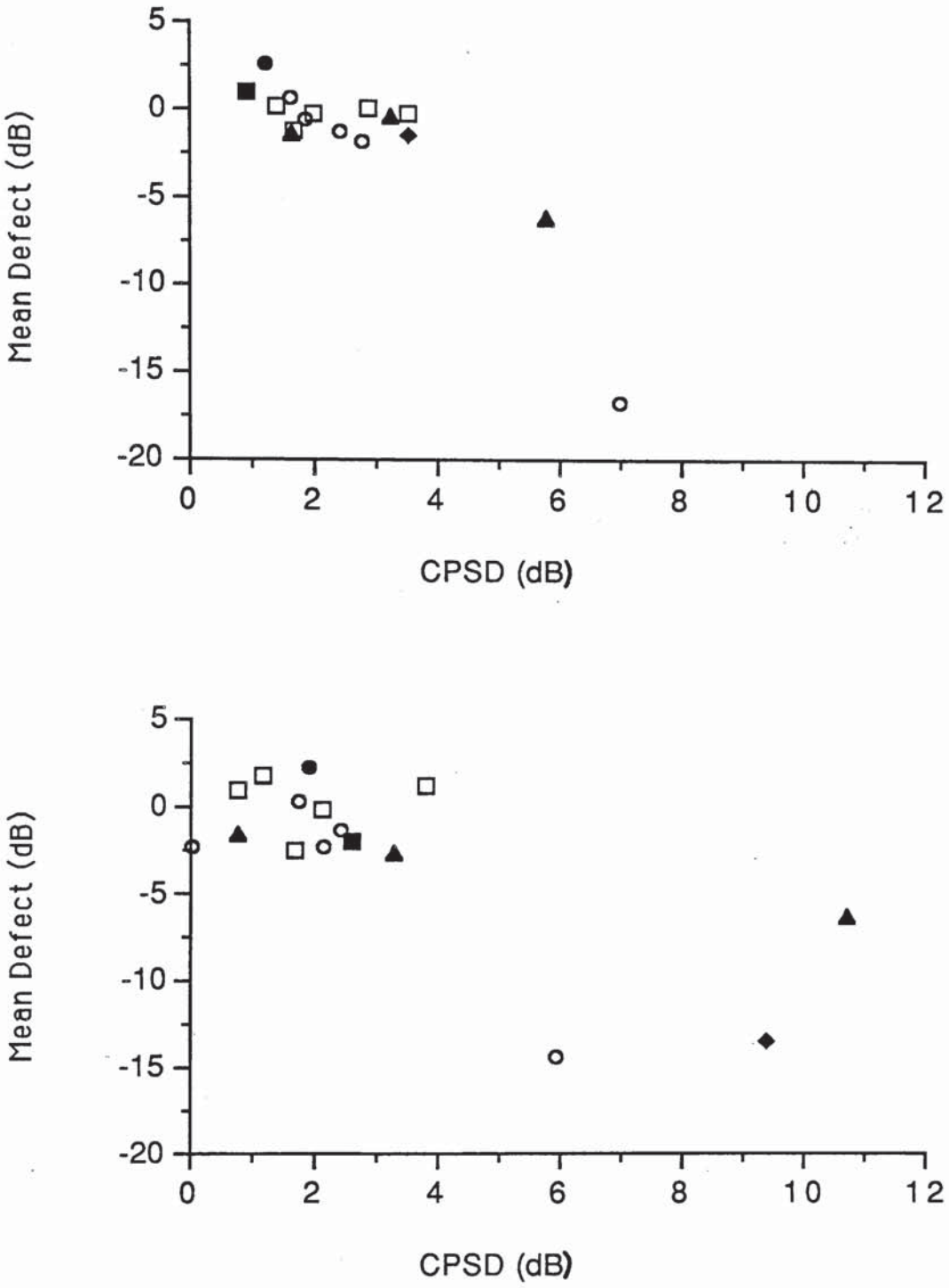


Figure 4.8. Illustrating the depth and type of field loss, derived from Humphrey program 30-2 after the follow-up examinations, using the classification of Caprioli & Sears (1987) showing mean deviation (diffuse loss) as a function of corrected pattern standard deviation (focal loss). Field loss is seen to be primarily of the diffuse type. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; low-tension glaucoma: closed diamonds; primary open-angle glaucoma: closed triangle). Top: right eyes; bottom: left eyes.

INDEX		EXAMINATION		
		Fourth	Follow-up (Day 1)	Follow-up (Day 2)
Global MS (dB)	R	20.88 (21.57;0.80)	20.97 (21.06;1.10)	20.18 (19.51;1.25)
	L	21.83 (20.67;1.28)	20.58 (21.16;0.96)	20.98 (19.96;1.09)
Central MS (dB)	R	28.22 (28.33;0.53)	27.03*** (26.73;0.89)	27.29 (27.05;0.88)
	L	27.38 (27.14;1.03)	26.12 (25.35;1.26)	27.78 (26.80;0.90)
Peripheral MS (dB)	R	18.61 (17.87;1.28)	17.76 (18.10;1.10)	17.55 (18.37;0.95)
	L	19.78 (18.42;1.30)	17.93 (17.02;1.36)	17.57 (16.92;1.23)
Superior peripheral MS MS (dB)	R	15.91 (16.39;1.11)	15.03 (15.59;1.21)	14.58 (15.45;1.48)
	L	17.15 (16.42;1.44)	16.17 (15.09;1.37)	14.08 (14.15;1.35)
Inferior peripheral MS (dB)	R	21.75 (21.62;0.94)	20.81 (20.49;1.13)	21.44** (21.76;0.83)
	L	21.64 (20.46;1.32)	21.91 (18.91;1.46)	21.14 (19.79;1.35)
Central MD (dB)	R	1.82 (1.62;0.48)	3.28*** (3.26;0.83)	2.19 (2.93;0.83)
	L	2.47 (2.85;1.06)	3.69 (4.63;1.25)	2.66 (3.19;0.88)
Central LV (dB squared)	R	6.03 (7.75;2.11)	7.13 (10.79;3.04)	5.59** (10.42;2.90)
	L	5.67 (10.95;3.56)	6.19 (2.12;0.90)	4.94** (10.81;5.79)

Table 4.4. Median visual field index against examination sequence for 16 patients. The significance level for comparison of a given examination with the previous examination are indicated in superscript. *** indicates a probability of $p<0.002$, ** $p<0.02$ and * $p<0.05$. The accompanying means and standard errors are given in parentheses.

INDEX		EXAMINATION		
		Fourth	Follow-up (Day 1)	Follow-up (Day 2)
Global SF (dB)	R	1.50 (1.68;0.16)	1.62 (1.84;0.21)	1.84 (1.86;0.22)
	L	1.27 (1.60;0.17)	1.96** (2.53;0.40)	2.35 (2.34;0.32)
No. of stimuli	R	401.0 (406.8;9.1)	405.0 (410.9;8.7)	423.0 (424.6;10.6)
	L	389.0 (401.7;8.4)	404.0* (424.1;14.4)	407.0 (420.4;10.41)
False negative responses (%)	R	0.0 (6.4;2.6)	10.1 (9.7;2.4)	7.1 (6.2;1.6)
	L	4.2 (11.4;4.1)	3.4 (12.9;4.1)	3.9 (11.1;4.0)
False positive responses (%)	R	0.0 (4.0;2.4)	0.0 (1.6;0.9)	0.0 (4.7;1.6)
	L	0.0 (5.0;2.4)	0.0 (1.8;1.0)	0.0 (0.8;0.8)
Fixation losses (%)	R	14.0 (18.3;5.7)	11.1 (18.1;5.6)	10.6 (18.5;4.6)
	L	11.7 (18.0;4.9)	9.3 (13.2;3.4)	4.5 (14.8;6.1)

Table 4.5. Median visual field index against examination sequence for 16 patients. The significance level for comparison of a given examination with the previous examination are indicated in superscript. *** indicates a probability of $p<0.002$, ** $p<0.02$ and * $p<0.05$. The accompanying means and standard errors are given in parentheses.

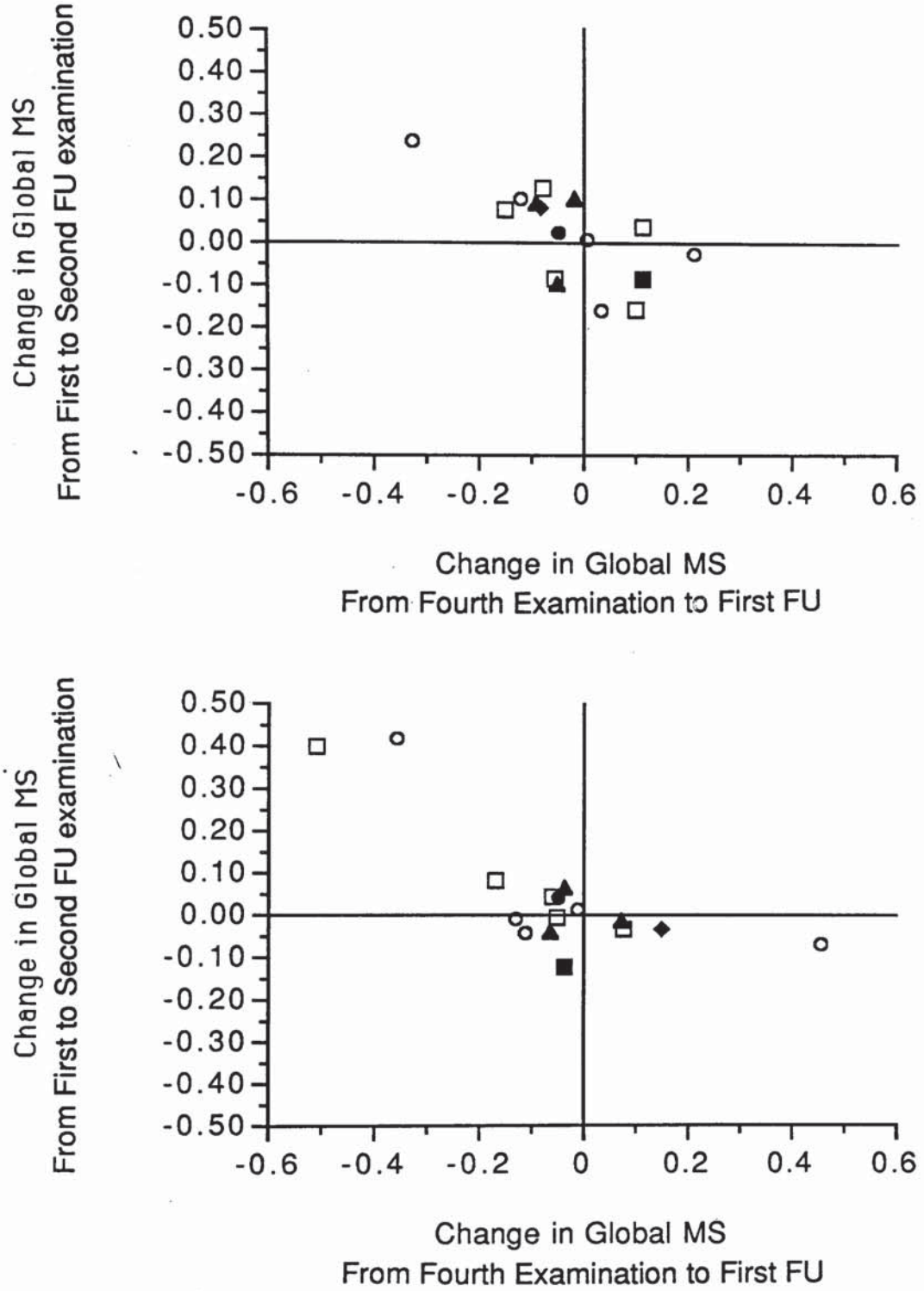


Figure 4.9. Proportionate change in global mean sensitivity (MS) from the first to second follow-up examinations against proportionate change in global mean sensitivity from the fourth examination to first follow-up. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle; low-tension glaucoma: closed diamond). Top: right eyes; bottom: left eyes.

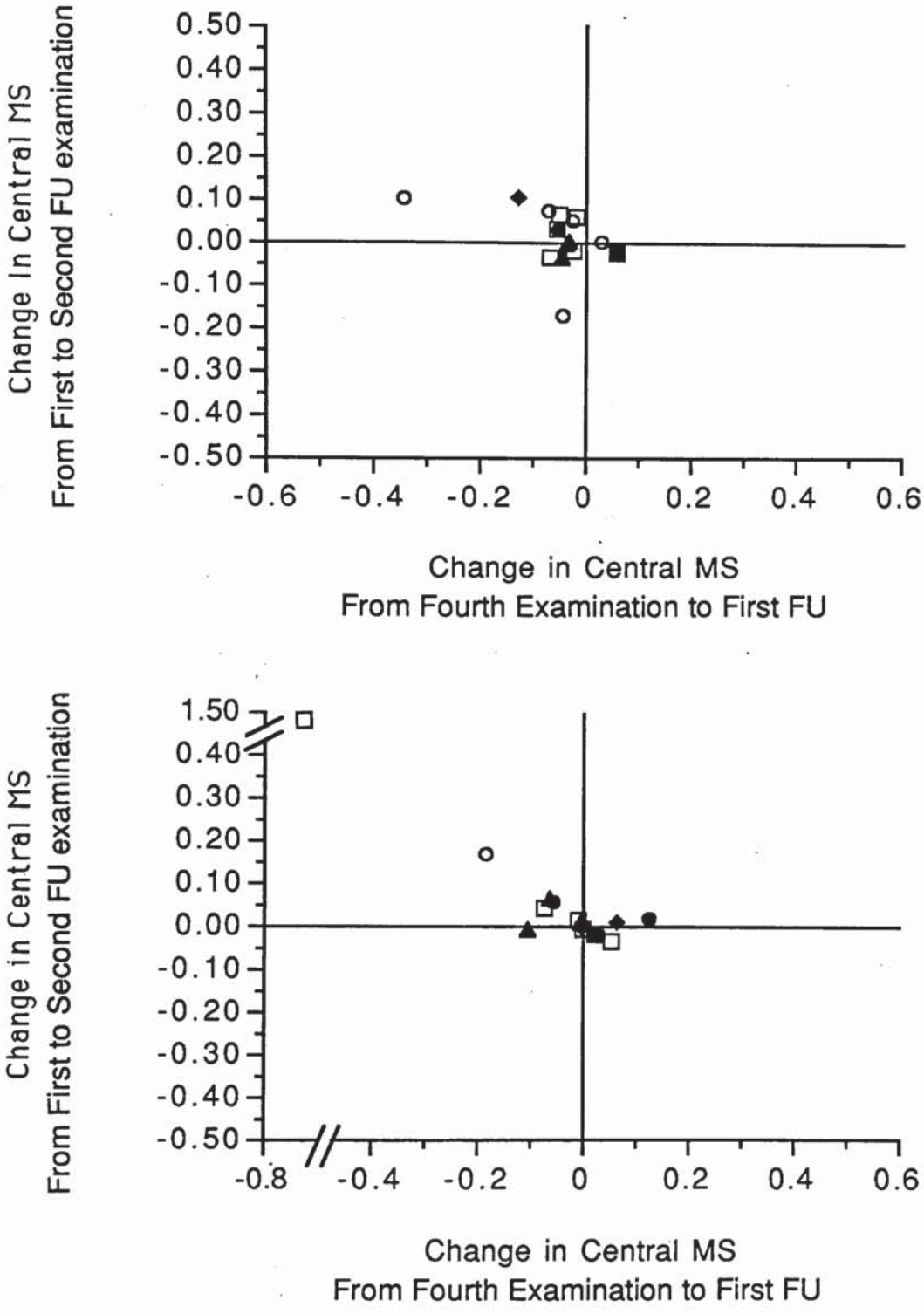


Figure 4.10. Proportionate change in central mean sensitivity (MS) from the first to second follow-up examinations against proportionate change in central mean sensitivity from the fourth examination to first follow-up. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle; low-tension glaucoma: closed diamond). Top: right eyes; bottom: left eyes.

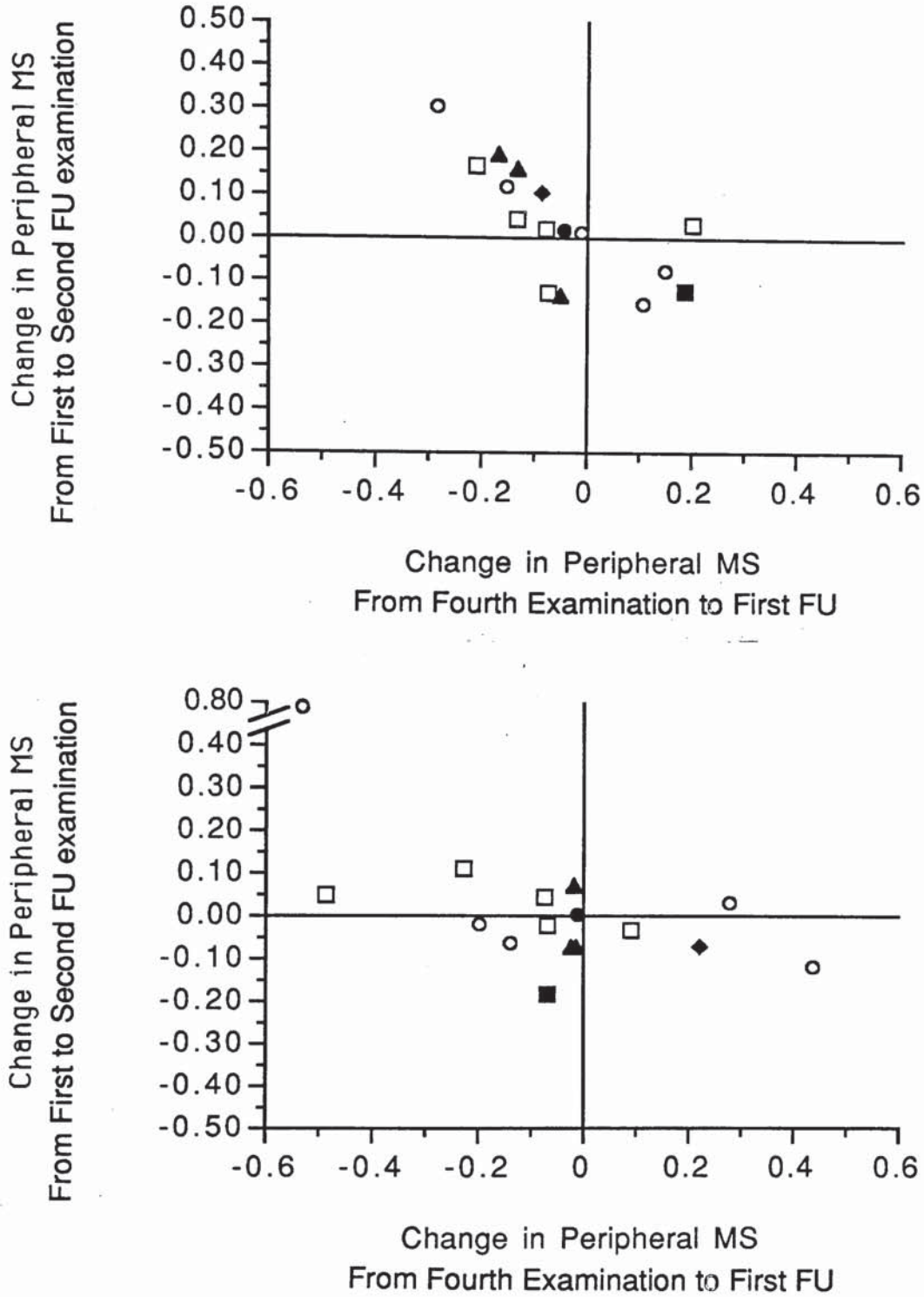


Figure 4.11. Proportionate change in peripheral mean sensitivity (MS) from the first to second follow-up examinations against proportionate change in peripheral mean sensitivity from the fourth examination to first follow-up. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle; low-tension glaucoma: closed diamond). Top: right eyes; bottom: left eyes.

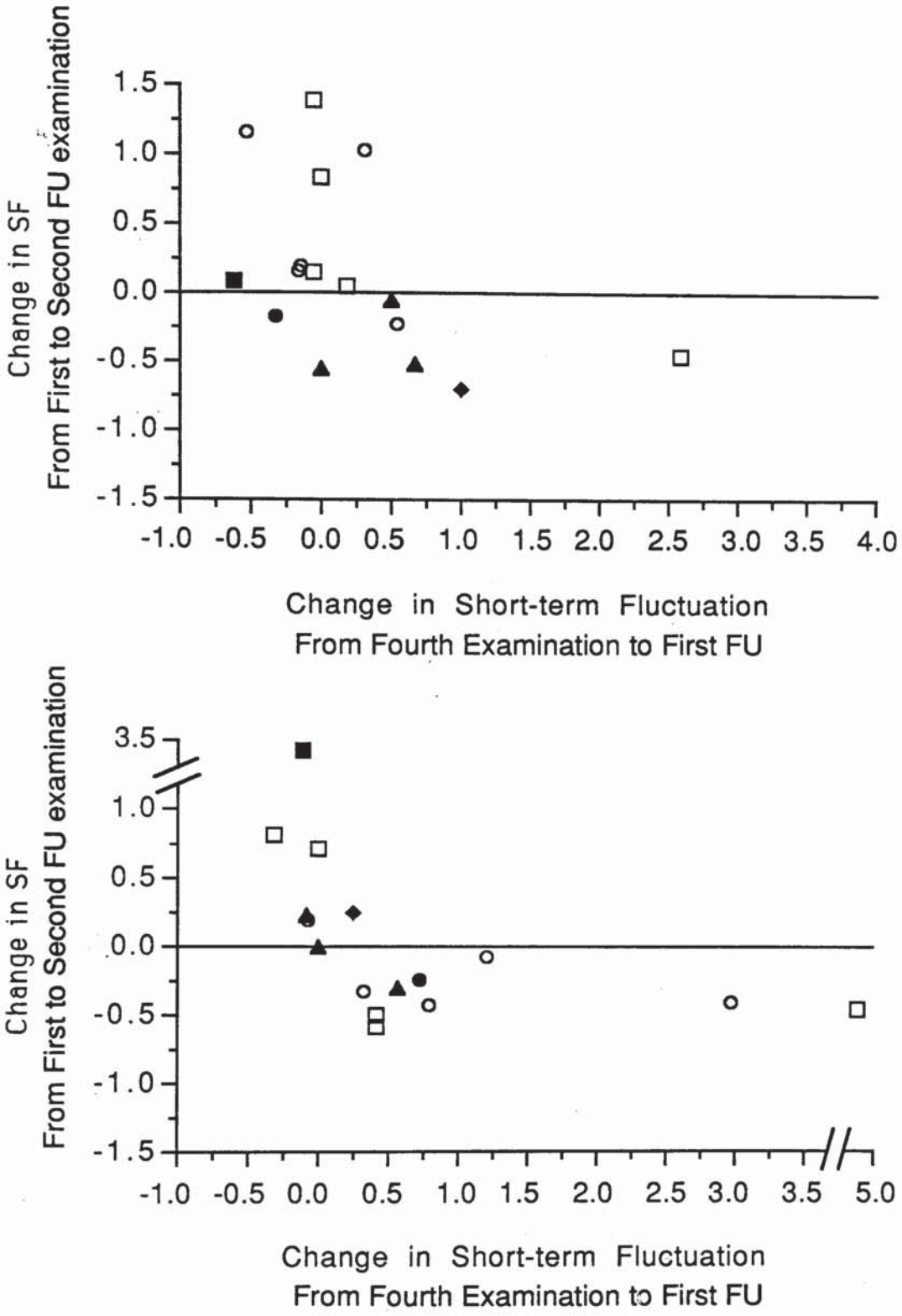


Figure 4.12. Proportionate change in short-term fluctuation from the first to second follow-up examinations against proportionate change in short-term fluctuation from the fourth examination to first follow-up. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle; low-tension glaucoma: closed diamond). Top: right eyes; bottom: left eyes.

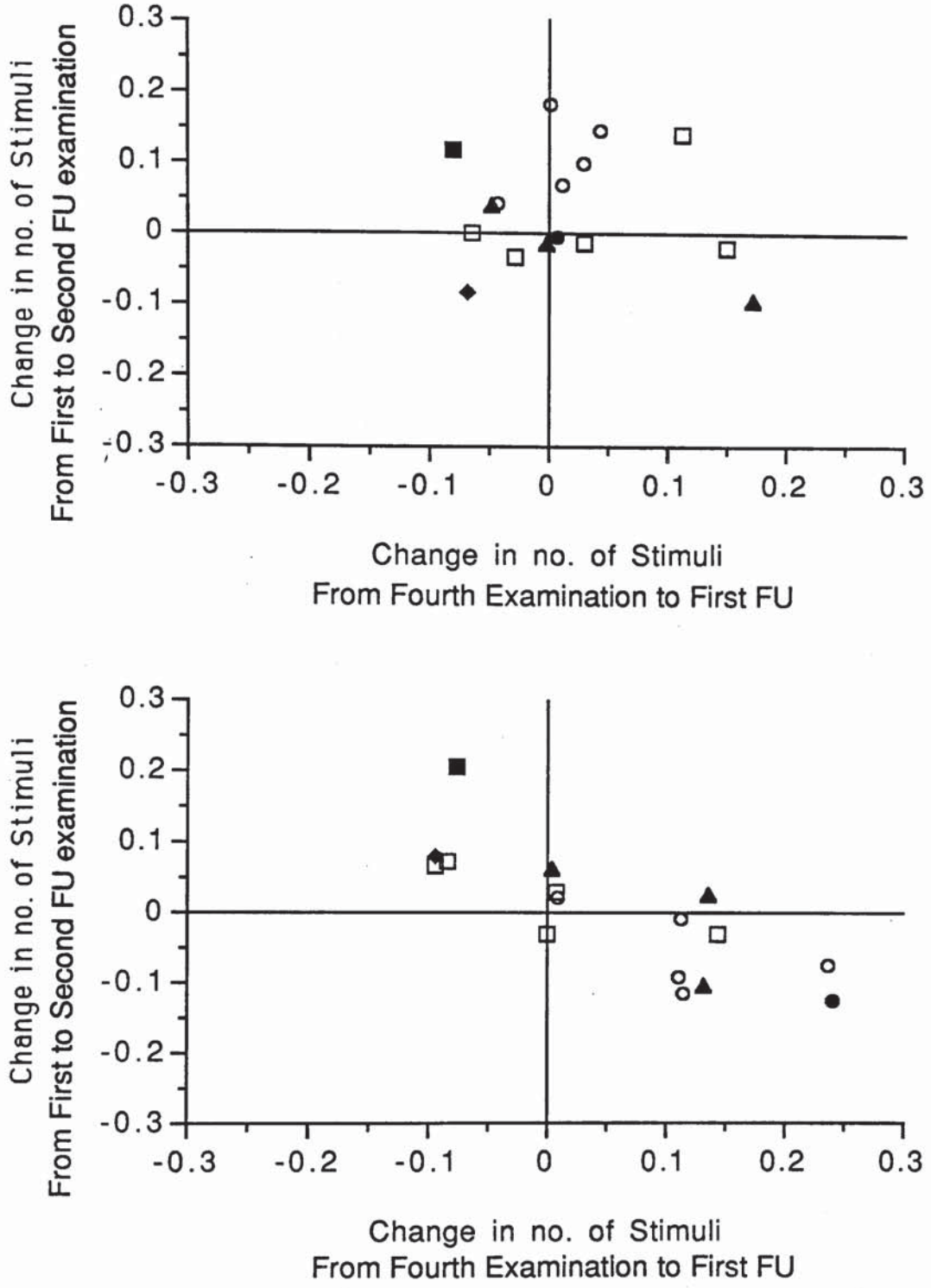


Figure 4.13. Proportionate change in the number of stimuli presented from the first to second follow-up examinations against proportionate change in the number of stimuli presented from the fourth examination to first follow-up. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle; low-tension glaucoma: closed diamond). Top: right eyes; bottom: left eyes.

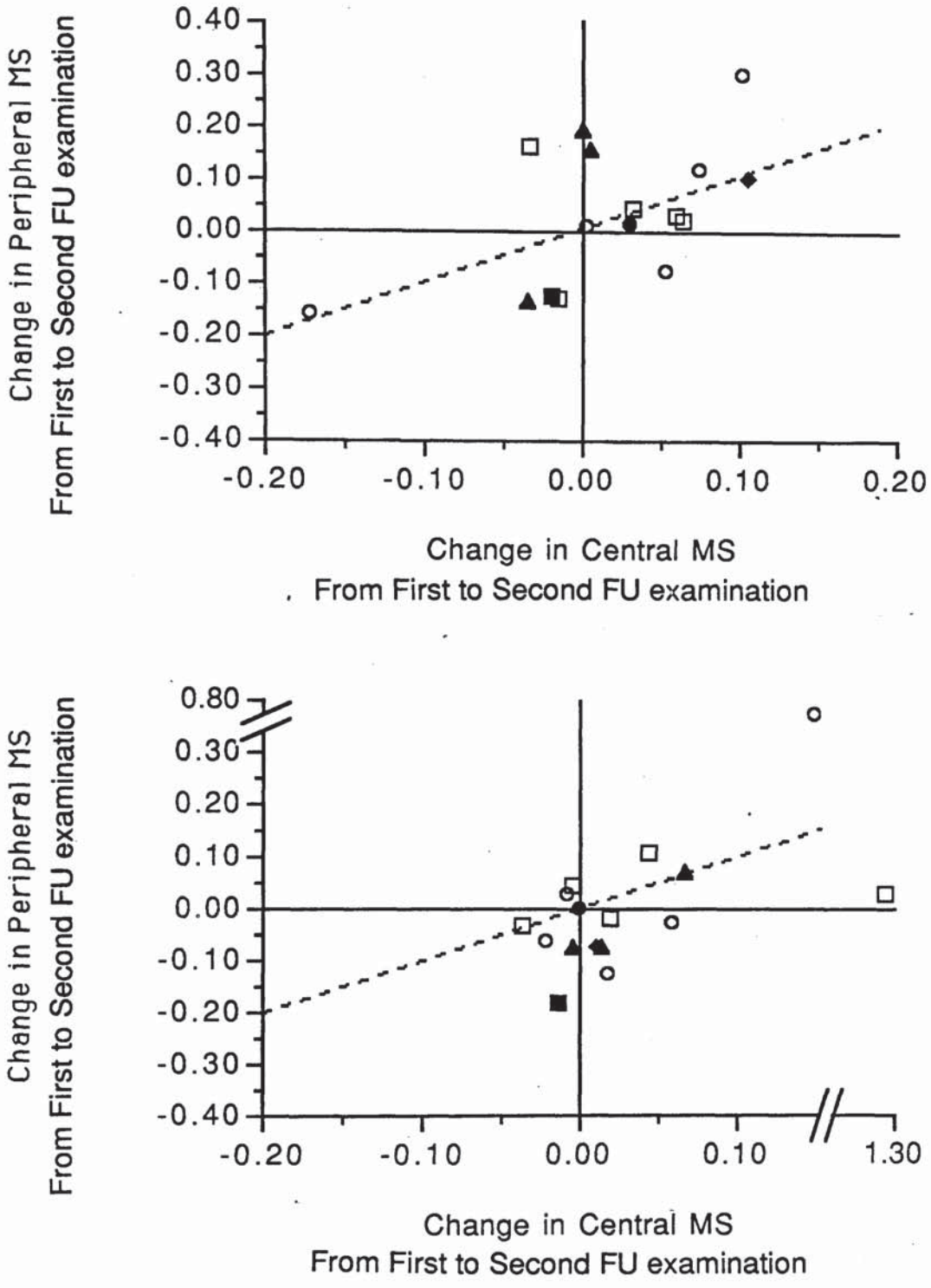


Figure 4.14. Proportionate change in peripheral mean sensitivity (MS) from the first to second follow-up examinations against proportionate change in central mean sensitivity (MS) from the first to second follow-up examinations. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; glaucoma suspect without therapy: open circles; glaucoma suspect with therapy: closed circles; primary open-angle glaucoma: closed triangle; low-tension glaucoma: closed diamond). Top: right eyes; bottom: left eyes. Dotted lines represent equal proportionate changes.

The relationship between the change in visual field indices from the first to the second follow-up examination plotted against the corresponding changes from the fourth examination to the first follow-up examination for the parameters global mean sensitivity, central mean sensitivity, peripheral mean sensitivity, short-term fluctuation and number of stimuli presented are shown in Figures 4.9. to 4.13. respectively. The relationship between the improvement in peripheral mean sensitivity plotted against central mean sensitivity from the first to second follow-up examinations is shown in Figure 4.14.

4.8. DISCUSSION

4.8.1. Short-term

The improvement in mean sensitivity (global, central and peripheral) of the right eye, which was maintained over a period of 12 days, and the concomitant decrease in short-term fluctuation with serial examination represent a "learning effect". The results are in agreement with the manual perimetric data of Aulhorn & Harms (1967, 1972) and also with other studies using automated perimetry (Gloor et al. 1980a,b, 1981; Parrish et al. 1984; Rabineau et al. 1985; Adelson et al. 1988; Niles & Trope 1988; Werner et al. 1988 and Heijl et al. 1989a). This improvement could be due to conditioned learning, perceptual learning or criteria alterations.

The lack of significant change in the number of fixation losses is in agreement with the work of Niles & Trope (1988), although a significant decrease in the number of false negative responses in the right eye was found from the first to second examinations which presumably represents a change in patient criterion for detection of the stimulus or improved attention.

Improvement in mean sensitivity was statistically more significant in the peripheral than the central field (see Table 4.2. and Figure 4.7.). This eccentricity dependency is in agreement with the work of Heijl (1987), Heijl et al. (1987b; 1989), Wood et al. (1987) and Adelson et al. (1988) and is in accord with Low's (1946) concept of the periphery as an unpractised sensory area. This heterogeneity of the learning effect tends to discount the theory that criterion changes are accountable. The eccentricity dependency could be explained by the fact that

short-term fluctuation increases with peripheral angle (Heijl et al. 1987a), or the patient learning to consciously raise the upper lid; fixation however was monitored on the video-screen throughout the examination and this tendency was not noted. Improvements in the superior areas of the field were not as great as those noted by Wood et al. (1987) due to the greater age of the sample, since the depressing influence of age on the field is greatest in the superior areas (Haas et al. 1986; Jaffe et al. 1986).

The relationship between the proportionate improvement and initial mean sensitivity in the right eyes, where fields that initially had the lowest sensitivity improved the most, is in agreement with the work of Heijl et al. (1989) in normal subjects and Drance et al. (1989) and Werner et al. (1990a) in glaucoma patients. This apparent depth dependency of the learning effect also appears to be related to the diagnosis. It may be seen from Figures 4.3. to 4.6. (right eyes) that glaucoma patients and suspects tended to have the lowest initial sensitivity and improved the most, whereas ocular hypertensive patients tended to have the highest initial sensitivity and showed less improvement in performance. This may result from the increased short-term and long-term fluctuations in glaucoma patients (Flammer et al. 1984b,c). It also argues against criterion changes accounting for the learning effect, as the patients individual criterion change would not be expected to be related to the diagnosis. Interestingly, the loss variance decreased over the course of the first three examinations, almost reaching statistical significance (df 2; chi squared=5.84; $p < 0.1$). It thus appears that the depth dependency of the learning effect may be applied on a pointwise basis within the same field i.e. those individual points having the lowest initial sensitivity improve the most leading to a smoothing of the hill of vision with practice. This is in agreement with the work of Heijl et al. (1989) who found a decrease in corrected pattern standard deviation with practice. The decrease in loss variance in this experiment could however be accounted for by the concomitant decrease in short-term fluctuation. Corrected loss variance was not calculated since the loss variance was only computed from the sixteen points within the central 30°, and short-term fluctuation from only eight points within 42° eccentricity (four of which were within 30° eccentricity).

Significant improvements in performance are seen to occur in the right eyes mainly from the

first to second examinations, and imply that the learning effect reaches a plateau after the second right eye examination. In the left eyes however, significant improvements in performance occurred only from the third to fourth examinations. This is thought to arise from an inter-ocular transfer of the learning effect (global mean sensitivity was higher in the left than the right eyes of 15/25 patients on the first examination), or some opposing influence to learning during examination of the second eye e.g. fatigue (Heijl 1977b; Heijl & Drance 1983).

The lack of significant change in the left eye from first to second examinations, and in right and left eyes from second to third examinations could result if the transfer of learning were counterbalanced by a fatigue effect resulting from previous examinations. This view is supported by the further improvements occurring in sensitivity after a break of 12 days where there is no counteracting fatigue element, and could indicate that fatigue effects last more than 24 hours and may be both intra and inter-test. The peripheral field shows a greater potential for improvement, however it seems to be more susceptible to fatigue since there are greater sensitivity increases in the peripheral than central areas after the break of 12 days.

Although statistically significant improvements occurred, these should be interpreted in relation to the long-term fluctuations. Only changes in the visual field indices greater than the long-term fluctuation may be considered as true improvement of the field due to learning effects. Some caution should be exercised in the use of the central visual field indices, mean sensitivity, mean defect and loss variance computed from the custom program since there were only 16 stimuli locations within the central 30°. However, the indices mean sensitivity and mean defect were considered representative of those obtained later on the same day from program 30-2. The correlation coefficients between the indices derived from the two programs were: right central mean sensitivity r_S=0.70; left central mean sensitivity r_S=0.92 and right central mean defect r_S=0.71; left central mean defect r_S=0.92. Loss variance correlated poorly with the pattern standard deviation of program 30-2: right loss variance r_S=0.24; left loss variance r_S=0.46, due to the diffuse nature of field loss in the sample.

It could be suggested that the learning effect was attributable to the commencement of

therapy, since, of those patients who showed the greatest improvements, the majority were on therapy. However, the first visual field examination was carried out 3 weeks after instigation of therapy and it is argued that, if the improvement were due to therapy, corresponding improvements would be expected in the fellow eye, which is clearly not the case.

4.8.2. Long-term

The majority of the visual field indices and parameters showed little change over the follow-up period, indicating that the learning effect is retained at least over the typical time periods as would be encountered between hospital out-patient visits.

Any improvement in the visual field indices and reliability parameters at the first long-term follow-up examination compared with those at the fourth examination could be attributed to continuation of the learning process or the effects of therapy. Deterioration in performance could be attributed to a regression of the learning skills ("forgetting") or progression of the disease process or a combination of both. Improvements between the first and second follow-up examinations would indicate a continuation of the learning process. The change from the fourth examination to the second follow-up examination is indicative of the change in the visual field resulting from the disease process alone. These patients were therefore followed up on two consecutive days to differentiate these factors.

The results were considered in terms of the proportionate change to account for the differing amounts of glaucomatous field loss within the sample. The statistically significant deterioration in right eye central mean sensitivity between the fourth examination and first follow-up examination compared with the insignificant change from the first to second follow-up examinations indicates that any change is mainly due to the disease process and learning effects are negligible over the follow-up examinations. The significant increase in left eye short-term fluctuation from the first to second examinations is indicative of a fatigue effect.

Weak relationships exist between the change in visual field indices and parameters from the

first to second follow-up examinations and the corresponding changes between the fourth examination and first follow-up examination as shown in Figures 4.9. to 4.13. That is, patients who have the longest interval to the follow-up examination show the greatest reduction in performance, however are capable of improving their performance more through further learning. This could imply a gradual regression of the learning skill as a function of time. Within the small sample, these relationships do not appear to be related to the diagnosis or instigation of therapy, since primary open-angle glaucoma patients would normally attend for ophthalmological examination more frequently than those with ocular hypertension.

4.9. CONCLUSIONS

The results are in agreement with the hypothesis of Hoskins et al. (1988) that, in the clinical situation, at least two baseline fields should be initially obtained before a diagnosis is made. This is particularly important in view of the "depth dependency" of the learning effect. The examinations should not, however, be carried out on consecutive days to avoid fatigue effects. In follow-up perimetry the order of eyes examined should always be noted. The skills required of the patient in automated perimetric assessment, once learned, appear to be retained.

CHAPTER 5

FATIGUE EFFECTS IN AUTOMATED PERIMETRY

5.1. INTRODUCTION

In early considerations of test logics and strategies for automated perimetry, it was assumed that the level of the differential light sensitivity remained constant over the duration of the test (Fankhauser et al. 1972; Heijl & Krakau 1975a; Spahr 1975; Bebie et al. 1976a).

In his pioneering studies on automated perimetry, Heijl (1977a) however reported that the performance of normal subjects appeared to deteriorate slightly with time. Heijl (1977a) did not document the magnitude of the change in sensitivity although the deterioration in sensitivity coincided with reports by patients that, after 5 minutes of testing, the background luminance appeared to vary. Heijl (1977b) further examined the influence of test time on sensitivity and on the number of fixation losses. The performance of 11 glaucoma patients and of 8 glaucoma suspects was compared with that of a control group of 12 normal subjects. Both patients and normal subjects had minimal experience of automated perimetry. The differential light sensitivity was continuously determined at eccentricities of 5°, 10° and 15° during a single examination lasting 30 minutes and fixation losses were monitored by presenting stimuli in the blind spot area. A reduction in sensitivity was found with increasing test time, although sensitivity remained relatively stable for the first 4 to 10 minutes of the examination. In normals the decrease in mean sensitivity was small, amounting to 1.5dB or less during the whole test session, whilst it was greater in the patient group, amounting to a reduction in sensitivity for certain stimulus locations of 6-12dB in those eyes with confirmed visual field defects. Test locations which exhibited pronounced time-dependent sensitivity reductions were found to be situated adjacent to visual field defects, although there were no differences between the sensitivity decreases for stimuli at 5° or 15° eccentricity in either the patient or the normal group. In the patient group the short-term fluctuation and the number of fixation losses also increased significantly with examination time. The deterioration in performance was attributed to a fatigue effect which was not considered to be age-related although the average age of the patient group was higher than that of the normal subjects.

Heijl (1977a,b) suggested that the continual presentation of automated static perimetric stimuli placed the patient under stress, and the resulting sensitivity decrease with time represented a functional loss in the development of early glaucomatous defects, since test locations showing large sensitivity reductions with time coincided with documented visual field defects. He therefore hypothesised that prolonged automated perimetric examination could function as a provocative test for the detection of early glaucomatous visual field loss and that the observed fatigue effects could explain the previously reported discrepancies between defects recorded with both manual and automated modes of testing (Heijl & Krakau 1975b; Schmied 1980), the extent of the defect depending on the total examination time.

