# NON-STANDARD TECHNIQUES FOR THE INVESTIGATION OF THE VISUAL FIELD

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# Non-standard techniques for the investigation of the visual field

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The study investigated the potential applications and the limitations of non-standard techniques of visual field investigation utilizing automated perimetry.

Normal subjects exhibited a greater sensitivity to kinetic stimuli than to static stimuli of identical size. The magnitude of physiological SKD was found to be largely independent of age, stimulus size, meridian and eccentricity. The absence of a dependency on stimulus size indicated that successive lateral spatial summation could not totally account for the underlying mechanism of physiological SKD. The visual field indices MD and LV exhibited a progressive deterioration during the time course of a conventional central visual field examination both for normal subjects and for ocular hypertensive patients. The fatigue effect was more pronounced in the latter stages and for the second eye tested. The confidence limits for the definition of abnormality should reflect the greater effect of fatigue on the second eye.

A 330 $cdm^{-2}$ yellow background was employed for blue-on-yellow perimetry. Instrument measurement range was preserved by positioning a concave mirror behind the stimulus bulb to increase the light output by 60%. The mean magnitude of SWS pathway isolation was approximately 1.4 log units relative to a 460nm stimulus filter. The absorption spectra of the ocular media exhibited an exponential increase with increase in age, whilst that of the macular pigment showed no systematic trend. The magnitude of ocular media absorption was demonstrated to reduce with increase in wavelength. Ocular media absorption was significantly greater in diabetic patients than in normal subjects. Five diabetic patients with either normal or borderline achromatic sensitivity exhibited an abnormal blue-on-yellow sensitivity; two of these patients showed no signs of retinopathy. A greater vulnerability of the SWS pathway to the diabetic disease process was hypothesized.

Statokinetic dissociation, fatigue effect, blue-on-yellow perimetry, pre-receptoral absorption, short wavelength sensitive pathway.

To

Carolyn

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# CHAPTER 1. A REVIEW OF AUTOMATED PERIMETRY.

## 1.1. Introduction.

The visual field is defined as "... that portion of the external environment of the observer wherein the steadily fixating eye(s) can detect visual stimuli" (Enoch, 1979) and is often described topographically as an island of vision in a sea of blindness (Traquair, 1927). The peak of the island of vision corresponds to the fovea, or the point of maximum sensitivity, while the slope of the island of vision illustrates the decline in sensitivity with increase in eccentricity from the fovea, ie the sensitivity gradient. Consequently, dim or small stimuli will only be detected proximal to the fovea, while bright or large stimuli will be detected at greater eccentricities from the fovea.

The aim of perimetry is to define the topography, or sensitivity gradient, of the island of vision. The minimum light intensity necessary to evoke a response is measured and this is termed the differential light threshold or increment threshold. Sensitivity is defined as the reciprocal of the differential light threshold. The normal monocular visual field varies between individuals and with test conditions but is generally accepted to have an overall extent of 60° superiorly, 60° nasally, 75° inferiorly and 100° temporally (Anderson, 1992). In addition, the emergence of retinal nerve fibres through the scleral canal results in an area of focal sensitivity loss approximately 5.5° wide and 7.5° high, termed the physiological blind spot, which is located in the visual field 15° temporal to fixation and 1.5° below the horizontal meridian (Reed and Drance, 1972).

Abnormality of visual function results in a departure of the topography of the hill of vision from normal limits and this loss of sensitivity is termed a visual field defect. A localized visual field defect is termed a scotoma, or alternatively is described as focal loss, whereas sensitivity loss over the whole field is described as diffuse loss. In addition, sensitivity loss can be relative or absolute. A relative visual field defect is of a depth that is within the measurement range of the perimeter, while an absolute defect represents sensitivity loss

of a greater magnitude than the available measurement range. In addition, the method of perimetric assessment can be divided into kinetic or static. Kinetic perimetry employs a stimulus of constant luminance and / or size and threshold is approached by moving the stimulus from non-seeing to seeing locations of the visual field, whilst in static perimetry the stimulus location is constant and threshold is determined by varying the luminance of the stimulus. Furthermore, manual perimetry describes a visual field examination that is controlled by the human examiner, while the term automated perimetry describes an examination in which the decision-making strategy is exclusively controlled by computer (Greve, 1982).

## 1.2. The evolution of perimetry.

Apparently David slayed Goliath in the knowledge that the giant had constricted visual fields (Griffin, 1980). Indeed, giantism is often associated with pituitary tumours which typically result in bitemporal hemianopic defects. The writings of Hippocrates show that the ancient Greeks were aware of the presence of hemianopic visual field defects as early as the 5th century BC. Ptolemy, in 150 AD, was the first to measure the visual field using a perimeter (Atchison, 1979). Precise details of the instrument employed were not recorded but the visual field was suggested to extend out to 45° eccentricity in all meridians.

As well as establishing the trichromatic theory of colour vision, Thomas Young (1801) reported the first exact measurement of the normal visual field using a luminous test object. The values reported, that is 50° superiorly, 60° nasally, 70° inferiorly and 90° temporally, were very similar to those currently accepted. Subsequently, von Graefe (1856) was the first to employ examination of the visual field as a diagnostic clinical tool. Targets in the form of pieces of chalk were moved across a small blackboard which was held by the patient. Various defects were reported including central scotomata, generalized contractions, hemianopias and enlargement of the blind spot. Using this simple technique, it was possible to distinguish between relative and absolute focal loss.

Aubert and Förster (1857) discovered that the extent of the visual field depended upon the angular subtense of the stimulus at the eye. As a result, the first commercially available arc perimeter was developed by Förster in 1869, which enabled measurement of the visual field at a greater eccentricity than the flat screen campimeter. The entire visual field was assumed to be normal using the arc perimeter if the overall extent was normal with a single large stimulus.

Bjerrum (1889) employed a tangent screen and different sized stimuli to examine the central visual field. He encouraged the examination of both the central and peripheral visual field in glaucoma and was the first to describe the arcuate scotoma. As a result, the campimeter gained clinical favour over other perimetric instruments, although it was to be a number of years before the "quantitative" technique of using different sized stimuli was to be clinically accepted (Walker, 1913).

By the early 20th Century, perimetry was an essential clinical tool of ophthalmological investigation and diagnosis. The conditions employed, however, were poorly controlled and lacked standardization. As a result, Ferree and Rand (1922) developed an arc perimeter with a constant adaptation level, a constant target reflectance and standarized coloured targets. In subsequent studies (Ferree and Rand, 1924. Ferree and Rand, 1927. Ferree et al, 1929), the influence of factors on the visual field such as adaptation level, target size, age and ametropia were investigated.

Kinetic perimetry was recognized to be prone to error due to variations in patient reaction time and in stimulus velocity. Consequently, Sloan (1939) was the first to emphasize the value of light-sense, or static threshold perimetry using an arc perimeter. This technique varied from kinetic perimetry in that a stationary stimulus of variable brightness was employed. Kinetic perimetry was less time-consuming, however, for the examination of the entire visual field.

The introduction of a projection bowl perimeter standardized the examination conditions employed for kinetic perimetry (Goldmann, 1945a; Goldmann, 1946). The Goldmann perimeter employed a constant adaptation level, a series of standardized target sizes, a fixation monitor and a calibration system to ensure a constant stimulus luminance. Similarly, Harms and Aulhorn (1959) designed the Tübinger perimeter, which standardized the conditions used for static perimetry.

Lynn and Tate (1975) were the first to propose the use of a microcomputer to control stimulus presentation and improve the speed of information processing in static perimetry. The development of automated static perimetry was motivated by the need to eradicate the errors associated with manual kinetic perimetry, that is, variations in patient reaction time and in stimulus velocity (Aulhorn, 1969; Fankhauser, 1969; Greve, 1973). The first commercially available automated perimeter, the Octopus automated perimeter, was developed as a result of research dealing with the theoretical aspects of automated perimetry (Fankhauser et al, 1972; Koch et al, 1972; Spahr, 1975). Other pioneering automated static perimeters included the Competer (Heijl and Krakau, 1975a and b), the Fieldmaster (Keltner et al, 1979), the Peritest (Greve, 1980a) and the Humphrey Field Analyzer (HFA) (Heijl, 1985). The HFA is now the most widely used automated perimeter.

## 1.3. Underlying principles of perimetry.

A number of underlying principles influence the format of the visual field for both manual and automated perimetry. Consideration must be given to these principles in the interpretation of the visual field and in perimeter design since the test conditions will influence the sensitivity, reliability and duration of the perimetric examination.

### 1.3.1. Units of measurement and dynamic range.

The maximum stimulus luminance varies between the different makes and models of perimeters. For example, the HFA and the Octopus bowl perimeters employ a maximum stimulus luminance of 10,000asb and 1,000asb respectively (Anderson, 1992), while the

maximum stimulus luminance of the Octopus 1-2-3 is 4,000asb (Octopus 1-2-3 Perimeter Digest, 1991). The unit of measurement used in perimetry to measure sensitivity is called the decibel (dB). A decibel is equal to 0.1 of a log unit and a 0dB stimulus represents the maximum stimulus luminance of the particular perimeter. Increasing sensitivity is denoted by a higher decibel value. Decibels are relative units, such that sensitivities of 10dB (=1 log unit), 20dB (=2 log units) and 30dB (=3 log units) correspond to stimulus intensities of one tenth, one hundredth and one thousandth respectively of the maximum possible luminance. Consequently, there is no direct conversion factor between sensitivity measured in decibels and the maximum stimulus luminance measured in apostilbs. Furthermore, the comparison of sensitivity between perimeters is confounded not only by differences in the maximum stimulus luminance but also by differences in the background luminance (Anderson et al, 1989).

The dynamic range has been defined as "... the measurement range over which the neurovisual system can be tested, using specific equipment with a given set of variables" (Fankhauser, 1979). In other words, it refers to the effective range of measurement rather than the entire operational range of either the visual system or of the perimeter. Dynamic range can be maximized by increasing the maximum stimulus luminance or by reducing the background luminance (Fankhauser, 1979).

### 1.3.2. Kinetic and static presentation.

Kinetic perimetry employs a stimulus of fixed luminance and size but variable position. The stimulus is generally moved towards fixation from non-seeing to seeing areas of the visual field and the position at which the stimulus is just seen is taken as threshold. By examining several meridians with a given stimulus an isopter or contour line can be plotted. Points along the isopter represent locations of equal sensitivity. The procedure is carried out for stimuli of different luminance and / or size in order to define the sensitivity gradient of the hill of vision. Manual kinetic perimetry permits a rapid assessment of the visual field but the results are influenced by variations in the reaction time of the patient and by differences in the stimulus velocity (Aulhorn, 1969; Fankhauser, 1969; Greve,

1973; Portney and Krohn, 1978; Calixto et al, 1979). Furthermore, shallow focal loss may be missed due to the phenomenon of successive lateral spatial summation whereby an infra-threshold stimulus is perceived if in motion due to the successive stimulation of individual receptors within a given receptive field (Greve, 1973). The introduction of automated perimeters capable of kinetic perimetry, such as the HFA 640 (Lynn et al, 1991; Minelli et al, 1991), has standardized stimulus velocity but the results are still susceptible to error as a result of patient reaction time. Indeed, stimulus velocities of 5° and 2° per second have been recommended for examination of the peripheral and central visual fields respectively using the Goldmann perimeter (Greve, 1973). Johnson and Keltner (1987) found that the optimal stimulus velocity was 4° per second, however, when evaluating the duration, reliability and sensitivity of the derived visual field using the Squid automated perimeter. Kinetic perimetry is the method of choice for the definition of prominent focal loss and in the assessment of residual visual function (Greve, 1973; Klewin and Radius, 1987).

Static perimetry employs a stimulus of fixed position and size but variable luminance (Sloan, 1939). The minimum light intensity necessary to evoke a response is taken as threshold. Stimulus luminance is varied in discrete steps rather than continuously in order to avoid any influence on the measured sensitivity due to the temporal interaction and the reaction times of the subject and perimetrist (Greve, 1973). The advantages of static perimetry are that the influence of stimulus velocity and patient reaction time are eliminated (Greve, 1973; Portney and Krohn, 1978). Unfortunately, manual static perimetry is time consuming (Portney and Krohn, 1978). Consequently, static perimetry had limited clinical use until the advent of automated static perimetry in the 1970s which permitted the thresholding of a greater number of stimulus locations within an acceptable time period. Static perimetry has been demonstrated to be more sensitive, however, than kinetic perimetry for the detection of small isolated areas of focal loss in glaucomatous patients (Harms, 1952; Drance et al, 1967a; Armaly, 1971; Aulhorn and Harms, 1972; Greve and Verduin, 1977; Portney and Krohn, 1978).

The interstimulus interval employed in static perimetry is of the order of 2 seconds (Greve, 1973), although some instruments such as the Octopus perimeters have the facility to employ an interstimulus interval appropriate to the reaction time of the patient (Octopus 1-2-3 Perimeter Digest, 1991). Similarly, the HFA employs an initial interval of 1.8 seconds during which a patient response will be accepted as valid and after 10 responses have been recorded an adjustment is made in the acceptance interval based on the average of the patients response time plus 0.85 seconds (Anderson, 1992). The acceptance interval may be subsequently lengthened if the patient slows down and in this manner the speed of the examination is optimized for a given patient.

Numerous studies have advocated the combination of both static and kinetic perimetry as a more effective means of visual field examination rather than relying on one particular technique (Harms, 1957; Aulhorn and Harms, 1972; Greve, 1973; Stewart et al, 1988; Miller et al, 1989; Ballon et al, 1992). Stewart and co-workers (1988) employed automated kinetic perimetry to examine the peripheral visual field in conjunction with supra-threshold automated static perimetry (with quantification of defects) within 30° eccentricity for both ocular hypertensive and glaucomatous patients. Approximately 23% of 600 ocular hypertensive or glaucomatous eyes were found to exhibit a central visual field defect and a normal peripheral visual field, while 1.0% of all eyes exhibited a peripheral visual field defect and a normal central visual field. In similarly designed studies, Miller and co-workers (1989) found that 7% of 599 "suspect" (ie elevated intra-ocular pressure or a suspicious appearance of the optic nerve head) or glaucomatous eyes exhibited a central visual field defect and a normal peripheral visual field, while 7% of all eyes exhibited a peripheral visual field defect and a normal central visual field. In addition, Ballon and co-workers (1992) found that 4% of 100 "suspect" or glaucomatous eyes exhibited a peripheral visual field defect and a normal central visual field. In all of these studies the kinetic component of the examination contributed approximately 25% of the total testing time.

1.3.3. Retinal adaptation.

Sensitivity is usually expressed as $\Delta L/L$ where $\Delta L$ is the minimum light intensity necessary to evoke a response and L is the background luminance. The relationship between L and $\Delta L$ is dependent upon L which determines the state of retinal adaptation (Aulhorn and Harms, 1972; Fankhauser, 1979). At photopic light levels (greater than 100asb), the Weber-Fechner Law describes a constant relationship between stimulus intensity and background luminance, that is:

$$\text{Constant} = \Delta L/L$$

At low photopic and mesopic light levels, however, the constant relationship between stimulus intensity and background luminance breaks down and the Rose-de-Vries Law is considered to be more appropriate (Fankhauser, 1979), that is:

$$\text{Constant} = \Delta L/L^{0.5}$$

Furthermore, at scotopic light levels (less than 1asb), $\Delta L$ is a constant independent of L, that is:

$$\text{Constant} = \Delta L$$

The levels of background luminance at which the Weber-Fechner and Rose-de-Vries Laws apply can show considerable overlap (Barlow,1972). Indeed, the state of retinal adaptation at the background luminances commonly employed in perimetry is controversial. Fankhauser (1979 and 1986) found that the Rose-de-Vries Law best described the retinal adaptation state at a background luminance of either 4asb (Octopus) or 31.5asb (HFA). Klewin and Radius (1986), however, suggested that the Weber-Fechner Law was only applicable at a background luminance of 31.5asb and did not hold at 4asb. Conversely, other studies have suggested that retinal adaptation under perimetric conditions is best described by the Weber-Fechner Law (Aulhorn and Harms, 1972; Greve, 1973; Wood et al, 1988a). In agreement with Barlow (1972), a recent study found considerable overlap between the levels of background luminance at which the Weber-Fechner (greater than 3.18asb) and Rose-de-Vries Laws (less than 31.8asb) was operative but concluded that the Rose-de-Vries Law was the most applicable for perimetry within 30° of fixation (Flanagan et al, 1991). In addition, retinal adaptation is also

influenced by factors such as pupil diameter and the extent of light absorption by the ocular media (Sections 1.11.2 and 1.11.3).

The dynamic range can be increased by reducing the background luminance (Fankhauser, 1979). Fankhauser (1979) found that reducing the background luminance from 31.5asb to 4asb resulted in a three-fold increase, or 5dB gain, in dynamic range. Indeed, the limitations imposed on dynamic range by the use of low wattage stimulus bulbs in the early automated perimeters necessitated the use of low background luminances (Heijl and Krakau, 1975a; Heijl, 1985). The advent of high intensity tungsten halogen lamps, however, has permitted the utilization of higher background luminances (ie typically 31.5asb) which require less adaptation time and are less susceptible to contamination by inadvertent ambient illumination (Heijl, 1985).

Early reports using manual perimetry have suggested that the utilization of different adaptation levels may provide additional diagnostic information to that obtained from conventional perimetry (Shiga, 1968; Greve et al, 1977; Hara, 1979). Greve and co-workers (1977) using the Friedmann Visual Field Analyzer found that meridional static perimetry at both mesopic and photopic adaptation levels aided the differential diagnosis of maculopathies and neuropathies, while Hara (1979) using a similar technique suggested that mesopic and scotopic perimetry accentuated the loss of visual field sensitivity in pigmentary retinal degenerations. Similarly, Drum and co-workers (1986) using manual static perimetry found an exaggerated loss of scotopic sensitivity compared to photopic sensitivity in glaucoma patients and suggested that the technique may be a more sensitive test for the detection of early glaucoma. In addition, the assessment of photopic and scotopic sensitivity (Marmor et al, 1983) using a modified automated static perimeter has been demonstrated to differentiate between the sub-groups of retinitis pigmentosa (Jacobson et al, 1986a; Apáthy et al, 1987) and to allow a more thorough investigation of the functional visual loss in rod and cone dysfunction (Jacobson et al, 1986b) and retinitis pigmentosa (Greenstein and Hood, 1986). Conversely, Kothe and co-workers (1991) could find no difference in the reduction of both scotopic and photopic

critical flicker frequency following an artificial increase in intra-ocular pressure. Recently, Moore and co-workers (1992), using dark adapted perimetry, have demonstrated focal sensitivity loss in areas of the visual field assessed as normal by manual kinetic techniques for retinitis pigmentosa patients. Furthermore, Denis and co-workers (1993) have advocated the use of a 0.3asb background luminance for the early detection of glaucomatous visual field loss.

Using a background luminance of 215 $cdm^{-2}$, Wilson (1967) demonstrated abnormalities of spatial summation in pre-geniculate lesions, while patients with post-geniculate lesions exhibited abnormalities of both spatial and temporal summation. Furthermore, using background luminances of 70 $cdm^{-2}$ and 223 $cdm^{-2}$, Shiga (1968) reported isopter depression in the early stages of third neuron and retinal diseases, including glaucoma, while normal subjects exhibited a general enlargement of the isopters. Similarly, the detection of early visual field defects has been demonstrated to be enhanced at high adaptation levels (greater than 200 $cdm^{-2}$) in progressive cone dysfunction (Elenius and Leinonen, 1986). Conversely, using automated perimetry, Asman and Heijl (1988) were unable to detect any difference in the magnitude of visual field loss for background luminances of approximately 1, 10 and 100 $cdm^{-2}$.

1.3.4. Spatial summation and stimulus size.

A range of stimulus sizes are available in modern projection perimeters. The HFA, for example, has five stimuli from Goldmann I to V with angular subtenses of 0.108° and 1.724° respectively. Increase in stimulus size results in a greater dynamic range (Fankhauser, 1979; Heijl, 1985; Choplin et al, 1990). For a background luminance of 4asb, Fankhauser (1979) found an increase in dynamic range of 12dB at 50° eccentricity and 3-4dB at fixation as a result of increasing the stimulus size from Goldmann I to III (0.431°). The greater dynamic range results from an increase in spatial summation with increase in stimulus size and with increase in eccentricity. Spatial summation describes the phenomenon by which a small infra-threshold stimulus is perceived as the stimulus

size is increased and both the luminance and the stimulus duration are held constant. Spatial summation can be described by the formula:

$$\text{Constant} = \Delta L \cdot A^{k}$$

where the constant represents threshold which varies with retinal position, $\Delta L$ is the stimulus intensity, A is the stimulus area and the exponent k represents the summation coefficient which increases with increase in eccentricity. When k=1, Ricco's Law is obeyed since complete spatial summation occurs.

Goldmann (1945a, 1945b and 1946) established the standard stimulus sizes, which are employed in the current automated perimeters, based on a single summation coefficient of 0.80 for the whole of the visual field. With this summation coefficient, a doubling of stimulus diameter is equivalent to a 5dB increase in stimulus intensity. In practice the relationship is an approximation since the empiric summation coefficient varies with eccentricity, adaptation level, stimulus size, defect depth and between individuals. Indeed, the magnitude of spatial summation increases not only with increase in stimulus size and eccentricity but also with decrease in adaptation level and stimulus duration (Barlow, 1958; Fankhauser and Schmidt, 1960; Sloan, 1961; Fankhauser, 1979; Brown et al, 1989). Furthermore, spatial summation is considered to be generally independent of age (Dannheim and Drance, 1971; Brown et al, 1989).

Goldmann size III was selected as the default stimulus for automated static perimetry, rather than the default kinetic size I stimulus, since it permitted a greater dynamic range (Fankhauser, 1979; Heijl, 1985) and was more resistant to the effects of optical defocus (Fankhauser, 1979; Heijl, 1985) and lens opacities (Radius, 1978; Fankhauser, 1979; Greve, 1980b; van den Berg, 1987). Fankhauser (1979) suggested that larger stimuli act as a filter minimizing the attenuation of sensitivity due to pre-retinal artifacts but detecting sensitivity loss derived from retinal and post-retinal disturbances of visual function. Furthermore, a Goldmann size V stimulus has been employed clinically to demonstrate and monitor residual vision in patients exhibiting an absolute sensitivity loss to a size III stimulus in both glaucoma (Wilensky et al, 1986; Zalta, 1991) and retinitis pigmentosa

(Wood et al, 1986a). Indeed, normative data has been established for stimulus size V (in addition to size III) (Choplin et al, 1990) and is now incorporated into the STATPAC software of the HFA.

Dubois-Poulsen (1952) suggested that sensitivity to early visual field loss could be increased by a reduction in stimulus size rather than luminance. Subsequently, various studies have demonstrated that the accuracy with which focal loss can be measured increases as stimulus size is decreased (Greve, 1973; Gramer, 1981; Bek and Lund-Andersen, 1989). Indeed, Greve (1973) suggested that an enhanced spatial summation in areas of focal loss within the visual field may produce an apparent reduction in the size of a visual field defect to larger diameter stimuli. Conversely, Dannheim and Drance (1974) could find no disturbance of spatial summation in glaucomatous subjects using manual static perimetry. In addition, smaller stimulus sizes have been recommended for the investigation of the central visual field since the Goldmann size III stimulus has been demonstrated to be relatively insensitive to early focal loss (Wood et al, 1986b; Wild et al, 1987a). Furthermore, Zalta and Burchfield (1990) found that a size I stimulus was more sensitive for the detection of shallow focal loss (6dB depth) in glaucoma patients compared with a size III stimulus, whilst Dengler-Harles and co-workers (1993) could find no significant difference in the visual field indices for stimulus sizes I and III. The difference in the findings was explained by a sample with predominantly diffuse field loss in the latter study and the utilization of a mathematical, rather than empirical, normal database for stimulus size I (Dengler-Harles et al, 1993).

Interestingly, the utilization of an increasing stimulus size with increase in eccentricity to produce an isosensitive profile and achieve equal cortical representation has been proposed (Wild et al, 1986a; Wild et al, 1987a; Wood et al, 1986b; Latham et al, 1993).

### 1.3.5. Temporal summation and stimulus duration.

The optimal stimulus duration is governed by the temporal summation properties of the visual system and by the need to eliminate eye movements away from fixation (Wild,

1988). Temporal summation describes the phenomenon by which a short duration infra-threshold stimulus is perceived as the stimulus duration is increased and both the luminance and the stimulus size are held constant (Anderson, 1992). Temporal summation can be described by the formula:

$$\text{Constant} = \Delta L \, . \, T^{k}$$

where the constant represents threshold which varies with retinal position, $\Delta L$ is the stimulus intensity, T is the stimulus duration and the exponent k represents the summation coefficient which increases with increase in eccentricity (Barlow, 1958; Saunders, 1975). When k=1, Bloch's Law is obeyed since complete temporal summation occurs. Bloch's Law applies to stimuli of short duration, that is less than the critical time, $T_c$. Therefore, when T is less than $T_c$ threshold determination obeys Bloch's Law (k=1) but as the neural mechanism becomes saturated, summation becomes incomplete (k less than 1) and eventually ceases (k=0). Consequently, when T is greater than $T_c$, threshold is independent of stimulus duration.

The value of the critical time varies with eccentricity, stimulus duration and adaptation level but is of the order of 60-100msec (Barlow, 1958; Greve, 1973; Saunders, 1975; Hart, 1987). Using manual perimetry, Harms (1952) found no further increase in threshold sensitivity for a stimulus duration of 100msec or longer, while Dannheim and Drance (1971) found that the critical time may exceed 100msec within 30° eccentricity for Goldmann stimulus size IV (0.862°) at background luminances of 10asb and 0.1asb. Conversely, Aulhorn and Harms (1972) found a critical time of 500msec. Temporal summation increases with increase in eccentricity and with decrease in adaptation level and is of a greater magnitude for smaller stimuli (Barlow, 1958; Saunders, 1975). In addition, the magnitude of temporal summation is independent of age (Dannheim and Drance, 1971) but varies according to the experimental design (Blackwell, 1963; Hart, 1987). Some investigations have implicated the higher centres of the visual system in the process of temporal summation (Battersby and Defabaugh, 1969; Hart, 1987).

Automated static perimetry generally employs stimulus durations of 100msec (Octopus) or 200msec (HFA) but durations of the order of 0.5 to 1.0 second have been proposed in order to eliminate the effects of temporal summation (Harms, 1952; Aulhorn and Harms, 1972). Longer stimulus durations (ie 0.5 to 1.0 second), however, may encourage eye movements away from fixation and will also increase the examination time (Aulhorn and Harms, 1972; Greve, 1973). Indeed, depending on the experimental technique employed, for stimuli within 30° eccentricity the latency of saccadic eye movements are approximately 75msec (Robinson, 1964) and the time taken for a saccade out to 30° eccentricity is approximately 90msecs (Robinson, 1964; Baloh et al, 1975; Bahill et al, 1981). Greve (1973) reported that inter-individual differences in temporal summation in normal subjects were small and considered that short stimulus durations were more suitable for the examination of patients with poor fixation. Furthermore, areas of focal loss within the visual field may only be revealed using short stimulus durations due to an enhanced temporal summation effect in diseased eyes (Wilson, 1967; Holmin et al, 1987; Krakau, 1989a).

1.3.6. Stimulus location and interstimulus separation.

The probability of detecting focal loss using static perimetry depends on the density of stimulus locations and the spatial arrangement of the stimuli (Greve, 1975; Fankhauser and Bebié, 1979; Johnson and Keltner, 1981). The spatial arrangement may vary according to which disease the test program is designed to detect (Johnson and Keltner, 1981). An increased density of stimulus locations, however, can only be incorporated at the expense of an increased examination time (Fankhauser and Bebié, 1979). Indeed, Greve (1975) calculated that 452 stimulus locations would be required to detect a 3° diameter circular area of focal loss within 30° of fixation with 95% confidence. Conversely, Johnson and Keltner (1981) demonstrated that the rate of detection of focal loss was not substantially improved by using more than 140-150 stimulus locations. Fankhauser and Bebié (1979) found that the probability of detecting focal loss of 8.4° diameter using a 6° interstimulus square grid was 100%, whilst that of a 6° diameter area of focal loss was 70%. Subsequently, it has been shown that focal loss the size and depth of the physiological

blind spot may be missed with a 6° interstimulus square grid (King et al, 1986; Wild et al, 1986b). Furthermore, for focal loss greater than 4° in diameter the probability of detection using a 6° interstimulus square grid was determined to be two to three times greater than that of a 1.5° interstimulus two-meridian grid (Fankhauser and Bebié, 1979). For focal loss of less than 2° diameter the probability of detection was low and was independent of the type of stimulus grid utilized (Fankhauser and Bebié, 1979).

A compromise must be reached between the efficiency of focal loss detection and the time to undertake a perimetric examination. Gutteridge (1984) summarized the three options for deciding the arrangement of stimuli within a visual field program. The alternatives are systematic sampling, higher density sampling in areas of the visual field at greater risk of sensitivity loss, or a combination of systematic and higher density sampling. Systematic sampling is employed in a square grid program, while higher density sampling is employed in the G1 program of the Octopus perimeter. The combination of systematic and higher density sampling has been employed in the Ocuplot and Fieldmaster perimeters. Indeed, Weber and Dobek (1986) advocated the utilization of a 3° interstimulus square grid within 10° eccentricity, a 4.2° grid between 10° and 20° eccentricity and a 6° grid between 20° and 30° eccentricity for the optimal detection of glaucomatous visual field defects. Similarly, the Octopus G1 program incorporates an increasing resolution with decrease in eccentricity, such that a 2.8° resolution is achieved within the macular area (Flammer et al, 1987). Subsequently, the G1 program has been demonstrated to improve both the detection and the assessment of visual field defects when compared to a 6° interstimulus square grid (Gloor and Gloor, 1986; Dannheim, 1987). A 6° interstimulus square grid is considered to be suitable, however, for the detection of visual field loss due to chiasmal and suprageniculate lesions.

Most automated perimeters provide facilities to increase the stimulus density in desired areas of the visual field by using custom programs, whilst stimulus density can be increased over the whole field by merging the results of two programs (eg programs 31 and 32 of the Octopus or programs 30-1 and 30-2 of the HFA). Interestingly, the Octopus

SAPRO program utilizes software that continually modifies the spatial resolution within an examination as a result of patient response. A coarse grid is employed in areas of normal sensitivity, while an increasingly finer grid is employed in areas of apparent visual field loss (Fankhauser et al, 1981; Häberlin et al, 1983; Funkhouser and Fankhauser, 1985). Asman and co-workers (1988) found that such spatially adaptive techniques did not improve sensitivity or specificity, however, when employed in conjunction with a threshold-related, supra-threshold screening program.

Recent studies have investigated the possibility of reducing the number of stimulus locations in order to reduce examination time whilst retaining sensitivity and specificity. Funkhouser and co-workers (1989a and b) found that the results of the Octopus G1 program could be accurately derived using an abbreviated program comprising approximately 30 of the original 59 stimulus locations. Krakau (1989b) suggested that by repeatedly thresholding 6 to 8 stimulus locations situated within 30° eccentricity, rather than a single threshold estimation of approximately 70 stimulus locations, nearly all abnormal visual fields could be detected. Similarly, de la Rosa and co-workers (1990 and 1992) suggested that 4 stimulus locations within 30° eccentricity (ie one stimulus location in each quadrant) can be thresholded to determine by means of multiple regression the sensitivity of the entire visual field (mean r=0.84). The standard error of the estimation was found to be similar to the magnitude of short-term fluctuation. For a single estimation of threshold, however, reducing the number of stimulus locations has been demonstrated to increase the mean sensitivity and reduce the short-term fluctuation (Fujimoto and Adachi-Usami, 1992a, b and c). In addition, Weber and Diestelhorst (1992) have demonstrated that programs with a reduced number of stimulus locations can be very accurate in the follow-up of glaucomatous visual fields. Indeed, theoretical calculations show that trend analysis can be improved if the reduction in examination time is combined with a greater frequency of examination (Weber and Diestelhorst, 1992). Furthermore, Zeyen and co-workers (1993) have suggested that by utilizing the stage concept in which the examination is divided into subsets of stimulus locations the option is provided to curtail the test if sufficient information has been gathered. All the stimulus locations in any

stage complete the thresholding procedure before the start of the ensuing stage and the visual field indices are updated at the end of each stage.

## 1.4. Stimulus generation.

Commercially available automated perimeters employ a variety of techniques to generate stimuli, including projection systems, light emitting diodes and fibre optics. The technique can influence the topography of the derived visual field and the efficiency of the perimetric examination.

### 1.4.1. Projection.

Projection systems offer the most flexible form of stimulus generation (Tate and Lynn, 1977; Fankhauser, 1979; Heijl, 1984). Indeed, the two most widely used perimeters, ie the HFA and Octopus automated perimeter, both employ projection systems. The stimulus intensity is controlled with a variable neutral density filter placed in front of an incandescent light source, while the stimulus size is governed by a rotating aperture plate in the stimulus light path. Furthermore, the stimulus position is varied by a number of rotating mirrors controlled by stepping motors and can be presented anywhere within the visual field with a resolution of 0.2° between adjacent stimuli (Fankhauser, 1979). In addition, the stimulus colour can be easily changed by placing a filter in the stimulus light path.

The dynamic range of a projection perimeter is determined mainly by the wattage of the stimulus bulb but consideration also needs to be given to the extent to which light is scattered beyond the geometrical boundaries of the spot stimulus (Fankhauser, 1979). Scattered light from a bright stimulus has been demonstrated to artificially reduce the depth and area of focal loss (Wilson, 1968; Weale and Wheeler, 1977; Fankhauser, 1979; Fankhauser and Haeberlin, 1980). Indeed, Fankhauser (1979) has proposed a maximum stimulus luminance of 1000asb in conjunction with a background luminance of 4asb to produce minimum straylight and allow a maximum dynamic range.

Due to the complicated design, projection systems are relatively expensive, vulnerable to damage and susceptible to mechanical failure (Heijl, 1984). The mirror controlled positioning of the stimulus must be frequently recalibrated (Heijl, 1985) and the stepping motors are audible which may result in an increased number of false-positive responses (Heijl, 1984; Taylor et al, 1984). Furthermore, ageing of the stimulus bulb necessitates the recalibration of the perimeter every time the instrument is switched on.

### 1.4.2. Light emitting diode (LED).

LED systems are able to operate at high luminance levels (Fankhauser, 1979) and are silent, robust and inexpensive (Taylor et al, 1984). A high frequency pulse current is employed to vary the intensity of the LED which is mounted on the surface of the perimeter bowl. As the position of each LED is fixed, a finite number of stimulus locations are available but this limitation can be overcome by the use of additional fixation targets providing the LEDs are closely spaced (Phelps, 1985). Unlike projection systems, the size of the LED generated stimulus is invariable and each LED requires individual calibration. In addition, the critical directional properties of LEDs necessitates precise mounting and the spectral nature of the LED stimulus may influence the differential light threshold (Fankhauser, 1979; Wild, 1988). Interestingly, the new Octopus 1-2-3 perimeter combines the merits of both projection and LED stimulus generation. A single LED is projected via a condensing lens directly onto the retina using a series of mirrors to vary the stimulus location (Octopus 1-2-3 Operating Instructions, 1990).

The LEDs of the early Dicon perimeter were mounted in apertures recessed within the surface of the perimeter bowl. Such "black hole" perimeters do not measure a true differential light threshold since the stimulus is not added to an even background (Heijl, 1985; Wood et al, 1986a). Indeed, the luminance of the LED at threshold may be less than the luminance of the background (Desjardins and Anderson, 1988). Consequently, the early Topcon perimeter employed LEDs that in the resting state were the same luminance as the background (ie 31.5asb) in order to measure a true differential light threshold. Furthermore, perimeters which employ "black hole" type presentations have

been criticised for producing changes in local retinal adaptation (Mills, 1985; Heijl, 1985). Flanagan and co-workers (1988) found that the Dicon perimeter produced a steeper sensitivity profile than perimeters utilizing other methods of stimulus generation, while Britt and Mills (1988) found that the "black hole" effect resulted in a higher variance of multiple threshold determinations ($p=0.0005$) contributing on average 0.8dB to the short-term fluctuation but considered this to be of minor clinical importance. Indeed, instruments such as the Competer and Medmont perimeters have avoided these artifacts by mounting the LEDs behind a diffusing coating to produce a homogenous bowl surface, while subsequent versions of both the Dicon and the Topcon perimeters have resorted to projection systems.

### 1.4.3. Fibre-optic.

Fibre-optic stimulus generation systems employ a centrally located light source from which light is guided down fibre optic light guides which terminate on the bowl surface. This system has been employed in the Fieldmaster (models 101PR, 200 and 225) and the Tubinger 2000 perimeters. Fibre-optic stimulus generation only permits stimuli of fixed location and size and is more expensive than either of the other two stimulus generation techniques.

The use of He Ne lasers for stimulus generation rather than incandescent sources has been proposed but the efficiency and suitability of these instruments is undetermined (Fankhauser, 1979).

## 1.5. Examination strategies.

The strategy employed for automated static perimetry depends largely on the purpose for which the examination is required. Furthermore, the perimetrist should be aware of the limitations of the method utilized by a particular strategy in order to accurately interpret the results of a derived visual field (Bebié, 1985a).

1.5.1. Supra-threshold (supraliminal) screening.

Supra-threshold screening procedures generally employ a stimulus luminance brighter than the age-matched normal threshold and normality is assumed if the first stimulus is seen (Asman, 1992). Stimulus luminances of 4dB to 6dB brighter than threshold have generally been employed. Supra-threshold strategies are very rapid and relatively simple to interpret compared to full threshold procedures which on average take 15 minutes to assess 70 stimulus locations within 30° eccentricity (Bebié, 1985a; Lewis et al, 1986). Supra-threshold strategies are unable to quantify the severity of a visual field defect (Bebié, 1985a). Consequently, supra-threshold strategies are employed to confirm normality in populations that are expected to be predominantly normal. Araujo and co-workers (1993) have recently suggested, however, that screening using supra-threshold luminance levels based on a previous full threshold examination provides similar information in the assessment of visual field progression as that obtained from a full threshold examination.

Numerous supra-threshold screening strategies are available. One-level screening employs a single stimulus luminance at all locations regardless of eccentricity (Keltner et al, 1979; Heijl, 1985; Wild, 1988). The reduction in normal sensitivity with increase in eccentricity is ignored and the efficacy of the procedure depends upon the initial choice of stimulus luminance. Consequently, the one-level screening technique exhibits poor specificity and is considered to be of limited value (Hong et al, 1981; Gramer et al, 1982). The procedure can be improved by employing two or more stimulus luminance levels one of which is the maximum in order to categorize visual field defects in terms of relative and absolute sensitivity loss (Keltner et al, 1979).

Gradient adapted screening strategies attempt to employ a stimulus luminance at a known and constant level above threshold for all eccentricities. The procedure relies on the prediction of the shape of the hill of vision (Heijl, 1985). Johnson and co-workers (1979) have demonstrated that gradient adapted supra-threshold automated static perimetry provides significantly better detection rates for visual field loss due to non-glaucomatous

optic nerve disease than manual kinetic perimetry. Indeed, gradient adapted supra-threshold screening procedures in conjunction with multiple stimulus presentation have been suggested as a means to further reduce the test duration (Greve, 1972 and 1973; Langerhorst et al, 1989). As with one-level screening, a maximum luminance stimulus can be employed to differentiate between relative and absolute sensitivity loss. Interestingly, the duration of the gradient adapted two luminance procedure is longer for older and for glaucomatous patients than for young and for normal subjects using a 120 point full field program, where as no such difference has been found using a full threshold program out to 30° eccentricity (Kosoko et al, 1986).

The gradient adapted threshold-related procedure thresholds one or more pre-determined locations at the onset of the examination and after correcting for the normal decay in sensitivity with increase in eccentricity, a predicted supra-threshold stimulus is presented at all other stimulus locations. If the initial threshold determination is performed in an area of focal loss or is erroneous, however, the choice of screening stimulus luminance will be incorrect. As a result, most instruments threshold two to four locations and take the most sensitive point as reference. In addition, more than one threshold assessment at each pre-determined location reduces the influence of erroneous responses (Heijl, 1985). Gradient adapted threshold-related techniques have been demonstrated to detect visual field defects earlier than manual kinetic perimetry (Heijl, 1976; Dyster-Aas, 1980). The procedure can be further improved by employing a "Quantify Defects" (Haley, 1987) or "Screening-with-Quantitation" (Bebié, 1985a) option. Using this option, stimulus locations that are missed during the screening phase of the examination are subsequently thresholded to determine the defect depth.

### 1.5.2. Full threshold.

Full threshold strategies provide a comprehensive assessment of the depth and area of the visual field and permit the detection of subtle defects, or the progression of existing defects more effectively, than supra-threshold procedures (Stewart et al, 1989). This is achieved at the expense of an increase in the test duration and consequently a limit on

the number of stimulus locations assessed. The specific nature of the thresholding algorithm determines not only the duration of the test but also the accuracy and reliability of the results (Bebié, 1985a). Most automated perimeters employ thresholding algorithms based on either the "method of limits" (Guilford, 1954) or on the "staircase method" (Stiles and Crawford, 1934). The method of limits utilizes an initial stimulus which is approximately 2dB to 4dB infra-threshold in relation to the age-matched normal values and is increased in intensity in constant steps of 2dB to 4dB until the stimulus is seen (Bebié et al, 1976a).

The majority of perimeters employ the "up-and-down" staircase or bracketing procedure to estimate threshold. Differences exist between instruments, however, in the details of the staircase procedure. Spahr (1975) developed the "optimal" staircase strategy, which is employed in the Octopus perimeter, by applying the principles of mathematical information theory in order to gain maximum information per stimulus presentation. Threshold is crossed initially using a 4dB step size and a starting luminance equal to the age-matched normal value for that particular location. For the second crossing of threshold the luminance direction is reversed and a 2dB step size is utilized to check and refine the estimate obtained in the first crossing. The starting luminance for the second crossing of threshold is the mean of the last two presentations of the first crossing and the final threshold value is taken as the mean of the last seen and not seen stimuli. This procedure requires approximately 5 stimulus presentations per location to estimate threshold (Spahr, 1975; Bebié et al, 1976b; Bebié, 1985a). Indeed, the average number of stimulus presentations per location is greater for the staircase method than the method of limits but the staircase method is considered to be more accurate (Bebié et al, 1976b).

For the HFA, threshold is determined twice at each of four primary stimulus locations, or seed points, one in each quadrant of the visual field and symmetrically placed 9° from both the horizontal and vertical meridians using an initial stimulus intensity of 25dB (Haley, 1987). Thresholding is then carried out at stimulus locations adjacent to, and radiating out from, the seed points using an initial stimulus luminance of 4dB greater than the predicted

sensitivity based on extrapolation from previously thresholded locations (Heijl, 1977a; Bebié et al, 1976b). The thresholding procedure is similar to that used by the Octopus perimeter except that the last seen stimulus value is taken as threshold. If sensitivity is 5dB or more different from age-matched normal data then a second threshold determination is carried out (Haley, 1987). Stimulus presentation is randomized by the computer for both the HFA and Octopus perimeters such that consecutive stimuli are rarely presented at the same location.

A greater number of reversals utilized in a thresholding algorithm permits a greater tolerance to erroneous patient responses but at the expense of an increase in the test duration (Bebié et al, 1976b; Heijl, 1977a). However, the effect of the number of reversals on the accuracy of the threshold estimation is controversial. Early studies (Spahr, 1975; Bebié et al, 1976b; Bebié, 1985a) suggested that the number of threshold reversals determined the accuracy of the threshold estimation, while a recent study (Johnson et al, 1992) has found little or no improvement in threshold accuracy with increase in the number of reversals. In agreement with the latter study, Gandolfo and co-workers (1985) using a computerized Goldmann perimeter demonstrated that mean sensitivity and short-term fluctuation were not significantly different for the estimation of threshold based on either the method of limits or on a bracketing procedure.

Numerous modifications to the bracketing procedure have been suggested in order to reduce the duration of the perimetric examination. The dynamic step unit (DSU) strategy initially employed in the Peristat 433 perimeter maintains a constant relationship between the step size employed in the thresholding algorithm and the slope of the frequency-of-seeing curve (Weber, 1991 and 1992). Areas of the visual field with a lower sensitivity exhibit a greater range of luminances over which the probability of stimulus detection varies between 0% and 100%, ie the slope of the frequency-of-seeing curve flattens with decrease in sensitivity (Chauhan and House, 1991; Weber and Rau, 1992). Consequently, by employing a larger step size in areas of the visual field exhibiting greater uncertainty the examination time is reduced. Vivell and co-workers (1991)

compared the conventional 4dB / 2dB staircase strategy employed in the HFA to the DSU strategy of the Peristat 433 and found that the DSU strategy provided a more rapid assessment of the visual field (by a factor of three) with comparable reproducibility in normals but at the cost of a reduced reproducibility of relative visual field defects (by a factor of 1.6).

The recently introduced FASTPAC strategy of the HFA utilizes a constant 3dB step size in the thresholding algorithm and a single crossing of threshold (Moss et al, 1992; Flanagan et al, 1993a). In addition, the initial stimulus luminance differs from that of the conventional strategy in that one half of the stimulus locations are presented 1dB brighter than the predicted threshold, while the other locations are presented 2dB dimmer than predicted. An approximate 40% reduction in the examination time of normal subjects was achieved but at the cost of a 24% increase in short-term fluctuation. In addition, the magnitude of the mean sensitivity was virtually identical for the two strategies. Furthermore, Flanagan and co-workers (1993b) have demonstrated that the time saving of the FASTPAC strategy is reduced in glaucomatous subjects as the severity of any visual field defect increases due to the larger initial step size of the conventional strategy. Consequently, FASTPAC is recommended as an alternative to gradient adapted threshold-related screening strategies (Flanagan et al, 1993a)

In a detailed study of the properties of staircase procedures, Johnson and co-workers (1992) concluded that the current strategies appear to be ideal in terms of efficiency and accuracy. Therefore, future thresholding procedures should depart from staircase based strategies in order to permit substantial improvements. The RIOTS (real-time interactive optimized test sequence) procedure employed a two phase heuristic test strategy (Johnson and Shapiro, 1991). A modified binary search procedure at critical primary stimulus locations was used in the first phase to permit a low resolution partitioning of the visual field which established expectations for the second high resolution phase of RIOTS. For the second phase, stimulus locations were alternated in an expected "seen" and "not seen" chequerboard pattern. Responses were evaluated by comparison with

neighbouring locations and the agreement between expected and obtained patient responses at each stimulus location was analyzed. Locations which suggested an erroneous response were re-checked. The chequerboard pattern was then reversed (previously "seen" locations become "expected not seen" and vice versa) and each stimulus location underwent a second stimulus presentation. The agreement between expected and obtained patient responses at each stimulus location was again determined and erroneous responses were checked. For stimulus locations which did not reach the expected agreement criteria the chequerboard was once more reversed and the process was repeated. The procedure relied on the fact that both normal and abnormal visual fields exhibited distinct and contiguous spatial patterns of sensitivity. The procedure reduced the test duration by at least 50%, provided greater accuracy and test-retest reliability, required fewer stimulus presentations, had a more consistent test time and avoided the need for catch trials since reliability could be assessed using the interstimulus agreement matrices (Johnson and Shapiro, 1991). However, the procedure has yet to be independently evaluated.

### 1.6. Reliability parameters.

Manual perimetry depends on the subjective judgement of the perimetrist to assess patient reliability, while automated perimetry provides an objective measure of performance by means of the reliability parameters or "catch trials" (Neuhann and Greite, 1981; Whalen, 1985a). The reliability parameters continually check for fixation losses, false-positive errors and false-negative errors. Approximately 10% of stimulus presentations are reserved for catch trials (Jenni and Flammer, 1987; Zulauf et al, 1992). In addition, reliability is partly reflected by the magnitude of the short-term fluctuation (Whalen, 1985a). Short-term fluctuation is recognized, however, to be a poor measure of patient reliability (Zulauf and Caprioli, 1991; Fankhauser, 1993) since the primary underlying factor influencing the magnitude of this function (See Section 1.0.1) is the level of threshold (Chauhan and House, 1991; Weber and Rau, 1992).

1.6.1. Fixation.

Fixation can be monitored continuously using an infra-red video camera. If a fixation loss or blink occurs, the test procedure is interrupted and only restarts when correct fixation has returned. In such situations any response is disregarded and the same stimulus is repeated at random later in the examination (Whalen, 1985a). This system is currently employed in the Octopus perimeter. Alternatively, a bright stimulus can be periodically presented into the blind spot (Heijl and Krakau, 1975a and b). If a fixation loss occurs a response will be recorded. This system is employed in the HFA and is termed the Heijl-Krakau technique. Both the Octopus and HFA perimeters also utilize a video monitor or a telescope system to allow the subjective monitoring of fixation by the perimetrist, while other perimeters such as the Medmont rely totally on the Heijl-Krakau technique. If the rate of fixation loss exceeds 20% of the blind spot presentations the field examination is flagged as unreliable (Haley, 1987).