Holmin & Krakau (1979) considered that the inherent variability of thresholds in glaucoma reduced the reliability of the recording and confounded the interpretation of change. They studied the sensitivity of relative scotomata during prolonged testing in glaucoma patients compared with normal areas in the same field, with the aim of identifying parameters that would minimise such variation e.g. the length of the test session and the stimulus duration. Their results were similar to those of Heijl (1977a,b). Glaucoma patients showed a decrease in sensitivity over time in areas of visual field loss; however, adjacent areas of normal sensitivity behaved in a similar manner to that of the normal control group, in whom sensitivity remained stable over a time period of 30 minutes. Short-term fluctuation also increased in defective areas compared with unaffected areas of the same field. A reduction of the stimulus duration from 500msec to 250msec resulted in a slight overall reduction in sensitivity and an increased inter-individual variation in normal subjects; the effect of a reduction in stimulus duration on the glaucomatous sample was however more marked, causing scotomata to become wider and deeper. Interestingly, an increase in the stimulus duration to 1sec resulted in the defective areas showing normal sensitivity values. Contrary to Heijl (1977a,b) there was no increase in the number of fixation losses with increase in examination time.

Heijl & Drance (1983) further studied the deterioration of sensitivity during prolonged testing with both automated (Competer) and manual (Tubingen) modes of testing. The dependence of the fatigue effect on background luminance was also investigated. Stimulus duration in

the automated mode of testing was 250msec, and the background luminances were 0.315, 3.15 and 31.5asb. For manual perimetry, the stimulus duration was 100msec at background luminances of 31.5 and 62.8asb. Greater changes in the differential threshold with time were found in the automated mode (mean threshold increment +0.67 log units) compared with the manual mode (+0.19 log units) during a test of 12 minutes duration. Similar sensitivity decrements were observed at all background luminances in both modes of testing. No differences were observed between patients with primary open-angle glaucoma and patients with low-tension glaucoma, or between those where the field was stable and those where the field showed recent progression. The test locations found to be most affected were situated in areas of relative visual field loss, or in adjacent locations.

Flammer & Niesel (1984) in a consideration of patient, disease and other factors affecting the reproducability of perimetric findings, noted a slight tendency for the short-term fluctuation to increase towards the end of the examination in a sample of glaucoma patients, although sensitivity remained constant and no change in short-term fluctuation was observed in normals. Flammer & Niesel (1984) attributed the increase in short-term fluctuation to an increase in the patients' reaction time with fatigue. Sensitivity in disturbed fields, however, showed a marked decrease with time, which correlated poorly with the patients' reaction times and which varied within the visual field of each patient. They considered that not only did this represent a general fatigue of the patient but also a so-called local "exhaustion phenomenon".

Sturmer et al. (1985) mapped the features of glaucomatous visual field defects using the fine-grid Octopus 'F' programs. The F2 program performs double determinations at each location examined whilst the F4 program measures the threshold four times at each location. These workers suggested that the F4 program exacerbated the effects of fatigue particularly in fields with low sensitivity, since a higher level of short-term fluctuation occurs in the measurement of these fields and thus a greater number of stimulus presentations would be required to determine the threshold 4 times.

Further work by Rabineau et al. (1985) on a sample of 7 normal subjects showed no

significant decrease in sensitivity or increase in short-term fluctuation during continual testing over a period of one hour with Octopus program 31. Three subjects were further subjected to an examination which consisted of 12 consecutive F2 programs and lasted 2.5-3.5 hours in total. No significant decreases in sensitivity or increases in short-term fluctuation with increase in time within the central 30° of the visual field were found in these subjects.

In a comparative study of quantitative testing with the Octopus, Humphrey and Tubingen perimeters, Mills et al. (1986) ensured that each test was performed on a different day to minimise the effects of fatigue on performance. Katz & Sommer (1986), in determining the assymetry and variation in the normal hill of vision, always examined the right eye of each patient first. They found consistently better results in one eye than the other, but could not attribute this to a fatigue effect, since the better eye was not always tested first. In a further study on the reliability indices of automated perimetric tests, Katz & Sommer (1988) found a greater proportion of 'unreliable' fields in glaucoma subjects than in normal patients, due to a higher rate of false negative responses. It could be hypothesised that this was due to a fatigue effect, since if sensitivity falls with time, a suprathreshold stimulus presented at a location where the threshold has been previously determined may no longer be suprathreshold and could therefore be missed by the patient.

Langerhorst et al. (1987, 1988) investigated whether the fatigue phenomenon that occurred during prolonged automated static testing could be a useful diagnostic tool. They used the Scoperimeter, a campimeter consisting of a large screen oscilloscope, with a background luminance of 0.315asb. The sample of 144 patients was divided into four groups, namely: normals, ocular hypertensives, glaucoma suspects and glaucoma patients. Tests of global and of local fatigue were performed. The global fatigue test consisted of a threshold program of 60 locations within 25°, measured five times in succession without a break, totalling 30 minutes. The local test consisted of thresholding at four locations between 5° and 15° eccentricity. These locations were customised for each subject such that for glaucoma patients the locations fell in a normal area, close to a defective area or actually within a defect. Results for the glaucoma group showed that the mean fatigue score (loss of mean sensitivity in dB/hour) for the glaucoma group was the highest. The mean local fatigue was twice that of

the global fatigue, and a small but significant age dependency (-0.18 dB/hour per year of age) was found i.e. the fatigue effect increased with increasing age. This age effect was similar in all four groups. Contrary to previous reports, no differences were found in glaucoma patients between the fatigue at test locations in normal areas and those in defective areas of the field in glaucoma patients. Division of the global results for different areas of the field (upper, lower, central and peripheral) suggested some eccentricity dependency of the fatigue effect, which was greater in peripheral areas. They concluded that the diagnostic use of fatigue effects was limited since considerable overlap of fatigue scores between the four groups rendered the test insensitive.

An eccentricity dependency of the fatigue effect was also shown by Suzumura (1988) using the Scoperimeter, where the effect was greater in the paracentral (5-19°) than the more peripheral field (19-25°). Fatigue effects were also noted to be greater in the hemi-field containing the defect than in the normal hemi-field.

The study of Johnson et al. (1988a) also argued against the diagnostic use of time-dependent sensitivity losses in glaucoma. Using a Digilab 750 automated perimeter (background luminance 31.5asb) a custom program was designed of 21 minutes duration, consisting of 14 intervals of 1.5 minutes. Within each 1.5 minute interval threshold determinations were made at eccentricities of 5°,10°,15° and 20° and catch trials were presented to estimate the false positive and negative responses. For the control group of 16 normal subjects the stimuli were presented along the four oblique meridians. The meridional locations of stimuli were altered for the patient group, which comprised 13 glaucomas and 3 with optic neuropathy, to avoid areas of significant field loss although the eccentricities remained constant. Selection of appropriate test locations for the patients were based on previous Humphrey Field Analyser 30-2 results. Only those visual field locations that were within 2dB of the normal age-related 95% confidence limits were utilised. Negligible changes were observed in the normal subjects over time for the stimuli presented at 5° and 10° eccentricity. An average sensitivity reduction of 1-2dB over the whole test was found for stimuli presented at 15° and 20° eccentricity whereas patients with visual field loss showed reductions in sensitivity at all eccentricities with increase in examination time. The average

reduction in sensitivity was 1-2dB for the stimuli at 5° and 10° eccentricity and of the order of 4dB for the stimuli at 15° and 20° eccentricity. Half of the normal subjects and half of the patients with visual field loss were given a break of 1.5 minutes mid-way through the examination. This resulted in a higher sensitivity during the second half of the test, particularly at 20° eccentricity, compared with those that had no rest. False positive rates we twice as high in patients compared with normals, and false negative rates 5-6 times greater. False response rates did not alter with time in the normal sample; the patient data suggested a slight decrease in false positive rates and an increase in false negative rates as a function of time, although there was considerable inter-patient variation. The brief rest did not appear to affect the false response rates in the normal subjects or in the patients. The rate of false responses was, however, significantly correlated with the overall time dependent sensitivity loss. The authors recommended that automated static perimetric testing should aim for a maximum test duration of 8-10 minutes to minimize the influence of fatigue on visual field sensitivity.

5.2. AIM OF THE STUDY

The experimental work described in Chapter 4 showed statistically significant improvements in performance mainly for the right eye (tested first) from the first to the second of 3 examinations carried out on 3 successive days and for the left eye (tested second) from the third to the fourth examination, which was carried out after a break of 12 days. The improvement in the performance of the right eye was attributed to learning effects. The improvement for the left eye was attributed to the absence of a between eye fatigue effect at the outset of the fourth left eye examination. Indeed, within the protocol adopted there was substantial potential both for learning and fatigue effects to occur and to interact. Such learning and fatigue effects can be intra- and inter-eye as well as intra- and inter-examination, as summarised in Figure 5.1. The learning effect, described in Chapter 4, was also shown to be greater for the peripheral than for the central visual field and this was discussed in terms of a depth-dependency of the learning effect as opposed to an eccentricity-dependency.

Several authors have documented the fatigue effects observed during prolonged perimetry in glaucoma patients, as reviewed in Section 5.1., with some suggestion that the fatigue

effect may also increase with increase in peripheral angle (Langerhorst et al. 1987, 1988; Suzumura 1988; Johnson et al. 1988a). Such studies, however, have only considered the central 30° of the visual field. The results of Chapter 4 suggested that the peripheral field could be more susceptible to fatigue since greater increases in sensitivity occurred in the peripheral field compared with the central field after the break of 12 days.

The aim of the first study in this Chapter was therefore to evaluate in glaucomatous patients any relationship between the fatigue effect and peripheral angle out to an eccentricity of 55°. Due to the impossibility of separating learning and fatigue effects in a naive patient sample, such as was utilised in Chapter 4, the investigation was carried out using a sample of well trained and highly motivated glaucomatous patients.

Figure 5.1. shows that inter-eye transfer of learning may occur at the first examination of naive glaucomatous patients. The results of Chapter 4, however, suggest that this did not occur in the sample under study: global mean sensitivity was greater in the second (left) eye than the first (right) eye at the first examination for 15 of the 25 patients studied, but this was not statistically significant. It was conjectured that the transfer of learning from the first to the second eye was counterbalanced by a fatigue effect occurring during examination of the second eye. It is impossible, however, to examine such an inter-eye transfer of the learning effect in glaucomatous patients since although there is substantial evidence to show that there is little difference between the mean sensitivity of right and left eyes in a normal sample (Brenton & Phelps 1986; Rutihauser et al. 1989; Feuer & Anderson 1989), the two eyes cannot be considered to represent the same sample from a glaucomatous population.

The aim of the second study was to examine further the interaction of intra and inter-eye (test) and intra and inter-examination (visit) learning and fatigue effects in naive glaucomatous patients using a similar protocol to that described in Section 4.6. The same eye was tested twice in succession at each examination in order to overcome the differences in field loss between the two eyes of any given patient. The first test therefore acted as a control for the second test and allowed better evaluation of the inter-eye transfer of learning and fatigue effects in a glaucomatous population .

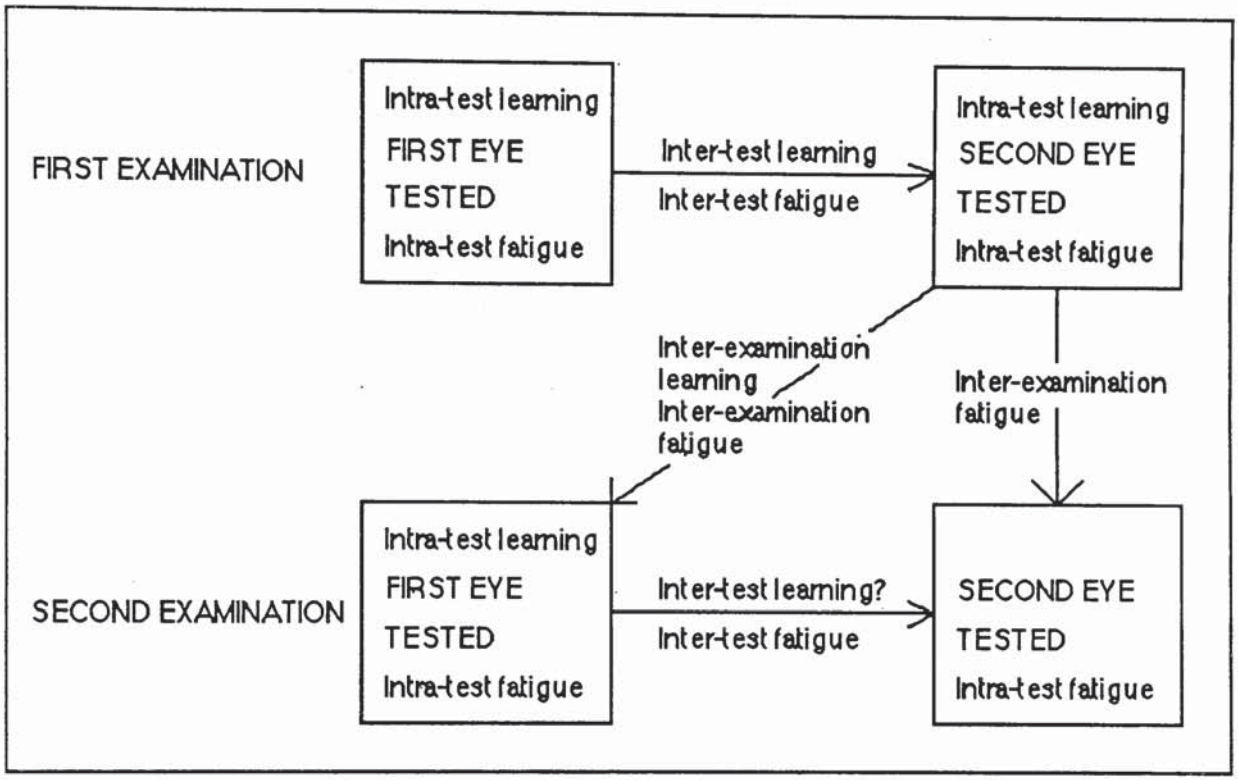


Figure 5.1. Showing how intra and inter-eye as well as intra and inter-examination (visit) learning and fatigue effects may interact in the examination of naive patients.

5.3. THE RELATIONSHIP BETWEEN INTRATEST FATIGUE EFFECTS AND PERIPHERAL ANGLE IN GLAUCOMATOUS PATIENTS

5.3.1. MATERIALS AND METHODS

The sample comprised 19 patients (9 males, 10 females; mean age 70.3 years, SD 5.9 years) all of whom had experienced a minimum of 3 automated perimetric examinations of the central field of each eye using a full-threshold strategy. Six of these patients had experienced a minimum of 7 automated perimetric examinations of the central and peripheral fields of both eyes using a full-threshold strategy.

Exclusion criteria comprised intraocular pressures greater than 30mm Hg, congenital or secondary glaucomas, pseudo-exfoliation and pigment dispersion, visual acuity worse than 6/12, previous intraocular surgery, diabetes or other systemic conditions with marked ocular complications, macula degeneration or other retinal disorders, contact lens wearers, those with abnormal anterior segments and those receiving CNS medication. Patients had no other ocular abnormality, open angles and clear media and were receiving topical ß-blocker therapy where appropriate. The diagnoses comprised 12 patients with ocular hypertension, 3 of whom were receiving therapy, 1 with low-tension glaucoma who was not receiving therapy and 6 with primary open-angle glaucoma all of whom were receiving therapy. Informed consent was obtained from all patients who were unaware as to the purpose of the study.

At the first visit, patients were examined with the Humphrey Field Analyser 630 using the standard 30-2 central thresholding program with stimulus size Goldmann III and stimulus duration 200msec. The depth and type of field loss within the sample, derived from program 30-2 is illustrated in Figure 5.2. after the classification of Caprioli & Sears (1987) and is seen to comprise patients with relatively pure diffuse loss.

The central and peripheral fields respectively were each examined on a separate occasion at the following two visits. Each visit was separated by a period of a week and comprised 5 consecutive tests of the central or peripheral field using a full-threshold program customised for the study (stimulus size Goldmann III and stimulus duration 200msec). The order of

examination of the central and peripheral field was randomised within the sample. The central field program examined 30 locations within 30° eccentricity using an interstimulus grid of 10°. The peripheral field program examined 30 locations between 30° and 55° eccentricity with an interstimulus grid of 10° in the nasal periphery and an interstimulus grid of 15° for the remaining peripheral area. The stimulus locations for both programs are shown in Figure 5.3. The time taken to complete each custom test was of the order of 6 minutes. Patients received a break of approximately 1 minute between each test while the results were saved on disk and the program restarted. Examination of the central field included measurement of the foveal threshold at the beginning ofeach of the 5 custom tests.

Patients were pre-adapted to the bowl luminance of 31.5asb for 5 minutes, and remained under the adaptation conditions of the perimeter bowl during the break between each test. Natural pupils were used; pupil size was measured under the adaptation conditions of the perimeter bowl via the video monitor and corrected for the effects of camera magnification. Intraocular pressure was measured after each examination (Goldmann tonometry). Ophthalmological examination was carried out, and the diagnosis confirmed at each patient's subsequent hospital out-patient visit a few weeks later.

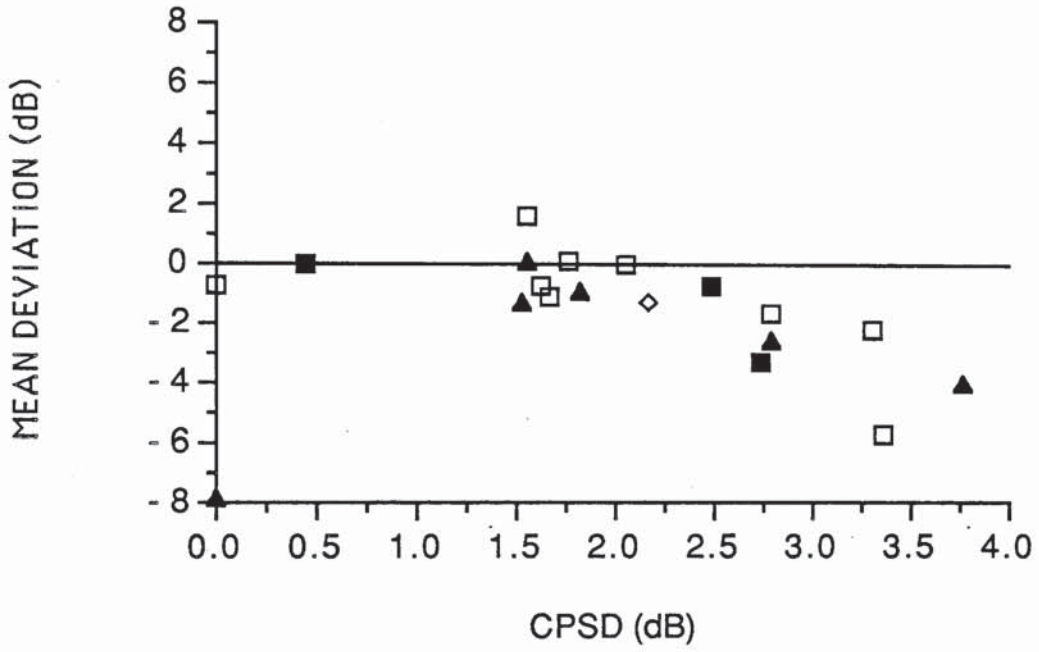


Figure 5.2. Illustrating the depth and type of field loss within the sample, derived from Humphrey program 30-2, after the classification of Caprioli & Sears (1987) which considers mean deviation (diffuse loss) as a function of corrected pattern standard deviation (focal loss). Field loss is seen to be primarily of the diffuse type. The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; low-tension glaucoma without therapy: open diamond; primary open-angle glaucoma with therapy: closed triangles).

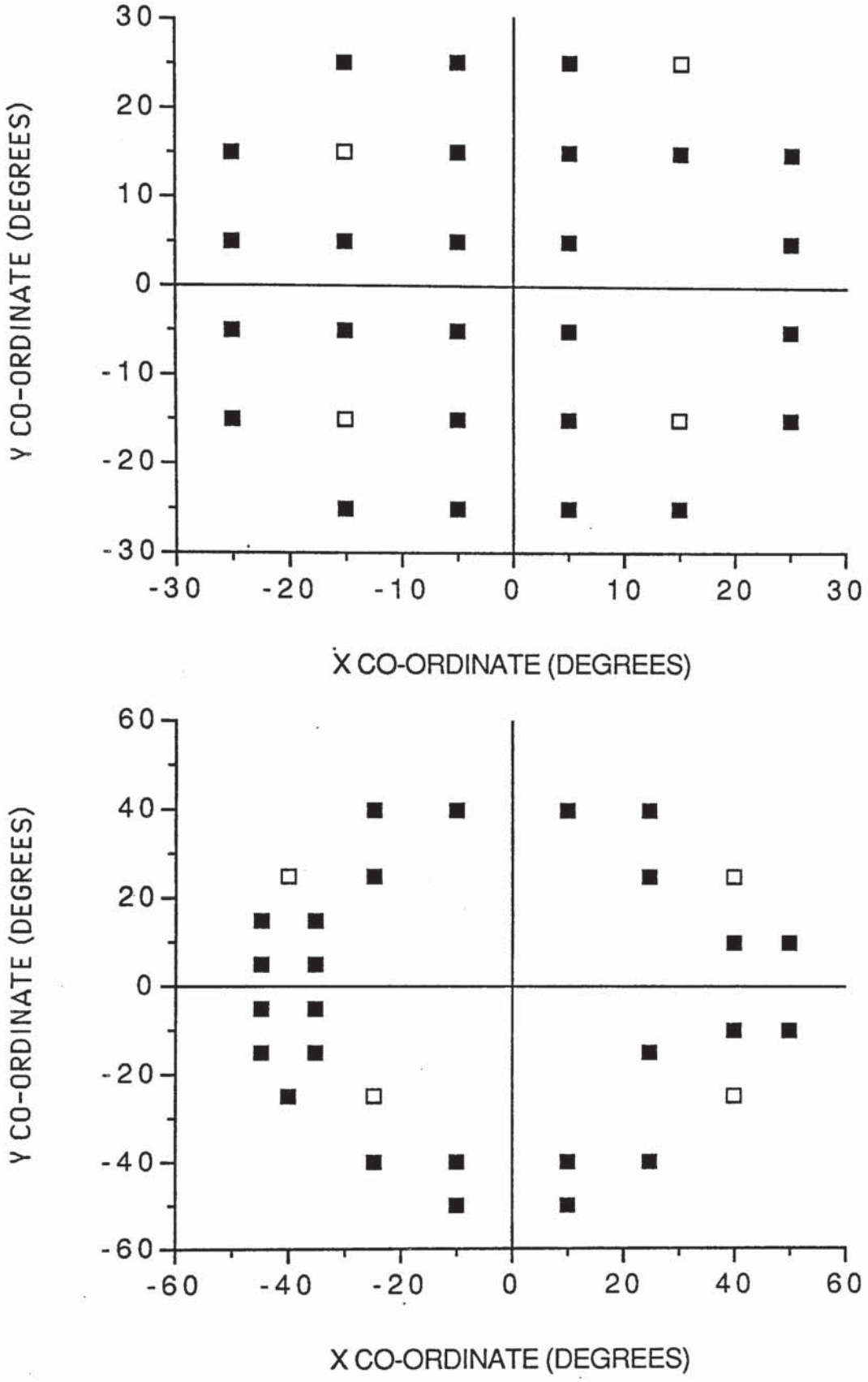


Figure 5.3. Showing stimulus locations of the custom programs for examination of the central (top) and peripheral (bottom) fields respectively. The program for examination of the central field consisted of 30 points within 30° eccentricity with an inter-stimulus separation of 10°. The program for examination of the peripheral field consisted of 30 points between 30°-55° eccentricity, with an inter-stimulus separation of 10° in the nasal periphery and 15° in the remaining peripheral field. Stimulus locations where double threshold determinations were made for the purpose of calculating short-term fluctuation are indicated with open squares.

The results were analysed in terms of the visual field indices calculated from the formulae of Flammer (1986). Data for both the central and peripheral fields was considered in terms of the visual field indices mean sensitivity and short-term fluctuation and also in terms of the reliability factors: the percentage of fixation losses, false positive and negative responses and the total number of stimuli presented. The mean defect and loss variance indices could not be calculated, since computation of these indices requires normative age-matched data, and there were no corresponding stimulus locations between the custom program and the standard central and peripheral programs for which normative data is available. Peripheral mean sensitivity was further considered in terms of hemi-fields, namely, superior, inferior, nasal and temporal peripheral mean sensitivity.

Statistical analysis for each of the 5 consecutive examinations of the central and peripheral fields was undertaken using the Friedmann two-way analysis of variance by ranks and the Wilcoxon signed rank test for matched pairs was used where the Friedmann ANOVA indicated a significant change.

5.3.2. RESULTS

Statistically significant decreases were found in the absolute values of the visual field indices for 19 glaucomatous patients over the course of 5 successive examinations using the Friedmann two-way ANOVA by ranks as shown in Table 5.1.

The results of the Wilcoxon signed-rank test for matched pairs are shown in Tables 5.2. and 5.3. of median visual field index and reliability parameters against examination sequence for 19 glaucomatous patients for the central and peripheral fields respectively.

Visual Field Index	df	Chi-squared	Significance level
Central MS	4	17.53	$p < 0.01$
Peripheral MS	4	33.18	$p < 0.001$
Superior peripheral MS	4	25.07	$p < 0.001$
Inferior peripheral MS	4	25.31	$p < 0.001$
Nasal peripheral MS	4	36.04	$p < 0.001$
Temporal peripheral MS	4	18.52	$p < 0.001$

Table 5.1. Showing the visual field indices which decreased significantly over five successive examinations (Friedmann two-way analysis of variance by ranks).

INDEX	EXAMINATION				
	1	2	3	4	5
Central MS (dB)	25.37 (25.29;0.44)	25.03* (24.77;0.46)	24.57* (24.27;0.55)	24.50 (23.91;0.59)	24.03 (23.73;0.58)
Foveal sensitivity (dB)	32.0 (32.16;0.61)	33.0 (33.21;0.41)	32.0 (32.21;0.40)	32.0 (32.37;0.45)	33.0 (32.63;0.41)
Central SF (dB)	1.22 (1.22;0.09)	1.22 (1.29;0.17)	1.73 (1.47;0.17)	1.58 (1.48;0.10)	1.58 (1.67;0.15)
% Fixation losses	7.7 (9.1;2.6)	0.0 (6.7;2.4)	0.0 (12.8;4.9)	0.0 (7.6;2.6)	7.1 (14.2;3.8)
% False positive responses	0.0 (10.8;3.9)	0.0 (7.4;5.3)	0.0 (2.6;2.6)	0.0 (3.4;2.3)	0.0 (5.3;2.0)
% False negative responses	0.0 (5.9;3.5)	0.0 (3.9;1.8)	0.0 (5.2;2.1)	0.0 (6.3;2.8)	0.0 (4.4;1.7)
Stimuli presented	201.0 (203.6;6.0)	196.0 (200.7;4.8)	207.0 (208.8;5.7)	197.0 (204.5;5.4)	207.0 (212.8;6.1)

Table 5.2. Median visual field index for the central field against examination sequence for 19 patients. The significance level for comparison of a given examination with the previous examination are indicated in superscript. * indicates a probability of $p<0.05$. The accompanying means and standard errors are given in parentheses.

INDEX	EXAMINATION				
	1	2	3	4	5
Peripheral MS (dB)	18.38 (18.62;0.56)	16.69*** (17.03;0.70)	16.73 (16.72;0.80)	14.95** (16.04;0.82)	14.09 (15.68;0.86)
Superior peripheral MS (dB)	17.86 (17.16;0.77)	14.71*** (14.93;0.94)	15.21 (14.75;0.91)	13.68** (13.92;0.98)	12.86 (13.83;1.05)
Inferior peripheral MS (dB)	19.63 (20.05;0.52)	18.25** (19.02;0.64)	17.88 (18.45;0.82)	17.00 (17.91;0.86)	16.56 (17.31;0.89)
Nasal peripheral MS (dB)	17.76 (17.69;0.66)	15.35** (15.80;0.81)	15.00 (14.92;1.02)	12.88** (13.91;1.06)	13.12 (13.01;1.15)
Temporal peripheral MS (dB)	19.62 (19.87;0.52)	19.27** (18.96;0.64)	18.77 (18.92;0.66)	18.27 (18.53;0.71)	18.38 (18.56;0.69)
Peripheral SF (dB)	1.41 (1.78;0.38)	1.73 (1.91;0.24)	1.73 (1.81;0.27)	1.73 (1.81;0.19)	1.73 (1.89;0.13)
% Fixation losses	0.0 (7.2;2.2)	0.0 (6.2;2.4)	6.7 (11.8;4.1)	12.5 (10.6;3.0)	0.0 (5.5;2.6)
% False positive responses	0.0 (5.4;2.9)	0.0 (9.1;4.0)	0.0 (2.3;1.2)	0.0 (1.8;1.4)	0.0 (1.1;0.8)
% False negative responses	0.0 (6.8;3.8)	0.0 (9.3;3.4)	0.0 (8.4;2.8)	14.3 (10.7;2.3)	12.5 (12.8;3.5)
Stimuli presented	211.0 (211.5;4.7)	208.0 (216.5;5.9)	209.0 (212.4;4.1)	222.0 (225.8;5.5)	223.0 (223.5;5.6)

Table 5.3. Median visual field index for the peripheral field against examination sequence for 19 patients. The significance level for comparison of a given examination with the previous examination are indicated in superscript. *** indicates a probability of $p<0.002$ and ** a probability of $p<0.02$. The accompanying means and standard errors are given in parentheses.

Statistically significant decreases occurred in the visual field indices central mean sensitivity, peripheral mean sensitivity, superior and inferior peripheral mean sensitivity and nasal and temporal peripheral mean sensitivity. The change in these parameters from the first to the fifth test was not only considered in absolute terms i.e. decibels, but also as a proportionate change to account for the differing amounts of field loss within the sample.

Group mean central mean sensitivity decreased by 1.56dB (-6.1%) from the first to the fifth test; group mean peripheral mean sensitivity decreased by 2.94dB (-16.2%). Group mean superior peripheral mean sensitivity decreased by 3.33dB (-21.1%) and group mean inferior peripheral mean sensitivity by 2.74dB (-14.2%); group mean nasal peripheral mean sensitivity decreased by 4.68dB (-27.7%) and group mean temporal peripheral mean sensitivity by 1.31dB (-6.8%). The Wilcoxon signed rank test showed these changes to be statistically significant mainly from the first to second tests, and to be statistically more significant for the peripheral field compared with the central field. Short-term fluctuation increased over the course of the 5 tests for both the central and the peripheral field although the changes were not statistically significant. Group mean central short-term fluctuation increased by 0.43dB (45.3%) and group mean peripheral short-term fluctuation by increased by 0.12dB (37.3%).

The group mean proportionate changes in mean sensitivity and in short-term fluctuation for the central and peripheral field over the course of the 5 tests relative to the baseline of the first test are illustrated in Figures 5.4. and 5.5. respectively. The proportionate changes in mean sensitivity and in short-term fluctuation from the first to the fifth test as a function of the absolute value at the first test for the central and peripheral field are shown in Figures 5.6. and 5.7. respectively. The standard errors were noted to be greater for the peripheral field than for the central field in both cases. When the proportionate change in central mean sensitivity from the first to the fifth test was compared with the corresponding proportionate change in peripheral mean sensitivity, the deterioration in the peripheral field (group mean proportionate change -0.16, SE 0.03, median -0.15) was significantly greater ($p<0.02$) than the deterioration in the central field (group mean proportionate change -0.06, SE 0.02, median -0.07).

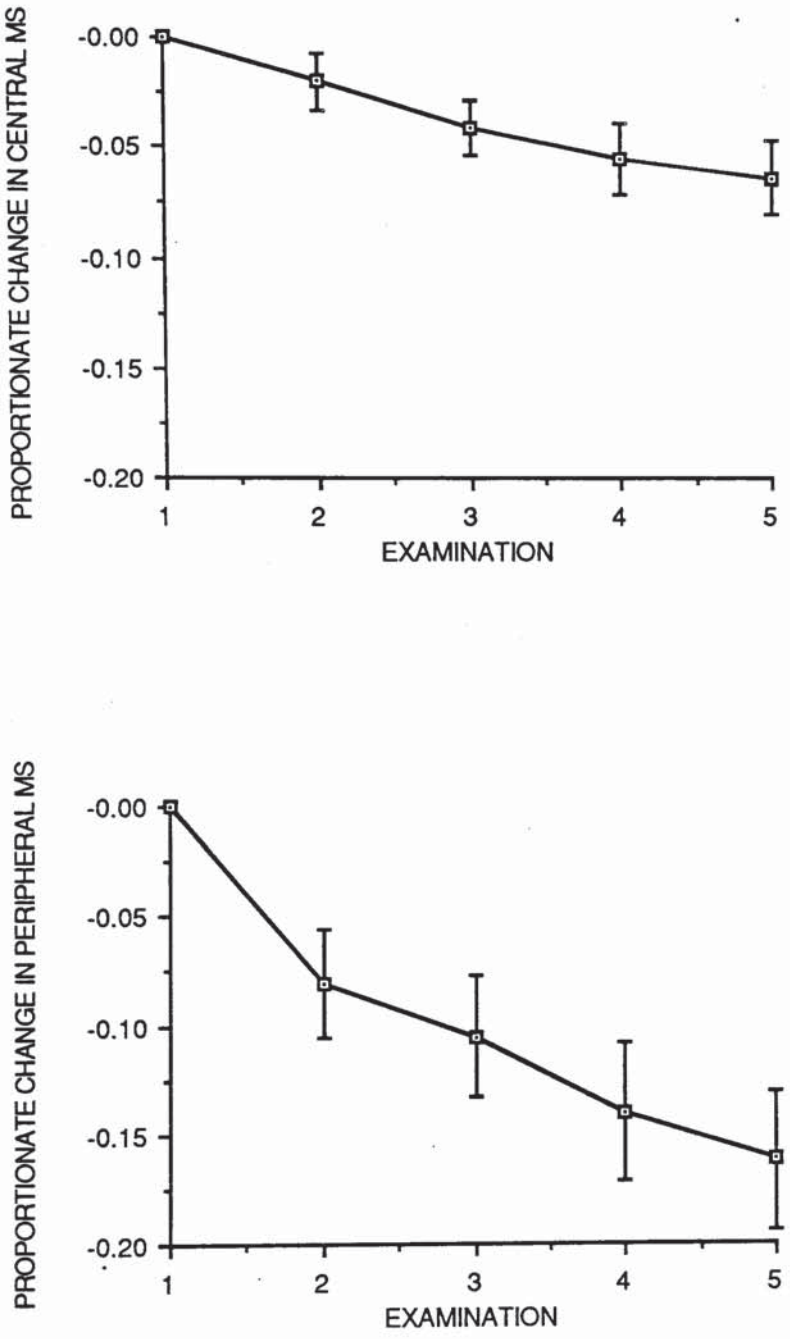


Figure 5.4. Group mean proportionate change in central (top) and peripheral (bottom) mean sensitivity considered relative to the first test as a function of test sequence. The error bars indicate 1 S.E. of the mean.

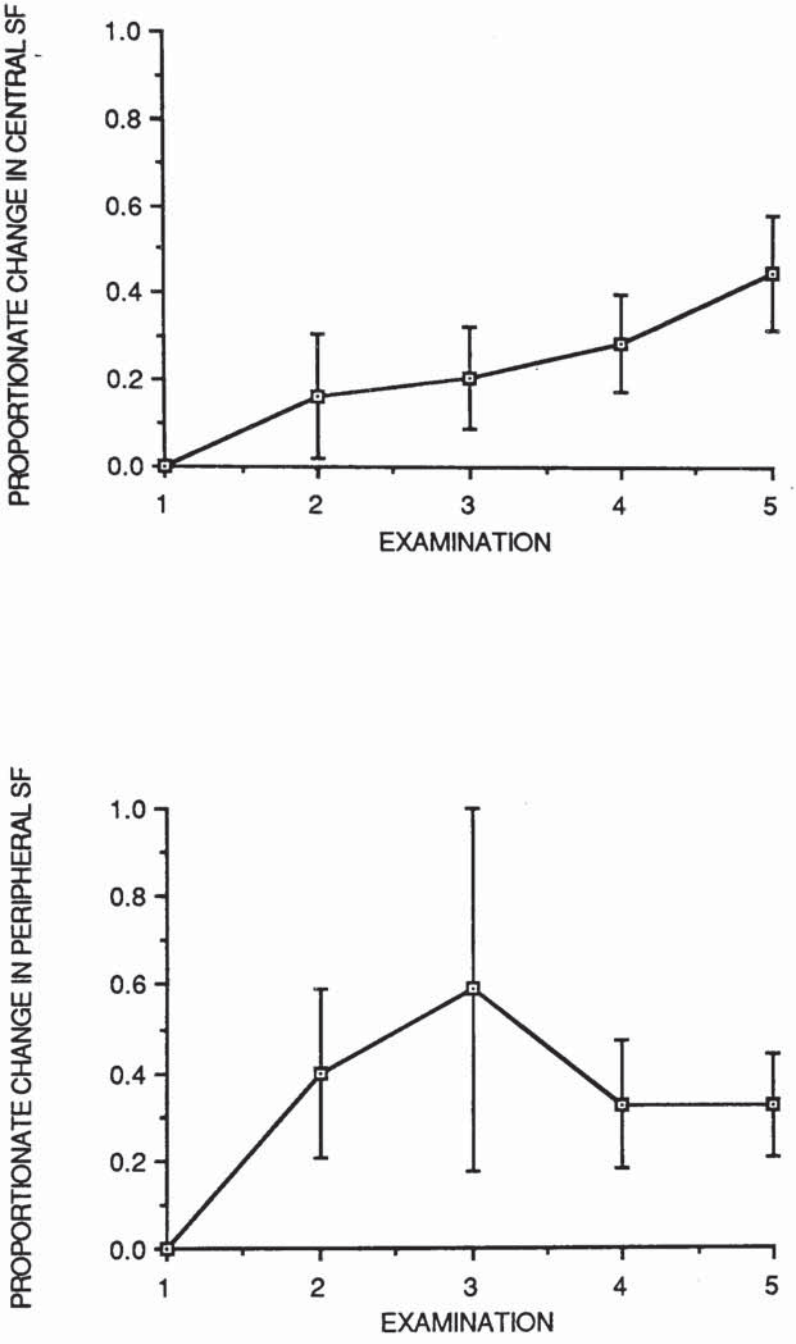


Figure 5.5. Group mean proportionate change in central (top) and peripheral (bottom) short-term fluctuation considered relative to the first test as a function of test sequence. The error bars indicate 1 S.E. of the mean.

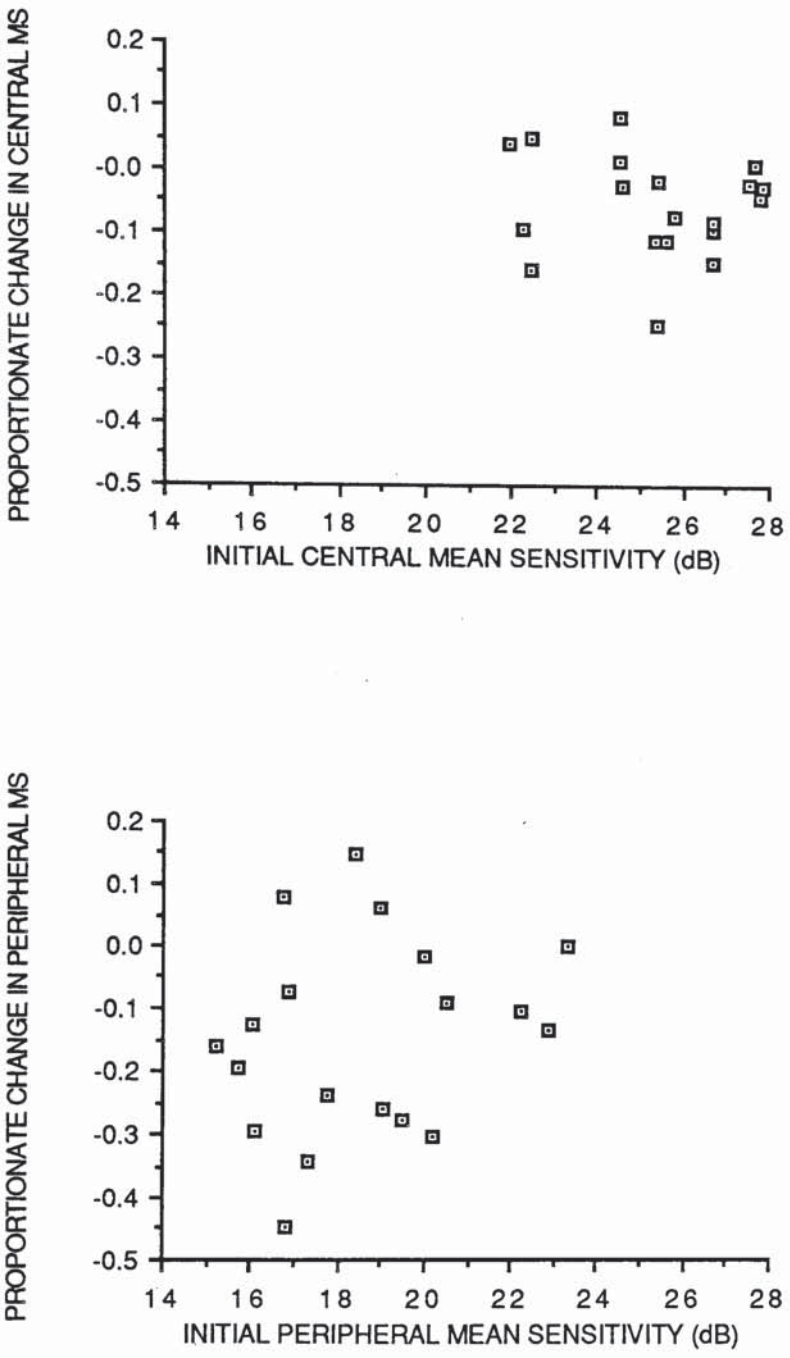


Figure 5.6. Proportionate change in central (top) and peripheral (bottom) mean sensitivity from the first to the fifth test as a function of the initial value recorded at the first test.

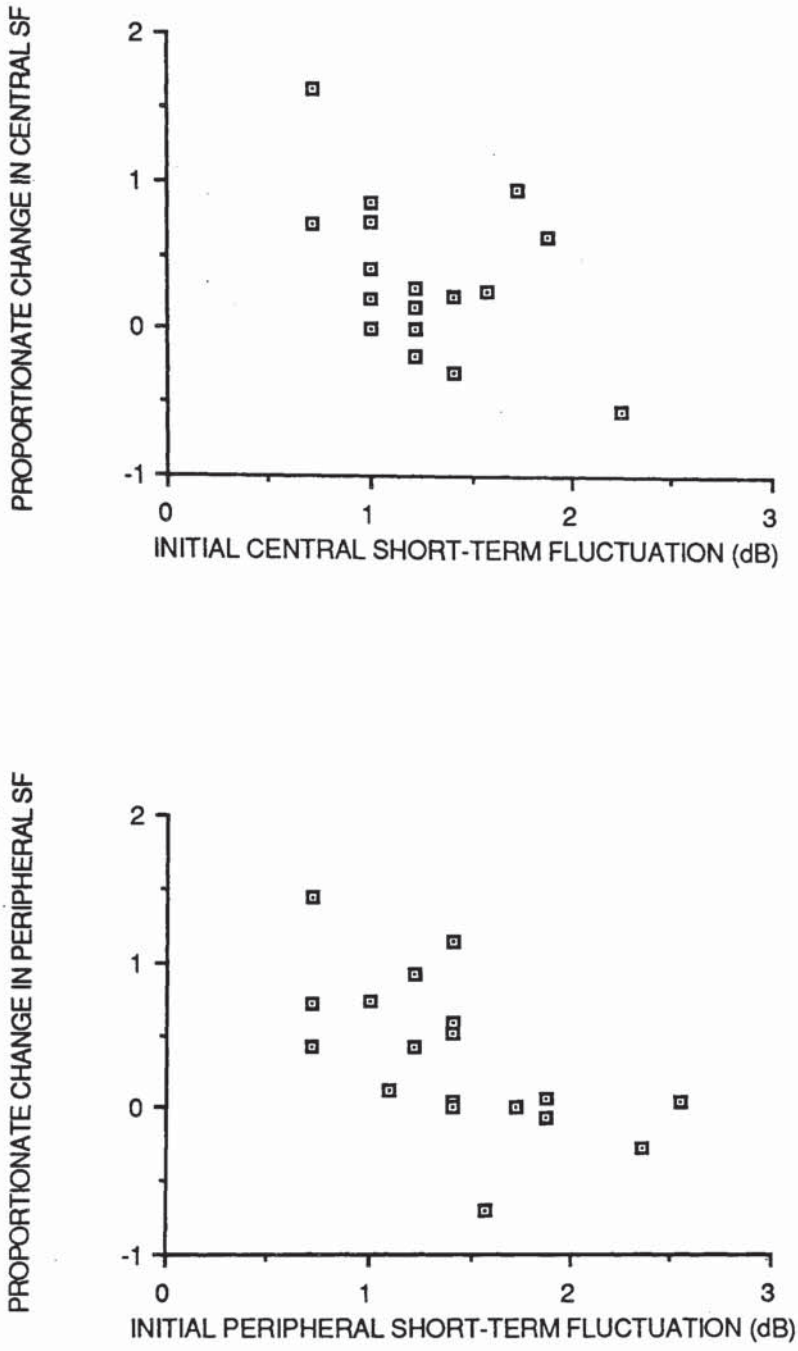


Figure 5.7. Proportionate change in central (top) and peripheral (bottom) short-term fluctuation from the first to the fifth test as a function of the initial value recorded at the first test.

No significant changes were observed in the foveal threshold or in any of the reliability indices of the percentage of fixation losses, false positive responses, false negative responses, number of stimuli presented or total test time over the course of 5 tests of the central or peripheral field.

5.3.3. DISCUSSION

The deterioration in mean sensitivity of the central and peripheral field over the course of 5 consecutive examinations is considered to represent a "fatigue effect". The results are in agreement with the manual perimetric data of Heijl & Drance (1983) and other studies on glaucomatous patients using automated perimetry (Heijl 1977b; Holmin & Krakau 1979; Heijl & Drance 1983; Flammer & Niesel 1984; Langerhorst et al. 1987, 1988; Suzumura 1988; Johnson et al. 1988a).

Deterioration in mean sensitivity was statistically significantly greater in the peripheral than the central field. This eccentricity dependency of the fatigue effect in glaucoma patients is in agreement with other authors (Langerhorst et al. 1987, 1988; Suzumura 1988; Johnson et al. 1988a), and also with the work of Wildberger & Robert (1988) in cases of optic neuropathy, but extends the finding to beyond 30° eccentricity. The eccentricity dependency of the fatigue effect could be explained by the increase in short-term fluctuation with peripheral angle (Heijl et al. 1987a). An alternative explanation could be mild ptosis occurring over the course of the 5 examinations. Fixation however was continually monitored on the video-screen during the examination and this tendency was not noted. Additionally, a greater deterioration was noted for the nasal compared with the temporal peripheral field over the 5 tests, and, if ptosis were the cause of this deterioration, it would be expected to have the same effects on the nasal and temporal areas of the field. Change in pupil diameter during the examinations was not thought to account for the greater deterioration in mean sensitivity in the peripheral field compared with the central field. Pupil diameter was measured for all tests under the adaptation conditions of the perimeter bowl via the video-monitor. Group mean pupil diameter was 4.0mm (SD 0.5mm) and 3.7mm (SD 0.7mm) for the first and fifth examinations respectively of the central field, and 4.5mm (SD 1.6mm) and 4.3mm (SD 1.6mm) for the first and fifth examinations respectively of the

peripheral field.

Similar decrements in performance have also been reported for the recording of the absolute light threshold (Ronchi 1970; Ronchi & Cetica 1972; Ronchi & Salvi 1973). The decay process in the measurement of the absolute threshold was described by an exponential function of the form $y=e^{-t/m}$ where e is the natural logarithm, t is the time and m is the time constant of the decay process. Ronchi & Salvi (1973) however reported the time constant to increase with eccentricity i.e. there was a slower decay process peripherally.

The relationship between the proportionate deterioration in mean sensitivity from the first to fifth examinations and the absolute value of mean sensitivity at the first examination, is inconclusive and cannot support a depth dependency of the fatigue effect. If the depth dependency of the fatigue effect were, however, applicable on a pointwise basis, it is hypothesised that fatigue would not only lead to a general constriction (depression) of the field but also a change in the form of the field i.e. the extent of focal loss. Due to the lack of age-matched normative data for the stimuli locations used in the study the visual field indices loss variance and corrected loss varience were not calculated, however it is hypothesised that fatigue could result in an increase in these parameters.

Improvements in sensitivity due to the learning effect, described in Chapter 4, were mainly attributed to an alteration in the patients' criterion for response. This however would not account for the apparent depth dependency of the fatigue effect, since the patients individual criterion for response would not be expected to be related to the depth of field loss or to the diagnosis. Additionally, if criterion changes were responsible for the fatigue effect, it would be expected that a similar deterioration in performance would also be observed in normal subjects. There is substantial evidence in the literature, however, suggesting that the differential light sensitivity remains relatively stable in normal subjects compared with glaucoma patients.

There are many references in the literature on visual fatigue and the effects of fatigue on the performance of visual tasks, using the test-stimulus itself as the fatiguing agent. As early as

1892, Clarke defined retinal fatigue as "exhaustion of the retinal sensibility induced by prolonged visual effort". Berger & Mahneke (1954) found visual acuity for a Landolt C, recorded continuously over a period of an hour, to decrease by 18%-32% although the variablity of the measurement showed no consistent change. Over a similar time period they also found central critical fusion frequency to decrease by an average of 10% although, again, there was no increase in the variability of the response. In studies on the effects of fatigue on a perceptual-motor task, Singleton (1953) and Haider & Dixon (1961) suggested that the decrement in performance resulted from an increase in the reaction time component of the skill although the movement time remained constant. In view of this, the average interstimulus duration was calculated for each of the 5 consecutive tests by dividing total test time by the number of stimuli presented. No significant change however was found in this parameter over the course of 5 tests, using the Friedmann two-way analysis of varience by ranks.

It was hypothesised that the "blankout" phenomenon, which occurs with a Ganzfeld stimulus, could be responsible for the fatigue effect. This phenomenon has been reported in relation to automated perimetry by Fuhr et al. (1990), who suggested that it resulted from binocular rivalry occurring under conditions in which there was approximately 0.75 log units of intensity difference in illumination between the two eyes. The phenomenon was eliminated when the bowl of a Humphrey Field Analyser was viewed binocularly, or when a translucent occluder was used for the eye not under test instead of an opaque occluder. Indeed, under such conditions, mean sensitivity was increased by 0.7dB and retest variability was reduced by 18.8%. The blankout phenomenon could account for any deterioration in performance observed in normal subjects, although would not account for the differences in fatigue effect between normal subjects and glaucoma patients, or for the eccentricity or possible depth dependency of the fatigue effect.

The substantial evidence showing that fatigue effects within the central 30° are minimal in normal subjects, and increase with increasing depth of glaucomatous visual field loss, suggests a physiological mechanism for the fatigue effect. An increased latency of the visual evoked response (VER), similar to that observed in demyelinating disease, is also seen in

patients with glaucoma (Atkin et al. 1983) and ocular hypertension and may precede the development of visual field loss (Quigley et al. 1981; Airaksinen et al. 1984). The increased latency of the VER is however frequently greater than would be accounted for by a slowing of the neuroconduction process in demyelination. It has been hypothesised therefore that a second source of visual delay might be located peripheral to the optic nerve, resulting from altered conduction within the retina, possibly at a pre-ganglionic level (Halliday et al. 1972; Heron et al. 1974). Indeed, Atkin (1985) has suggested that raised intraocular pressure may impair transport of neurotransmitter from the retinal ganglion cells to their axon terminals in the lateral geniculate nucleus. If there is diffuse loss of retinal ganglion cell function with little effect on vision there may nevertheless be a considerable effect on the time taken to excite corticopetal cells in the lateral geniculate nucleus through the reduced neurotransmitter availability. Atkin (1985) thus proposes that synaptic depletion of neurotransmitter is partially responsible for the fatigue effects observed in multiple sclerosis as well as in glaucoma.

5.4. THE INTERACTION OF LEARNING AND FATIGUE EFFECTS IN NAIVE GLAUCOMA SUSPECT PATIENTS

5.4.1. MATERIALS AND METHODS

The sample comprised 10 patients with suspected glaucoma (3 male and 7 female; mean age 63.5 years, SD 9.6 years) referred by optometrists or general practitioners to the Birmingham General Hospital. No patient had any previous experience of automated perimetry.

The same exclusion criteria were applied as detailed in Section 4.6. for the recruitment of patients by the consultant ophthalmologist namely, intraocular pressures greater than 30mm Hg, congenital or secondary glaucomas, pseudo-exfoliation and pigment dispersion, visual acuity of worse than 6/12, previous intraocular surgery, diabetes or other systenmic conditions with marked ocular complications, macula degeneration or other retinal disorders, contact lens wearers, those with abnormal anterior segments and those receiving CNS medication. Apart from the suspicion of glaucoma, patients had no other ocular abnormality and had open angles and clear media. Informed consent was obtained from all patients who

were unaware as to the purpose of the study.

All patients underwent a full ophthalmological examination prior to automated perimetry, consisting of ophthalmoscopic disc assessment, gonioscopy, Goldmann tonometry (average of 3 measurements), slit-lamp assessment of the anterior chamber and blood pressure measurement. ß-blocker therapy was commenced where appropriate.

Patients were examined with the Humphrey Field Analyser 630, using a full-threshold program customised for the study, with stimulus size Goldmann III (0.431°) and a stimulus duration of 200msec. The single program examined the same 60 locations across the field as described in Section 5.3.1 using an interstimulus grid of 10° out to an eccentricity of 30° and in the nasal periphery and an interstimulus grid of 15° for the remaining peripheral (30-55°) area. Thirty stimuli were located in the central and in the peripheral areas of the field, as shown in Figure 5.8. The program included additional stimulus locations in the nasal periphery in view of the recent evidence showing isolated peripheral visual field defects, with normal central fields, to occur in up to 12% of early glaucoma patients (Seamone et al. 1988; Haas et al. 1989). The time taken to complete the program was in the order of 12 minutes.

Patients were examined on three consecutive days, and again after a break of 7 days, since the experimental work of Chapter 4 on short-term learning effects had identified an inter-eye inter-test fatigue effect that lasted more than 24 hours but less than 12 days. All examinations were carried out at the same time of day, and intraocular pressure was measured after each examination (Goldmann tonometry). The right eye was examined twice in succession on each day, with a break of 5 minutes between each examination. The order of examination of the peripheral and central field was randomised at each visit.

Patients were pre-adapted to the bowl luminance of 31.5asb for 5 minutes, natural pupils were used with the appropriate near refractive correction and fixation constantly monitored. All patients were given the same instruction, and the examinations were all controlled by the same perimetrist. One week after completion of the last custom field, patients were examined using the standard 30-2 central thresholding program. The depth and type of field loss within

the sample, derived from program 30-2 is illustrated in Figure 5.9. after the classification of Caprioli & Sears (1987). The diagnosis was confirmed at the next ophthalmological examination using the results of program 30-2.

Results for the custom program were considered in terms of the visual field indices as described by Flammer et al. (1985) and calculated for the custom program using the formulae of Flammer (1986). Data for the full field, and for the central and peripheral areas in isolation, was considered in terms of the visual field indices mean sensitivity and short-term fluctuation and in terms of the reliability factors: the percentage of fixation losses, false positive and false negative responses and the total number of stimuli presented.

The proportionate difference between the visual field indices recorded from the first and second eyes tested was calculated for each day, and statistical analysis for the first 3 daily sucessive examinations undertaken using a Friedmann two-way analysis of variance by ranks, to determine whether the interaction of learning and fatigue effects varied as a function of examination sequence. The Wilcoxon signed-rank matched pairs test was used to examine the change between the third daily successive examination and the fourth examination, carried out after a break of 10 days.

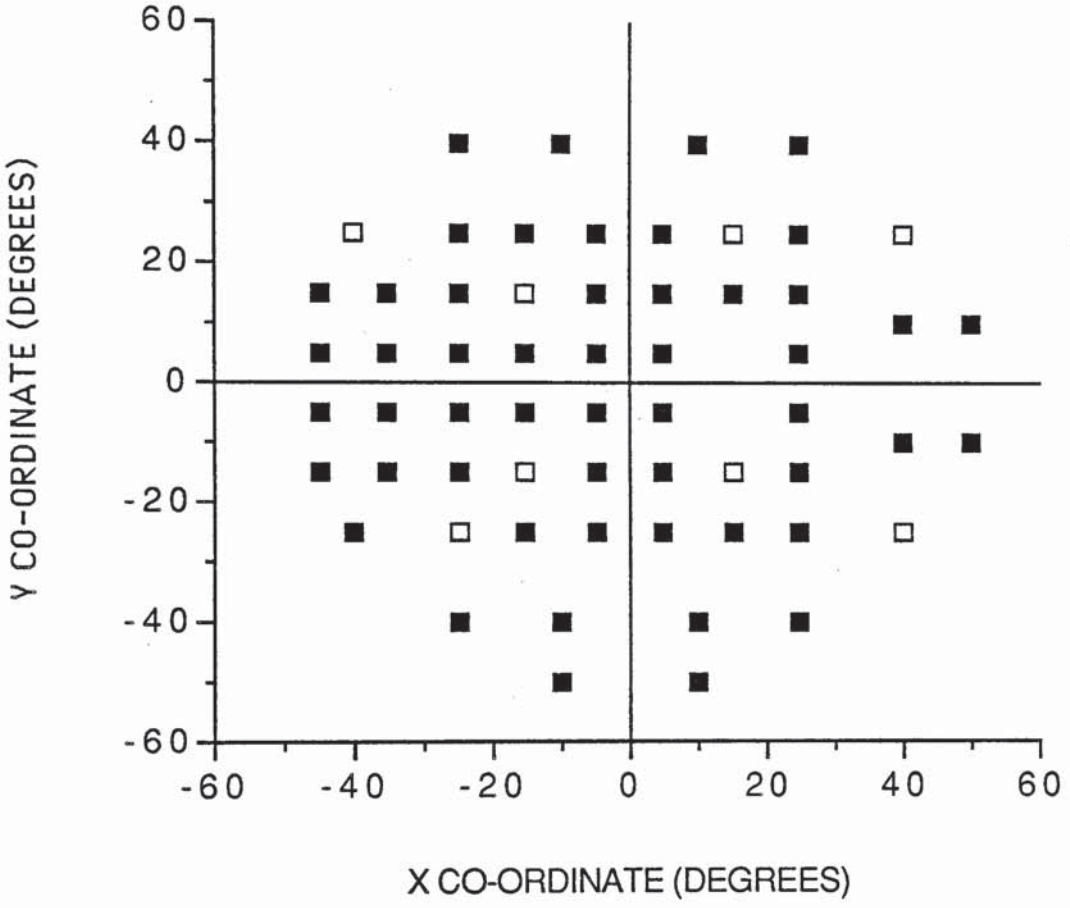


Figure 5.8. Showing stimuli locations of the custom program. The program consisted of 60 points, comprising 30 points within 30° eccentricity and 30 points between 30°-55° eccentricity. The inter-stimulus separation was 10° within 30° eccentricity and in the nasal periphery and 15° in the remaining peripheral (30-55°) field. Stimulus locations where double threshold determinations were made for the purpose of calculating short-term fluctuation are indicated with open squares.

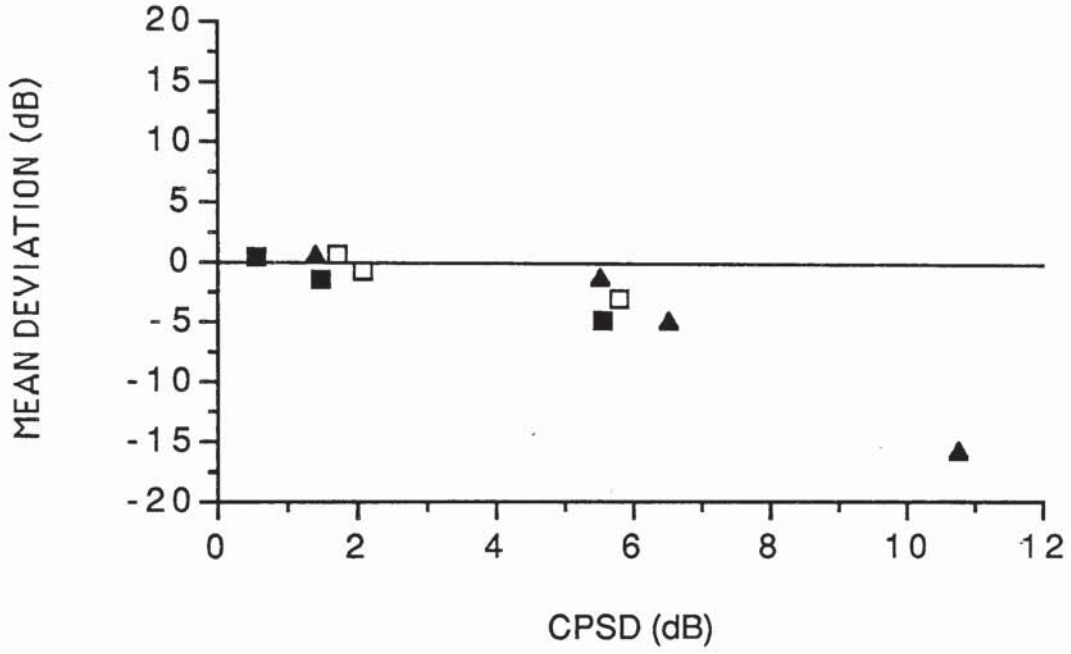


Figure 5.9. Illustrating the depth and type of field loss, derived from Humphrey program 30-2 after the classification of Caprioli & Sears (1987), which considers mean deviation (diffuse loss) as a function of corrected pattern standard deviation (focal loss). The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; primary open-angle glaucoma: closed triangles).

5.4.2. RESULTS

The diagnoses comprised 6 patients with ocular hypertension, 3 of whom were receiving therapy, and 4 patients with primary open-angle glaucoma, all of whom were receiving therapy.

The median visual field indices and reliability parameters against examination sequence for the 10 patients are shown in Tables 5.4. and 5.5. respectively. The accompanying means and standard errors are shown in parentheses.

The Friedmann two-way ANOVA by ranks showed no significant change in the proportionate difference between the first and second eye examined as a function of examination sequence over the first 3 examinations for each of the visual field indices global mean sensitivity, central mean sensitivity, peripheral mean sensitivity, superior peripheral mean sensitivity, inferior peripheral mean sensitivity or short-term fluctuation.

The Wilcoxon signed-rank matched pairs test showed no significant change in the proportionate difference between the visual field indices derived from the two tests carried out on the third daily successive examination and those carried out at the follow-up examination 10 days later.

INDEX		DAY			
		1	2	3	10
Global MS (dB)	R1	20.20 (19.24;1.49)	20.65 (19.90;1.47)	20.35 (19.95;1.64)	20.85 (20.54;1.50)
	R2	19.85 (18.76;1.59)	20.30 (18.92;1.78)	19.35 (18.68;1.94)	19.45 (19.66;1.53)
Central MS (dB)	R1	24.95 (23.25;1.55)	24.70 (23.70;1.58)	24.85 (24.22;1.43)	25.50 (24.87;1.42)
	R2	23.70 (22.65;1.61)	25.05 (22.76;1.85)	22.90 (22.46;1.85)	24.95 (23.69;1.49)
Peripheral MS (dB)	R1	15.45 (15.21;1.54)	17.15 (15.92;1.41)	15.2 (15.68;1.97)	16.25 (16.21;1.73)
	R2	15.25 (14.88;1.66)	15.75 (15.19;1.76)	15.35 (14.88;2.12)	14.05 (15.69;1.69)
Superior peripheral MS MS (dB)	R1	12.60 (12.86;1.78)	14.25 (13.10;1.82)	12.05 (12.88;2.39)	12.70 (13.20;2.17)
	R2	12.40 (12.46;1.71)	11.75 (12.32;2.08)	12.95 (12.08;2.57)	9.00 (12.42;2.13)
Inferior peripheral MS (dB)	R1	17.85 (17.28;1.64)	18.20 (17.54;1.42)	18.25 (18.14;1.81)	20.50 (18.85;1.64)
	R2	18.20 (16.96;1.83)	19.55 (17.70;1.62)	18.85 (17.36;1.87)	19.65 (18.54;1.62)

Table 5.4. Median visual field index for first (R1) and second (R2) test of the right eye against examination sequence (days) for 10 glaucomatous suspects. The accompanying means and standard errors are given in parentheses.

INDEX		DAY			
		1	2	3	10
Global SF (dB)	R1	1.77 (2.22;0.34)	1.90 (2.32;0.39)	1.77 (2.10;0.24)	2.70 (2.65;0.46)
	R2	2.25 (2.19;0.35)	1.78 (2.07;0.28)	2.30 (2.38;0.38)	1.65 (1.63;0.17)
Central SF (dB)	R1	1.80 (2.47;0.54)	1.22 (1.49;0.19)	1.58 (2.02;0.38)	2.18 (2.61;0.56)
	R2	1.79 (1.95;0.39)	1.66 (1.70;0.29)	1.85 (2.27;0.44)	1.37 (1.53;0.30)
Peripheral SF (dB)	R1	2.12 (1.98;0.18)	2.24 (2.83;0.55)	1.93 (1.97;0.29)	1.80 (2.40;0.51)
	R2	1.93 (2.16;0.46)	1.94 (2.14;0.44)	1.57 (2.30;0.46)	1.50 (1.49;0.16)
No. of stimuli	R1	423.0 (399.9;41.9)	438.5 (433.8;14.4)	419.5 (412.4;10.7)	412.5 (411.7;10.1)
	R2	431.0 (433.6;18.5)	400.0 (413.7;11.5)	414.0 (418.6;12.8)	414.5 (411.7;8.4)
False negative responses (%)	R1	14.6 (17.9;4.4)	9.6 (11.4;2.6)	9.2 (12.3;3.9)	10.6 (1.3;3.6)
	R2	10.4 (13.3;4.6)	6.3 (14.5;6.4)	0.0 (7.1;5.2)	3.9 (10.8;4.4)
False positive responses (%)	R1	2.8 (5.7;2.3)	0.0 (3.6;2.7)	0.0 (1.7;1.1)	0.0 (4.2;2.2)
	R2	0.0 (2.8;1.4)	0.0 (2.7;2.7)	0.0 (2.5;1.3)	0.0 (1.4;0.9)
Fixation losses (%)	R1	8.5 (10.5;3.6)	4.1 (9.8;4.2)	5.7 (9.5;3.3)	7.9 (12.8;3.9)
	R2	4.6 (6.0;1.7)	9.3 (11.1;2.3)	3.9 (5.0;21.9.4)	6.4 (10.4;4.7)

Table 5.5. Median reliability parameters against examination sequence (days) for 10 glaucomatous suspects. The accompanying means and standard errors are given in parentheses.

5.4.3. DISCUSSION

Learning effects would result in an increase in the visual field indices and parameters (i.e. an improvement in performance) from the first to the second test on each day, whereas fatigue effects would result in a decrease in the indices. The lack of significant change in the difference between the visual field indices recorded each day as a function of examination sequence indicates that the balance between learning and fatigue effects is constant over the course of three successive daily examinations.

The results are in agreement with the earlier psychophysical studies of Haider & Dixon (1961) and Singleton (1953). The former authors examined the differential light threshold over 3 sessions; the second session was a week after the first and the third 3 weeks after the second. Each session consisted of 2 tests, each test lasting 14 minutes. An increase in threshold, attributable to fatigue, was found in all but the first of the 6 tests. Haider & Dixon (1961) considered that the lack of a deterioration in sensitivity during the first test occurred since the fatigue was masked by training effects. A similar conclusion was reached by Singleton (1953), who studied the effects of fatigue on a perceptual-motor task. The subject sat in front of a display consisting of 4 lights situated at 3,6,9 and 12 o'clock. One of the 4 lights was illuminated in turn and the task was to move a lever in the direction of the illuminated light. Singleton (1953) found a decrement in both the rate and accuracy of performance of the task, although this was not noted during the first trial since the fatigue was masked by learning effects. Other authors have also considered the learning effect in automated perimetry to be counterbalanced by fatigue arising from the examination itself (Brenton et al. 1986; Katz & Sommer 1986; Kosoko et al. 1986a). Indeed, Jaffe et al. (1986) felt that this assumption was justifiable in normal subjects.

When the absolute values of the visual field indices obtained from 2 tests at the first daily examination were compared using the Wilcoxon signed-rank test, no statistically significant difference was found. This indicates that, at the first examination of a naive glaucoma suspect patient, learning and fatigue effects counterbalance since two successive tests of the same eye may be considered to represent a single test of duration 20-25 minutes.

The rationale for this study was the finding in Chapter 4 that improvements in sensitivity occurred between the first and second examinations for the first (right) eye tested and also between the third and fourth examinations for the second (left) eye tested. When the corresponding absolute values of the visual field indices were compared in this study, no statistically significant differences were found, indicating a lack of improvement in performance due to learning between the first and second examinations of the first eye tested, and the presence of a fatigue effect between the third and fourth examinations of the second eye tested.

5.5. CONCLUSIONS

The fatigue effect has several implications for clinical perimetry. The development and progression of visual field defects leads to an increase in the short-term fluctuation, requiring a greater number of stimuli presentations to measure the threshold and thus prolonging test time. The study of Section 5.3. also showed the fatigue effect to increase with increasing test time. The duration of perimetric examination should therefore be noted and, where possible, standardised to increase the accuracy of follow-up examinations. Automated perimetry also allows for repeated threshold determinations and statistical analysis of the data. If, however, sensitivity decreases with time an increased accuracy of measurement through averaging procedures cannot be assumed.

This study, together with the study of Chapter 4 suggests that learning effects are greater than fatigue effects in the initial examination of glaucomatous patients, although if the initial examination is prolonged, learning and fatigue effects are equal, resulting in a stable threshold. In subsequent examinations, once patients are fully trained in automated perimetry, fatigue effects are more prominent than learning, resulting in a deterioration of sensitivity.

The renewed interest in the examination of the peripheral field in glaucoma using both automated static (Seamone et al. 1988; Haas et al. 1989) and automated kinetic (Stewart et al. 1988) techniques should be considered in the light of the eccentricity-dependency (and possible depth-dependency) of the fatigue effect. The validity of age-matched normative

data for use in calculation of the visual field indices for the second eye examined is also questioned, in view of the possible inter-eye transfer of the fatigue effect.

CHAPTER 6

THE OPTIMUM STIMULUS PARAMETERS FOR THE EARLY DETECTION OF GLAUCOMATOUS VISUAL FIELD LOSS

6.0. INTRODUCTION

Various studies have hypothesised that different combinations of stimulus parameters presented by a given instrument can, in certain ocular and / or neurological disorders, be manipulated to provide diagnostic information additional to that obtained from the conventional perimetric examination (Dubois-Poulsen 1952; Dubois-Poulsen & Magis 1957; Sloan 1961; Sloan & Brown 1962; Wilson 1967; Greve et al. 1976; Flanagan et al. 1984a,b; Wild et al. 1984; Paige et al. 1985).

The general aim of the current study was to investigate the optimum conditions for the earliest detection of glaucomatous visual field loss by automated perimetry using certain novel combinations of adaptation level, stimulus size, stimulus duration and stimulus configuration.

6.1.1. THE DUPLICITY THEORY OF VISION

The relative contribution of the retinal photoreceptors in visual processing is dependent upon the luminance level. At low luminance levels (scotopic vision) contribution from the rods is greatest and at high luminance levels (photopic vision) the greatest contribution is from the cones; this is the basis of the duplicity theory of vision. In the study of visual function, the wavelength composition, spatial and temporal properties and other characteristics of the stimulus can be selected to emphasise the relative contribution of the rods and cones and thereby provide a measure of scotopic and photopic function.

6.1.2. DARK AND LIGHT ADAPTATION

Adaptation allows the visual system to maintain its ability to detect contrast (sensitivity) despite large changes in the luminance level. It is still not clear to what extent adaptation results from changes in retinal synaptic connections i.e. a neural reorganisation, and how much is mediated in the photoreceptors i.e. photochemical changes; for a review see Green (1986). It is generally assumed that rods are mainly responsible for vision below about 0.1asb although there is some cone activity at luminances as low as 0.0014asb. The transition from rod-mediated to cone-mediated vision is not abrupt and the two systems operate together over the mesopic range, which may extend up to 1000 times the threshold for cone vision (Davson 1980). In addition, the rod system may function at high adaptation levels of up to 628asb (Sloan 1947, 1950).

At high levels of illumination (above 120-300 cd/m2; corresponding to 377-942.5 asb) the rods become "saturated" in the sense that they respond to light but are incapable of responding to changes in illumination. The differential light threshold $\Delta L/L$, defined in Section 1.2., becomes infinitely high so there is no awareness of contrast (Aguilar & Stiles 1954; Fuortes et al. 1961; Blakemore & Rushton 1965; Sakitt 1976; Klingaman 1979; Yeh et al. 1989). Aguilar & Stiles (1954) showed saturation to occur when each rod absorbs 1,000 quanta of light per second. Saturation is thought to be a property of the light transducer

mechanism of the rod, it does not result from inhibition of rods by cones at high luminances (Fuortes et al. 1961). The exact mechanism of saturation is however uncertain; there is evidence to show that it occurs primarily at the level of the rod outer segments, athough post-receptoral mechanisms may also be involved under certain experimental conditions (Alexander et al. 1986). Indeed, electrophysiological recordings from cat retinal ganglion cells have demonstrated that, in this species, saturation of individual rod responses does not occur; it is a property of pooled signals from rods (Lennie et al. 1976).

It is an open question as to whether individual rod receptors in the mammalian retina show any light adaptation. There is evidence in cold-blooded vertebrates that these cells do adapt to light (Dowling & Ripps 1972; Hemila 1977; Green 1986), although in mammals there is evidence against light adaptation (Green 1986; Baylor et al. 1984). Recently, Tamura et al. (1989) have shown rod adaptation to light in the cat; since the cone system of the cat retina has a high light threshold, the rods need to adapt so they do not saturate before the cones take over at higher light intensities. Tamura et al. (1989) thus proposed that the operating range of the rod system in the cat is composed of a lower intensity range set by neural network adaptation, and a higher intensity range determined by receptor adaptation.

Rod responses tend to be more "sluggish" than cone responses (Klingaman 1976); thus, when signals from both receptors reach a ganglion cell, the faster cone response can cancel the rod response by rendering the ganglion cell refractory (Gouras & Link 1966). Indeed, Drum (1984a) has shown that cone response latency and log sensitivity are proportional to light adaptation.

6.1.3. ROD AND CONE INTERACTION

Older psychophysical studies support the notion of rod-cone independence (Stiles 1939; Flamant & Stiles 1948; Westheimer 1970), however there is no active division between rod and cone functioning (Lythgoe 1940); the rod and cone systems are believed to interact and combine into the same pathways and do not adapt independently (Granit 1943; D'Zmura & Lennie 1986) except in rod or cone free regions of the retina.

Rod-cone interaction may be either summatory or inhibitory (Denny et al. 1989). At a given mesopic adaptation level, Hough (1968) showed the luminosity curve could not be constructed by linear addition of pure photopic and scotopic curves. Drum (1982) also demonstrated summation betwen subthreshold rod and cone responses at absolute threshold which was less than the linear addition. More recently, an inhibitory form of rod-cone interaction has been demonstrated, where dark-adapted unstimulated rods exert an inhibitory influence on cone pathways which is removed by selective rod light adaptation (Alexander & Fishman 1984; Coletta & Adams 1984). An analogous influence of cones upon rods has also been described (Frumkes et al. 1986) although little is known about this third form of rod-cone interaction. There is substantial evidence of rod-cone interaction in the retina from anatomical studies (Dowling & Boycott 1966; Kolb 1970; Raviola & Giula 1973) and from physiological studies (Gouras & Link 1966; Steinberg 1969; Niemeyer & Gouras 1973) which show that such interactions could occur via direct rod-cone gap junctions, via pathways involving the horizontal cells or through the neural convergence of rod and cone signals on the same ganglion cell. These studies are paralleled by psychophysical studies of rod-cone interaction in the human visual system showing that cones may influence rod thresholds and vice versa (Ikeda & Urakubo 1969; Frumkes & Temme 1977; Temme & Frumkes 1977; Latch & Lennie 1977; Drum 1981; Benimoff et al. 1982; Sugita & Tasaki 1988). Studies demonstrate that the interrelationship between rod and cone systems is highly dependent on spatial and temporal variables (Frumkes & Temme 1977).

6.1.4. ABSOLUTE AND DIFFERENTIAL LIGHT THRESHOLDS

The simplest way to study the light sense is to measure the threshold or minimum light stimulus necessary to evoke the sensation of light, known as the absolute light threshold. The subject is dark-adapted and the illumination of a test patch increased until it is perceived. The test patch may be illuminated continuously or presented in flashes of varying luminance. Measurement of the absolute threshold in darkness immediately following exposure to light results in the characteristic dark adaptation curve with cone and rod mediated portions.

The technique of static perimetry (Sloan 1939) involves measurement of the differential light threshold. This is the amount a stimulus, which itself produces a sensation of light, must be

increased or decreased to produce a change in the sensation. The subject views a field of luminance L, and a smaller concentric field of variable luminance is projected onto this. The luminance of the smaller field is (L+ΔL), such that the observer may just detect a difference (ΔI) of brightness between the fields i.e. contrast. The increment ΔL is called the liminal brightness increment or differential light threshold.

6.1.5. THE WEBER-FECHNER LAW

The differential light threshold (ΔL) varies with the adapting luminance (L). Over a certain range of adaptation levels the differential light threshold is a constant proportion of the adapting luminance i.e. ΔL/L is a constant. This is the basis of Weber's law of sensation (extended to visual discrimination by Fechner) which applies approximately to all sensory modalities, namely that the difference threshold is proportional to the prevailing stimulus. For example, if L is 1000 asb then ΔL is about 20 asb; if L is 10000 asb then ΔL is about 200 asb

ΔL may be determined for a range of background luminances L. When the background luminance is zero, very little additional light (ΔL) must be added to reach threshold. Over a range of low background luminances the increment ΔL remains constant or may even decrease slightly since, although the low background luminances may not be perceptible the sum of (L+ΔL) is a constant (Baumgardt & Smith 1965). As the background intensity rises, ΔL increases and the function of ΔL/L over a range above threshold is linear i.e. ΔL/L=constant, thus demonstrating a constant Weber-Fechner fraction for the detection of scotopic incremental thresholds. This was originally attributed to rod activity (Aguilar & Stiles 1954) on the assumption that the rods and cones adapt independently although Sharpe et al. (1989) suggest that Weber's law for incremental thresholds is achieved only by rods acting in conjunction with cones and not by rods alone. As the adaptation level is increased further ΔL becomes a constant as the threshold intensity for cone function is reached; visual acuity improves markedly and colours become perceptible. The Weber-Fechner fraction (ΔL/L) later remains constant over a range of at least 3 log units for cone function. If data were to be collected at very high adaptation levels, the cone mechanism eventually becomes saturated and no longer detects differences between the test spot and background. Early investigators found ΔL/L to increase again at high intensities, however Steinhardt (1936)

showed it to remain constant to a value in excess of 1.5×10^6 asb. At these high levels of radiant intensity, energy transfer to the retina can become high enough to cause thermal damage, resulting in oedema and photocoagulation of the tissue. In the cone dominated region of the central retina, the absolute threshold for light is higher than for the peripheral retina and the rod-cone transition is less easily discerned.

At photopic adaptation levels the fraction $\Delta L/L$ is fairly constant at about 0.02-0.03 indicating that a change of 2-3% in luminance can be detected. At low luminances however, the power to discriminate falls off sharply so that at 0.001 asb, two patches of light must differ by about 50% in luminance to be discriminated.

Two models have been proposed to describe photoreceptor responses in the presence of adapting background illumination (Valeton 1983). The "increment light model" describes increment responses to light increments on a background whereas the "incident light model" describes total receptor response as a function of total light intensity i.e. increment plus background. In the dark adapted condition, with no background present, the two models are identical. If the receptor adapts to light according to Weber's law, the changes in these two functions with adapting light are similar, however the incident light model is of greater relevence in studying contrast sensitivity (Hemila 1987).

6.1.6. THE ROSE-DE-VRIES LAW

The relationship describing the transition between ΔL=constant and $\Delta L/L$=constant is, according to Barlow (1972), $\Delta L/(L+DL)$=constant where DL is the "dark light" or photon and neuron noise of the eye. Thus, at low luminances the formula would approximate to ΔL=constant, while at higher levels the Weber-Fechner law applies with a transitional zone inbetween. It is frequently stated that the Rose-de-Vries law holds in the low photopic or mesopic ranges. This law states that $\Delta L/\sqrt{L}$=constant although Barlow (1972) suggests that the Weber-Fechner law may hold well into the scotopic regions and the Rose-de-Vries law may be applicable in the photopic region. It seems that an equation of the form $\Delta L/L^k$=constant is appropriate, with k ranging from 0.5 to 1.0, depending on such variables as background luminance, stimulus size, wavelength and duration.

The transition from Rose-de-Vries to Weber behaviour occurs at a lower luminance for the peripheral than the central visual field (Koenderink et al. 1978); thus, at a particular adaptation level peripheral incremental thresholds may demonstrate Weber behavior whereas central thresholds conform to the Rose-de-Vries law.

6.1.7. THE DIFFERENTIAL LIGHT THRESHOLD IN CLINCAL PERIMETRY

Measurement of the differential light threshold is a measure of the contrast sensitivity of the retina under particular conditions of exposure to light; the differential light threshold is determined by whichever system is the most sensitive channel of information under the given stimulus conditions, not necessarily involving one class of photoreceptor signals or even one colour mechanism (Frumkes & Temme 1977). An understanding of increment sensitivity is thus basic to an appreciation of the techniques used in clinical perimetry. In practice, a single background adapting luminance is selected for testing all regions of the retina. Aulhorn (1964) has determined the threshold gradient for the horizontal meridian at adaptation levels of 100asb to darkness. When absolute thresholds are measured in the fully dark adapted eye a small relative depression of visual sensitivity can be demonstrated at the fovea. This is a physiological scotoma caused by the absence of rods from the fovea. With adaptation to mesopic and photopic levels of background illumination, increment sensitivity (1/threshold) decreases for all regions of the retina, but drops to a greater extent for the rod-dominated portions of the extra-foveal retina. Consequently, the profile of the visual field at mesopic and photopic adapting luminances shows a peak of sensitivity at fixation.

Normal sensitivity at various adaptation levels has been shown to be dependent upon the meridian tested. The inferior field has been reported to become relatively more sensitive than the superior field with dark adaptation (Wolf & Zigler 1963; Zeuge & Drance 1967; Krill et al. 1968; Abraham et al. 1983; Drum et al. 1986; Birch et al. 1987). Wolf & Zigler (1963) considered this difference to be embryological in origin, although Birch et al. (1987) related it to the finding in other species that rod outer segments are longer (Batelle & LaVail 1978) and rhodopsin content greater (Rapp et al. 1985) in the superior retina.

6.1.8. CHOICE AND LIMITATIONS OF ADAPTATION LEVEL IN PERIMETRY

The degree of dark or light adaptation depends on how much light reaches the retina. This is influenced not only by the background luminance but also by the pupil size and the extent of media absorbtion. A given level of background luminance may be in the photopic range for a normal sized pupil, but may fall into the mesopic range for a miosed pupil in the presence of media opacities (Klewin & Radius 1986; Baldwin & Smith 1987).