The disadvantages of systems that continuously monitor fixation are that the examination will be prolonged by frequent interruptions and that false interruptions can occur due to minor head movements (Haley, 1987). The disadvantages of the Heijl-Krakau technique are that fixation is only checked periodically rather than continually monitored and that the initial localization of the blind spot by the computer determines the accuracy of the technique (Zulauf and Caprioli, 1991). Consequently, pericoecal focal loss will reduce the effectiveness of the Heijl-Krakau technique since the stimulus will not be detected despite substantial fixation loss (Fankhauser, 1993). Furthermore, the differentiation between a fixation loss and false-positive response is impossible (Fankhauser, 1993) whilst a false-negative response during a fixation catch trial will indicate correct fixation despite erroneous eye movements (Fankhauser, 1993).

It is generally agreed that fixation loss is the most common cause of unreliable automated perimetry results (Katz and Sommer, 1988; Nelson-Quigg et al, 1989; Bickler-Bluth et al, 1989a; Katz et al, 1991; Johnson and Nelson-Quigg, 1993). Consequently, an increase in the reliability limit for fixation losses from 20% to 33% has been proposed (Katz and

Sommer, 1988; Bickler-Bluth et al, 1989a; Johnson and Nelson-Quigg, 1990). The fixation loss rate has been demonstrated to decrease with perimetric experience (Bickler-Bluth et al, 1989a; Johnson and Nelson-Quigg, 1993). Katz and Sommer (1990a) found that glaucoma patients with high fixation loss rates (≥20%) exhibited a higher mean sensitivity and a lower pattern standard deviation than those with good fixation, while Cascairo and co-workers (1991) found mean deviation to be significantly decreased (ie deteriorated) at a fixation loss rate of 33% in normal subjects. Furthermore, Henson and Bryson (1991) have shown that fixation loss results in an increased short-term fluctuation. As a result, any increase in the reliability limit for fixation losses must take into account concomitant changes to the sensitivity and specificity of automated perimetry.

The requirement to maintain central fixation over long periods may account for inaccurate and unreliable results in automated perimetry (Trope et al, 1989; Eizenman et al, 1992). Consequently, Trope and co-workers (1989) have investigated the use of eye movement perimetry in which the patient signals detection by making a saccade towards the stimulus. With this technique the patient is actively encouraged to change fixation and eye movements are recorded using a sensitive eye tracker. The technique still needs to be clinically evaluated.

### 1.6.2. False-positive and false-negative errors.

A false-positive error is recorded when a patient responds to the noise of the perimeter in the absence of a stimulus presentation, while a false-negative error occurs when a patient fails to respond to a supraliminal stimulus presented at a location that has previously been thresholded (Whalen, 1985a; Heijl et al, 1987a). High false-positive error rates are generally exhibited by anxious and over-eager (often termed "trigger-happy") patients and result in "white scotomata" of the grey-scale printout due to abnormally high sensitivity values (Whalen, 1985a; Zulauf and Caprioli, 1991). High false-negative error rates are exhibited by inattentive or fatigued patients and result in an abnormally low sensitivity (Whalen, 1985a). If the rate of false-positive or false-negative errors exceeds 33% the field examination is flagged as unreliable (Haley, 1987).

The percentage of subjects exceeding the 33% false-positive and false-negative error criteria is equivocal. One study found approximately 30% to 40% of automated perimetry results to be unreliable based upon the 33% false-positive and false-negative error criteria (Enger and Sommer, 1987; Katz and Sommer, 1988; Katz and Sommer, 1990a; Katz, Sommer and Witt, 1991), while others have found a considerably lower incidence of unreliable results (Nelson-Quigg et al, 1989; Hardage and Stamper, 1989; Bennett et al, 1991; Johnson and Nelson-Quigg, 1993). This controversy has been attributed to differences in the testing protocol and in the patient populations between studies (Bickler-Bluth et al, 1989b; Johnson and Nelson-Quigg, 1990; Katz and Sommer, 1990b). Somewhat surprisingly, Johnson and co-workers (1993) found that intermittent or continuous patient monitoring did not influence the error rate. It is generally agreed, however, that glaucomatous subjects exhibit a higher false-negative error rate than normal subjects (Heijl et al, 1987a; Jenni and Flammer, 1987; Katz and Sommer, 1988; Katz, Sommer and Witt, 1991; Johnson and Nelson-Quigg, 1993) which has been attributed to increased fatigue and variability (Katz and Sommer, 1988). Indeed, reliability parameter rates, in general, are related to the defect depth in glaucomatous visual fields (Jenni and Flammer, 1987; Reynolds et al, 1990).

Various studies have investigated the influence of false-positive and false-negative errors on the outcome of automated perimetry. Katz and Sommer (1990a) found that high false-positive error rates (≥10%) resulted in a higher mean sensitivity for both glaucoma patients and normal subjects, while high false-negative error rates (≥33%) resulted in a lower mean sensitivity both for glaucoma patients and normal subjects and in a higher pattern standard deviation for normal subjects (Katz and Sommer, 1990a). Similarly, Cascairo and co-workers (1991) demonstrated that the global indices mean deviation and short-term fluctuation were significantly increased from baseline in normal subjects at a false-positive error rate of 33% and were significantly decreased at a false-negative error rate of 20%, while pattern standard deviation was found to be significantly increased for both false-positive and false-negative error rates of 20% and 10% respectively.

The false-positive error rate is positively correlated with the rate of fixation loss (Reynolds et al,1990). Indeed, the fixation loss rate is frequently contaminated by artifacts such as false-positive errors (Sanabria et al, 1991). All but one study (Reynolds et al, 1990) have found the reliability parameters to be independent of age (Heijl et al, 1987a; Jenni and Flammer, 1987; Katz and Sommer, 1988; Nelson-Quigg et al, 1989; Bickler-Bluth et al, 1989a).

### 1.6.3. Other measures of reliability.

In a letter to the editor, Fankhauser (1993) advocated alternative measures of reliability since the current parameters are contaminated by noise. The information within the thresholding algorithms can be utilized to assess the decision making properties and accuracy of a subject's response (Johnson and Shapiro, 1991; Olsson et al, 1989). Such techniques need to be clinically evaluated but may provide a more accurate estimation of reliability than the current parameters (Olsson et al, 1989). In addition, an excessive number of stimulus presentations can be an indicator of unreliability (Whalen, 1985a; Zulauf et al, 1992). Zulauf and co-workers (1992) have suggested the use of a new reliability parameter, termed the "stimulus discrepancy", which represents the difference between the estimated and actual number of stimulus presentations for a given visual field.

## 1.7. Fluctuation.

The outcome of any psychophysical quantitative test is known to fluctuate (Flammer, 1985a). Fluctuation of the visual field is defined as reversible changes of the differential light threshold of unknown origin that include measurement error, sampling error and physiological variation (Zulauf and Caprioli, 1991). The definition excludes explainable sources of change in visual field sensitivity such as learning and fatigue.

The frequency-of-seeing curve (Figure 1.1) illustrates that as stimulus intensity is increased the probability of detection is also increased (Flammer et al, 1984a; Flammer et

al, 1984b; Flammer, 1985a; Bebié et al, 1976a; Bebié et al, 1976b; Zulauf and Caprioli, 1991; Asman, 1992). Furthermore, the slope of the frequency-of-seeing curve is a reflection of the magnitude of fluctuation. A flat curve indicates a high fluctuation since large changes in stimulus intensity result in only small changes in the frequency-of-seeing (Zulauf and Caprioli, 1991). Threshold is defined as the intensity at which a stimulus is detected for 50% of presentations (Flammer et al, 1984a; Flammer et al, 1984b; Flammer, 1985a; Zulauf and Caprioli, 1991). The measurement of threshold at a single stimulus location, therefore, requires many stimulus presentations and is time-consuming (Flammer, 1985a; Zulauf and Caprioli, 1991).

Quantitative automated static perimetry dictates that threshold is assessed at a number of stimulus locations throughout the visual field (Flammer et al, 1984a). A staircase or bracketing procedure is employed to reduce the number of stimulus presentations (Bebié et al, 1976b; Heijl, 1977a). In effect, threshold is estimated rather than measured at each stimulus location and the concept of the frequency-of-seeing curve is ignored. As a result, the repeated assessment of threshold at a single stimulus location will produce a scatter of threshold values (Bebié et al, 1976a).

The total variance ($\sigma_T^2$) is comprised of two components, that is the short-term fluctuation and the long-term fluctuation, such that:

$$\sigma_T^2 = \sigma_{SF}^2 + \sigma_{LF}^2$$

where $\sigma_{SF}^2$ and $\sigma_{LF}^2$ are the short-term fluctuation and the long-term fluctuation components respectively (Flammer, 1985a; Flammer, 1985b).

1.7.1. Short-term fluctuation (SF).

Short-term fluctuation "... represents the scatter observed when the same threshold is measured independently (twice or repeatedly) during a single examination of the visual field" (Flammer, 1986). It is the average of the local scatter over the whole of the visual field and is calculated using the equation:

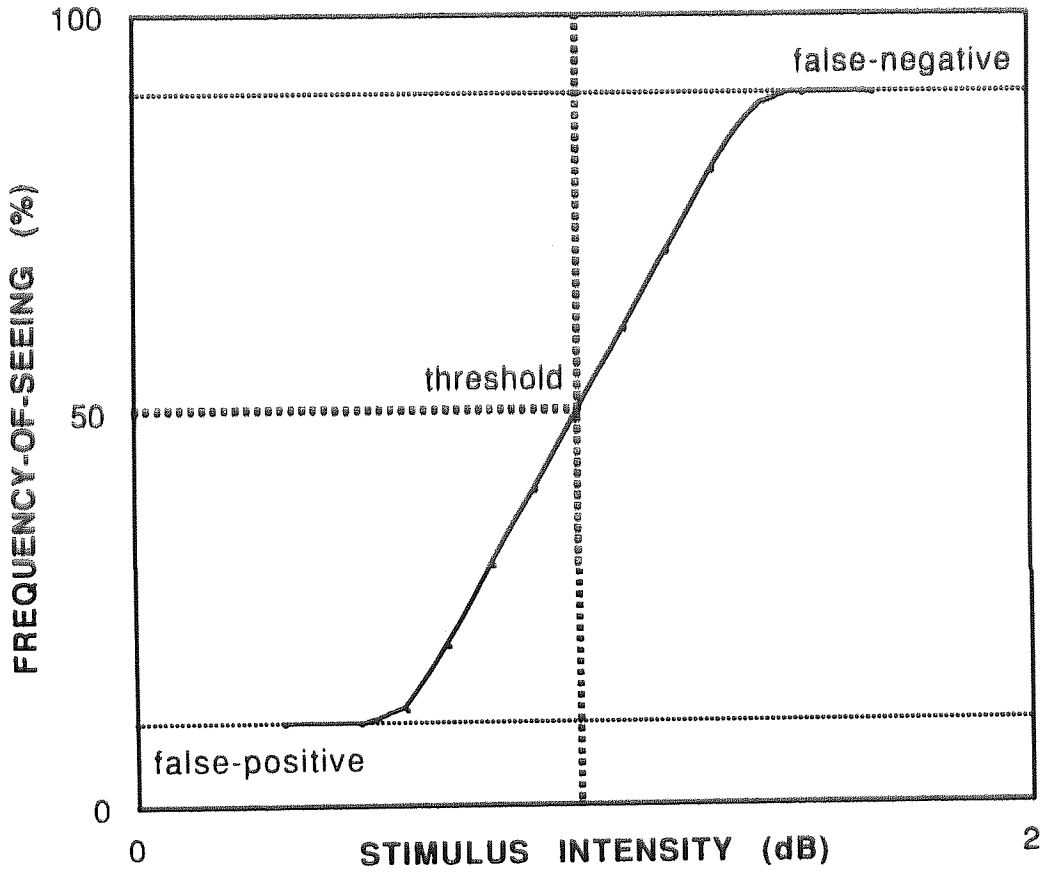



Fig. 1.1. Schematic frequency-of-seeing curve. As stimulus intensity increases, the frequency-of-seeing the stimulus also increases. The frequency-of-seeing may not reach 0% or 100% due to false-positive and false-negative responses respectively. Threshold is defined as the stimulus luminance at which 50% of the presentations are seen.

$$SF = \sqrt{\frac{\sum_{i=1}^{m}\sum_{k=1}^{n}(x_{ik} - x_i)^2}{m(n-1)}}$$

where m is the number of test locations used for the estimation of SF, n is the number of repetitions of threshold and $X_{ik}$ is the kth threshold determination taken at each point i (Flammer et al, 1985). The equation effectively calculates the root mean square (RMS) of the differences between double determinations of threshold. Alternatively, the calculation of the goodness of fit of a polynomial surface to the visual field has been suggested as a means of estimating SF (Schulzer et al, 1990; Mills et al, 1991).

The SF limits the accuracy of threshold determination at a single visual field examination and is generally attributed to the zone of uncertain responses for stimuli near threshold (Flammer, 1985b). An abnormally high SF can indicate poor patient reliability but can also be a sign of early disease and in some instances can precede manifest visual field loss (Flammer et al, 1984b; Stürmer et al, 1985; Werner and Drance, 1977). In addition, the magnitude of the SF is determined by the slope of the frequency-of-seeing function (Flammer, 1985b).

Methodological influences on the estimation of SF include the starting value of the threshold algorithm and the bracketing procedure employed in the determination of threshold (Lewis et al, 1986; Brenton and Argus, 1987; Fankhauser et al, 1988). These factors may in part explain the difference found in the magnitude of SF between the Octopus and Humphrey perimeters. In addition, an increased SF has been found for Goldmann stimulus sizes I and II compared to stimulus size III, whilst no further reduction in SF was found when comparing stimulus size III to stimulus sizes IV and V (Gilpin et al, 1990). The SF is also influenced by the number of stimulus locations and the number of determinations of threshold (Bebié et al, 1976b; Casson et al, 1990; Chauhan et al, 1991; Dengler-Harles et al, 1993; Flanagan et al, 1993c). Five threshold determinations at each of 4 stimulus locations has been suggested to provide an optimal estimation of SF

(Casson et al, 1990). The effect of stimulus duration on the SF is equivocal. It was suggested that shorter stimulus durations (ie 100 or 200msec) would result in a higher SF (Krakau, 1989a) but a recent study could find no dependency of SF on stimulus duration (Pennebaker et al, 1992). In addition, poor patient reliability in the form of fixation losses (Henson and Bryson, 1991), false-positive responses (Flammer et al, 1984a; Katz and Sommer, 1990a) and false-negative responses (Katz and Sommer, 1988) all increase the SF. An increase in the brightness of the fixation spot has also been found to increase the SF (Safran et al, 1992).

The SF increases with increase in eccentricity (Flammer et al, 1984a; Heijl et al, 1987c; Rutishauser et al, 1989; Heijl and Asman, 1989; Chauhan et al, 1990) and also increases as the depth of sensitivity loss increases (Heijl, 1977a; Flammer et al, 1984a; Langerhorst et al, 1987). It reaches a maximum of approximately 5dB at a sensitivity level of 10dB but diminishes with further reduction in sensitivity due to a constricted measurement range (Flammer et al, 1984a; Heijl et al, 1991a). Furthermore, SF is higher in glaucomatous patients than in normal subjects (Werner and Drance, 1977; Flammer et al, 1984b) and is particularly pronounced at stimulus locations adjacent to focal loss (Haefliger and Flammer, 1991; Zulauf and Caprioli, 1991). The relationship between SF and age is equivocal. Some reports have suggested that SF increases with increase in age (Katz and Sommer, 1987; Autzen and Work, 1990; Chauhan et al, 1990; Chauhan and House, 1991), while others have found no dependency (Flammer at al, 1984a; Brenton and Phelps, 1986; Heijl et al,1987a; Nelson-Quigg et al, 1989).

The level of threshold is the primary underlying physiological influence on SF (Chauhan and House, 1991; Weber and Rau, 1992). Previous studies have assumed that the frequency-of-seeing function was invariant (Bebié et al, 1976b; Spahr, 1975). However, recent work has shown that the slope of the frequency-of-seeing curve flattens with increase in threshold (Chauhan and House, 1991; Weber and Rau, 1992). The influence of eccentricity, sensitivity loss and age can be explained by the fact that these factors co-vary with the threshold level.

Unlike the Octopus perimeter, the Humphrey Field Analyzer gives a greater weighting to central stimulus locations in the calculation of global SF than peripheral locations in order to compensate for the increased variability in threshold with increase in eccentricity (Heijl et al, 1987b). The effect of the weighting function is to slightly reduce the SF (Flanagan et al, 1993c). Furthermore, the Octopus and Humphrey perimeters differ in the number of stimulus locations that are employed to determine SF. The G1 program of the Octopus perimeter thresholds all 59 stimulus locations twice to derive the SF, whilst program 30-2 of the HFA utilizes 10 double determinations of threshold from predetermined stimulus locations. The calculation of SF from 10 double determinations, however, is only a rough indication of the true value (ie within 44% of the true SF at a 95% confidence level) (Bebié et al, 1976b). Consequently, the upper limits of normality for SF are 2.0dB and 2.3dB for the Octopus and Humphrey perimeters respectively. A recent study has demonstrated that the difference in the adaptation levels, however, between the Octopus (4asb) and Humphrey (31.5asb) perimeters does not significantly influence the SF (Crosswell et al, 1991). Conversely, Dengler-Harles and co-workers (1993) found that the interaction of adaptation level and stimulus duration (ie Octopus; 4asb and 100msec respectively: HFA; 31.5asb and 200msec) resulted in a higher mean sensitivity ($p<0.002$) and a higher SF ($p<0.02$) for the Octopus automated perimeter when compared to the HFA.

### 1.7.2. Long-term fluctuation (LF).

Long-term fluctuation is defined as "... the variation in the threshold measurements over time, when the variation due to repeated measurements at a given time has been removed" (Flammer et al, 1983; Flammer et al, 1984b; Flammer, 1985a; Flammer, 1985b). The LF has both homogenous and heterogenous components. Uniform change in sensitivity over the entire visual field is indicated by the homogenous component of the LF, while the heterogenous component reflects localized change in sensitivity over time (Bebié et al, 1976a; Flammer et al, 1983; Flammer et al, 1984c).

An analysis of variance model can be employed to calculate the LF of several test locations:

$$Y_{ilk} = \mu + L_i + V_l + LV_{ik} + E_{ilk}$$

where $Y_{ilk}$ is the threshold measurement of test location i in visual field test l for replication k, $\mu$ is the overall mean value, L (test location) is the effect of the test location and V (visual field) is the effect of the individual field examination. V is mainly determined by the homogenous LF. LV is the interaction between L and V, which is mainly determined by the heterogenous LF. E is the experimental error, or the SF, evaluated on the basis of two replications of threshold (Flammer et al, 1983; Flammer, 1985b).

The LF confounds the interpretation of change in the visual field from one examination to another and is generally attributed to an actual change in the sensitivity of the visual system (Flammer et al, 1983; Flammer, 1985b). The magnitude of LF in the normal eye is approximately 2.0dB (Heijl et al, 1987c). The LF increases, however, with increase in the time interval between visual field examinations (Katz and Sommer, 1986; Krakau, 1991). Furthermore, an increased LF can be an early sign of retinal disease (Zulauf and Caprioli, 1991). The magnitude of the homogenous component of the LF has been found to be significantly higher in glaucomatous and glaucoma suspect patients ($p<0.001$) than in normal subjects (Flammer at al, 1984c). The LF increases with increase in SF, although the association is of only borderline statistical significance (Flammer et al, 1984c). It increases with increase in defect depth (Heijl, 1977a; Flammer et al, 1984b; Crick et al, 1985; Heijl et al, 1989a; Piltz and Starita, 1990; Werner et al, 1991; Zulauf et al, 1991) and also with increase in eccentricity (Heijl et al, 1987c; Rutishauser and Flammer, 1988; Young et al, 1990; Werner et al, 1991; Zulauf et al, 1991). Indeed, the LF exhibited by a single test location of a glaucomatous eye increases by approximately $0.5dB^2$ for each 1.0dB increase in defect depth (Zulauf et al, 1991). Furthermore, an increased LF has been documented in patients with raised intra-ocular pressure, although the association is of only borderline statistical significance (Flammer et al, 1984c). The influence of age on the LF is controversial. Some studies have found an increase in LF with increase in age (Katz and Sommer, 1987), while others have found no association between age and LF (Heijl et al, 1988).

## 1.8. Visual field indices.

Automated perimetry generates a large amount of numeric data. Consequently, visual field indices were developed to aid interpretation, reduce any inherent noise and simultaneously emphasize sensitivity loss (Flammer et al, 1985; Flammer, 1986). Indices are simple global descriptive statistics of the state of the visual field derived from pointwise sensitivity values which can be used to determine whether a particular examination is within normal criteria or whether significant trends have occurred in a series of examinations (Bebié and Fankhauser, 1981). The main use of indices is to quantitatively compare a series of examinations since deviation maps and probability maps provide more information concerning the spatial position of any visual field loss (Heijl et al, 1987b).

### 1.8.1. Mean sensitivity (MS).

The mean sensitivity represents the arithmetic mean of sensitivity of all stimulus locations tested within the visual field.

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

$$\text{where } X_i = {}^{1}/_{n} \cdot \sum_{k=1}^{n} X_{ik}$$

and $X_{ik}$ is the sensitivity at test location i for replication k, $X_i$ is the average local sensitivity at stimulus location i, n is the number of threshold replications (independent measurements within the same examination) and m is the number of stimulus locations. The calculation of MS does not involve any age-matched normal data. MS is particularly sensitive to diffuse visual field damage. If the number of stimulus locations are sufficiently large MS is independent of SF and the homogenous component of LF (Flammer et al, 1983; Bebié, 1985b).

1.8.2. Mean defect (MD).

The mean defect is the arithmetic mean of the difference between the measured sensitivity and normal sensitivity at each of the stimulus locations (Bebié, 1985b; Flammer, 1986). Mathematically MD is the first central moment of the distribution of loss scores (Hirsch, 1985).

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

where $Z_i$ is the age-matched normal sensitivity at stimulus location i. The MD represents the mean depression (or elevation) of the measured field compared to the age-matched normal reference field. Consequently, for a normal field the MD approximates to zero, while a positive value indicates a loss of sensitivity (Augustiny and Flammer, 1985; Flammer et al, 1985). MD is sensitive to diffuse damage but is relatively unaffected by localized loss or SF.

The mean defect of the Octopus perimeter is analagous to the mean deviation (also abbreviated to MD) used in the HFA. The calculation of mean deviation in the STATPAC analysis of the HFA, however, involves the subtraction of the normal age-matched values from the measured threshold and consequently a negative value indicates a loss of sensitivity (Heijl et al, 1987b). Furthermore, the mean deviation is weighted to compensate for the greater variability of threshold at each stimulus location with increase in eccentricity. The more central stimulus locations are given a greater weighting in the calculation of mean deviation compared with the peripheral stimulus locations where the fluctuation of the differential light threshold is greater (Heijl et al, 1987b; Heijl et al, 1987c).

1.8.3. Loss variance (LV).

The loss variance is the intraindividual variance of the distribution of the measured sensitivity minus the sum of the MD and the age-matched normal sensitivity (Bebié, 1985b; Flammer, 1986). Mathematically LV is the second central moment of the distribution of loss scores (Hirsch, 1985).

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

LV represents the degree to which the shape of the measured field departs from normal. A high LV indicates the presence of either focal sensitivity loss (ie an irregular hill of vision) or an increased SF and as a result can be helpful in the detection of early visual field defects (Flammer, 1986). For a normal visual field or a uniformly depressed abnormal visual field the LV approximates to zero (Heijl et al, 1987b). LV can only be expressed as a positive value since the calculation involves squaring each difference (Bebié, 1985b).

The LV of the Octopus perimeter is analagous to the pattern standard deviation (PSD) used in the HFA. PSD, however, is calculated from the standard deviation of the pointwise differences between the measured and the age-matched normal visual fields (Heijl et al, 1987b). Therefore, the PSD and LV have different units, that is dB and $dB^2$, respectively. Furthermore, the calculation of PSD in the STATPAC analysis of the HFA is weighted to compensate for the greater variability of threshold at each stimulus location with increase in eccentricity. The weighting function minimizes the magnitude of the PSD (and SF) in normal subjects (Heijl et al, 1987b) but has been found to slightly increase the PSD and CPSD in patients with primary open-angle glaucoma (Flanagan et al, 1993c).

1.8.4. Corrected loss variance (CLV).

Corrected loss variance is the LV from which is subtracted the square of the measured SF (Bebié, 1985b; Hirsch, 1985; Flammer, 1986).

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

CLV separates real deviation of the shape of the measured field from that due to SF (Flammer et al, 1985; Augustiny and Flammer, 1985; Flammer, 1986). A high CLV indicates the presence of focal sensitivity loss within the visual field. The corrected loss variance of the Octopus perimeter is analagous to the corrected pattern standard deviation (CPSD) used in the HFA (Heijl et al, 1987b). Negative estimates of CPSD are assigned a value of zero since variances cannot be negative (Heijl et al, 1987b).

Flammer and co-workers (1985) found that the relationship between MD and CLV in glaucoma patients was correlated (r = 0.66) and emphasized that an abnormal value of one index could frequently be accompanied by a normal value of the other. In addition, Liao and co-workers (1988) found that the CLV, rather than MS, MD or SF, was the only index that permitted discrimination of ocular hypertensive (OHT) patients from normal subjects. Gollamudi and co-workers (1988) evaluated the use of MD and CLV in patients with established or advancing glaucoma. They found that the relationship between MD and CLV was much weaker (r = 0.32) and that the CLV remained relatively constant as the MD deteriorated over a maximum period of six years. Similarly, Pearson and co-workers (1990) investigated the relationship of MD and CLV both in glaucomatous and OHT patients. The relationship between MD and CLV was found to be weak in OHT patients (r=0.57), statistically significant in glaucoma patients with early to moderate (MD less than 18dB) visual field loss (r=0.92) and poor in glaucoma patients with severe (MD greater than 18dB) visual field loss. Differences in selection criteria and methodology may explain the difference in findings between studies (Pearson et al, 1990).

1.8.5. Third central moment (M3).

The third central moment of the distribution of the deviation of measured sensitivity from age-matched normal sensitivity is sensitive to deviations restricted to a small number of stimulus locations (Brechner and Whalen, 1984; Bebié, 1985b; Hirsch, 1985; Flammer, 1986).

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

By raising the difference between the measured sensitivity and the normal age-matched sensitivity to the third power, a small number of reduced sensitivity values will have an exaggerated influence on the M3. The M3 was suggested to be particularly helpful in the detection of very early visual field defects (Brechner and Whalen, 1984).

1.8.6. Skewness (Q).

Effectively, skewness reveals the same information as the M3 ie Q is sensitive to deviations restricted to a small subset of stimulus locations since the difference between the measured sensitivity and the normal age-matched sensitivity is raised to the third power (Bebié, 1985b; Hirsch, 1985; Flammer, 1986; Pearson et al, 1989).

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

Both the M3 and the Q will be less sensitive to diffuse defects than MD, LV or CLV (Bebié, 1985b; Hirsch, 1985) and have only been reported for use with the Octopus perimeter (Flammer, 1986; Pearson et al, 1989) but can also be applied to other instruments.

Bebié (1985b) and Hirsch (1985) both emphasized that the usefulness of the M3 and the Q was questionable since the indices had not undergone clinical validation. Pearson and co-workers (1989) found no correlation between Q and MD, or between Q and CLV, in OHT and glaucomatous patients. Indeed, repeated testing revealed that positive Q values were not predictive of increasing abnormality as assessed by MD and CLV criteria. It was concluded that the Q was of little or no use in the management of ocular hypertension and glaucoma.

1.8.7. Spatial correlation (SC).

The spatial correlation is the average of the value obtained when the corrected loss at each point is multiplied by the loss at each of its adjacent points (Bebié, 1985b; Flammer, 1986).

$$SC = {}^{1}/_{p} \cdot \sum_{(i,j)} (Z_i - MD - X_i) \cdot (Z_j - MD - X_j)$$

where summation extends over all pairs ( i, j ) and p is the number of pairs involved in the summation. Unlike the indices mentioned so far, SC accounts for the location or clustering of individual stimulus locations with reduced sensitivity (Bebié, 1985b). SC will be largest when two adjacent points exhibit a large sensitivity loss but will be reduced if an

adjacent point exhibits normal sensitivity. In addition, SC will be low if defects are randomly distributed throughout the visual field but will be high if the defects are clustered.

Bebié (1985b) emphasized that the usefulness of SC was questionable since the index had not been clinically validated. Three indices that are a measure of the spatial correlation of visual field loss have been developed (Chauhan and Henson, 1987; Chauhan et al, 1988; Chauhan et al, 1989). SIZ represents the total number of clustered points depressed greater than 5dB below the age-matched normal data. CLUS represents the mean depth of the clustered stimulus locations. PCLUS represents the percentage of mean defect that is clustered (Chauhan et al, 1989). Chauhan and co-workers (1990) employed MD, CLV, SIZ, CLUS and PCLUS to determine the use of visual field indices in detecting changes in the glaucomatous visual field. The indices generally performed very poorly in the detection of visual field deterioration. The most sensitive index of visual field deterioration, however, was PCLUS which still only attained a sensitivity of 65% and a specificity of 74%. Asman and Heijl (1993) developed an index which was sensitive to clustered stimulus locations arranged in an arcuate pattern and was therefore designed to permit the earlier detection of glaucomatous visual field loss. Artifacts were de-emphasized by taking into account the volume of the clustered defect, rather than the area, since deeper defects were more likely to be due to true field loss. The discrimination of normal and glaucomatous eyes was found to be significantly better with arcuate cluster analysis (sensitivity 88%; specificity 98%) than with traditional cluster analysis (sensitivity 69 - 75%; specificity 98%).

1.8.8. Defect volume (DV).

The defect volume employs a three-dimensional representation of the visual field and is defined as the fall in volume of this three-dimensional form due to visual field defects (van den Berg et al, 1985; Langerhorst et al, 1985).

$$DV = VOL_{norm} - VOL_{ind}$$

where $VOL_{norm}$ is the age-matched normal volume and $VOL_{ind}$ is the volume of the measured visual field. A subsequent study has attempted to optimize the determination

of the normal reference visual field (van den Berg et al, 1987) but to date the DV index has not been applied clinically. Volumetric analysis has been employed, however, to study the effects of ageing on the visual field (Suzumura et al, 1985; Jaffe et al, 1986) and to study the effects of learning on static perimetry (Wild et al, 1987b; Wood et al, 1987a).

### 1.8.9. Indices currently under development.

Indices which are currently under development include the diffuse loss (DL) and the learner's index (LI). DL is particularly sensitive to general depression of the visual field (Funkhouser, 1991; Funkhouser et al, 1992) and yields similar information to that of the cumulative defect curve which graphically illustrates the cumulative distribution of the local defect values (Bebié et al, 1989). The interpretation of the cumulative defect curve, however, is subjective and can be ambiguous (Bebié et al, 1989; Funkhouser, 1991; Funkhouser et al, 1992). The DL index has been developed to provide a single numeric value of the magnitude of diffuse visual field loss which, unlike the cumulative defect curve, avoids empirical estimation (Funkhouser, 1991; Funkhouser et al, 1992).

The LI is designed to identify individuals exhibiting learning effects (Asman et al, 1993). It is effectively sensitive to mid-peripheral depression of the visual field which is a characteristic of the typical inexperienced patient. Consequently, the interpretation of unreliable visual field results can be avoided.

## 1.9. Graphical data presentation.

Global visual field indices provide very little information concerning the spatial characteristics of any visual field defect (Heijl et al, 1987b). Consequently, various graphical methods of data presentation have been developed to depict the location, size and depth of any visual field defect. These graphical techniques are designed to aid interpretation, reduce any inherent noise and simultaneously emphasize visual field loss.

1.9.1. Sensitivity value table.

The simplest form of graphical data presentation is the sensitivity value table which shows the threshold sensitivity in decibels at each stimulus location. Locations which have been thresholded twice are represented by two decibel values. The sensitivity value table can be difficult to interpret because of the large amount of unrefined data (Greve, 1982) but can also be particularly useful to locate areas of high SF (Zulauf and Caprioli, 1991). Indeed, Krakau (1978) represented pointwise abnormal sensitivity with a number of zero symbols in order to facilitate the recognition of visual field defects. The sensitivity value table has the advantage, however, that the visual field data is free from mathematical manipulation (Whalen, 1985b).

1.9.2. Grey grid and grey scale.

The grey grid represents the sensitivity with a symbols, such as a squares, at each stimulus location. Symbol shades range from black to white and the darker the symbol the lower the differential light sensitivity (Whalen, 1985b).

Grey scale maps carry the grey grid concept one step further by filling areas between stimulus locations with interpolated symbols (Fankhauser and Bebié, 1979). As with the grey grid, the darker the symbol the lower the differential light sensitivity. Each actual or interpolated sensitivity value is assigned to a symbol generally with a 5dB sensitivity range. As a result, adjacent symbols may represent either a 1dB or 9dB difference in sensitivity (Whalen, 1985b). Due to differences in dynamic range, grey scales are not comparable between instruments (Wild, 1988). The grey scale gives a quick general impression of the visual field (Whalen, 1985b; Weber and Geiger, 1989) but provides a poor representation of diffuse sensitivity loss (Flammer, 1986) and tends to exaggerate the congruence of neurological visual field defects (Whalen, 1985b).

The use of interpolation in automated static perimetry was suggested by Fankhauser and co-workers (1972). Interpolated estimates of sensitivity have been demonstrated to be only slightly less accurate than direct measurements for an interstimulus separation of 6°

or less (Fankhauser and Bebié, 1979). Using rectangular stimulus locations, Weber and Geiger (1989) have shown that interpolation from four points gives the smoothest grey scale appearance but is the least exact method, while linear interpolation (Weber and Spahr, 1976) is the method of choice clinically since the grey scale more closely resembles the accepted morphological appearance of the visual field. A combination of the two methods, that is mixed interpolation, is recommended for research purposes because the results are the most accurate (Weber and Geiger, 1989).

1.9.3. Profile and three dimensional plots.

The profile plot resembles a manual static perimetry profile carried out along a single meridian. Most of the points along the profile plot are interpolated, however, rather than direct measurements of sensitivity (Whalen, 1985b). Three dimensional plots depict the topography of the visual field but the format depends upon the software employed (Wild et al, 1987c). Variables such as stimulus location, sensitivity scaling, resolution and angle of orientation must be standardized to allow comparison between visual fields (Hart and Hartz, 1982; Wild et al, 1987c).

1.9.4. Comparison printout.

The comparison printout of the Octopus perimeter shows the numeric difference at each stimulus location between the measured threshold and the age-matched reference threshold (Whalen, 1985b). The Octopus model of the normal visual field assumes, however, a Gaussian distribution of normal sensitivity deviations, a constant shape of the hill of vision with increasing age and a constant fluctuation (SD ±2.4dB) across the visual field (Bebié et al, 1976a; Fankhauser and Bebié, 1979; Bebié, 1985b; Hirsch, 1985; Le Blanc, 1985). Therefore, the normal values used in the comparison printout are not based on empiric data (Heijl et al, 1987b).

1.9.5. Empiric deviation and probability plots.

Schwartz and Nagin (1985), using the Octopus model of the normal visual field (Heijl and Asman, 1989), were the first to suggest the use of pointwise statistical significance values

for the analysis of automated perimetric data. Heijl and co-workers (1987b) found that the distribution of sensitivity deviations in a sample of 487 normal empirical visual fields, however, were significantly non-Gaussian, that is the distribution exhibited negative skewness and positive kurtosis, and that the fluctuation increased with increasing eccentricity (Heijl et al, 1987b; Heijl et al, 1987c). Furthermore, the shape of the visual field was found to change with age (Heijl et al, 1987b).

In a subsequent study (Heijl and Asman, 1989), the empirical model of the visual field was found to produce greater sensitivity and improved specificity in the separation of glaucomatous and normal visual fields than a Gaussian based model using statistical significance limits derived for each stimulus location, now termed probability plots. Furthermore, as the probability plots were based on empiric data, false-positive defects in the periphery were found to be de-emphasized, while subtle paracentral focal loss was emphasized (Heijl et al, 1987b; Heijl et al, 1989b). Inexperienced or unreliable patients could produce false defects, however, since the empiric data was derived from trained normal subjects that met the standard reliability criteria. This empirical model of the normal visual field was incorporated into the HFA under the name STATPAC and is the basis for the total deviation and pattern deviation plots (Heijl et al, 1987b). A similar empirical model of the normal visual field was developed for FASTPAC. The sensitivity and specificity of empirical analytical programs, however, is determined by the quality of the data employed to establish the normal sensitivity values (Iwase et al, 1989).

The total deviation plot of the HFA illustrates the pointwise difference between the measured threshold and the age-matched normal value (Heijl et al, 1987b; Heijl and Asman, 1989; Heijl et al, 1989b). A numeric display shows the magnitude of the deviation in decibels of each threshold at each stimulus location, while a probability symbol display is utilized to show the frequency of occurrence of each threshold within an age-matched normal population (Asman, 1992). The total deviation plot is sensitive to both generalized and localized sensitivity loss (Haley, 1987; Heijl et al, 1987b; Heijl and Asman, 1989; Heijl et al, 1989b).

The pattern deviation plot of the HFA illustrates the pointwise deviation of the shape of the visual field from the age-matched normal field (Heijl et al, 1987b; Heijl and Asman, 1989; Heijl et al, 1989b). This is achieved by correcting for generalized shifts in the overall sensitivity which emphasizes localized sensitivity loss. Those points that have the highest measured sensitivities are assumed to be unaffected by localized visual field loss. The general sensitivity level for the pattern deviation plot is calculated from the stimulus location with the seventh highest sensitivity having excluded points in areas of the visual field with the highest fluctuation (Heijl et al, 1987b). The pattern deviation plot is illustrated using both numerical and probability symbol pointwise displays.

### 1.9.6. Cumulative defect (Bebié) curve.

The cumulative defect curve provides a cumulative distribution of the pointwise sensitivity values of the G1 examination sorted from left to right in descending order (Bebié et al, 1989). The N5, N95 and N99 curves represent the 5th, 95th and 99th percentiles of distribution of the pointwise sensitivity values of a normal visual field. A normal visual field would be expected to yield a curve between the N5 and N95 curves. The cumulative defect curve differentiates between localized and diffuse visual field loss, but provides no information concerning the topography of any defect and should be used in conjunction with comparison plots or grey scales (Kaufmann and Flammer, 1989).

### 1.9.7. Glaucoma hemifield test.

It can be argued that empiric probability maps may fail to detect subtle early focal loss due to the inherent threshold fluctuation within the normal population values. Focal loss may be detected, however, by means of a comparison with other areas within the same visual field rather than with pointwise normal population values (Heijl and Asman, 1989). This is the basis of the glaucoma hemifield test (GHT) which was introduced to the HFA with the STATPAC 2 update (Heijl et al, 1991b). Five zones in the upper hemifield are compared with five mirror-image zones in the lower hemifield and a score is assigned to each zone based on the percentile deviation in the pattern deviation plot. The percentile deviation score of the five upper zones is compared to the five lower zones to determine whether

these differences fall outside or within the limits of normality (Heijl et al, 1991b). Generalized shifts in sensitivity are also recognized and noted.

## 1.10. Analytical programs.

Despite the introduction of indices and graphical data presentation techniques, experience is required for the interpretation of visual field printouts. Furthermore, the comparison of sequential visual fields is crucial for the determination of progression or regression of ocular disease and to evaluate the efficacy of any treatment. Various analytical programs have been introduced to aid interpretation in both of these tasks.

### 1.10.1. Program Delta.

An early attempt towards the computerized evaluation of serial visual field change was program Delta of the Octopus perimeter (Bebié and Fankhauser, 1981). A paired comparison *t*-test was undertaken to estimate the statistical probability of a difference over serial visual fields for mean sensitivities calculated for a number of sectors within the visual field. Hills and Johnson (1988) subsequently demonstrated, however, that the paired comparison *t*-test had limited clinical use because it was extremely sensitive to small diffuse changes in sensitivity, but highly insensitive to localized sensitivity loss.

### 1.10.2. Octosmart.

The Octosmart program, used in conjunction with program G1 of the Octopus perimeter, was introduced to make visual field evaluation clearer by translating data into evaluative statements concerning the degree of sensitivity loss and the reliability of the patient (Bebié, 1990; Funkhouser et al, 1991). The program provides analytical statements automatically but is unable to answer questions and does not relieve responsibility from the clinician for diagnosis (Bebié, 1990). The Octosmart program has been found to make highly accurate judgements when compared to human observers in cases of obvious field loss (Funkhouser et al, 1991) and avoids the unpredictable, non-standardized

interindividual differences of human observers in borderline cases (Hirsbrunner et al, 1990).

### 1.10.3. STATPAC.

The STATPAC program of the HFA also includes a number of facilities based on empirical data for the analysis of change in serial visual fields (Heijl et al, 1987b). The change analysis feature allows the overview of grey scales, total deviation and pattern deviation probability plots for up to 16 consecutive visual fields. This form of data presentation allows an easy overview of a large amount of data. In addition, box plots are available which provide a five number summary of a given visual field. The line in the middle of the box indicates the median threshold value and the box extends from the fifteenth to the eighty-fifth percentile, while the outlying bars represent the highest and lowest sensitivity values. Serial visual field results are displayed consecutively alongside a normal box plot derived from empiric data (Heijl et al, 1987b). The box plot data presentation technique has been used to develop a system for the classification of glaucomatous visual field defects (Shin et al, 1991). Furthermore, if five or more consecutive visual fields are available, a linear regression analysis of MD is automatically performed. With increasing sensitivity loss MD will become more negative and the series of data points will have a negative slope. The resulting slope and the level of significance of the slope are displayed. This form of data presentation represents a high degree of data reduction (Heijl et al, 1987b).

Improved facilities for the analysis of change in glaucomatous visual fields were introduced with STATPAC 2 (Heijl et al, 1991b). Empirical significance limits of visual field change were established from the repeated thresholding of 51 stable glaucoma patients over a one month period. These limits were employed to derive change probability plots showing the significance of sensitivity change at each stimulus location (Heijl et al, 1991b). The utilization of pathophysiological test-retest data is unique but it does not correct for the homogenous component of LF and as a result statistically significant changes can come and go (Zulauf and Caprioli, 1991). The STATPAC 2 change

probability analysis has been found to correlate well with the interpretation of visual fields by human observers and may indeed offer improved sensitivity and specificity (Tuulonen and Airaksinen, 1991; Morgan et al, 1991).

### 1.10.4. PERIDATA.

PERIDATA was designed for the transmission, storage and processing of visual field data from the Octopus and HFA perimeters (Brusini et al, 1991) and contains a number of unique features. The conformity visual field index assesses the similarity between the shape of a measured scotoma and that of 7 standard patterns stored in the computer (Peridata 6.0). The graphical analysis of numerical trends (GANT) illustrates a cumulative curve of initial sensitivity values and superimposes upon this curve a series of bars which indicate the magnitude and direction of any change in sensitivity of each particular value between the first and last visual field (Peridata 6.0). GANT depicts the amount of change in the visual field between examinations and whether the change has occurred in an area of the field with high or low sensitivity. The graphical analysis of topographical trends (GATT) superimposes the grey scale plots of two fields to illustrate topographical sensitivity changes (Weber and Krieglstein, 1989). Areas of visual field change are indicated by stripes, while areas of high LF are indicated by a chequerboard pattern. The contrast between the stripes is a measure of the magnitude of the change. Horizontal stripes indicate visual field deterioration, while vertical stripes indicate improvement. GATT is limited, however, by the information content of the interpolated grey scale (Weber and Krieglstein, 1989).

Methods of improved analysis for both single and serial visual fields that are currently under development include visual field indices which assess the spatial relationship of sensitivity loss (Asman et al, 1992), the use of neural networks (Kelman et al, 1991; Nagata et al, 1991), the employment of multi-dimensional vector field analysis (Cyrlin et al, 1991) and the pointwise topographical and longitudinal modelling of visual field change using univariate linear regression (Noureddin et al, 1991; O'Brien and Schwartz, 1990;

O'Brien et al, 1991) and polynomial and multiple regression techniques (Wild et al, 1991; Wild et al, 1993).

## 1.11. Extraneous factors.

The differential light threshold is influenced not only by disease and by the inherent subjective nature of the threshold response but also by various extraneous factors (Wild, 1988). Some of these factors, such as refractive error and lens rim artifact, can be avoided by the careful implementation of the examination by the perimetrist. Conversely, unavoidable factors include media opacities since conditions such as glaucoma are frequently associated with the concomitant development of cataract. An understanding of the influence of these factors on the differential light threshold is essential if artifactual attenuation of sensitivity is to be differentiated from that due to a disease process (Wild, 1988; Zulauf and Caprioli, 1991).

### 1.11.1. Age.

Perimetric sensitivity is known to decrease with increase in age. Indeed, studies using manual kinetic perimetry have found a general contraction of isopters with advancing age (Ferree et al, 1929; Goldmann, 1945b; Drance et al, 1967b; Egge, 1984). The rate of decay of sensitivity, however, is equivocal. Some workers (Ferree et al, 1929; Suzumura et al, 1985) have found sensitivity to be relatively stable up to 40 years of age and then to deteriorate with further increase in age, while others (Drance et al, 1967b; Egge, 1984; Williams, 1983) have described a linear deterioration of sensitivity for normal subjects up to 80 years of age. Furthermore, Suzumura and co-workers (1985) found that the decay of sensitivity with increase in age was more pronounced for the central isopters.

The effect of advancing age on manual static perimetry is to produce a uniform depression of the hill of vision (Goldmann, 1945b). Similarly, a deterioration of sensitivity with increase in age has been reported using automated perimetry (Haas and Flammer, 1985; Jaffe et al, 1986; Brenton and Phelps, 1986; Katz and Sommer, 1986; Iwase et al,

1988; Collin et al, 1988), although Jacobs and Patterson (1985) were unable to demonstrate any loss of sensitivity with increasing age. As with manual perimetry, the rate of decay of sensitivity is equivocal. Numerous studies have found a linear relationship between deterioration of sensitivity and age (Haas and Flammer, 1985; Jaffe et al, 1986; Brenton and Phelps, 1986), while more recent studies have described a deterioration of sensitivity only after 40 years of age (Iwase et al, 1988; Collin et al, 1988). Furthermore, the influence of ageing on the sensitivity gradient is also controversial. Some studies have found a steepening of the sensitivity gradient with increase in age (Katz and Sommer, 1986; Jaffe et al, 1986), while others suggest a uniform depression of sensitivity (Brenton and Phelps, 1986; Iwase et al, 1988). Conversely, Haas and co-workers (1986) found that the pericentric area deteriorated to a lesser extent than either the centre or periphery within 30° eccentricity and that the upper hemifield deteriorated to a greater extent than the lower hemifield. A greater deterioration of sensitivity in the upper hemifield has also been described by Katz and Sommer (1986). In addition, Collin and co-workers (1988) found that sensitivity decay with increasing age was greater within 30° eccentricity up to 40 years of age and was greater between 30° and 60° eccentricity up to 60 years of age.

The deterioration of sensitivity with advancing age can be explained by numerous factors including an increase in the optical density of the ocular media (van Norren and Vos, 1974; Pokorny et al, 1987), a decrease in pupil diameter (Weale, 1991), a decrease in the density of the photopigments (van Norren and van Meel, 1985) and the loss of neural components involved in the transmission of visual impulses (Marshall, 1985). Johnson and co-workers (1989) separated preretinal from neural factors and concluded that the deterioration of sensitivity in the normal eye with advancing age can be primarily explained by neural losses.

### 1.11.2. Media opacity.

Media opacities result in the attenuation of the differential light threshold due to both light absorption and light scatter. Light absorption will reduce the intensity of both the

background and stimulus but light scatter is recognized to be the main cause of image degradation (Greve, 1980b; Bettelheim and Ali, 1985). In clinical practice, the commonest cause of media opacity is cataract but other causes of image degradation, such as corneal dystrophy (Faschinger, 1987) are potential sources of perimetric attenuation.

Various studies have shown that the effect of cataract on manual kinetic perimetry is to produce a concentric contraction of the isopters, pseudo scotomata and to exaggerate existing focal loss (Lyne and Phillips, 1969; Bigger and Becker, 1971; Radius, 1978; Greve, 1980b). The attenuating effects of cataract can be minimized, however, by the use of larger stimuli (Radius, 1978; Greve, 1980b). Furthermore, it has been demonstrated that the effect of cataract on semi-automated static perimetry is to produce a general reduction in sensitivity which is more marked for central stimulus locations (Greve, 1973; Greve, 1980b).