Currently, the choice of adaptation level is based on considerations of dynamic range. The Friedmann Visual Field Analyser utilises a luminance of 0.8asb (Bedwell 1967) and the Tubinger perimeter 10asb. Early computerised perimeters used low background luminances, since the stimulus light output was limited (Spahr 1973). The Competer operated at adaptation levels of 0.3asb and 3asb (Heijl & Krakau 1975a; Heijl 1977a) and the Peritest (Greve 1980a) and Periscope (Greve et al. 1980) used backgrounds of 3asb and 0.3asb respectively. Indeed, Fankhauser (1979) found that an adaptation level of 4asb, used in the Octopus Automated Perimeter, increased the dynamic range by 0.5 log units (about 3 times) compared with a background of 31.5asb. The limited stimulus light output is however no longer a problem, indeed, the Competer 750 utilises a background luminance of 31.5asb and this is also used in the Humphrey Field Analyser. The recently introduced Octopus 123 and Dicon TKS4000 instruments also employ a background luminance of 31.5asb.

It is important to operate on a linear portion of the Weber-Fechner curve in clinical perimetry. If an adaptation level is chosen that is at the low end of Weber behaviour or in the mesopic range where the Rose-de-Vries law applies, a small change in L, resulting from light output alterations or a lowering of retinal adaptation due to a constricted pupil or the presence of media opacities will have different effects on L and ΔL. This could result in production of a pseudo-defect. On the linear portion, these changes would be affect the background and threshold equally and thus the ratio between them would remain constant.

In clinical perimetric studies the Weber-Fechner law has been shown to be valid over adaptation levels of 100-100,000asb (Aulhorn et al. 1966; Aulhorn & Harms 1972). Fankhauser (1979) considered the Weber-Fechner law to be valid over adaptation levels

greater than 65asb and concluded that changes in pupil size would not affect the threshold above a background luminance of 94asb. From a consideration of Blackwell's curve (1963) of the $\Delta L/L$ function, Dubois-Poulsen (1967), however, suggests the Weber-Fechner law is valid above 9.4 asb. Fankhauser (1979) suggests that the Rose-de-Vries law holds for adaptation levels of the currently available perimeters although many workers consider the levels conform to the Weber-Fechner law (Greve 1973; Klewin & Radius 1986).

The success of modern perimetric techniques, using the angular size and contrast of white test objects as variables, depends on the fact that most eye diseases impair both rod and cone function. Sloan (1950) has shown that, at an adaptation level of 7asb, the thresholds of light adapted rods and cones are similar in the peripheral field and thus perimetric examination with a white target will not reveal defects affecting one receptor system only. Indeed, Sloan's (1950) studies of two patients, one with congenital night blindness and the other with congenital achomatopsia showed normal fields at an adaptation level of 7asb. Further studies of patients with selective impairment of cone function also showed normal fields at similar adaptation levels (Goodman et al. 1963; Sloan & Feiock 1971). Sloan (1950) also found similar thresholds for both dark and light-adapted (7asb) cones, although Drum (1980a) does not support this; under similar experimental conditions he found the thresholds to differ over the central 30° with dark adapted cones demonstrating enhanced parafoveal sensitivity.

Normal Goldmann kinetic fields at an adaptation level of 31.5asb have been demonstrated in patients with Retinitis Pigmentosa who have no significant rod function (Massof & Finkelstein 1979), in a case of progressive cone dysfunction (Elenius 1985; Elenius & Leinonen 1986) and in a patient with retinal degenerative disease (Jacobson 1990) thought to be a type of congenital night blindness (Marmor 1989). In the latter case, the normal field was accounted for by a "hypersensitivity" of the short-wavelength cone system, despite severely impaired rod function and abnormal mid-spectral cone sensitivity.

The International Perimetric Society (IPS) standards commitee (1979) have recommended that perimetry should be performed under photopic conditions within the range of

background luminances over which the Weber fraction remains constant for the following reasons: 1) this background level requires less sensitive calibration equipment, 2) the test is less sensitive to fluctuations or modest changes in the light source output, 3) the result is less dependent on changes in pupil size, 4) visual functions are tested at clearly defined photopic levels and 5) fixation control is easier than at low adaptation levels. Thus, a background luminance of no less than 31.5asb is recommended; this is in agreement with the work of Aulhorn & Harms (1967) in their investigation of early glaucomatous visual field defects. This level is considered to be below, but close to the level where $\Delta L/L$ becomes constant. The IPS standards committee also recommended that instruments are constructed such that they may be calibrated over a range of background levels since additional diagnostic information may be obtained by testing at other adaptation levels in certain disease conditions.

6.1.9. ENHANCED DEFECT DETECTION AT VARYING ADAPTATION LEVELS

The rationale for examination at a different adaptation level is that one of the receptor systems may be selectively affected in certain ocular disease. Some authors however suggest that the detection of early glaucomatous field loss is not enhanced by examination at higher or lower adaptation levels. Mogil et al. (1985) found no significant differences between the results of comparable tests performed on the Octopus automated perimeter (4asb) and the Humphrey Field Analyser (31.5asb). Indeed, Heijl (1985) did not consider perimetry at background luminances of lower than 31.5asb to offer any diagnostic advantages; this was substantiated by Asman & Heijl (1988) who found no difference in the depth of glaucomatous defects at adaptation levels of 3asb, 31.5asb and 315asb using the Humphrey Field Analyser. In a study of Retinitis Pigmentosa patients Wood et al. (1986b) found no differences in apparent field retention using the Dicon AP3000 at adaptation levels of 10asb, 31.5asb and 45asb.

6.1.9.1. Lower adaptation levels

Earlier authors, who were not concerned with enlargement of the dynamic range, proposed that low adaptation levels (mesopic or even scotopic) facilitated the detection and differential

diagnosis of disturbed visual function (Feree et al. 1931; Marlow 1932, 1947, 1957; Weekers & Roussel 1945; Jayle et al. 1963). Adaptation levels of 0.7-2.2asb were commonly used although Ferree & Rand (1936) suggested the adaptation level should be increased in cases of advanced pathology. Van Wien (1952) however considered there was no diagnostic advantage in the recognition of early glaucoma with dark adapted fields. Bair (1940) recommended an adaptation level of 0.1asb on the assumption that at this level the sensitivity of rods and cones was similar and the results were less affected by ametropia. In all studies, sensitivity losses at low adaptation levels were considered as a function of background luminance without consideration of the accuracy of determination.

Using a modified Friedmann Visual Field Analyser (FVFA) Greve et al. (1977) showed that examination at mesopic and photopic adaptation levels could differentiate between maculopathies and central neuropathies. Greater defects were observed under mesopic conditions in cases of maculopathy, although the defects were similar at both adaptation levels in central neuropathies. No difference was reported for glaucomatous defects under the two conditions, although the luminance levels were not reported. Hara (1979) also reported enhanced detection and differentiation of retinal degenerative conditions when using the FVFA at scotopic adaptation levels after dark-adaptation.

Woo et al. (1984), using Goldmann perimetry, demonstrated a scotoma in a patient whom it was thought had previously suffered an attack of optic neuritis; the scotoma disappeared when the fields were repeated under conditions of reduced luminance when the patient wore dark red sunglasses.

Fellman et al. (1984) and Fellmann & Lynn (1985) found greater defects in glaucoma patients at an adaptation level of 4 asb compared with 31.5 asb. Starita et al. (1987) however found the visual field index mean defect to be similar in glaucoma patients at adaptation levels of 4asb and 31.5asb, although corrected loss variance was greater at the lower background luminance.

Following early studies which showed abnormalities of extrafoveal dark adaptation in

glaucomatous patients (Zeuge & Drance 1967; Lakowski et al. 1976), Drum (1984b, 1985) and Drum et al. (1986, 1988) investigated the glaucomatous visual field at low adaptation levels. He found glaucoma patients to have more pronounced sensitivity losses, both diffuse and local, under scotopic conditions (Drum 1984b) although later work suggested that the increased defects under scotopic conditions were mainly diffuse (Drum 1985; Drum et al. 1986). A more detailed analysis showed that defect depth was greater under scotopic levels although photopic defects tended to be larger at the earliest stages of loss. In the latter case he acknowledged that the trend may have been influenced by a small sub-section of the sample (Drum 1988). Generally, diffuse losses were greater under scotopic (<0.01asb) than photopic conditions (125asb) although localised threshold elevations were similar at both adaptation levels (Drum 1986).

Dark and light adapted static perimetry has been shown to permit assessment of visual disability and classification of sub-types of Retinitis Pigmentosa (Marmor et al. 1983; Lyness et al. 1985; Kemp et al. 1988). Indeed, a knowledge of the state of the rod function relative to cone function in a particular area of the field is valuable in the diagnosis and management of many retinal disorders. Measurements with white light cannot provide this information. To identify which mechanism is operative it is necessary to vary the spectral composition of the stimulus. A practical method of performing this using only two colours (blue-green and deep red) has been developed by Massof & Finkelstein (1979, 1981) using the Tubinger perimeter. Ernst et al. (1983) have adapted a perimeter using LEDs of two colours as stimuli and Jacobson et al. (1986) later modified a Humphrey Field Analyser for this purpose. Modifications to the Humphrey Field Aanlyser involved the insertion of blue-green and red stimuli into the optical pathway, and a 1.2 log unit neutral density filter so the normal upper limit for dark-adapted sensitivity to the blue-green stimulus did not exceed 63dB, the maximum allowable by the data collection algorithms. For dark-adapted testing, the two lamps that provide the background of 31.5asb were turned off under computer control. The yellow LED fixation targets were replaced with red ones and an infra-red system was used to monitor fixation. These techniques were subsequently applied to the further study of Retinitis Pigmentosa (Kemp et al. 1988) and cone-rod dystrophies (Yagasaki & Jacobson 1989).

Arguments against the use of scotopic and low adaptation levels include the increased adaptation time, the necessity of excluding light from the apparatus and the examination room and the difficulty of checking fixation at scotopic levels.

6.1.9.2. Higher adaptation levels

Wilson (1967) demonstrated, at an adaptation level of 674asb, abnormalities of both spatial and temporal summation in lesions of the post-geniculate pathways and abnormalities of spatial summation only in pre-geniculate lesions. Shiga (1968) showed contraction of isopters in cases of retinal (including glaucoma) and third neurone disease at adaptation levels of 220asb and 700asb compared with 22asb. Conversely, the visual field enlarged under these conditions for normal control eyes although some narrowing of the isopters occured above 1500asb. Paige (1985) found enhanced detection of subtle visual field defects at an adaptation level of 315asb compared with 31.5asb in a mixed sample of glaucoma suspects, glaucoma patients and neuro-ophthalmological patients using a modified Humphrey Field Analyser. Perimetry at an adaptation level of 628asb showed a large paracentral ring scotoma in a patient with progressive cone dysfunction but normal rod function whose Goldmann fields at 31.5asb were full (Elenius 1985; Elenius & Leinonen 1986). Other authors have also reported enhanced detection of focal glaucomatous visual field loss at an adaptation level of 31.5asb compared with 4asb. Indeed, Fitzke (1988) considers perimetry at photopic adaptation levels to be an important area of future research.

6.1.9.3. Variation in accuracy of threshold determination

Literature concerning the effect of threshold fluctuations at different adaptation levels is also somewhat equivocal. Some authors have found fluctuations to increase at lower adaptation levels. Aulhorn & Harms (1967) noted a monotonic increase in fluctuations using manual static perimetry with decrease in background luminance from 100asb to darkness. Both Steinhardt (1936) and Kishto (1970) showed an increased spread of results at background luminances above 628asb. Rose (1977) suggested that although the dynamic range could be increased further by using adaptation levels well into the mesopic range, this would be at the expense of increased photon noise making the detection of the threshold end-point more difficult because of a lower signal to noise ratio. Brenton & Argus (1987) found both

short-term fluctuation and heterogenous long-term fluctuation to be greater at the lower adaptation level of the Octopus automated perimeter (4asb) compared with the Humphrey Field Analyser (31.5asb) although Fankhauser et al. (1988) attributed this to the different thresholding strategies employed by the two instruments. In a study using the Humphrey Field Analyser at background luminances of 0.0315asb, 0.315asb, 3.15asb and 31.5asb, Crosswell et al. (1990) showed short-term fluctuation, intra-individual variation and the heterogeneous component of the long-term fluctuation to be higher at the two lower adaptation levels, although no such trend was observed for the homogeneous component of the long-term fluctuation.

A higher background luminance will increase the precision of threshold determination since it favours a steeper frequency-of-seeing curve. Indeed, Jayle et al. (1965) found fluctuations to decrease with decreasing illumination. However, Fankhauser & Schmidt (1960) found fluctuations to be similar when operating the Goldmann perimeter at adaptation levels of 0.04asb, 0.4asb, 4asb and 40asb. Greve (1973) also noted no significant difference in threshold fluctuations with change in background luminance and Starita et al. (1987) found no difference in short-term fluctuation when operating the Squid automated perimeter at backgrounds of 4asb and 31.5asb, while maintaining all other stimulus parameters constant.

6.1.10. CONE ISOLATION PERIMETRY

Many retinal diseases are accompanied by acquired blue-yellow colour vision defects, a generalisation recognised by Kollner (1912). Indeed, several studies of foveal colour vision in glaucoma have indicated that hue discrimination is reduced selectively in the blue-yellow axis of colour discrimination (Lakowski & Drance 1979; Drance et al. 1981; Flammer & Drance 1984) and this has been related to diffuse retinal nerve fibre loss (Airaksinen et al. 1986). Since such colour vision defects have also been reported in ocular hypertensive patients it has been suggested that they may precede glaucomatous visual field loss (Drance et al. 1981; Adams et al. 1982, 1987; Heron et al. 1988). Attempts have therefore been made to isolate the short-wavelength sensitive (SWS) pathways which subserve blue-yellow colour vision. Bright yellow backgrounds (luminances of 635-1570asb) are used to depress the sensitivity of medium and long-wavelength cones and deep blue stimuli are presented

against these to preferentially stimulate the SWS cones system (Adams et al. 1987).

Subsequently, a Humphrey Field Analyser was modified to allow perimetry of the SWS cone system (Johnson et al. 1988b; Johnson et al. 1989a). Three modifications were made to the Humphrey Field Analyser: 1) a custom ROM chip allowed the normal background illumination to be turned off while maintaining independent control of stimulus illumination; 2) an auxiliary background lighting system was installed with yellow filter of 530nm cutoff and 3) a blue filter with cutoff 500nm was inserted into the stimulus light beam. Selective loss of SWS foveal pathways (Eisner et al. 1987; Haegerstrom-Portnoy et al. 1989) as well as SWS sensitivity over the central 30° of the visual field (Johnson et al. 1988b) have been found with increasing age. This has been attributed to neural losses as opposed to pre-retinal factors (Johnson et al. 1989a). When compared with age-matched normals, glaucoma patients and ocular hypertensives have been reported to show significant sensitivity losses, both diffuse and local, for the SWS pathways throughout the central visual field (Heron et al. 1988; Johnson et al. 1989b). Further longitudinal studies are however required to show whether the ocular hypertensive patients who demonstrated defects by this method do in fact progress to develop glaucoma.

Various hypotheses have been advanced to account for this apparent preferential sensitivity loss within the blue cone system. The SWS cones represent less than 10% of the total number of cones (Marc & Sperling 1977; DeMonasterio et al. 1981; Williams et al. 1981) and less than 0.5% of all photoreceptors (Osterberg 1935). The SWS cone mechanism has some electrophysiological and psychophysical properties which differ greatly from those of the red and green sensitive mechanisms; indeed, in some respects SWS cones have more properties in common with rods (Zrenner 1982). SWS cones send signals only to the chromatic pathways and do not contribute to the luminance response or resolution (Eisner & MacLeod 1980). There is some evidence based on cell body size, conduction latency and receptive field size for Macaque monkey retinal ganglion cells at comparable retinal eccentricities, that SWS cones send signals to larger parvocellular axons than those processing red-green information (DeMonasterio 1979), and this observation is consistent with the work of Quigley who showed that larger ganglion cells appear to be preferentially

damaged in glaucoma (Quigley et al. 1986, 1987, 1988, 1989). Greenstein et al. (1989a) have studied SWS cone sensitivity in retinal diseases that differ in their primary locus of sensitivity loss, namely retinitis pigmentosa, diabetes mellitus and glaucoma. Their finding that all three diseases resulted in decreased SWS cone pathway sensitivity implied that multiple sites were involved and the deficit could not be attributed solely to the photoreceptors. Indeed, Greenstein et al. (1990) found SWS cone pathway loss to be more highly correlated with the degree of diabetic retinopathy than the Farnsworth-Munsell colour vision score. Interestingly, Greenstein et al. (1989b) have evaluated the relative sensitivity losses of medium wavelength (MWS) and SWS cones in retinitis pigmentosa and diabetes mellitus. Although they found a preferential SWS loss in both diseases, losses of the MWS mechansim were found to be dependent on adaptation level, which was in agreement with the earlier study of Sandberg & Berson (1977).

Drum et al. (1989) however found no difference between chromatic (both red-green and blue-yellow) and achromatic sensitivity losses in glaucoma patients and considered that tests of chromatic sensitivity were unlikely to be better than achromatic tests at detecting early glauomatous damage. Indeed, Airaksinen et al. (1986) found a significant number of eyes in their study with advanced glaucomatous visual field loss but no abnormality of colour discrimination.

6.1.11. UNDERLYING RETINAL ARCHITECTURE IN RELATION TO GLAUCOMA

The primary site of retinal damage in glaucoma occurs at the ganglion cells. Many ganglion cells of the primate retina share both rod and cone inputs (Polyak 1941; Dowling & Boycott 1966; Wiesel & Hubel 1966; Enroth-Cugell et al. 1977), although midget ganglion cells (corresponding to the P-beta class of Perry et al. 1984) seem to convey pure cone signals (Polyak 1941; Dowling & Boycott 1966). This was substantiated by the work of D'Zmura & Lennie (1986) who suggested that ganglion cells with small receptive fields receive a pure cone input whereas those with larger receptive fields receive inputs from both rods and cones. They suggested however that this division into two pathways did not necessarily reflect the morphological and physiological distinction between the two major classes of

ganglion cell that project to different laminae of the lateral geniculate nucleus of the Macaque (Wiesel & Hubel 1966; Leventhal et al. 1981; Perry et al. 1984). Indeed, Wiesel & Hubel (1966) found some parvocellular neurons driven by rods as well as by cones. Thus, although the P-beta system in the fovea may be driven exclusively by cones, it seems that in the near peripheral retina some of the larger P-beta ganglion cells also receive input from rods. Indeed, Sterling et al. (1986) have suggested that near the area centralis, about 1500 rods converge on a beta ganglion cell. There is good evidence however that many of the larger P-alpha ganglion cells that project principally to the magnocellular lateral geniculate nucleus receive inputs from rods (Gouras & Link 1966; Wiesel & Hubel 1966).

Sterling et al. (1986) have traced two neural circuits in the cat retina from photoreceptors to P-alpha and P-beta ganglion cells. The "cone bipolar circuit" appears to convey centre-surround receptive field arrangement to both ganglion cell types, using cones at higher luminance levels and and rods (via gap junctions to cones) in low luminance levels. A "rod bipolar circuit" appears to convey the quantal signal and the pure centre-receptive field to the ganglion cells in low luminance levels. Thus, Drum et al. (1986) hypothesised that the greater diffuse glaucomatous loss observed under scotopic conditions was related to the fact that larger ganglion cells, which are preferentially damaged in glaucoma (Quigley et al. 1986, 1987, 1988, 1989) receive a substantially greater rod input than the small ganglion cells. Indeed, it has been known for some time that larger ganglion cells are more susceptible to pressure-induced damage (Gasser & Erlanger 1929). It should be noted however that magnocellular ganglion cells constitute 10% of the total ganglion cell population, whereas parvocellular neurons comprise 80% (Perry et al. 1984).

6.1.12. INFLUENCE OF PUPIL SIZE

Although, as reviewed in Section 6.1.9., some authors have claimed that additional diagnostic information may be obtained, and the detection of visual field defects enhanced, by examination under varying adaptation levels, only the study of Drum has considered the effect that a concurrent change in pupil size may have on the threshold.

A pupil of varying size performs three main functions (Davson 1990): 1) It modifies the amount of light entering the eye, thus permitting useful vision over a wide range of luminance levels. The amount of light entering the eye is directly proportional to the area of the pupil or square of the pupil diameter. The pupil is thought to account for 1 log unit of a total adaptation ability of 10 log units; 2) As a result of constriction, the pencils of light entering the eye are smaller and the depth of focus of the optical system is increased. This is particularly important at near, where the depth of field becomes small; 3) Spherical aberrations are minimised by the reduction in the aperture of the optical system. Under scotopic conditions, form is only vaguely perceived and the advantage of more light entering a dilated pupil far outweighs the effects of aberrations. Under photopic conditions however the reverse is true.

The pupil therefore may either enhance or degrade the retinal image quality and variations in the pupil size have a number of implications for the perimetrist (Tate 1985).

Retinal illumination is partially determined by the surface area of the pupil, and may be expressed by the formula (Le Grand 1968a):

$$E = 0.36\ L.S.t_{\partial}$$

where E is the retinal illumination in lumens/m^2; S is the pupil surface area in cm^2; L is the luminance of the stimulus or background in candelas/m^2 and t_{∂} is the transmission factor of the ocular media which varies betwen 0.1 and 0.7 for the wavelength and observer considered. For white light it is about 0.5 (Ludvigh & McCarthy 1938). Variations in pupil size may be enough to change the retinal adaptation state from photopic to mesopic or even scotopic.

The effect of the pupil on the resolving power of the eye is more important than the way in which it limits the extent of the visual field. The retinal image quality reflects the combined effects of refraction and diffraction. Refractive effects may either improve or degrade image quality, whereas diffractive effects always degrade the image. The degrading refractive influences of lens aberrations and shallow depth of field increase with large pupil apertures, however diffractive effects become significant at smaller pupil sizes where they are the

limiting factor for resolution (Westheimer 1964; Campbell & Green 1965). The eye's optimum optical performance thus occurs at a pupil size of 2.4mm (Campbell & Gubisch 1966).

The pupil diameter also limits the size of the retinal blur circle, and thus affects the depth-of-field of the eye. Ogle & Schwartz (1959) reported a depth-of-field decrease of 0.12 Dioptres per mm of pupil diameter increase for pupil sizes 2.5-8mm, however Tucker & Charman (1975) found depth-of-field to be insensitive to pupil diameters above 4mm. The depth-of-field also varies inversely with pupil diameter for constant retinal illumination (Campbell 1957), however for pupil diameters smaller than 2.5mm this relationship breaks down due to the Stiles-Crawford effect. Charman & Whitefoot (1977) have reported that the depth-of-field decreases for pupil diameters up to 5mm and then remains at an approximately constant value of 0.3D.

The effective surface area of the pupil becomes steadily smaller at more oblique angles since the available pupillary area for light to pass to the peripheral retina decreases more slowly than the cosine of the angle of eccentricity (Spring & Stiles 1948; Jay 1962). This is compensated for by greater spatial summation in the retinal periphery and reduced retinal image projection (Drasdo & Fowler 1974; Holden et al. 1987) so that retinal illumination is constant to an eccentricity of 80° (Bedell & Katz 1982; Koojiman 1983). Beyond 80° the reduction in pupil area is greater then the decrease in retinal image area. Perimetrically, this effect is constant for a given patient and therefore can be neglected in comparing one field with another. Nevertheless, it is very small, amounting to 0.07dB at 40° and 2.8dB at 70° eccentricity (Greve 1973). At retinal level the effect of a larger pupil diameter is however reduced by the Stiles-Crawford effect which results from the directional sensitivity of the retinal cones. Rays of light which enter the pupil peripherally may give a subjective brightness of only 15% of those entering the pupil centrally (Stiles & Crawford 1933).

6.1.13. INFLUENCE OF PUPIL SIZE ON VISUAL FUNCTION

The natural pupil adopts a size very close to the optimum for visual resolution over a wide range of luminance and contrast levels (Campbell & Gregory 1960; Woodhouse 1975). Leibowitz (1952) showed grating acuity to vary as a function of pupil diameter. As pupil

diameter increased a concomitant improvement in acuity resulted which reached a peak at 2.77mm and then decreased for pupils larger than this. Conversely, Kay & Morrison (1985, 1987) showed changes in pupil size of 2-8mm had little effect on contrast sensitivity over a wide range of spatial frequencies, except at low spatial frequencies (0.5-3c/deg.) when a reduction occured at pupil sizes ≤2mm. These latter authors used natural pupils in the study and did not correct for the change in retinal illumination with variation in pupil size. Small pupils were shown by Charman (1979) to render the effects of refractive error on contrast sensitivity less significant at all spatial frequencies, particularly low ones, and contrast sensitivity was optimal for pupil diameters of the order of 3mm. Similarly, Tucker & Charman (1975) obtained optimum Snellen acuity at a pupil diameter of 3mm.

Alpern & Spencer (1953) showed critical flicker frequency to be higher in the peripheral than the central field for fixed pupils. The high frequency (2Hz) component of accommodative fluctuations, present for a pupil diameter of 7mm, was shown to be diminished or absent for pupils of 1mm diameter due to the increased depth of focus (Campbell et al. 1959). Lindstrom et al. (1968) found dark adaptation to be impaired in subjects with Pilocarpine-induced miosis. Sundet (1972) showed that the reversal of the colour stereopsis effect which occurs with changes in illumination also occurred when pupil size was varied and the concomitant change in illuminance accounted for with neutral density filters.

Karpe & Wulfing (1962) noted a considerable decrease in the amplitude of the scotopic b-wave of the electro-retinogram (ERG) for drug-induced miosis, which could be compensated for by increasing the luminance of the stimulus. Similar results were reported by Holder & Huber (1984) for the flash ERG, but they found the pattern ERG to be insensitive to pupil size. Thompson & Drasdo (1989) however found the amplitude of the pattern-onset ERG to be greater with a miotic pupil although the pattern specific response remained similar. Skalka & Holman (1972) reported that pupil dilation did not significantly alter the amplitude or latency of the visual evoked potential (VEP); conversely, Hawkes & Stow (1981) observed that amplitude of the VEP was depressed with both small and large pupils and the latency was increased with a small pupil and decreased with a large one. They considered this latency change to be due to the total flux entering the eye and not related to

the change in acuity. An increased latency of the positive component of the VEP with a miotic pupil was also found by Penne & Fonda (1981) and Holder & Huber (1984).

6.1.14. INFLUENCE OF PUPIL SIZE ON PERIMETRIC THRESHOLDS

It has been suggested that variation in pupil size does not account for the inter-individual differences in visual field threshold or the age-related changes in sensitivity in normal eyes for either manual kinetic (Drance et al. 1967a) or automated static perimetry (Brenton & Phelps 1986). Contrary to this, Williams (1983) showed variation in pupil size to account for 32% of inter-individual variation in the I2 isopter area although age accounted for 17% of variation in pupil diameter. Variation in pupil size has little effect on the magnitude of the short-term fluctuation (Flammer et al. 1984c) nor is it a covariate of the homogenous componant of the long term-fluctuation (Flammer et al. 1984a).

6.1.14.1. Manual kinetic perimetry

Engel (1942) reported a narrowing of the Bjerrum field to 5mm red and 1mm white targets at 300mm after instillation of Physostigmine. Day & Scheie (1953) also examined the effects of drug induced miosis, using 1% Pilocarpine, on the tangent screen fields of a sample of normal and glaucomatous eyes. In normals, miosis led to concentric contraction of the central fields and enlargement of the blind spot. In glaucomas, a more marked constriction of the visual field occurred, which simulated progression of the glaucomatous process. A similar conclusion was reached by Forbes (1966) who charted the fields of a sample of glaucoma patients on miotic therapy, and then repeated the examination after dilating each patient. He found miosis to cause general depression (non-specific contraction of the isopters) and enlargement of glaucomatous defects, particularly those with shallow margins. In various case reports he suggested that miosis could simulate glaucomatous loss, create the impression of progression of loss, simulate low tension glaucoma, simulate advanced loss in the presence of lens opacities or simulate recovery of optic nerve function under conditions of an enlarging pupil.

Miosis results in a general depression of both central and peripheral isopters, and may exaggerate the size and density of visual field defects (Scott 1957; Harrington 1981; Shields

1987). Lindstrom et al. (1968) found a mean reduction in pupil diameter of 1.32mm, induced by Pilocarpine 2%, to lead to a maximal field constriction of 10° which was most marked in the supero-temporal field. McCluskey et al. (1986) found a good correlation between change in Goldmann isopter area and change in pupil area, modified with 2% Pilocarpine. Only subjects who attained a pupil diameter ≤2mm after miosis were included in the analysis, and negative lenses corrected the ciliary spasm. The smallest isopter (I2e) was affected most and it was considered that this was due to diffraction leading to a defocussed image, which would be of more significance for the central field. Gabriel et al. (1988), using soft contact lenses with artificial pupils, found that a decrease in pupil area from 6.8mm to 3mm reduced the I2 isopter area by 20%. This was attributed to the reduction in retinal illumination.

6.1.14.2. Manual static perimetry

Greve (1973) considered a reduction in pupil diameter from 6-2mm, produced by illuminating the eye which was not under examination, to have a negligible effect on the visual field. Indeed, it amounted to approximately 0.2 log units at an eccentricity of 25° using the Friedmann Visual Field Analyser (FVFA). Similarly, Bedwell and Davies (1977) determined a maximum variation in threshold of 0.14 log units with the FVFA for variations in pupil size of 3.5 to 9.5mm, induced by 0.2% Thymoxamine and 5% Ephedrine respectively.

6.1.14.3. Automated perimetry

There has been little work reported so far concerning the effect of pupil size on the automated perimetric profile. Fankhauser (1979) found the effect of 3% Pilocarpine induced miosis amounted to only 0.2 log units, and this was similar at luminance levels of 4asb and 40asb. Brenton & Phelps (1986) found a good correlation between pupil size and mean sensitivity for both central and peripheral areas of the field of normal subjects using Humphrey programs 30-2 and 30/60-2. This relatonship however became insignificant once age-effects were considered, therefore pupil size alone does not account for the variation in mean sensitivity with age, nor the intra-individual variation in normal eyes. Mikelberg et al. (1987) found a positive correlation between the proportionate change in pupil diameter, modified using 0.5% Thymoxamine, and proportionate change in mean sensitivity as determined by Octopus program G1 in a sample of normals. Wood et al. (1988a) investigated

the effect of pupil size on the outcome of automated perimetry with the LED stimulus of the Dicon AP3000 instrument at adaptation levels of 10asb and 45 asb. They found perimetric sensitivity to increase with increasing pupil diameter over a range of pupil sizes modified using the miotic Thymoxamine and the mydriatic Phenylephrine; in addition, the effect of pupil size change was found to be similar at both adaptation levels and to increase with peripheral angle. Lindenmuth et al. (1989) found drug-induced miosis caused an increase in the visual field index mean deviation derived by Humphrey program 30-2 in normal subjects. However, they chose Pilocarpine 2% as miotic and additional negative lenses were required to correct the myopia due to ciliary spasm. Mean defect increased by an average of 0.67dB in constricted fields compared with baseline fields, the greatest change occurring at more eccentric locations (20-30°) and least centrally (≤10°). Lindenmuth et al. (1990) also reported an increase in mean defect of 0.83dB compared with baseline fields following pupil dilation with Tropicamide 1%. Interestingly, the corrected pattern standard deviation also increased by 0.60dB following pupil dilation. No change was noted in the short-term fluctuation or reliability indices in either study (Lindenmuth et al. 1989, 1990).

6.1.15. AIM OF THE STUDY

The long-term aim of the investigation was to investigate the hypothesis that the detection of focal glaucomatous visual field loss may be enhanced at higher adaptation levels.

The initial aim of the investigation was thus to develop the methodology for the use of higher adaptation levels than those utilised in currently available automated perimeters. This involved firstly, ensuring the validity of the Weber-Fechner law at the higher adaptation levels employed and secondly determining the accuracy and reliability of the threshold recorded at the various adaptation levels compared with that of the control response at 31.5asb. The experimental work was to be performed on a sample of clinically normal young emmetropic subjects in order to investigate the suitability of the protocol using optimum perimetric observers free from the contaminating influence of intraocular light scatter. A further criterion under study was to be the role of pupil size.

6.1.16. MATERIALS AND METHODS

The sample comprised 10 clinically normal volunteer emmetropic subjects (4 male, 6 female; mean age 21.7 years; SD 0.6 years). The subjects were free of any ocular or systemic medication, and were experienced in psychophysical techniques of examination. Subjects with a history of cardiovascular disease or migraines were excluded from the study.

Before each subject participated in a session, visual acuity and pupil diameter were measured, a full slit-lamp examination of the anterior eye was performed including assessment of the angle by the technique of Van Herrick and intraocular pressure was measured. The purpose of the study was explained to each subject and informed consent was obtained.

Three modifications were made to the Humphrey Field Analyser 630 to allow the background luminance to be raised above the standard 31.5asb level: 1) a custom ROM (read only memory) chip was introduced to permit the normal background luminance to be turned off while maintaining independent control of stimulus luminance; 2) a separate background illumination system was installed to provide a uniform high intensity white adaptation field. This consisted of six 60 watt, 221mm tungsten filament striplights, mounted vertically on the inside of the perimeter three each side of the chin-rest. The illumination level of the perimeter bowl was varied by placing neutral density filters over the striplights; 3) a neutral density filter was placed over the CCD camera to facilitate monitoring of patient fixation at the higher adaptation levels. Adaptation levels of 77.0asb, 141.5asb, 314.5asb and 1195.0asb were used to give a range of adaptation levels that were evenly distributed when considered in logarithmic terms. The highest adaptation level ensured rod saturation. The background luminances were measured using a spectra minispot photometer. As a control, perimetric sensitivity was also measured at the standard 31.5asb background luminance supplied by the Humphrey Field Analyser.

Pupil size was modified pharmacologically. All drugs used in the study were obtained from Smith and Nephew single-dose unpreserved "Minims". The instillations were made with a micro-pipette such that each drop comprised 25µl of drug. One drop of Benoxinate HCl

0.4% was instilled to inhibit reflex tear formation and facilitate penetration of the ophthalmic agents used subsequently, due to its effect on the lipid barrier anterior to the corneal epithelium (O'Connor Davies 1981). Pupil size was then modified using one drop of Thymoxamine HCl 0.5% for miosis or one drop of Phenylephrine HCl 2.5% for mydriasis. These latter two agents both act on alpha adrenoreceptors present on the smooth muscle of the dilator pupillae. Thymoxamine induces pupillary miosis as a result of antagonist action on alpha receptors; Phenylephrine induces pupillary mydriasis as a result of agonist action on alpha receptors. In addition, both agents act on the ciliary body vasculature but the interference with ciliary muscle function is minimal in young subjects and unlikely to affect the sustained accommodative response required for fixation at the perimetric viewing distance of 33cm (Mordi et al. 1986). To check that the action of the drugs was constant, the pupil diameter was monitored throughout each examination, measured via the video camera and corrected for the effects of camera magnification. The value for pupil diameter was the mean of the measurements taken every two minutes throughout the examination. Saline 0.9% was employed as the control solution. All possible side effects of the drugs used were explained to each subject prior to the study.

Perimetry was undertaken 30 minutes after instillation of the appropriate drugs. Perimetric sensitivity was determined using program 30-2, which tests 76 locations out to an eccentricity of 30°, with a full-threshold strategy, stimulus size Goldmann III and stimulus duration 200msec. In addition, a foveal threshold measurement was made. The order of bowl luminance and pupil size was randomised throughout the sample. Subjects were pre-adapted to the given bowl luminance for 3 minutes, and fixation monitored throughout the examination via the video camera.

Each subject attended 8 sessions with a minimum washout period of 2 days between each session; two field examinations were undertaken at each session, with a break of 10 minutes between each. The first session comprised a training period consisting of two 30-2 programs at the 31.5asb adaptation level. Following each session visual acuity was measured again and a full examination of the anterior eye was performed including intraocular pressure measurement. Pupil size and recovery was monitored using a pupillometer. In order to

comply with the recommendations of Aston University ethical committee it was stipulated that subjects should live on campus, or have easy access to the Department without having to drive or cycle. Subjects were also required to bring a pair of sunglasses for use following pupil dilation.

The pointwise decibel values at each adaptation level printed out by the instrument were considered in terms of the differential light threshold logΔL. The general form of the equation relating decibels to ΔL is:

$$dB = \text{constant} + 10 \log_{10} L/\Delta L \text{.....(equation 1)}$$

where the value of the constant, k, is dependent on the background luminance (L) and maximum stimulus luminance (ΔL) i.e. the dynamic range of the instrument. Rearranging equation 1, we can say:

$$dB = k + 10 \log_{10} L - 10 \log_{10} \Delta L \text{.....(equation 2)}$$

If, however, the backgound luminance is turned off and an external luminance source supplied, the version of the software employed in the perimeter refers the dB scale to a value of L=0, and thus equation 2 becomes:

$$dB = k - 10 \log_{10} \Delta L \text{.....(equation 3)}$$

For the Humphrey Field Analyser, a sensitivity of 0dB corresponds to the maximum stimulus luminance ΔL of 10,000asb, thus giving a value of k=40. Thus, equation 3 gives:

$$\log_{10} \Delta L \text{ (asb)} = (40 - dB) / 10$$

6.1.17. RESULTS

The group mean and standard deviation of the pupil diameter for the 10 subjects as a function of adaptation level and pharmacological agent is shown in Table 6.1.

Group mean log differential light threshold logΔL increased linearly with increase in log adaptation level L for the saline control and was independent of pupil size over the range employed in the study (Figure 6.1.).

When logΔL is plotted against logL for eccentricities of 0° and 27° temporally (Figure 6.2.) the

relationship for the peripheral field is seen to be linear, although for the fovea there was some suggestion that the linear relationship broke down at the control adaptation level of 31.5asb.

The dependence of mean sensitivity on pupil size is shown in Figures 6.3.a. and 6.3.b. No relationship was evident between the proportionate change in mean sensitivity relative to that recorded with the natural pupil and the proportionate change in pupil diameter relative to that of the natural pupil for any of the adaptation levels employed.

Similarly, no obvious relationship was found between group mean short-term fluctuation and adaptation level for any pupil size as shown in Figure 6.4., or between the proportionate change in short-term fluctuation relative to that recorded with the natural pupil and the proportionate change in pupil diameter relative to that of the natural pupil, as shown in Figures 6.5.a. and 6.5.b.

The group median reliability parameters of fixation losses, false positive and false negative responses and number of stimuli presented are shown in Tables 6.2.a., 6.2.b., 6.2.c. and 6.2.d. as a function of pupil size and adaptation level. No change in the reliability parameters was noted as a function of adaptation level or pupil size.

	ADAPTATION LEVEL (asb)				
	31.5	77.0	141.5	314.5	1195.0
MIOTIC	3.7	3.1	3.1	2.7	2.5
0.5% Thymoxamine	(0.8)	(0.6)	(0.6)	(0.6)	(0.5)
SALINE	5.6	4.1	3.7	3.6	3.0
	(0.5)	(0.8)	(0.9)	(0.8)	(0.5)
MYDRIATIC	7.2	7.0	6.5	6.0	4.8
2.5% Phenylephrine	(0.8)	(1.5)	(1.4)	(1.2)	(1.1)

Table 6.1. Group mean pupil diameter (mm) as a function of pharmacological agent and adaptation level. The standard deviations are shown in brackets.

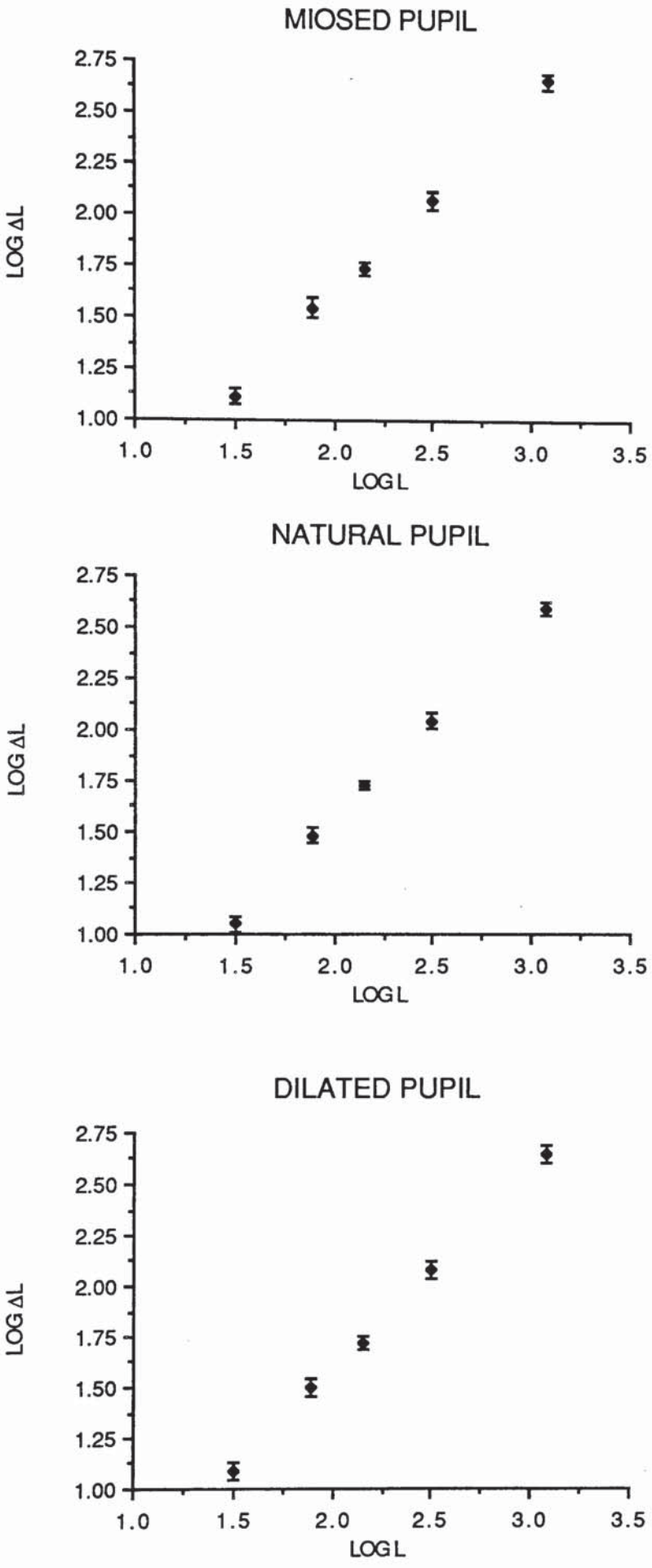


Figure 6.1. Group mean log differential light threshold against log adaptation level as a function of pupil size. Error bars indicate 1 S.E.M.

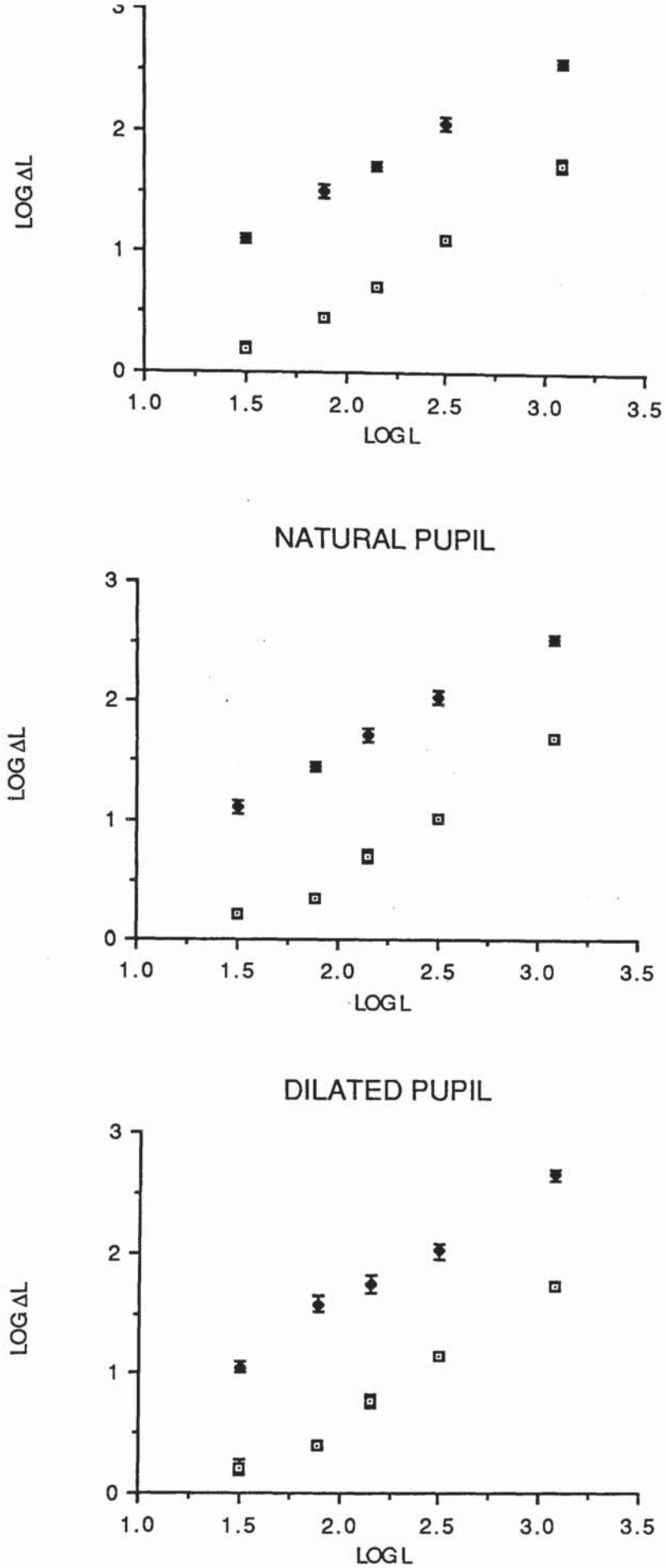


Figure 6.2. Group mean log differential light threshold against log adaptation level as a function of eccentricity (open squares: 0°; closed diamonds: 27° temporal for miotic (top), natural (middle) and dilated (bottom) pupils. Error bars indicate 1 S.E.M.

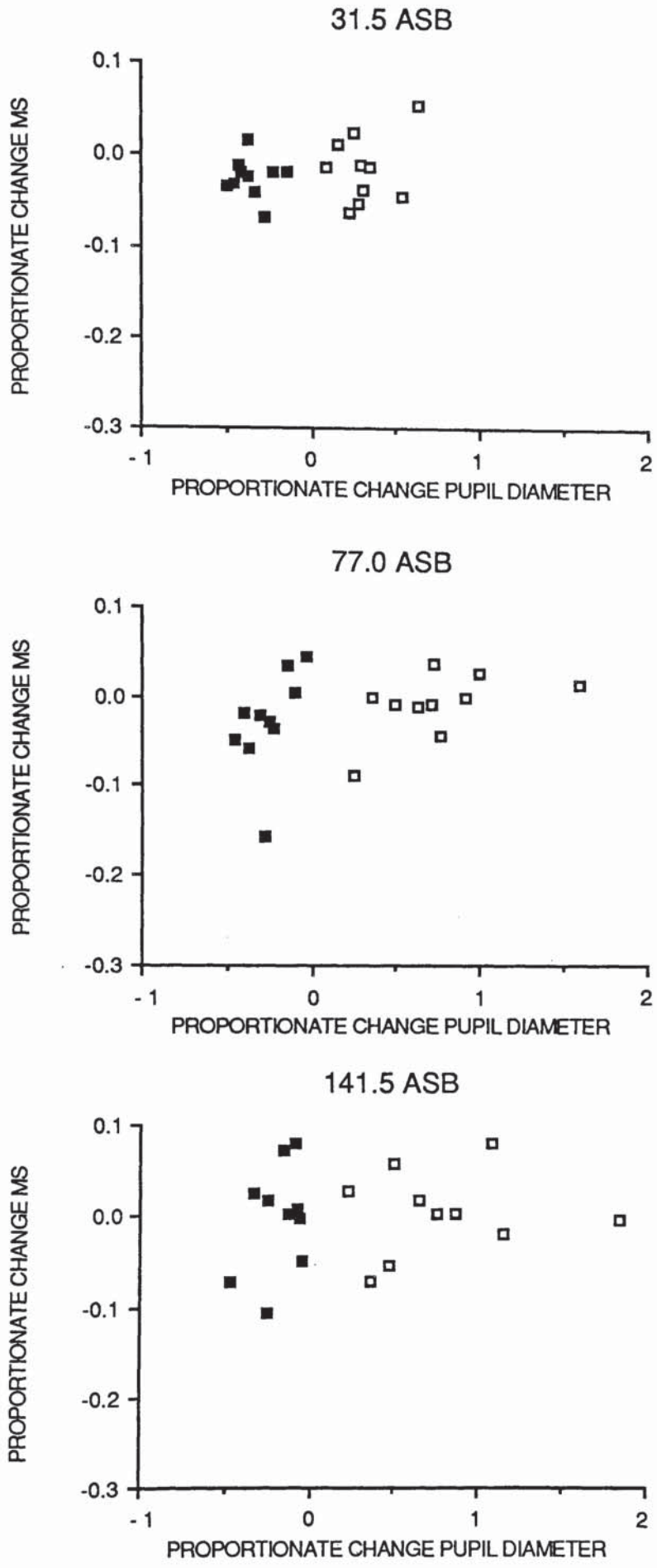


Figure 6.3.a. Proportionate change in global mean sensitivity against proportionate change in pupil diameter for adaptation levels of 31.5asb (top), 77.0asb (middle) and 141.5asb (bottom). Closed squares indicate miosed pupils, open squares indicate dilated pupils.

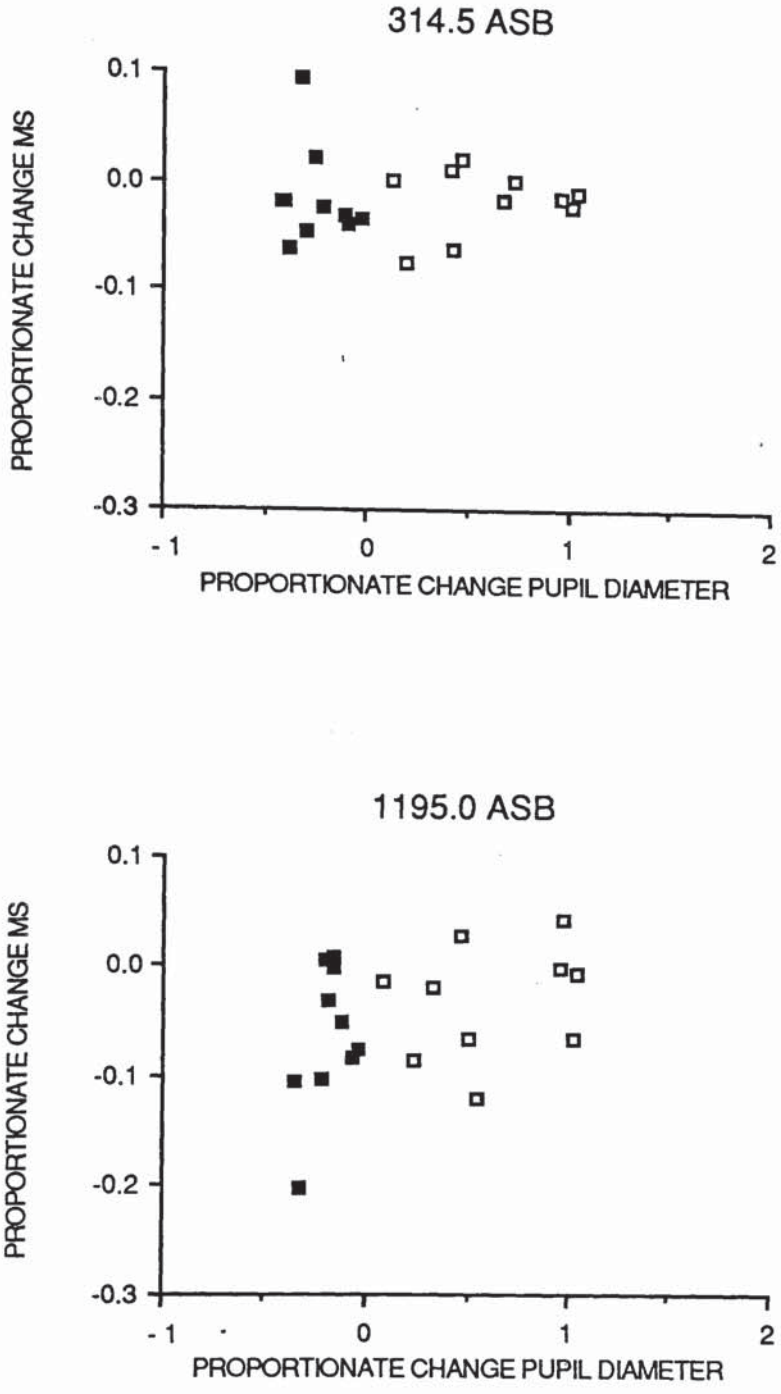


Figure 6.3.b. Proportionate change in global mean sensitivity against proportionate change in pupil diameter for adaptation levels of 314.5asb (top) and 1195.0asb (bottom). Closed squares indicate miosed pupils, open squares indicate dilated pupils.

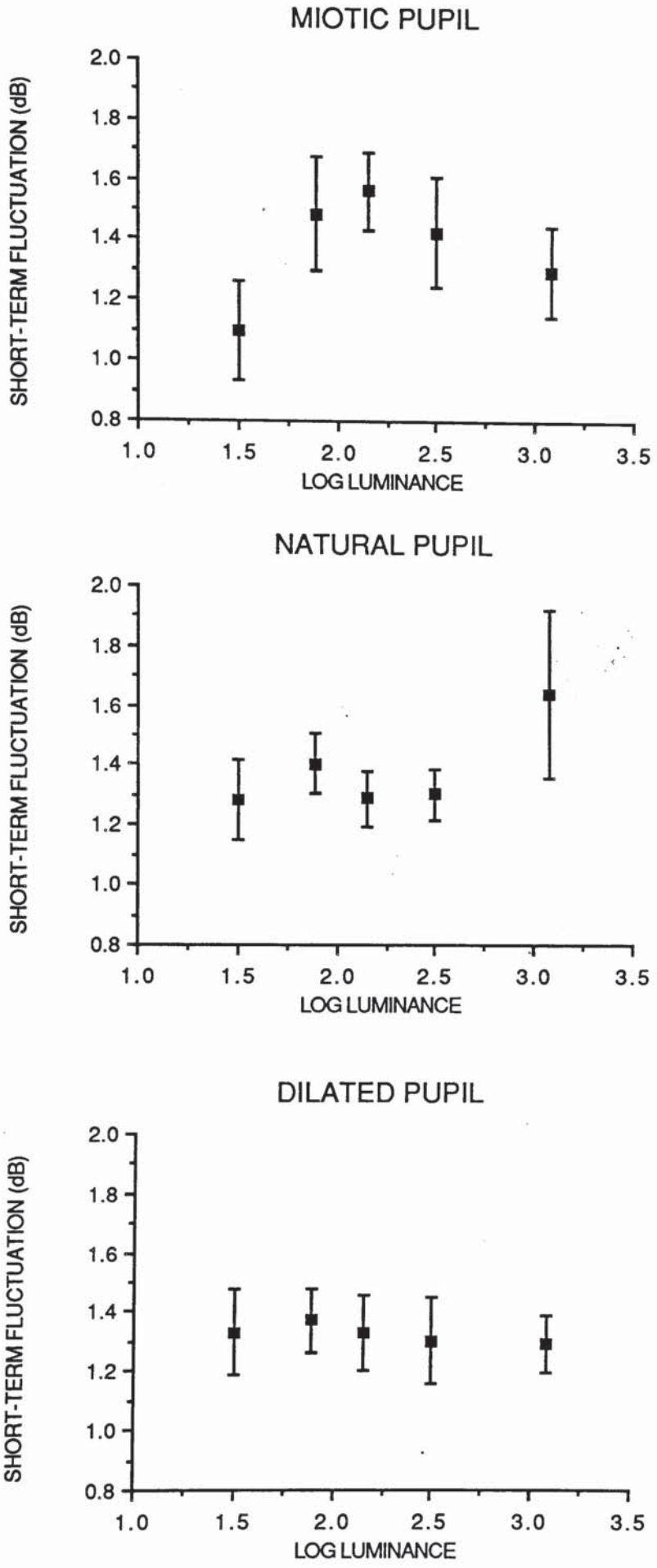


Figure 6.4. Group mean short-term fluctuation against adaptation level as a function of pupil size. Error bars indicate 1 S.E.M.

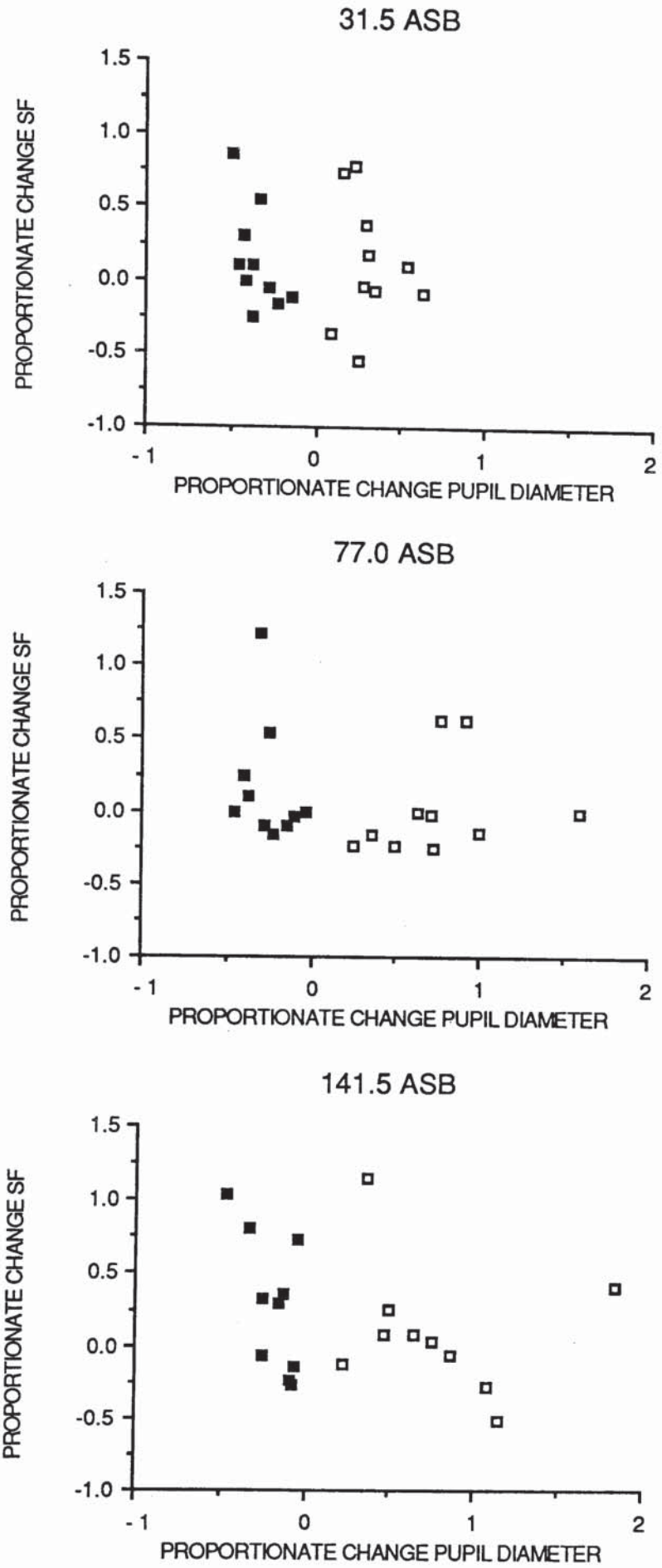
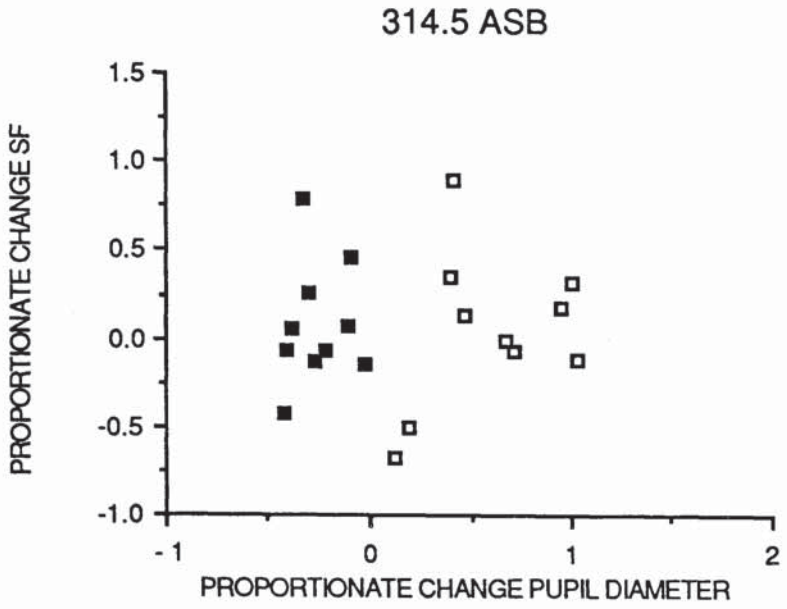


Figure 6.5.a. Proportionate change in short-term fluctuation against proportionate change in pupil diameter for adaptation levels of 31.5asb (top), 77.0asb (middle) and 141.5asb (bottom). Closed squares indicate miosed pupils, open squares indicate dilated pupils.



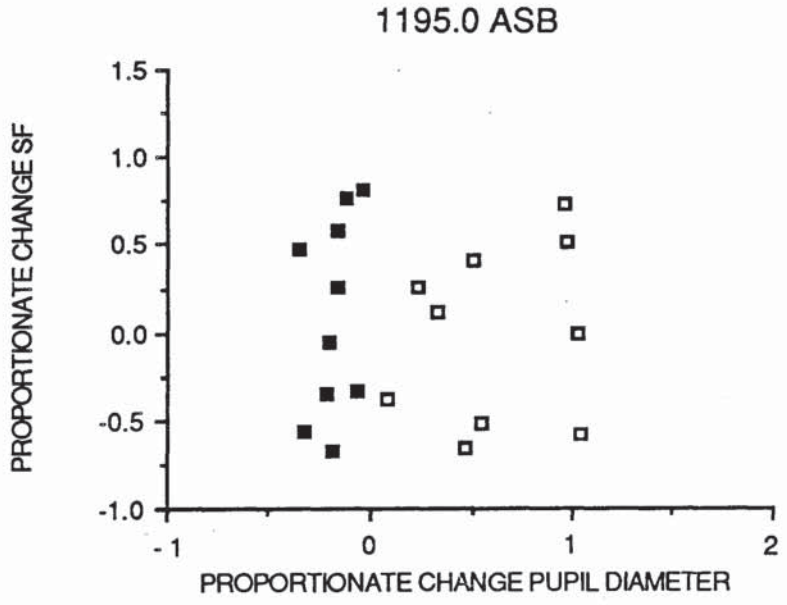


Figure 6.5.b. Proportionate change in short-term fluctuation against proportionate change in pupil diameter for adaptation levels of 314.5asb (top) and 1195.0asb (bottom). Closed squares indicate miosed pupils, open squares indicate dilated pupils.

	ADAPTATION LEVEL (asb)				
	31.5	77.0	141.5	314.5	1195.0
MIOTIC	4.1	0.0	0.0	0.0	0.0
0.5% Thymoxamine	(4.2;1.4)	(1.9;1.4)	(2.2;1.3)	(1.7;0.9)	(0.8;0.6)
SALINE	2.0	0.0	0.0	0.0	0.0
	(3.3;1.4)	(1.8;1.0)	(1.0;0.6)	(1.9;0.8)	(2.1;0.9)
MYDRIATIC	4.2	0.0	0.0	0.0	4.0
2.5% Phenylephrine	(4.9;1.6)	(3.8;1.9)	(0.5;0.5)	(1.4;0.7)	(4.1;1.5)

Table 6.2.a. Median % of fixation losses against adaptation level for 10 normal subjects. The accompanying means and standard errors are given in parentheses.

	ADAPTATION LEVEL (asb)				
	31.5	77.0	141.5	314.5	1195.0
MIOTIC	0.0	0.0	1.3	0.0	0.0
0.5% Thymoxamine	(0.5;0.5)	(6.1;3.1)	(5.0;2.1)	(3.8;1.9)	(3.4;2.3)
SALINE	0.0	0.0	0.0	0.0	0.0
	(3.7;1.7)	(3.9;2.1)	(4.0;3.1)	(3.8;2.3)	(4.0;2.8)
MYDRIATIC	3.9	3.8	6.3	0.0	0.0
2.5% Phenylephrine	(6.2;2.6)	(6.2;2.4)	(6.2;1.9)	(5.4;2.8)	(0.0;0.0)

Table 6.2.b. Median % of false negative responses against adaptation level for 10 normal subjects. The accompanying means and standard errors are given in parentheses.

	ADAPTATION LEVEL (asb)				
	31.5	77.0	141.5	314.5	1195.0
MIOTIC	0.0	0.0	0.0	0.0	0.0
0.5% Thymoxamine	(0.0;0.0)	(0.6;0.6)	(0.0;0.0)	(0.8;0.8)	(2.2;2.2)
SALINE	0.0	0.0	0.0	0.0	0.0
	(2.6;1.8)	(0.8;0.8)	(2.5;1.7)	(2.6;1.4)	(3.1;3.1)
MYDRIATIC	0.0	0.0	0.0	0.0	0.0
2.5% Phenylephrine	(1.4;0.9)	(0.0;0.0)	(2.9;1.5)	(0.0;0.0)	(1.2;1.2)

Table 6.2.c. Median % of false positive responses against adaptation level for 10 normal subjects. The accompanying means and standard errors are given in parentheses.

	ADAPTATION LEVEL (asb)				
	31.5	77.0	141.5	314.5	1195.0
MIOTIC	447.0	447.0	433.5	445.5	432.0
0.5% Thymoxamine	(450.0;9.3)	(463.3;17.8)	(438.9;10.3)	(447.6;10.2)	(452.2;13.7)
SALINE	443.5	438.0	440.0	443.0	442.5
	(452.8;12.2)	(442.6;7.0)	(441.8;11.8)	(445.0;9.9)	(444.8;6.7)
MYDRIATIC	448.5	435.0	440.0	444.0	458.0
2.5% Phenylephrine	(454.8;9.6)	(447.7;14.8)	(438.1;7.4)	(451.9;10.4)	(455.4;8.3)

Table 6.2.d. Median number of stimuli presented against adaptation level for 10 normal subjects. The accompanying means and standard errors are given in parentheses.

6.1.18. DISCUSSION

Several studies have suggested that the detection of focal glaucomatous visual field loss may be enhanced using higher adaptation levels than are utilised in currently available automated perimeters (Shiga 1968; Paige 1985; Drum et al. 1986; Mills et al. 1986; Lustgarten et al. 1990).

The study of Drum et al. (1986) suggested that the detection of diffuse glaucomatous visual field loss was enhanced at scotopic adaptation levels compared with photopic adaptation levels. Drum's study was, however, limited to only 6 stimulus locations, 3 situated 7.5° above and 3 situated 7.5° below the horizontal meridian in the nasal field with 2 stimuli at each of th eccentricities 5°, 10° and 15°. In addtion, the depth and type of visual field loss in Drum's glaucoma sample was not specified although the younger glaucoma patients were reported to have very early localised field loss which rarely coincided with the stimulus locations. The study thus limited the category of localised loss to positions in the field separated by a few degrees and extended the category of diffuse defects to those that were actually localised but equally severe at the superior and inferior test locations. Although the scotopic adaptation level revealed a greater extent of diffuse loss, the localised losses were found to be equal under scotopic and photopic adaptation levels. His result was consistent with Drance's earlier hypothesis (1985a), namely that two different mechanisms of neural damage are present in glaucoma. Damage to large ganglion cells might lead to diffuse visual field loss whereas damage to small ganglion cells, which receive a substantially greater cone input, could cause localised defects. Since the ability to discriminate between stimuli of similar luminance i.e. contrast sensitivity, increases with increasing adaptation level (Blackwell 1963), Drum et al. (1986) hypothesised that higher adaptation levels should be more efficient for the detection of focal glaucomatous visual field loss. The highest adaptation level therefore selected, namely 1195.0asb, was chosen to saturate the rod mechanism (Aguilar & Stiles 1954; Yeh et al. 1989). This current study has defined the normal perimetric response in young subjects at a range of adaptation levels higher than those that would be normally encountered in clinical perimetry.

The linear relationship between logΔL and logL shown in Figure 6.1. implies that the

Weber-Fechner law applies for the four higher adaptation levels employed in the study. This conclusions is further validated by the independence of threshold at the higher adaptation levels on pupil diameter. The results are in agreement with the work of Aulhorn et al. (1966) and Aulhorn & Harms (1972) who suggested that the Weber-Fechner law was valid above 100asb and Fankhauser (1979), who found it to be valid above 65asb for the conditions of clinical perimetry. The aim of the study was not to investigate whether the Weber-Fechner law was applicable at an adaptation level of 31.5asb. This is a controversial area: Fankhauser (1979) suggests that the Rose-de-Vries law holds for such an adaptation level although although many workers consider 31.5asb to conform to the Weber-Fechner law (Dubois-Poulsen 1967; Greve 1973; Klewin & Radius 1986). The study of Heuer et al. (1985) suggests that the adaptation level of 4asb employed in the Octopus Automated Perimeter does not conform to the Weber-Fechner law and this has been substantiated by Baldwin & Smith (1987). Validation of the Weber-Fechner law for an adaptation level of 31.5asb would require the use of several adaptation levels both above and below this figure to determine the exact form of the $\Delta L/L$ curve in this region.

Figure 6.2. implies that, although the Weber-Fechner law holds for the four higher adaptation levels at an eccentricity of 27°, this may not be the case for the fovea at the control adaptatio level of 31.5asb since there is some suggestion that the logΔL against logL function may become flatter at the lowest adaptation level. The transition from Rose-de-Vries to Weber behaviour is highly dependent on the spatial and temporal variables of the stimulus (Van Nes & Bouman 1967; Van Nes et al. 1967). In addition, Koenderink et al. (1978) have demonstrated that the transition from Rose-de-Vries to Weber behaviour occurs at a retinal illumination of 2-3 log units less at an eccentricity of 50° compared with an eccentricity of 0°. It would seem that the data shown in Figure 6.4. supports this.

Although the four higher adaptation levels were supplied from an external source of illumination, the internal illumination system of the Humphrey Field Analyser was utilised for the adaptation level of 31.5asb. It is possible that colour temperature differences between the illumination sources might affect the threshold recorded.

The increased retinal illumination which occurs with mydriasis would be expected to cause an increase in perimetric sensitivity at adaptation levels below which the Weber-Fechner law is valid. This expected improvement may be reduced or eliminated by increased aberrations associated with a larger pupil and the Stiles-Crawford effect, whereby rays of light entering the eye through the centre of the pupil elicit a greater sensation of brightness than rays of light that pass through the pupil eccentrically.

The data in Figure 6.3. implies that, for the higher adaptation levels employed, change in mean sensitivity is largely independent of pupil size change. This is in agreement with the study of Fankhauser (1979) who found mean sensitivity to be independent of pupil diameter change above an adaptation level of 94asb. Although there was a slight trend at all adaptation levels towards an increase in mean sensitivity with increase in pupil diameter, the data could not be fitted with any accuracy. The coefficients of determination (R^2) were 0.06, 0.28, 0.01, 0.04 and 0.06 for adaptation levels of 31.5, 77.0, 141.5, 314.5 and 1195.0asb respectively. The group mean miosed pupil diameter at an adaptation level of 31.5asb was 3.7mm (SD 0.8mm); it should be noted however that patients on miotic therapy frequently have pupils smaller than this e.g. 2mm diameter.

As seen from Figure 6.4., short-term fluctuation showed no correlation with adaptation level. Previous literature concerning threshold fluctuations at varying adaptation levels is somewhat equivocal, as reviewed in Section 6.9.3., although most authors have only considered the adaptation levels employed in commercially available perimeters i.e. below 40asb. The studies of Steinhardt (1936) and Kishto (1970) have investigated fluctuations at adaptation levels of 628asb or higher, where they demonstrated an increased spread of threshold data.

Figures 6.5.a. and 6.5.b. show the short-term fluctuation to be also independent of pupil diameter, a finding which is in agreement with the work of previous authors (Flammer 1984c; Lindenmuth et al. 1989, 1990) on normal subjects. Conversely, Wood et al. (1988a) found an increase in short-term fluctuation with decrease in pupil size for LED perimetry performed on normal subjects out to an eccentricity of 50°. Interestingly, Flammer (1984c) reported that

a decrease in pupil diameter was associated with increased fluctuations in glaucoma patients, although the effect was not quantified. It is, however, possible that the reported decrease in pupil diameter may have been related to miotic therapy given to patients with visual field loss and Flammer (1984c) reported that the main factor influencing the magnitude of the short-term fluctuation was the level of the differential light sensitivity itself.

6.1.19. CONCLUSIONS

Global mean sensitivity within 30° eccentricity obeyed the Weber-Fechner law for the four higher adaptation levels studied and was independent of pupil size change in a sample of young normal subjects.

This investigation has laid the groundwork for subsequent studies which will determine similar normative data for elderly subjects, and also define the threshold / luminance response in glaucoma patients with purely diffuse and purely focal visual field loss. The adaptation level at which any anomalous response was maximal should be determined. Such anomalous behaviour could then be evaluated as a potential diagnostic indicator of early glaucomatous damage.

Although perimetric sensitivity was independent of pupil diameter, it should be noted that patients on long-term miotic therapy frequently have smaller pupils than those measured in the study. In addition, pupil miosis may have a greater effect on threshold for eccentricities greater than 30°. Indeed, Wood et al. (1988a) found the effect of pupil miosis on perimetric sensitivity to increase with increasing peripheral angle to an eccentricity of 50° using an LED stimulus. This latter observation is of importance in view of the renewed interest in examination of the peripheral visual field in glaucoma (Seamone et al. 1988; Stewart et al. 1988; Haas et al. 1989).

6.2.1. INTRODUCTION

The development of automated perimetry has resulted in a variety of commercially available instruments. The design characteristics of these projection instruments stem largely from those of earlier manual instruments notably the Goldmann and Tubinger perimeters. The choice of stimulus variables for a given perimeter results mainly from tradition and from empirical development limited by engineering constraints rather than from considerations of the optimum detection of visual field loss. Indeed, one of the goals for future development in automated perimetry has been defined as the standardisation of stimulus conditions and data representation (Keltner 1979; Keltner & Johnson 1986). Considerations regarding the choice of stimulus type, size, duration and location as well as adaptation level and strategy have been reviewed in detail in Chapter 1.

Larger stimuli are employed in automated perimetry than are traditionally used in manual kinetic perimetry since they enhance the dynamic range and, until recently, were considered to be resistant to the effects of uncorrected refractive error and media opacities, as reviewed in Section 1.6.2. The default stimulus is a Goldmann size III but a size V stimulus has been proposed to quantify severely disturbed visual fields in glaucoma (Wilensky et al. 1986) and retinitis pigmentosa (Wood et al. 1986b) and studies have been carried out to establish empirical normative data for larger stimuli (Choplin et al. 1990). In screening for early glaucomatous visual field defects, however, the aim is to detect shallow paracentral scotomata and the increased dynamic range available with larger targets is of little value. Consequently, several authors have proposed the use of smaller stimuli (e.g. Goldmann size I) for the earliest detection of glaucomatous loss in the central visual field (Gramer et al. 1981) since the use of a Goldmann size III stimulus has been shown to saturate the central visual field area, and theoretically to be insensitive for the detection of early field loss (Wood et al. 1986a; Wild et al. 1986b). Indeed, Rolando et al. (1987) showed a highly significant correlation between intraocular pressure and the differential light sensitivity measured over the central 10° of the visual field using a Goldmann size I stimulus. The principle of increasec detection of defects with a smaller stimulus is explained by reduced spatial summation; it is

the converse to that of using a size V stimulus to increase the dynamic range and so map severely disturbed fields.

The optimum choice of stimuli locations is also equivocal. According to Fankhauser & Bebie (1979) the probability of detecting a 4.2° scotoma using a 6° square stimulus grid is 100%. King et al. (1986) however demonstrated that this grid resolution was not adequate for the identification of a scotoma the size and depth of the blind spot, a finding supported by Wild et al. (1986c) who considered that stray light effects (Fankhauser & Haeberlin 1980) masked the physiological scotoma. Indeed, Weber & Dobek (1986) demonstrated that the most effective method for detecting glaucomatous visual field loss using the Humphrey Field Analyser would be to develop a program with a 3° grid within 10° eccentricity, a 4.2° grid between 10° and 20° eccentricity and a 6° grid between 20° and 30° eccentricity. This recommendation coincided with the introduction of the Octopus program G1, in which the grid resolution has a maximal value of 2.8° in the macula area (Flammer et al. 1987). Nevertheless, Weber (1987) considered a 6° grid to be adequate for the detection of visual field loss secondary to chiasmal and supra-geniculate lesions.

A variety of adaptation levels have also been utilised in commercially available instruments. Heuer et al. (1987b, 1988) hypothesised that threshold measurements at the 31.5asb background of the Humphrey Field Analyser would be affected to a greater extent by light scattering than at the 4asb background employed by the Octopus Automated Perimeter. Conversely, they also considered that the absorbing effects of media opacities would be greater at the lower background luminance of the Octopus Automated Perimeter.

6.2.2. AIM OF THE STUDY

The aim of the study was to investigate the efficacy of variations in stimulus size, stimulus duration, stimulus location and adaptation level for the earliest detection of glaucomatous visual field loss. The range of possible stimulus options for the study was restricted to those offered by the two automated projection perimeters which have become the standard, namely the Octopus Automated Perimeter and the Humphrey Field Analyser.

6.2.3. MATERIALS AND METHODS

The sample comprised 20 patients (mean age 62.5 years, SD 10.5 years) with minimal or no visual field defects by previous quantitative perimetry (defined as kinetic Goldmann examination or Octopus program 33). The diagnoses comprised 9 patients with primary open-angle glaucoma, 8 with ocular hypertension, 1 with low-tension glaucoma and 2 glaucoma suspects. All patients had visual acuities of 6/9 or better, clear media and, where appropriate, were receiving topical ß-blocker therapy only. Exclusion criteria comprised intraocular pressures greater than 30mm Hg, miotic therapy, abnormal angles or irides, congenital or secondary glaucomas, pseudoexfoliation and pigment dispersion glaucoma, aphakia or pseudophakia, retinal degenerative conditions, diabetes and other systemic conditions with marked ocular complications. The depth and type of visual field loss, derived from Octopus program G1 is shown in Figure 6.6. based on the classification of Caprioli & Sears (1987).

The study was divided into three parts. In the first part, one eye of each patient was examined using program G1 (both phases) and program 32 of the Octopus 201 Automated Perimeter. This enabled a comparison of sensitivity recorded with two different stimulus grids while maintaining the same adaptation level, stimulus size (Goldmann III), stimulus duration (100msec) and thresholding strategy. The stimulus grids of program G1 and program 32 are illustrated in Figures 6.7. and 6.8. respectively.

In the second part, the same eye was examined with program 30-2 on the Humphrey Field Analyser 630, using Goldmann stimuli sizes I and III. This permitted a comparison of sensitivity recorded using different stimulus sizes while maintaining the same stimulus grid, adaptation level, stimulus duration (200msec) and thresholding strategy. The Humphrey Field Analyser Statpac program only contains a normal database for a Goldmann size III stimulus, and therefore normal data for a size I stimulus was obtained by two methods. Firstly, data for a size I stimulus was collected from a sample of 18 normal subjects (mean age 58.2 years; SD 12.5 years) to create an empirical normal database. Due to the vast amount of time and resources required for the establishment of a database for a size I stimulus (the empirical Statpac database of Heijl et al. (1987b) consisted of 487 examinations of 239 normal individuals) a

linear regression analysis was performed for the mean sensitivity recorded with the size I stimulus against age in a similar manner to that of Heijl et al. (1987b). This enabled the prediction of the normal value of mean sensitivity for stimulus size I for each age and thus allowed calculation of mean defect; such a small normal sample however precluded calculation of the loss variance index, since this would necessitate a regression for each stimulus location. Secondly, the Humphrey Field Analyser mathematically derived normal database for a size I stimulus was employed. In this mathematical model, the perimeter calculates an expected normal visual field contour for each stimulus size based on a slope equation which assumes a constant decrease in sensitivity for each degree of eccentricity from the central reference level. A slope value of 0.4dB per degree is used for a size I stimulus (the corresponding value for a size III stimulus is 0.31dB per degree). The mathematical model enabled calculation of both mean defect and loss variance indices.

The previous two parts permitted a comparison of sensitivity recorded with Octopus program 32 (size III) and Humphrey 30-2 (size III) using different adaptation levels, stimulus durations and thresholding strategy while maintaining the same stimulus grid. The comparison of sensitivity data between automated perimeters is however frequently confounded by the fact that the measured sensitivity, expressed in decibels (dB), is a logarithmic representation of the projected stimulus luminance referenced to the maximum stimulus luminance, the value of which varies between different instruments. In addition, instruments can employ different adaptation levels. The relationship between the differential light sensitivity ($L/\Delta L$) and sensitivity expressed in dB, for the Octopus and Humphrey Field Analyser is shown below:

$$\text{Octopus sensitivity (dB)} = 24 + 10 \log_{10} (L/\Delta L)$$

$$\text{Humphrey sensitivity (dB)} = 25 + 10 \log_{10} (L/\Delta L)$$

where L = 4asb for the Octopus Automated Perimeter and 31.5asb for the Humphrey Field Analyser. The measured and normal sensitivity values for each program were therefore considered in terms of $\log_{10}(L/\Delta L)$ to calculate the visual field indices, thus enabling a comparison of sensitivity between the two decibel scales.

The order of sessions, and order of examinations within each session were randomised. All

examinations were performed within a period of 2 weeks. Natural pupils were used throughout, and the pupil diameter measured at each perimeter bowl via the video fixation monitor. Patients were pre-adapted to the bowl luminance for 5 minutes, and the appropriate near refractive correction used.

The visual field indices mean sensitivity, mean defect, loss variance and short-term fluctuation were calculated for Octopus program 32 and Humphrey 30-2 (Goldmann size III) using the equations of Flammer (1986), in the absence of the weighting function for the normal variation in in short-term fluctuation with increase in peripheral angle used by Heijl et al. (1987b). These visual field indices are automatically printed out with Octopus program G1. Age-matched normative data for a size III stimulus, necessary in the calculation of the mean defect and loss variance indices was obtained from the appropriate Humphrey Statpac or Octopus printout. The blind spot locations were omitted in the calculation of indices for the Octopus 32 and Humphrey 30-2 programs, since there are no stimuli in the blind spot area of program G1.

The visual field indices from the first two sections, expressed in decibels, were compared using the non-parametric Wilcoxon signed rank test, as the indices did not follow a normal distribution. In the case of the third section the visual field indices were transformed to $\log_{10}(L/\Delta L)$ and evaluated in a similar manner with the Wilcoxon signed rank test.