The effect of cataract on automated static perimetry has been assessed using methodologies which attempt to simulate the optical effects of cataract, or which compare the difference in perimetric attenuation between eyes in patients with unilateral cataracts or which compare the difference in perimetric attenuation in pre- and postoperative intra-ocular lens implant patients. Methodologies which attempt to simulate the optical effects of cataract include the use of neutral density filters (Heuer et al, 1987; Eichenberger et al, 1987; Baldwin and Smith, 1987; Heuer et al, 1989), diffusing filters (Urner-Block, 1987; Heuer et al, 1987; Eichenberger et al, 1987; Heuer et al, 1988; Budenz et al, 1993) and latex beads suspended in solution (Wood et al, 1987b; Wood et al, 1987c; Dengler-Harles et al, 1990).

The employment of neutral density filters produced a uniform depression of the automated static visual field (ie a deterioration of MS and MD) (Heuer et al, 1987; Heuer et al, 1989) which was most marked for central stimulus locations resulting in an increase in localized loss (ie a deterioration in LV) in normal subjects (Eichenberger et al, 1987). Neutral density filters do not provide a good simulation of the optical effects of cataract,

however, since they absorb rather than scatter light (Baldwin and Smith, 1987). Similarly, the use of diffusing filters produced a uniform depression of the automated static visual field (ie a deterioration of MS and MD) (Heuer et al, 1988) which was most marked for central stimulus locations (Urner-Block, 1987; Eichenberger et al, 1987). In addition, sensitivity decreased with increase in light scatter. The influence of diffusing filters in the presence of focal sensitivity loss, however, is equivocal. Urner-Block (1987) found an apparent reduction in the magnitude of localized loss (ie an improvement of CLV) with diffusing filters, whilst Budenz and co-workers (1993) found little difference in perimetric attenuation resulting from diffusing filters both within "normal" and focal loss areas of the glaucomatous visual field. Furthermore, light scatter which has minimal influence on visual acuity can result in the significant attenuation of perimetric sensitivity (Heuer et al, 1988). This finding is in agreement with that of van den Berg (1987) who measured the effect of media disturbances on the point spread function and concluded that perimetric attenuation could be reduced by the use of larger diameter stimuli.

Induced intra-ocular light scatter using latex beads (500nm diameter) suspended in solution was found to result in an overall depression of perimetric sensitivity and to steepen the Octopus perimetric profile and flatten the Dicon profile of normal subjects (Wood et al, 1987b; Wood et al, 1987c). The steepening of the Octopus profile was explained by the use of a size III (0.431°) stimulus which was considered to saturate the central visual field and be relatively insensitive to the effects of light scatter. Attenuation of sensitivity was also found to be greater at lower bowl luminances using the Dicon perimeter (Wood et al, 1987b; Wood et al, 1987c). The magnitude of perimetric attenuation was highly correlated with forward intra-ocular light scatter as assessed by contrast sensitivity in the presence and absence of a glare source. In the glaucomatous eye, induced intra-ocular light scatter was found to decrease MS linearly and decrease LV curvilinearly (Dengler-Harles et al, 1990). The change in LV, however, was explained by the failure to account for the effects of light scatter on the format of the normal reference age-matched data. After correction for this artifact MD decreased linearly, while CLV remained unchanged. This suggests that forward light scatter results in the uniform loss

of sensitivity (Dengler-Harles et al, 1990), while the apparent under estimation of localized loss reported by a previous study (Urner-Block, 1987) is a calculation artifact. Indeed, computer simulation of glaucomatous visual fields suggests that an increase in MD without alteration of CLV should occur as a result of cataract development (Augustiny and Flammer, 1985). The model of perimetric attenuation arising in the normal eye (Wood et al, 1987b; Wood et al, 1987c) was compared with that arising from unilateral cataract (Wood et al, 1987b; Wood et al, 1989). Non-nuclear cataracts produced a steepening of the Octopus perimetric profile and a flattening of the Dicon profile, while nuclear cataracts produced a flattening of the perimetric profile for both the Octopus and Dicon automated perimeters.

Studies which have compared the results of automated static perimetry (Octopus program G1) to either Scheimflug densitometry (Guthauser et al, 1987; Guthauser and Flammer, 1988) or to photopapillometry (Hendrickson et al, 1987) techniques in pre- and postoperative intra-ocular lens implant patients have found that the effect of cataract is to produce a diffuse reduction in sensitivity which is more marked for central stimulus locations. Post-operative improvement in MS has been found to be highly correlated ($r=0.9$; $p<0.001$) with the magnitude of backward light scatter (Guthauser et al, 1987; Guthauser and Flammer, 1988), but not to be as pronounced as the improvement in imaging quality as shown by photopapillometry (Hendrickson et al, 1987). The influence of cataract on the visual field might be predicted, therefore, by the measurement of backward light scatter from the crystalline lens (Guthauser and Flammer, 1988; De Natale et al, 1988). This technique assumes that the magnitude of backward and forward light scatter are related since image degradation in the presence of media opacities primarily occurs due to forward light scatter (Bettelheim and Ali, 1985). The measurement of backward light scatter in cases of posterior subcapsular cataracts, however, shows poor correlation with the improvement in the postoperative visual field (De Natale and Flammer, 1989).

In pre- and postoperative intra-ocular lens implant patients with otherwise normal eyes, cataract has been shown to produce a uniform depression of the automated static visual field since the postoperative percentage threshold recovery did not vary with eccentricity and PSD did not change systematically between pre- and postoperative examinations (Lam et al, 1991). Conversely, a similar study of the influence of cataract in otherwise normal subjects and in glaucomatous patients concluded that the differential light threshold showed a wide variance to the extent that CLV could not clearly separate glaucomatous from cataractous visual field damage (Heider et al, 1991).

### 1.11.3. Pupil size.

Variation in pupil size will change the intensity of both the perimetric stimulus and background. Consequently, the contrast of the stimulus will be unchanged. Stimulus detection is dependent, however, upon the state of retinal adaptation. At photopic levels, variation in pupil size will have minimal effect upon stimulus detection whilst at mesopic levels variation in pupil size will induce change in sensitivity. The state of retinal adaptation at the background luminances commonly employed in perimetry, however, is equivocal (Aulhorn and Harms, 1972; Greve, 1973; Wood et al, 1988a; Fankhauser, 1979; Flanagan et al, 1991). In addition, diffraction (Mikelberg et al, 1987; Lindenmuth et al, 1989) and depth of focus (Mikelberg et al, 1987) have been suggested as factors that may influence the differential light threshold as a result of variation in pupil size.

Drug induced miosis has been demonstrated to result in the contraction of isopters (Ferree et al, 1934; Engel, 1942; Day and Scheie, 1953) and also to produce pseudo glaucomatous focal loss and the exaggeration of existing focal loss (Engel, 1942; Forbes, 1966). Conversely, information gained from clinical data suggested that change in pupil size has a negligible effect on the manual kinetic visual field (Drance et al, 1967b; Williams, 1983). Subsequent studies have demonstrated, however, that the extent of the manual kinetic visual field decreases with reduction in pupil size (McCluskey et al, 1986; Nugent et al, 1987; Gabriel et al, 1988).

Greve (1973) demonstrated that a 4mm reduction in the pupil diameter of normal subjects resulted in a 0.2 log unit uniform depression of sensitivity, while Bedwell and Davies (1977) found a 0.14 log unit depression of sensitivity for a 6mm reduction in pupil diameter. Similarly, using the Octopus automated perimeter, Fankhauser (1979) found a 2dB decrease in the MS of normal subjects out to 30° eccentricity. Furthermore, using automated perimetry drug induced miosis has been demonstrated to accentuate glaucomatous visual field loss (De Natale et al, 1984). Physiological inter-individual variations in pupil size, however, have been shown not to influence the magnitude of MS (Brenton and Phelps, 1986) or SF (Flammer et al, 1984a) using automated static perimetry.

Subsequent studies utilizing automated perimetry have found a deterioration in sensitivity with induced miosis for both normal subjects (Mikelberg et al, 1987; Wood et al, 1988a; Lindenmuth et al, 1989) and glaucoma patients (Rebolleda et al, 1992). These results are explained by a concomitant reduction in retinal luminance with pupil miosis (Heuer et al, 1987; Heuer et al, 1989). Furthermore, the loss of sensitivity with induced miosis has been demonstrated to be greater for peripheral stimulus locations (Wood et al, 1988a; Rebolleda et al, 1992). Conversely, Lindenmuth and co-workers (1990) found a significant deterioration of MD ($p=0.001$) and CPSD ($p=0.006$) in normal subjects as a result of induced mydriasis.

### 1.11.4. Interocular asymmetry.

The extent to which the two visual fields of an individual are symmetrical is an important consideration in perimetry because between eye comparisons of data are frequently made in cases of unilateral or asymmetric disease. Indeed, using program 30-2 of the HFA, Brenton and co-workers (1986) found that pointwise asymmetry between the two visual fields of normal subjects ranged from 0.0dB to 9.0dB with the greatest difference occurring in the superior hemifield. A pointwise asymmetry exceeding 6.0dB was found to occur for fewer than 1% of stimulus locations, while an asymmetry of global MS exceeding 1.4dB was found to occur for fewer than 1% of normal subjects. Furthermore,

Rutishauser and co-workers (1989) found that the root mean square values for the component of variance attributable to differences between the two eyes of a normal individual, as assessed with program JO of the Octopus perimeter, lay between 0.0dB and 3.3dB depending on the test location. In addition, using program 30-2 of the HFA, Feuer and Anderson (1989) determined that the MS was effectively identical between the two eyes of a normal subject ie the difference in MS between the two eyes (0.65dB) was less than the measurement error incurred for testing the same eye twice (0.70dB). Confidence limits were established for the definition of abnormality. Abnormality was indicated by a 2.0dB between-eye difference in MS at a single examination, or by a 1.5dB between-eye difference in MS confirmed at a second examination, or by a 1.0dB between-eye difference in MS exhibited over four examinations (Feuer and Anderson, 1989).

### 1.11.5. Learning and fatigue.

Learning and fatigue effects, whereby sensitivity increases and decreases respectively during and between examinations, are known to influence the magnitude of the differential light threshold. Both factors are reviewed fully in Chapter 4.

### 1.11.6. Refractive defocus.

A defocused stimulus will result in diminished contrast and decreased intensity of the retinal image since the stimulus is spread over a greater area of the retina. Indeed, Ogle (1960) found that foveal sensitivity decreased with increasing defocus, but that the effect was reduced for larger diameter stimuli. Similarly, Ronchi and Barca (1981) demonstrated that the use of either larger diameter or longer duration stimuli reduced the attenuation of sensitivity due to optical defocus, particularly with increase in eccentricity. An increase in spatial and temporal summation with increase in eccentricity was proposed to explain the resistance to optical defocus. Furthermore, optical defocus has been demonstrated to reduce contrast sensitivity over a broad range of spatial frequencies (Marmor and Gawande, 1988).

It was recognized at an early stage in the development of kinetic perimetry that failure to correct ametropia led to a reduction in the extent of the visual field (Ferree et al, 1929). Serra (1983) found that 2.50 diopters sphere of refractive defocus resulted in a 50% reduction of the II2e manual kinetic isopter, while Benedetto and Cyrlin (1985) have also reported an overall depression and an exaggerated loss of central sensitivity (ie a flattening of the island of vision) of the kinetic visual field as a result of defocus.

An increase in the attenuation of sensitivity within 30° eccentricity with increase in refractive defocus has also been shown for both manual (Sloan, 1961; Fankhauser and Enoch, 1962; Atchison, 1987) and automated (Fankhauser, 1979; Benedetto and Cyrlin, 1985; Weinreb and Perlman, 1986; Goldstick and Weinreb, 1987; Heuer et al, 1987) static perimetry. Furthermore, the attenuation of sensitivity due to defocus is reduced with increase in stimulus size (Sloan, 1961; Fankhauser, 1979; Atchison, 1987) and with increase in eccentricity (Sloan, 1961; Fankhauser and Enoch, 1962; Maguire, 1971; Atchison, 1987; Benedetto and Cyrlin, 1985). In effect, a sinking and a flattening of the island of vision with refractive defocus has been described (Benedetto and Cyrlin, 1985). Conversely, using automated perimetry Goldstick and Weinreb (1987) found a deterioration in MD with defocus, while CLV and SF remained largely unaffected. In automated perimetry, however, the attenuation of sensitivity attributable to peripheral refractive error can be ignored (Wild, Wood and Crews, 1988). In addition, the attenuation of sensitivity due to defocus for the high pass resolution perimeter (Frisén, 1987) is particularly pronounced due to the complex stimulus employed in this instrument (House et al, 1990).

The effect of refractive defocus due to accommodative microfluctuations is equivocal. Tate (1985) suggested that accommodative microfluctuations resulted in a depression of central sensitivity, while Wood et al (1988b) found that the magnitude of sensitivity loss due to accommodative microfluctuations was minimal within 5° eccentricity and insignificant between 5° and 27.5° eccentricity.

The trial lens used to correct ametropia can be a source of perimetric attenuation due to prismatic effects (Greve, 1973; Atchison and Johnston, 1979; Miller and Gelber, 1990) or lens rim artifact (Zalta, 1989). Greve (1973) calculated that a +15.00 diopters sphere corrective lens could induce an alteration in stimulus position of 2.5° at an eccentricity of 12°, while Atchison and Johnston (1979) suggested that corrective lens powers between -6.00 and +10.00 diopters sphere at a vertex distance of 14mm could result in a 3dB attenuation of perimetric sensitivity for Goldmann stimulus size I. Consequently, the use of contact lenses to correct high ametropic and aphakic patients for perimetry has been recommended (Zalta, 1989; Miller and Gelber, 1990).

1.11.7. Medication and drugs.

Gandolfo (1983) studied the effect of a blood alcohol level of 0.05% on both manual kinetic and static perimetry. Perimetry was carried out at photopic and mesopic adaptation levels and a critical flicker fusion frequency technique was also employed. The ingestion of alcohol resulted in an increased central sensitivity for both photopic and mesopic static perimetry, enlargement of the blindspot and angioscotomata, contraction of kinetic peripheral isopters and a deterioration of critical flicker fusion frequency. The results can also be explained by flaws in the experimental design, however, since the subjects were untrained, the order of examinations was not randomized and a control condition was not employed.

Riedel (1985) employed program 51 of the Octopus automated perimeter to assess the effect of a high blood alcohol level (greater than 1‰) on the differential light threshold. A significant decrease in sensitivity of the peripheral temporal (60°-90°) visual field was reported in addition to a concentric contraction. Furthermore, significant increases were found in the SF and in the number of false-positive and false-negative responses. Zulauf and co-workers (1986) found that perimetric sensitivity within 30° eccentricity (Octopus program JO) was not influenced by a blood alcohol level of 0.08% in untrained subjects. A significant increase, however, in the number of false-positive responses was reported ($p=0.05$). A trend towards an increased number of false-negative responses, a higher SF

and an increased number of stimulus presentations was also noted. Using program 30-2 of the HFA, Wild and co-workers (1990) found a 1.0dB increase in MD ($p=0.002$) and a $0.6dB^2$ increase in the PSD ($p=0.003$) and CPSD ($p=0.046$) in trained normal subjects with on average a blood alcohol level of 69.5mg%. In addition, the number of stimulus presentations increased by 6% ($p=0.006$) and the number of false-negative responses increased by 4% ($p=0.019$). The change in sensitivity represented a sinking and a steepening of the island of vision ($p=0.046$).

Haas and Flammer (1985) determined the effect of a 5mg and 10mg diazepam dosage four hours before perimetry on the central visual field (program JO) of normal subjects using the Octopus automated perimeter. The influence of short-term diazepam therapy was found to be statistically insignificant, although there were general trends towards an increase in sensitivity, an increase in reaction time, a reduction in the number of false-positive responses and an increase in the number of false-negative responses. In addition, Mann and co-workers (1989) could find no effect of chloroquine and hydroxychloroquine on the visual field indices MS, MD, SF and CLV using program JO of the Octopus perimeter. Similarly, both CNS and non-CNS acting anti-histamine drugs have been found to have a minimal effect on the central visual field (HFA program 30-2) of trained normal subjects (Wild et al, 1989). Although the global SF was found to be significantly higher for the non-CNS acting anti-histamine ($p<0.05$), the effects on the other parameters did not reach statistical significance.

Martin and Rabineau (1987) could find no measurable effect on the visual field of topical guttae timolol 0.5% using program G1 of the Octopus perimeter. Topical timolol therapy is thought to reduce the incidence of glaucomatous damage in OHT patients (Epstein et al, 1989; Kass et al, 1989). The relative effects, however, of various topical beta-blockers on the visual field is controversial. Messmer and co-workers (1991) assessed the effect of betaxolol 0.5% and timolol 0.5% on the visual field (Octopus program G1) of 40 patients with primary open-angle glaucoma. The visual fields of both groups tended to improve during the first 6 months of treatment but the betaxolol treated group showed greater

improvement (p=0.041). Subsequently, Flammer and co-workers (1992) could find no difference in the treatment effect between carteolol and timolol in 142 patients with primary open-angle glaucoma.

1.11.8. Other factors.

Facial features such as deep-set eyes and lid ptosis can influence the differential light threshold (Fisher, 1967). Using automated perimetry, upper lid ptosis in particular has been demonstrated to result in a depression of the superior visual field close to fixation (Meyer et al, 1993). In addition, a diurnal variation in visual field sensitivity of approximately 0.5dB in normal subjects has been documented (Mizutani and Suzumura, 1985). The diurnal variation was found to be higher in OHT (ie greater than 1.0dB) and glaucoma patients (ie greater than 1.5dB) than in normal subjects and was suggested to be related to fluctuations in intra-ocular pressure.

# CHAPTER 2. RATIONALE AND LOGISTICS.

## 2.1. Aims of the study.

The study had two broad concurrent aims. Firstly, to expand the work previously undertaken within the Department of Vision Sciences, Aston University, Birmingham, using conventional automated perimetry with particular reference to statokinetic dissociation and to within-test changes in sensitivity. Secondly, to develop a system for blue-on-yellow perimetry for application in various ocular conditions but particularly with reference to diabetic maculopathy.

## 2.2. Rationale.

Research within the Department by Wood and co-workers (1986a) had shown that retinitis pigmentosa patients exhibited a relative sparing of sensitivity to kinetic stimuli in the presence of a marked reduction of sensitivity to static stimuli; a phenomenon termed statokinetic dissociation. Other researchers had also documented statokinetic dissociation in numerous diseases affecting all levels of the visual pathway (Zappia et al, 1971; Safran and Glaser, 1980; Plant and Wilkins, 1988; Wedemeyer at al, 1989; Osako et al, 1991a and b). In addition, a "physiological" statokinetic dissociation was known to occur in some normal subjects (Fankhauser and Schmidt, 1960; Safran and Glaser, 1980; Wedemeyer at al, 1989; Osako et al, 1991a and b). The only dedicated study which had systematically examined physiological statokinetic dissociation, however, had utilized manual perimetry (Fankhauser and Schmidt, 1960). Furthermore, the incidence, magnitude and factors influencing physiological statokinetic dissociation were unclear and the extent to which this physiological function might contribute to statokinetic dissociation in visual pathway abnormality was also equivocal. The aim of the study was to investigate physiological SKD as a function of age, meridian, stimulus size and eccentricity using the HFA 640. The HFA 640 was a recently introduced automated

perimeter which was capable of both kinetic and static perimetry and which provided identical stimulus conditions for each method of visual field assessment.

A considerable proportion of the automated perimetry research carried out within the Department had examined within- and between-test changes in sensitivity (Wood et al, 1987a; Wild et al, 1989 and 1991; Searle et al, 1991). In particular, the study of Searle and co-workers (1991) had described a progressive decline in sensitivity both within- and between-eyes during the time course of a single perimetric examination; a phenomenon termed the fatigue effect. These findings were in agreement with the results of other researchers (Heijl, 1977b and c; Johnson et al, 1988a). In all of these studies, the fatigue effect was assessed by repeatedly thresholding a limited number of stimulus locations. The effect of fatigue on the entire visual field within 30° eccentricity, however, was unknown. The aim of the study, therefore, was to determine the time course of the fatigue effect during a routine visual field examination. The introduction of the Octopus 1-2-3 facilitated the assessment of within-test changes in sensitivity since the examination procedure with this perimeter was divided into 8 distinct and separate stages; the stimulus locations within a given stage were thresholded before the start of the ensuing stage and were, in general, randomly distributed across the visual field.

The second half of the study was devoted to a relatively new method of visual field investigation, namely blue-on-yellow perimetry. The technique employs a blue stimulus to preferentially stimulate the short wavelength sensitive (SWS) cones and a high luminance yellow background to saturate the remaining retinal receptors. Initial studies of blue-on-yellow perimetry had suggested that the technique permitted the detection of glaucomatous visual field loss at an earlier stage of the disease process than conventional white-on-white perimetry (Johnson et al, 1993a and b; Sample et al, 1993a). Furthermore, laboratory based studies had demonstrated a reduction of SWS sensitivity before achromatic sensitivity loss in a variety of other ocular diseases including diabetic retinopathy (Adams et al, 1987a; Greenstein et al, 1989a; Greenstein et al, 1992), age-related maculopathy (Applegate et al, 1987; Haegerstrom-Portnoy and Brown, 1989) and

retinitis pigmentosa (Greenstein et al, 1989a). The clinical relevance of blue-on-yellow perimetry in the investigation of these conditions was unknown.

Short-wavelength stimuli are preferentially absorbed in the normal eye by the pre-receptoral filters, namely the components of the ocular media and the macular pigment. In addition, the magnitude of pre-receptoral absorption exhibits considerable between-subject variation which confounds the interpretation of SWS sensitivity.

Diabetic retinopathy is the leading cause of blindness among adults of working age in the Western World (Klein, 1988) and diabetic maculopathy in particular is one of the commonest causes of loss of visual function in diabetic patients. Prompt laser photo-coagulation, however, can halt the further progression of diabetic maculopathy (Verougstraete, 1988). Diabetic maculopathy was selected for study since the assessment of SWS sensitivity may permit the earlier detection of visual dysfunction than the procedures currently available particularly that of visual acuity (Zwas et al, 1980; Adams, 1982; Zisman and Adams, 1982; Adams et al, 1987a; Greenstein et al, 1989a; Greenstein et al, 1990 and 1992) and therefore enable earlier medical intervention.

The aim of the second part of the study was to develop a technique for blue-on-yellow perimetry, to investigate the influence of pre-receptoral absorption on the blue-on-yellow hill of vision and to apply the procedure to cases considered to be at risk of developing diabetic maculopathy. The study of blue-on-yellow perimetry necessitated the modification of a commercially available HFA 640. In addition to the hardware modifications, experiments were undertaken, firstly, to determine the peak wavelength of the SWS spectral sensitivity function with the chosen background conditions and having defined the stimulus wavelength, secondly, to ensure and quantify the magnitude of SWS isolation. The investigation of pre-receptoral absorption was also undertaken with this particular stimulus.

Modifications were also made to the HFA for the assessment of pre-receptoral absorption. A clinical procedure was already established for the assessment of ocular media absorption based on the determination of scotopic sensitivity (Sample et al, 1988a; Johnson et al, 1988b). As a result of the current study, suggestions were made to reduce the influence of ocular media absorption since the scotopic sensitivity procedure was found to be time consuming. In addition, the influence of macular pigment on the blue-on-yellow hill of vision required investigation if blue-on-yellow perimetry was to be employed for the assessment of visual function within the macula region. Macular pigment absorption was assessed utilizing a previously described psychophysical procedure which was considered suitable for application with the HFA (Pease et al, 1987).

In the diabetic study a number of control stimulus and background combinations were utilized in addition to blue-on-yellow perimetry. An alternative stimulus filter, with a broader spectral transmission, was employed for this aspect of the study since it permitted a greater dynamic range and had previously been shown to provide adequate SWS isolation (Johnson et al, 1988b). Furthermore, the employment of a filter with a broader spectral transmission reduced the attenuation of sensitivity due to the macular pigment. It was recognized that the macular pigment assessment procedure was unsuitable for application in diseased eyes since it depended on the underlying assumption of normal spectral sensitivity.

## 2.3. Logistics.

The research was carried out within the Department of Vision Sciences, Aston University, Birmingham and the study had approval from the Aston University Human Science Ethical Committee and where applicable from the East Birmingham Health Authority Research and Ethics Sub-Committee.

Normal control subjects were recruited from old age pensioner associations and from students and staff of the University. The nature of the procedures were fully explained

both with an information sheet and verbally and on arrival subjects were requested to sign a consent form.

Ocular hypertensive patients were recruited from the Birmingham and Midland Eye Hospital (BMEH) and were selected with the full cooperation of the consultant ophthalmologist who provided confirmation of diagnosis and ensured that volunteers satisfied the necessary inclusion and exclusion criteria. Patients were required to attend the Department for one visit but all had previously under gone numerous examinations with the HFA. Initial contact was made by letter which explained the nature of the procedures involved. Patients were requested to return a form stating whether or not they were prepared to volunteer for the study. Appointments were then made by telephone and confirmed by letter.

Diabetic patients were recruited from the Birmingham Heartlands Hospital (formerly East Birmingham Hospital) and were selected by research nurses with the full cooperation of the consultant diabetic physician and consultant ophthalmologist who provided confirmation of diagnosis and ensured that volunteers satisfied the necessary inclusion and exclusion criteria. The recruitment procedures were identical to those of the ocular hypertensive patients. Patients were required to attend the Department for four appointments and subsequently to attend the Birmingham Heartlands Hospital for retinal photography within a maximum period of two weeks after the last appointment at the Department. The consultant ophthalmologist considered that fluorescein angiography of patients within the study was not appropriate on ethical grounds. Blood sugar level was recorded at the end of each visit to the Department.

There were few logistical problems associated with the project. Recruitment of the diabetic subjects proved to be difficult, however, due to the fact that four appointments were required from each volunteer. Access to the modified HFA 640 was shared equally with a concomitant study of blue-on-yellow perimetry in glaucoma and ocular hypertension but this did not create any difficulties.

# CHAPTER 3. THE ASSESSMENT OF PHYSIOLOGICAL STATOKINETIC DISSOCIATION.

## 3.1. Introduction.

Statokinetic dissociation (SKD) describes a reduced sensitivity to a static stimulus relative to the identical kinetic stimulus in clinical perimetry.

This phenomenon was first reported by Riddoch (1917) using manual perimetric techniques in 9 patients with occipital lobe injuries. Moving stimuli were readily detected in areas of the visual field that exhibited severely depressed or an absence of sensitivity to stationary stimuli of equivalent size. It was hypothesized that motion perception and form and colour perception were mediated by different areas of the occipital cortex. This dissociation of functions, therefore, resulted in the total preservation of motion perception mechanisms and SKD was a phenomenon limited to lesions of the occipital cortex. Furthermore, the absence of SKD was considered to be a poor prognostic sign for recovery.

SKD has been confirmed in patients with lesions of the occipital cortex (Holmes, 1918; Plant and Wilkins, 1988; Charlier et al, 1989; Finkelstein and Johnson, 1989; Yabuki et al, 1989), but has also been documented in patients with lesions of the optic radiations (Plant, 1986; Yabuki et al, 1989), optic tract (Zappia et al, 1971; Bender and Bodis-Wollner, 1978), optic chiasma (Zappia et al, 1971; Safran and Glaser, 1980; Charlier et al, 1989; Yabuki et al, 1989) and optic nerve (Safran and Glaser, 1980; Charlier et al, 1989; Yabuki et al, 1989). It has also been documented in retinitis pigmentosa (Wood et al, 1986a), optic neuritis (Wedemeyer et al, 1989; Osako et al, 1991a; Osako et al, 1991b) and glaucoma (Katsumori et al, 1991).

3.1.1. Mechanisms of SKD in visual pathway abnormality.

Holmes (1918) found that sensitivity to a moving stimulus in cases of occipital cortex injury was usually restricted to particular areas of the scotoma. It was argued that rather than a complete preservation of motion sensitivity, SKD represented a relative loss of form sensitivity. Motion sensitivity was regarded as being more resistant to disease or injury although both functions exhibited diminished sensitivity. Indeed, only one of the cases described by Riddoch (1917) exhibited SKD over the whole area of the scotoma; in all other cases SKD was restricted to subregions of the scotoma. Furthermore, in discussions of the Riddoch phenomenon both Polyak (1957) and Teuber and co-workers (1960) suggested that SKD could be explained by an increased fragility of the form detection mechanisms.

Using Goldmann perimetry Zappia and co-workers (1971) demonstrated SKD in a patient with a lesion of the optic tract and in a patient with a lesion of the optic chiasma. They concluded that SKD was not limited to lesions of the occipital cortex and had no prognostic significance for recovery. SKD was explained by a relative loss of form sensitivity. An association of SKD with an enhanced local adaptation or Troxler effect to static stimuli (Bay, 1953) or a fatigue effect with repeated static presentations (Sunga and Enoch, 1970) was also suggested.

Safran and Glaser (1980) demonstrated SKD for the achromatic detection of white and red stimuli using Goldmann perimetry in normal subjects and in patients with lesions of the anterior visual pathway. Evidence from electrophysiological and psychophysical studies also suggested that kinetic stimuli were detected by movement-dependent channels (analagous to Y-type, transient, phasic, M-cell) that responded preferentially to temporally changing stimuli of low spatial frequency, while static stimuli were detected by movement-independent channels (analagous to X-type, sustained, tonic, P-cell) that were responsible for the perception of spatial contrast, form and colour (Ikeda & Wright, 1972a; Kulikowski & Tolhurst, 1973; Tolhurst, 1973). Furthermore, the receptive fields of the movement-dependent channels were proposed to be larger with expandable borders

(Ikeda and Wright, 1971; Ikeda & Wright, 1972a; Ikeda & Wright, 1972b). SKD was explained by a selective loss of the movement-independent channels. The detection of moving stimuli at the edge of scotoma was attributed to the larger receptive fields of the movement-dependent channels. SKD was not demonstrated, however, when the end point was the colour recognition of red stimuli. This latter finding was attributed to the processing of colour information through the movement-independent channels.

The effect of varying stimulus parameters and test conditions for 17 patients with retinitis pigmentosa was studied by Wood and co-workers (1986a) using manual static, automated static and manual kinetic perimetry. All 17 patients exhibited SKD and the magnitude of this function increased with increase in stimulus size. An enhanced spatial summation was speculatively proposed to explain the mechanism of SKD in retinitis pigmentosa.

The spatial and temporal properties of patients exhibiting SKD were investigated using sinusoidal wave gratings by Plant (1986) and Plant and Wilkins (1988). It was reasoned that conventional perimetric techniques were unsuitable for determining the underlying mechanism of SKD because the ability to detect a moving stimulus was velocity dependent (Johnson and Keltner, 1987). A preferential loss for stimuli of high spatial and low temporal frequencies was found in a patient with an optic radiation lesion (Plant,1986) and in a patient with an occipital cortex lesion (Plant and Wilkins, 1988) despite an overall reduction in contrast sensitivity. The results suggested a relative sparing of mechanisms responsible for the detection of low spatial and high temporal frequency stimuli rather than a separate pathway. Direction discrimination was also demonstrated suggesting that the residual mechanisms subserved motion perception (Plant and Wilkins, 1988). The existence, however, of a functionally distinct but anatomically contiguous pathway for the detection of moving stimuli was not excluded.

The velocity dependent characteristics of SKD were studied by Wedemeyer and co-workers (1989) using automated perimetry and a Goldmann size I stimulus in normal subjects and patients with a history of optic neuritis. Although both groups exhibited

SKD, the magnitude was found to be relatively large for optic neuritis patients and to be independent of stimulus velocities between 1° and 8° per second both for normal subjects and for optic neuritis patients. A selective loss of function of the tonic (X-type, sustained, P-cell) ganglion cells was suggested to explain the mechanism of SKD in optic neuritis. Indeed, chromatic and flicker sensitivity studies have suggested a selective loss of function of the tonic ganglion cells in various optic nerve diseases (Alvarez and King-Smith, 1984; King-Smith et al, 1984).

Yabuki and co-workers (1989) employed automated static and manual kinetic perimetric techniques in a retrospective study of 162 eyes of patients with lesions located throughout the visual pathway. Approximately 20% of patients exhibited SKD; the magnitude of this function was independent of the location of the lesion within the visual pathway. There was no evidence to suggest that SKD had any prognostic significance for recovery. Successive lateral spatial summation (Greve, 1973) in areas of reduced retinal sensitivity was proposed to explain the presence of SKD.

Charlier and co-workers (1989) employed automated perimetry to assess SKD in 83 patients with various types of neuro-ophthalmic disorders. SKD was exhibited by 12 patients with either lesions of the optic chiasma or occipital cortex and was explained by the processing of motion and form information by separate channels. Furthermore, the sparing of subcortical visual pathways responsible for the phenomenon of "selective attention" (Singer et al, 1977) was hypothesized as the specific underlying mechanism. Similar conclusions were made by Finkelstein and Johnson (1989) in a case report of a patient with an occipital lobe infarction. It was suggested, however, that the specific mechanism of SKD in this case might be the phenomenon of "blindsight" (Sanders et al, 1974), in which the superior colliculus or extrastriate cortex have been suggested to process movement information (Weiskrantz, 1987).

Automated static and manual kinetic perimetric techniques were used by Katsumori and co-workers (1991) to assess SKD in glaucomatous eyes with early visual field defects.

The difference in sensitivity between the upper and lower visual fields was compared between the two techniques. Approximately 11% of stimulus locations exhibited SKD greater than ±5dB; peripheral stimulus locations exhibited the greatest magnitude of SKD. SKD was speculatively explained by a greater vulnerability of the large ganglion cells to selective damage in glaucoma (Quigley et al, 1987; Quigley, 1987).

The spatial summation characteristics of 5 optic neuritis patients with demonstrable SKD were compared to those of 8 glaucoma patients and 12 normals by Osako and co-workers (1991a). Automated static perimetry was employed using Goldmann stimulus sizes III and V. The magnitude of spatial summation, measured by the increase in sensitivity for stimulus size V compared to size III, was found to be greater for both patient groups in regions of the visual field with reduced sensitivity and to be considerably higher for the optic neuritis patients. It was, therefore, suggested that SKD in optic neuritis might be explained by an abnormal spatial summation effect.

Osako and co-workers (1991b) assessed both the temporal response and spatial summation characteristics of 9 optic neuritis patients and 9 normals using automated static perimetry for Goldmann stimulus sizes III and V and sinusoidal flicker modulation (contrast) thresholds at 2, 8 and 20 Hz. In addition, SKD was assessed using automated kinetic and static perimetry for stimulus size I. Optic neuritis patients exhibited a non-selective loss of flicker sensitivity for all 3 temporal frequencies; regions of the visual field that could detect a kinetic stimulus often exhibited an absolute loss of flicker sensitivity to one or more frequencies. A preferential loss of P-cells (tonic, X-type, sustained) would be expected to produce a selective reduction in sensitivity to low temporal frequencies. SKD in optic neuritis was suggested to be unrelated to the temporal characteristics of M- and P-cells. Furthermore, the magnitude of spatial summation was found to be considerably higher for the optic neuritis patients than the normal subjects suggesting that SKD in optic neuritis might be explained by an enhanced spatial summation effect.

In a review of the temporal properties of spatial vision, Plant (1991) suggested that SKD in both anterior and posterior visual pathway abnormality can be explained by the preferential loss of anatomically distinct visual pathways which mediate sensitivity for stimuli of high spatial and low temporal frequencies. These spatiotemporal losses were thought to reflect the properties of the magnocellular and parvocellular systems systems rather than the neuronal receptive field characteristics. Distinction was drawn between the SKD described by Plant (1986) and Plant and Wilkins (1988) and that of "blindsight" (Sanders et al, 1974) in which there is no conscious perception of the stimulus by the patient despite directional specific eye movements and that of the residual vision phenomenon described by Barbur and co-workers (1980) in which the magnitude of the sensitivity loss is much greater.

### 3.1.2. Physiological SKD.

A "physiological" SKD was first documented by Fankhauser and Schmidt (1960). Twenty normal subjects were assessed using Goldmann manual perimetry and stimulus sizes 0 to V presented at a velocity of 1° per second. In general, a greater sensitivity (approximately 2dB) was demonstrated to kinetic stimuli. Within 2° eccentricity, however, sensitivity to static stimuli was greater.

Using manual perimetric techniques, seven of the 15 normal subjects studied by Safran and Glaser (1980) exhibited physiological SKD. Each subject demonstrated a greater sensitivity to kinetic stimuli and the magnitude of SKD varied between 6° and 9°. Furthermore, using automated perimetry Wedemeyer and co-workers (1989) found the mean magnitude of physiological SKD to be 6° (SD 2.00°) in a sample of five normal subjects, while Osako and co-workers (1991b) found the mean magnitude of this function to be 4.5° (SD 1.25°) in a sample of nine normal subjects.

### 3.1.3. Mechanisms of physiological SKD.

Greve (1973) hypothesized that an infra-threshold stimulus (defined by static perimetry) may be perceived if in motion. The successive stimulation of individual receptors within a

given receptive field would result in a lateral spatial summation effect and, therefore, the stimulus would be detected. This hypothesis of "successive lateral spatial summation" was also proposed to explain physiological SKD in later studies (Safran and Glaser, 1980; Osako et al, 1991b).

Safran and Glaser (1980) hypothesized that the mechanism of physiological SKD was related to a larger receptive field size of the transient ganglion cells (Ikeda and Wright, 1971; Ikeda & Wright, 1972a; Ikeda & Wright, 1972b). Electrophysiological and psychophysical studies suggested that information relating to motion detection was mediated by the transient ganglion cells (Ikeda & Wright, 1972a; Kulikowski & Tolhurst, 1973; Tolhurst, 1973). Furthermore, motion detection by the phasic mechanisms (Y-type, transient, M-cell) was hypothesized to be slightly more sensitive than form detection by the tonic mechanisms (X-type, sustained, P-cell) under the conditions employed in perimetry (Wedemeyer et al, 1989).

### 3.1.4. Aim of the study.

Physiological SKD has received relatively little attention. Indeed, previous studies of SKD in visual pathway abnormality have ignored the possibility of a physiological component of this function (Charlier et al, 1989; Katsumori et al, 1991). The magnitude and incidence of physiological SKD is equivocal (Fankhauser and Schmidt, 1960; Safran and Glaser, 1980; Wedemeyer et al, 1989; Osako et al, 1991b). Discrepancies in findings have arisen from a lack of standardisation in perimetric procedures (Safran and Glaser, 1980). Furthermore, the variation in the magnitude of physiological SKD as a function of such factors as age, meridian, stimulus size, stimulus duration and adaptation level, together with the interaction of these factors with eccentricity are unknown.

The aim of the study, therefore, was: (1) to examine the relationship between static and kinetic measurements of the visual field using the standardized procedures of automated perimetry; (2) to determine the incidence of physiological SKD; and (3) to determine the

effects of age, meridian, stimulus size and eccentricity together with their interactions on physiological SKD.

## 3.2. Materials and methods.

### 3.2.1. Sample.

The sample consisted of two groups: 20 age-matched young subjects (10 males and 10 females; mean age 21.21 years, SD 1.37 yrs) and 20 age-matched elderly subjects (10 males and 10 females; mean age 69.05 years, SD 8.03 yrs). Exclusion criteria included systemic conditions with known ocular involvement, systemic medication with known CNS effects, a past history of eye disease, the use of topical eye treatment, the use of contact lenses, a positive family history of glaucoma in a first degree relative, a history of diabetes mellitus and neurological or psychiatric illness. All subjects had intraocular pressures of less than 21 mmHg, normal media, normal fundi and normal static threshold central visual fields by Humphrey automated perimetry (program 30-2). Subjects in the young group had distance refractive errors within ±0.75 diopter sphere and ±0.75 diopter cylinder and a visual acuity of 6/6 or better. Subjects in the elderly group had distance refractive errors within ±3.50 diopter sphere and ±1.50 diopter cylinder and a visual acuity of 6/9 or better.

### 3.2.2. Perimetry.

Perimetry was undertaken for the right eye of each subject using the HFA 640 (software version 5.2). This is an automated projection perimeter, capable of both static and kinetic visual field examination, which employs a bowl luminance of 31.5 asb at a viewing distance of 33 cm. Static stimuli are presented for a duration of 200 msec, using a 4-2 decibel double staircase strategy based upon a starting value at an intensity slightly brighter than the subjects expected threshold (Haley, 1987). The last seen stimulus value is identified as the threshold at that point. The sensitivity scale measured in decibels is referred to a maximum stimulus luminance of 10,000 asb. The default static stimulus size is Goldmann III (0.431°). Kinetic stimuli corresponding to Goldmann equivalent sizes I to V and

Goldmann equivalent intensities 0dB to 49dB are presented at a default stimulus velocity of 4° per second (Kinetic Perimetry, 1989). The default kinetic stimulus is I-2e (0.108°).

SKD can be assessed variously. The sensitivity to a static stimulus can be determined and compared to the sensitivity of an identical kinetic stimulus. The difference in sensitivity between the two stimuli is expressed in terms of degrees (Charlier et al, 1989; Osako et al, 1991a). Alternatively, the threshold for a kinetic stimulus can be determined and the static sensitivity can then be assessed at the same point. The latter method measures SKD in decibels.

The kinetic stimuli were chosen to produce a spread of discrete eccentricities for Goldmann equivalent sizes I and III along the 15° and 195° meridians. For the young group, the I-2e, I-2c, I-1e, I-1c, I-1a, I-4˜d (20, 22, 25, 27, 29, 31dB respectively) and the III-4˜c, III-3˜e, III-3˜d, III-3˜c, III-3˜b (32, 35, 36, 37, 38dB) stimuli were used. For the elderly group the I-3b, I-2e, I-2c, I-2a, I-1e, I-1d (18, 20, 22, 24, 25, 26dB) and III-4˜e, III-4˜c, III-4˜a, III-3˜e, III-3˜d (30, 32, 34, 35, 36dB) were used. Preliminary studies had shown that kinetic targets could not be consistently detected within 10° eccentricity for a stimulus velocity of 4° per second. The selection of the luminance values between the two age groups was influenced by the steepening of the sensitivity gradient with age.

All kinetic stimuli were presented randomly along the 15° and the 195° meridians using the manual mode facility of the kinetic program (Figure 3.1). The kinetic stimuli automatically commenced travel towards fixation from 75° eccentricity. For stimulus values which were detected within 20° of fixation, the kinetic stimuli were presented from 30° eccentricity using the "Zoom to 30°" option on the touch screen of the HFA in order to save time and to reduce subject fatigue.

Seven repetitions of each of the 11 kinetic stimuli (six size I & five size III) were presented along each of the two meridians. The mean location of the 7 presentations for each stimulus was determined and then expressed in terms of the respective x and y

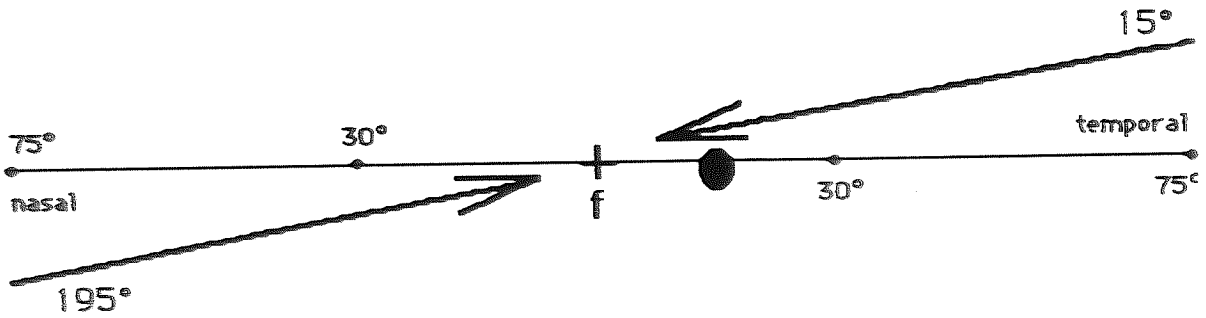



Figure 3.1. Diagram illustrating the direction of travel of kinetic stimuli.

coordinates. Static sensitivity for the corresponding stimulus size was then determined 7 times using a custom static threshold program at each of the mean locations of the kinetic stimuli. In addition, 7 repetitions of the static foveal threshold for both stimulus sizes were carried out during the custom program. A maximum of four custom static threshold programs were required to accommodate all the eccentricities.

The kinetic and static examinations for stimulus sizes I and III each lasted a maximum of 45 minutes, and were carried out on four separate days. All tests were undertaken within a maximum period of 4 weeks and generally within 14 days. Subjects were given frequent rest periods during each examination. The order of examination was varied within the constraint that the kinetic investigation for a given stimulus size had to precede the static investigation for that size in order to obtain the eccentricities for the custom static threshold programs.

Prior to the investigation, all subjects undertook four practice sessions to minimize any learning effects (Wood et al, 1987a; Heijl et al, 1989; Searle et al, 1991). The static training consisted of two examinations carried out with program 30-2 using stimulus sizes I and III. This program thresholds 76 points out to an eccentricity of 30°. The order of stimulus size was randomised between the two examinations which were carried out on separate days. The kinetic training consisted of two examinations using the six size I and the five size III stimuli presented along the 15° and 195° meridians, with six repetitions of the 3 inner isopters and three repetitions of the outer isopters. The order of stimulus size was again randomised between the two examinations which were also carried out on separate days. Consequently, a total of 4 separate training sessions each lasting approximately 30 minutes were carried out on separate days. The order of the kinetic and static training sessions was further randomised.

Static stimuli were presented at the integer closest to the mean eccentricity of the seven repetitions for each kinetic stimulus. The resolution of the custom program within 30° eccentricity was 1°. Locations beyond 30° eccentricity were limited to 2° resolution.

Together with potential rounding errors the maximum disparity between the kinetic and static stimulus locations amounted to 1.5°. This compares to an amplitude of physiological eye movement of 0.5° (Carpenter, 1988).

The distance refractive correction was employed, together with the appropriate near addition in the elderly group, to correct for the viewing distance of 33 cm. Refractive correction was not employed for the static or kinetic stimuli located greater than 30° from fixation in order to avoid artifacts due to the trial lens rim. Natural pupils were used throughout. The pupil diameter was measured on two occasions during the four sessions using the video monitor. The measurement was corrected for the magnification of the optical system; group mean pupil diameter for the young subjects was 5.46 mm (SD 1.21 mm) and for the elderly subjects 3.91 mm (SD 0.71 mm).

Operator involvement during the examinations was kept to a minimum; subjects were realigned when necessary. The Heijl-Krakau blind spot technique for monitoring the quality of fixation is not operative during kinetic perimetry. Fixation was monitored qualitatively using the video eye monitor. All perimetry was performed by one operator to minimise inter-examiner variation (Berry et al, 1966; Ross et al, 1984).

### 3.2.3. Statistical Analysis.

In order to permit analysis of the kinetic and static sensitivity gradients, both within- and between-age groups and within- and between-stimulus sizes, the area under each sensitivity gradient for each subject was calculated. This standardized the data for the four combinations of age and stimulus size. To study the influence of eccentricity and meridian on SKD, the area under each sensitivity gradient was calculated separately for four zones: 25° to 40° temporally, 10° to 25° temporally, 10° to 25° nasally and 25° to 40° nasally. The dimensions of the zones were selected empirically to provide, wherever possible, three stimulus locations within each zone. The area under each zone was then determined by the Trapezium Rule. An additional three data points per zone were interpolated at fixed locations from the measured data. The region within 10° eccentricity was not analysed

due to the absence of kinetic isopters in this area. Similarly, the region beyond 40° eccentricity was not evaluated due to an absence of points within this region which arose from the steeper hill of vision in the elderly group.

A repeated measures analysis of variance (ANOVA) was undertaken on the area values. The effects of stimulus type (ie kinetic or static), stimulus size (ie I or III), meridian (ie temporal or nasal) and eccentricity were the within-subject factors. Age was treated as a between-subjects factor. The within-subject factors stimulus size, meridian and eccentricity, together with their associated interaction terms, defined the shape of the hill of vision. The within-subject factor stimulus type, together with the associated interaction terms, described the SKD as a function of stimulus size, meridian and eccentricity. The between-subjects factor, age, identified the differences between the young and elderly age groups.

## 3.3. Results.

The static and kinetic sensitivity gradients corresponding to each age group for the two stimulus sizes are shown in Figure 3.2. The standard errors of the group mean static sensitivity data were larger for the size I stimulus and for the older age group. The standard errors of the group mean kinetic sensitivity data were larger for the older age group, for stimulus size III and with increasing eccentricity.

The relationship between the area underneath the static hill of vision derived by the Trapezium Rule and the static mean sensitivity of each stimulus size for each age group is shown in Figure 3.3. The distribution of area values parallel to the abscissa shows that the area measure of sensitivity was a more representative indicator of the between-subject variation in the shape of the sensitivity gradient.