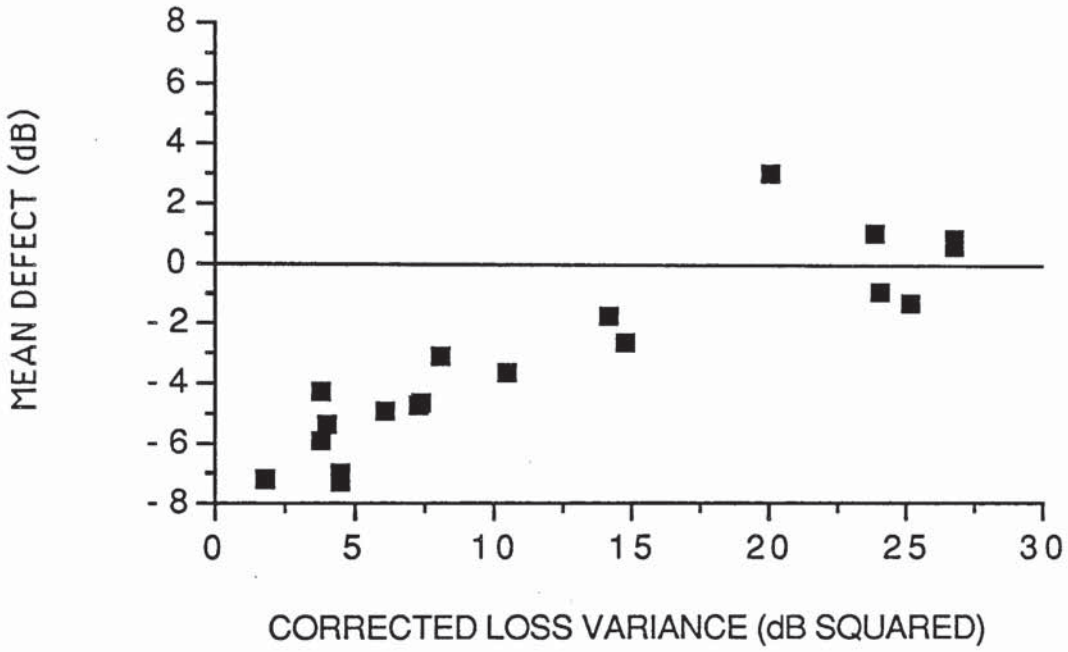


Figure 6.6. Illustrating the depth and type of visual field loss, derived from Octopus program G1 (size III), after the classification of Caprioli & Sears (1987) which considers mean defect (diffuse loss) as a function of corrected loss variance (focal loss). Field loss is seen to be primarily of the diffuse type.

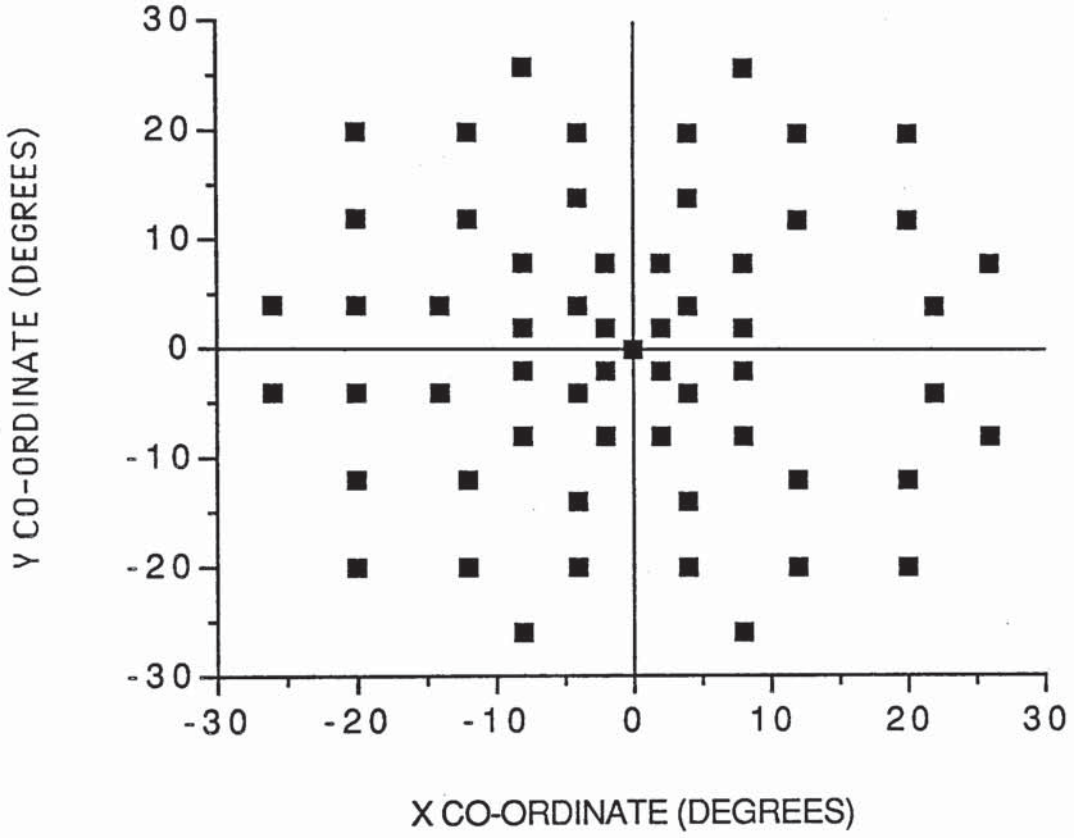


Figure 6.7. Illustrating the stimulus grid of Octopus program G1. Short-term fluctuation is calculated from double threshold determinations at each stimulus location.

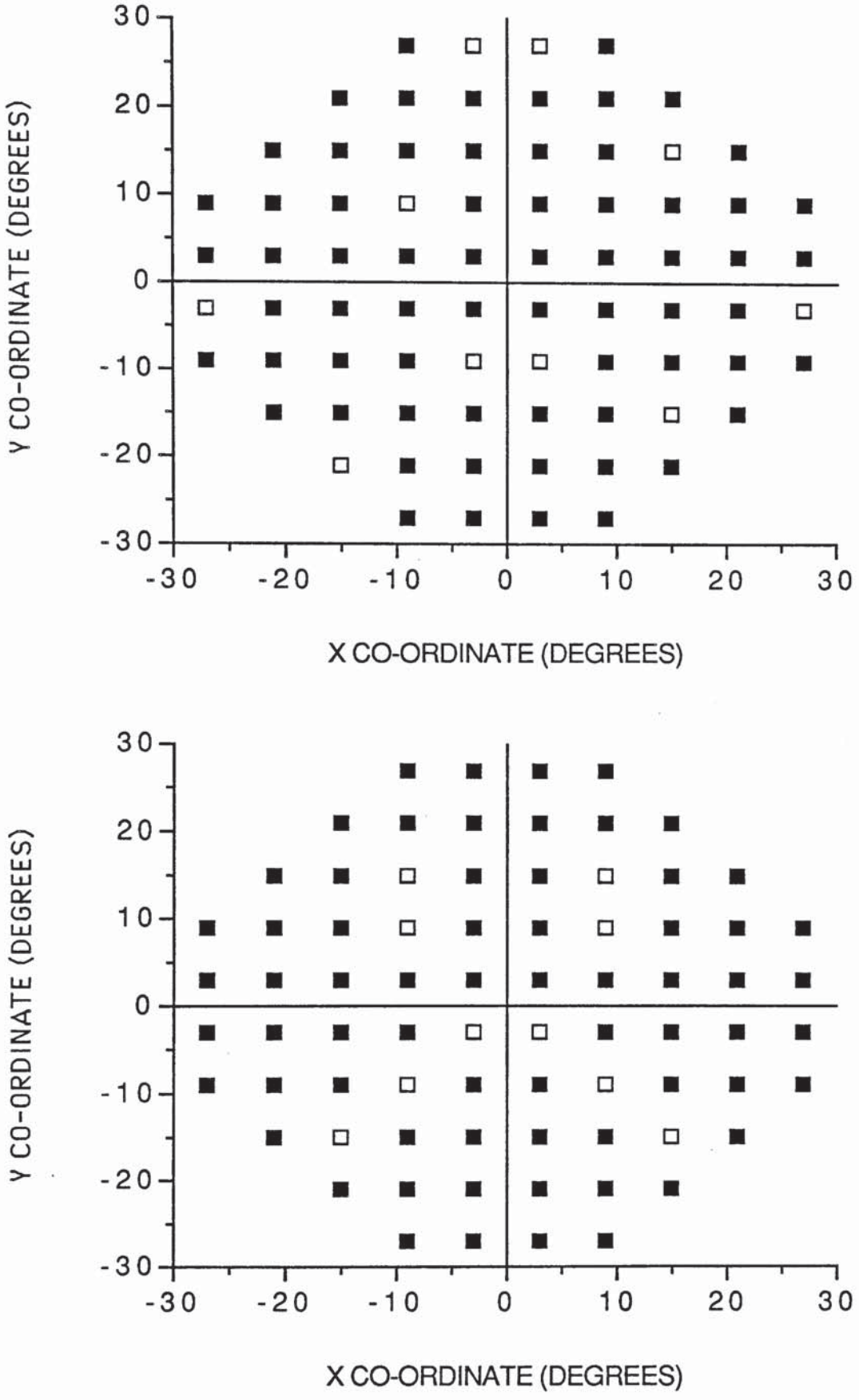


Figure 6.8. Illustrating the stimulus grids of programs Octopus 32 (top) and Humphrey 30-2 (bottom). Locations where double threshold determinations are made for the purpose of calculating short-term fluctuation are indicated with open squares.

6.2.4. RESULTS

Data from one patient was excluded from the analysis since a significant arcuate defect was detected by automated perimetry which was not evident on previous manual Goldmann testing (mean defect 15.2dB; corrected loss variance 82.7dB^2 recorded with Octopus program G1); this data was excluded since the purpose of the study was to define the optimum stimulus parameters for the detection of early glaucomatous visual field loss. All fields were considered reliable according to the criteria of less than 33% false positive and false negative responses and less than 20% fixation losses, except in 5 cases of Humphrey Field Analyser 30-2 programs. In 4 of these 5 cases fixation losses exceeded 20% (3 using stimulus size III and 1 using stimulus size I), and it was necessary to replot the blind spot. In the remaining case, the number of false negative reponses exceeded 33%.

Group mean pupil diameter for the Octopus 201 was 5.6mm (SD1.2mm); group mean pupil diameter for the Humphrey Field Analyser was 5.0mm (SD 1.1mm). In the case of the Humphrey Field Analyser pupil diameter was corrected for the magnification effects of the camera. This was not necessary for the Octopus perimeter, since the scale of the ruler placed across the monitor to measure pupil diameter is already corrected for the effects of camera magnification.

Influence of stimulus grid configuration: Octopus programs G1 and 32

Results of the group mean visual field indices and standard deviations, considered in decibels, for Octopus program 32 and for both phases of program G1 are summarised in Table 6.3., using the sign convention of Flammer (1986) i.e. increasing mean defect is positive. Group mean mean sensitivity for both phases of program G1 was 30.02dB (SD 3.16dB); this was significantly better ($p<0.002$) than the group mean mean sensitivity recorded with program 32 (27.10dB; SD 4.24dB). Mean sensitivity was significantly better ($p<0.002$) in the second phase of program G1 (30.23dB; SD 3.07dB) compared with the first phase (29.82dB; SD 3.28dB), although there was a good correlation between both phases of the program ($r_S=0.972$).

Mean defect derived by program 32 and program G1 was not statistically significantly

different. Mean defect was however significantly less ($p<0.02$) in the second phase of program G1 (-3.31dB; SD 2.97dB) compared with the first phase (-2.90dB; SD 3.17dB). When the stimuli within 10° eccentricity were analysed separately, mean defect was found to be significantly higher ($p<0.05$) for program 32 (-4.91dB; SD 2.57dB) than for both phases of program G1 (-5.78dB; SD 1.62dB).

Loss variance was significantly higher ($p<0.02$) with program 32 (20.52 dB^2; SD 9.82 dB^2) than for both phases of program G1 (15.63dB^2; SD 9.36dB^2). Loss variance was also significantly lower ($p<0.02$) in the second phase of program G1 (14.53dB^2; SD 9.06dB^2) compared with the first phase (16.66dB^2; SD 9.91dB^2). Corrected loss variance was not statistically significantly different between program G1 and program 32.

Short-term fluctuation was significantly lower ($p<0.002$) with program G1 (1.73dB; SD 0.42dB) compared with program 32 (2.82dB; 0.98dB).

INDEX	G1 (phase 1)	G1 (phase 2)	G1 (mean)	32
Mean sensitivity (dB)	29.82 (3.28)	30.23 (3.07)	30.02 (3.16)	27.10 (4.24)
Mean defect (dB)	-2.90 (3.17)	-3.31 (2.97)	-3.10 (3.06)	-2.38 (4.24)
Mean defect within 10° eccentricity (dB)	-5.60 (1.72)	-5.91 (1.57)	-5.78 (1.62)	-4.91 (2.57)
Loss variance (dB^2)	16.66 (9.91)	14.53 (9.06)	15.63 (9.36)	20.52 (9.82)
Corrected loss variance (dB^2)			16.02 (18.01)	13.94 (10.38)
Short-term fluctuation (dB)			1.73 (0.42)	2.82 (0.98)

Table 6.3. Group mean visual field index expressed in decibels for Octopus program G1 (phase 1 and 2 and mean of both phases) and program 32. The accompanying standard deviations are given in parentheses.

Influence of stimulus size: stimulus sizes I and III with Humphrey Field Analyser program 30-2

The group means and standard deviations for the visual field indices recorded with stimulus sizes I and III, for both mathematically and empirically derived normal databases, and considered in decibels are summarised in Table 6.4. The Statpac stimulus size III visual field indices which are weighted for the normal variance at each stimulus location are also summarised in the table. The sign convention of Heijl et al. (1987b) is employed i.e. increasing mean defect is negative, to allow comparison with the weighted indices. Since the indices loss variance and corrected loss variance of Flammer (1986) are quadratic indices, and their weighted Statpac counterparts pattern standard deviation and corrected pattern standard deviation are not, the weighted Statpac indices are expressed as the square of the index.

The results of the regression of empirical sensitivity data for the size I stimulus against age are shown in Figure 6.9. for both global mean sensitivity and for mean sensitivity within 10° eccentricity. The corresponding regression equations are:

$$\text{Global mean sensitivity} = 27.13 - 0.17.\text{age} \quad (R^2=0.42)$$

$$\text{Central mean sensitivity} = 28.42 - 0.12.\text{age} \quad (R^2=0.46)$$

Group mean mean sensitivity for a size I stimulus was 15.24dB (SD 3.37dB) and for a size III stimulus 25.48dB (SD 2.94dB).

Group mean global mean defect was higher for the mathematical size I database (3.13dB; SD 3.20dB) compared with the mathematical size III database (1.90dB; SD 2.24dB) although the difference was not statistically significant ($p<0.1$). Group mean global mean defect calculated from the empirical size I database (1.00dB; SD 3.71dB) was not significantly different from the group mean global mean defect calculated using the size III mathematical database ($p<0.1$), or from the unweighted index calculated using the Statpac database (2.91dB; SD 3.38dB; $p<0.1$) or from the weighted Statpac index (1.86dB; SD 2.56dB; $p<0.1$).

Similarly, there was no statistically significant difference between the group mean mean defect within 10° eccentricity calculated using the size I mathematical database (3.17dB; SD 2.65dB) and the size III mathematical database (1.78dB; SD 1.85dB; $p<0.1$). Group mean mean defect within 10° eccentricity calculated from the empirical size I database (1.09dB; SD 3.22dB) was not significantly different from the group mean global mean defect calculated using the size III mathematical database ($p<0.1$), or from the unweighted index calculated using the Statpac database (3.38dB; SD 1.72dB; $p<0.1$).

There was no statistically significant difference between the loss variance or corrected loss variance indices recorded with each stimulus size and calculated using the mathematical normal databases. Group mean loss variance for a size I stimulus was 14.98dB^2 (SD 10.35dB^2) and for a size III stimulus 16.20dB^2 (SD12.64dB^2). These values were not statistically significantly different from the group mean unweighted loss variance calculated using the Statpac database (14.24dB^2; SD 11.99dB^2) or the group mean weighted Statpac index, pattern standard deviation squared (16.73dB^2; SD 16.89dB^2).

Group mean corrected loss variance for a size I stimulus was 10.53dB^2 (SD 8.57dB^2) and for a size III stimulus 12.15dB^2 (SD 11.79dB^2) calculated using the mathematical database for both stimulus sizes. These values were not statistically significantly different from the group mean unweighted corrected loss variance calculated using the Statpac database (10.78dB^2; SD 12.48dB^2) or the group mean weighted Statpac index, corrected pattern standard deviation squared (9.65dB^2; SD 11.96dB^2).

Group mean short-term fluctuation was also similar for stimulus sizes I (2.08dB; SD 0.78dB) and III (2.00dB; SD 0.88dB).

INDEX	30-2 size I empirical	30-2 size I mathematical	30-2 size III unweighted	30-2 size III weighted	30-2 size III mathematical
Mean sensitivity (dB)	15.24 (3.45)		25.48 (2.94)		
Mean defect (dB)	1.00 (3.71)	3.13 (3.20)	2.91 (3.38)	1.86 (2.56)	1.90 (2.24)
Mean defect within 10° eccentricity (dB)	1.09 (3.22)	3.17 (2.65)	3.38 (1.72)		1.78 (1.85)
Loss variance (dB^2)		14.98 (10.35)	14.24 (11.99)	16.73 (16.89)	16.20 (12.64)
Corrected loss variance (dB^2)		10.53 (8.57)	10.78 (12.48)	9.65 (11.96)	12.15 (11.79)
Short-term fluctuation (dB)	2.08 (0.78)		2.00 (0.88)	1.77 (0.77)	

Table 6.4. Group mean visual field indices expressed in decibels for stimulus sizes I and III recorded with Humphrey Field Analyser program 30-2. The accompanying standard deviations are given in parentheses.

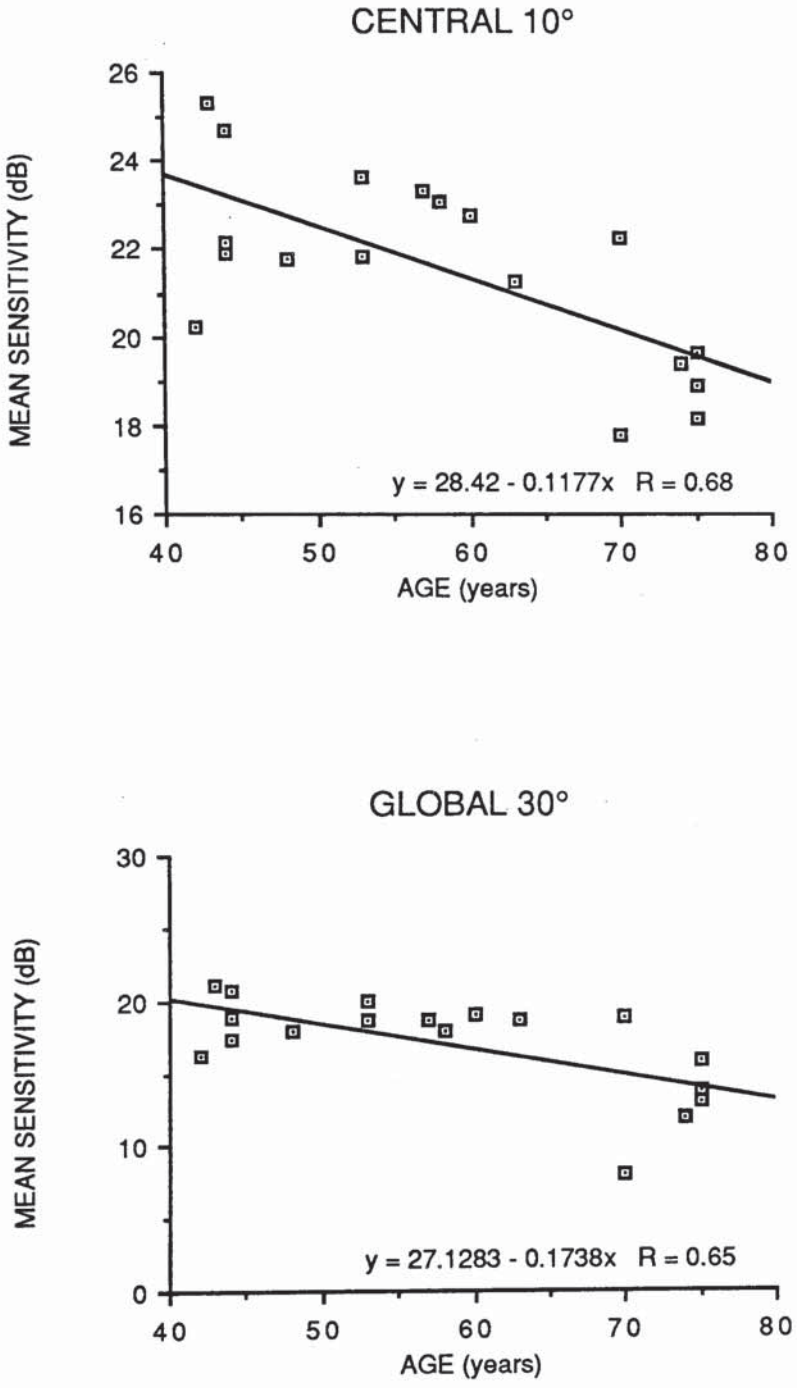


Figure 6.9. Regression of empirical sensitivity data for a size I stimulus against age for mean sensitivity within the central 10° (top) and for global mean sensitivity (bottom). The corresponding regression equations are: Central mean sensitivity = 28.42-0.12.age (R^2=0.46) and Global mean sensitivity = 27.13-0.17.age (R^2=0.42)

Interaction of adaptation level and stimulus size: Octopus program 32 and Humphrey program 30-2

The relationships between the indices calculated in decibels from the formulae of Flammer (1986) are shown in Figures 6.10.-6.11. A linear relationship is present for the indices mean sensitivity, mean defect and loss variance recorded by each instrument although there appears to be no such relationship for short-term fluctuation. The correlations between the indices recorded in decibels are: mean sensitivity r_S=0.85 ($p<0.001$), mean defect r_S=0.78 ($p<0.001$) and loss variance r_S=0.73 ($p<0.001$). The effect of introducing a weighting function for the normal variance at each stimulus location in the calculation of the Humphrey Statpac indices is also illustrated.

Short-term fluctuation was significantly lower ($p<0.02$) for the Humphrey Field Analyser (2.00dB; SD 0.88dB) compared with the Octopus 201 (2.82dB; SD 0.98dB). The number of stimuli presented by each instrument was not significantly different (481.7 stimuli; SD 39.3 for Octopus program 32 and 509.0 stimuli; SD 55.9 for Humphrey Field Analyser program 30-2).

The group mean indices calculated in terms of $\log_{10}(L/\Delta L)$ are summarised in Table 6.5. The relationship between the visual field indices calculated in terms of $\log_{10}(L/\Delta L)$ are shown in Figure 6.12.

When the visual field indices were recalculated considering pointwise sensitivity values and normative age-matched data in terms of $\log_{10}(L/\Delta L)$, group mean mean sensitivity was found to be significantly lower ($p<0.02$) on the Humphrey Field Analyser (0.07; SD 0.29) compared with the Octopus (0.31; SD 0.42). Similarly, group mean mean defect was significantly higher ($p<0.002$) recorded with the Humphrey Field Analyser (0.28; SD 0.33) compared with the Octopus (-0.24; SD 0.42). Mean defect is expressed using the formula of Flammer (1986) i.e. increasing mean defect is positive.

Group mean loss variance was significantly higher ($p<0.02$) recorded with the Octopus (0.21;

SD 0.10) compared with the Humphrey Field Analyser (0.14; SD 0.12). Corrected loss variance, which is the loss variance corrected for the short-term fluctuation, was however not statistically significantly different. Group mean corrected loss variance recorded with the Octopus program 32 was 0.12 (SD 0.75) and that recorded with the Humphrey Field Analyser program 30-2 was 0.10 (SD 0.11).

Short-term fluctuation recorded with Octopus program 32 (0.28; SD 0.10) was significantly higher ($p<0.02$) than that recorded with Humphrey program 30-2 (0.18; SD 0.08).

INDEX	Octopus 32	Humphrey 30-2
Mean sensitivity	0.31 (0.42)	0.07 (0.29)
Mean defect	-0.24 (0.42)	0.28 (0.33)
Loss variance	0.21 (0.10)	0.14 (0.12)
Corrected loss variance	0.12 (0.75)	0.10 (0.11)
Short-term fluctuation	0.28 (0.10)	0.18 (0.08)
Number of stimuli	481.7 (39.3)	509.0 (55.9)

Table 6.5. Group mean visual field indices calculated from considering pointwise sensitivity data in terms of $\log_{10}$ (L/ΔL) for program 32 (size III) of the Octopus 201 and 30-2 (size III) of the Humphrey Field Analyser. The accompanying standard deviations are given in parentheses.

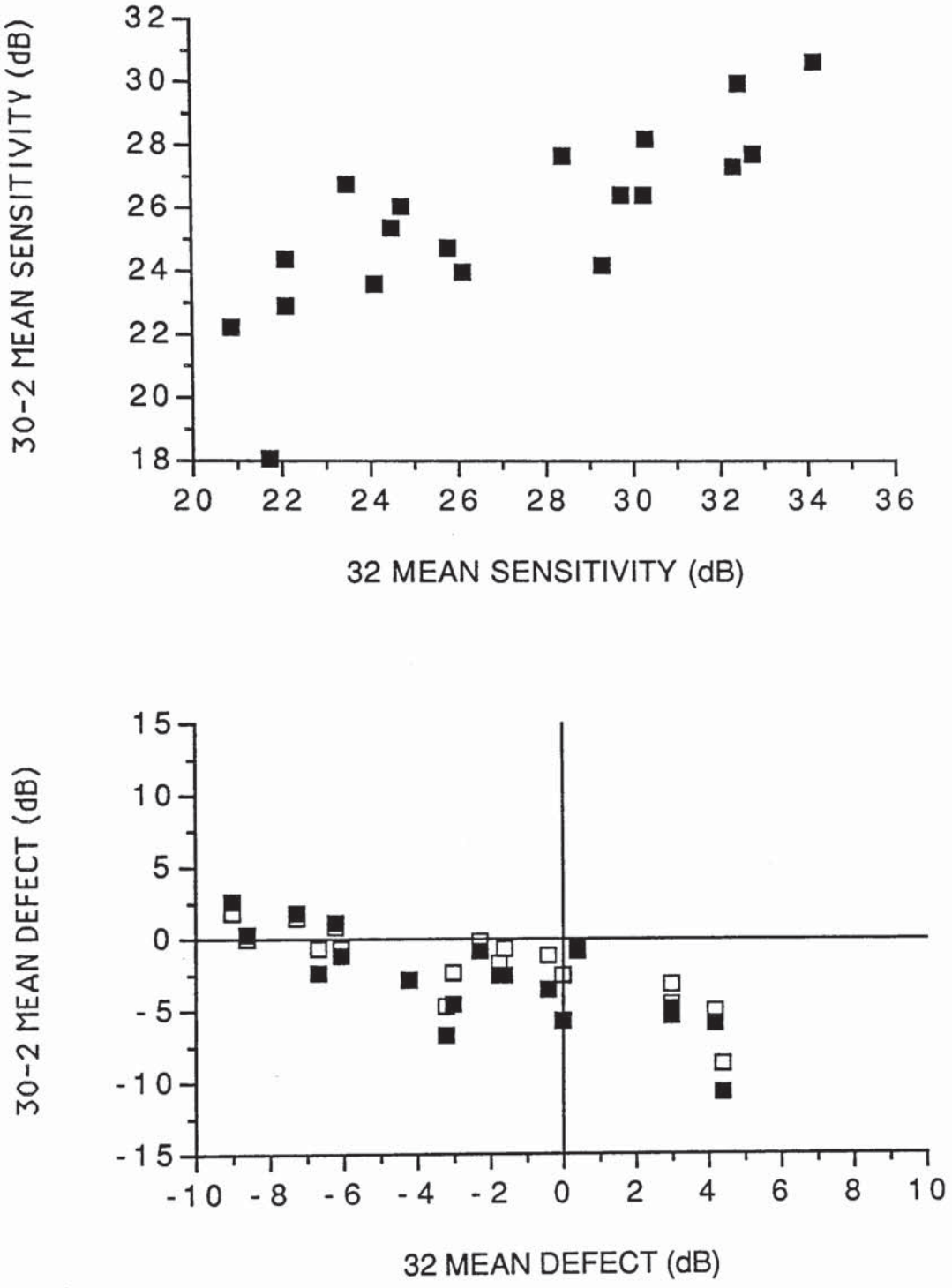


Figure 6.10. Showing the decibel relationship (closed squares) between the visual field indices mean sensitivity (top) and mean defect (bottom) recorded with Humphrey Field Analyser program 30-2 (stimulus size III) compared with those recorded with Octopus program 32 (stimulus size III), calculated from the formulae of Flammer (1986). The effect of introducing a weighting function for the normal variance at each stimulus location in calculation of the Humphrey Statpac indices is also illustrated in these figures (open squares).

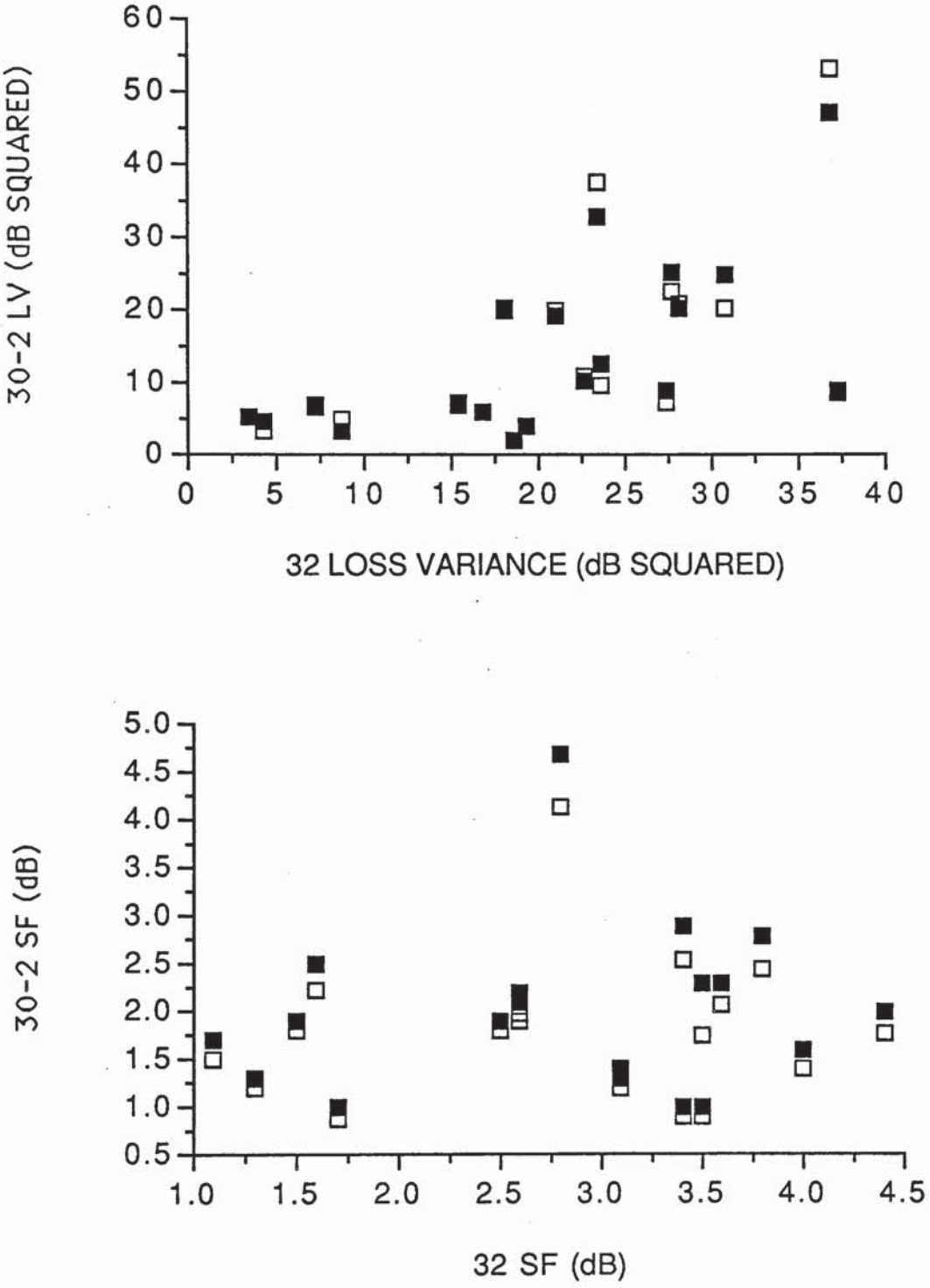


Figure 6.11. Showing the decibel relationship (closed squares) between the visual field indices loss variance (top) and short-term fluctuation (bottom) recorded with Humphrey Field Analyser program 30-2 (stimulus size III) compared with those recorded with Octopus program 32 (stimulus size III), calculated from the formulae of Flammer (1986). The effect of introducing a weighting function for the normal variance at each stimulus location in calculation of the Humphrey Statpac indices is also illustrated in these figures (open squares).

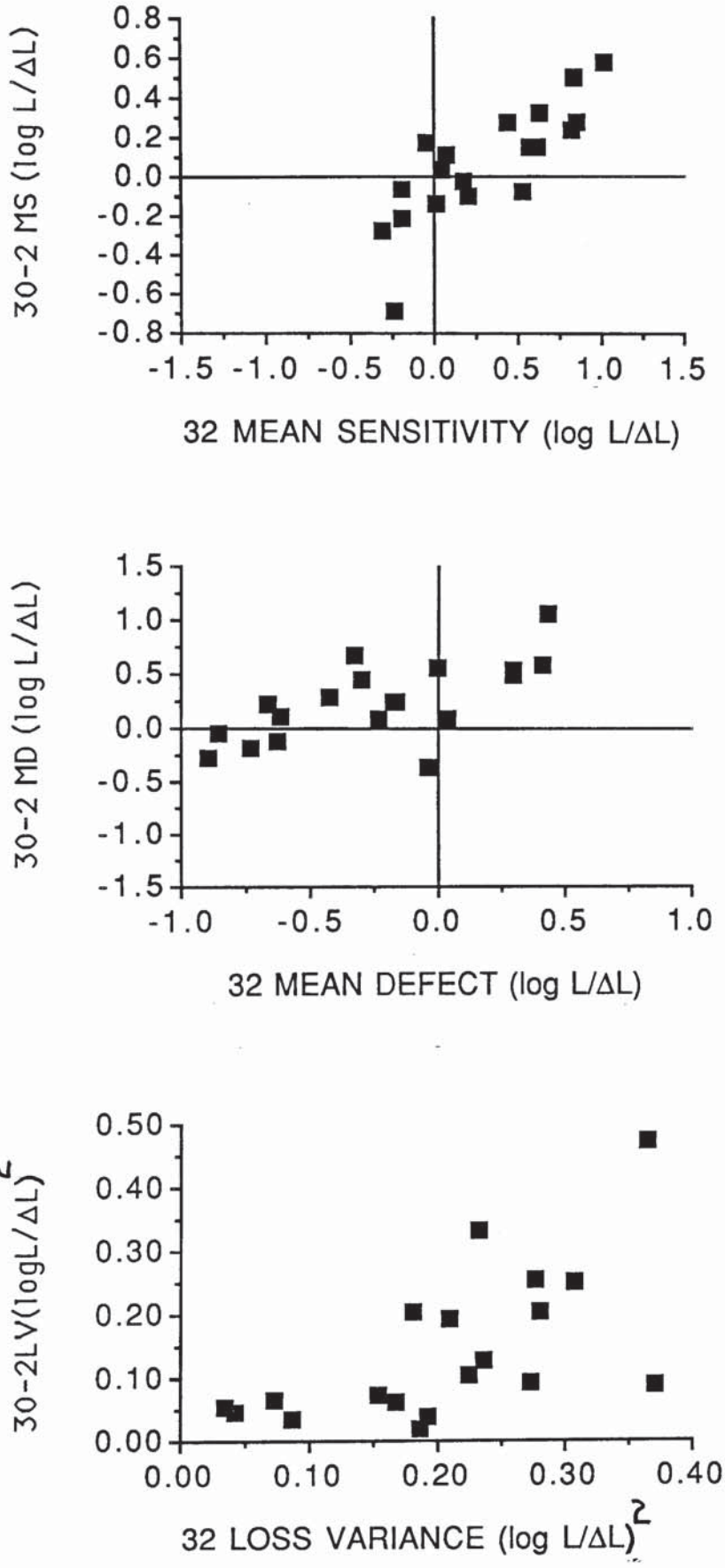


Figure 6.12. Showing the relationship between the visual field indices mean sensitivity (top), mean defect (middle) and loss variance (bottom) recorded with the Humphrey Field Analyser program 30-2 (size III) compared with those recorded with Octopus program 32 (size III) when the visual field indices were recalculated using the formulae of Flammer (1986) considering pointwise sensitivity and age-matched normative data in terms of $\log_{10}(L/\Delta L)$.

6.2.5. DISCUSSION

The higher mean sensitivity recorded with program G1 compared with program 32 may be due to the inclusion of a greater number of stimuli locations in the central area of the field and to measurement of the macula threshold (program G1 has 17 points within the central 10° whereas program 32 has 12 points). The similarity of the mean defect indices recorded with the two different stimulus grids indicates that, for the sample in question, use of the centrally weighted grid does not enhance the detection of glaucomatous loss when considering the global visual field indices. This finding however is not totally in agreement with Gloor & Gloor (1986) who compared the detection of glaucomatous visual field defects with the program G1 to that with the 6° square stimulus grids of Octopus programs 31 and 32. They also founc mean sensitivity to be significantly higher with program G1, but mean defect to be lower due to the test pattern of program G1 being more centrally weighted. Conversely, Dannheim (1987) considered program G1 to improve the detection and assessment of defects compared with the 6° square stimulus grid.

Weber & Dobek (1986) have suggested that the detection of scotomata is enhanced by the use of a more dense grid within the central 10° area. When data from the central 10° was analysed separately, mean defect was found to be greater ($p<0.05$) recorded with program 32 (-4.91dB; SD 2.57 dB) than with program G1 (-5.78dB; SD 1.62 dB). The higher density of stimuli in the central area of program G1 did not improve the detection of early diffuse glaucomatous defects in the sample under study.

The higher mean sensitivity, and lower mean defect, in the second phase of program G1 may also be due to learning effects despite employing a randomised design and patients who were experienced in perimetric techniques.

The lower degree of focal loss (loss variance) recorded with program 32 compared with program G1 may be due to the inclusion of a greater number of stimulus locations within the central 10° of the field, where early focal glaucomatous visual field defects are not to be expected. It could also have resulted from the difference in grid resolution between the programs. Interestingly, the loss variance was also significantly lower in the second phase of

program G1 ($p<0.02$). This might be attributed to a learning effect, since the visual field index corrected pattern standard deviation has been reported to diminish with perimetric experience in normal subjects (Heijl et al. 1989a). The finding of a higher degree of focal loss with program 32 compared with program G1 again conflicts with Gloor & Gloor (1986) who found the loss variance index to be similar in both programs.

The lower short-term fluctuation found with program G1 compared with program 32 is most likely due to the increased accuracy of calculation from the greater number of double determinations (59) of program G1 compared with the 10 double determinations used to calculate the root mean square (RMS) fluctuation in program 32. Indeed, the precision of the RMS as an estimate of the short-term fluctuation depends on the number of points replicated and the number of replications at these points (Bebie et al. 1976b); these authors showed that 10 double determinations gives the short-term fluctuation to an accuracy of only +/-25%.

Several authors have proposed that the use of a size I stimulus may be more sensitive for the detection of early defects within the paracentral area (Gramer et al. 1981; Wood et al. 1986a; Wild et al. 1986b). This hypothesis has recently been substantiated by Zalta & Burchfield (1990) who found a size I stimulus to be more sensitive for the detection of shallow scotomata (6dB depth) in the central visual field compared with a size III stimulus. In the current study, however, use of either the empirically derived or mathematical databases for a size I stimulus did not result in an increased mean defect for the field within either 10° or 30° eccentricity. The normal decline in sensitivity with age for the size I stimulus may not, however, be linear as assumed in the regression analysis to calculate an empirical size I normal database. A linear relationship between mean sensitivity and age is however assumed in the mathematical database. In addition, the effects of forward intraocular light scatter, which increase with age, are greater for a smaller stimulus (Radius 1978; Greve 1979). The mediocre correlation between mean sensitivity and age for the empirically derived database is in agreement with the study of Haas et al. (1986) who examined the influence of age on the results of automated perimetry in 203 eyes of 153 normal subjects.

The detection of focal loss was not enhanced by the use of a size I compared with a size III stimulus. It should be noted, however, that the sample comprised patients with primarily diffuse glaucomatous field loss.

The independence of short-term fluctuation with respect to stimulus size is in accord with the work of Gilpin et al. (1989) who found no differences in the short-term fluctuation or homogeneous component of the long-term fluctuation using the Humphrey Field Analyser for Goldmann stimuli I to V in normal subjects. The heterogeneous component of long-term fluctuation was however found to decrease with increasing stimulus size.

Johnson et al. (1987) devised a linear least squares regression equation to predict the sensitivity (recorded in dBs) for normal subjects on a given type of automated perimeter from sensitivity data obtained with a different type of automated perimeter. Their results suggested that a simple linear conversion was able to predict decibel sensitivity values, despite variations in background luminance and the other stimulus parameters. Anderson et al. (1989) confirmed the linear relationship between sensitivity data of automated perimeters in normal subjects, but found a lower correlation for abnormal points within the field. The current study confirms the linear relationship existing between the visual field indices of the Octopus and Humphrey instruments expressed in decibels. Further work may be required on the relationship between the indices determined on different instruments for more disturbed fields.

When the visual field indices were recalculated considering sensitivity in terms of $\log_{10}(L/\Delta L)$ mean sensitivity recorded with the Humphrey Field Analyser was lower than that recorded with the Octopus. This is in agreement with the study of Sucs & Verriest (1987). They compared the Humphrey Field Analyser 610 with the Octopus 500 in a sample of 10 young normals and transformed the results in terms of $\log_{10}(L/\Delta L)$ to standardise the different decibel scales. They found mean sensitivity to be lower with the Humphrey Field Analyser 610 both when considered in terms of decibels and also when converted to $\log_{10}(L/\Delta L)$.

The lower mean sensitivity recorded with the Humphrey Field Analyser when the results were transformed to $\log_{10}(L/\Delta L)$ is also in agreement with studies on glaucomatous samples Mogil et al. (1985) found the Humphrey Field Analyser to record a higher frequency of more extensive visual field loss compared with the Octopus 2000R in a sample of 26 glaucoma patients. Similarly, in a sample of 40 glaucoma patients with mild to moderate defects, Mills et al. (1986) found that defects recorded with the Humphrey Field Analyser 620 tended to be deeper and wider than with the Octopus 201, although this trend was not consistent and did not reach statistical significance. This conclusion has since been supported in a sample of 29 patients with ocular hypertension or early glaucoma by Lustgarten et al. (1990). They found the Humphrey Field Analyser to be slightly more sensitive for the detection of early glaucomatous visual field defects compared with the Octopus 2000R, although again the trend was not statistically significant.

The lower mean sensitivity recorded with the Humphrey Field Analyser could be attributed to the smaller pupil size at the higher adaptation level of 31.5asb compared with the 4asb background of the Octopus Automated Perimeter. This factor would not however account for the significant difference in mean defect since, in the computation of this index, measured thresholds are compared with age-matched normative threshold values for each perimeter, and therefore a control for the pupil size difference exists in the normal database. Furthermore, Fankhauser (1979) has shown that a pharmacologically induced pupil constriction from 4mm to 2mm in diameter (i.e. a four factor decrease in pupil area) resulted in a decrease in mean sensitivity of 2dB for the central 30° of the visual field, and this reduction was the same at adaptation levels of 4asb and 40asb.

From consideration of the Weber-Fechner and Rose-de-Vries laws, it would be expected that $(L/\Delta L)$ would be similar for both instruments or would be greater at the higher adaptation level of the Humphrey Field Analyser. This latter hypothesis has been verified empirically in normals (Hoskins & Migliazzo 1985; Lewis et al. 1986; Sucs & Verriest 1987; Brenton & Argus 1987) but does not account for the lower mean sensitivity found on the Humphrey Field Analyser in the glaucomatous sample. Hoskins & Migliazzo (1985) found a significantly higher sensitivity of 4dB per test location recorded with the Humphrey Field Analyser

compared with the Octopus 201 Automated Perimeter in a normal sample, employing similar stimulus grid patterns for the central field (Octopus program 31 and Humphrey Field Analyser program 30-1). The maximum stimulus intensity for the Humphrey Field Analyser is 10,000asb presented on a 31.5asb background, giving a Weber fraction of 10000/31.5=317, whereas the maximum stimulus intensity of the Octopus is 1000asb presented on a 4asb background, giving a Weber fraction of 1000/4=250. This difference in the Weber fraction would account for 1dB higher sensitivity recorded with the Humphrey Field Analyser since (log 317)-(log 250)=1dB. The remaining 3dB difference in recorded sensitivity was considered by Hoskins & Migliazzo (1985) to result from the difference in stimulus duration. The Octopus has a stimulus duration of 100msec and the Humphrey Field Analyser 200msec. From the temporal summation data of Aulhorn & Harms (1972) it may be seen that the difference in measured sensitivity for these stimulus durations when corrected for the difference in background luminance is of the order of 3dB.

Another factor which could account for the lower mean sensitivity recorded with the Humphrey Field Analyser is the strategy employed in determining threshold. The Octopus 201 employs a 4-2-1 strategy, taking as threshold the average of the last seen and last unseen stimuli, the final 1dB step being achieved by interpolation. The Humphrey Field Analyser employs a 4-2-2 strategy and takes the last seen stimulus as threshold, thus the Humphrey Field Analyser would record a sensitivity value that is apparently 1dB lower than that recorded by the Octopus. The dB scales however cannot be directly compared for the reasons outlined in Section 6.2.3.

The respective stimulus durations employed by the two instruments are not thought to account for the difference in sensitivity. The critical time for the background luminance used in the Octopus system (4asb) has been shown to be less than 100msec (Bahler 1975) and the critical time decreases with increasing adaptation level (Barlow 1958). Indeed, temporal summation has not been found to be altered in glaucoma patients (Dannheim & Drance 1974). The longer stimulus duration employed by the Humphrey Field Analyser would however prolong test time compared with the Octopus 201, and thus a decrease in sensitivity due to fatigue could be more apparent (Heijl 1977b; Heijl & Drance 1983).

Conversely, Holmin & Krakau (1979) reported sensitivity to be decreased and fluctuations to increase with the use of a 250msec stimulus on the Competer instrument compared with a stimulus duration of 500msec.

The different model used to create the normal database for each perimeter could account for the recorded difference in mean defect. The normal model used in the Octopus system implies that the shape of the normal hill of vision remains unchanged with age, the sensitivity decreasing by 1dB per decade, and that the normal intraindividual variation is constant throughout the field (Bebie 1985). The normal model used in Statpac software on the Humphrey Field Analyser, described by Heijl et al. (1987a,b), was empirically determined. It allows for a depression of the hill of vision with age that is eccentricity dependent i.e. the hill of vision becomes steeper with age, and for the intra- and interindividual variability which varies with test location. The difference in normal databases would not however account for the higher mean sensitivity recorded with the Octopus 201 automated perimeter, since the computation of mean sensitivity does not involve reference to normative data.

The lower short-term fluctuation recorded with the Humphrey Field Analyser compared with the Octopus Automated Perimeter is in agreement with studies on normal subjects (Lewis et al. 1986; Brenton & Argus 1986; Crosswell 1990). In contrast, Sucs & Verriest (1987) found interindividual variation in mean sensitivity to be higher using the Humphrey Field Analyser 610 compared with the Octopus 500. It should be noted however that the Octopus 500, also used in the study of Lewis et al. (1986), employs a "rapid check strategy" and only performs a full staircase threshold procedure at locations where the measured sensitivity differs from the age-corrected value in the normal database. Fankhauser et al. (1988) has considered the difference in fluctuation to be artefactual, attributing it to the different bracketing strategies used and the end-point taken as threshold. This would cause the Humphrey Field Analyser to underestimate short-term fluctuation compared with the Octopus 201 thresholding strategy since the Humphrey Field Analyser cannot produce odd differences between two determinations of the same threshold whereas the Octopus 201 may yield both odd and even differences.

The effect of adaptation level on short-term fluctuation is somewhat equivocal, as reviewed in Section 6.1.9.3.; the higher short-term fluctuation observed at the lower 4asb adaptation level of the Octopus 201 compared with the 31.5asb of the Humphrey Field Analyser is in accord with the work of Aulhorn & Harms (1972), who used manual static perimetry. There is no literature to date on the effect of stimulus duration on the level of the short-term fluctuation. The difference in short-term fluctuation in this study was mainly attributed to the different locations where double determinations are made for the purpose of calculating short-term fluctuation. These are distributed more centrally in Humphrey program 30-2 compared with Octopus program 32, as shown in Figures 6.7. and 6.9. Indeed, there is substantial evidence in the literature showing an increase in short-term fluctuation with peripheral angle for automated perimetry (Van den Berg et al. 1985; Brenton & Phelps 1986; Lewis et al. 1986; Heijl et al. 1987a,b; Langerhorst 1988; Rutihauser et al. 1989).

The higher degree of focal losses recorded on the Octopus 201, represented by the index loss variance, was considered to be artefactual. The loss variance index is representative of local scatter as well as true deviations whereas the visual field index corrected loss variance is the loss variance corrected for short-term fluctuation. Corrected loss variance therefore separates true local deviations from scatter, and this index was found to be similar recorded with each instrument. This latter result must be viewed with caution however since the short-term fluctuation was only determined with limited accuracy from 10 double determinations from different locations in each program.

6.2.6. CONCLUSIONS

The stimulus parameters and configuration of the Humphrey Field Analyser appear to show greater diffuse glaucomatous visual field loss compared with those offered by the Octopus. The Humphrey Field Analyser may therefore be more sensitive for the earlier detection of diffuse glaucomatous visual field loss. To the extent to which focal losses can be compared, there was no difference between the two instruments.

CHAPTER 7

STUDIES OF TEMPORAL SUMMATION IN GLAUCOMA

7.1. INTRODUCTION

Although photoreceptor absorbtion of a single quantum of light can trigger a neural response in the dark-adapted eye (Hallett 1969), several quanta must be absorbed to elicit a sensation (Hecht et al. 1942). A group of quantal absorbtions must occur within a certain retinal area (spatial summation) and during a limited period of time (temporal summation) to constitute an adequate stimulus. During this period the effects of individual quantum absorptions are summed along the visual pathway i.e. additional photons, in striking a given receptor, cause an increase in the receptor's potential if they arrive before the effects of the preceding photons have worn off completely.

7.2. BLOCH'S LAW AND THE CRITICAL DURATION

Temporal summation is described by the relationship $\Delta L.t^k$=constant, where ΔL is the incremental threshold, t is the stimulus duration and k is the summation coefficient. When k=1, the product of luminance and presentation time is constant, temporal summation is said to be complete and Bloch's law (1885) applies. The maximum time over which complete temporal summation can occur is termed the critical duration, represented by the symbol t_c. Bloch's law states that, within the limit of the critical duration, a given amount of luminous energy will have the same effect regardless of its distribution in time. For longer durations of stimulus presentation i.e. $t>t_c$, temporal summation becomes partial and the summation coefficient lies between zero and one ($0<k<1$). When k=0.5, the square root or Pieron's law of temporal summation applies. For still longer stimuli, the effect of a stimulus becomes dependent on its luminance alone rather than on the product of its luminance and duration i.e. ΔL=constant.

When thresholds are being measured, it is therefore necessary to specify whether the threshold is being determined with the minimum amount of energy or with the minimum level of luminance. Measurement of threshold energy requires stimuli shorter than the critical duration whereas measurement of the threshold luminance, important in the assessment of

visual function, requires stimuli longer than the critical duration. Clinical perimetry employs stimuli of duration longer than the critical time, which eliminates time as a variable for the perception of the stimulus. Stimuli presented for longer than the critical duration are visible solely as a function of their luminance, relative to the adapting level of luminance i.e. the contrast.

The Bunsen-Roscoe law of photochemistry is an analog of Bloch's law of vision. It describes the physical phenomenon of temporal summation of light energy by light-driven chemical reactions. Identical photochemical effects can be achieved by low levels of illumination introduced over long periods of time and by higher levels of illumination applied over shorter intervals. This reciprocal property is of value to photographers who use balanced variations in diaphragm aperture size and exposure duration to achieve equivalent degrees of film exposure with greater or less motion blur and depth of field. The total effect of exposure is determined by the number of quanta absorbed by the photosensitive emulsion on the film surface.

Many studies have estimated the critical duration for specified stimulus parameters. Brindley (1952) found the minimum period over which the law applied to be as short as 4.1×10^{-7}sec for a light flash with peak intensity of 3×10^{8} Trolands viewed foveally. In the same study Brindley (1952) found that the maximum critical duration was of the order of 30msec whereas Baumgardt & Hillman (1961) found an upper limit for Bloch's law of 100msec at absolute threshold for both red and blue-green light at 20° eccentricity for stimuli up to 8° in diameter. I has been shown that temporal summation for the background level used in the Octopus Automated Perimeter (4asb) is complete at 100msec (Bahler 1975).

7.3. THEORIES OF TEMPORAL SUMMATION

Evidence against the theory that temporal summation for brightness is based on purely photochemical events has been summarised by Boynton (1961). Hood & Grover (1974) have shown Bloch's law to apply to the cone electroretinogram of the frog. Kahneman (1965) concluded that perfect temporal summation, as indicated by the reciprocity law, occurs at a locus which integrates information from an extensive area of the retina. Indeed, Van der Brink

& Boumann (1954) found temporal summation to occur for stimuli presented to different areas of the retina. Other studies implicate the chromatically opponent systems in temporal integration (Mitsuboshi et al. 1987a,b; Ejima & Takahashi 1988). Temporal summation has also been demonstrated for binocularly presented stimuli thus implicating a central mechanism (Matin 1962; Kahnemann et al. 1967; Battersby & Defaubaugh 1969; Baron & Westheimer 1973). The influence of higher centres in the process of temporal summation is shown in the fact that auditory stimuli may have some effect on performance (Treisman 1964; Bernstein et al. 1973). These findings suggest that temporal summation of incremental stimuli by the visual system is a complex process, presumably involving more than a single mechanism. Indeed, Kahnemann et al. (1967) have noted that while the time-intensity reciprocity for brightness is probably mediated at retinal level, the reciprocity observed in the perception of form indicates central factors.

7.4. FACTORS AFFECTING TEMPORAL SUMMATION

The capacity of the visual system for demonstrating the properties of temporal summation, both complete and partial, is not a constant but depends on many parameters of the stimulus and background.

7.4.1. Stimulus size

Temporal summation increases with decrease in stimulus size (Pieron 1920; Graham & Margaria 1935; Baumgardt 1947; Barlow 1957,1958). Saunders (1975) however showed that, at absolute threshold, the critical duration for achromatic stimuli of size 0.05°, 0.17° and 0.53° presented at eccentricities of 0.67° and 4° was 80msec and this value was independent of stimulus size or location. Under increment threshold conditions, however, the critical duration decreased with increase in stimulus size. The results of Barlow (1958) also indicate little dependence of the critical duration on stimulus area at low adaptation levels but a decrease in the critical duration with increase in stimulus area at higher adaptation levels.

7.4.2. Adaptation level

Temporal summation increases with decrease in adaptation level (Stiles & Crawford 1934;

Graham & Kemp 1938; Barlow 1958) and during dark adaptation, with most of the increase in the critical duration occurring during the first few seconds of dark adaptation (Stewart 1972; Montellese et al. 1979). Indeed, Biersdorf (1955) found the critical time to be inversely proportional to the background luminance. Dannheim & Drance (1971b) found the critical duration for a Goldmann size IV stimulus to be 320msec at 30° eccentricity at an adaptation level of 0.1asb whereas the corresponding value at 10asb was 100msec. The increase in temporal summation with decreasing adaptation level involves neural processes (Boynton 1961) and cannot take place at a photochemical level alone (Battersby & Schuckman 1970) since the increase in temporal summation occurs faster than the time required for photopigment regeneration (Alpern 1971; Alpern & Hollins 1973). The increase in temporal summation with dark adaptation is not thought to be attributable to a change from dominant cone to dominant rod function (Brown & Black 1976; Montellese et al. 1979; Skottun et al. 1982) although this has recently been disputed by Sharpe et al. (1988) in a study of a rod monochromat. Although these latter authors found similar critical durations under dark adapted conditions for the rod monochromat and for a normal control subject, the critical duration was found to be longer for the monochromat than for the normal subject at an adaptation level of 314asb. Sharpe et al. (1988) attributed the discrepancy between their study and those of the previous authors to instrumental differences.

7.4.3. Eccentricity

Temporal summation is greater at the periphery of the visual field than at the centre. Dannheim & Drance (1971) found the critical duration to be 32msec foveally and up to 100msec at 30° eccentricity using a stimulus equivalent to Goldmann size IV (0.862°). The differences in temporal summation between centre and periphery of the field, however, are smaller than in the case of spatial summation; indeed, some authors consider there is no difference in the temporal integrative properties between the centre and periphery of the field (Bouman & Van Den Brink 1952; Kishto & Saunders 1970).

7.4.4. Spectral composition

The temporal responsiveness of the visual system to coloured stimuli varies in a complex manner. For small foveal stimuli (≤0.02°) wavelength has no effect on temporal summation

(Rouse 1952). For larger stimuli (≥0.08°), however, wavelength does have an effect (Sperling & Jolliffe 1965; Saunders 1975). Measurements of the critical duration for different wavelengths have indicated that short wavelength stimuli are integrated over longer intervals than are long wavelength stimuli (Sperling & Jolliffe 1963; Uetsuki & Ikeda 1971; Ueno 1976; Granda et al. 1986) i.e. the critical duration for blue light is greater than that for red light for large stimuli (0.75°). At photopic luminance levels the critical duration for red light is approximately 100msec whereas for blue light it is of the order of 250msec. Conversely, King-Smith & Carden (1976) showed that the critical duration was shortest for light of middle wavelengths and longest for stimuli at the spectral extremes. They analysed the data in terms of a hypothesis involving the luminance channel and the chromatically opponent channels. According to their model the luminance system, for which the critical duration is short, is more sensitive to yellow light whereas the opponent colour systems, where the critical duration is long, are more sensitive to light at the spectral extremes. This apparent separation of the colour channels indicates that temporal summative properties are at least partially diferentiated at an early stage of visual perception (Krauskopf & Mollon 1971). Threshold detection for changes in wavelength depends on the product of wavelength change and the duration over which the change in wavelength occurs (Regan & Tyler 1971a,b). Beyond this period, threshold detection of wavelength change depends on the magnitude of wavelength change alone. The temporal responsiveness of the visual system is related to the length of the critical duration; the visual system responds more rapidly to changes in luminance than to changes in spectral composition and, in general, responds more rapidly to changes in spectral composition at the red than the blue end of the spectrum.

7.4.5. Cognitive element

The critical duration is longer for complex perceptual tasks e.g. correct identification of a Snellen letter than for the relatively simple task of light detection, a fact which implicates cortical factors in temporal summation (Blackwell 1963). Indeed, the critical duration has been reported to be of the order of 400msec for an acuity related task (identification of the break in Landolt C), whereas for luminance detection it is of the order of 100msec (Kahnemann 1964; Kahnemann & Norman 1964; Baron & Westheimer 1973). The critical duration also varies as a function of the acuity required for the task; it is shorter for the detection of low spatial

frequencies than for higher spatial frequencies (Schober & Hilz 1965; Nachmias 1967; Arend 1976; Breitmeyer & Ganz 1977; Legge 1978; Gorea & Tyler 1986).

7.4.6. Age

Temporal summation is considered to be independent of age for the detection of perimetric spot stimuli (Danheim & Drance 1971b) and for the detection of gratings (Sturr et al. 1988) although Eriksen et al. (1970) found the critical duration to increase with increasing age for the identification of the position of the gap in Landolt C stimuli.

7.4.7. Inter-individual variation

Greve (1973) found a high inter-individual variation in a group of 20 normal subjects in the value of the summation coefficient k, which he concluded could have implications for the significance that may be attached to changes in temporal summation in areas of visual field loss. Indeed, Brown & Black (1976) found the maximum critical duration to vary between 250msec and 370msec for 3 subjects at an acuity level of 6/30.

7.5. AIM OF THE STUDY

Empirical evidence has indicated that different combinations of stimulus parameters presented by a given instrument can, in certain ocular and neurological disorders, be manipulated to provide diagnostic information additional to that obtained from the conventional perimetric examination. It has been claimed that abnormalities of spatial summation may be evident at an earlier stage than visual field defects in certain pathological conditions including glaucoma (Dubois-Poulsen 1952; Dubois-Poulsen & Magis 1957; Sloan 1961; Sloan & Brown 1962; Furuse 1966). Flanagan et al. (1984b) suggested that the perimetric response in Retinitis Pigmentosa (RP) was atypical over a range of stimulus combinations and strategies. Indeed, Wood et al. (1986b) found RP patients to show enhanced perimetric sensitivity to a stimulus of duration 100msec compared with a stimulus of 500msec duration. This surprising finding was contrary to conventional perimetric theory: a greater sensitivity would be expected using the longer duration stimulus by virtue of the increase in dynamic range, provided the presentation time remains within the critical duration.

Dannheim & Drance (1974) investigated temporal summation in a sample of primary open-angle glaucoma patients with manual kinetic and static perimetry. Using a Goldmann size IV stimulus, they found the temporal summative properties in areas of relative scotomata under both photopic (10asb) and mesopic (0.1asb) adaptation conditions and the value of the critical duration (100msec) to be similar to those found in normal areas of the same field. The temporal summation curves of the glaucoma patients were also similar to those obtained in a comparable study of normal subjects (Dannheim & Drance 1971b).

The automation of perimetry offers many advantages over manual methods, as reviewed in Section 1.5., including superior reproducibility of the examination strategy and greater precision in the mapping of the extent and depth of visual field defects. In addition, software is now available for use with automated perimeters enabling the stimulus duration to be varied. The aim of this pilot study was to investigate the temporal summative properties of glaucomatous patients using automated perimetry, and to determine whether this data could be used to provide additional diagnostic information for the earliest detection of glaucomatous visual field loss.

7.6. MATERIALS AND METHODS

The sample comprised 10 patients (4 male; 6 female) consisting of 4 patients with primary open-angle glaucoma (mean age 67.8 years, SD 3.4 years), all of whom were receiving therapy and 6 patients with ocular hypertension (mean age 63.3 years, SD 3.0 years), 3 of whom were receiving therapy. The grand mean age of the sample was 65.1 years (SD 6.3 years). Patients had no other ocular abnormality, open angles, clear media and where appropriate, were receiving topical ß-blocker therapy only. Exclusion criteria comprised visual acuity worse than 6/12, refractive errors greater than 5 Dioptres spherical and 2 Dioptres cylindrical, intraocular pressures greater than 30mm Hg, contact lens wearers, those with abnormal anterior segments, congenital or secondary glaucomas, pseudo-exfoliation and pigment dispersion, previous intraocular surgery, macula degeneration or other retinal disorders, diabetes or other systemic conditions with marked ocular complications and those receiving CNS medication. All patients had experienced a minimum of 3 previous automated perimetric examinations of the central visual field and were experienced in psychophysical

measurement techniques. Informed consent was obtained from all patients, who were themselves naive as to the purpose of the study.

One eye of each patient was examined with the Humphrey Field Analyser 630 using program 24-2 with foveal threshold measurement and stimulus size Goldmann III. The program was repeated 6 times at stimulus durations of 75, 100, 150, 200, 350 and 500 msec. The stimulus duration was varied via a custom ROM chip.

Patients attended for 2 sessions and performed three 24-2 programs at each session, within a period of 2 weeks. The order of examination with each stimulus duration was randomised within each session and between sessions for each patient. Intraocular pressure was measured after each session (Goldmann tonometry). Patients were pre-adapted to the bowl luminance of 31.5asb for 5 minutes and received a break of 10 minutes between each program. Natural pupils were used throughout; the pupil diameter was measured via the video fixation monitor and corrected for the effects of camera magnification. Fixation was constantly monitored and the appropriate near refractive correction used. The time taken to complete each program was of the order of 9 minutes.

The experimental procedure was repeated on a group of clinically normal age-matched subjects (mean age 61.8 years, SD 7.0 years; 6 male and 4 female) with visual acuity better than or equal to 6/6. Subjects had good general health and were free of any systemic or ocular medication. All patients were experienced observers in psychophysical techniques and were given preliminary training in automated perimetry consisting of two 24-2 programs with measurement of foveal threshold using a Goldmann size III stimulus and the default stimulus duration of 200msec.

Data for the patient sample was initially considered in terms of the visual field indices mean sensitivity and short-term fluctuation, calculated from the formulae of Flammer (1986) and the reliability parameters: the percentage of fixation losses, false positive and negative responses and total number of stimuli presented. Data for those patients with ocular hypertension and for the normal control group was additionally considered on an eccentricity

basis, taking the mean of 4 threshold determinations at each eccentricity along the oblique meridians, namely 0°, 4.2°, 12.7° and 21.2°.

Data was further analysed by considering the temporal summative properties in psychophysical terms. The model describing temporal summation is:

$$\Delta L.t^{k}=\text{constant}$$

It follows that,

$$\log \Delta L + k \log t = \log \text{constant}$$

where log ΔL is expressed in the decibel values of sensitivity. Log ΔL (directly proportional to the decibel scale) was therefore plotted against log t, to give the temporal summation curve, and the slope of the curve (proportional to the temporal summation coefficient k) determined by linear regression. Each patient was age-matched to the normal control group on an individual basis and the slopes of the patient and normal groups compared. The slopes of the normal and ocular hypertensive groups were similarly compared at corresponding meridians.

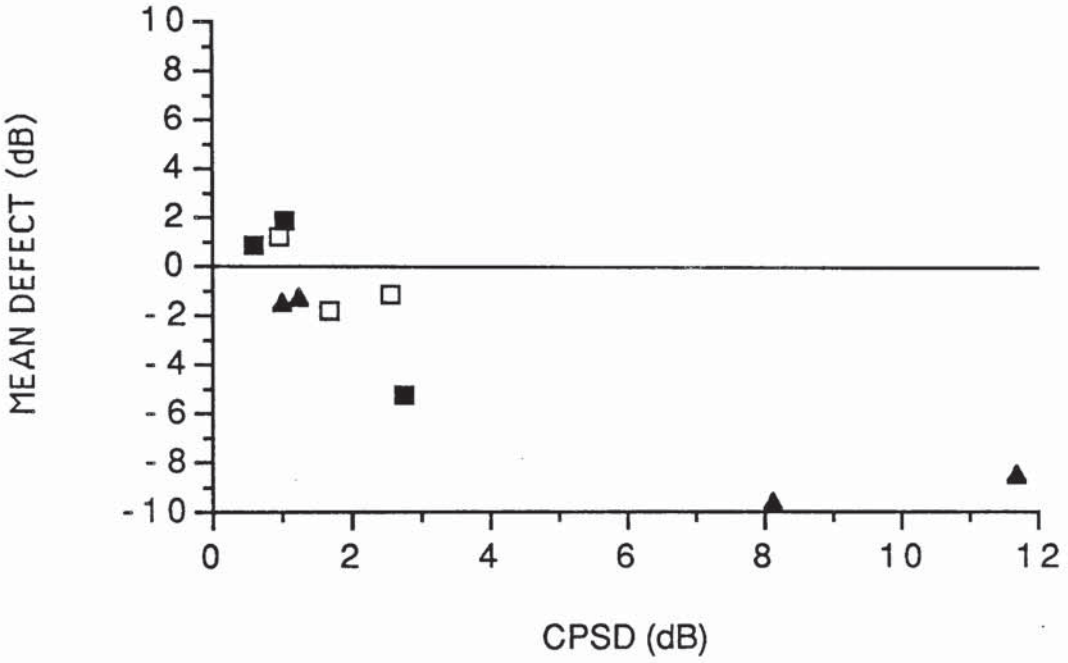


Figure 7.1. Illustrating the depth and type of field loss, derived from Humphrey program 24-2 at a stimulus duration of 200msec, after the classification of Caprioli & Sears (1987) which considers mean defect (diffuse loss) as a function of corrected pattern standard deviation (focal loss). The diagnoses are indicated (ocular hypertension without therapy: open squares; ocular hypertension with therapy: closed squares; primary open-angle glaucoma: closed triangles).

7.6. RESULTS

The depth and type of visual field loss, derived from program 24-2 with Statpac analysis at a stimulus duration of 200msec, is shown in Figure 7.1.

Global mean sensitivity increased with increasing stimulus duration for both the glaucomatous patients and normal controls, as illustrated in Figure 7.2. Global mean sensitivity increased from 26.1dB (SE 0.87dB) to 29.7dB (SE 0.64dB) with increase in stimulus duration from 75msec to 500msec. The corresponding increase in mean sensitivity for 10 glaucomatous patients was from 23.7dB (SE 1.66dB) to 28.2dB (SE 0.98dB). The standard errors were found to be higher in the glaucomatous patients than for the normal controls.

Short-term fluctuation was found to decrease with increase in stimulus duration for the normal controls, as shown in Figure 7.3., although this data could not be fitted with any accuracy by a linear function (R^2=0.47). No relationship was observed between global short-term fluctuation and stimulus duration for the glaucomatous patients.

A Friedmann analysis of variance by ranks showed no statistically significant differences in the percentage of fixation losses (normals $p<0.2$; glaucomatous $p<0.2$), false negative responses (normals $p<0.1$; glaucomatous $p<0.1$) or false positive responses (normals $p<0.2$; glaucomatous $p<0.1$) with increase in stimulus duration. The number of stimuli presented at each stimulus duration for both the normal controls and glaucomatous patients approximated to a normal distribution (Kolmogorov-Smirnov one sample test) and therefore a parametric one-way analysis of variance with repeated measures was carried out on the raw data; again, no statistically significant difference was found in the number of stimuli presented at each stimulus duration in either group (normals $p<0.2$; glaucomatous $p<0.1$).

When global mean sensitivity was plotted against log stimulus duration, and the slope of the summation curve (proportional to the temporal summation coefficient) determined by linear regression, the group mean slopes for the normal subjects and glaucomatous patients were 4.58 and 5.84 respectively as shown in Figure 7.4. When the glaucomatous sample was

additionally divided into those patients with ocular hypertension (n=6) and those with primary open-angle glaucoma (n=4) , as shown in Figure 7.5. the group mean slopes were 4.69 and 7.13. respectively. The standard errors of global mean sensitivity at each stimulus duration were higher in the ocular hypertensive patients than in the normal controls and higher still in the primary open-angle glaucoma patients than in the ocular hypertensives.

To relate the slope to the temporal summation coefficient k, such that $0 \leq k \leq 1$, the decibel values of mean sensitivity were converted to the differential light sensitivity $L/\Delta L$ using the equation $dB=25+10\log_{10}(L/\Delta L)$, where L and ΔL are in apostilbs, and $\log_{10} (L/\Delta L)$ plotted against log stimulus duration. It was found that the slope of the summation curve expressed in decibels was greater than the slope expressed in terms of $\log_{10} (L/\Delta L)$ by a factor of 10, giving group mean temporal summation coefficients of 0.46, 0.47 and 0.71 for the normal, ocular hypertensive and primary open-angle glaucoma groups respectively.

The slopes for both the glaucomatous and age-matched control subjects followed a normal distribution (Kolmogorov-Smirnov one-sample test). Comparison of the slopes for both groups using a paired Student's t-test however revealed no statistically significant difference between the patient and control groups, when age-matched on an individual basis. The slopes for each of the 10 patients and age-matched controls are shown in Table 7.1.

Temporal summation increased with increase in peripheral angle for the normal subjects as shown in Figure 7.6.; this was manifested as an increase in the slope of the temporal summation curve with increase in eccentricity. The slopes for the normal control group at eccentricities of 0°, 4.2°, 12.7° and 21.2° were 1.04, 2.96, 3.19 and 4.89 respectively. The corresponding slope values at similar eccentricities for the 6 ocular hypertensive patients were 0.66, 2.46, 3.45 and 5.11, as shown in Figure 7.7. Within the limits of the small sample (n=6) the slope values were not significantly different (p=0.65) between the ocular hypertensives and the normal controls (Student's t-test).

Temporal summation curves were further plotted for clusters of 2 or 3 adjacent points of visual field loss (defined as those in which sensitivity was depressed by more than 5dB below

the age-corrected normal value by Statpac analysis) in the glaucoma patients, and compared with summation curves obtained from clusters at corresponding eccentricities in unaffected areas of the same field. In 2 patients with advanced glaucomatous visual field loss, the slopes of the temporal summation curves were greater in the defective than in the corresponding normal area of the field, as shown in Table 7.2. Slopes from normal areas of the field in the 2 glaucoma patients with advanced loss were, however, greater than the slopes for the same test locations determined from the age-matched control subjects. In the remaining 2 patients, who displayed minimal loss, the slopes for the normal and for the defective areas of the field were found to be similar.

When the slope of the temporal summation curves for the patient group were considered as a function of the visual field indices mean defect and corrected pattern standard deviation, derived from program 24-2 at a stimulus duration of 200msec, the slope was found to increase with increasing diffuse and increasing focal glaucomatous visual field loss, shown in Figure 7.8.

PATIENT	AGE		DIAGNOSIS	SLOPE OF SUMMATION CURVE	
	Patient	Control		Patient	Control
1	72	70	OH	4.37	4.33
2	71	69	OH	5.44	5.16
3	71	69	OH	3.93	7.57
4	69	67	OH	2.46	4.39
5	68	63	OH	4.21	3.41
6	66	62	OH	8.95	4.08
7	63	58	POAG	12.80	2.98
8	59	55	POAG	6.78	5.39
9	58	54	POAG	5.13	4.06
10	54	51	POAG	3.80	4.57

Table 7.1. Showing slopes of the temporal summation curves for 10 patients and age-matched normal control subjects by diagnosis (OH: ocular hypertensive; POAG: primary open-angle glaucoma).

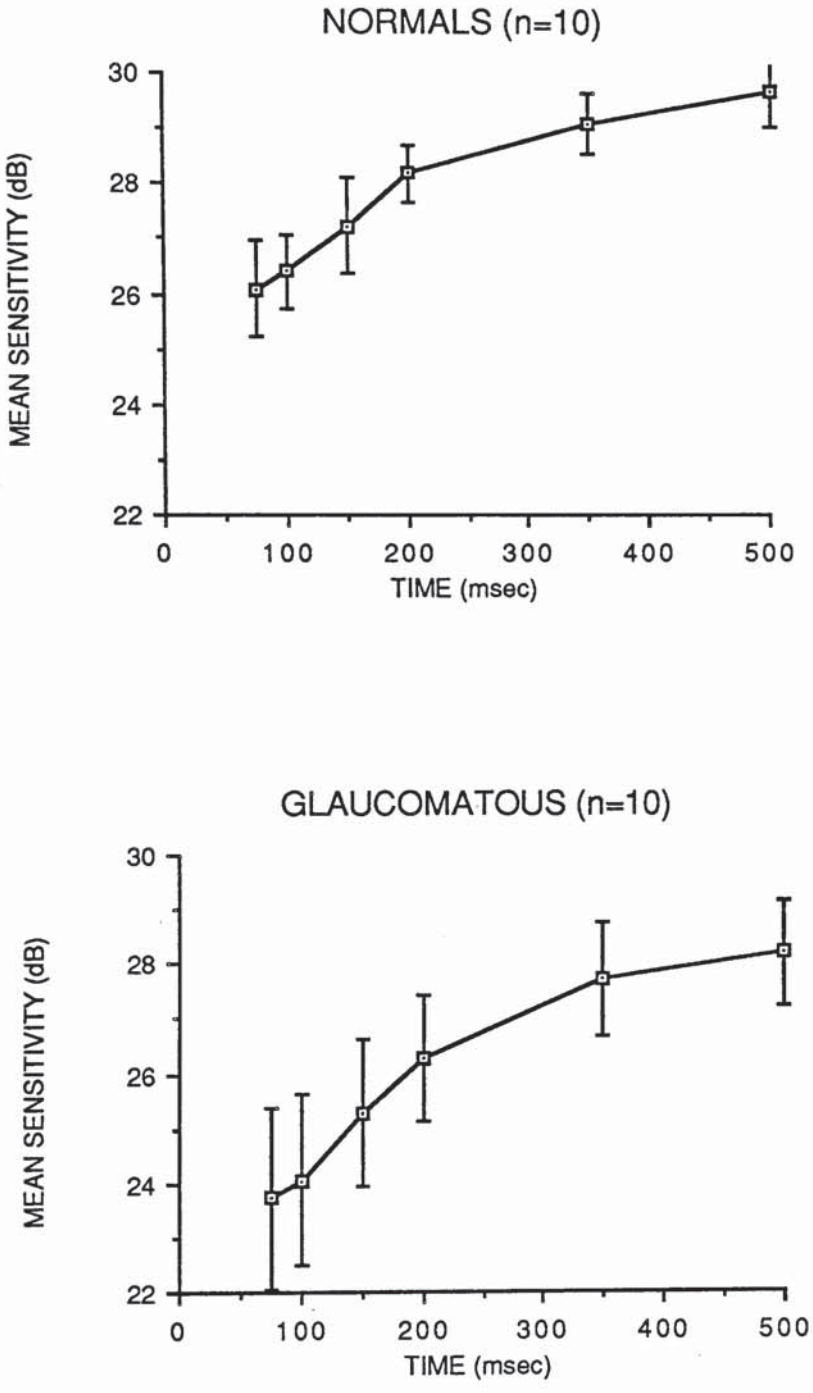


Figure 7.2. Group mean global mean sensitivity as a function of stimulus duration for the normal group (top) and glaucomatous group (bottom). Error bars indicate one standard error of the mean.

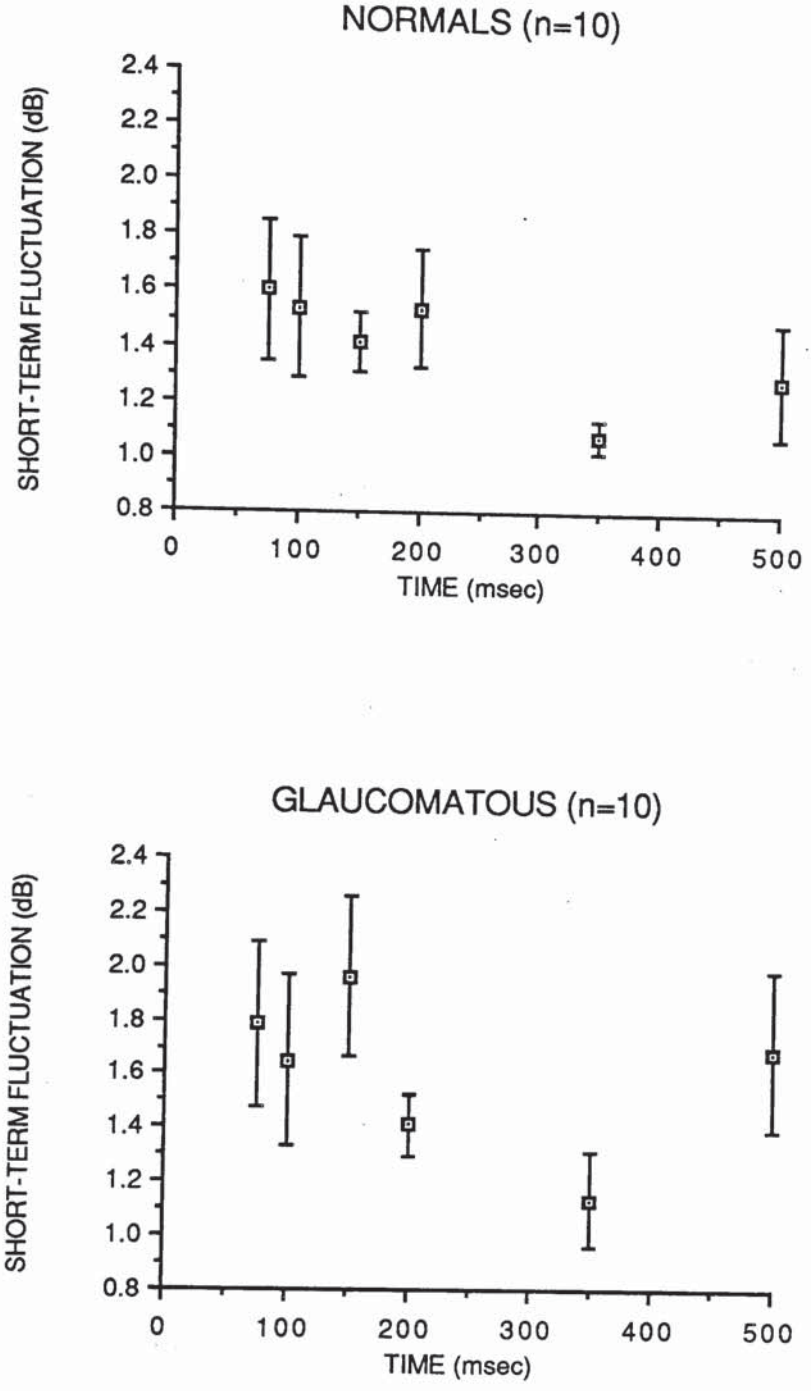


Figure 7.3. Group mean global short-term fluctuation as a function of stimulus duration for the normal group (top) and glaucomatous group (bottom). Error bars indicate one standard error of the mean.

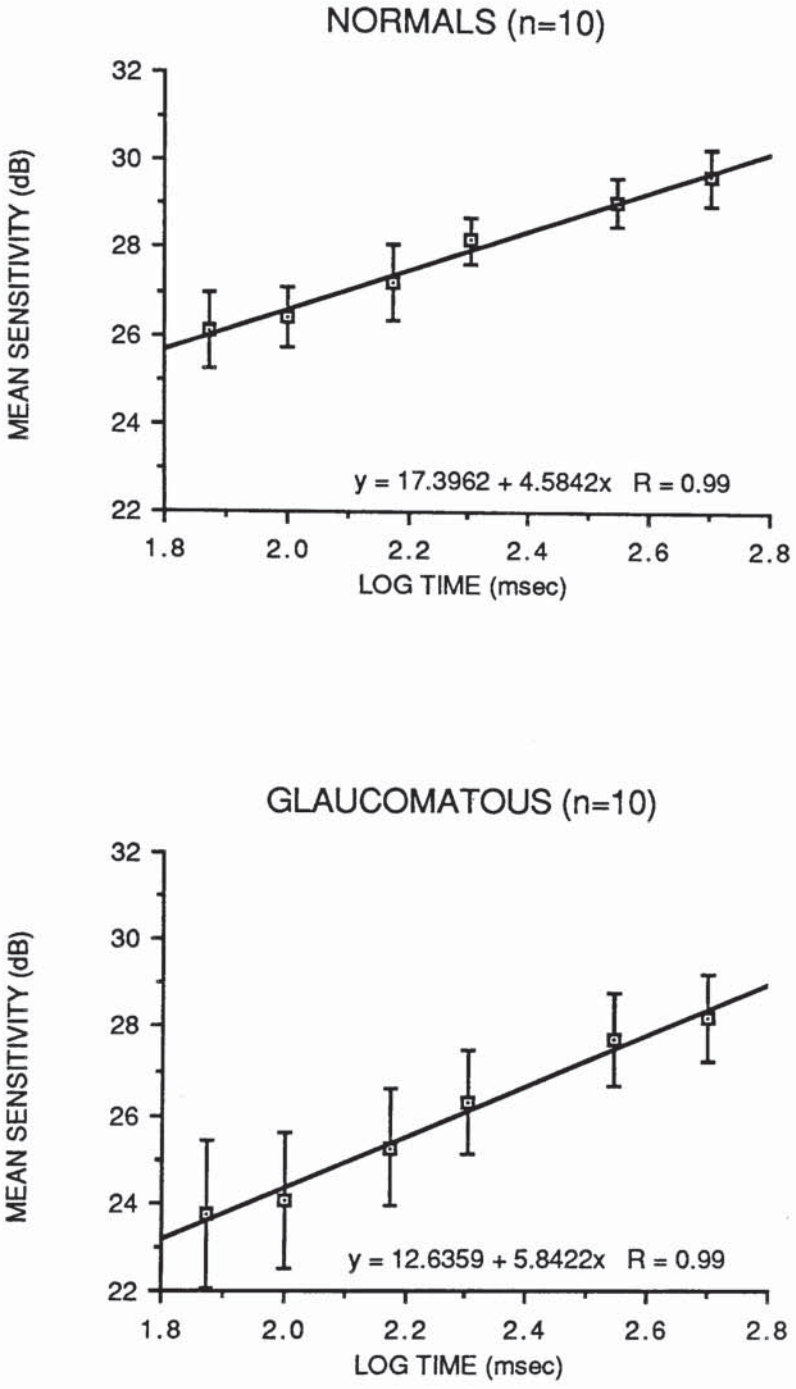


Figure 7.4. Group mean global mean sensitivity as a function of log stimulus duration for the normal group (top) and glaucomatous group (bottom). Error bars indicate one standard error of the mean.