The results of the ANOVA are given in Table 3.1. The area underneath the hill of vision was greater for the temporal meridian than for the nasal meridian ($p=0.010$) and was

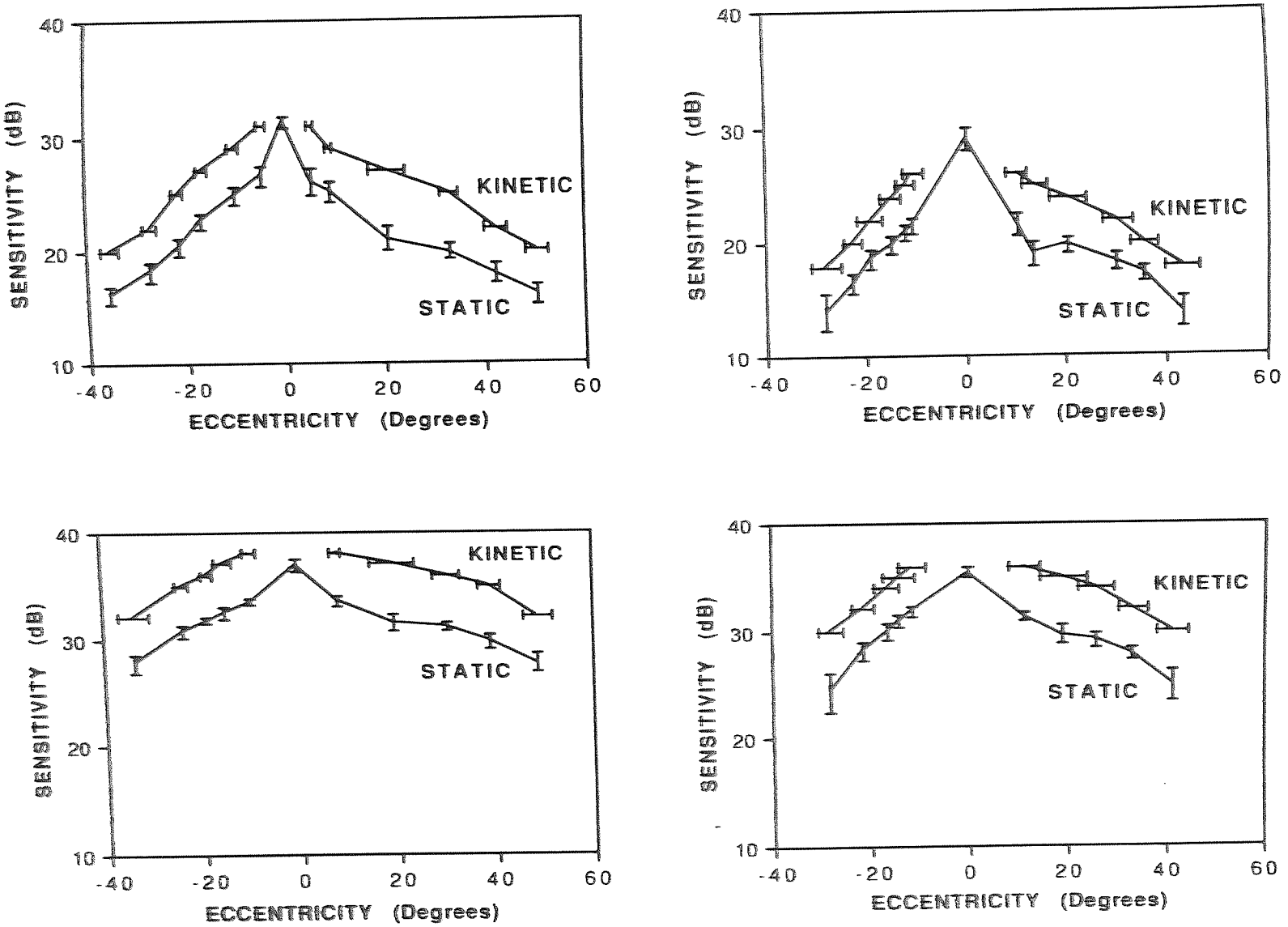



Fig. 3.2. Group mean static and kinetic sensitivity profiles. Top left: young age group, size I. Bottom left: young age group, size III. Top right: elderly age group, size I. Bottom right: elderly age group, size III. (+ve eccentricity indicates the temporal meridian and -ve eccentricity the nasal meridian). The error bars represent two standard errors of the mean.

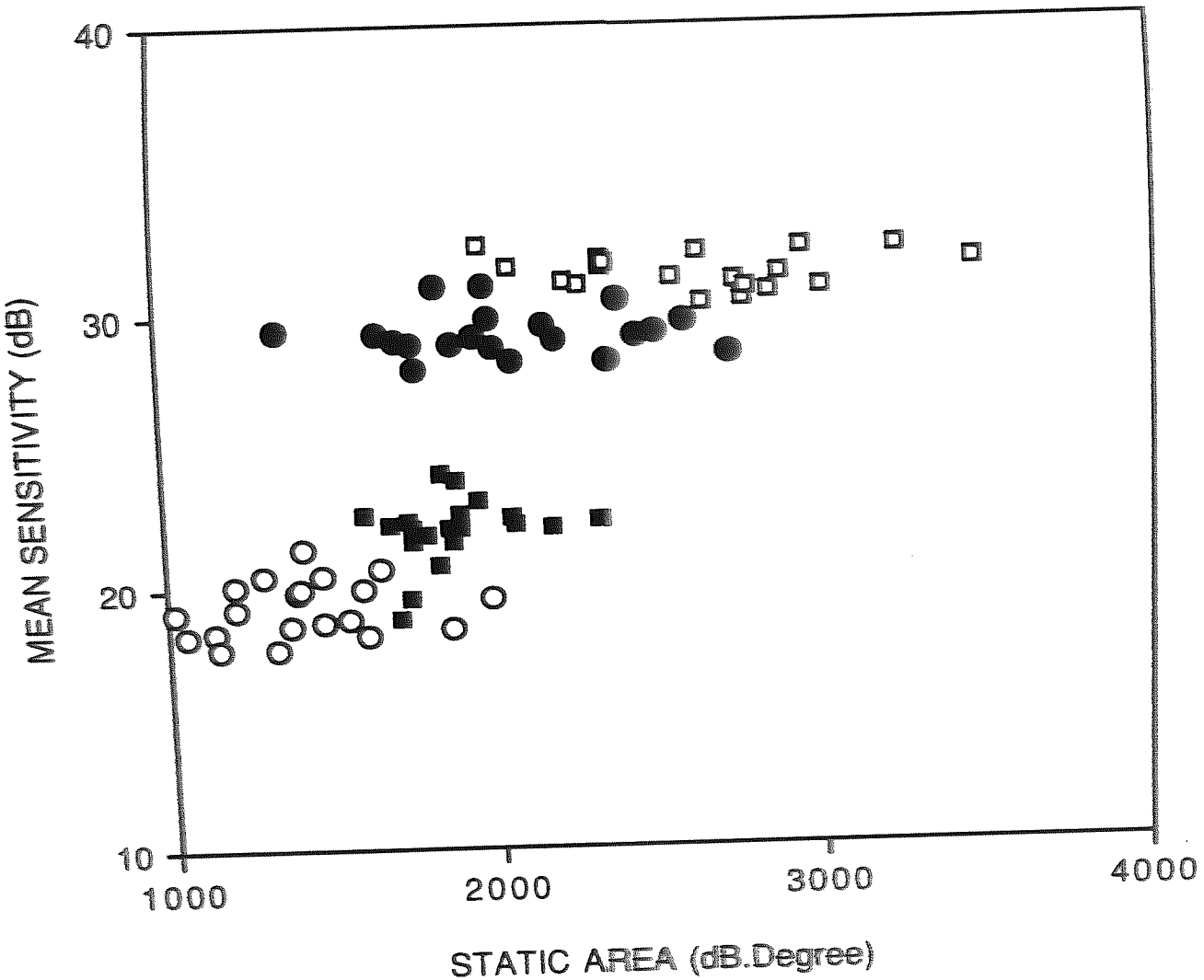



Fig. 3.3. Static mean sensitivity as a function of the area beneath the static sensitivity profile. (Filled squares: young age group, size I. Open squares: young age group, size III. Open circles: elderly age group, size I. Filled circles: elderly age group, size III).

greater for the 10°- 25° zones than for the 25°- 40° zones (p=0.014) particularly for the older age group (p=0.003). The increase in area from the 25°- 40° zone to the 10°- 25° zone was greater for the nasal meridian than for the temporal meridian (p<0.001). These effects are due to a steeper profile of the hill of vision in the nasal visual field, the gradient of which increases with increasing eccentricity and with increasing age.

As would be expected, the area underneath the hill of vision increased with increase in stimulus size (p<0.001). This increase was more marked for the temporal meridian than for the nasal meridian (p=0.038) particularly within the 10° - 25° zone (p=0.006). Also, the increase in area with increase in stimulus size was greater for the younger age group (p=0.032). The kinetic and static sensitivities were lower for the elderly age group (p<0.001).

The kinetic profiles for both stimulus sizes were significantly higher than the corresponding static profiles (p<0.001), particularly within the 10° - 25° zone of the temporal meridian (p=0.024). This latter effect is due to a greater influence of the reduced sensitivity in the blind spot region on the static sensitivity gradient compared to the kinetic sensitivity gradient.

The magnitude and variation of physiological SKD for all stimulus locations as a function of age and stimulus size is shown in Figure 3.4. The mean SKD for stimulus sizes I and III in the young age group was 4.41dB (SE 0.14, median 4.15) and 4.64dB (SE 0.12, median 4.43) respectively and in the elderly group 4.02dB (SE 0.16, median 3.86) and 4.82dB (SE 0.20, median 4.43). The steep slope of the cumulative frequency curves illustrates the minimal variation in SKD both within- and between-subjects.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Age | 1 | 1022240.75 | 102240.75 | 36.73 | <0.001 |
| Error | 38 | 1057450.48 | 27827.64 | | |
| Type | 1 | 261376.56 | 261376.56 | 43.67 | <0.001 |
| Type X age | 1 | 84.10 | 84.10 | 0.01 | =0.906 |
| Error | 38 | 227444.87 | 5985.39 | | |
| Stimulus size | 1 | 82455.12 | 82455.12 | 116.27 | <0.001 |
| Stimulus size X age | 1 | 3496.90 | 3496.90 | 4.93 | =0.032 |
| Error | 38 | 26947.82 | 709.15 | | |
| Meridian | 1 | 85380.84 | 85380.84 | 7.38 | =0.010 |
| Meridian X age | 1 | 25150.22 | 25150.22 | 2.18 | =0.148 |
| Error | 38 | 439357.55 | 11562.04 | | |
| Eccentricity | 1 | 74120.06 | 74120.06 | 6.71 | =0.014 |
| Eccentricity X age | 1 | 111513.60 | 111513.60 | 10.10 | =0.003 |
| Error | 38 | 419503.12 | 11039.55 | | |

Table 3.1. Repeated measure analysis of variance of the area values.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Type X Size | 1 | 568.82 | 568.82 | 1.88 | =0.178 |
| Type X Size X Age | 1 | 652.05 | 652.05 | 2.15 | =0.150 |
| Error | 38 | 11499.53 | 302.61 | | |
| Type X Meridian | 1 | 15675.04 | 15675.04 | 3.79 | =0.059 |
| Type X Meridian X Age | 1 | 1316.75 | 1316.75 | 0.32 | =0.576 |
| Error | 38 | 157346.98 | 4140.71 | | |
| Type X Eccentricity | 1 | 1105.56 | 1105.56 | 0.22 | =0.638 |
| Type X Eccentricity X Age | 1 | 4233.30 | 4233.30 | 0.86 | =0.359 |
| Error | 38 | 187139.18 | 4924.71 | | |
| Size X Meridian | 1 | 1176.49 | 1176.49 | 4.63 | =0.038 |
| Size X Meridian X Age | 1 | 232.80 | 232.80 | 0.92 | =0.344 |
| Error | 38 | 9653.68 | 254.04 | | |
| Size X Eccentricity | 1 | 64.80 | 64.80 | 0.27 | =0.604 |
| Size X Eccentricity X Age | 1 | 660.15 | 660.15 | 2.78 | =0.103 |
| Error | 38 | 9029.78 | 237.62 | | |

Table 3.1. (Continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Meridian X Eccentricity | 1 | 138532.84 | 138532.84 | 19.45 | <0.001 |
| Meridian X Eccentricity X Age | 1 | 1107.75 | 1107.75 | 0.16 | =0.695 |
| Error | 38 | 270611.24 | 7121.35 | | |
| Type X Size X Meridian | 1 | 29.16 | 29.16 | 0.11 | =0.746 |
| Type X Size X Meridian X Age | 1 | 38.02 | 38.02 | 0.14 | =0.712 |
| Error | 38 | 10453.20 | 275.08 | | |
| Type X Size X Eccentricity | 1 | 33.06 | 33.06 | 0.16 | =0.693 |
| Type X Size X Eccentricity X Age | 1 | 81.22 | 81.22 | 0.39 | =0.537 |
| Error | 38 | 7972.37 | 209.79 | | |
| Type X Meridian X Eccentricity | 1 | 13806.25 | 13806.25 | 5.55 | =0.024 |
| Type X Meridian X Eccentricity X Age | 1 | 1452.02 | 1452.02 | 0.58 | =0.449 |
| Error | 38 | 94586.50 | 2489.11 | | |
| Size X Meridian X Eccentricity | 1 | 1672.81 | 1672.81 | 8.55 | =0.006 |
| Size X Meridian X Eccentricity X Age | 1 | 562.50 | 562.50 | 2.87 | =0.098 |
| Error | 38 | 7436.40 | 195.69 | | |

Table 3.1. (Continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Type X Size X Meridian X Eccentricity | 1 | 6.25 | 6.25 | 0.05 | =0.827 |
| Type X Size X Meridian X Eccentricity X Age | 1 | 2.75 | 2.75 | 0.02 | =0.885 |
| Error | 38 | 4940.43 | 130.01 | | |



Table 3.1. (Continued).

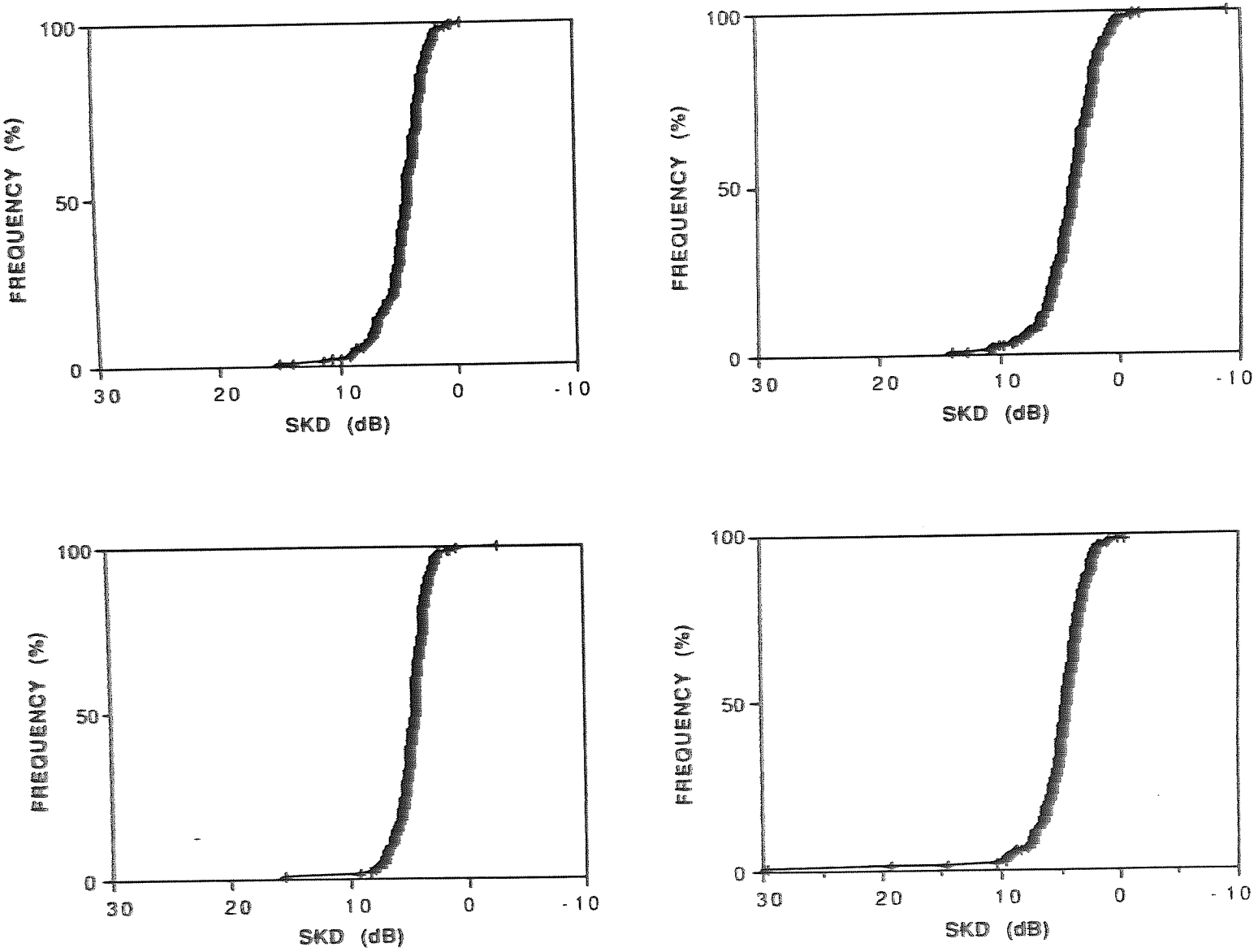



Fig. 3.4. Cumulative frequency curves showing the magnitude and variation of physiological SKD. Top left: young age group, size I. Bottom left: young age group, size III. Top right: elderly age group, size I. Bottom right: elderly age group, size III.

## 3.4. Discussion.

The data shows that the results of kinetic and static perimetry are not quantitatively the same. All subjects demonstrated a greater sensitivity to a kinetic stimulus. An "inverse SKD", whereby a greater sensitivity is demonstrated for a static stimulus rather than a kinetic stimulus, was present in only 8 of the 880 determinations.

The findings are in agreement with previous studies which show that SKD can be demonstrated in normal subjects (Fankhauser and Schmidt, 1960; Safran and Glaser, 1980; Wedemeyer et al, 1989; Osako et al, 1991b). In this study, physiological SKD was present in all subjects for both stimulus sizes using a stimulus velocity of 4° per second. Physiological SKD was found to be largely independent of eccentricity contrary to a previous study which employed manual perimetry (Fankhauser and Schmidt, 1960). The incidence of SKD is higher than that reported previously for manual perimetry using stimulus sizes I to V and a stimulus velocity of 3° per second (Safran and Glaser, 1980).

In this study, physiological SKD was assessed in terms of luminance rather than position (i.e. a vertical rather than a horizontal approach to the hill of vision). The thresholding strategies of the two methods of perimetric examination may contribute to the magnitude of physiological SKD. There is a reduction of the given kinetic isopter when a stimulus is moved from unseen to seen regions of the visual field due to the reaction time of the subject. This effect, however, is diminished by an apparent increase in the given isopter caused by the greater temporal and spatial summation of a moving stimulus (Tate and Lynn, 1977). Furthermore, kinetic isopters for I-4e (10dB), I-2e (20dB) and I-1e (25dB) stimuli have been found to be constant for stimulus velocities between 1° and 4° per second and only a slight reduction in sensitivity was found for a stimulus velocity of 6° per second (Johnson and Keltner, 1987). The magnitude of simple reaction time is approximately 200 msec and shows no consistent deterioration from 20-60 years of age; above 60 years of age the deterioration is minimal (Keele, 1986). Assuming no summation effects, reaction time would account for the inward displacement of the kinetic

isopters by approximately 0.8°. This effect is comparable to the magnitude of physiological eye movements (Carpenter, 1988). The anticipated effect of a longer reaction time would be to displace the kinetic isopters inward, thus potentially producing a larger mismatch between the positions of the static and kinetic thresholds. Assuming a reaction time of 500 msec, the combined error from the mismatch of the threshold positions and the resolution of the static threshold positioning offered by the perimeter would total a maximum of 3.5°. However, the interaction of age and SKD was not statistically significant (p=0.906).

The thresholding algorithm employed for the determination of static sensitivity will also influence the magnitude of SKD. Threshold estimation varies as a function of the direction and the step size employed in the crossing of threshold (Anderson et al, 1989; Johnson et al, 1992). The algorithm used by the HFA includes a final 2dB crossing of threshold that will probably occur in an ascending direction but can also occur in a descending direction; threshold is taken as the last seen stimulus at that location. The measurement error associated with the thresholding procedure is ± 1dB. This is contaminated further by the local short-term fluctuation of the threshold estimate.

Refractive correction was not employed for the assessment of kinetic and static sensitivity beyond 30° eccentricity. The reduction in perimetric sensitivity due to defocus (Sloan, 1961; Fankhauser and Enoch, 1962), however, is reduced with increase in stimulus size (Fankhauser, 1979; Wild et al, 1988) and with increase in eccentricity (Benedetto and Cyrlin, 1985; Wild et al, 1988). Although peripheral refractive error has a major influence on motion thresholds in the peripheral retina (Leibowitz et al, 1972; Johnson and Leibowitz, 1974), it would appear that in relation to static automated perimetry the effect is insignificant (Wild et al, 1988). In addition, defocus induces similar changes in sensitivity for both static and kinetic stimuli (Benedetto and Cyrlin, 1985).

The determination of the mechanism of physiological SKD was not a specific aim of this study and, therefore, any explanation can only be speculative.

The magnitude of physiological SKD might be expected to increase with increase in stimulus size if "successive lateral spatial summation" was the mechanism responsible for the detection of kinetic stimuli. Physiological SKD, however, was found to be independent of stimulus size ($p=0.178$). The ratio of summation for the kinetic stimulus (influenced by area and velocity) relative to summation for the same diameter static stimulus (influenced by area alone) was identical for both stimulus sizes I and III. This does not necessarily exclude the hypothesis of "successive lateral spatial summation" as one of the underlying mechanisms of physiological SKD. It might, however, indicate a saturation point in terms of stimulus velocity (less than 4° per second) or stimulus size (less than 0.108° diameter) at which further summation cannot occur.

The suggestion of Safran and Glaser (1980) that SKD can be explained by the receptive field properties of the transient ganglion cells is controversial. The distinction between X and Y cells made on the basis of transient and sustained responses has been demonstrated to be dependent on contrast level, such that at low contrast (corresponding to threshold detection) the properties of the two cell types are similar (Lennie, 1980a). In addition, there is no evidence to suggest any segregation of information from X and Y cells in the occipital cortex (Lennie, 1980b). The hypothesis made by Wedemeyer and co-workers (1989) that motion detection by the phasic mechanisms (Y-type, transient) might be more sensitive than form detection by the tonic mechanisms (X-type, sustained) under the conditions employed in perimetry are neither substantiated nor denigrated as a result of the findings of this study.

Electrophysiological evidence suggests that ganglion cells which project to the magnocellular layers (analogous to the phasic mechanisms) of the lateral geniculate body and cortex are responsible for the detection of low contrast, moving stimuli (Hicks et al, 1983; Cavanagh et al, 1984; Derrington and Lennie, 1984; Kaplan et al, 1990). It is feasible, therefore, that the magnocellular system is more sensitive to the conditions employed in kinetic perimetry rather than those of static perimetry. This explanation of

SKD suggests an increased sensitivity of the magnocellular system to kinetic stimuli rather than the detection of static and kinetic stimuli by different mechanisms.

## 3.5. Conclusions.

The quantitative comparison of static and kinetic measurements of the visual field is confounded by physiological SKD. In general, the kinetic technique over-estimated the static perimetric profile by an average of 4.5dB. Minimal variation was found in the magnitude of this function both within- and between-subjects. Physiological SKD was exhibited by all individuals for both stimulus sizes and all kinetic stimulus values using a stimulus velocity of 4° per second. In addition, the magnitude of physiological SKD was found to be largely independent of age, stimulus size, meridian and eccentricity.

Any future studies of SKD in visual pathway abnormality should consider the physiological component of this function and ensure that equivalent conditions are employed for the assessment of static and kinetic perimetry. Further research should investigate the underlying mechanisms of SKD both in normal subjects and in patients with visual pathway abnormalities. In particular, techniques which exclude the influence of stimulus velocity, such as flicker perimetry or modulated sinusoidal wave gratings, should be employed to elucidate the variations in spatial and temporal sensitivity with eccentricity. The generation of spatiotemporal threshold surfaces (ie three-dimensional plots which illustrate the relationship between spatial and temporal sensitivity) for various stimulus locations should provide a more complete analysis of the characteristics of functional loss in visual pathway abnormality.

# CHAPTER 4. FATIGUE EFFECTS DURING A SINGLE SESSION OF AUTOMATED STATIC PERIMETRY IN NORMAL SUBJECTS AND OCULAR HYPERTENSIVE PATIENTS.

## 4.1. Introduction.

Automated perimetry has improved the reproducibility of clinical visual field testing when compared to manual perimetric techniques. The outcome of a visual field examination, however, is influenced by various extraneous factors. The influence of optical factors such as pupil size (Fankhauser, 1979; Mikelberg et al, 1987; Lindenmuth et al, 1989; Heuer et al, 1989), refractive error (Benedetto and Cyrlin, 1985; Weinreb and Perlman, 1986; Atchinson, 1987; Heuer et al, 1987) and media opacities (Guthauser et al, 1987; Heuer et al, 1989; Wood et al, 1989; Dengler-Harles et al, 1990) are well documented (see Chapter 1).

Other extraneous factors which influence the outcome of a visual field examination include psychological effects such as learning and fatigue. Indeed, variability of response is common during and between examinations in many types of psychophysical tests. Low (1946) measured peripheral visual acuity in 43 normal subjects on 8 successive occasions after noticing an improvement in performance between the first and the second eyes at a single examination. A modified perimeter was employed to present Landolt rings of varying angular subtense in any one of four positions. The subject identified the position of the break in the Landolt ring. On average, subjects responded to stimuli eleven times more efficiently after training. The improvement in performance, however, varied markedly between subjects (ie 4 to 144 fold improvement). In order to achieve an optimum performance 25 hours of training was considered necessary. The peripheral retina was hypothesized to be an unpractised sensory area.

Haider and Dixon (1961) measured threshold over a period of 14 minutes in ten normal subjects. The brightness of two constantly presented spots of light differing in intensity

by 0.05 log units were simultaneously adjusted by the subject until only one of the stimuli was visible. Subjects attended for six sessions over a period of approximately 4 weeks. Group mean threshold was relatively stable during the first session but tended to rise over subsequent sessions indicating a within-examination fatigue effect. It was suggested that the improvement due to training effects masked the effect of fatigue during the first session. In addition, the threshold was considerably lower at the start of the second session indicating a learning effect between the first and second sessions.

Sunga and Enoch (1970) described a "short-term saturation" or fatigue effect in patients with optic nerve and cortical lesions. A modified Goldmann perimeter was employed to present continuous or tachistoscopic stimuli at selected locations in the visual field. Sensitivity declined in a progressive time-related manner to repeated stimuli. This effect occurred even in areas of the visual field with normal levels of sensitivity. In addition, reduction of the background luminance resulted in a reduced fatigue effect.

Ronchi and Salvi (1973) continuously measured absolute threshold to a stimulus 6' of arc in diameter, presented for 100 msec over a period of 2 hours for nine normal dark-adapted subjects. Subjects were experienced in the psychophysical procedures and were tested under binocular viewing conditions. During the first hour an oscillatory decline in sensitivity was reported, after which time sensitivity oscillated around a baseline sensitivity level. The deterioration in sensitivity over time was less pronounced with increase in eccentricity beyond 30° and in monocular areas of the binocular visual field. Large variations were recorded between individuals. It was suggested that a decline in vigilance might explain the fatigue effect.

Aspinall (1974) employed the Farnsworth-Munsell 100-hue test to measure performance in two groups of normal subjects. One group had been previously trained in the test procedure. The trained group exhibited an improved performance and a reduced between-subject variation when compared to the untrained group. The results were

explained by changes in the response criterion of the untrained group as a result of unfamiliarity with the test conditions.

The Nicolet CS-2000 Vision Tester was employed by Kelly and Tomlinson (1987) to assess monocular contrast sensitivity functions over 5 consecutive days in a group of 20 normal young subjects. The sample was then divided into four groups of five subjects and contrast sensitivity was assessed either 1, 3, 5 or 7 days after the initial training period to determine the time course of any deterioration in the learning effect. A further group of five subjects underwent the the same training program and repeated the test 7 days after training but both eyes were assessed at each session. There was no obvious increase in contrast sensitivity over the 5 day training period. Contrast sensitivity also remained stable after the training period. Furthermore, there was no obvious evidence of a transfer of learning between eyes at a single session or between sessions. It was suggested that the variability of the technique was too high to detect the subtle alterations in sensitivity due to learning or fatigue.

The Farnsworth-Munsell 100-hue test was also employed by Breton and co-workers (1988) to study the learning effect in a group of 26 normal untrained subjects and in a group of 30 normal trained subjects. A significant improvement in performance over at least four successive tests was demonstrated by the untrained group, while the trained group exhibited no clear trend towards improvement. It was hypothesized that the source of this learning effect was cognitive rather than a change in colour discrimination.

4.1.1. Learning effects in perimetry.

Learning effects, whereby sensitivity increases during and between perimetric examinations, have been reported in both manual and automated perimetry. Manual static profile perimetry was employed by Aulhorn and Harms (1967) to study the within-test change in sensitivity in normal subjects at 5 stimulus locations between 0° and 18° eccentricity. Threshold was determined twenty times over a period of one day at each stimulus location. The learning effect varied from zero to one log unit between individuals.

Furthermore, the improvement in sensitivity generally occurred over the first ten sessions and then plateaued. The level of sensitivity attained at the end of the training session was retained when the test was repeated up to seven days later.

Although recognising the presence of a learning effect in manual static perimetry, Greve (1973) suggested that differences obtained between successive examinations were insignificant because the improvement in sensitivity was diffuse. The magnitude of a field defect, therefore, would not change in relation to the sensitivity of the surrounding visual field. The learning effect was explained in part by a steepening of the slope of the frequency of seeing curve. The range of luminances over which the chance of detection of a stimulus varied between 1% and 99% was found to be approximately 0.50 log units for untrained normal subjects and 0.30 log units for trained normal subjects. In addition, Tate and Lynn (1977) attributed the learning effect to a change in the criterion for stimulus detection. As familiarity with the test procedure was gained the patient would respond to stimuli that were previously ignored. The learning process could be accelerated if feedback or encouragement was given to the patient.

Gloor and co-workers (1980) employed Program 31 of the Octopus perimeter to study the long-term fluctuation in 32 glaucomatous eyes and suggested that learning could result in an increase in sensitivity of up to 2 decibels at each stimulus location. Subsequently, the between-examination alteration in sensitivity was assessed by Gloor and co-workers (1981) in 120 eyes of 66 patients, with ocular hypertension or glaucoma, using Program 31 of the Octopus perimeter. A learning effect was found between the first and second examinations which was characterized by a reduction in the size of any scotoma and an increase in sensitivity of up to 2dB per stimulus location. A similar increase in sensitivity, however, was not found between the second and third examinations. Gloor and co-workers (1981) stated that there was a need to differentiate between true change in the visual field and learning effects.

In a study of visual field reproducibility Parrish and co-workers (1984) employed Program 30 of the Perimetron automated perimeter to assess static sensitivity along the superotemporal (45°) meridian on five occasions over a period of 30 days in 18 eyes of 13 normal subjects. The variability was higher than expected and was attributed to the fact that the subjects were not previously trained. Furthermore, to determine the magnitude of short- and long-term fluctuation in automated perimetry Flammer and co-workers (1984b) arbitrarily ignored the first automated perimetry result in order to avoid contamination of the data by learning effects. Similarly, Wilensky and Joondeph (1984) considered that it was necessary to ignore the results of the first two examinations. Kosoko and co-workers (1986) could find no evidence of a between-eye learning effect, however, as indicated by a reduced test duration for the second eye examined.

Wood and co-workers (1987a) employed Program 21 of the Octopus 201 automated perimeter in conjunction with stimulus size III to assess the change in the sensitivity over time of the visual field of the right eye in 10 naive normal subjects during eight serial examinations each carried out on separate days (days 1-5 inclusive and days 15, 16 and 44). Eight subjects exhibited a learning effect which was more pronounced in the superior hemifield and for stimulus locations beyond 30° eccentricity, while two subjects exhibited no obvious improvement in sensitivity. The exact pattern of the learning effect, however, differed between subjects: some exhibited a large increase in sensitivity at the second examination, while others showed a gradual increase in sensitivity up to the fifth examination. Furthermore, the learning effect was retained when the test was repeated on days 15, 16 and 44.

In a retrospective study, Werner and co-workers (1988) employed program 32 of the Octopus 201 automated perimeter to examine 20 glaucomatous eyes on four separate occasions. The four examinations were carried out over a mean period of 20 months and the patients were experienced in Goldmann manual perimetry. No obvious change over the four visits was found in the indices mean sensitivity, total loss, or in the number of disturbed stimulus locations (a disturbed stimulus location was defined as a point with a

sensitivity value 5dB or more below the age-matched normal value). A significant decrease in the short-term fluctuation was reported, however, between the first and second visits ($p<0.001$). It was concluded that the learning effect was insignificant in glaucoma patients who had previous experience of manual perimetry and that a single baseline examination would probably be sufficient in this population.

Heijl and co-workers (1989) employed Program 30-2 of the HFA to assess the sensitivity in both eyes of 74 normal subjects on three occasions (an interval of two months between each examination) and for a separate group of 10 normal subjects on ten occasions (an interval of one week between each examination). Mean sensitivity increased with training particularly for the second eye at the first session compared to the first eye at the first session and for the first eye at the second session. A concomitant improvement in the visual field indices mean deviation, short-term fluctuation and corrected pattern standard deviation was also reported. Furthermore, the learning effect was retained when the test was repeated two and four months later. For the 74 normal subjects, the group mean mean sensitivity improved by 1.3dB between the first and third visits. This improvement in sensitivity was more pronounced for peripheral stimulus locations. Subjects with a low mean sensitivity at the first examination exhibited a greater learning effect. They concluded that a single visual field examination was inadequate to provide accurate baseline information.

A HFA 630 was employed by Wild and co-workers (1989) in conjunction with stimulus size III to assess static sensitivity for 19 naive patients with suspected glaucoma. A custom program consisting of 60 stimuli arranged in a square grid with a 12° interstimulus spacing and extending to 60° eccentricity was utilised for the study. The visual field of the right eye followed by the left eye was examined on 4 separate days (days 1-3 inclusive and day 15). The global, superior, inferior, central and peripheral mean sensitivity indices of the right eye exhibited a significant increase over the first three visits ($p\leq0.01$), while the global short-term fluctuation, central mean deviation and the number of stimulus presentations exhibited a concomitant significant decrease ($p\leq0.01$). These changes

occurred mainly between the first and second visits. The improvement in performance of the left eye was less pronounced. Furthermore, both the right and left eyes showed significant improvements in sensitivity between the third and fourth visits, but the changes were more pronounced for the left eye ($p<0.001$). The increase in mean sensitivity was greater for peripheral stimuli than for the central stimuli. They concluded that the results of a clinical visual field examination were influenced by the order of examination between eyes and by the interval between visits.

The effect of learning on the visual field indices mean sensitivity and short-term fluctuation was reported by Autzen and Work (1990). They utilized program 32 of the Octopus 2000R automated perimeter in conjunction with stimulus size III. They examined each eye of 33 naive normal subjects on two occasions separated by between 3 and 34 days (mean 12.5 days). Mean sensitivity improved by 0.95dB ±1.75 ($p<0.05$) for both eyes between the two visits and short-term fluctuation declined by 0.30dB$^2$ ($p=0.009$). The improvement of mean sensitivity in the upper temporal quadrant, however, failed to reach statistical significance.

In a retrospective study, Werner and co-workers (1990) reported on the results from 29 eyes of patients with suspected glaucoma examined on four separate occasions with program 32 of the Octopus 201 automated perimeter. The four examinations were carried out over a mean period of 24 months and subjects were experienced in Goldmann kinetic and multiple stimulus suprathreshold static perimetry. There was no obvious improvement over the four visits for global mean sensitivity or for mean sensitivity within 20° eccentricity. A significant increase in mean sensitivity occurred, however, for stimulus locations beyond 20° eccentricity ($p=0.012$). Furthermore, statistically significant improvements between the first and second visits were also reported for short-term fluctuation, total loss and the number of disturbed stimulus locations ($p<0.01$). The results suggested that the learning effect was small and limited to peripheral stimulus locations in glaucoma suspects who had previous experience of manual perimetric techniques. They concluded that two baseline examinations would be sufficient to minimize any learning effects.

In a similar type of retrospective study based upon the results of 45 clinically stable glaucoma patients Kulze and co-workers (1990) attempted to determine the factors associated with the learning effect using program 30-2 of the HFA. One eye from each subject was studied over the first two visits. The group mean mean defect decreased by 1.7dB between the two visits ($p<0.05$), while at the same time the central reference level increased significantly ($p<0.05$). Previous experience of manual or automated suprathreshold static perimetry had no significant effect on learning. They suggested that predicting which patient required a second baseline field examination in order to minimize learning effects was difficult.

Searle and co-workers (1991) utilized a custom program of the HFA 640 (stimulus size III) which consisted of 30 stimuli situated between 9° and 24° eccentricity to assess static sensitivity for each eye of 38 normal naive subjects. The custom program was approximately 5 minutes in duration and was repeated three times without interruption for each eye on each of two separate visits with an interval of approximately 2 weeks between visits. Stimulus durations of 100 and 200 msecs were randomly assigned to each subject ($n=20$ and $n=18$ respectively). For the 200msec stimulus duration, group mean global and pointwise sensitivity decreased for both eyes over the three programs indicating a within-eye fatigue effect. The within-eye decrease in sensitivity was greater for the second eye at each visit. At the second visit, however, group mean mean sensitivity improved by 1.4dB for the first eye examined relative to the first visit indicating a between-visit learning effect. Similarly, the short-term fluctuation, the number of stimulus presentations and the test duration increased for both eyes over the three programs suggesting a within-eye fatigue effect, but were lower for the second visit indicating a between-visit learning effect. Peripheral stimulus locations exhibited a greater change in sensitivity due to fatigue and learning. Although, as would be expected, the mean sensitivity was lower, similar trends were noted for the 100 msec stimulus duration. It was concluded that confidence limits for the definition of abnormality should account for the order in which the eyes of an individual are examined.

Long-term changes in perimetric sensitivity were studied by Wild and co-workers (1991). The methodology was the same as that employed for an earlier study of serial learning effects (Wild et al, 1989). Perimetry was undertaken for both eyes of 16 patients with suspect glaucoma using a HFA 630 automated perimeter and a custom program consisting of 60 stimuli within 60° eccentricity. The initial training program (four examinations on 3 successive days and again after an interval of 12 days) was followed after a period of between 5 and 15 months (mean 8.7 months) by two examinations on 2 successive days. The group mean central mean sensitivity (ie stimulus locations within 30° eccentricity) of the first eye deteriorated by 1.6dB between the final examination of the training period and the first long-term follow-up examination ($p<0.002$). Furthermore, between the final examination of the training period and the first long-term follow-up examination both the global short-term fluctuation (54.3%; $p<0.01$) and the number of stimulus presentations (3.8%; $p<0.05$) increased significantly. After an appropriate training regime, therefore, the presence of any further learning effect at long-term follow-up is insignificant.

The first four visual field examinations of 15 clinically stable glaucomatous eyes assessed using the G1 program of the Octopus 2000 automated perimeter were retrospectively evaluated by Marchini and co-workers (1991). The mean interval between each examination varied between 2 and 4 months. There was a statistically significant reduction ($p<0.05$) in the indices mean defect and short-term fluctuation between the first and second visits and this improvement in performance was retained over the subsequent visits. Furthermore, there was a significant reduction ($p<0.05$) in the number of disturbed points in the whole field (and in all quadrants except the inferior nasal quadrant) between the first and second visits and also in the peripheral field and in the number of stimulus presentations. It was concluded, therefore, that a single baseline field would not be sufficient in this population to avoid learning effects.

Program J1 of the Octopus automated perimeter was employed by Marra and Flammer (1991) to consecutively measure static threshold twelve times at 3 stimulus locations

between 3° and 28° eccentricity over a time period 5 to 8 minutes. Seventy normal subjects, 16 "early" glaucoma patients and 14 cataract patients were recruited for the study. One eye of each volunteer was chosen at random. Sensitivity remained stable for the three stimulus locations in the majority of eyes over each repetition of the custom program and no obvious difference was demonstrated between trained and untrained subjects or between normal and diseased eyes. A statistically significant learning effect was exhibited, however, by subjects with large refractive errors ($p<0.05$), particularly myopes ($p<0.01$). The learning effect was suggested to be small and to occur between examinations rather than during a given examination.

In summary, the learning effect results in an increase in sensitivity particularly for peripheral stimulus locations during and between perimetric examinations in both normal and diseased eyes. The increase in sensitivity due to the learning effect is most noticeable for the second eye at the first session compared to the first eye at the first session and for the first eye at the second session compared to the first eye at the first session if the order of eye examined remains constant between the two visits. The clinical consequence of the learning effect is a noticeable improvement in the visual field indices MD, SF and CPSD between perimetric examinations which is retained over a period of months.

4.1.2. Fatigue effects in perimetry.

Fatigue effects, whereby sensitivity decreases during a perimetric examination, have been reported in both manual and automated perimetry. Greve (1973) recognised the influence of fatigue on manual perimetry and suggested that fatigue could be minimized by allowing the patient rest periods during the examination. Furthermore, Heijl and Krakau (1975) and Heijl and Drance (1983) reported that the fatigue effect was generally more pronounced for automated perimetry than for manual perimetry.

The Competer automated static perimeter (Heijl and Krakau, 1975) was employed by Heijl (1977a and b) to assess the fatigue effect in a group of 12 normal subjects and in a group

of 19 glaucoma patients. Threshold was repeated over a continuous period of approximately 30 minutes for one eye of each volunteer at 6 stimulus locations located at 5°, 10° and 15° eccentricity. Sensitivity was generally stable for the first 4 to 10 minutes but decreased over the duration of the test. The deterioration in mean threshold was less than 1.5dB for the normal group but was higher for the glaucomatous group reaching up to 6dB to 10dB at some stimulus locations. Stimulus locations that exhibited a pronounced fatigue effect were often situated close to a visual field defect; otherwise, the magnitude of the fatigue effect was found to be independent of stimulus eccentricity. Both short-term fluctuation and the number of fixation losses increased over the duration of the test for the glaucomatous group. The development of faster test procedures was encouraged to avoid fatigue and the use of the fatigue effect as a provocative test for disease was suggested.

Holmin and Krakau (1979) utilized the Competer automated perimeter to study the effect of fatigue on 5 normal and 13 glaucomatous eyes. Threshold was repeatedly assessed over a 30 minute test session for 6 stimulus locations on 12 occasions using a stimulus duration of 0.5 seconds. Normal subjects exhibited a stable sensitivity. The glaucoma patients, exhibited a decrease in sensitivity in areas of field loss, with adjacent areas of normal sensitivity exhibiting no obvious decline in sensitivity. An increased stimulus duration of 1 second overcame the fatigue effect.

The fatigue effect was studied by Heijl and Drance (1983) using both manual and automated static perimetry in 21 patients with primary open angle glaucoma and in two patients with suspected glaucoma. Six stimulus locations between 5° and 20° eccentricity were continuously assessed using a 0.25 second stimulus duration with the Competer automated perimeter over a period of 30 minutes. Background luminances of 0.1, 1.0 or 10.0 $cdm^{-2}$ were randomly employed for each individual. Manual static perimetry was undertaken using the Tübingen perimeter at background luminances of 10 and 20 $cdm^{-2}$ with a 100 msec stimulus duration for stimulus locations in or adjacent to scotomata. Each stimulus location was tested for approximately 12 minutes. The glaucoma patients

demonstrated a significant rise in the differential threshold during prolonged continuous testing, which was more pronounced in scotomatous or adjacent areas of the visual field. Furthermore, the fatigue effect was found to be independent of background luminance but was of a greater magnitude for automated perimetry. The use of the fatigue effect as a provocative test for glaucoma was suggested.

Rabineau and co-workers (1985) assessed the effect of fatigue on 8 normal trained subjects. Program 31 of the Octopus 201 automated perimeter was repeated 4 times for the right eye of each volunteer over a period of 1 hour. Short-term fluctuation and mean sensitivity was determined for each of the four consecutive examinations. Group mean mean sensitivity and short-term fluctuation showed no obvious deterioration over the four examinations. It was concluded that for practical test situations fatigue had no influence on perimetric threshold or on fluctuation in well motivated normal subjects over a period of 1 hour.

Langerhorst and co-workers (1987) assessed the fatigue effect in 44 normal subjects, 26 ocular hypertensives, 38 glaucoma suspects and 36 glaucoma patients. The Scoperimeter was utilized to continuously measure threshold at either 60 stimulus locations within 25° eccentricity over 30 minutes or at 4 stimulus locations between 5° and 15° eccentricity over twenty minutes. Although the deterioration in group mean mean sensitivity over time was greatest for the glaucoma group, considerable overlap occurred between the four groups. The use of fatigue as a provocative test for disease was therefore regarded as unreliable. Furthermore, the fatigue effect was found to be more pronounced with increase in age for all four groups. Nevertheless, the proximity of visual field loss was found to have no influence on the magnitude of the fatigue effect. A lack of correlation between fatigue in the central and in the full visual field suggested an eccentricity dependency of the fatigue effect.

The Scoperimeter was employed by Suzumura (1988) to study the fatigue effect in 26 normal eyes, 34 eyes with suspected glaucoma and 24 eyes with primary open angle

glaucoma. A static threshold custom program consisting of 60 stimulus locations was repeated five times in succession for each volunteer. All three groups of subjects exhibited a deterioration in sensitivity over time but the glaucomatous group showed the greatest reduction. The magnitude of the fatigue effect was found to be greater for an annulus between 5° and 19° compared with an annulus between 19° and 25° eccentricity and for the hemifield containing the visual field defect. It was suggested that an enhanced fatigue effect might precede identifiable glaucomatous visual field defects.

The Digilab 750 automated perimeter was employed by Johnson and co-workers (1988) to continuously measure sensitivity at 5°, 10°, 15° and 20° eccentricity at 1.5 minute intervals over a period of 21 minutes for each eye. The sample consisted of 16 normal subjects and 16 patients (13 glaucomas and 3 optic neuropathies) with "early to moderate" visual field loss. Both groups exhibited a reduction in sensitivity as a function of test duration. The magnitude of the fatigue effect was greater for the patient group, however, and increased with increase in stimulus eccentricity. The normal group exhibited negligible change in sensitivity over time at 5° and 10° eccentricity and a mean reduction of 1dB to 2dB at 15° and 20° eccentricity, while the patient group exhibited a 1dB to 2dB reduction at 5° and 10° and a 4dB reduction at 15° and 20°. In addition, a brief rest midway through the test reduced the magnitude of the fatigue effect. The patient group exhibited a higher rate of false-positive and false-negative responses, but no obvious time dependency was noticed for either of these functions. The development of faster test procedures and the introduction of rest periods during the examination was encouraged. In addition, the use of the fatigue effect as a provocative test was considered to be unreliable due to the large variation in results between both normal and pathological eyes.

The phase concept of program G1 of the Octopus perimeter was utilised by Wildberger and Robert (1988) to assess fatigue in 49 eyes of 29 patients with optic neuropathy and in 37 eyes of 28 age-matched normal subjects. Both groups were allowed a short training period prior to the test and regular breaks were allowed during the procedure. Thirty two

per cent of normal subjects and 70 to 77% of patients exhibited a lower mean sensitivity in phase 2 compared to phase 1 for all 59 stimulus locations. The difference in group mean mean sensitivity between the two groups was statistically significant. In addition, the loss of sensitivity was greater for peripheral rather than for central stimulus locations. A corresponding deterioration between phase 1 and phase 2 in the visual field indices mean defect and corrected loss variance was also reported. Using the Arden contrast sensitivity test, however, a similar deterioration in sensitivity was not obvious for either group.

Changes in sensitivity within 10° eccentricity were investigated by Fujimoto and Adachi-Usami (1993) for 10 normal subjects, 10 patients with recovered optic neuritis and 10 glaucoma patients. Program 31 of the Octopus 201 automated perimeter was repeated three times without interruption for one eye of each volunteer. Eight of the 25 stimulus locations of program 31 were selected for the calculation of mean sensitivity and short-term fluctuation. The glaucoma group exhibited a statistically significant deterioration in group mean mean sensitivity from the second to the third test ($p<0.025$), while the other two groups showed no obvious change over time. Short-term fluctuation was found to be significantly higher in the group with recovered optic neuritis than in the normal group ($p<0.025$).

In summary, the fatigue effect leads to a progressive deterioration of sensitivity as a function of test duration particularly for peripheral stimulus locations. Furthermore, the fatigue effect is more pronounced in diseased rather than in normal eyes and also in scotomatous or adjacent areas of the visual field. Fatigue effects have, in general, been investigated using the repeated thresholding of selected stimulus locations and the outcome of fatigue on the complete field within 30° eccentricity for the first and second eyes tested is unknown. In addition, the influence of rest periods on the fatigue effect within- and between-eyes at a single session of automated perimetry is also unknown.

4.1.3. Interocular asymmetry in automated static perimetry.

Despite a relative lack of information concerning the interaction between learning and fatigue effects within- and between-eyes at a single examination, various criteria for abnormality have been proposed based upon an interocular asymmetry in the visual field.

In a study of the between-subject variation of the hill of vision in 146 normal eyes, Katz and Sommer (1986) reasoned that an interocular difference in sensitivity might indicate a learning effect, a fatigue effect or a true asymmetry of sensitivity. No consistent changes in sensitivity, however, could be found between the two eyes despite the fact that the right eye was always tested first. Any interocular differences in sensitivity were considered to represent a true asymmetry of the visual field.

The interocular asymmetry of the normal visual field was assessed by Brenton and co-workers (1986) in 20 trained normal subjects. Program 30-2 of the HFA 610 was employed and the right eye was always examined first. The interocular difference in group mean mean sensitivity between the first and second examinations was minimal (+0.3dB, SD ±0.5), while the pointwise difference ranged from 0dB to 9dB, with greater asymmetry occurring in the upper hemifield. Short-term fluctuation was not statistically different between the two eyes. A difference of interocular mean sensitivity greater than 1.4dB was suggested to indicate abnormality ($p<0.001$). The fatigue effect was assumed to be counterbalanced by a learning effect that enhanced the sensitivity of the second eye.

Feuer and Anderson (1989) employed program 30-2 of the HFA to assess the visual field of both eyes of ten inexperienced normal subjects. One eye was tested twice and the order of testing was randomized to reduce the influence of learning and fatigue. The difference in mean deviation between the two eyes (0.65dB) was less than the test-retest value for the eye tested twice (0.70dB). The sensitivity of the two eyes of the normal subjects, therefore, was within the resolution of the measurement procedure. An interocular asymmetry of mean deviation greater than 2dB, or a difference of 1.5dB if confirmed on a second occasion, were suggested to be suspicious. Artifactual causes of

visual field asymmetry, however, should be excluded for the finding to represent early visual field loss.

Program G1 of the Octopus 201 automated perimeter was employed by Zulauf and co-workers (1991) to study the asymmetry between the right and left visual fields of 138 normal subjects. Mean sensitivity was significantly higher for the first eye tested ($p<0.04$). The difference in mean sensitivity between the first and second eyes of trained subjects was 0.4dB (95th percentile 1.7dB), while that of untrained subjects was 0.6dB (95th percentile 2.4dB). It was concluded that an asymmetry in mean sensitivity of greater than 2dB was indicative of early visual field loss.

A retrospective study by Thölen and co-workers (1992) examined whether lateral (ie interocular) differences in visual field sensitivity indicated the future onset of glaucoma. The sample initially comprised 47 patients exhibiting ocular hypertension, 22 of whom eventually developed glaucoma. Mean sensitivity was calculated for stimulus locations within 30° eccentricity for either programs 31/32 or program G1 of the Octopus 201 perimeter. The interocular difference in sensitivity was significantly higher ($p=0.027$) in the group that developed glaucoma despite the fact that the visual field indices for both eyes were within normal limits. Furthermore, the same eye repeatedly demonstrated the lower sensitivity. An ocular hypertensive patient with an interocular difference in mean sensitivity, therefore, was at greater risk of developing glaucoma.

In summary, any interocular difference in the perimetric sensitivity of normal subjects is considered to be less than that of the resolution of the measurement procedure. An exaggerated interocular difference of sensitivity, however, has been suggested to indicate abnormality assuming that artifactual causes of visual field asymmetry such as learning and fatigue effects have been excluded.

It can be hypothesized that within-eye learning and fatigue effects oppose each other during any given examination and that the resultant effect on perimetric sensitivity

changes with the number and frequency of follow-up examinations. That is, the influence of the learning component is initially prevalent and consequently the fatigue component is masked. The learning component diminishes, however, with gain in experience of the test procedure by the patient. At some point in time, the influence of the learning component plateaus and the fatigue component prevails. At this stage, the resultant effect on perimetric sensitivity is influenced to a greater extent by the fatigue component which increases with test duration. In addition, it can also be hypothesized that the resultant is different between the first and second eyes at the same visit due to an increased influence of the fatigue effect.

### 4.1.4. Aim of the study.

By using subjects experienced in automated static perimetry the aim of the study was to determine; (1) the time course of the fatigue effect within the first and second eye at a given examination across the visual field out to 30° eccentricity; (2) the influence of a rest period during the examination of a given eye; and (3) whether any differences in the fatigue effect are present between ocular hypertensive patients and age-matched normal subjects. Such information might provide insight into the underlying basis for the interocular asymmetry recorded at a given visual field examination.

## 4.2. Materials and methods.

### 4.2.1. Sample.

The sample consisted of two groups: 20 normal subjects (9 males and 11 females; mean age 67.21 years, SD 8.21) and 20 ocular hypertensive patients (8 males and 12 females; mean age 66.55 years, SD 6.50). Subjects were age-matched between the two groups. All individuals had normal central fields and had previously experienced a minimum of 6 static threshold central visual field examinations with the HFA program 30-2. All had distance refractive errors of not greater than ±3.00DS and / or ±2.50DC, a visual acuity of 6/9 or better, normal media and normal fundi.

Normal subjects had an intraocular pressure of less than 21 mmHg, while the ocular hypertensives had a recorded intraocular pressure greater than 21 mmHg on more than one prior occasion. Exclusion criteria included systemic conditions with known ocular involvement, systemic medication with known CNS effects, a past history of eye disease, the use of pilocarpine topical eye treatment, the use of contact lenses, a history of diabetes mellitus and neurological or psychiatric illness. Exclusion criteria for the normal group additionally included a positive family history of glaucoma in a first degree relative and the use of any topical eye treatment.

### 4.2.2. Perimetry.

Perimetry was undertaken for both eyes of each individual using program G1X of the Octopus 1-2-3 perimeter. The stimulus approximates to a Goldmann size III (0.564°) and is generated by a broad band light emitting diode (592nm +78nm / -32nm at 10%) presented for a duration of 100 msecs. The maximum stimulus intensity of 4000 asb is referenced to a value of 0dB and the background luminance is 31.5 asb (Octopus 1-2-3 Operating Instructions, 1990). The direct projection of both the stimulus and the fixation target from infinity with the Octopus 1-2-3 removes any need for a near correction. Program G1X thresholds 59 stimulus locations, including the fovea, out to an eccentricity of 28.3°. The program is divided into two phases. During phase 1, all 59 locations are thresholded. Stimuli are presented, using a 4-2dB bracketing strategy based upon a starting intensity 4dB brighter than the age-corrected normal values. The final threshold value is adjusted by ±1dB depending on whether the final stimulus is seen or not seen respectively. During phase 2, all the locations are re-thresholded using a starting intensity corresponding to that recorded in phase 1. Each phase consists of 4 stages, with phase 1 comprising stages 1 to 4, and phase 2 comprising stages 5 to 8. The location of the stimuli in stage 1 are identical to those of stage 5, and likewise for stages 2 and 6, 3 and 7 and 4 and 8. The thresholding of all points in any stage is completed before the start of the ensuing stage (Octopus 1-2-3 Perimeter Digest, 1991; Messmer and Flammer, 1991).

The Octopus 1-2-3 perimeter was selected for three reasons. Firstly, the stimuli are thresholded in a relatively random order with respect to eccentricity (Figure 4.1) unlike the HFA which measures sensitivity at four primary seed points to determine the starting intensity of neighbouring stimulus locations. As the seed points of the HFA are located at 12.7° eccentricity the order of threshold determination is inherently biased towards central stimulus locations earlier in the test program (Heijl, 1985). Secondly, the examination routine of program G1X is divided into two phases thereby providing a convenient means of assessing the effect of a within-examination rest period. Thirdly, the two phases are each divided into four stages thereby providing a means of assessing within-examination changes in sensitivity.

The designated first eye for a given subject was randomly assigned. A rest period of 60 seconds was given to each subject at the end of phase 1 and a further break of 3 minutes was allowed before the examination of the second eye. The distance refractive correction was employed throughout and pupil size was measured for each eye using the video eye monitor. The measurement was corrected for the magnification of the optical system. Mean pupil sizes were 4.25 mm (SD 0.80) and 4.05 mm (SD 0.60) for the first and second eyes respectively of the normal group and 4.40 mm (SD 0.90) and 4.60 mm (SD 1.00) for the first and second eyes respectively of the ocular hypertensive group.

Throughout the examination the Octopus 1-2-3 displays a rolling (ie continually updated) value of the visual field indices on the monitor which represent the field at any given time. The indices displayed during the examination are only an approximation, however, since they are derived from sensitivity values gathered both from completely and incompletely thresholded stimulus locations. As stimuli are presented at an initial value brighter than the expected threshold, the incompletely thresholded locations exhibit an apparent under estimation of sensitivity. This error in the displayed value is then compounded throughout each of the stages. The indices displayed on the print-out, however, are not subject to this error.

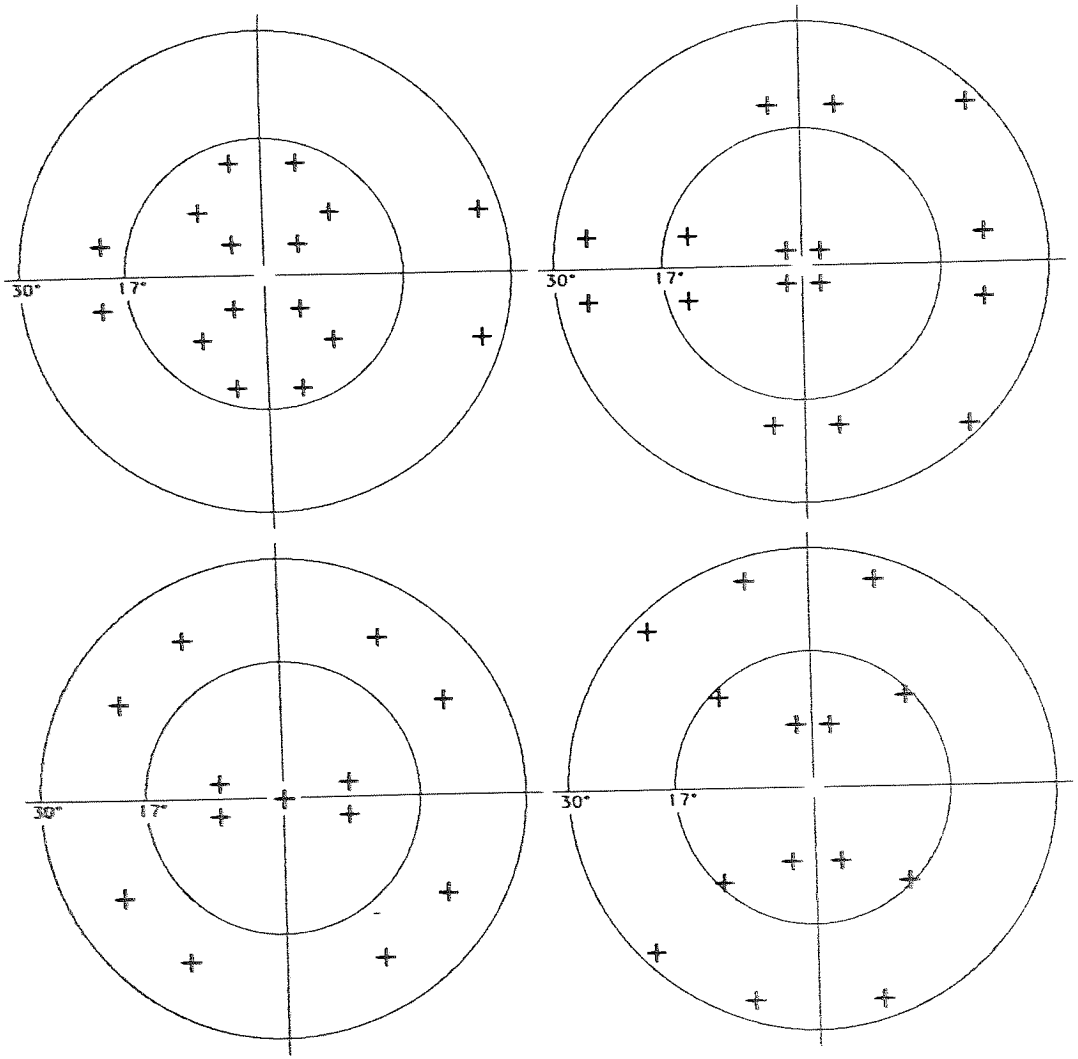



Fig. 4.1. The spatial arrangement of stimulus locations for each stage of the GIX program (Top left; stages 1 and 5. Top right; stages 2 and 6. Bottom left; stages 3 and 7. Botttom right; stages 4 and 8).

The results for each stage cannot be accessed via the instrument printer without the premature curtailment of the examination. The phase 1 results were therefore documented photographically, under the room illumination of the examination using 125 ASA FP4 film without flash, whilst the patient rested between phases. The equations of Flammer (1986) were used to recalculate the mean defect and loss variance corresponding to the end of each of the eight individual stages. The stimulus locations corresponding to each stage were identified from the G1X literature (Octopus 1-2-3 Operating Instructions, 1990; Octopus 1-2-3 Perimeter Digest, 1991). The phase 2 results were calculated from the final print-out which displays the sensitivity values in terms of the mean of phase 1 and phase 2. The appropriate normal values necessary for the calculations were provided by the manufacturer (Personal communication Interzeag AG, Schlieren, Switzerland). The short-term fluctuation was similarly calculated for each of the stages 5 to 8. The time to complete each stage, the total number of stimulus presentations and the number of catch trials were also recorded.

4.2.3. Primary analysis.

A repeated measures ANCOVA was separately carried out for mean defect and loss variance with ocular condition as a between-subjects factor and stage, phase, and eye as within-subject factors and age as a covariate. The ANCOVA is an analysis of variance technique which was used to correct for the effect of the differing ages within the sample. Each stage of program G1X was considered to be an ordinal categorical variable (ie stage 1, stage 2, stage 3, etc). Where appropriate, the Greenhouse-Geisser correction was applied to account for the lack of compound symmetry due to the serial correlation between the repeated measures. In the case of short-term fluctuation, which was only calculated over phase 2, the within-subject factors were stage and eye. To account for accumulating Type I errors (the possibility of finding a significant difference for a particular parameter when no such difference actually exists) a Bonferroni correction was applied. The conventional 0.05 level was divided by the number of analyses (=3) and the outcome of statistical testing was considered to be significant only at the $p \leq 0.017$ level.

4.2.4. Secondary analysis.

To identify potential differences in the fatigue effect between hemifields, indices were calculated for each of the four hemifields. Separate ANCOVA were then undertaken to identify for each index, differences between the superior and inferior hemifields and between the nasal and temporal hemifields. The influence of stimulus eccentricity was investigated by separately calculating the indices for locations within and beyond 17° eccentricity. An eccentricity of 17° was chosen in order to achieve an approximately equal distribution of stimulus locations between the selected annuli: 31 stimuli were located inside 17° eccentricity and 28 stimuli were located beyond 17° eccentricity. The bias arising over the various stages from the inequality in the distribution of the stimulus locations between the two annuli (Figure 4.1) was reduced by undertaking the ANCOVA on the central and peripheral annuli indices calculated cumulatively over stage. A Bonferroni correction was applied both to the hemifield and to the annulus analysis. Only tests significant at $p \leq 0.017$ are discussed.

The Bonferroni correction is only appropriate if the analyses are independent of each other. Some dependency, however, is present in that mean defect covaries with loss variance (albeit more in severe loss), the indices representing the global field are highly correlated with those from each of the hemifields and from each of the annuli and the indices of one hemifield are correlated with those of the opposite hemifield. As a result, the inferences are more conservative than if the analyses were completely independent.

## 4.3. Results.

### 4.3.1. Global mean defect (MD).

The group mean global MD for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.2 and Table 4.1 respectively. The MD was poorer (ie more positive) with increase in age ($p=0.003$). Furthermore, the MD was poorer in the second eye ($p<0.001$) irrespective of diagnosis and declined (ie became more positive) over stage for both groups ($p<0.001$). The deterioration in the group mean global MD over stage was 2.57dB and 2.44dB for the first and second eyes respectively of the normal group and 2.14dB and 2.33dB for the ocular hypertensive group. The decline over stage was greater for phase 1 than for phase 2 ($p<0.001$). The MD was worse in phase 2 compared with phase 1 ($p<0.001$) and this difference was more pronounced for the ocular hypertensive group ($p=0.009$) with the difference between groups increasing with increase in age ($p=0.012$).

### 4.3.2. Global loss variance (LV).

The group mean global LV for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.3 and Table 4.2 respectively. The LV was poorer (ie more positive) with increase in age ($p=0.004$). Furthermore, the LV was poorer in the second eye ($p=0.007$) irrespective of diagnosis and declined (ie became more positive) over stage for both groups ($p<0.001$). The deterioration in the group mean global LV over stage was 4.29dB$^2$ and 7.23dB$^2$ for the first and second eyes respectively of the normal group and 5.32dB$^2$ and 6.02dB$^2$ for the ocular hypertensive group. The LV was greater in phase 2 compared to phase 1 ($p<0.001$) and the difference between phases was greatest in the first eye of the elderly ocular hypertensives ($p=0.016$). The overall decline in sensitivity over stage and phase was greater in the normal group compared to the ocular hypertensive group ($p=0.012$).

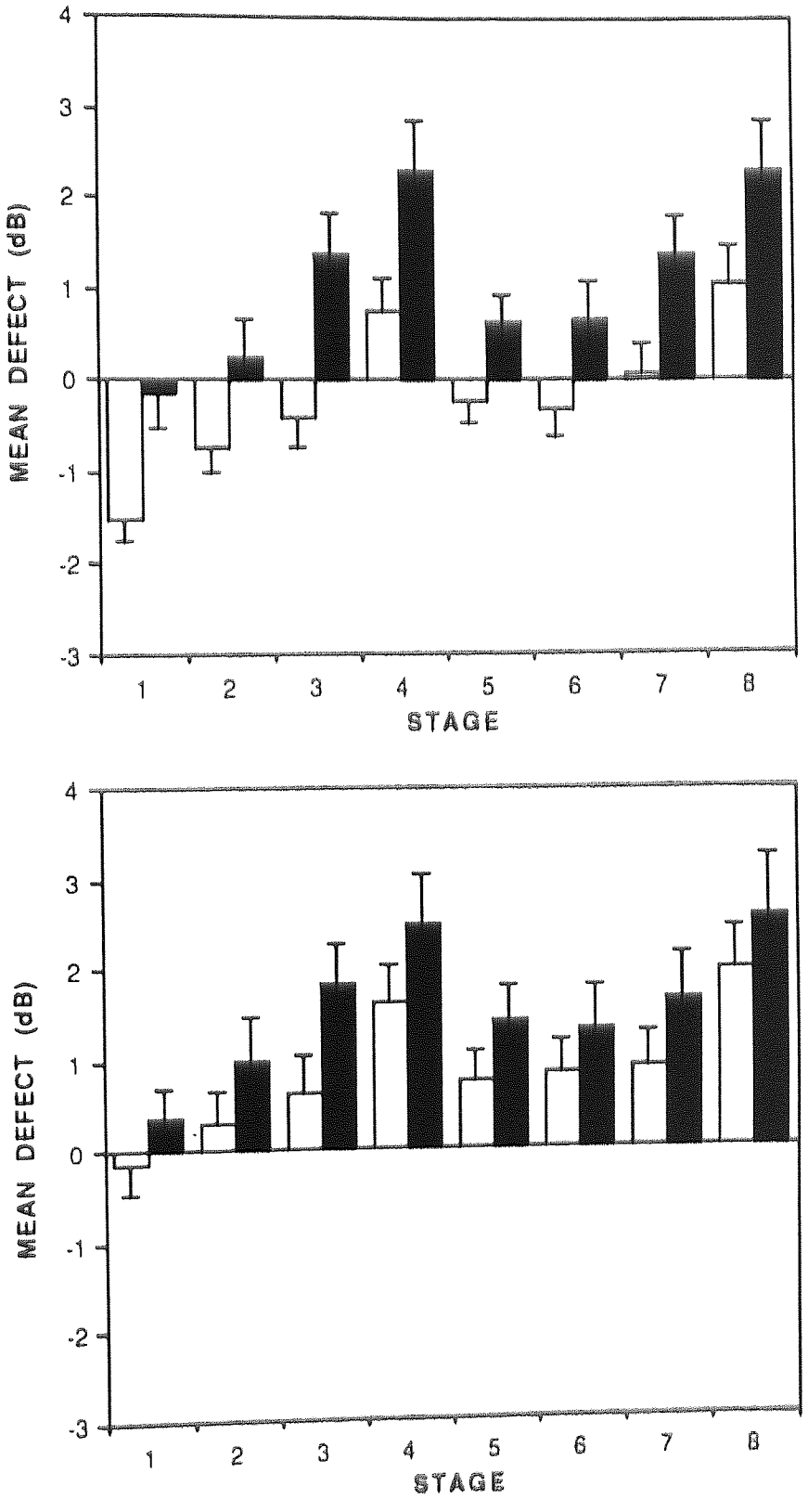



Fig. 4.2. Bar charts of global mean defect (dB) against stage for the normal subjects (top) and ocular hypertensive patients (bottom); Open bars first eye; closed bars second eye. The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.568 | 0.568 | 0.79 | =0.379 |
| Age | 1 | 7.327 | 7.327 | 10.23 | =0.003 |
| Age X group | 1 | 0.845 | 0.845 | 1.18 | =0.284 |
| Error | 36 | 25.786 | 0.716 | | |
| Eye | 1 | 3.237 | 3.237 | 57.01 | <0.001 |
| Eye X group | 1 | 0.194 | 0.194 | 3.42 | =0.072 |
| Eye X age | 1 | 0.085 | 0.085 | 1.51 | =0.227 |
| Eye X age X group | 1 | 0.145 | 0.145 | 2.56 | =0.118 |
| Error | 36 | 2.044 | 0.056 | | |
| Stage | 3 | 5.528 | 1.842 | 80.00 | <0.001 |
| Stage X group | 3 | 0.026 | 0.008 | 0.38 | =0.691 |
| Stage X age | 3 | 0.224 | 0.074 | 3.24 | =0.043 |
| Stage X age X group | 3 | 0.017 | 0.005 | 0.25 | =0.789 |
| Error | 108 | 2.487 | 0.023 | | |

Table 4.1. Repeated measures analysis of co-variance for global MD.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Phase | 1 | 0.848 | 0.848 | 51.63 | <0.001 |
| Phase X group | 1 | 0.123 | 0.123 | 7.50 | =0.009 |
| Phase X age | 1 | 0.033 | 0.033 | 2.02 | =0.164 |
| Phase X age X group | 1 | 0.116 | 0.116 | 7.06 | =0.012 |
| Error | 36 | 0.591 | 0.016 | | |
| Eye X stage | 3 | 0.113 | 0.037 | 3.15 | =0.034 |
| Eye X stage X group | 3 | 0.023 | 0.007 | 0.65 | =0.566 |
| Eye X stage X age | 3 | 0.048 | 0.016 | 1.33 | =0.269 |
| Eye X stage X age X group | 3 | 0.025 | 0.008 | 0.69 | =0.539 |
| Error | 108 | 1.297 | 0.012 | | |
| Eye X phase | 1 | 0.105 | 0.105 | 5.69 | =0.022 |
| Eye X phase X group | 1 | 0.032 | 0.032 | 1.76 | =0.193 |
| Eye X phase X age | 1 | 0.018 | 0.018 | 1.02 | =0.319 |
| Eye X phase X age X group | 1 | 0.034 | 0.034 | 1.90 | =0.177 |
| Error | 36 | 0.664 | 0.018 | | |

Table 4.1. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Phase X stage | 3 | 0.624 | 0.208 | 24.66 | <0.001 |
| Phase X stage X group | 3 | 0.006 | 0.002 | 0.27 | =0.823 |
| Phase X stage X age | 3 | 0.007 | 0.002 | 0.29 | =0.805 |
| Phase X stage X age X group | 3 | 0.005 | 0.001 | 0.22 | =0.860 |
| Error | 108 | 0.911 | 0.008 | | |
| Eye X phase X stage | 3 | 0.023 | 0.007 | 1.05 | =0.368 |
| Eye X phase X stage X group | 3 | 0.031 | 0.010 | 1.40 | =0.248 |
| Eye X phase X stage X age | 3 | 0.026 | 0.008 | 1.19 | =0.314 |
| Eye X phase X stage X age X group | 3 | 0.034 | 0.011 | 1.57 | =0.205 |
| Error | 108 | 0.799 | 0.007 | | |

Table 4.1. (continued).

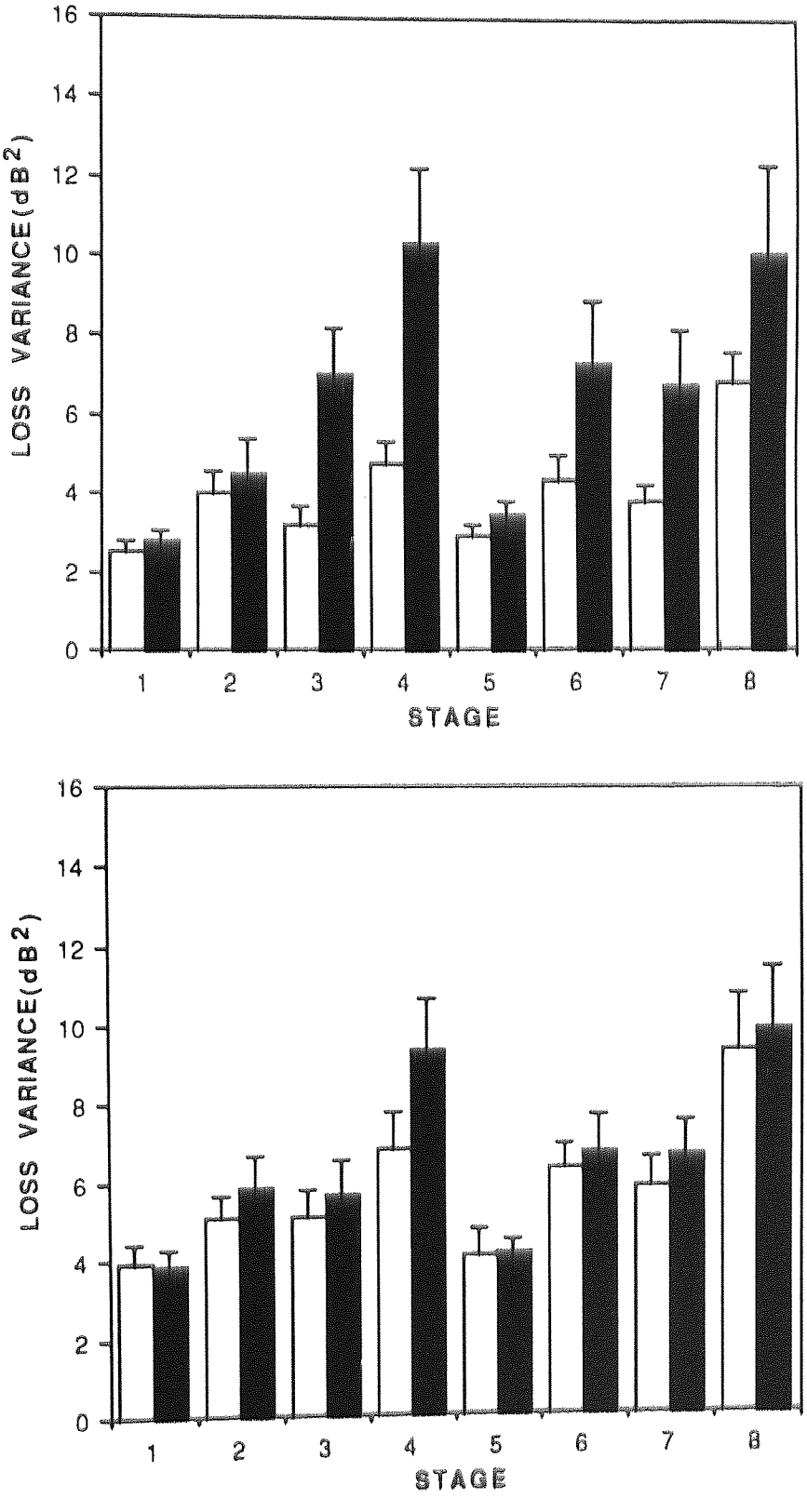



Fig. 4.3. Bar charts of global loss variance ($dB^2$) against stage for the normal subjects (top) and ocular hypertensive patients (bottom); Open bars first eye; closed bars second eye. The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.731 | 0.731 | 0.46 | =0.504 |
| Age | 1 | 15.473 | 15.473 | 9.62 | =0.004 |
| Age X group | 1 | 0.257 | 0.257 | 0.16 | =0.691 |
| Error | 36 | 57.884 | 1.607 | | |
| Eye | 1 | 6.501 | 6.501 | 8.16 | =0.007 |
| Eye X group | 1 | 0.031 | 0.031 | 0.04 | =0.843 |
| Eye X age | 1 | 0.766 | 0.766 | 0.96 | =0.333 |
| Eye X age X group | 1 | 0.092 | 0.092 | 0.12 | =0.735 |
| Error | 36 | 28.673 | 0.796 | | |
| Stage | 3 | 46.194 | 15.398 | 33.94 | <0.001 |
| Stage X group | 3 | 0.053 | 0.017 | 0.04 | =0.989 |
| Stage X age | 3 | 0.743 | 0.247 | 0.55 | =0.652 |
| Stage X age X group | 3 | 0.067 | 0.022 | 0.05 | =0.985 |
| Error | 108 | 48.993 | 0.453 | | |

Table 4.2. Repeated measures analysis of co-variance for global LV.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Phase | 1 | 4.022 | 4.022 | 30.67 | <0.001 |
| Phase X group | 1 | 0.001 | 0.001 | 0.01 | =0.923 |
| Phase X age | 1 | 0.065 | 0.065 | 0.50 | =0.483 |
| Phase X age X group | 1 | 0.001 | 0.001 | 0.00 | =0.945 |
| Error | 36 | 4.722 | 0.131 | | |
| Eye X stage | 3 | 1.488 | 0.496 | 2.04 | =0.123 |
| Eye X stage X group | 3 | 0.145 | 0.048 | 0.20 | =0.870 |
| Eye X stage X age | 3 | 0.344 | 0.114 | 0.47 | =0.673 |
| Eye X stage X age X group | 3 | 0.216 | 0.072 | 0.30 | =0.797 |
| Error | 108 | 26.312 | 0.243 | | |
| Eye X phase | 1 | 0.213 | 0.213 | 1.03 | =0.316 |
| Eye X phase X group | 1 | 1.233 | 1.233 | 5.96 | =0.020 |
| Eye X phase X age | 1 | 0.503 | 0.503 | 2.43 | =0.127 |
| Eye x phase X age X group | 1 | 1.317 | 1.317 | 6.36 | =0.016 |
| Error | 36 | 7.453 | 0.207 | | |

Table 4.2. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Phase X stage | 3 | 0.392 | 0.130 | 1.19 | =0.315 |
| Phase X stage X group | 3 | 1.266 | 0.422 | 3.85 | =0.012 |
| Phase X stage X age | 3 | 0.303 | 0.101 | 0.92 | =0.433 |
| Phase X stage X age X group | 3 | 1.106 | 0.368 | 3.37 | =0.021 |
| Error | 108 | 11.832 | 0.109 | | |
| Eye X phase X stage | 3 | 1.490 | 0.496 | 3.34 | =0.024 |
| Eye X phase X stage X group | 3 | 0.266 | 0.088 | 0.60 | =0.609 |
| Eye X phase X stage X age | 3 | 0.535 | 0.178 | 1.20 | =0.312 |
| Eye X phase X stage X age X group | 3 | 0.352 | 0.117 | 0.79 | =0.496 |
| Error | 108 | 16.055 | 0.148 | | |

Table 4.2. (continued).

4.3.3. Global short-term fluctuation (SF).

The group mean global SF for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.4 and Table 4.3 respectively. The SF was unaffected by increase in age ($p=0.081$). It was similar between the two eyes ($p=0.061$), regardless of group ($p=0.890$) and the alteration over stage was not statistically significant ($p=0.066$).

4.3.4. Superior / inferior hemifield mean defect.

The group mean superior and inferior hemifield MD for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.5 and Table 4.4 respectively.

The MD of both the superior and inferior hemifields deteriorated with increase in age ($p=0.002$). Both hemifield MDs were poorer in the second eye ($p<0.001$), particularly for the ocular hypertensive group ($p=0.017$). The MD of both hemifields deteriorated over stage ($p<0.001$) and this deterioration was greater with increase in age ($p=0.003$). The deterioration over stage of both hemifield MDs was greater for phase 1 than for phase 2 ($p<0.001$) and this deterioration was different between the two eyes ($p=0.004$). The MD of both hemifields were poorer in phase 2 than phase 1 for the older patients of the ocular hypertensive group ($p=0.001$).

The inferior hemifield MD was poorer than that of the superior hemifield ($p<0.001$) and this difference was greater with increase in age ($p=0.009$). Although not statistically significant overall ($p=0.199$), the trend was to a greater deterioration over stage of the inferior hemifield MD compared to that of the superior hemifield, which increased with increase in age ($p<0.001$) and was greater for the ocular hypertensive group ($p<0.001$) particularly as age increased ($p<0.001$). Furthermore, the greater deterioration over stage of the inferior hemifield MD with increase in age compared to that of the superior hemifield was more pronounced for the second eye ($p=0.009$). The difference between hemifield MDs over stage was also more pronounced for the first phase ($p<0.001$).

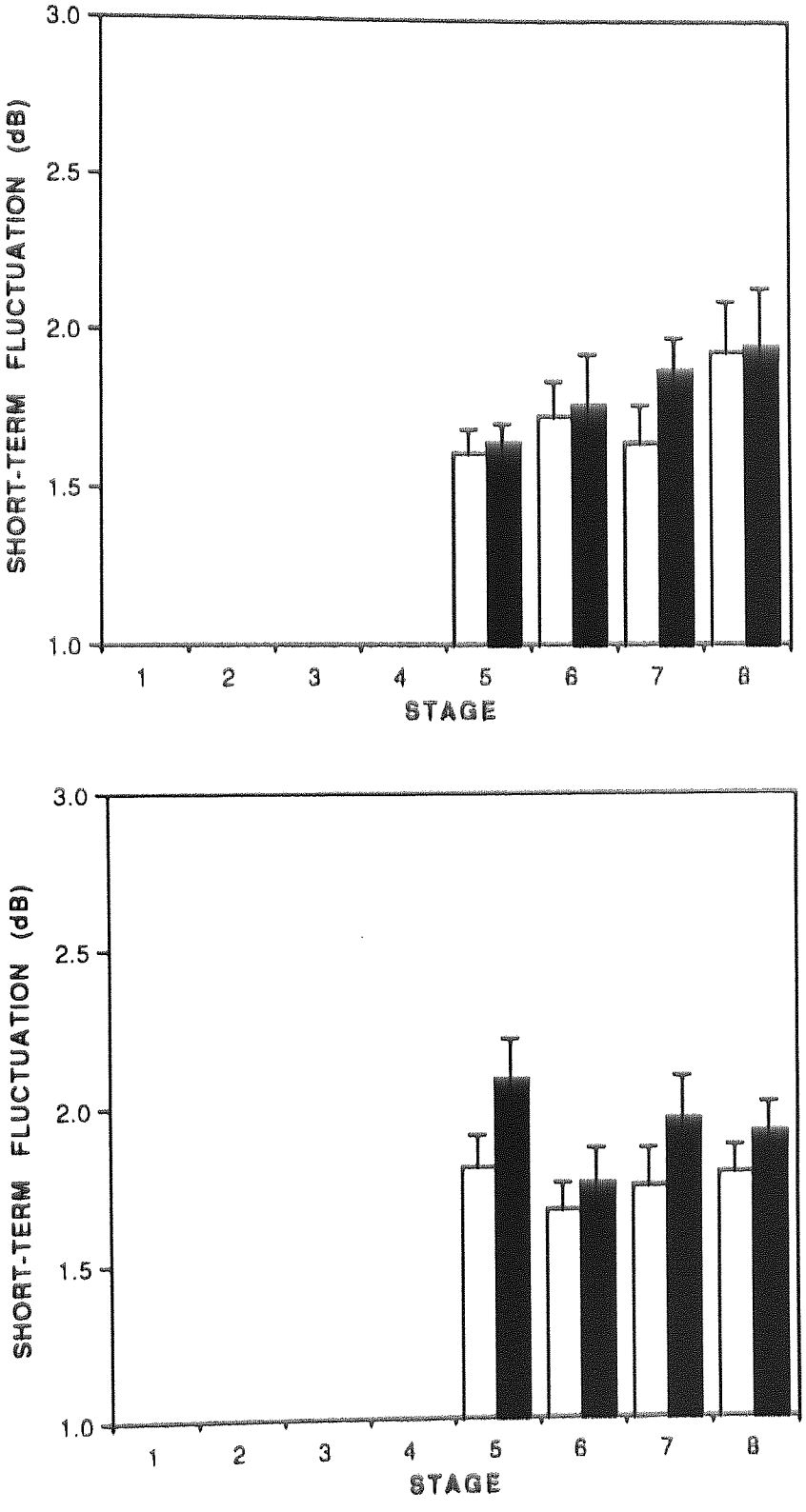



Fig. 4.4. Bar charts of global short-term fluctuation (dB) against stage for the normal subjects (top) and ocular hypertensive patients (bottom); Open bars first eye; closed bars second eye. The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.045 | 0.045 | 0.26 | =0.609 |
| Age | 1 | 0.557 | 0.557 | 3.22 | =0.081 |
| Age X group | 1 | 0.071 | 0.071 | 0.41 | =0.525 |
| Error | 36 | 6.227 | 0.172 | | |
| Eye | 1 | 0.377 | 0.377 | 3.73 | =0.061 |
| Eye X group | 1 | 0.001 | 0.001 | 0.02 | =0.890 |
| Eye X age | 1 | 0.009 | 0.009 | 0.09 | =0.765 |
| Eye X age X group | 1 | 0.004 | 0.004 | 0.04 | =0.836 |
| Error | 36 | 3.639 | 0.101 | | |
| Stage | 3 | 0.472 | 0.157 | 2.58 | =0.066 |
| Stage X group | 3 | 0.110 | 0.036 | 0.60 | =0.593 |
| Stage X age | 3 | 0.017 | 0.005 | 0.09 | =0.948 |
| Stage X age X group | 3 | 0.122 | 0.040 | 0.67 | =0.554 |
| Error | 108 | 6.588 | 0.061 | | |

Table 4.3. Repeated measures analysis of co-variance for global SF.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X stage | 3 | 0.020 | 0.006 | 0.11 | =0.944 |
| Eye X stage X group | 3 | 0.087 | 0.029 | 0.49 | =0.676 |
| Eye X stage X age | 3 | 0.265 | 0.088 | 1.48 | =0.226 |
| Eye X stage X age X group | 3 | 0.108 | 0.036 | 0.60 | =0.601 |
| Error | 108 | 6.445 | 0.059 | | |



Table 4.3. (continued).

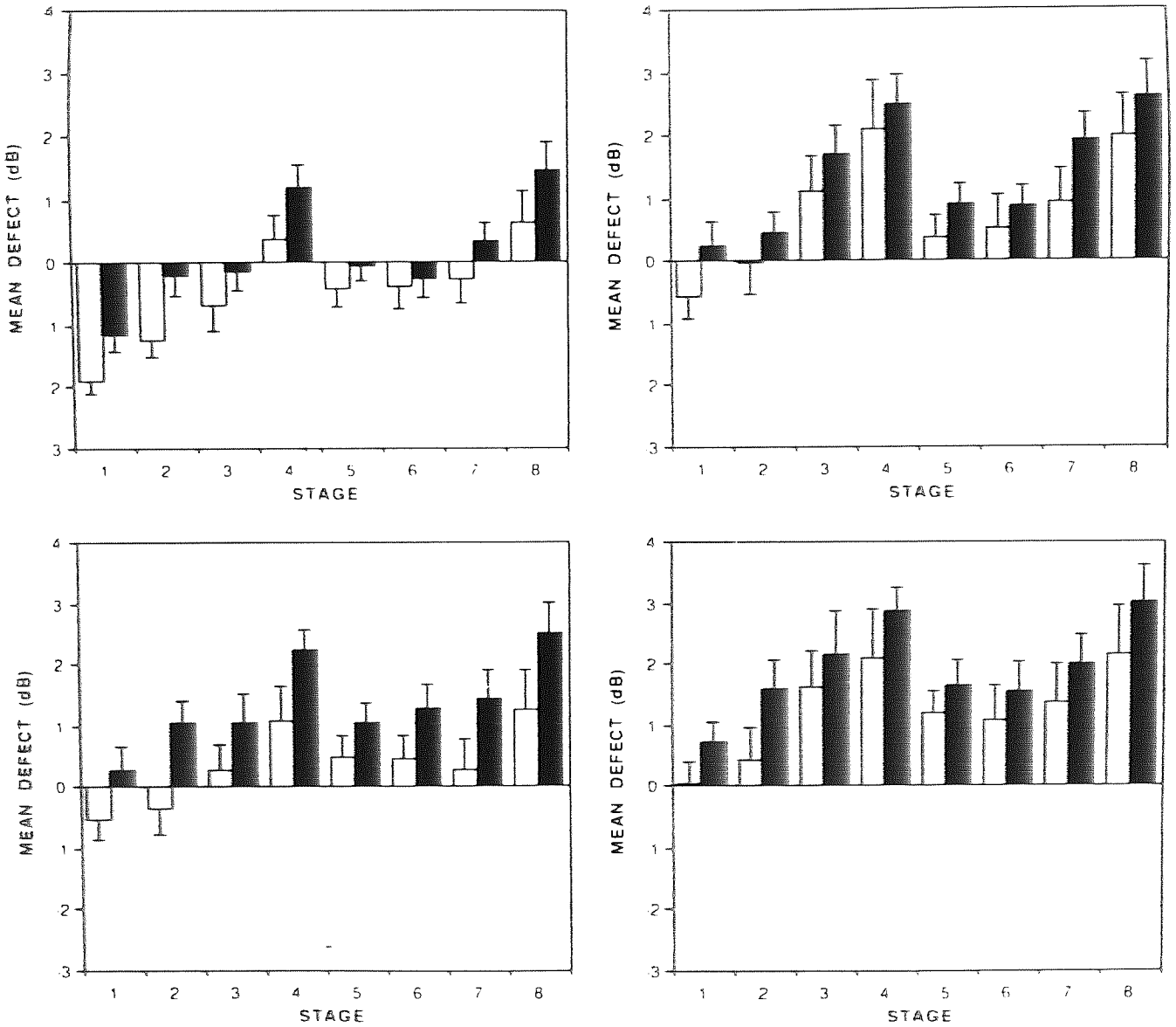



Fig. 4.5. Bar charts of superior (open bars) and inferior hemifield (closed bars) mean defect (dB) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 1.700 | 1.700 | 1.15 | =0.292 |
| Age | 1 | 16.454 | 16.454 | 11.08 | =0.002 |
| Age X group | 1 | 2.340 | 2.340 | 1.58 | =0.217 |
| Error | 36 | 53.473 | 1.485 | | |
| Superior / inferior (S/I) | 1 | 5.781 | 5.781 | 36.32 | <0.001 |
| S/I X group | 1 | 0.391 | 0.391 | 2.46 | =0.125 |
| S/I X age | 1 | 1.234 | 1.234 | 7.76 | =0.009 |
| S/I X age X group | 1 | 0.360 | 0.360 | 2.26 | =0.141 |
| Error | 36 | 5.730 | 0.159 | | |
| Eye | 1 | 6.173 | 6.173 | 52.68 | <0.001 |
| Eye X group | 1 | 0.731 | 0.731 | 6.25 | =0.017 |
| Eye X age | 1 | 0.328 | 0.328 | 2.80 | =0.103 |
| Eye X age X group | 1 | 0.588 | 0.588 | 5.02 | =0.031 |
| Error | 36 | 4.218 | 0.117 | | |

Table 4.4. Repeated measures analysis of co-variance for superior / inferior (S/I) MD.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 9.582 | 3.194 | 69.93 | <0.001 |
| Stage X group | 3 | 0.357 | 0.119 | 2.61 | =0.079 |
| Stage X age | 3 | 0.857 | 0.285 | 6.26 | =0.003 |
| Stage X age X group | 3 | 0.282 | 0.094 | 2.06 | =0.133 |
| Error | 108 | 4.933 | 0.045 | | |
| Phase | 1 | 1.365 | 1.365 | 32.76 | <0.001 |
| Phase X group | 1 | 0.553 | 0.553 | 13.28 | <0.001 |
| Phase X age | 1 | 0.222 | 0.222 | 5.34 | =0.027 |
| Phase X age X group | 1 | 0.514 | 0.514 | 12.34 | =0.001 |
| Error | 36 | 1.500 | 0.041 | | |
| S/I X eye | 1 | 0.041 | 0.041 | 1.11 | =0.299 |
| S/I X eye X group | 1 | 0.006 | 0.006 | 0.17 | =0.686 |
| S/I X eye X age | 1 | 0.199 | 0.199 | 5.36 | =0.026 |
| S/I X eye X age X group | 1 | 0.007 | 0.007 | 0.21 | =0.652 |
| Error | 36 | 1.339 | 0.037 | | |

Table 4.4. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| S/I X stage | 3 | 0.103 | 0.034 | 1.61 | =0.199 |
| S/I X stage X group | 3 | 0.595 | 0.198 | 9.25 | <0.001 |
| S/I X stage X age | 3 | 0.931 | 0.310 | 14.47 | <0.001 |
| S/I X stage X age X group | 3 | 0.557 | 0.185 | 8.66 | <0.001 |
| Error | 108 | 2.317 | 0.021 | | |
| Eye X stage | 3 | 0.369 | 0.123 | 5.02 | =0.004 |
| Eye X stage X group | 3 | 0.117 | 0.039 | 1.60 | =0.199 |
| Eye X stage X age | 3 | 0.187 | 0.062 | 2.55 | =0.068 |
| Eye X stage X age X group | 3 | 0.121 | 0.040 | 1.65 | =0.189 |
| Error | 108 | 2.649 | 0.024 | | |
| S/I X phase | 1 | 0.060 | 0.060 | 3.58 | =0.066 |
| S/I X phase X group | 1 | 0.005 | 0.005 | 0.31 | =0.583 |
| S/I X phase X age | 1 | 0.008 | 0.008 | 0.52 | =0.476 |
| S/I X phase X age X group | 1 | 0.004 | 0.004 | 0.27 | =0.608 |
| Error | 36 | 0.604 | 0.016 | | |

Table 4.4. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X phase | 1 | 0.185 | 0.185 | 4.66 | =0.037 |
| Eye X phase X group | 1 | 0.092 | 0.092 | 2.32 | =0.136 |
| Eye X phase X age | 1 | 0.069 | 0.069 | 1.74 | =0.195 |
| Eye X phase X age X group | 1 | 0.100 | 0.100 | 2.53 | =0.120 |
| Error | 36 | 1.435 | 0.039 | | |
| Phase X stage | 3 | 1.580 | 0.526 | 25.60 | <0.001 |
| Phase X stage X group | 3 | 0.121 | 0.040 | 1.97 | =0.129 |
| Phase X stage X age | 3 | 0.078 | 0.026 | 1.27 | =0.289 |
| Phase X stage X age X group | 3 | 0.121 | 0.040 | 1.97 | =0.129 |
| Error | 108 | 2.222 | 0.020 | | |
| S/I X eye X stage | 3 | 0.003 | 0.001 | 0.06 | =0.981 |
| S/I X eye X stage X group | 3 | 0.012 | 0.004 | 0.23 | =0.878 |
| S/I X eye X stage X age | 3 | 0.232 | 0.077 | 4.04 | =0.009 |
| S/I X eye X stage X age X group | 3 | 0.013 | 0.004 | 0.23 | =0.873 |
| Error | 108 | 2.073 | 0.019 | | |

Table 4.4. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| S/I X eye X phase | 1 | 0.030 | 0.030 | 3.15 | =0.084 |
| S/I X eye X phase X group | 1 | 0.006 | 0.006 | 0.69 | =0.412 |
| S/I X eye X phase X age | 1 | 0.015 | 0.015 | 1.61 | =0.212 |
| S/I X eye X phase X age X group | 1 | 0.009 | 0.009 | 0.97 | =0.330 |
| Error | 36 | 0.350 | 0.009 | | |
| S/I X phase X stage | 3 | 0.253 | 0.084 | 7.56 | <0.001 |
| S/I X phase X stage X group | 3 | 0.061 | 0.020 | 1.83 | =0.146 |
| S/I X phase X stage X age | 3 | 0.029 | 0.009 | 0.90 | =0.446 |
| S/I X phase X stage X age X group | 3 | 0.063 | 0.021 | 1.89 | =0.136 |
| Error | 108 | 1.206 | 0.011 | | |
| Eye X phase X stage | 3 | 0.025 | 0.008 | 0.63 | =0.587 |
| Eye X phase X stage X group | 3 | 0.019 | 0.006 | 0.48 | =0.686 |
| Eye X phase X stage X age | 3 | 0.012 | 0.004 | 0.31 | =0.805 |
| Eye X phase X stage X age X group | 3 | 0.022 | 0.007 | 0.56 | =0.633 |
| Error | 108 | 1.435 | 0.013 | | |

Table 4.4. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| S/I X eye X phase X stage | 3 | 0.018 | 0.006 | 0.76 | =0.501 |
| S/I X eye X phase X stage X group | 3 | 0.015 | 0.005 | 0.64 | =0.571 |
| S/I X eye X phase X stage X age | 3 | 0.010 | 0.003 | 0.43 | =0.703 |
| S/I X eye X phase X stage X age X group | 3 | 0.013 | 0.004 | 0.55 | =0.624 |
| Error | 108 | 0.875 | 0.008 | | |



Table 4.4. (continued).