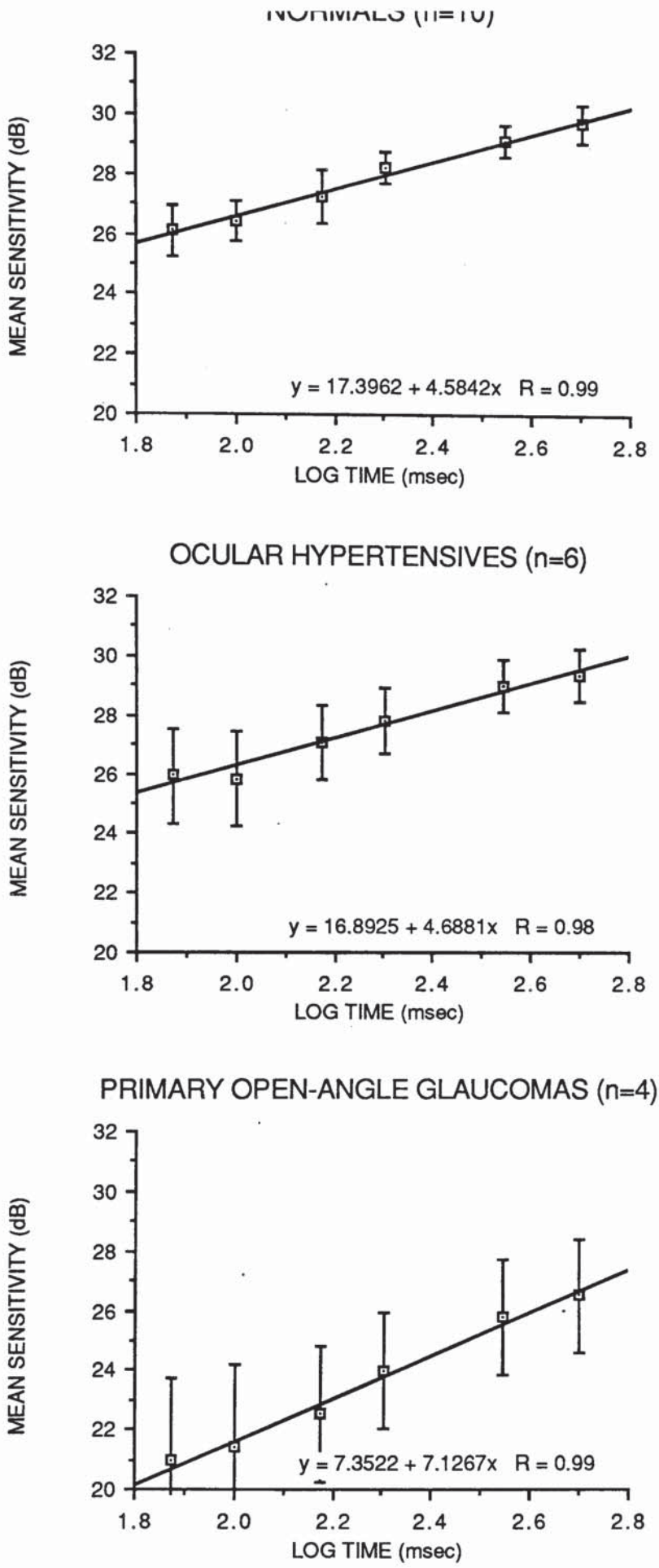


Figure 7.5. Group mean global mean sensitivity as a function of log stimulus duration for the normal group (top), ocular hypertensive patients (middle) and primary open-angle glaucoma patients (bottom). Error bars indicate one standard error of the mean.

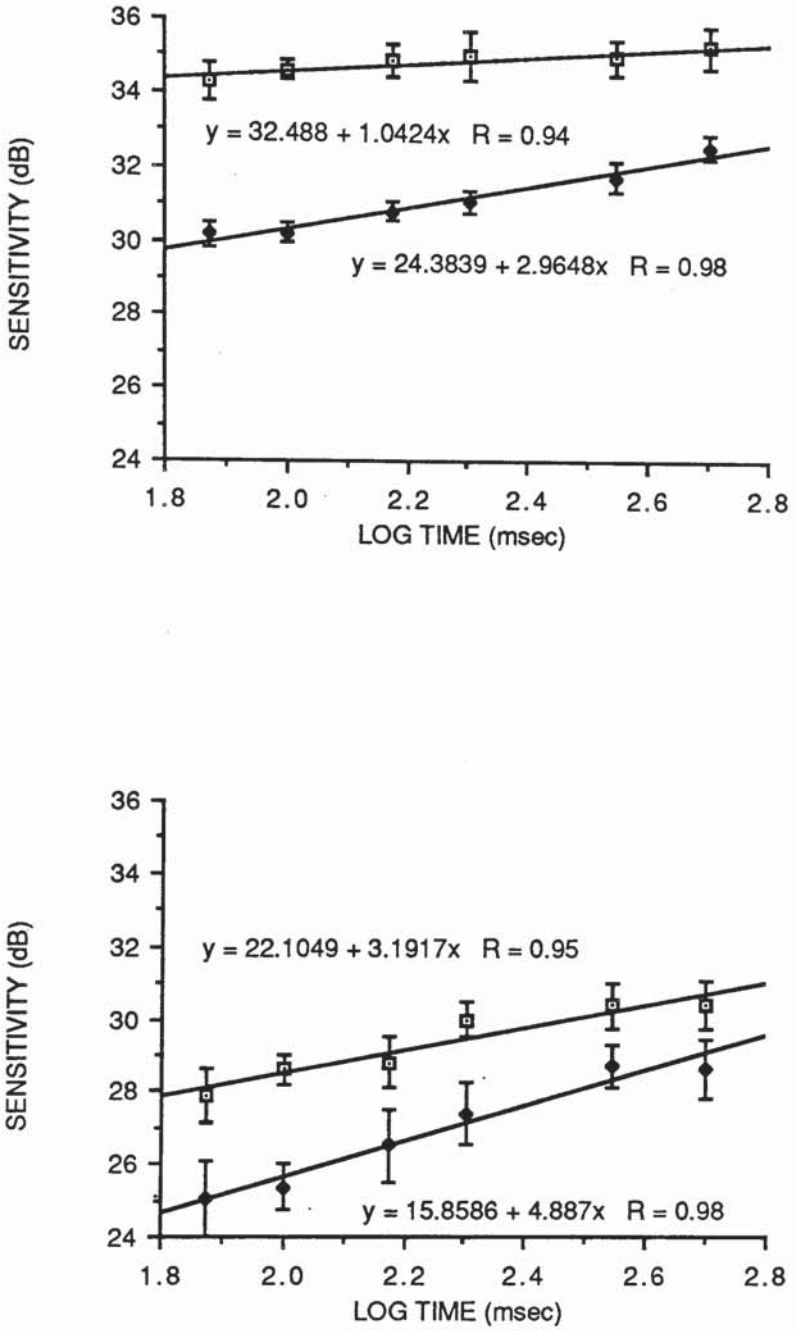


Figure 7.6. Group mean sensitivity as a function of log stimulus duration for 10 normal subjects at eccentricites of (top) 0° (open squares) and 4.2° (closed diamonds) and (bottom) 12.7° (open squares) and 21.2° (closed diamonds).

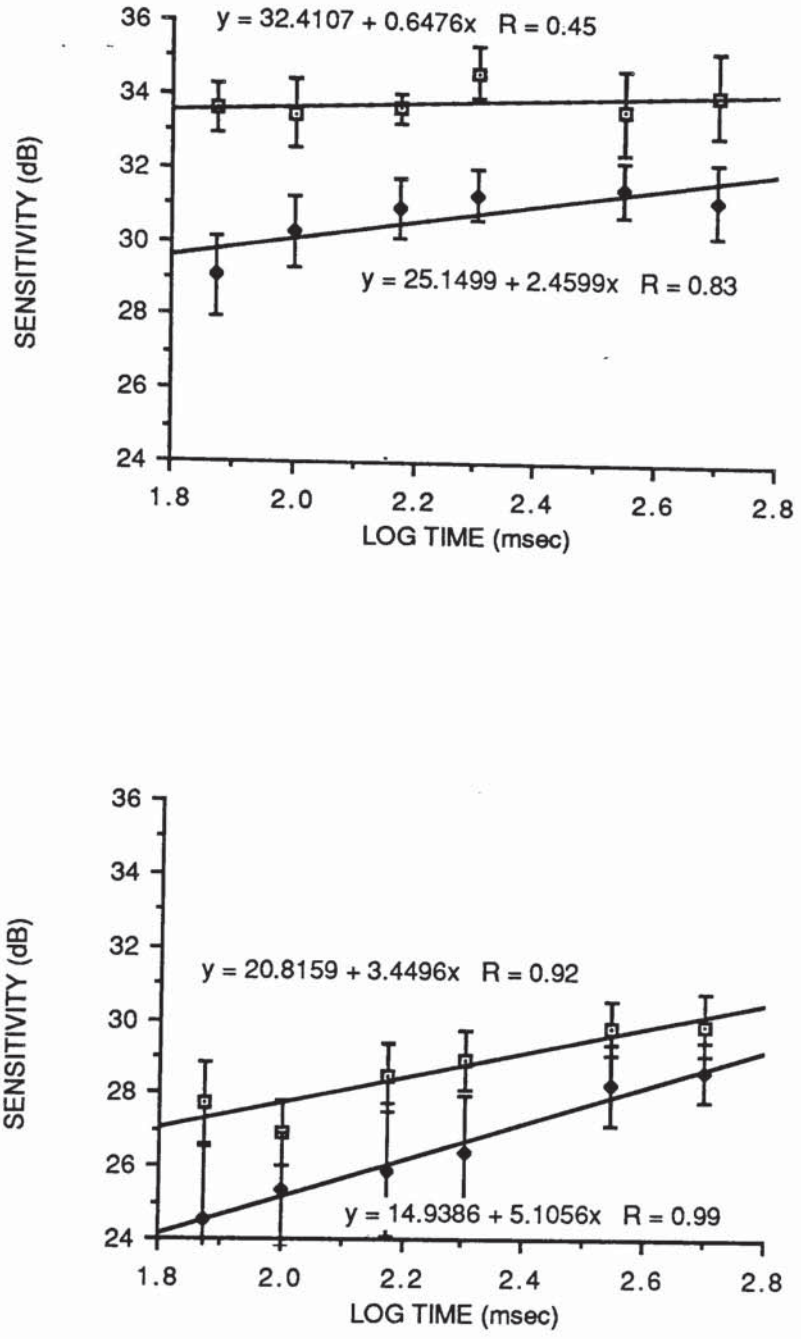


Figure 7.7. Group mean sensitivity as a function of log stimulus duration for 6 ocular hypertensive patients at eccentricites of (top) 0° (open squares) and 4.2° (closed diamonds) and (bottom) 12.7° (open squares) and 21.2° (closed diamonds).

GLAUCOMA PATIENT	MD	CPSD	SLOPE (VF loss)	SLOPE (Normal area)	SLOPE (Age-matched)
1	-9.57	8.11	14.93	9.47	3.12
2	-8.47	11.68	23.60	7.91	4.84
3	-1.22	1.25	4.44	2.10	4.56
4	-1.43	1.01	4.20	4.56	2.59

Table 7.2. Slopes of the temporal summation curves for 4 glaucoma patients plotted from clusters of depressed points ("VF loss") and corresponding clusters of points in normal areas of the same field at similar eccentricities ("Normal area"). These latter values are compared with corresponding slopes from age-matched control subjects ("Age-matched").

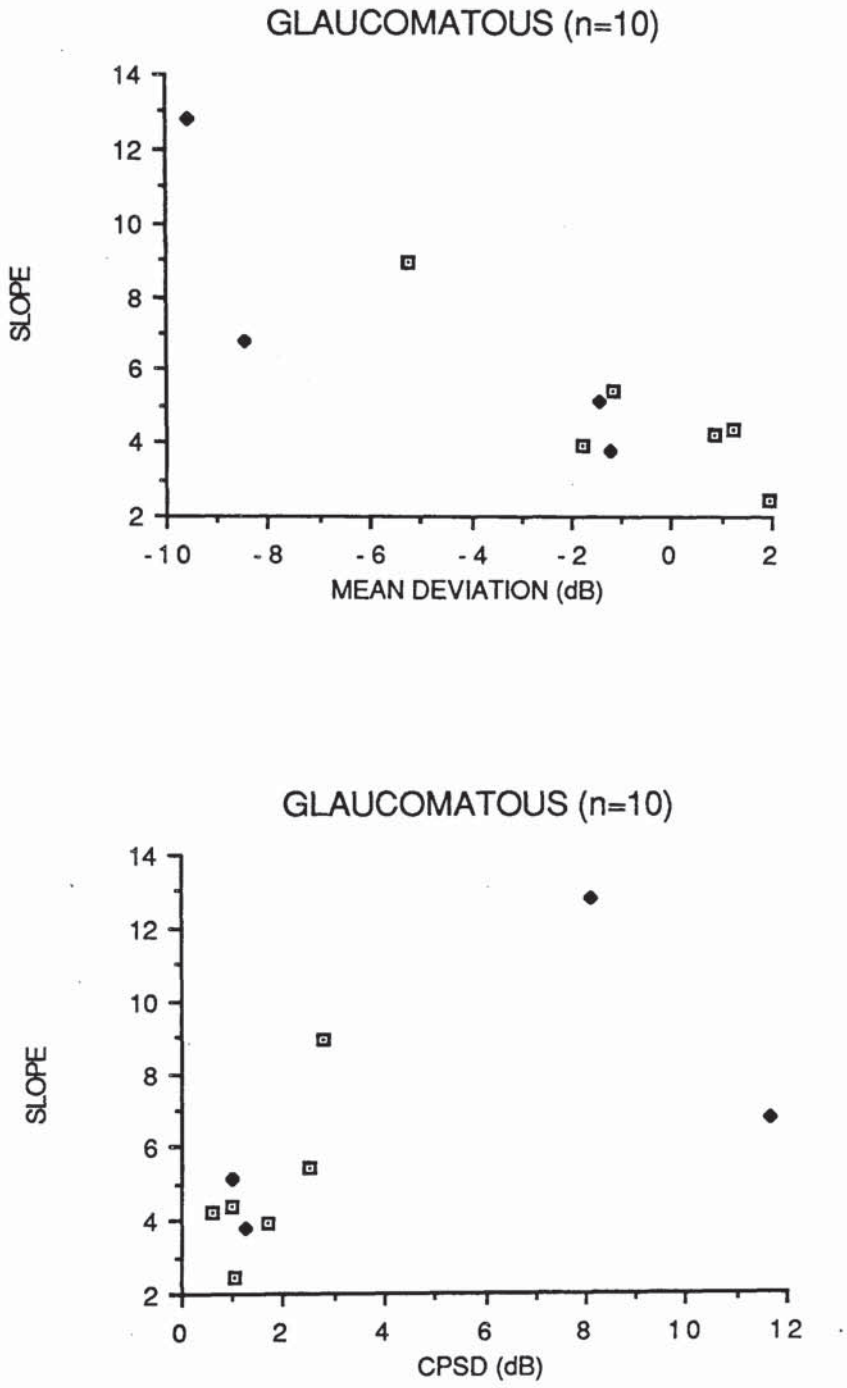


Figure 7.8. Slope of the temporal summation curve as a function of the visual field indices mean deviation (top) and corrected pattern standard deviation (bottom), derived from Humphrey program 24-2 at a stimulus duration of 200msec. The diagnoses are indicated (open squares: ocular hypertension; closed diamonds: primary open-angle glaucoma).

7.8. DISCUSSION

Previous studies of temporal summation in ocular disease are somewhat equivocal. Wilson (1967) showed anomalies of temporal summation at an adaptation level of 628asb using a stimulus subtending 1.3° in post-geniculate lesions and normal temporal summation in pre-geniculate lesions; the greater the reduction in sensitivity caused by the lesion, the more nearly complete was the temporal summation. In pre-geniculate lesions no further temporal summation was found for stimuli of duration greater than 317msec; this value was the same as for normal visual fields. In contrast, for post-geniculate lesions, temporal summation was observed for stimuli of up to 950msec duration. Anomalies of temporal summation were however only found in areas of the visual field already identified as defective by conventional perimetry.

Dannheim & Drance (1974), using manual perimetry with a Goldmann size IV stimulus, investigated temporal summation in a glaucomatous sample. They found normal temporal summation curves in areas of relative scotomata to be similar to those obtained from unaffected areas of the the same field and the critical duration to be comparable in the glaucomatous sample to that obtained in normal subjects (Dannheim & Drance 1971b).

Wood et al. (1986b), using manual static perimetry at an adaptation level of 10asb, found some retinitis pigmentosa patients to show enhanced sensitivity to a Goldmann size V stimulus of duration 100msec, compared with a size V stimulus of 500msec.

Using the Competer perimeter (background luminance 0.315asb) Holmin et al. (1987) found that a reduction in stimulus duration from 500msec to 250msec resulted in a general decrease of sensitivity, an enlargement and deepening of relative defects and the appearance of new defects in a sample of glaucomatous patients whereas normal areas of the same fields remained unchanged. The shorter stimulus duration also resulted in an increase in the short-term fluctuation in defective areas compared with normal areas during a prolonged (30 minute) test. If the stimulus duration was however increased to 1000msec it was found that defective areas showed normal sensitivity. The increase in depth of relative defects with decrease in stimulus duration was explained by Krakau (1989) in terms of a

hypothetical model based on rarefaction of optic nerve fibres, as follows: in the normal retina, which contains a great number of nerve fibres in the stimulated area, the probability of detection of the stimulus with negligible delay is high; in a scotomatous area where the number of fibres is reduced there may be a delay until elements of sufficient sensitivity respond to the stimulus.

Brown & Lovie-Kitchen (1989) found the critical duration to be longer in patients with age-related maculopathy compared with a normal control group, although this difference was not statistically significant. Under photopic conditions (10.5asb), using a Goldmann size II stimulus presented at 10° eccentricity, the critical duration was 92msec for the patient group and 58msec for the normal control group whereas under scotopic conditions the critical durations were 304msec and 283msec respectively.

In the current study, the increase in mean sensitivity with increase in stimulus duration is in accord with conventional perimetric theory, whereby the dynamic range can be extended by increasing the stimulus duration. The lack of change in short-term fluctuation with increasing stimulus duration is in agreement with the work of Greve (1973), who used manual static perimetry on normal subjects.

The coefficient of temporal summation was greater in the glaucomatous patients than in the normal control group (0.584 compared with 0.458 respectively), i.e. temporal summation was apparently more complete in the glaucomatous sample. This finding is in agreement with the studies of Wilson (1967) and Brown & Lovie-Kitchen (1989), who found temporal summation to be enhanced in neurological and ocular disease, although, as described above, Wilson (1967) only considered summation to be disturbed in lesions posterior to the lateral geniculate body. If temporal summation is increased in ocular disease, this is an argument for using short stimulus durations.

For studies of temporal summation to provide additional diagnostic information to that of the conventional perimetric examination for the detection of early glaucoma it would be necessary to show a difference in temporal summative properties between the ocular

hypertensive group and the normal control group. The glaucomatous sample was therefore divided into those with ocular hypertension and those with primary open-angle glaucoma, as seen in Figure 7.5. Although the group mean slope was greater in the 4 glaucoma patients compared with 6 ocular hypertensives (4.69 and 7.13 respectively), there was little difference between the ocular hypertensive group and the normal subjects.

The increase in temporal summation with increase in peripheral angle is in agreement with the study of Dannheim & Drance (1971), who used manual static perimetry. No differences were found in the slopes at any of the four eccentricities studied between the normal controls and the ocular hypertensive patients.

The relationship between the coefficient of temporal summation and the visual field indices indicates that the temporal integrative properties of the visual system increase with increasing diffuse and increasing focal glaucomatous visual field loss. This is in agreement with the work of Wilson (1967) who found a statistically significant positive correlation between the slope of the temporal summation curve and mean differential light threshold in post-geniculate lesions.

An increase in temporal summation in glaucoma would also be in accord with previous studies showing defects of flicker sensitivity (i.e. poorer temporal resolution) in glaucoma (Tyler 1981; Atkin et al. 1983; Toi et al. 1990).

Furthermore, several studies have shown an increase in temporal summation with increase in spatial frequency for both square (Schober & Hilz 1965; Nachmias 1967) and sine wave (Arend 1976; Breitmeyer & Ganz 1977; Gorea & Tyler 1986) gratings. Assuming that transient channels operate at low spatial frequencies and sustained channels at higher spatial frequencies, as proposed by Tolhurst (1975), we can infer that transient channels have a shorter critical duration than sustained channels. An increase in temporal integration in glaucoma would therefore also be in agreement with the work of Quigley and co-workers (1986, 1987, 1988, 1989) who showed preferential loss of large ganglion cells, which have mainly transient responses, in glaucoma.

7.10. CONCLUSIONS

Changes in temporal summation occur in glaucoma and coexist with both diffuse and focal visual field loss recorded by automated perimetry. The increase in temporal summative properties is greater with increasing glaucomatous visual field loss. Whether , however, the changes in temporal summation precede glaucomatous visual field loss is open to conjecture. Use of the technique is limited by the high inter-individual variation of the summation coefficient in normal subjects and the fact that temporal summation is not determined solely at retinal ganglion cell level, where glaucomatous damage occurs. In addition, the higher standard errors in mean sensitivity and short-term fluctuation recorded for each stimulus duration in a heterogenous glaucomatous sample will also limit the accuracy with which the coefficient of temporal summation may be determined for each patient. It is hypothesised that temporal summation recorded with automated perimetry may be greater than that with manual methods due to the greater cognitive demands of automated perimetry. It is therefore essential that, in any follow-up of this pilot study, patients are fully trained in automated perimetry.

CHAPTER 8

CONCLUSIONS

The aims of this study were twofold. Firstly, to isolate the effects of certain extraneous factors and potential artefacts on the sensitivity gradient of the abnormal eye, with particular reference to primary open-angle glaucoma and ocular hypertension, since these factors might limit the early detection and accurate monitoring of visual field loss. Secondly, to clinically investigate the optimum stimulus combinations for the earliest detection of glaucomatous visual field loss using automated perimetry.

Although automated static perimetry has many advantages over manual kinetic and static methods, a review of the literature summarised certain factors which might influence the measurement and interpretation of perimetric data. It was considered that the effects of these factors, previously reported for manual perimetry, might differ for the examination techniques used in automated perimetry. This study has shown that the various extraneous factors examined exert a significant influence on the outcome of automated perimetry and impede the detection and monitoring of both diffuse and focal glaucomatous visual field loss.

The design of automated perimeters stems mainly from traditional manual techniques, however the advanced technology utilised in automated perimetry has facilitated manipulation of the given stimulus parameters. This study also showed that the choice of stimulus parameters may indeed expedite the detection of glaucomatous visual field loss.

The experimental work of Chapters 3-5 was designed to isolate the effects of three extraneous factors on the format of the sensitivity gradient of the glaucomatous eye, namely, intraocular light scatter, prior perimetric experience and perimetric fatigue.

Media opacities cause an increase in intraocular light scatter leading to perimetric attenuation through optical degradation. Perimetric attenuation arising from optical degradation must, therefore, be differentiated from that due to neural dysfunction. The results of this current study have many implications in the context of an increasingly elderly population where

glaucoma and cataract frequently coexist. Induced forward intraocular light scatter was found to cause a general depression of the sensitivity gradient of the glaucomatous eye, with an apparent decrease in the extent of focal visual field loss. The apparent decrease in focal loss was attributed to the use of inappropriate age-matched normative data in the software package for calculation of the visual field indices by the perimeter. The current study concluded that diffuse glaucomatous visual field loss is more difficult to recognise in the presence of media opacities and the increase in diffuse loss leads to an underestimation of the focal loss. The study thus clinically substantiated an earlier computer simulation of the effects of media opacities on the perimetric profile (Augustiny & Flammer 1985). The study also emphasised the limitations of age-matched normative databases in software used for computation of the visual field indices. The normative age-matched threshold data in the software, used to calculate the visual field indices, only takes into account that amount of intraocular light scatter which would be "normally" expected for each given age and does not consider a patient with abnormally high values of intraocular light scatter for their age.

Assessment of forward intraocular light scatter by the measurement of contrast sensitivity depression under glare conditions is however time-consuming. Further studies are required to develop simple methods for assessing forward intraocular light scatter, and to evaluate the relationship between the results of these various methods (e.g. measurement of low contrast acuity under glare conditions with, for example, the Pelli-Robson chart) and perimetric attenuation. Alternatively, it is suggested that a grating and glare source could be incorporated into future perimeter bowls employing a back projection system and glare sensitivity measured following perimetric examination. Such results could then be used by the perimeter software to correct, for the effects of forward intraocular light scatter, firstly the threshold data of a given patient and secondly the normal age-matched database since the study has illustrated the inadequacies of visual field indices calculated from age-matched normative databases at baseline examination and follow-up. The procedure outlined would establish patient-specific data free from the effects of forward intraocular light scatter and permit calculation of the visual field indices on an individual patient basis. Futher studies are required on the development of algorithms for determining such reference fields. The study is in agreement with other authors who have advocated the use of patient specific normal

reference fields (Wild et al. 1986c; Van den Berg & Nooteboom 1987; Van den Berg et al. 1987). The results of glare sensitivity testing could also be incorporated in the analysis of data by expert systems, which have recently been applied to automated perimetry (Sturmer et al. 1989; Bebie 1990; Hirsbrunner et al. 1990).

The light scatter simulation employed in the current study constituted a source of light absorption as well as forward induced light scatter. It is hypothesised that the absorption effects, which would lead to an apparent increase in diffuse loss, were also partially responsible for the apparent reduction in focal losses. This hypothesis could be further investigated using neutral density filters of similar absorbance to the cells to differentiate the effects of absorption from those due to scatter. The current study also showed that the position of the lenticular opacity affected the forward light scattering properties. Further studies are required to determine the effects of corneal and vitreous opacities on the sensitivity gradient.

Other recent studies have defined the perimetric attenuation arising from optical degradation utilising the method of back light scatter measurement for the assessment of media opacities (Guthauser et al. 1986, 1987; Guthauser & Flammer 1988; DeNatale & Flammer 1989). It is generally accepted, however, that visual impairment due to media opacities results from an increase in forward intraocular light scatter. The current study showed a poor relationship between forward and backward intraocular light scatter, implying that the technique of back light scatter measurement would not reveal the full extent of perimetric attenuation due to media opacities and thus could not fully differentiate optical from neural attenuation in glaucoma. This study therefore verified the use of forward intraocular light scatter measurement techniques, as opposed to back scatter, for the assessment of perimetric attenuation (Heuer et al. 1987b, 1988; Wood et al. 1987a,b, 1989). Recent interest in perimetry at higher photopic adaptation levels (Elenius 1985; Elenius & Leinonen 1986) and in blue-yellow cone isolation perimetry in glaucoma (Heron et al. 1988; Johnson et al. 1989b; Sample & Weinreb 1990) has emphasised the importance of considering the effects of intraocular light scatter at the high adaptation levels of 600-700asb employed with these techniques. In relation to the technique of cone isolation perimetry, the dependence of

intraocular light scatter on wavelength should be re-examined since, as reviewed in Section 3.3.7., previous studies are equivocal (Hemenger 1982; Wooten & Geri 1987).

Perimetric sensitivity in glaucomatous patients was found to improve with repeated examination over a short time period of a few days. This finding was published during the development of the thesis (Wild et al. 1989) and has since been substantiated, using a retrospective study over a period of several months, by Werner et al. (1990b). The skills required of the patient, in perimetric assessment, were also found to be retained over a longer time period (mean 8.7 months). The short-term and long-term findings have implications for the initial assessment and for the follow-up of glaucoma patients, particularly with regard to the possible beneficial effects of ocular therapy. The results also emphasise the need for patients who are fully trained in the techniques of automated perimetry during the trials of both ocular and systemic therapeutic agents. Perimetric sensitivity was found to increase heterogeneously with serial examination, with greater improvements occurring for eccentricities beyond 30°. This finding is highly relevant considering the recently renewed interest in the examination of the peripheral visual field in glaucoma, using both automated static (Seamone et al. 1988; Haas et al. 1989) and automated kinetic (Stewart et al. 1988) techniques. The eccentricity dependency of the learning effect was, however, shown to be depth-related i.e. those areas of the field with the lowest initial sensitivity improved the most with practice. This latter finding was also substantiated in the study of Werner et al. (1990b). The depth-dependency of the learning effect in glaucoma suspect patients naive to automated perimetry suggested that both central (i.e. cortical) and peripheral (i.e. retinal) mechanisms are involved in the learning process. The main effects of learning were found by the second examination, thus discarding the results of the first examination may negate the learning effect. The probable transfer of learning from the first to the second eye examined at the first session calls into question the validity of using age-matched normative data particularly for the first eye examined in patients naive to automated perimetry. The presence of a learning effect highlights the need to quantify the perimetric experience of subjects used to establish age-matched normative databases.

The increase in perimetric sensitivity with learning was not as great in the superior peripheral

field, as that reported by Wood et al. (1987c). This discrepancy was attributed to the difference in the age of the samples employed, since an increase in age leads to a reduction in sensitivity which is greatest in the peripheral regions (Haas et al. 1986; Jaffe et al. 1986; Heijl et al. 1987a). The mean age of the young normal sample studied by Wood et al. (1987c) was 23.8years, whereas the mean age of the elderly glaucomatous sample employed in the current study was 62.8years. Subsequently, however, Heijl et al. (1989a) and Autzen & Work (1990) have shown no correlation between age and learning effects in normal subjects. Heijl (1987) has suggested that the influence of age on the shape of the hill of vision is greater in untrained than in trained subjects. It would be of interest to investigate the influence of age on the learning effect, and the effect of training on the change in shape in the hill of vision with age in a sample of glaucomatous patients, since this information is of importance in the design of age-matched databases. An obvious limitation in this proposal would be the limited age range of patients with glaucoma. Further work is also required to devise a method of assessing the potential for learning on an individual basis. A short program undertaken prior to the main examination is envisaged which assesses the rate of change in perimetric sensitivity with repeated measurement at a limited number of locations across the visual field. This information could be used to adjust the normative database for the effects of training for both the first and the second eye examined, and could be applied in perimetric expert systems.

As summarised in Chapter 4, learning effects have been demonstrated in many psychophysical paradigms including peripheral motion thresholds, hyperacuity, colour vision and contrast sensitivity. Recent research has been directed towards these and other psychophysical methods, e.g. pattern discrimination (Drum et al. 1989) and peripheral displacement thresholds (Fitzke et al. 1989), that will identify the earliest visual loss in glaucoma and predict which of the 10% of ocular hypertensive patients will develop glaucomatous visual field loss. The results of the current study imply that learning effects are likely to be associated with these newer methods of psychophysical investigation and thus trained patients are required for their evaluation. Indeed, significant learning effects have been reported in high-pass resolution perimetry both in normal subjects and in glaucoma patients (Drance et al. 1989; Martin-Boglind & Wanger 1989). Studies are also required to

determine the effects of learning in automated perimetry for novel combinations of stimulus size and duration. It is hypothesised that the learning effect would be greatest for small stimuli of short duration. The development of perimetric and other psychophysical techniques that employ a forced-choice paradigm, and thus are criterion-free, would also minimise the effects of training.

Prolonged automated perimetric assessment of glaucomatous patients was found to lead to a decrease in sensitivity which exhibited an eccentricity-dependency although, unlike the study on learning effects, the data did not support a depth-dependency whereby those fields initially showing the lowest sensitivity deteriorated the most with prolonged examination. With the exception of the first automated perimetric examination, the fatigue effects were more prominent than the learning effects. Perimetric sensitivity decreased heterogeneously with prolonged examination in fully-trained patients, with greater deterioration occurring in the peripheral field than in the central field. Comparison of the learning and fatigue studies suggest that in the initial examination of naive glaucoma suspect patients learning and fatigue effects counterbalance although fatigue effects are considered to be more prominent in the examination of patients experienced in automated perimetry. The fatigue effect therefore has several implications in monitoring the progression of visual field loss. The length of the examination should be noted and, where possible, standardised. The decrease in sensitivity with time implies that an increased accuracy of threshold measurement by repeated determinations and averaging procedures cannot be assumed. The interocular transfer of fatigue calls into question the validity of normative data in calculation of the visual field indices for the second eye examined. The order of examination of the two eyes should also be noted. As with the learning effect, the eccentricity-dependency of the fatigue effect is important in the light of renewed interest in examination of the peripheral field using automated static and kinetic techniques. If 2 or 3 examinations are carried out to establish a baseline with which to compare subsequent results, as suggested by Hoskins et al. (1988), it is important that these examinations are not carried out within too short a time period because of the inter-examination transfer of fatigue.

It is hypothesised that the fatigue effect, like the learning effect, also exhibits a depth as well

as an eccentricity dependency. It is suggested that this was not manifested in the current study for the following reason: A depth-dependency presumes that those fields initially showing the lowest sensitivity would deteriorate the most with prolonged examination. Measurement of the deterioration of these fields was, however, limited by the constraints of the dynamic range. Further studies are required to determine the time of onset of the fatigue effect, such that recommendations may be made regarding the optimum length of examination. In addition, the stimulus parameters that minimise the fatigue effect should also be studied; it is hypothesised that the effects of fatigue may be greatest for small, short duration stimuli. Further work is also required to devise a method of assessing perimetric fatigue on an individual basis. A short program which examines a limited number of locations across the whole field is suggested. This program would be undertaken prior to and after the main examination and would thus assess the deterioration in perimetric sensitivity over the course of the main examination. This information could be used to adjust the normative database for the effects of fatigue on an individual basis for each eye, and the information used in perimetric expert systems for the monitoring of visual field progression.

The experimental work of Chapters 6 and 7 was designed to clinically determine the optimum combination of stimuli for the earliest detection of glaucomatous visual field loss by automated perimetry. In addition, a further extraneous factor which may influence the outcome of automated perimetric assessment, namely that of pupil size, was further examined in Chapter 6.

The Weber-Fechner law was shown to be valid in two ways for the adaptation levels employed in this current study: The differential light threshold was found to be a constant proportion of the adapting luminance and the recorded threshold was independent of pupil size change for adaptation levels above 77.0asb. A deterioration in the accuracy of response was not noted at the higher adaptation levels; no relationship was observed between the adaptation level and the short-term fluctuation or the patient reliability parameters. This study on young normal subjects has laid the groundwork for subsequent studies which will firstly determine similar normative data for elderly subjects and, secondly, define the threshold response of glaucomatous patients, both with diffuse and focal visual field loss, at higher

adaptation levels. Although perimetric sensitivity for the central 30° of the visual field was independent of pupil size change, pupil miosis may have a significant effect on threshold for eccentricities greater than this, an important finding in view of the renewed interest in the examination of the peripheral visual field in glaucoma mentioned previously. A consideration of the effects of intraocular light scatter is also imperative for perimetry at high photopic adaptation levels.

The finding that the standard stimulus parameters offered by the Humphrey Visual Field Analyser, namely a Goldmann size III stimulus of duration 200msec at an adaptation level of 31.5asb, showed a higher level of diffuse visual field loss than those of the Octopus Automated Perimeter, namely a Goldmann size III stimulus of duration 100msec at an adaptation level of 4asb, has implications for the choice of stimulus parameters in the design of future instruments and software packages. Indeed, a bowl luminance of 31.5asb was selected for the recently introduced Octopus 123 and Dicon TKS4000 instruments. The study also supports the recommendations of Keltner (1979) and Keltner & Johnson (1986) that future developments in automated perimetry should aim to standardise the stimulus conditions and data representation.

Use of a Goldmann size I stimulus compared with a size III stimulus, with both stimulus sizes at an adaptation level of 31.5asb and stimulus duration of 200msec, did not appear to enhance the detection of diffuse glaucomatous visual field loss. A review of relevent literature however suggests that a size I stimulus may improve the detection of shallow paracentral scotomata i.e. focal loss; however, the sample employed in this study consisted of patients with mainly diffuse loss. Further studies are therefore required on a sample of patients with relatively pure focal loss to determine the stimulus parameters that reveal the greatest extent of focal loss.

Recent studies (e.g. Heijl & Bengtsson 1989; Drance et al. 1989a) have been directed towards a correlation of the structural changes observed in glaucoma, e.g. by computerised optic nerve head evaluation and retinal nerve fibre layer photography, with the functional changes found e.g. by automated perimetry. Such studies have not, however, considered

the effects of cortical magnification. A future objective would be to design perimetric routines which incorporate different stimulus sizes, based on the coverage factor of retinal ganglion cells, such that the stimulus size increases with increase in peripheral angle. The stimuli would then be scaled in proportion to the decreased cortical representation of the peripheral field compared with the central field (M-scaled), thus avoiding saturation, and would result in an isosensitive profile in the normal eye. Even then, the assumption that cortical magnification and psychophysics are well correlated may be erroneous, as pointed out in a recent paper by Drasdo (1989). The current cortical magnification equations are based on total retinal ganglion cell counts and not on population counts of specific subtypes. Recent anatomical and physiological findings in the primate visual system suggest that different components of visual information are processed in largely independent, parallel pathways. In the primate a segregation of neurones is first apparent in the lateral geniculate nucleus, with its clear division into magnocellular and parvocellular layers. These two layers receive input separately from two major classes of retinal ganglion cells, the P-alpha and P-beta cells (Perry et al. 1984) which differ anatomically and physiologically even though they are not physically separated. Parvo neurons have small receptive fields, exhibit high spatial and low temporal resolution and possess colour-opponency, thus responding selectively to different wavelengths. Magno neurons have large receptive fields, exhibit high luminance contrast sensitivity, low spatial and high temporal resolution (Schiller & Malpeli 1978; Kaplan & Shapley 1982). The segregation into parvo and magno processing streams is maintained to the cortex (Livingstone & Hubel 1987). Recent histologic evidence suggests that there is a selective loss of the larger (magnocellular) cell pathways in glaucoma (Quigley et al. 1986, 1987, 1988, 1989) and thus, in the future design of psychophysical tests for the earliest detection of glaucomatous visual field loss, stimuli should be selected which preferentially stimulate the magnocellular system e.g. measurement of luminance contrast sensitivity to low spatial and high temporal frequencies. These, combined with estimates of the density and distribution of P-alpha ganglion cells by histological or psychophysical techniques (e.g. Drasdo 1989), would allow M-scaling for the magnocellular system and the earlier detection of glaucomatous visual field loss.

In a pilot study, temporal summation was found to be more complete with increase in both

diffuse and focal glaucomatous visual field loss, although the change in temporal summation properties did not reach statistical significance compared with a normal age-matched control sample. The changes in temporal summation were also found to be greater in areas of visual field loss compared with normal areas of the same field, although again this difference was not statistically significant in the sample employed. If temporal summation were indeed enhanced in glaucoma, this would be an argument for the use of a short stimulus duration for the earliest detection of glaucomatous visual field loss. Whether the changes in temporal summation precede glaucomatous visual field loss could not, however, be concluded from the study, which was limited by the high intraindividual variation in the temporal summation coefficient of the normal subjects. It is also important to consider the increase in temporal summative properties with increase in eccentricity in respect of the renewed interest in examination of the peripheral visual field by automated static perimetry mentioned previously.

The pilot study on temporal summation should be extended to a longitudinal study of a larger sample both of glaucoma and of ocular hypertensive patients to determine whether an increase in temporal summation precedes the development of glaucomatous visual field loss. It is suggested that use of the technique could be improved by selecting conditions which would enhance temporal summation e.g. a lower adaptation level and a smaller stimulus size, and also by extending the study of temporal summation to the visual field beyond 24° eccentricity. The effects of age and perimetric experience on temporal summation should also be investigated. It is hypothesised that temporal summative properties recorded with automated perimetry may be greater than that with manual methods due to the greater cognitive demands of automated perimetry. A study could be undertaken to verify this hypothesis using identical stimulus parameters and adaptation level for both manual and automated modes.

The development of automated perimetry has revolutionised the role of visual field investigation in the diagnostic procedure. The current study has identified the influence of certain extraneous factors on the format of the sensitivity gradient of the abnormal eye; this work should lead to the application of correction factors for patient specific variables. The

standard approach of using a single combination of stimulus parameters for the detection of visual field loss caused by one particular known condition, and also for monitoring cases of visual field loss with different aetiologies should be refined. Measurement of temporal summation by automated perimetry will, it is hoped, allow the utilisation of this phenomenon as a diagnostic tool. Greater understanding of the mechanisms underlying the processing of perimetric and other psychophysical stimuli will lead to the earlier detection and diagnosis of abnormality.

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APPENDIX: SUPPORTING PUBLICATIONS

1. Wild J.M., **Dengler-Harles M.**, Cole M.D., O'Neill E.C. & Crews S.J. (1989) Regression techniques in the analysis of visual field loss. In: Perimetry Update 1988/1989. Proceedings of the VIIIth International Perimetric Society Meeting. Ed: A. Heijl. Kugler & Ghedini, Amsterdam. p207-216

2. Wild J.M., **Dengler-Harles M.**, Searle A.E.T., O'Neill E.C. & Crews S.J. (1989) The influence of the learning effect on automated perimetry in patients with suspected glaucoma. Acta Ophthalmologica 67:537-545

3. **Dengler-Harles M.**, Wild J.M., Cole M.D., O'Neill E.C. & Crews S.J. (1990) The influence of forward light scatter in the visual field indices in glaucoma. Graefe's Arch Clin Exp Ophthalmol 228:326-331

4. **Dengler-Harles M.**, Wild J.M., Searle A.E.T. & Crews S.J. The relationship between backward and forward intraocular light scatter. Accepted for publication in the Proceedings of the IXth International Perimetric Society Meeting, Malmo, June 1990

The relationship between backward and forward intraocular light scatter

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