4.3.5. Superior / inferior hemifield loss variance.

The group mean superior and inferior hemifield LV for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.6 and Table 4.5 respectively. Both the superior and inferior hemifield LVs deteriorated with increase in age ($p=0.003$). The LV of both hemifields was worse for the second eye ($p=0.010$). Both hemifield LVs deteriorated over stage ($p<0.001$), particularly in the second eye ($p=0.012$) and over phase ($p<0.001$). The deterioration over stage of both hemifield LVs was greater for phase 2 than for phase 1 ($p=0.011$). The deterioration over phase of both hemifields was greater for the second eye of the normal group ($p=0.017$).

Although the overall magnitude of the LV was similar for the two hemifields ($p=0.987$), the deterioration in the superior hemifield LV over stage was greater than that of the inferior hemifield ($p=0.009$).

4.3.6. Superior / inferior hemifield short-term fluctuation.

The group mean superior and inferior hemifield SF for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.7 and Table 4.6 respectively. The SF was unaffected by age ($p=0.267$) and was similar between the two eyes ($p=0.028$), regardless of group ($p=0.859$).

There was no difference in the SF of the two hemifields ($p=0.397$) or in the magnitude of the deterioration over stage between hemifields ($p=0.529$).

4.3.7. Nasal / temporal hemifield mean defect.

The group mean nasal and temporal hemifield MD for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.8 and Table 4.7 respectively. The MD of both hemifields was poorer with increase in age ($p=0.003$). Both the nasal and temporal hemifield MDs were poorer in

the second eye ($p<0.001$). Both hemifield MDs deteriorated over stage ($p<0.001$), with the deterioration over stage increasing with increase in age ($p=0.007$) and between eyes ($p=0.003$). Both hemifield MDs deteriorated over phase ($p<0.001$), with the deterioration over phase greater for the ocular hypertensive group ($p=0.001$) particularly with increase in age ($p=0.002$). The deterioration over stage of both hemifield MDs was greater for phase 1 than for phase 2 ($p<0.001$).

There was no difference, however, in the MD of the two hemifields ($p=0.406$) or in the magnitude of the deterioration over stage between the two hemifields ($p=0.644$).

4.3.8. Nasal / temporal hemifield loss variance.

The group mean nasal and temporal hemifield LV for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.9 and Table 4.8 respectively. Both the nasal and temporal hemifield LVs were unaffected by age ($p=0.021$). The LV of both hemifields was poorer in the second eye ($p=0.002$). Both hemifield LVs deteriorated over stage ($p<0.001$) and phase ($p<0.001$), with the deterioration over phase greater for the second eye of the elderly normal subjects ($p=0.013$).

The deterioration over stage in the nasal hemifield LV was greater than that of the temporal hemifield ($p<0.001$) and the difference between the hemifields over stage was different between phases ($p=0.012$).

4.3.9. Nasal / temporal hemifield short-term fluctuation.

The group mean nasal and temporal hemifield SF for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.10 and Table 4.9 respectively. The LV of both hemifields was unaffected by age ($p=0.146$). There was no difference in the magnitude of the SF of the two hemifields ($p=0.288$). The nasal hemifield SF, however, exhibited greater deterioration over stage than that of the temporal hemifield ($p=0.002$).

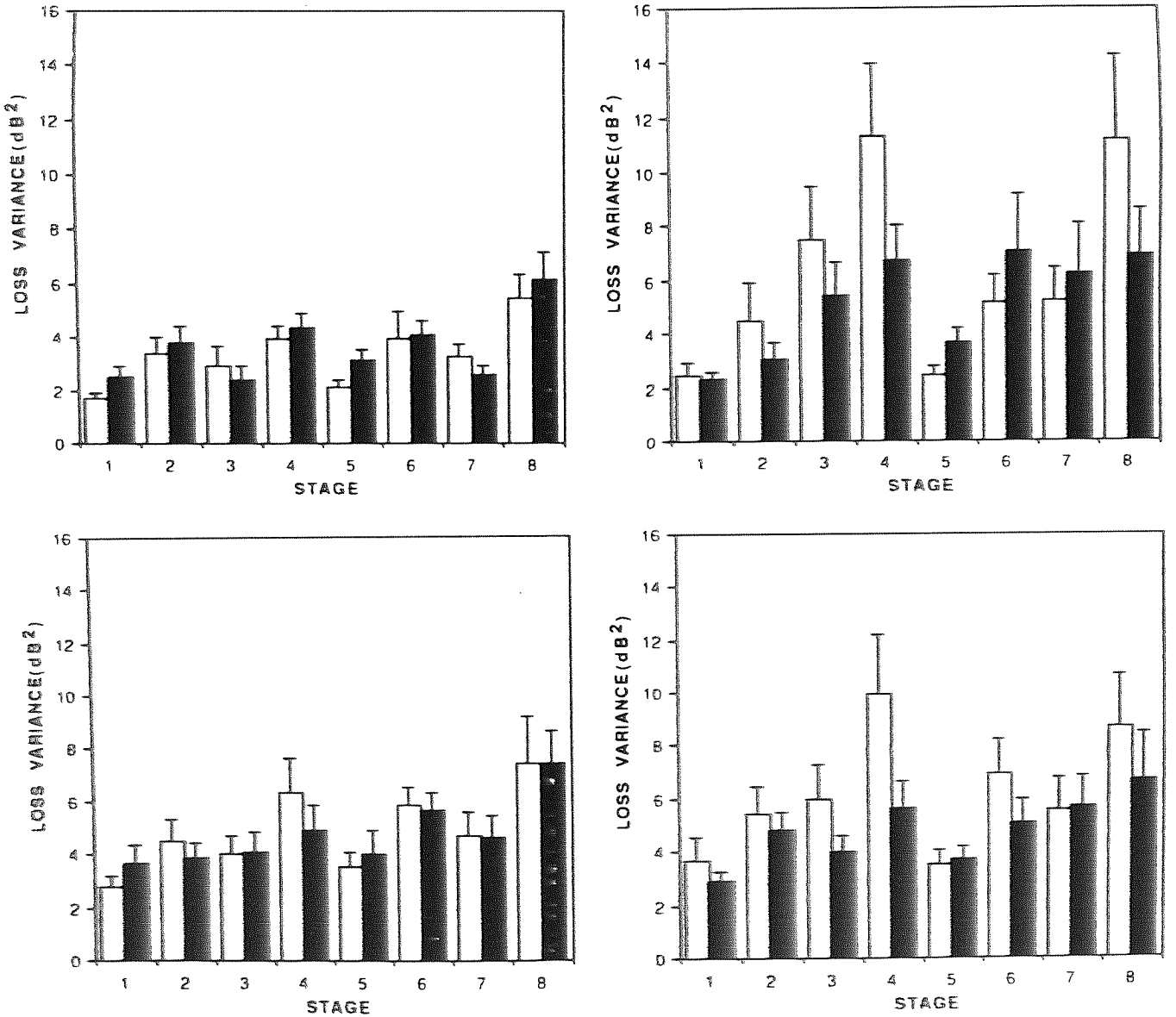



Fig. 4.5. Bar charts of superior (open bars) and inferior hemifield (closed bars) loss variance ($dB^2$) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.013 | 0.013 | 0.00 | =0.951 |
| Age | 1 | 37.416 | 37.416 | 10.33 | =0.003 |
| Age X group | 1 | 0.099 | 0.099 | 0.03 | =0.869 |
| Error | 36 | 130.375 | 3.621 | | |
| Superior / Inferior (S/I) | 1 | 0.001 | 0.001 | 0.00 | =0.987 |
| S/I X group | 1 | 0.418 | 0.418 | 0.29 | =0.591 |
| S/I X age | 1 | 4.924 | 4.924 | 3.46 | =0.071 |
| S/I X age X group | 1 | 0.313 | 0.313 | 0.22 | =0.642 |
| Error | 36 | 51.214 | 1.422 | | |
| Eye | 1 | 11.576 | 11.576 | 7.29 | =0.010 |
| Eye X group | 1 | 0.001 | 0.001 | 0.00 | =0.987 |
| Eye X age | 1 | 3.204 | 3.204 | 2.02 | =0.164 |
| Eye X age X group | 1 | 0.022 | 0.022 | 0.01 | =0.906 |
| Error | 36 | 57.188 | 1.588 | | |

Table 4.5. Repeated measures analysis of co-variance for superior / inferior (S/I) LV.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 74.418 | 24.806 | 25.73 | <0.001 |
| Stage X group | 3 | 2.185 | 0.728 | 0.76 | =0.521 |
| Stage X age | 3 | 3.089 | 1.029 | 1.07 | =0.366 |
| Stage X age X group | 3 | 1.918 | 0.639 | 0.66 | =0.576 |
| Error | 108 | 104.105 | 0.963 | | |
| Phase | 1 | 9.384 | 9.384 | 28.45 | <0.001 |
| Phase X group | 1 | 0.096 | 0.096 | 0.29 | =0.591 |
| Phase X age | 1 | 0.150 | 0.150 | 0.46 | =0.504 |
| Phase X age X group | 1 | 0.089 | 0.089 | 0.27 | =0.607 |
| Error | 36 | 11.877 | 0.329 | | |
| S/f X eye | 1 | 1.804 | 1.804 | 2.06 | =0.159 |
| S/f X eye X group | 1 | 0.245 | 0.245 | 0.28 | =0.599 |
| S/f X eye X age | 1 | 0.208 | 0.208 | 0.24 | =0.628 |
| S/f X eye X age X group | 1 | 0.278 | 0.278 | 0.32 | =0.576 |
| Error | 36 | 31.480 | 0.874 | | |

Table 4.5. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| S/I X stage | 3 | 5.581 | 1.860 | 4.09 | =0.009 |
| S/I X stage X group | 3 | 1.512 | 0.504 | 1.11 | =0.349 |
| S/I X stage X age | 3 | 1.153 | 0.384 | 0.85 | =0.472 |
| S/I X stage X age X group | 3 | 1.615 | 0.538 | 1.18 | =0.319 |
| Error | 108 | 49.127 | 0.454 | | |
| Eye X stage | 3 | 6.229 | 2.076 | 4.11 | =0.012 |
| Eye X stage X group | 3 | 0.508 | 0.169 | 0.34 | =0.770 |
| Eye X stage X age | 3 | 1.166 | 0.388 | 0.77 | =0.496 |
| Eye X stage X age X group | 3 | 0.709 | 0.236 | 0.47 | =0.677 |
| Error | 108 | 54.511 | 0.504 | | |
| S/I X phase | 1 | 1.259 | 1.259 | 3.69 | =0.063 |
| S/I X phase X group | 1 | 0.088 | 0.088 | 0.26 | =0.614 |
| S/I X phase X age | 1 | 0.177 | 0.177 | 0.52 | =0.475 |
| S/I X phase X age X group | 1 | 0.089 | 0.089 | 0.26 | =0.612 |
| Error | 36 | 12.281 | 0.341 | | |

Table 4.5. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X phase | 1 | 1.221 | 1.221 | 3.21 | =0.082 |
| Eye X phase X group | 1 | 2.365 | 2.365 | 6.21 | =0.017 |
| Eye X phase X age | 1 | 2.334 | 2.334 | 6.13 | =0.018 |
| Eye X phase X age X group | 1 | 2.283 | 2.283 | 5.99 | =0.019 |
| Error | 36 | 13.715 | 0.380 | | |
| Phase X stage | 3 | 3.655 | 1.218 | 3.89 | =0.011 |
| Phase X stage X group | 3 | 2.803 | 0.934 | 2.98 | =0.035 |
| Phase X stage X age | 3 | 0.663 | 0.221 | 0.71 | =0.551 |
| Phase X stage X age X group | 3 | 2.597 | 0.865 | 2.76 | =0.046 |
| Error | 108 | 33.863 | 0.313 | | |
| S/I X eye X stage | 3 | 1.580 | 0.526 | 0.67 | =0.555 |
| S/I X eye X stage X group | 3 | 3.715 | 1.238 | 1.57 | =0.207 |
| S/I X eye X stage X age | 3 | 3.127 | 1.042 | 1.32 | =0.273 |
| S/I X eye X stage X age X group | 3 | 3.563 | 1.187 | 1.51 | =0.222 |
| Error | 108 | 85.229 | 0.789 | | |

Table 4.5. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| S/I X eye X phase | 1 | 0.228 | 0.228 | 0.80 | =0.376 |
| S/I X eye X phase X group | 1 | 0.001 | 0.001 | 0.00 | =0.983 |
| S/I X eye X phase X age | 1 | 0.515 | 0.515 | 1.81 | =0.187 |
| S/I X eye X phase X age X group | 1 | 0.004 | 0.004 | 0.02 | =0.902 |
| Error | 36 | 10.239 | 0.284 | | |
| S/I X phase X stage | 3 | 0.400 | 0.133 | 0.36 | =0.767 |
| S/I X phase X stage X group | 3 | 0.872 | 0.290 | 0.79 | =0.495 |
| S/I X phase X stage X age | 3 | 0.382 | 0.127 | 0.35 | =0.780 |
| S/I X phase X stage X age X group | 3 | 0.839 | 0.279 | 0.76 | =0.511 |
| Error | 108 | 39.719 | 0.367 | | |
| Eye X phase X stage | 3 | 2.317 | 0.772 | 1.98 | =0.130 |
| Eye X phase X stage X group | 3 | 0.360 | 0.120 | 0.31 | =0.792 |
| Eye X phase X stage X age | 3 | 1.966 | 0.655 | 1.68 | =0.182 |
| Eye X phase X stage X age X group | 3 | 0.468 | 0.156 | 0.40 | =0.725 |
| Error | 108 | 42.083 | 0.389 | | |

Table 4.5. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| S/I X eye X phase X stage | 3 | 0.667 | 0.222 | 0.73 | =0.527 |
| S/I X eye X phase X stage X group | 3 | 1.017 | 0.339 | 1.12 | =0.343 |
| S/I X eye X phase X stage X age | 3 | 0.221 | 0.073 | 0.24 | =0.855 |
| S/I X eye X phase X stage X age X group | 3 | 1.037 | 0.345 | 1.14 | =0.334 |
| Error | 108 | 32.677 | 0.302 | | |

Table 4.5. (continued).

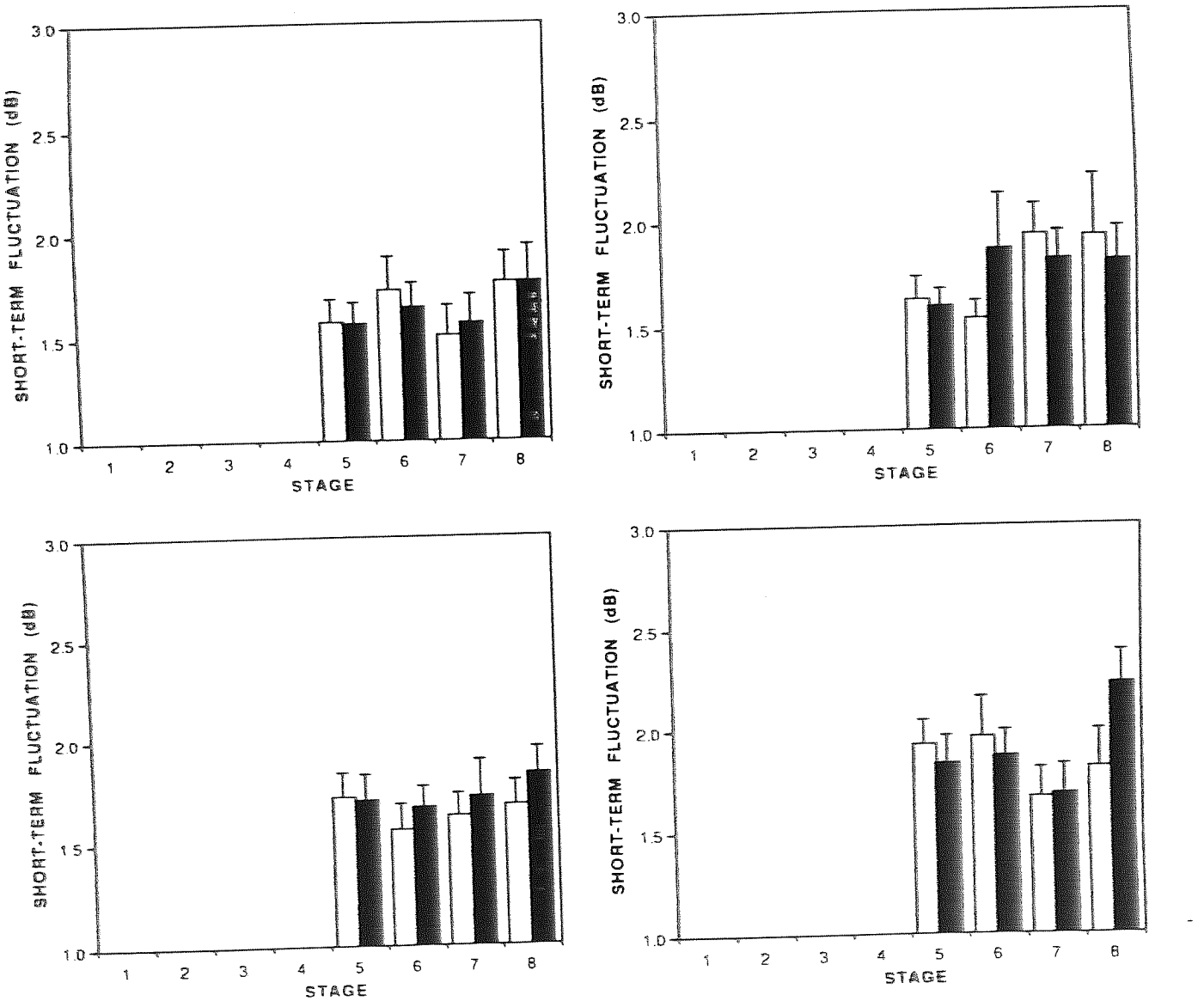



Fig. 4.7. Bar charts of superior (open bars) and inferior hemifield (closed bars) short-term fluctuation (dB) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.001 | 0.001 | 0.01 | =0.940 |
| Age | 1 | 0.426 | 0.426 | 1.27 | =0.267 |
| Age X group | 1 | 0.010 | 0.010 | 0.03 | =0.862 |
| Error | 36 | 12.096 | 0.336 | | |
| Superior / Inferior (S/I) | 1 | 0.120 | 0.120 | 0.73 | =0.397 |
| S/I X group | 1 | 0.000 | 0.000 | 0.00 | =0.996 |
| S/I X age | 1 | 0.029 | 0.029 | 0.18 | =0.674 |
| S/I X age X group | 1 | 0.001 | 0.001 | 0.01 | =0.920 |
| Error | 36 | 5.903 | 0.163 | | |
| Eye | 1 | 1.073 | 1.073 | 5.26 | =0.028 |
| Eye X group | 1 | 0.006 | 0.006 | 0.03 | =0.859 |
| Eye X age | 1 | 0.007 | 0.007 | 0.04 | =0.852 |
| Eye X age X group | 1 | 0.010 | 0.010 | 0.05 | =0.822 |
| Error | 36 | 7.348 | 0.204 | | |

Table 4.6. Repeated measures analysis of co-variance for superior / inferior (S/I) SF.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 0.706 | 0.235 | 1.88 | =0.155 |
| Stage X group | 3 | 0.243 | 0.081 | 0.65 | =0.541 |
| Stage X age | 3 | 0.185 | 0.061 | 0.49 | =0.633 |
| Stage X age X group | 3 | 0.278 | 0.092 | 0.74 | =0.464 |
| Error | 108 | 13.544 | 0.125 | | |
| S/I X eye | 1 | 0.001 | 0.001 | 0.02 | =0.884 |
| S/I X eye X group | 1 | 0.073 | 0.073 | 1.12 | =0.298 |
| S/I X eye X age | 1 | 0.025 | 0.025 | 0.38 | =0.541 |
| S/I X eye X age X group | 1 | 0.070 | 0.070 | 1.07 | =0.307 |
| Error | 36 | 2.371 | 0.065 | | |
| S/I X stage | 3 | 0.284 | 0.094 | 0.72 | =0.529 |
| S/I X stage X group | 3 | 0.189 | 0.063 | 0.48 | =0.679 |
| S/I X stage X age | 3 | 0.069 | 0.023 | 0.18 | =0.899 |
| S/I X stage X age X group | 3 | 0.168 | 0.056 | 0.43 | =0.717 |
| Error | 108 | 14.130 | 0.130 | | |

Table 4.6. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X stage | 3 | 0.133 | 0.044 | 0.45 | =0.697 |
| Eye X stage X group | 3 | 0.099 | 0.033 | 0.33 | =0.779 |
| Eye X stage X age | 3 | 0.343 | 0.114 | 1.16 | =0.328 |
| Eye X stage X age X group | 3 | 0.113 | 0.037 | 0.38 | =0.744 |
| Error | 108 | 10.706 | 0.099 | | |
| S/I X eye X stage | 3 | 0.210 | 0.070 | 0.61 | =0.590 |
| S/I X eye X stage X group | 3 | 0.403 | 0.134 | 1.16 | =0.326 |
| S/I X eye X stage X age | 3 | 0.391 | 0.130 | 1.12 | =0.339 |
| S/I X eye X stage X age X group | 3 | 0.463 | 0.154 | 1.33 | =0.270 |
| Error | 108 | 12.535 | 0.116 | | |

Table 4.6. (continued).

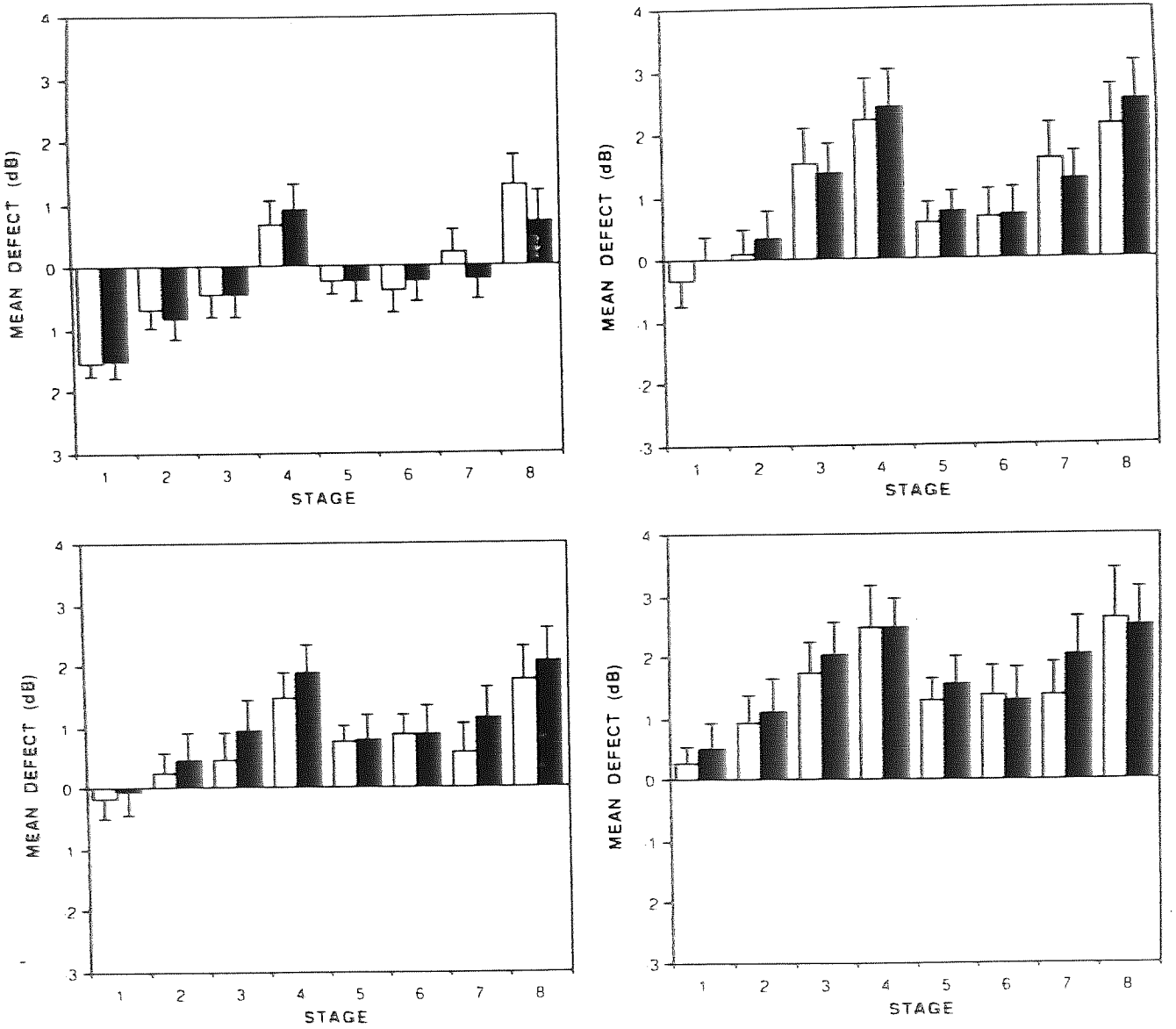



Fig. 4.8. Bar charts of nasal (open bars) and temporal hemifield (closed bars) mean defect (dB) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 1.274 | 1.274 | 0.89 | =0.353 |
| Age | 1 | 14.975 | 14.975 | 10.41 | =0.003 |
| Age X group | 1 | 1.867 | 1.867 | 1.30 | =0.262 |
| Error | 36 | 51.806 | 1.439 | | |
| Nasal / Temporal (N/T) | 1 | 0.079 | 0.079 | 0.71 | =0.406 |
| N/T X group | 1 | 0.134 | 0.134 | 1.19 | =0.282 |
| N/T X age | 1 | 0.127 | 0.127 | 1.13 | =0.295 |
| N/T X age X group | 1 | 0.119 | 0.119 | 1.06 | =0.309 |
| Error | 36 | 4.063 | 0.112 | | |
| Eye | 1 | 6.509 | 6.509 | 57.74 | <0.001 |
| Eye X group | 1 | 0.590 | 0.590 | 5.24 | =0.028 |
| Eye X age | 1 | 0.218 | 0.218 | 1.94 | =0.173 |
| Eye X age X group | 1 | 0.461 | 0.461 | 4.10 | =0.050 |
| Error | 36 | 4.058 | 0.112 | | |

Table 4.7. Repeated measures analysis of co-variance for nasal / temporal (N/T) MD.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 10.019 | 3.339 | 77.36 | <0.001 |
| Stage X group | 3 | 0.195 | 0.065 | 1.51 | =0.224 |
| Stage X age | 3 | 0.623 | 0.207 | 4.81 | =0.007 |
| Stage X age X group | 3 | 0.152 | 0.050 | 1.17 | =0.319 |
| Error | 108 | 4.662 | 0.043 | | |
| Phase | 1 | 1.394 | 1.394 | 36.04 | <0.001 |
| Phase X group | 1 | 0.474 | 0.474 | 12.27 | =0.001 |
| Phase X age | 1 | 0.170 | 0.170 | 4.40 | =0.043 |
| Phase X age X group | 1 | 0.441 | 0.441 | 11.40 | =0.002 |
| Error | 36 | 1.393 | 0.038 | | |
| N/T X eye | 1 | 0.023 | 0.023 | 0.24 | =0.628 |
| N/T X eye X group | 1 | 0.132 | 0.132 | 1.37 | =0.250 |
| N/T X eye X age | 1 | 0.001 | 0.001 | 0.02 | =0.899 |
| N/T X eye X age X group | 1 | 0.151 | 0.151 | 1.57 | =0.218 |
| Error | 36 | 3.484 | 0.096 | | |

Table 4.7. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| N/T X stage | 3 | 0.042 | 0.014 | 0.49 | =0.644 |
| N/T X stage X group | 3 | 0.087 | 0.029 | 0.99 | =0.385 |
| N/T X stage X age | 3 | 0.056 | 0.018 | 0.65 | =0.547 |
| N/T X stage X age X group | 3 | 0.079 | 0.026 | 0.91 | =0.419 |
| Error | 108 | 3.158 | 0.029 | | |
| Eye X stage | 3 | 0.382 | 0.127 | 5.43 | =0.003 |
| Eye X stage X group | 3 | 0.071 | 0.023 | 1.01 | =0.382 |
| Eye X stage X age | 3 | 0.112 | 0.037 | 1.60 | =0.199 |
| Eye X stage X age X group | 3 | 0.073 | 0.024 | 1.05 | =0.367 |
| Error | 108 | 2.530 | 0.023 | | |
| N/T X phase | 1 | 0.012 | 0.012 | 1.08 | =0.305 |
| N/T X phase X group | 1 | 0.001 | 0.001 | 0.00 | =0.946 |
| N/T X phase X age | 1 | 0.001 | 0.001 | 0.06 | =0.804 |
| N/T X phase X age X group | 1 | 0.001 | 0.001 | 0.03 | =0.864 |
| Error | 36 | 0.408 | 0.011 | | |

Table 4.7. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X phase | 1 | 0.134 | 0.134 | 3.11 | =0.086 |
| Eye X phase X group | 1 | 0.061 | 0.061 | 1.42 | =0.242 |
| Eye X phase X age | 1 | 0.038 | 0.038 | 0.89 | =0.353 |
| Eye X phase X age X group | 1 | 0.069 | 0.069 | 1.60 | =0.214 |
| Error | 36 | 1.552 | 0.043 | | |
| Phase X stage | 3 | 1.425 | 0.475 | 22.30 | <0.001 |
| Phase X stage X group | 3 | 0.087 | 0.029 | 1.36 | =0.262 |
| Phase X stage X age | 3 | 0.067 | 0.022 | 1.06 | =0.362 |
| Phase X stage X age X group | 3 | 0.086 | 0.028 | 1.36 | =0.262 |
| Error | 108 | 2.301 | 0.021 | | |
| N/T X eye X stage | 3 | 0.043 | 0.014 | 0.59 | =0.599 |
| N/T X eye X stage X group | 3 | 0.011 | 0.003 | 0.16 | =0.898 |
| N/T X eye X stage X age | 3 | 0.084 | 0.028 | 1.14 | =0.333 |
| N/T X eye X stage X age X group | 3 | 0.014 | 0.004 | 0.19 | =0.876 |
| Error | 108 | 2.682 | 0.024 | | |

Table 4.7. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| N/T X eye X phase | 1 | 0.002 | 0.002 | 0.11 | =0.740 |
| N/T X eye X phase X group | 1 | 0.006 | 0.006 | 0.34 | =0.565 |
| N/T X eye X phase X age | 1 | 0.006 | 0.006 | 0.36 | =0.554 |
| N/T X eye X phase X age X group | 1 | 0.006 | 0.006 | 0.33 | =0.568 |
| Error | 36 | 0.662 | 0.018 | | |
| N/T X phase X stage | 3 | 0.004 | 0.001 | 0.10 | =0.950 |
| N/T X phase X stage X group | 3 | 0.039 | 0.013 | 0.93 | =0.421 |
| N/T X phase X stage X age | 3 | 0.020 | 0.006 | 0.47 | =0.689 |
| N/T X phase X stage X age X group | 3 | 0.032 | 0.010 | 0.77 | =0.504 |
| Error | 108 | 1.528 | 0.014 | | |
| Eye X phase X stage | 3 | 0.023 | 0.007 | 0.58 | =0.617 |
| Eye X phase X stage X group | 3 | 0.032 | 0.010 | 0.78 | =0.500 |
| Eye X phase X stage X age | 3 | 0.017 | 0.005 | 0.43 | =0.713 |
| Eye X phase X stage X age X group | 3 | 0.036 | 0.012 | 0.89 | =0.441 |
| Error | 108 | 1.484 | 0.013 | | |

Table 4.7. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| N/T X eye X phase X stage | 3 | 0.023 | 0.007 | 0.78 | =0.498 |
| N/T X eye X phase X stage X group | 3 | 0.037 | 0.012 | 1.24 | =0.299 |
| N/T X eye X phase X stage X age | 3 | 0.036 | 0.012 | 1.23 | =0.304 |
| N/T X eye X phase X stage X age X group | 3 | 0.029 | 0.009 | 0.98 | =0.399 |
| Error | 108 | 1.074 | 0.009 | | |



Table 4.7. (continued).

4.3.10. Central / peripheral annuli mean defect.

The group mean cumulative central and peripheral annuli MD for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.11 and Table 4.10 respectively. The MD of both annuli was poorer with increase in age ($p=0.010$) and was poorer in the second eye ($p<0.001$) and in phase 2 ($p<0.001$). Furthermore, the MD of both annuli deteriorated over stage ($p<0.001$), particularly for the normal group ($p=0.006$) and with increase in age for both groups ($p=0.002$). This effect was most pronounced in the elderly normal group ($p=0.015$). The decline of both annuli MDs over stage was greater for phase 1 than for phase 2 ($p<0.001$) and was different between the two eyes ($p=0.012$).

The peripheral annulus MD deteriorated more over stage than that of the central ($p<0.001$) and this change was more pronounced in phase 1 ($p<0.001$). In addition, the difference between the central and peripheral annuli MDs was most pronounced in phase 2 compared to phase 1 ($p<0.001$) and this difference was greater for the normal group ($p=0.008$), particularly as age increased ($p=0.009$).

4.3.11. Central / peripheral annuli loss variance.

The group mean cumulative central and peripheral annuli LV for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.12 and Table 4.11 respectively. The LV of both annuli was poorer with increase in age ($p=0.008$) and deteriorated over stage ($p<0.001$). Both the central and peripheral annuli LVs were larger in phase 2 ($p<0.001$) and also in the second eye ($p=0.013$). The deterioration of both annuli LVs over stage was greater for phase 1 than for phase 2 ($p<0.001$).

The peripheral annulus LV was greater than that of the central ($p<0.001$) and this difference became more marked over stage ($p<0.001$) and phase ($p<0.001$), with the difference over stage being more pronounced for phase 2 compared to phase 1 ($p<0.001$).

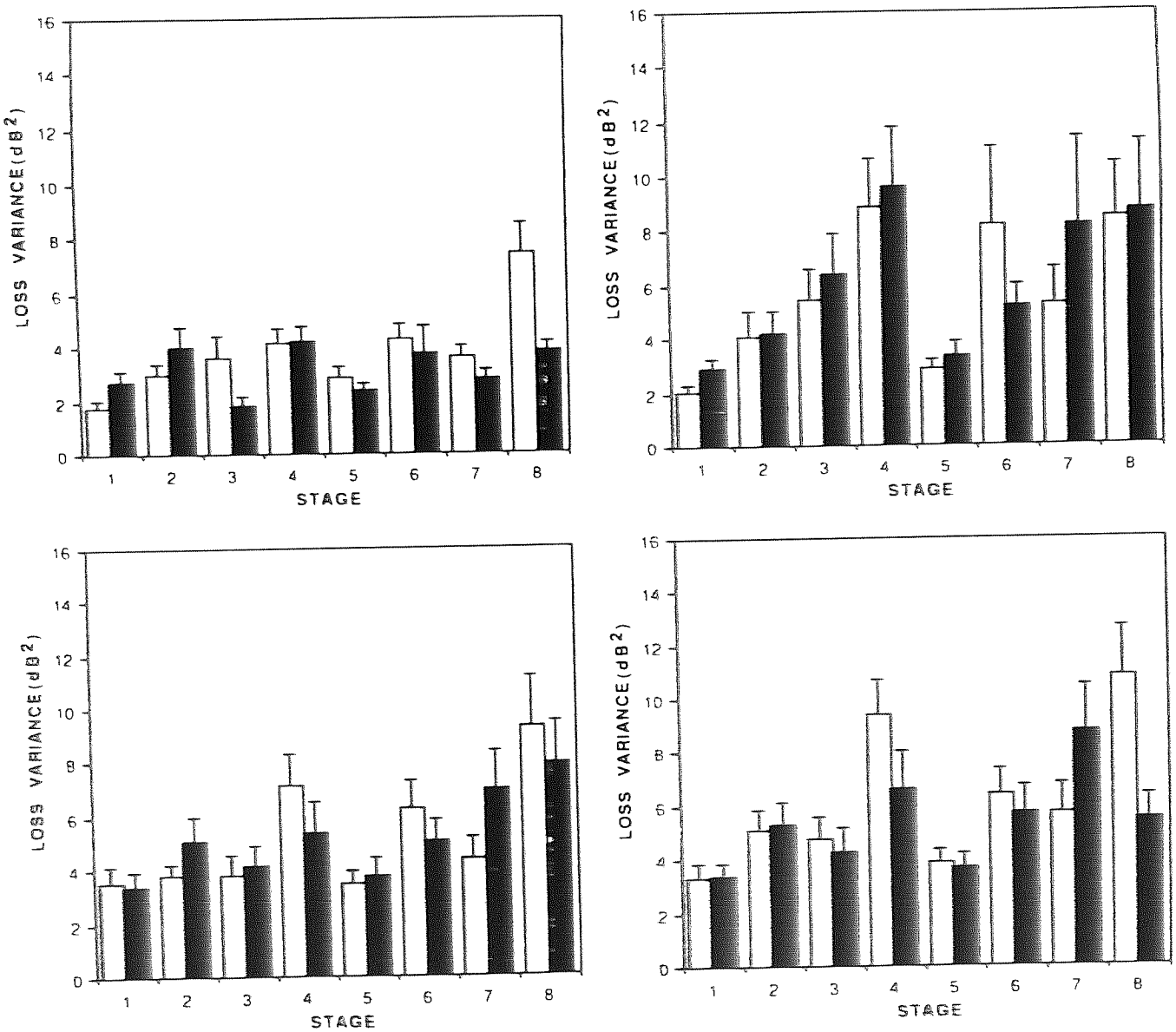



Fig. 4.9. Bar charts of nasal (open bars) and temporal hemifield (closed bars) loss variance ($dB^2$) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.920 | 0.920 | 0.28 | =0.598 |
| Age | 1 | 19.049 | 19.049 | 5.85 | =0.021 |
| Age X group | 1 | 0.226 | 0.226 | 0.07 | =0.793 |
| Error | 36 | 117.216 | 3.256 | | |
| Nasal / Temporal (N/T) | 1 | 1.729 | 1.729 | 2.08 | =0.157 |
| N/T X group | 1 | 1.901 | 1.901 | 2.29 | =0.139 |
| N/T X age | 1 | 1.024 | 1.024 | 1.23 | =0.274 |
| N/T X age X group | 1 | 1.833 | 1.833 | 2.21 | =0.146 |
| Error | 36 | 29.873 | 0.829 | | |
| Eye | 1 | 14.723 | 14.723 | 10.71 | =0.002 |
| Eye X group | 1 | 0.381 | 0.381 | 0.28 | =0.601 |
| Eye X age | 1 | 1.052 | 1.052 | 0.77 | =0.387 |
| Eye X age X group | 1 | 0.173 | 0.173 | 0.13 | =0.725 |
| Error | 36 | 49.489 | 1.374 | | |

Table 4.8. Repeated measures analysis of co-variance for nasal / temporal (N/T) LV.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 78.456 | 26.152 | 27.81 | <0.001 |
| Stage X group | 3 | 0.942 | 0.314 | 0.33 | =0.786 |
| Stage X age | 3 | 1.322 | 0.440 | 0.47 | =0.690 |
| Stage X age X group | 3 | 0.954 | 0.318 | 0.34 | =0.783 |
| Error | 108 | 101.556 | 0.940 | | |
| Phase | 1 | 12.437 | 12.437 | 40.04 | <0.001 |
| Phase X group | 1 | 0.633 | 0.633 | 2.04 | =0.162 |
| Phase X age | 1 | 0.001 | 0.001 | 0.01 | =0.938 |
| Phase X age X group | 1 | 0.647 | 0.647 | 2.08 | =0.157 |
| Error | 36 | 11.180 | 0.310 | | |
| N/T X eye | 1 | 0.663 | 0.663 | 0.55 | =0.463 |
| N/T X eye X group | 1 | 1.301 | 1.301 | 1.08 | =0.305 |
| N/T X eye X age | 1 | 0.201 | 0.201 | 0.17 | =0.685 |
| N/T X eye X age X group | 1 | 1.667 | 1.667 | 1.38 | =0.247 |
| Error | 36 | 43.374 | 1.204 | | |

Table 4.8. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| N/T X stage | 3 | 9.387 | 3.129 | 5.87 | <0.001 |
| N/T X stage X group | 3 | 1.270 | 0.423 | 0.80 | =0.499 |
| N/T X stage X age | 3 | 3.445 | 1.148 | 2.16 | =0.097 |
| N/T X stage X age X group | 3 | 1.846 | 0.615 | 1.16 | =0.330 |
| Error | 108 | 57.533 | 0.532 | | |
| Eye X stage | 3 | 2.937 | 0.979 | 2.00 | =0.128 |
| Eye X stage X group | 3 | 0.735 | 0.245 | 0.50 | =0.654 |
| Eye X stage X age | 3 | 0.014 | 0.004 | 0.01 | =0.997 |
| Eye X stage X age X group | 3 | 0.880 | 0.293 | 0.60 | =0.591 |
| Error | 108 | 52.811 | 0.488 | | |
| N/T X phase | 1 | 0.737 | 0.737 | 2.18 | =0.148 |
| N/T X phase X group | 1 | 0.325 | 0.325 | 0.96 | =0.332 |
| N/T X phase X age | 1 | 0.228 | 0.228 | 0.68 | =0.416 |
| N/T X phase X age X group | 1 | 0.438 | 0.438 | 1.30 | =0.262 |
| Error | 36 | 12.156 | 0.337 | | |

Table 4.8. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X phase | 1 | 0.439 | 0.439 | 1.03 | =0.316 |
| Eye X phase X group | 1 | 2.583 | 2.583 | 6.08 | =0.019 |
| Eye X phase X age | 1 | 0.732 | 0.732 | 1.72 | =0.197 |
| Eye X phase X age X group | 1 | 2.883 | 2.883 | 6.78 | =0.013 |
| Error | 36 | 15.303 | 0.425 | | |
| Phase X stage | 3 | 0.790 | 0.263 | 0.99 | =0.389 |
| Phase X stage X group | 3 | 1.385 | 0.461 | 1.73 | =0.177 |
| Phase X stage X age | 3 | 0.130 | 0.043 | 0.16 | =0.882 |
| Phase X stage X age X group | 3 | 1.104 | 0.368 | 1.38 | =0.257 |
| Error | 108 | 28.857 | 0.267 | | |
| N/T X eye X stage | 3 | 1.996 | 0.665 | 1.28 | =0.285 |
| N/T X eye X stage X group | 3 | 1.997 | 0.665 | 1.28 | =0.285 |
| N/T X eye X stage X age | 3 | 0.762 | 0.254 | 0.49 | =0.662 |
| N/T X eye X stage X age X group | 3 | 2.250 | 0.750 | 1.44 | =0.238 |
| Error | 108 | 56.068 | 0.519 | | |

Table 4.5. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| N/T X eye X phase | 1 | 0.173 | 0.173 | 0.50 | =0.484 |
| N/T X eye X phase X group | 1 | 0.389 | 0.389 | 1.13 | =0.296 |
| N/T X eye X phase X age | 1 | 0.226 | 0.226 | 0.66 | =0.423 |
| N/T X eye X phase X age X group | 1 | 0.330 | 0.330 | 0.96 | =0.334 |
| Error | 36 | 12.447 | 0.345 | | |
| N/T X phase X stage | 3 | 5.430 | 1.810 | 4.11 | =0.012 |
| N/T X phase X stage X group | 3 | 0.579 | 0.193 | 0.44 | =0.697 |
| N/T X phase X stage X age | 3 | 2.646 | 0.882 | 2.00 | =0.127 |
| N/T X phase X stage X age X group | 3 | 0.568 | 0.189 | 0.43 | =0.703 |
| Error | 108 | 47.529 | 0.440 | | |
| Eye X phase X stage | 3 | 2.541 | 0.847 | 2.69 | =0.057 |
| Eye X phase X stage X group | 3 | 0.190 | 0.063 | 0.20 | =0.875 |
| Eye X phase X stage X age | 3 | 1.459 | 0.486 | 1.54 | =0.212 |
| Eye X phase X stage X age X group | 3 | 0.301 | 0.100 | 0.32 | =0.789 |
| Error | 108 | 34.044 | 0.315 | | |

Table 4.5. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| N/T X eye X phase X stage | 3 | 0.301 | 0.100 | 0.32 | =0.789 |
| N/T X eye X phase X stage X group | 3 | 0.409 | 0.136 | 0.44 | =0.707 |
| N/T X eye X phase X stage X age | 3 | 1.594 | 0.531 | 1.70 | =0.176 |
| N/T X eye X phase X stage X age X group | 3 | 0.507 | 0.169 | 0.54 | =0.637 |
| Error | 108 | 33.680 | 0.311 | | |



Table 4.8. (continued).

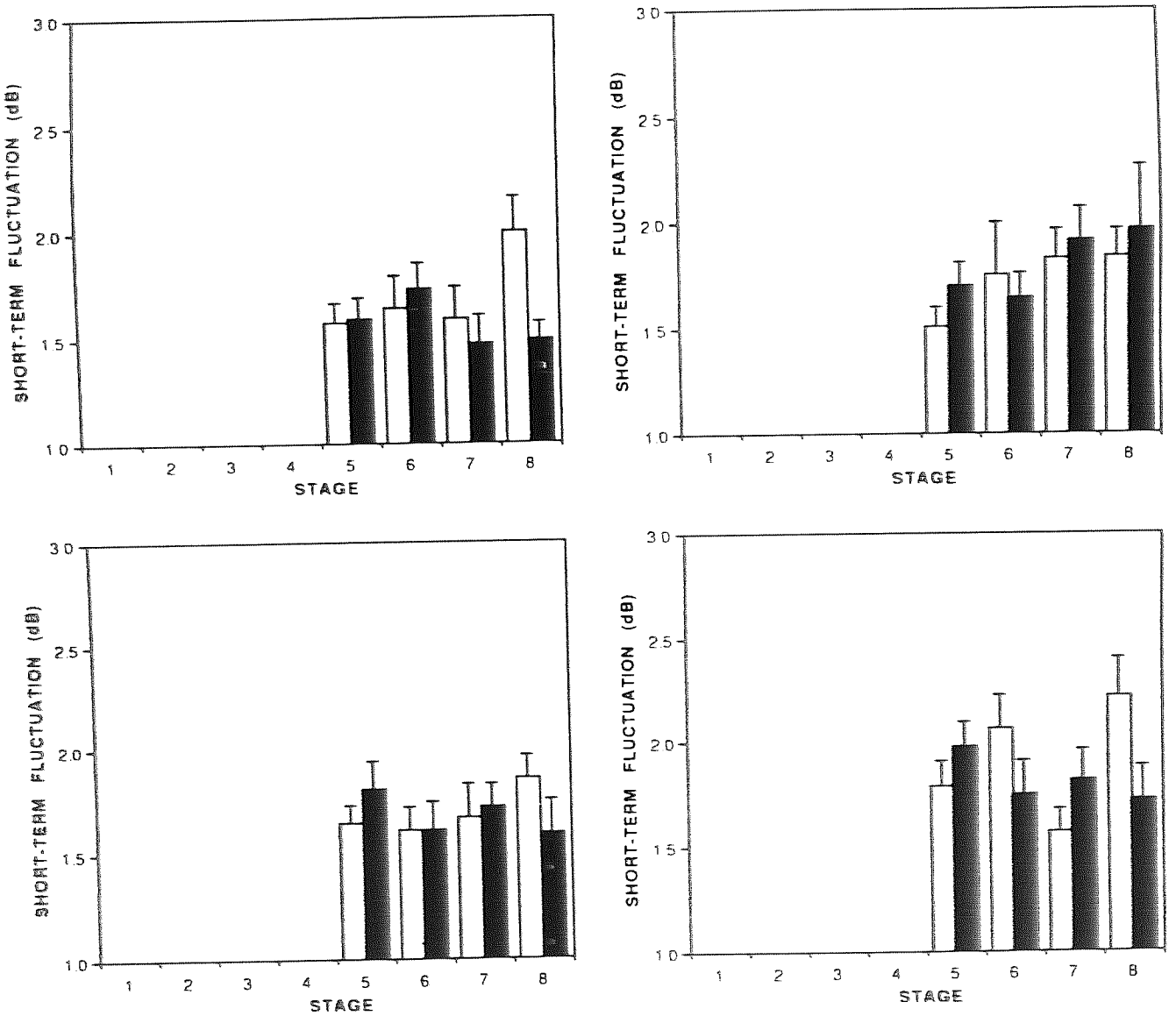



Fig. 4.10. Bar charts of nasal (open bars) and temporal hemifield (closed bars) short-term fluctuation (dB) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.050 | 0.050 | 0.14 | =0.706 |
| Age | 1 | 0.768 | 0.768 | 2.20 | =0.146 |
| Age X group | 1 | 0.080 | 0.080 | 0.23 | =0.633 |
| Error | 36 | 12.564 | 0.349 | | |
| Nasal / Temporal (N/T) | 1 | 0.139 | 0.139 | 1.16 | =0.288 |
| N/T X group | 1 | 0.021 | 0.021 | 0.18 | =0.674 |
| N/T X age | 1 | 0.123 | 0.123 | 1.03 | =0.317 |
| N/T X age X group | 1 | 0.025 | 0.025 | 0.22 | =0.645 |
| Error | 36 | 4.304 | 0.119 | | |
| Eye | 1 | 1.031 | 1.031 | 4.75 | =0.036 |
| Eye X group | 1 | 0.001 | 0.001 | 0.00 | =0.967 |
| Eye X age | 1 | 0.001 | 0.001 | 0.01 | =0.931 |
| Eye X age X group | 1 | 0.001 | 0.001 | 0.01 | =0.944 |
| Error | 36 | 7.823 | 0.217 | | |

Table 4.9. Repeated measures analysis of co-variance for nasal / temporal (N/T) SF.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 0.405 | 0.135 | 1.08 | =0.356 |
| Stage X group | 3 | 0.317 | 0.105 | 0.84 | =0.457 |
| Stage X age | 3 | 0.091 | 0.030 | 0.24 | =0.834 |
| Stage X age X group | 3 | 0.329 | 0.109 | 0.88 | =0.442 |
| Error | 108 | 13.520 | 0.125 | | |
| N/T X eye | 1 | 0.020 | 0.020 | 0.16 | =0.692 |
| N/T X eye X group | 1 | 0.023 | 0.023 | 0.18 | =0.674 |
| N/T X eye X age | 1 | 0.308 | 0.308 | 2.36 | =0.133 |
| N/T X eye X age X group | 1 | 0.037 | 0.037 | 0.28 | =0.597 |
| Error | 36 | 4.704 | 0.130 | | |
| N/T X stage | 3 | 1.737 | 0.579 | 5.92 | =0.002 |
| N/T X stage X group | 3 | 0.025 | 0.008 | 0.09 | =0.946 |
| N/T X stage X age | 3 | 0.105 | 0.035 | 0.36 | =0.741 |
| N/T X stage X age X group | 3 | 0.008 | 0.002 | 0.03 | =0.984 |
| Error | 108 | 10.565 | 0.097 | | |

Table 4.9. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X stage | 3 | 0.112 | 0.037 | 0.33 | =0.788 |
| Eye X stage X group | 3 | 0.315 | 0.105 | 0.94 | =0.420 |
| Eye X stage X age | 3 | 0.274 | 0.091 | 0.82 | =0.480 |
| Eye X stage X age X group | 3 | 0.400 | 0.133 | 1.20 | =0.314 |
| Error | 108 | 12.067 | 0.111 | | |
| N/T X eye X stage | 3 | 0.238 | 0.079 | 0.75 | =0.501 |
| N/T X eye X stage X group | 3 | 0.422 | 0.140 | 1.33 | =0.272 |
| N/T X eye X stage X age | 3 | 0.051 | 0.017 | 0.16 | =0.891 |
| N/T X eye X stage X age X group | 3 | 0.443 | 0.147 | 1.39 | =0.253 |
| Error | 108 | 11.453 | 0.106 | | |

Table 4.9. (continued).

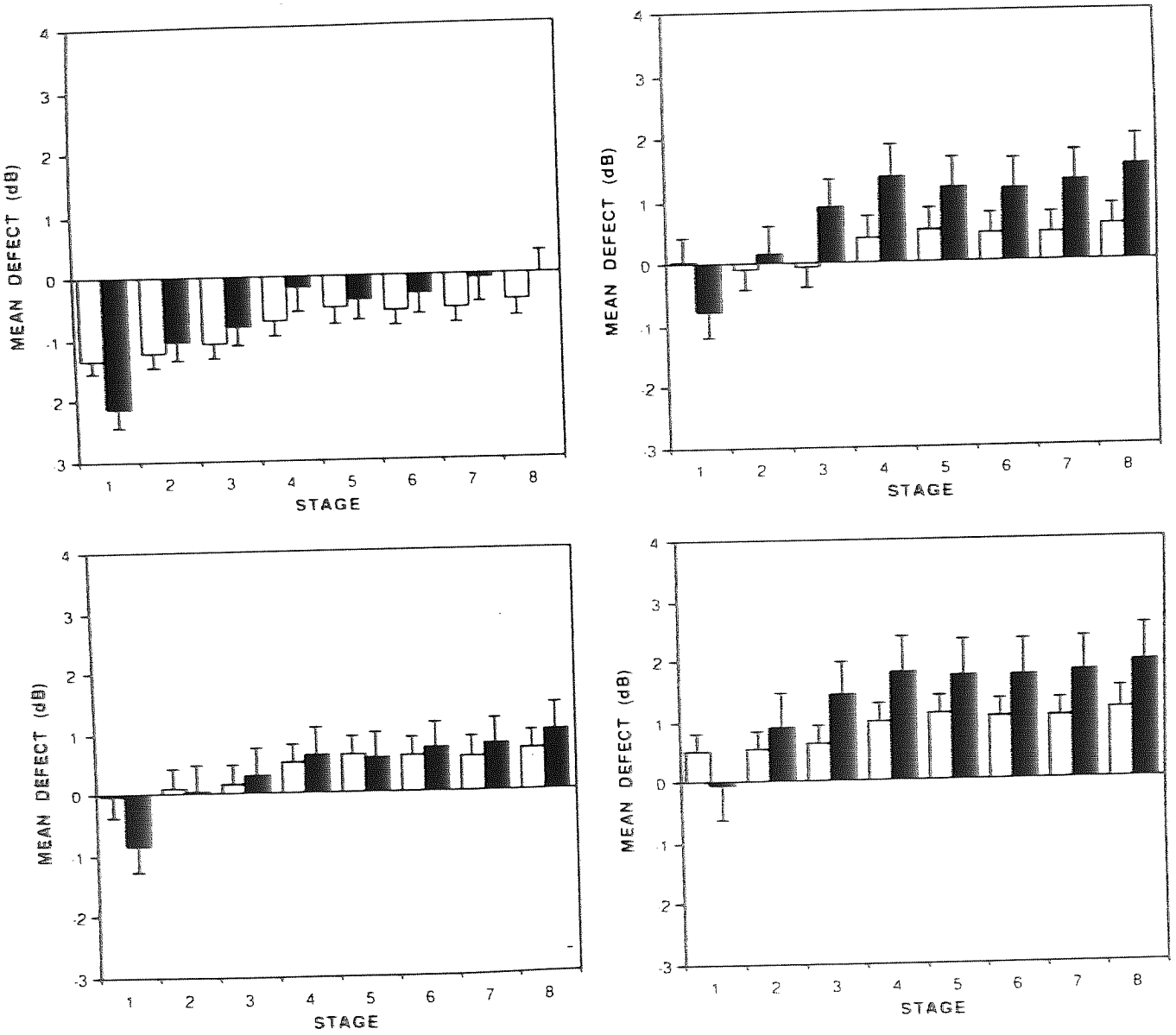



Fig. 4.11. Bar charts of cumulative central (open bars) and peripheral annuli (closed bars) mean defect (dB) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.689 | 0.689 | 0.31 | =0.583 |
| Age | 1 | 16.547 | 16.547 | 7.36 | =0.010 |
| Age X group | 1 | 1.311 | 1.311 | 0.58 | =0.450 |
| Error | 36 | 80.966 | 2.249 | | |
| Central / Peripheral (C/P) | 1 | 0.065 | 0.065 | 0.17 | =0.680 |
| C/P X group | 1 | 0.030 | 0.030 | 0.08 | =0.777 |
| C/P X age | 1 | 0.390 | 0.390 | 1.03 | =0.316 |
| C/P X age X group | 1 | 0.017 | 0.017 | 0.05 | =0.830 |
| Error | 36 | 13.600 | 0.377 | | |
| Eye | 1 | 12.032 | 12.032 | 67.21 | <0.001 |
| Eye X group | 1 | 0.257 | 0.257 | 1.44 | =0.238 |
| Eye X age | 1 | 0.005 | 0.005 | 0.03 | =0.863 |
| Eye X age X group | 1 | 0.151 | 0.151 | 0.85 | =0.364 |
| Error | 36 | 6.444 | 0.179 | | |

Table 4.10. Repeated measures analysis of co-variance for central / peripheral (C/P) MD.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 3.962 | 1.320 | 134.70 | <0.001 |
| Stage X group | 3 | 0.127 | 0.042 | 4.34 | =0.006 |
| Stage X age | 3 | 0.154 | 0.051 | 5.24 | =0.002 |
| Stage X age X group | 3 | 0.107 | 0.035 | 3.66 | =0.015 |
| Error | 108 | 1.058 | 0.009 | | |
| Phase | 1 | 6.265 | 6.265 | 183.91 | <0.001 |
| Phase X group | 1 | 0.158 | 0.158 | 4.66 | =0.038 |
| Phase X age | 1 | 0.124 | 0.124 | 3.65 | =0.064 |
| Phase X age X group | 1 | 0.130 | 0.130 | 3.84 | =0.058 |
| Error | 36 | 1.226 | 0.034 | | |
| C/P X eye | 1 | 0.381 | 0.381 | 6.14 | =0.018 |
| C/P X eye X group | 1 | 0.127 | 0.127 | 2.05 | =0.161 |
| C/P X eye X age | 1 | 0.007 | 0.007 | 0.12 | =0.727 |
| C/P X eye X age X group | 1 | 0.128 | 0.128 | 2.06 | =0.160 |
| Error | 36 | 2.235 | 0.062 | | |

Table 4.10. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| C/P X stage | 3 | 1.733 | 0.577 | 59.98 | <0.001 |
| C/P X stage X group | 3 | 0.107 | 0.035 | 3.66 | =0.050 |
| C/P X stage X age | 3 | 0.056 | 0.018 | 1.92 | =0.169 |
| C/P X stage X age X group | 3 | 0.091 | 0.030 | 3.11 | =0.073 |
| Error | 108 | 1.058 | 0.009 | | |
| Eye X stage | 3 | 0.111 | 0.037 | 5.19 | =0.012 |
| Eye X stage X group | 3 | 0.025 | 0.008 | 1.19 | =0.305 |
| Eye X stage X age | 3 | 0.049 | 0.016 | 2.30 | =0.116 |
| Eye X stage X age X group | 3 | 0.030 | 0.010 | 1.42 | =0.248 |
| Error | 108 | 0.773 | 0.007 | | |
| C/P X phase | 1 | 0.482 | 0.482 | 33.84 | <0.001 |
| C/P X phase X group | 1 | 0.113 | 0.113 | 7.93 | =0.008 |
| C/P X phase X age | 1 | 0.050 | 0.050 | 3.51 | =0.069 |
| C/P X phase X age X group | 1 | 0.108 | 0.108 | 7.59 | =0.009 |
| Error | 36 | 0.513 | 0.014 | | |

Table 4.10. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X phase | 1 | 0.140 | 0.140 | 5.17 | =0.029 |
| Eye X phase X group | 1 | 0.074 | 0.074 | 2.72 | =0.108 |
| Eye X phase X age | 1 | 0.090 | 0.090 | 3.33 | =0.076 |
| Eye X phase X age X group | 1 | 0.083 | 0.083 | 3.07 | =0.088 |
| Phase X stage | 3 | 2.385 | 0.795 | 98.83 | <0.001 |
| Phase X stage X group | 3 | 0.065 | 0.021 | 2.70 | =0.096 |
| Phase X stage X age | 3 | 0.063 | 0.021 | 2.62 | =0.101 |
| Phase X stage X age X group | 3 | 0.057 | 0.019 | 2.37 | =0.121 |
| Error | 108 | 0.868 | 0.008 | | |
| C/P X eye X stage | 3 | 0.014 | 0.004 | 0.70 | =0.473 |
| C/P X eye X stage X group | 3 | 0.003 | 0.001 | 0.18 | =0.789 |
| C/P X eye X stage X age | 3 | 0.037 | 0.012 | 1.80 | =0.180 |
| C/P X eye X stage X age X group | 3 | 0.003 | 0.001 | 0.18 | =0.797 |
| Error | 108 | 0.746 | 0.006 | | |

Table 4.10. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| C/P X eye X phase | 1 | 0.000 | 0.000 | 0.01 | =0.903 |
| C/P X eye X phase X group | 1 | 0.000 | 0.000 | 0.02 | =0.896 |
| C/P X eye X phase X age | 1 | 0.008 | 0.008 | 0.54 | =0.467 |
| C/P X eye X phase X age X group | 1 | 0.000 | 0.000 | 0.02 | =0.895 |
| Error | 36 | 0.536 | 0.014 | | |
| C/P X phase X stage | 3 | 1.019 | 0.339 | 41.29 | <0.001 |
| C/P X phase X stage X group | 3 | 0.052 | 0.017 | 2.11 | =0.150 |
| C/P X phase X stage X age | 3 | 0.031 | 0.010 | 1.26 | =0.277 |
| C/P X phase X stage X age X group | 3 | 0.043 | 0.014 | 1.77 | =0.191 |
| Error | 108 | 0.889 | 0.008 | | |
| Eye X phase X stage | 3 | 0.037 | 0.012 | 2.19 | =0.134 |
| Eye X phase X stage X group | 3 | 0.005 | 0.001 | 0.34 | =0.646 |
| Eye X phase X stage X age | 3 | 0.025 | 0.008 | 1.48 | =0.236 |
| Eye X phase X stage X age X group | 3 | 0.007 | 0.002 | 0.47 | =0.571 |
| Error | 108 | 0.608 | 0.005 | | |

Table 4.10. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| C/P X eye X phase X stage | 3 | 0.025 | 0.008 | 1.64 | =0.207 |
| C/P X eye X phase X stage X group | 3 | 0.003 | 0.001 | 0.25 | =0.717 |
| C/P X eye X phase X stage X age | 3 | 0.034 | 0.011 | 2.18 | =0.135 |
| C/P X eye X phase X stage X age X group | 3 | 0.004 | 0.001 | 0.31 | =0.671 |
| Error | 108 | 0.562 | 0.005 | | |



Table 4.10. (continued).

4.3.12. Central / peripheral annuli short-term fluctuation.

The group mean cumulative central and peripheral annuli SF for each eye of the normal and ocular hypertensive groups as a function of stage and the associated ANCOVA summary table are shown in Figure 4.13 and Table 4.12 respectively. The SF of both annuli was unaffected by age ($p=0.075$) but deteriorated over stage ($p=0.009$).

The peripheral annulus SF was greater than that of the central ($p<0.001$) and this difference decreased over stage ($p<0.001$).

4.3.13. Time results.

The time to complete all 8 stages, expressed cumulatively as a function of eye and of group, is shown in Figure 4.14 and the associated ANCOVA summary table is shown in Table 4.13. The time to complete all 8 stages was unaffected by age ($p=0.568$). The examination time was longer for the ocular hypertensive group ($p=0.046$). It was greater in the second eye irrespective of diagnosis ($p=0.004$) and the difference between eyes increased with increase in age ($p=0.016$). As would be expected, time increased over stage ($p<0.001$) and over phase ($p<0.001$), with the increase over phase greater with increase in age ($p=0.047$) and greater for phase 1 of the second eye of the ocular hypertensive group ($p=0.049$). The increase in time over stage was greater for phase 1 ($p<0.001$) particularly for the second eye ($p=0.024$).

4.3.14. Number of stimulus presentations.

The difference in the number of stimulus presentations between the first and second eyes as a function of the average mean sensitivity for the first and second eyes of a given individual is shown in Figure 4.15. There is a general trend for a greater number of stimulus presentations in the second eye. The data shows no obvious differences, however, between the normal subjects and ocular hypertensive patients.

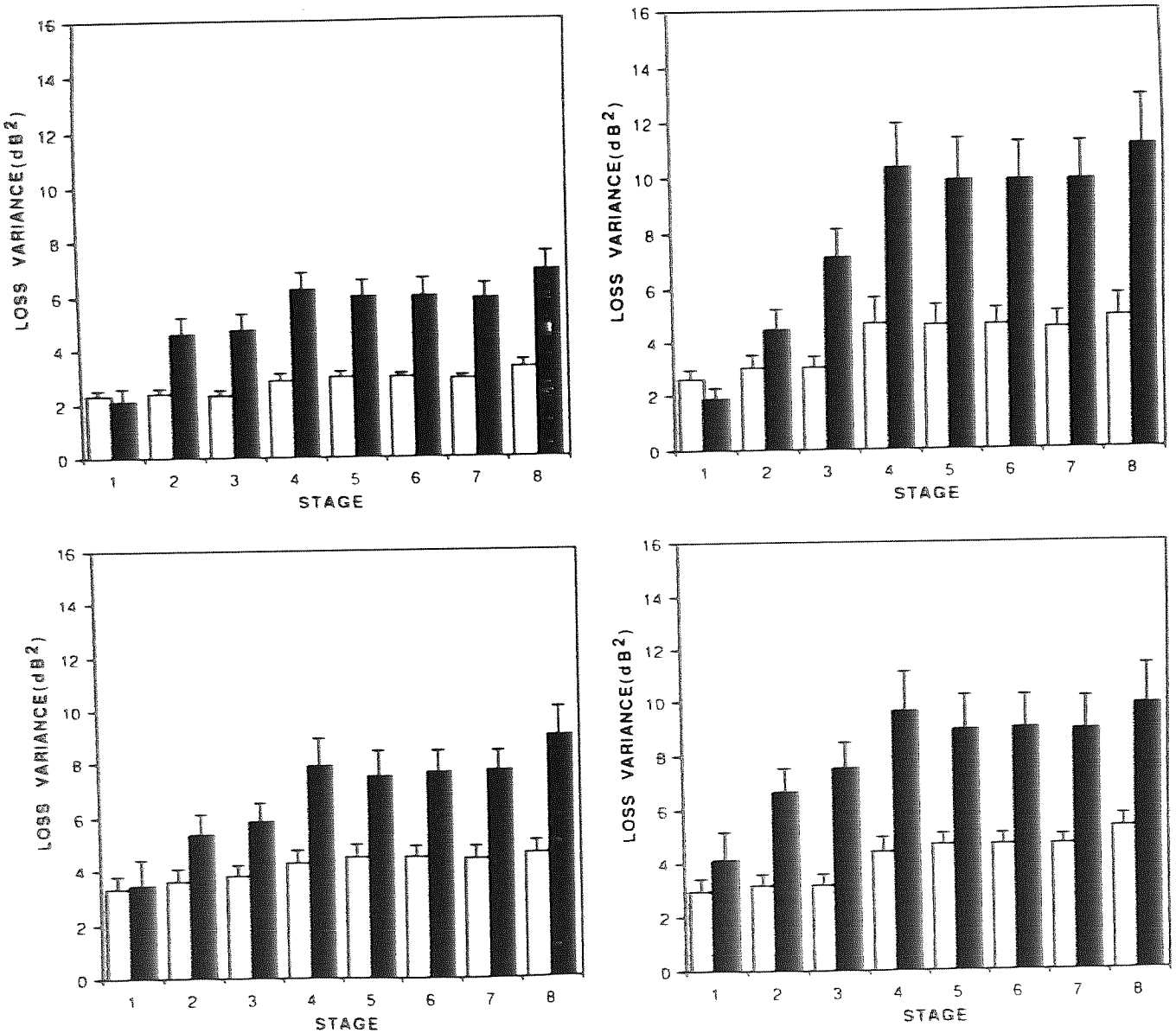



Fig. 4.12 Bar charts of cumulative central (open bars) and peripheral annuli (closed bars) loss variance ($dB^2$) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 1.747 | 1.747 | 0.56 | =0.460 |
| Age | 1 | 25.048 | 25.048 | 8.01 | =0.008 |
| Age X group | 1 | 0.898 | 0.898 | 0.29 | =0.595 |
| Error | 36 | 112.618 | 3.128 | | |
| Central / peripheral (C/P) | 1 | 81.968 | 81.968 | 74.24 | <0.001 |
| C/P X group | 1 | 3.999 | 3.999 | 3.62 | =0.065 |
| C/P X age | 1 | 1.437 | 1.437 | 1.30 | =0.261 |
| C/P X age X group | 1 | 3.829 | 3.829 | 3.47 | =0.071 |
| Error | 36 | 39.746 | 1.104 | | |
| Eye | 1 | 9.120 | 9.120 | 6.80 | =0.013 |
| Eye X group | 1 | 1.186 | 1.186 | 0.88 | =0.353 |
| Eye X age | 1 | 0.389 | 0.389 | 0.29 | =0.593 |
| Eye X age X group | 1 | 1.636 | 1.636 | 1.22 | =0.277 |
| Error | 36 | 48.264 | 1.340 | | |

Table 4.11. Repeated measures analysis of co-variance for central / peripheral (C/P) LV.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 41.668 | 13.889 | 121.23 | <0.001 |
| Stage X group | 3 | 0.179 | 0.059 | 0.52 | =0.618 |
| Stage X age | 3 | 0.412 | 0.137 | 1.20 | =0.310 |
| Stage X age X group | 3 | 0.149 | 0.049 | 0.44 | =0.674 |
| Error | 108 | 12.374 | 0.114 | | |
| Phase | 1 | 62.057 | 62.057 | 340.67 | <0.001 |
| Phase X group | 1 | 0.193 | 0.193 | 1.06 | =0.310 |
| Phase X age | 1 | 0.258 | 0.258 | 1.42 | =0.241 |
| Phase X age X group | 1 | 0.134 | 0.134 | 0.74 | =0.396 |
| Error | 36 | 6.557 | 0.182 | | |
| C/P X eye | 1 | 0.517 | 0.517 | 0.89 | =0.352 |
| C/P X eye X group | 1 | 0.001 | 0.001 | 0.00 | =0.957 |
| C/P X eye X age | 1 | 0.142 | 0.142 | 0.24 | =0.624 |
| C/P X eye X age X group | 1 | 0.010 | 0.010 | 0.02 | =0.894 |
| Error | 36 | 20.925 | 0.581 | | |

Table 4.11. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| C/P X stage | 3 | 16.067 | 5.355 | 38.51 | <0.001 |
| C/P X stage X group | 3 | 0.020 | 0.006 | 0.05 | =0.938 |
| C/P X stage X age | 3 | 0.237 | 0.079 | 0.57 | =0.548 |
| C/P X stage X age X group | 3 | 0.027 | 0.009 | 0.07 | =0.978 |
| Error | 108 | 15.018 | 0.139 | | |
| Eye X stage | 3 | 0.472 | 0.157 | 1.47 | =0.239 |
| Eye X stage X group | 3 | 0.582 | 0.194 | 1.81 | =0.177 |
| Eye X stage X age | 3 | 0.130 | 0.043 | 0.41 | =0.640 |
| Eye X stage X age X group | 3 | 0.547 | 0.182 | 1.70 | =0.194 |
| Error | 108 | 11.590 | 0.107 | | |
| C/P X phase | 1 | 4.514 | 4.514 | 16.77 | <0.001 |
| C/P X phase X group | 1 | 0.298 | 0.298 | 1.11 | =0.299 |
| C/P X phase X age | 1 | 0.000 | 0.000 | 0.00 | =0.996 |
| C/P X phase X age X group | 1 | 0.383 | 0.383 | 1.42 | =0.241 |
| Error | 36 | 9.688 | 0.269 | | |

Table 4.11. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X phase | 1 | 1.083 | 1.083 | 5.31 | =0.027 |
| Eye X phase X group | 1 | 0.817 | 0.817 | 4.01 | =0.053 |
| Eye X phase X age | 1 | 0.327 | 0.327 | 1.61 | =0.213 |
| Eye X phase X age X group | 1 | 0.744 | 0.744 | 3.65 | =0.064 |
| Error | 36 | 7.339 | 0.203 | | |
| Phase X stage | 3 | 26.942 | 8.980 | 86.17 | <0.001 |
| Phase X stage X group | 3 | 0.167 | 0.055 | 0.53 | =0.573 |
| Phase X stage X age | 3 | 0.401 | 0.133 | 1.28 | =0.282 |
| Phase X stage X age X group | 3 | 0.122 | 0.040 | 0.39 | =0.659 |
| Error | 108 | 11.256 | 0.104 | | |
| C/P X eye X stage | 3 | 0.199 | 0.066 | 0.53 | =0.569 |
| C/P X eye X stage X group | 3 | 0.861 | 0.287 | 2.31 | =0.112 |
| C/P X eye X stage X age | 3 | 0.089 | 0.029 | 0.24 | =0.763 |
| C/P X eye X stage X age X group | 3 | 0.833 | 0.277 | 2.24 | =0.120 |
| Error | 108 | 13.403 | 0.124 | | |

Table 4.11. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| C/P X eye X phase | 1 | 0.181 | 0.181 | 0.66 | =0.423 |
| C/P X eye X phase X group | 1 | 0.740 | 0.740 | 2.68 | =0.110 |
| C/P X eye X phase X age | 1 | 0.024 | 0.024 | 0.09 | =0.765 |
| C/P X eye X phase X age X group | 1 | 0.609 | 0.609 | 2.21 | =0.146 |
| Error | 36 | 9.945 | 0.276 | | |
| C/P X phase X stage | 3 | 13.360 | 4.453 | 40.81 | <0.001 |
| C/P X stage X phase X group | 3 | 0.031 | 0.010 | 0.10 | =0.869 |
| C/P X stage X phase X age | 3 | 0.461 | 0.153 | 1.41 | =0.251 |
| C/P X stage X phase X age X group | 3 | 0.014 | 0.004 | 0.04 | =0.929 |
| Error | 108 | 11.785 | 0.109 | | |
| Eye X phase X stage | 3 | 0.757 | 0.252 | 2.43 | =0.109 |
| Eye X phase X stage X group | 3 | 0.481 | 0.160 | 1.54 | =0.225 |
| Eye X phase X stage X age | 3 | 0.111 | 0.037 | 0.36 | =0.650 |
| Eye X phase X stage X age X group | 3 | 0.444 | 0.148 | 1.42 | =0.248 |
| Error | 108 | 11.242 | 0.104 | | |

Table 4.11. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| C/P X eye X phase X stage | 3 | 0.201 | 0.067 | 0.50 | =0.564 |
| C/P X eye X phase X stage X group | 3 | 1.054 | 0.351 | 2.63 | =0.093 |
| C/P X eye X phase X stage X age | 3 | 0.084 | 0.028 | 0.21 | =0.757 |
| C/P X eye X phase X stage X age X group | 3 | 1.059 | 0.353 | 2.64 | =0.093 |
| Error | 108 | 14.455 | 0.133 | | |



Table 4.11. (continued).

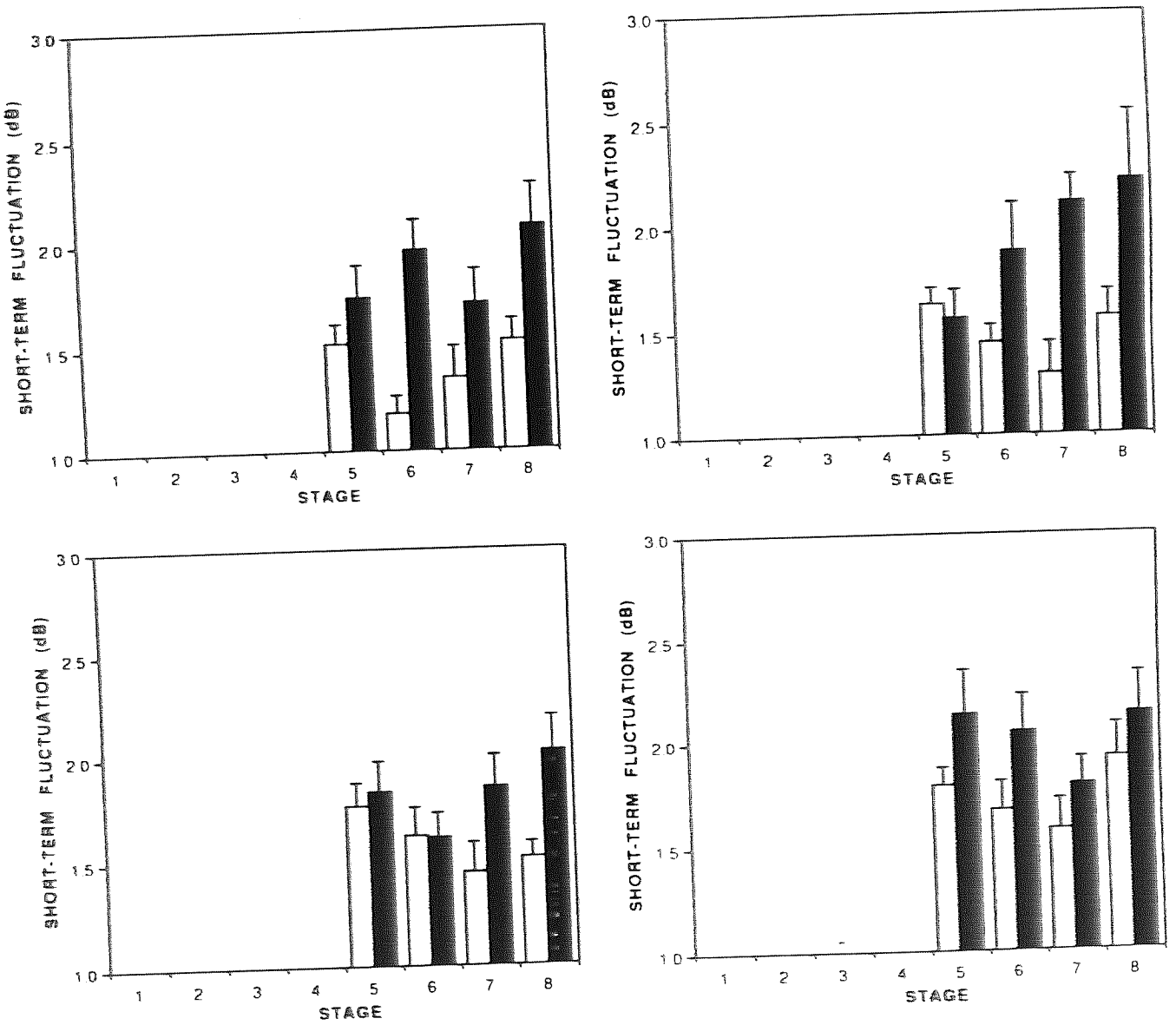



Fig. 4.13. Bar charts of cumulative central (open bars) and peripheral annuli (closed bars) short-term fluctuation (dB) against stage for the normal subjects (top left first eye; top right second eye) and ocular hypertensive patients (bottom left first eye; bottom right second eye). The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.149 | 0.149 | 0.48 | =0.492 |
| Age | 1 | 1.038 | 1.038 | 3.35 | =0.075 |
| Age X group | 1 | 0.260 | 0.260 | 0.84 | =0.366 |
| Error | 36 | 11.148 | 0.309 | | |
| Central / peripheral (C/P) | 1 | 2.461 | 2.461 | 13.53 | <0.001 |
| C/P X group | 1 | 0.356 | 0.356 | 1.96 | =0.170 |
| C/P X age | 1 | 0.001 | 0.001 | 0.00 | =0.948 |
| C/P X age X group | 1 | 0.288 | 0.288 | 1.59 | =0.216 |
| Error | 36 | 6.548 | 0.181 | | |
| Eye | 1 | 0.601 | 0.601 | 2.16 | =0.151 |
| Eye X group | 1 | 0.039 | 0.039 | 0.14 | =0.709 |
| Eye X age | 1 | 0.007 | 0.007 | 0.03 | =0.875 |
| Eye X age X group | 1 | 0.057 | 0.057 | 0.21 | =0.653 |
| Error | 36 | 10.049 | 0.279 | | |

Table 4.12. Repeated measures analysis of co-variance for central / peripheral (C/P) SF.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Stage | 3 | 0.379 | 0.126 | 5.34 | =0.009 |
| Stage X group | 3 | 0.084 | 0.028 | 1.19 | =0.308 |
| Stage X age | 3 | 0.006 | 0.002 | 0.09 | =0.901 |
| Stage X age X group | 3 | 0.112 | 0.037 | 1.59 | =0.214 |
| Error | 108 | 2.561 | 0.023 | | |
| C/P X eye | 1 | 0.000 | 0.000 | 0.00 | =0.972 |
| C/P X eye X group | 1 | 0.001 | 0.001 | 0.01 | =0.923 |
| C/P X eye X age | 1 | 0.017 | 0.017 | 0.11 | =0.746 |
| C/P X eye X age X group | 1 | 0.010 | 0.010 | 0.07 | =0.796 |
| Error | 36 | 5.834 | 0.162 | | |
| C/P X stage | 3 | 0.642 | 0.214 | 8.67 | <0.001 |
| C/P X stage X group | 3 | 0.116 | 0.038 | 1.58 | =0.214 |
| C/P X stage X age | 3 | 0.012 | 0.004 | 0.16 | =0.843 |
| C/P X stage X age X group | 3 | 0.156 | 0.052 | 2.11 | =0.130 |
| Error | 108 | 2.666 | 0.024 | | |

Table 4.12. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Eye X stage | 3 | 0.078 | 0.026 | 0.95 | =0.371 |
| Eye X stage X group | 3 | 0.048 | 0.016 | 0.59 | =0.512 |
| Eye X stage X age | 3 | 0.032 | 0.010 | 0.39 | =0.615 |
| Eye X stage X age X group | 3 | 0.051 | 0.017 | 0.62 | =0.496 |
| Error | 108 | 2.984 | 0.027 | | |
| C/P X eye X stage | 3 | 0.046 | 0.015 | 0.55 | =0.527 |
| C/P X eye X stage X group | 3 | 0.013 | 0.004 | 0.16 | =0.786 |
| C/P X eye X stage X age | 3 | 0.008 | 0.002 | 0.11 | =0.839 |
| C/P X eye X stage X age X group | 3 | 0.015 | 0.005 | 0.19 | =0.761 |
| Error | 108 | 3.007 | 0.027 | | |

Table 4.12. (continued).

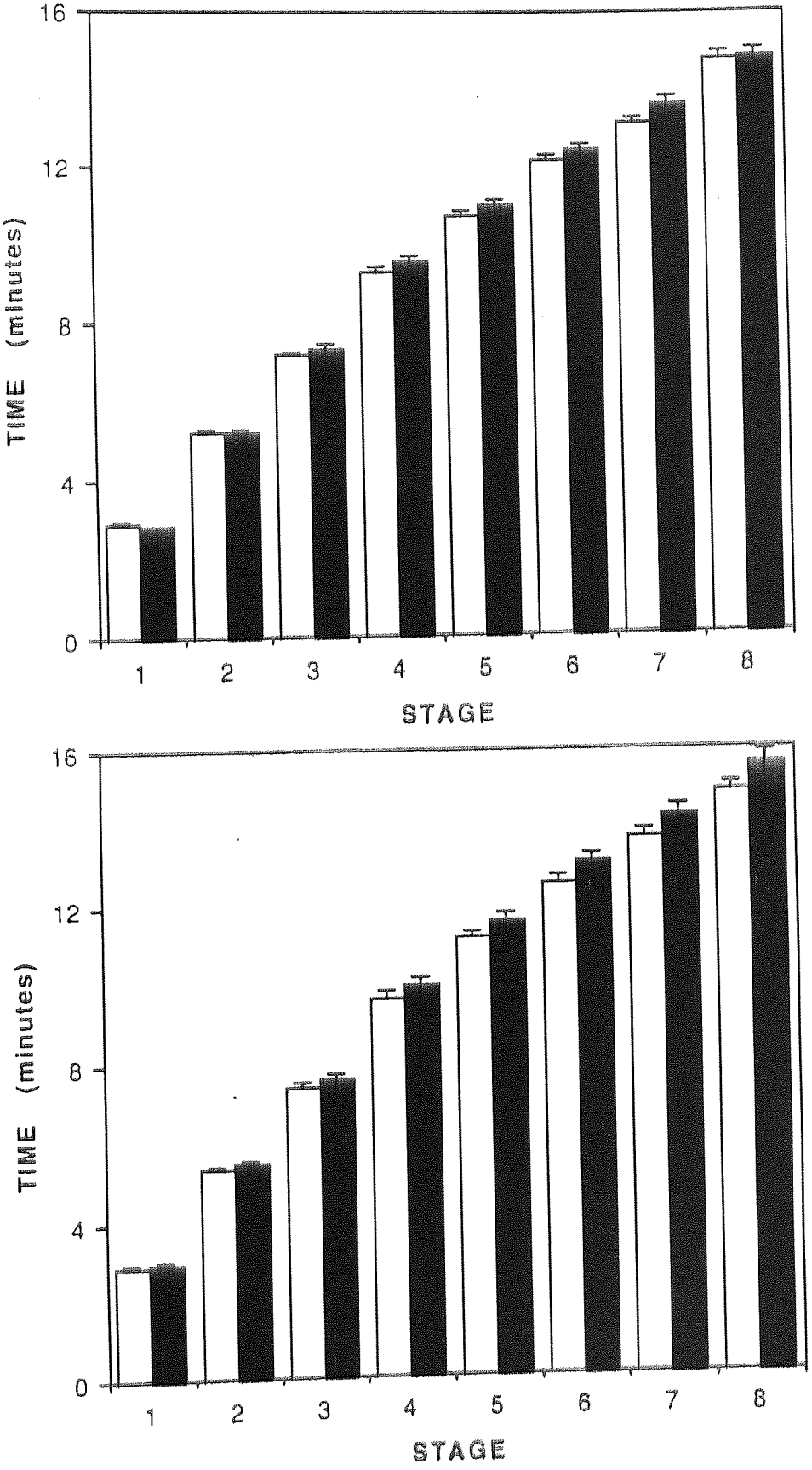



Fig. 4.14. Bar charts of cumulative time (minutes) against stage for the normal subjects (top) and ocular hypertensive patients (bottom); Open bars first eye; closed bars second eye. The error bars represent one standard error of the mean.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Group | 1 | 0.196 | 0.196 | 4.27 | =0.046 |
| Age | 1 | 0.015 | 0.015 | 0.33 | =0.568 |
| Age X group | 1 | 0.156 | 0.156 | 3.40 | =0.073 |
| Error | 36 | 1.656 | 0.046 | | |
| Eye | 1 | 0.083 | 0.083 | 9.23 | =0.004 |
| Eye X group | 1 | 0.007 | 0.007 | 0.81 | =0.372 |
| Eye X age | 1 | 0.057 | 0.057 | 6.35 | =0.016 |
| Eye X age X group | 1 | 0.004 | 0.004 | 0.55 | =0.464 |
| Error | 36 | 0.325 | 0.009 | | |
| Stage | 3 | 50.906 | 16.968 | 21067.85 | <0.001 |
| Stage X group | 3 | 0.003 | 0.001 | 1.58 | =0.217 |
| Stage X age | 3 | 0.008 | 0.002 | 3.33 | =0.054 |
| Stage X age X group | 3 | 0.003 | 0.001 | 1.65 | =0.204 |
| Error | 108 | 0.086 | 0.001 | | |

Table 4.13. Repeated measures analysis of co-variance for time.

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Phase | 1 | 108.011 | 108.011 | 25328.39 | <0.001 |
| Phase X group | 1 | 0.006 | 0.006 | 1.43 | =0.239 |
| Phase X age | 1 | 0.017 | 0.017 | 4.21 | =0.047 |
| Phase X age X group | 1 | 0.007 | 0.007 | 1.69 | =0.201 |
| Error | 36 | 0.153 | 0.004 | | |
| Eye X stage | 3 | 0.005 | 0.001 | 2.13 | =0.136 |
| Eye X stage X group | 3 | 0.004 | 0.001 | 1.87 | =0.170 |
| Eye X stage X age | 3 | 0.002 | 0.001 | 1.06 | =0.340 |
| Eye X stage X age X group | 3 | 0.004 | 0.001 | 1.90 | =0.166 |
| Error | 108 | 0.086 | 0.001 | | |
| Eye X phase | 1 | 0.008 | 0.008 | 3.31 | =0.077 |
| Eye X phase X group | 1 | 0.010 | 0.010 | 4.14 | =0.049 |
| Eye X phase X age | 1 | 0.004 | 0.004 | 1.88 | =0.179 |
| Eye X phase X age X group | 1 | 0.009 | 0.009 | 4.00 | =0.053 |
| Error | 36 | 0.088 | 0.002 | | |

Table 4.13. (continued).

| Source | Degrees of freedom | Sums of squares | Mean square | F value | Significance level |
|---|---|---|---|---|---|
| Phase X stage | 3 | 19.096 | 6.365 | 9535.41 | <0.001 |
| Phase X stage X group | 3 | 0.002 | 0.001 | 1.32 | =0.273 |
| Phase X stage X age | 3 | 0.003 | 0.001 | 1.71 | =0.186 |
| Phase X stage X age X group | 3 | 0.003 | 0.001 | 1.79 | =0.173 |
| Error | 108 | 0.072 | 0.001 | | |
| Eye X phase X stage | 3 | 0.007 | 0.002 | 4.45 | =0.024 |
| Eye X phase X stage X group | 3 | 0.002 | 0.001 | 1.37 | =0.259 |
| Eye X phase X stage X age | 3 | 0.001 | 0.001 | 1.09 | =0.329 |
| Eye X phase X stage X age X group | 3 | 0.001 | 0.001 | 1.08 | =0.331 |
| Error | 108 | 0.061 | 0.001 | | |

Table 4.13. (continued).

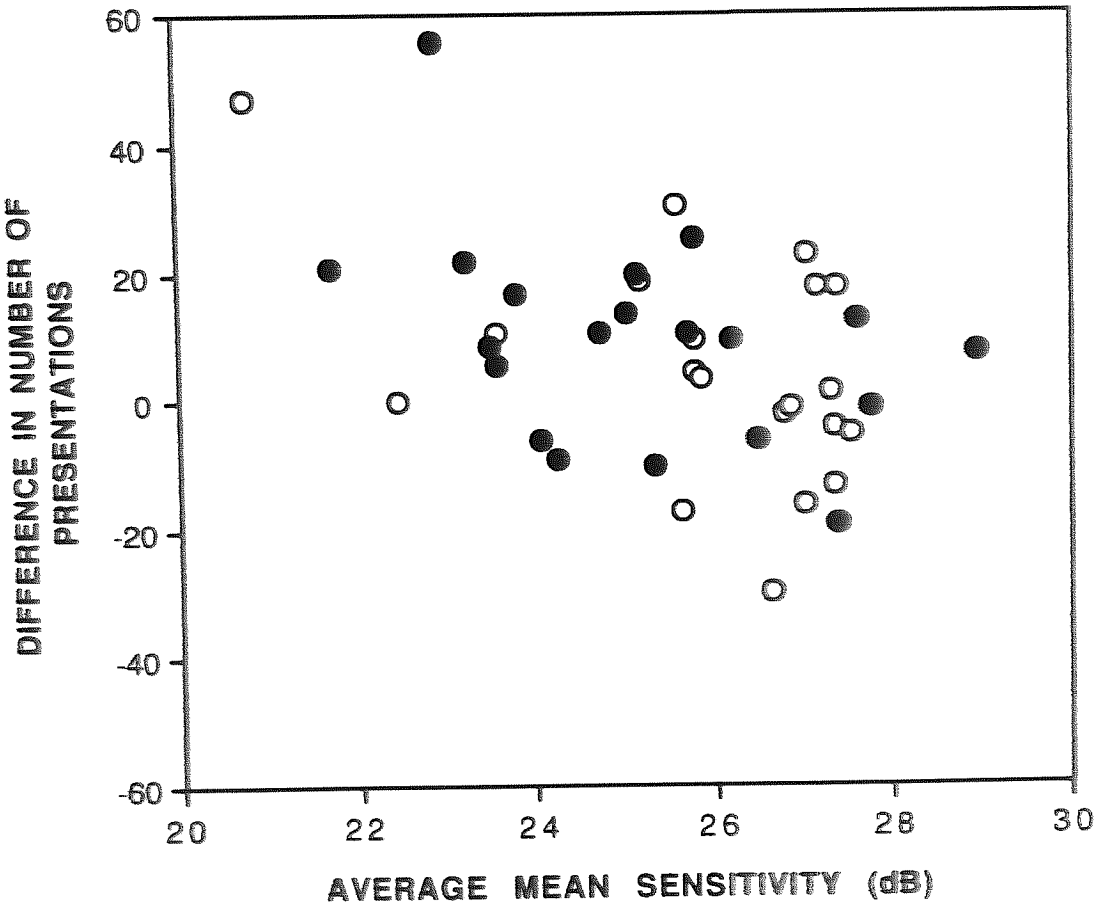



Fig. 4.15. Scatterplot of the difference in the number of stimulus presentations between the first and second eyes (second minus first) as a function of the average mean sensitivity for the first and second eyes for each individual. (Open circles; normal subjects. Closed circles; ocular hypertensive patients).

4.3.15. Fixation losses and catch trials.

The number of fixation losses, false-positives and false-negative responses obtained was minimal and insufficient to warrant any form of analysis.

In summary, the results show a progressive deterioration over stage of the global indices MD and LV despite the introduction of breaks within the examination procedure. In addition, the deterioration of MD was greater for the inferior hemifield and for the peripheral annulus, whilst that of LV was greater for the superior and nasal hemifields and for the peripheral annulus. Global SF exhibited no significant alteration over stage. The deterioration of SF was greater, however, for the nasal hemifield. In general, these changes were more pronounced for phase 2 and for the second eye and with increase in age but varied differently between the two groups.

4.4. Discussion.

The progressive deterioration in perimetric sensitivity over stage found in this study compare favourably with the results of Searle and co-workers (1991) who reported a decline in sensitivity over time at each of two separate examinations with the deterioration being greater in the second eye. In contrast, the results do not agree with those of Marra and Flammer (1991) who reported no obvious change in sensitivity both in trained and inexperienced normal subjects and cataract and glaucoma patients for the repeated thresholding of 3 stimulus locations over a period of 5 to 8 minutes using the Octopus perimeter. The use of 59 stimulus locations in the current study, however, will result in a considerably greater uncertainty as to where in the visual field the next stimulus will be presented. The greater demands on subject vigilance, therefore, could conceivably result in a more pronounced fatigue effect (Fujimoto and Adachi-Usami, 1992a).

The poorer sensitivity in phase 2 compared to phase 1 reinforces the finding of a decline in sensitivity over stage. It would also suggest that the break of one minute between phases at best only retards the progressive decline in sensitivity for a relatively short

period of time. In addition, the poorer sensitivity in the second eye would suggest that a between-examination break of three minutes is insufficient to overcome the between-eye transfer of the fatigue effect resulting from the examination of the first eye.

The use of fatigue as a provocative diagnostic test for glaucoma has been proposed (Heijl, 1977b & c; Heijl and Drance, 1983; Suzumura, 1988). This has proved to to be unreliable, however, due to the considerable overlap of results between normal subjects and glaucoma patients (Langerhorst et al, 1987; Johnson et al, 1988a). In broad agreement with this latter finding, the performance of the normal and ocular hypertensive groups in the current study were found to be almost indistinguishable. Indeed, between-eye differences in pointwise sensitivity of up to 9dB have previously been reported in normal subjects (Brenton et al, 1986).

The results indicate a progressive overall depression of the hill of vision during the course of the examination, together with a localised loss (ie a shape change). The depression was more marked in the inferior field than the superior field but similar between the nasal and the temporal fields, whilst the localised loss was more pronounced in the superior and nasal fields. The alterations in sensitivity were also greater for the peripheral annulus. In general, the shape change was more exaggerated for the second eye but the components of the shape change varied differently between the two groups. When considered overall, the results suggest a sinking together with a steepening of the hill of vision. This finding is compatible with earlier studies which have found a pronounced fatigue effect for peripheral stimulus locations (Langerhorst et al, 1987; Johnson et al, 1988a; Wildberger and Robert, 1988). The change in LV, however, may also reflect additional shape changes which are independent of eccentricity.

The fatigue effect was investigated for a given number of completed stimulus locations. An alternative experimental design would have been to study the fatigue effect over a predefined and fixed time. The duration of each individual stage (Figure 4.14), however,

was such that any between stage analysis was considered to be clinically acceptable for all between-phase, between-eye and between-group comparisons.

It might be argued that the deterioration of the visual field indices over the eight stages of the G1X examination could occur as a result of the increase in information arising from the progressive inclusion of newly thresholded stimulus locations. That is, the initial thresholded stimulus locations might be excessively influenced by false-positive responses and / or subsequent stimulus locations might be excessively influenced by false-negative responses. The visual field indices express, however, the difference between the measured sensitivity and that of the established normal values and as such should approximate to zero in the normal field. Any change in the visual field indices must therefore represent a real change in sensitivity and not an artifact due to the progressive inclusion of thresholded values from additional stimulus locations.

The precise pattern of the decline in sensitivity may be contaminated by the difference between the number of central and peripheral stimulus locations over stage (Figure 4.1). From Figure 4.1, it can be seen that the number of peripheral stimulus locations is greatest for stage 2 and for stage 6, while for stages 3 to 4 and 7 to 8 respectively the proportion of central to peripheral locations is similar. Fatigue effects are known to greater for peripheral stimulus locations (Langerhorst et al, 1987; Johnson et al, 1988a; Wildberger and Robert, 1988) and, therefore, the results could be subject to an artifact in that a greater reduction in sensitivity could occur between stages 1 and 2 and particularly between stages 5 and 6 (phase 2) due to the difference in the proportion of central to peripheral stimuli. The data, however, shows little sign of this.

The difference in the starting luminance of the staircase procedure might have influenced the magnitude of the threshold estimation between the two phases. However, the starting position of the staircase relative to the threshold influences the efficiency of threshold determinations but not the accuracy (Johnson et al, 1992).

4.4.1. An explanation of the mechanism of the fatigue effect.

The mechanism of the fatigue effect in perimetry is unknown. The shape change in the superior field might be associated with a progressive upper lid ptosis although no obvious reduction in palpebral aperture size was noted on the video monitor. Such a loss, however, is small relative to the decline in sensitivity of the inferior field.

Ganzfeld blankout (Fuhr et al, 1990) or the Troxler phenomenon (Davson, 1980), due to the suppression of eye movements and the subsequent formation of a stabilised retinal image (Steinman and Levinson, 1990; Campbell and Andrews, 1992), have been proposed to explain the fatigue effect. The Troxler phenomenon results in a preferential fading of the peripheral visual field and is frequently reported by patients undergoing routine perimetric examination. The underlying mechanism can be explained by an increase in receptive field size when presented with a motionless stimulus (Campbell and Andrews, 1992). This hypothesis is consistent with the greater deterioration in mean defect and loss variance for the more peripheral regions of the visual field.

Psychological factors such as attention or vigilance may also have a bearing on perimetric fatigue (Coren and Ward, 1989). The influences on performance during monotonous tasks which require sustained attention are not totally understood (Mackworth, 1969). However, performance is known to decline in situations of sustained attention and this decline occurs due to a loss of vigilance soon after commencement of the task (Warm, 1984). The process by which performance deteriorates is described as the "vigilance decrement", which typically occurs within 20 to 35 minutes and at least 50% of the loss occurs within the first 15 minutes (Teichner, 1974). The theory of habituation, that is the waning of neural responsiveness due to repetitive stimulation, is often used to explain the vigilance decrement (Warm, 1984). As a result, the background event rate (ie the frequency of stimulation) is a very important determinant of performance (Jerison and Pickett, 1964). An increased frequency of stimuli leads to a greater decline of the rate of detection. In addition, by the phenomenon of dishabituation, performance can recover following changes in the mode of stimulation (Mackworth, 1968; Mackworth, 1969). In

other words, a stimulus is more likely to be detected if it is new, unexpected or difficult to interpret due to an increased arousal response. The fact that performance can suddenly recover as a result of dishabituation distinguishes the vigilance decrement from fatigue.

## 4.5. Conclusions.

The increase in the visual field indices mean defect and loss variance in a time-related manner, particularly for the second eye, questions the currently accepted duration of a perimetric examination. The use of alternative and faster measurement strategies, such as the dynamic step unit (DSU) strategy of the Peristat 433 perimeter (Weber, 1991 and 1992; Vivell et al, 1991), RIOTS (real-time interactive optimized test sequence) (Johnson and Shapiro, 1991) and the FASTPAC strategy of the HFA (Moss et al, 1992; Flanagan et al, 1993a; Flanagan et al, 1993b) seem to be a clear and logical direction for the development of automated perimetry. Alternatively, the possibility of reducing the number of stimulus locations in order to reduce examination time has been suggested to be clinically feasible (Funkhouser et al, 1989a and b; de la Rosa et al, 1990 and 1992; Fujimoto and Adachi-Usami, 1992a, b and c; Weber and Diestelhorst, 1992). The goal should obviously be to produce reliable and reproducible test procedures which avoid fatigue.

Alternatively, if the conventional algorithms are to be utilised, then confidence limits for the definition of abnormality should reflect the more pronounced effect of fatigue on the second eye and be different between the two eyes. In addition, the introduction of breaks during an examination, although insufficient to reverse the fatigue effect, may retard the progressive decline in sensitivity due to fatigue.

Further study should be directed towards the influence of the Troxler phenomenon and vigilance decrement on perimetric fatigue. The development of stabilised retinal images should be discouraged using the appropriate stimulus and background conditions, while

the employment of warning cues before the presentation of a stimulus might result in a greater arousal response thereby suppressing the vigilance decrement (Solso, 1988).

# CHAPTER 5. THE MODIFICATION OF A HUMPHREY FIELD ANALYZER 640 FOR BLUE-ON-YELLOW PERIMETRY AND THE QUANTIFICATION OF PRE-RECEPTORAL ABSORPTION.

## 5.1. Introduction.

Blue-on-yellow perimetry employs a blue stimulus to preferentially stimulate the SWS pathway and a high luminance yellow background to saturate both the medium wavelength sensitive (MWS) and the long wavelength sensitive (LWS) pathways and to simultaneously suppress rod activity.

### 5.1.1. The development of blue-on-yellow perimetry.

Numerous laboratory based studies have shown that blue-yellow colour vision abnormalities can be an early sign of ocular disease.

#### 5.1.1.1. Hue discrimination and colour matching tests.

Hue discrimination and colour matching tests, both of which employ foveal fixation, have demonstrated a blue-yellow colour vision deficit prior to the manifestation of visual field loss in glaucoma (Lakowski et al, 1972a; Lakowski and Drance, 1979; Drance, 1981; Drance et al, 1981; Motolko and Drance, 1981; Adams et al, 1982; Flammer and Drance, 1984; Airaksinen et al, 1986; Sample et al, 1988b and c; Steinschneider and Ticho, 1991). Indeed, Foulds and co-workers (1974) using the Farnsworth-Munsell 100 Hue test found that an artificial increase in the intra-ocular pressure of normal subjects resulted in a blue-yellow deficit, which disappeared when the intra-ocular pressure returned to normal. Conversely, Hamill and co-workers (1984) found no correlation between acquired colour vision deficits and the presence of early glaucomatous cupping of the optic disc. A blue-yellow deficit, however, has been demonstrated in diabetic patients without diabetic retinopathy or with early retinopathy (Kinnear et al, 1972; Lakowski et al, 1972b; Adams, 1982; Aspinall et al, 1983; Roy et al, 1984 and 1986; Mäntyjärvi, 1987; Trick et al, 1988; Greenstein et al, 1990; Lagerlöf, 1991; Birch et al, 1991; Hardy et al, 1992).

5.1.1.2. Chromatic adaptation and spectral sensitivity techniques.

Chromatic adaptation and spectral sensitivity techniques have also demonstrated a selective loss of the short-wavelength sensitive (SWS) pathway to foveal stimuli prior to the presence of visual field loss in glaucoma (Zwas et al, 1982; Adams et al, 1982; Alvarez et al, 1983a; Vola et al, 1985; Alvarez and Mills, 1985; Zwas and Shin, 1987; Adams et al, 1987b and c; Sucs and Verriest, 1989; Yamazaki et al, 1989; Lakowski et al, 1989; Greenstein et al, 1989a and b; Zwas et al, 1991). In addition, such techniques have also demonstrated a selective loss of the short-wavelength sensitive (SWS) pathway to foveal stimuli in diabetics without retinopathic abnormality (Marré and Marré, 1984; Zwas et al, 1980; Zisman and Adams, 1982; Vola et al, 1982; Adams et al, 1987a and b; Greenstein et al, 1989a, b and c; Greenstein et al, 1990; Terasaki et al, 1990; Schefrin et al, 1991; Greenstein et al, 1992). Indeed, a number of studies have found that the selectivity of the SWS pathway attenuation is greater in diabetes than in glaucoma since the reduction of sensitivity of the achromatic mechanism is less in diabetes (Adams, 1982; Greenstein et al, 1989a and b). Furthermore, a selective loss of the short-wavelength sensitive (SWS) pathway to foveal stimuli has been demonstrated in numerous other diseases including age-related maculopathy (Marré, 1973; Alvarez et al, 1983b; Applegate et al, 1987; Haegerstrom-Portnoy and Brown, 1989), retinitis pigmentosa (Hansen, 1977; Sandberg and Berson, 1977; Young, 1982; Greenstein and Hood, 1986; Greenstein et al, 1989a, b and c), central serous choroidopathy (Verriest and Uvijls, 1977; Adams, 1982; Terasaki et al, 1990), optic neuritis (Zisman et al, 1978; Alvarez et al, 1982; Terasaki et al, 1990), optic atrophy (Krill et al, 1970), toxic amblyopia (Zisman et al, 1978) and familial macular dystrophy (Bresnick et al, 1989).

Early glaucomatous visual field loss generally occurs beyond the foveal region (Aulhorn and Harms, 1967; Drance, 1969; Aulhorn and Karmeyer, 1976; Werner et al, 1977; Hart and Becker, 1982; Mikelberg and Drance, 1984; Caprioli and Sears, 1987). Laboratory based studies of colour vision deficits in glaucoma, however, have generally employed foveal fixation. A clinical procedure to assess SWS pathway sensitivity over the central (ie within 30° eccentricity) visual field, namely blue-on-yellow perimetry, was developed by

Heron and co-workers (1988). Subsequently, other clinical studies have demonstrated that blue-on-yellow perimetry detects glaucomatous visual field loss at an earlier stage of the disease process than conventional white-on-white perimetry (Johnson et al, 1989a; Sample and Weinreb, 1990; De Jong et al, 1990; Weinreb and Sample, 1991; Flanagan et al, 1991; Johnson et al, 1991; Adams et al, 1991; Sample and Weinreb, 1992; Johnson et al, 1993a and b; Lewis et al, 1993; Sample et al, 1993a).

The clinical utilization of blue-on-yellow perimetry in diseases other than ocular hypertension and glaucoma, however, has been minimal (Lutze et al, 1989; Jacobson et al, 1990). The evidence from laboratory based studies would suggest that blue-on-yellow perimetry may permit the earlier detection of numerous ocular diseases. Indeed, it would seem that the potential benefits of this clinical technique have not been fully explored.

5.1.2. Optimum parameters for blue-on-yellow perimetry.

The optimum stimulus parameters for blue-on-yellow perimetry have yet to be standardized. A background filter transmitting all visible wavelengths above 530nm (eg Wratten #12 or Schott OG530) is generally utilized. The magnitude of the required background luminance is equivocal (Johnson et al, 1989a; Sample and Weinreb, 1990). Background luminances of 180 $cdm^{-2}$ (De Jong et al, 1990), 200 $cdm^{-2}$ (Johnson et al, 1989a; Johnson et al, 1991; Adams et al, 1991; Johnson et al, 1993a and b; Lewis et al, 1993), 300 $cdm^{-2}$ (Flanagan et al, 1991) and 500 $cdm^{-2}$ (Heron et al, 1988) have been utilized. A background luminance of 80.9 $cdm^{-2}$ for blue-on-yellow perimetry has also been advocated on the basis that higher adaptation levels only raise SWS pathway thresholds rather than increase isolation (Sample and Weinreb, 1990; Weinreb and Sample, 1991; Sample and Weinreb, 1992; Sample et al, 1993a). However, Yeh and co-workers (1989) found that the maximum isolation of the SWS pathway in the normal eye was only achieved above an adaptation level of approximately 140 $cdm^{-2}$ for a pupil diameter of 3mm, whilst Aguilar and Stiles (1954) demonstrated that background luminances of up to 300 $cdm^{-2}$ were necessary to suppress rod activity. In addition, Wald and co-workers (1955) demonstrated that the scotopic mechanism is more sensitive to

blue light compared with the photopic mechanism. Furthermore, the proportion of rods to cones is known to increase with increase in eccentricity (Davson, 1980). Consequently, it is plausible that at a relatively low background luminance a loss of sensitivity of the SWS pathway may result in the detection of the stimulus by the scotopic mechanism. Indeed, rod dominated vision at photopic light levels (ie 310 $cdm^{-2}$) has been demonstrated to be a feature of advanced optic nerve and retinal disease (Kalloniatis et al, 1993).

The choice of stimulus filter is also equivocal. A stimulus filter with a discrete spectral transmission in the short-wavelength region of the visible spectrum (eg 440nm; half point bandwidth less than 20nm) has been used to promote isolation of the SWS cone response, but such a filter attenuates the dynamic range of the perimeter (Sample and Weinreb, 1990; Weinreb and Sample, 1991; Sample and Weinreb, 1992; Sample et al, 1993a). Alternatively, a stimulus filter with a broader spectral transmission in the short-wavelength region (eg OCLI blue dichroic, transmitting wavelengths below 500nm) has been used to permit a greater dynamic range (Johnson et al, 1989a; De Jong et al, 1990; Johnson et al, 1991; Adams et al, 1991; Flanagan et al, 1991; Johnson et al, 1993a and b; Lewis et al, 1993). A broadband stimulus filter does not guarantee the same degree of isolation as a narrowband filter, however, since the transmission of wavelengths up to 500nm may allow detection of the stimulus by the MWS cones in the presence of an SWS cone deficit (Sample and Weinreb, 1990; Weinreb and Sample, 1991). Fortunately, SWS pathway isolation is encouraged by the use of a larger stimulus diameter (ie greater than 1°) and a longer stimulus duration (ie 200 msec) (King-Smith and Carden, 1976; Harwerth et al, 1993) both of which increase the dynamic range of the perimeter.

In summary, the magnitude of SWS isolation can be increased by the use of a blue stimulus filter with a narrow spectral transmission (Sample and Weinreb, 1990; Weinreb and Sample, 1991; Sample and Weinreb, 1992; Sample et al, 1993a) or by a higher background luminance (Yeh et al, 1989). However, the narrower the spectral transmission of the blue filter the lower the maximum stimulus intensity, while the higher the background luminance the lower the sensitivity of the visual system (see Section 1.3.3);

the combined effect is to substantially attenuate (ie by approximately 1.3 log units) the dynamic range. Consequently, the conditions which favour SWS isolation are in conflict with those which allow a maximum dynamic range. A fundamental requirement of perimeter design, however, is the attainment of maximum dynamic range (Fankhauser, 1979). This goal is particularly pertinent for blue-on-yellow perimetry since any increase in the maximum stimulus intensity can be employed to increase the dynamic range *per se* but also to provide a greater choice of stimulus and background conditions to further improve SWS isolation.

### 5.1.3. Pre-receptoral absorption.

Short-wavelength stimuli are preferentially absorbed by the ocular media (Said and Weale, 1959; Ruddock, 1965a; Mellerio, 1971; Coren and Girgus, 1972; Norren and Vos, 1974; Zigman, 1978; Werner and Wooten, 1980; Werner, 1982; Wyszecki and Stiles, 1982; Zeimer and Noth, 1984; Pokorny et al, 1987; Weale, 1988; Sample et al, 1988a and 1989; Johnson et al, 1988b; Johnson et al, 1989b; Savage et al, 1993; Johnson et al, 1993) and by the macular pigment (Ruddock, 1963 and 1965b; Bone and Sparrock, 1971; Yasuma et al, 1981; Wyszecki and Stiles, 1982; Pease and Adams, 1983; Moreland and Bhatt, 1984; Norren and Tiemeijer, 1986; Pease et al, 1987; Werner et al, 1987; Bone et al, 1988; Kilbride et al, 1989; Hammond and Fuld, 1992; Bone et al, 1992) which confounds the interpretation of SWS sensitivity. In addition, ocular media absorption increases with increase in age (Said and Weale, 1959; Mellerio, 1971; Coren and Girgus, 1972; Zigman, 1978; Werner and Wooten, 1980; Werner, 1982; Pokorny et al, 1987; Weale, 1988; Sample et al, 1988a; Johnson et al, 1988b; Johnson et al, 1989b; Savage et al, 1993). Furthermore, the magnitude of absorption due to the ocular media (Coren and Girgus, 1972; Norren and Vos, 1974; Werner and Wooten, 1980; Werner, 1982; Pokorny et al, 1987; Sample et al, 1988a; Johnson et al, 1988b; Johnson et al, 1989b; Savage et al, 1993) and due to the macular pigment (Wyszecki and Stiles, 1982; Pease and Adams, 1983; Pease et al, 1987; Werner et al, 1987; Bone et al, 1992) exhibits a large variation between individuals of the same age. The attenuation of short-wavelength light arising both from the ocular media and from the macular pigment

therefore needs to be separated from any loss of SWS pathway sensitivity due to the disease process.

Techniques have already been developed for the assessment of ocular media absorption and applied clinically to blue-on-yellow perimetry (Sample et al, 1988a and 1989; Johnson et al, 1989b). The influence of the macular pigment, however, on the outcome of blue-on-yellow perimetry is unknown (de Jong et al, 1990; Sample and Weinreb, 1990). Indeed, such information is essential if the potential benefits of blue-on-yellow perimetry are to be exploited for the detection of macular disease.

### 5.1.4. Spectral sensitivity.

Spectral sensitivity is known to be influenced by factors such as the chromatic composition (Auerbach and Wald, 1955; Marks and Bornstein, 1973; Kalloniatis and Harwerth, 1991) and intensity of the adapting background (Brindley, 1953; Wald, 1964; Ingling, 1969; Kalloniatis and Harwerth, 1990 and 1991); the size (King-Smith and Carden, 1976; Kuyk, 1980; Johnson and Massof, 1982; Kokoschka and Adrian, 1985) and duration of the stimulus (Ronchi, 1974; King-Smith and Carden, 1976) and the eccentricity at which the stimulus is presented (Kuyk, 1980; Kitahara et al, 1983; Hibino, 1992). It was therefore necessary to assess spectral sensitivity using the parameters employed for blue-on-yellow perimetry since the resultant effect of the interaction of the parameters was unknown. The wavelength of the stimulus filter utilized for blue-on-yellow perimetry was determined by the peak sensitivity of the derived SWS pathway spectral sensitivity function.

### 5.1.5. Aim.

The aim was: (1) to modify a HFA 640 for blue-on-yellow perimetry taking into account the conflicting requirements of SWS pathway isolation and dynamic range; (2) to further modify the HFA to permit the quantification of pre-receptoral absorption particularly that due to the macular pigment; (3) to determine the peak wavelength of the SWS spectral

sensitivity function with the chosen background conditions; and (4) to quantify the magnitude of SWS pathway isolation obtained with the chosen stimulus conditions.

## 5.2. Materials and methods.

### 5.2.1. General modifications and theoretical considerations.

Humphrey 5.3 software was utilized to extinguish the intrinsic background illumination for all investigations. Two auxiliary lamp housings, designed to provide a high intensity adapting field and to facilitate the easy interchange of background filters, were mounted on either side of the HFA close to the intrinsic background sources. Both housings consisted of an ELE/ELT 80 Watt / 30 volt tungsten halogen lamp (General Electric, Cleveland, Ohio), an infra-red filter, the appropriate background filter and an opal diffusing filter. The opal diffusing filter was positioned flush with the surface of the perimeter cupola to ensure uniform illumination over the cupola surface.

The uniform diffusion of light leaving the lamp housing is desirable to avoid any non-uniformity of illumination on the cupola surface. A self-luminous surface will distribute light over a wide range of directions and will have a certain luminous intensity (defined as the luminous flux emitted per unit solid angle in any given direction) in each direction. If an elementary area, $A_S$, of a self luminous-surface has a luminous intensity d I in a direction inclined to the normal at an angle, Ø, the projected area in direction Ø is $A_S \cos Ø$ and the luminance (defined as the luminous intensity per unit projected area) is given by:

$$\text{Luminance} = dI / A_S \cos Ø$$

Observation of a self-luminous surface indicates that the brightness of the surface is independent of the angle of inclination of the surface to the direction of observation. The equation above shows that the luminous intensity of any element, d I, is proportional to cos Ø (Longhurst, 1973). This is known as Lambert's cosine law of emission. A surface which obeys this law is termed a uniform diffusing surface. No surface provides totally

uniform diffusion but opal glass is close to this ideal condition, such that transmitted light is radiated approximately according to Lambert's cosine law of emission.

The diffusing properties of the lamp housing and accompanying filters were verified by placing the housing with the front diffusing filter at the centre of rotation of a degree scaled turntable. The luminous intensity of the diffusing surface was then recorded with a mini-spot photometer at a distance of 4 metres so that the diffusing surface fell within the sight-ring of the photometer for all angles of Ø. The lamp was run at 15 volts to obtain a full scale reading on the photometer for a 0° angle of inclination to the direction of observation of 3000 $cd/m^2$ (the units used are insignificant since the recorded measurement is the ratio of luminous intensity for the various angles of Ø). Measurements of luminous intensity were taken to the left side of the lower lamp housing since it was from this side that incident light entered the perimeter bowl.

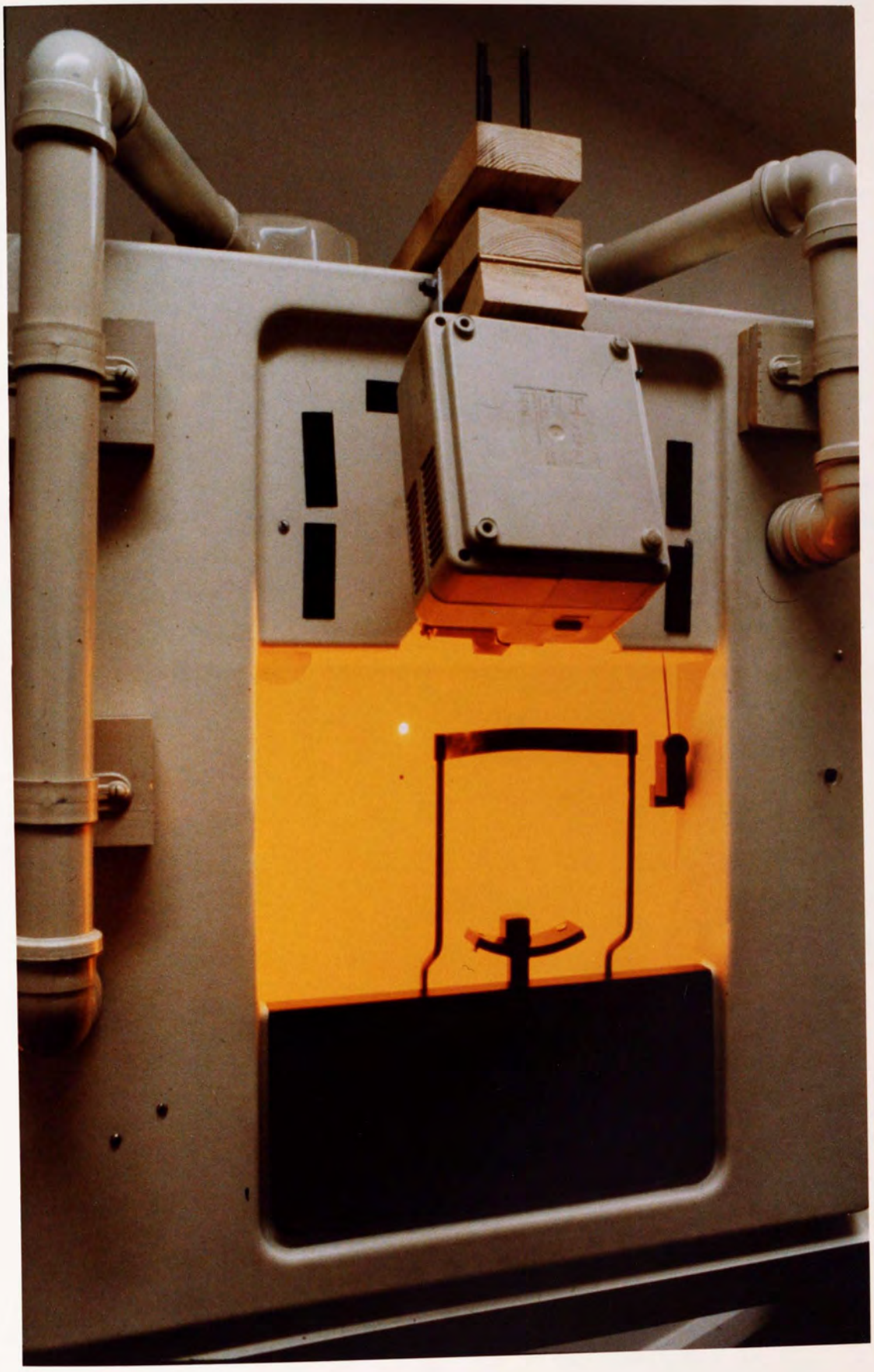
The diffusing properties of the lamp housing were found to be a good approximation to an ideal uniform diffuser. For an angle of inclination, Ø, of up to 30° the photometer reading was within ±1.50% of the theoretical value of a uniform diffusing surface and for a Ø of up to 70° within ±5.00% (Table 5.1.). Furthermore, the integrating sphere properties of the cupola will tend to reduce any residual non-uniformity of illumination. Indeed, direct photometric measurement with both auxiliary lamp housings in operation revealed that the illumination on the perimeter cupola was within ±2.00% of the mean value within 30° of fixation in all meridians.

The ELE/ELT tungsten halogen lamps were powered by a stabilized Farnell power unit (Farnell Instruments Ltd, Wetherby, Yorkshire, UK) and the life of the lamps was extended by deliberately under running the voltage at 28.5 volts. In addition, the stability of the auxiliary background luminance was routinely checked by direct photometric measurement. The body of each lamp housing acted as a heat sink and cool air was drawn over the housing via ducting to further dissipate heat (Figure 5.1.). A removable filter

| Ø (degrees) | Photometer reading ($cd/m^2$) | Theoretical value d I = 3000 X Cos Ø | Deviation (%) |
|---|---|---|---|
| 0 | 3000 | 3000.00 | 0 |
| 10 | 2995 | 2954.42 | +1.35 |
| 20 | 2800 | 2819.07 | -0.68 |
| 30 | 2600 | 2598.07 | +0.07 |
| 40 | 2200 | 2298.13 | -4.46 |
| 50 | 1900 | 1928.36 | -1.49 |
| 60 | 1450 | 1500.00 | -3.44 |
| 70 | 1000 | 1026.06 | -2.60 |

Table. 5.1. The percentage deviation of the photometer reading from the theoretical value of an ideal uniform diffusing surface as determined by Lambert's cosine law of emission for various angles of inclination, Ø, of up to 70°.

Figure 5.1. The modified Humphrey Field Analyzer 640 showing the yellow background employed for blue-on-yellow perimetry and a stationary size V blue stimulus situated above fixation.



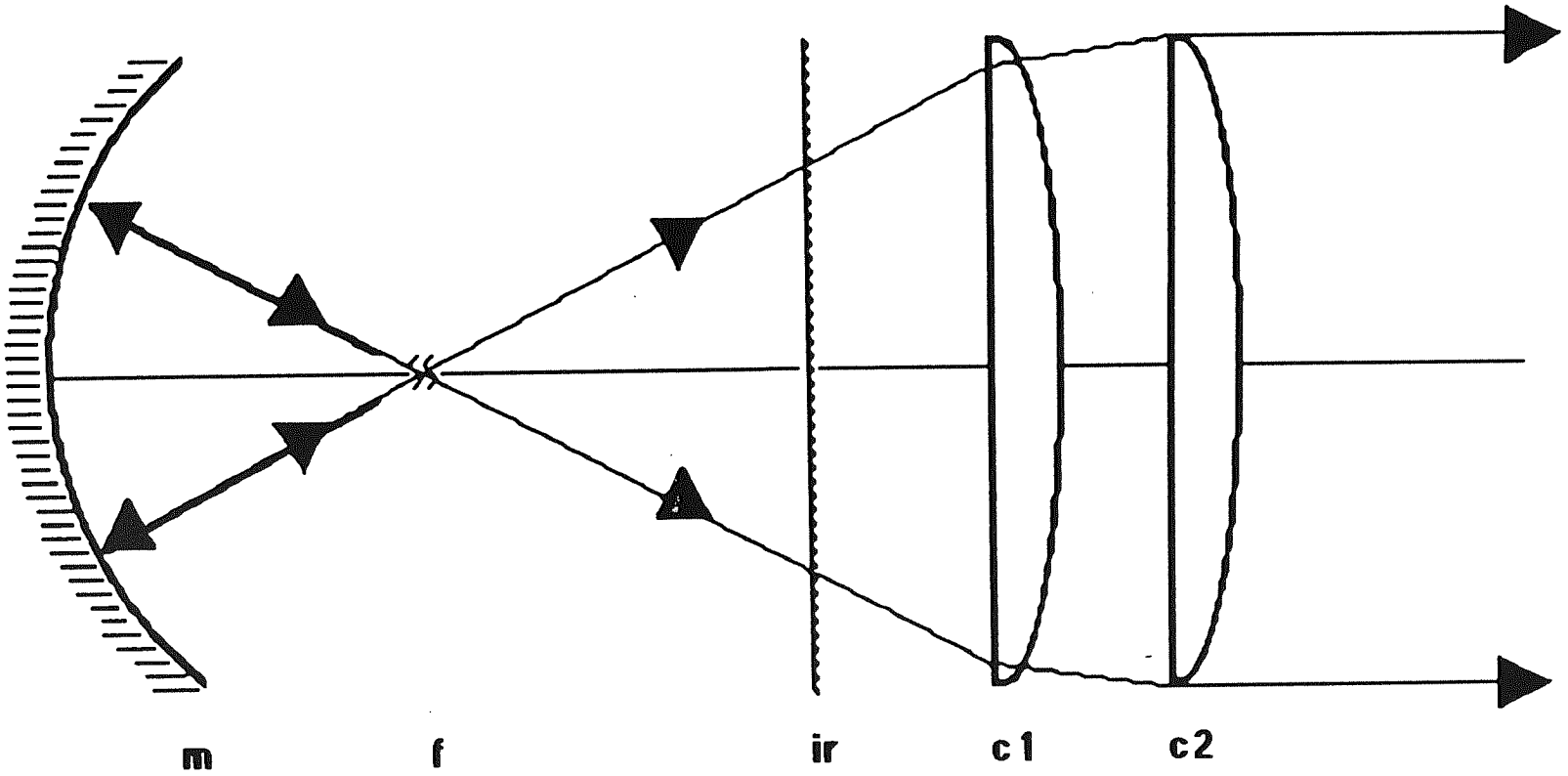



Figure 5.2. Schematic diagram showing how a concave mirror (m) is positioned behind the stimulus bulb filament (f) of the HFA in order to increase the maximum stimulus luminance (ir: infra red filter, c1 and c2: condensing lens system consisting of two plano convex lenses).

holder was attached to the projector arm of the HFA, which allowed the easy interchange of stimulus filters.

In order to cater for the conflicting interests of maximum SWS pathway isolation and maximum dynamic range, a method was devised to increase the maximum stimulus luminance of the HFA. Concave spherical reflectors are often used to increase the light output of illumination or projection systems. This is achieved by locating the centre of curvature of the reflector at the source (Figure 5.2.) so that the reflector images the source back on itself (Smith, 1966).

A focused image of the stimulus bulb filament in situ was projected onto the surface of the perimeter cupola by gaining access to the command structure software and then positioning a +3.00 diopter lens in front of the projector arm. The optical system of the HFA was then adjusted to ensure that the filament image was central in relation to the size V (1.724°) stimulus patch (Figure 5.3.). Direct measurement of the projected image showed that the height of the filament covered approximately 65% of the diameter of the stimulus patch, while the filament width covered the whole diameter.

The stimulus bulb was then removed from the HFA and mounted on an optical bench to produce, with the aid of a +10.00 diopter lens, a magnified sharp filament image. The height of the filament image and the distance from the lens to the focused image were measured and the actual height of the filament was calculated to be 1.45mm.

Where:

Distance from lens to image, $l'$ = 1341.00mm

Focal length of lens, $f$ = 100.00mm

Height of filament image, $h'$ = 18.00mm

and magnification, $m$ $= {}^{l'-f}/_{f}$ $= {}^{1241}/_{100}$

$= 12.41$

Therefore, actual height of filament, $h$ $= {}^{h'}/_{m}$

$= {}^{18.00}/_{12.41}$ = 1.45mm

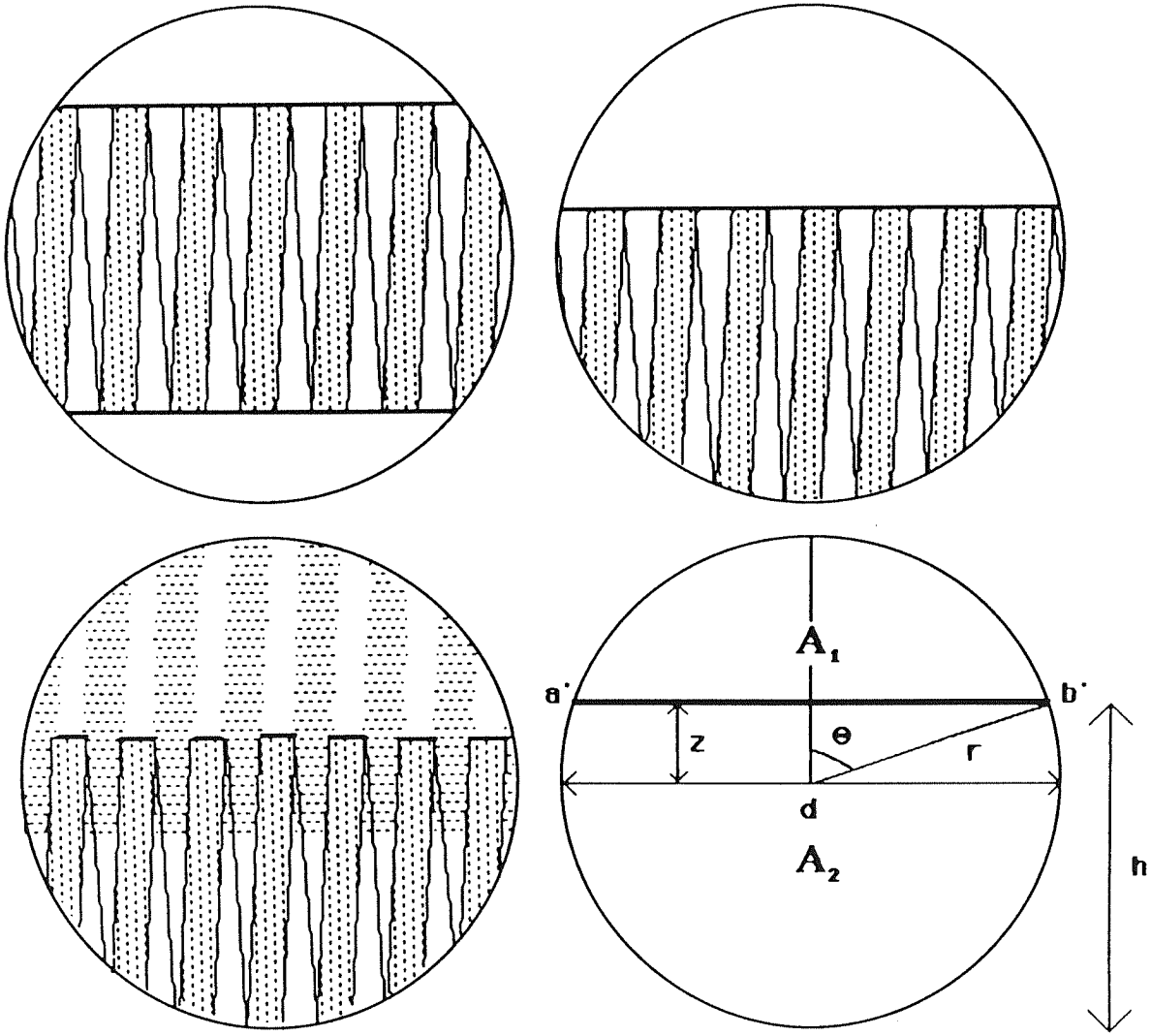



Figure 5.3. Schematic diagram showing: Top left: the conventional position of the filament within the size V stimulus margin. Top right: the position of the decentred filament. Bottom left: the defocused second filament image above and interleaved between the original filament outline. Bottom right: the measured and calculated dimensions of the decentred filament.

The effective diameter of the size V field stop (ie in the filament plane) was 2.23mm.

Where:

Effective diameter of size V field stop $= 1.45 \times {}^{100}/_{65} = 2.23\text{mm}$

The extent to which the filament could be decentred whilst remaining within the field stop was 0.39mm.

Where:

Filament decentration $= {}^{(2.23 - 1.45)}/_{2} = 0.39\text{mm}$

Both terminals of the stimulus bulb were then machined to remove 0.39mm of length, using a custom made jig. When the bulb was placed back in the socket of the HFA, a decentred projected filament image was obtained just within the size V stimulus margin (Figure 5.3.). A small reduction in stimulus intensity was noted (-3.57%) but this was within the permitted calibration tolerance of the instrument (Table 5.2.).

A first-surface concave mirror with a 28.00mm radius of curvature and a 40.00mm diameter was then positioned 28.80mm behind the filament centre (Figure 5.2.) to produce a slightly reduced defocused image of the filament within the confines of the size V projected stimulus margin. This increased the uniformity of luminance across the stimulus spot. The image of the filament was thus reduced by a factor of 0.95.

Where:

Radius of curvature of mirror, r $= 28.00\text{mm}$

Mirror vertex to filament, l $= 28.80\text{mm}$

and mirror vertex to image, l'

$= ({}^{2}/_{r} - {}^{1}/_{l})^{-1}$

$= ({}^{2}/_{28.00} - {}^{1}/_{28.80})^{-1} = 27.24\text{mm}$

Therefore, magnification, m

$= {}^{l'}/_{l}$

$= {}^{27.24}/_{28.80} = 0.95$

The concave mirror was adjusted to give a filament image partly above and partly overlapping and interleaved between the original filament profile for 30% of the size V

| Stimulus bulb set up | Stimulus luminance (asb) | Change in luminance (%) |
|---|---|---|
| Theoretical 0dB | 10,000 | — |
| Bulb centred | 10,540 | +5.40 |
| Bulb lowered | 9,643 | -3.57 |
| Mirror uncovered | 16,002 | +60.02 |

Table. 5.2. The percentage difference in stimulus luminance, relative to 10,000 apostilbs, for the various combinations of stimulus bulb position. Luminance values in apostilbs are also shown. A stationary 0dB size V stimulus was projected onto the perimeter bowl surface to permit measurement with a photometer and positioning clamp supplied by Humphrey Instruments Inc.

stimulus patch diameter (Figure 5.3.) to further ensure uniformity of luminance and to minimize filament heating. Prior to switching on the HFA, a matt black deflector angled at 30° to the horizontal and sloping away from the stimulus bulb, was placed in front of the concave mirror. The deflector was removed on completion of the calibration procedure. As the calibration procedure is only activated when the HFA is switched on, the instrument remains unaware of the increase in stimulus intensity.

An increase in stimulus intensity of 60% on the HFA default 0dB value of 10,000asb (Table 5.2.) was achieved ie the maximum stimulus luminance without any filter in place was 16002asb. The increase in light output by the concave mirror can be attributed to both the formation of a second filament image and the increase in temperature of part of the filament which results from the return of radiation by the mirror. The contribution of the second filament image to the overall increase in light output was calculated to be 45%.

Where (Figure 5.3.):

The filament height was measured to cover approximately 65% of the diameter of the size V stimulus.

Filament height, h = 1.45mm

Diameter of stop image in filament plane, d $= {}^{1.45}/_{0.65}$ = 2.23mm

Radius of stop image in filament plane, r = 1.115mm

Extent of filament above horizontal of stop image, z

=1.450mm - 1.115mm =0.335mm

Cos Ø $= {}^{0.335}/_{1.115}$ = 0.3004

Ø = 1.266 radians

Sin Ø = 0.9535

Therefore, area not illuminated by filament (ie area above line a' - b'), $A_1$,

$= 2\,({}^{Ø}/_{2} - \text{Sin}Ø\ \text{Cos}{}^{Ø}/_{2})\ r^2$

$= 0.979\ r^2$

and total area $= \pi\ r^2$

Hence, area illuminated by filament (ie area below line a' - b'), $A_2$,

$$= \text{Total area} - A_1$$

$$= (\pi - 0.979)\, r^2$$

$$= 2.163\, r^2$$

Increase in light output due to the formation of the filament image

$$= A_1 / A_2$$

$$= 0.979 / 2.163 \qquad = 0.45$$

ie $\qquad = 45\%$

A further increase in light output occurred due to the rise in temperature of the stimulus bulb filament as a result of the return of 15% of the total radiation to the filament from the mirror.

Where (Figure 5.3.):

Half cone (plane) angle subtended by the mirror at the source, $\phi$,

$$= \text{Sin}^{-1}(20/28) \qquad = 45.6°$$

The solid angle subtended by the mirror at the source, $\omega$,

$$= 2\pi\,(1 - \text{Cos}\phi)$$

Without the mirror in place the energy from the filament is radiated into $4\pi$ Steradians.

Therefore, proportion of the total energy returned from the mirror to the filament

$$= 2\pi\,(1 - \text{Cos}\phi) / 4\pi$$

$$= 0.30 / 2.0 \qquad = 0.15$$

ie $\qquad = 15\%$

(The mirror reflectance is assumed to be approximately 98% taking into account the complete visual spectrum).

The temperature of the filament was increased by 4.5% in the area of overlap and was reduced by only 1.0% (due to an increase in the electrical resistance of the hotter part of the filament) where no overlap occurred.

Where:

Without the mirror in operation, filament radiation, $E^2/R$

$$= \beta T_o^4$$

and filament resistance, $R = \alpha T_o$

Therefore, $E^2 = \alpha \beta T_o^5$

E is the stimulus bulb voltage, $\alpha$ is a constant describing the increase in the resistance of the filament with increase in temperature, $\beta$ is a constant for the particular lamp (dependent upon the filament design) and $T_o$ is the filament temperature without the mirror in operation. The supply to the HFA stimulus bulb is voltage controlled. The total voltage with the mirror in operation can be considered to consist of two part fractions: $E_1$ for part p of the filament at temperature $T_1$ (in the area of overlap) and $E_2$ for part 1-p of the filament at temperature $T_2$ (where no overlap occurs).

Where:

With the mirror in operation, for part p of the filament of resistance, $R_1$,

$$= \alpha p T_1$$

and $(E_1)^2 = \alpha \beta . 0.85 p^2 T_1^5$.....(i)

With the mirror in operation, for part (1-p) of the filament of resistance, $R_2$,

$$= \alpha (1\text{-}p) T_2$$

and $(E_2)^2 = \alpha \beta . (1\text{-}p)^2 T_2^5$.....(ii)

Also, $E_1/E_2 = R_1/R_2$

$$= p T_1 / (1\text{-}p) T_2 \text{.....(iii)}$$

Hence, $T_1/T_2 = (0.85)^{-1/3}$ $\left(\text{ie } (i)/(ii) = (iii)^2\right)$

and $T_1 = 1.055 T_2 = s T_2$.....(iv)

With the mirror in operation, for the whole filament, $E^2$

$$= \alpha \beta \left(pT_1 + (1\text{-}p)\, T_2\right) \left(0.85pT_1^4 + (1\text{-}p)\, T_2^4\right)$$

Therefore,

$$T_o^5 = \left(pT_1 + (1\text{-}p)\, T_2\right) \left(0.85pT_1^4 + (1\text{-}p)\, T_2^4\right)$$

$$= \left(p\, s + (1\text{-}p)\right) \left(0.85p\, s^4 + (1\text{-}p)\right) T_2^5$$

Fraction of area overlap between filament and image (Figure 5.3d.),

$$= 2\, z/h$$

$$= 2 \times 0.335/1.45 \qquad = 46\%$$

This area is to be considered to be receiving reflected radiation.

For p = 0.46, (1-p) = 0.54 and s from equation (iv)

Therefore, $T_2 = 0.99\, T_o$

ie $T_2$ is 1.0% less than $T_o$

and $T_1 = 1.045\, T_o$

ie $T_1$ is 4.5% greater than $T_o$

The luminosity of a tungsten source taken over the visible spectrum is proportional to $T^{8.25}$, where T is the temperature of the source ($T^{8.25}$ is derived by considering luminosity contributions with respect to wavelength throughout the whole of the visible spectrum). The relative increase in light output due to returned radiation and the consequent alteration in the filament temperature was calculated to be 16%.

Where:

Relative increase in luminosity $= \left(p\, (T_1/T_o)^{8.25}\right) + \left((1\text{-}p)\, (T_2/T_o)^{8.25}\right)$

$$= (0.54.(0.990)^{8.25}) + (0.46.(1.045)^{8.25})$$

$$= 1.158$$

ie $= 16\%$

Therefore, a 61% theoretical increase in the stimulus bulb output was derived (45% increase in light output due to the formation of the second filament image and 16% due to the heating of the filament) which showed close agreement to the observed increase in light output of 60%.

The 4.5% rise in the filament temperature was equivalent to a 11.6% increase in the voltage supply to the stimulus bulb without the mirror. This resulted in an effective voltage supply to the filament of 10.60 volts.

Where:

$$E'/E = (T_1/T_o)^{2.5}$$

$$= (1.045)^{2.5} = 1.116$$

ie $= 11.6\%$

Therefore, the effective voltage supply, E' $= 1.116 \times 9.5 = 10.60$ volts

E' and E are the voltages of the stimulus bulb with and without the mirror in operation respectively.

The nominal life of the stimulus bulb was 50 operating hours for a default voltage of 12 volts (Osram Lighting Catalogue '93/94). The voltage supply to the stimulus bulb in the conventional HFA, however, is deliberately under run at 9.5 volts to produce an extended filament life of approximately 1117 operating hours. The life of the filament with the mirror in operation at the effective voltage of 10.60 volts was calculated to be 260 operating hours using the equation (Cayless and Marsden, 1983):

$$\text{Actual filament life} = \text{Nominal Filament Life} \times (E'/E)^{-13.3}$$

$$= 50 \cdot (10.60/12.00)^{-13.3}$$

$$= 260 \text{ hours}$$

where E' is the applied voltage and E is the rated voltage.

The increase in measurement range as a result of the concave mirror was 0.20 log units.

Where:

Default maximum stimulus luminance, $\Delta L$ = 10, 000asb = 4.00 log units

Modified maximum stimulus luminance, $\Delta L'$ = 16,002asb = 4.20 log units

Therefore, increase in dynamic range = $\log \Delta L' - \log \Delta L$ = 0.20 log units.

5.2.2. Modifications for the assessment of ocular media absorption.

The modifications to the HFA and methodology for the assessment of ocular media absorption were similar to those of Sample and co-workers (1988a,1989 and 1991). The technique is based upon the deviation of scotopic spectral sensitivity from the absorption spectrum of rhodopsin.

Blocking material was fixed within the HFA to reduce the leakage of light from the stimulus bulb onto the cupola surface. The resultant luminance of the background was less than 0.01 $cdm^{-2}$. In addition, a red filter (Cinelux; 406 red) (Strand Lighting Ltd, Isleworth, Middlesex, UK) was positioned over the fixation target to ensure dark adaptation. Fixation was monitored during the measurement of ocular media absorption with the aid of an infra-red source, which consisted of an M94 20 Watt / 12 volt tungsten halogen lamp (Osram Ltd, Wembley, Middlesex, UK) mounted behind a Schott RG830 "black light" filter (only transmitting wavelengths above 750nm). The assembly was encased within a steel tube and fixed to the frame of the HFA such that infra-red radiation was reflected off the bowl surface and onto the subject. The technique for the assessment of ocular media absorption is described in full in Chapter 6.

5.2.3. Modifications for the assessment of macular pigment absorption.

The psychophysical technique utilized for the assessment of macular pigment absorption was similar to that of Pease and Adams (1983) and Pease and co-workers (1987). This particular technique was chosen because of the relative ease of applying the methodology to the HFA.

A light box, consisting of an ELC 250 Watt / 24 volt tungsten halogen lamp (General Electric, Cleveland, Ohio) mounted behind a series of infra-red filters and cooled by a squirrel cage fan, was suspended above the forehead rest of the HFA. Four achromatic lenses were arranged to project a uniform (within ± 2.00% of the mean) 26° diameter central field from the light box on to the cupola. A red 460 $cdm^{-2}$ central adapting field of 26° diameter was produced by the combination of light from the light box and from the two

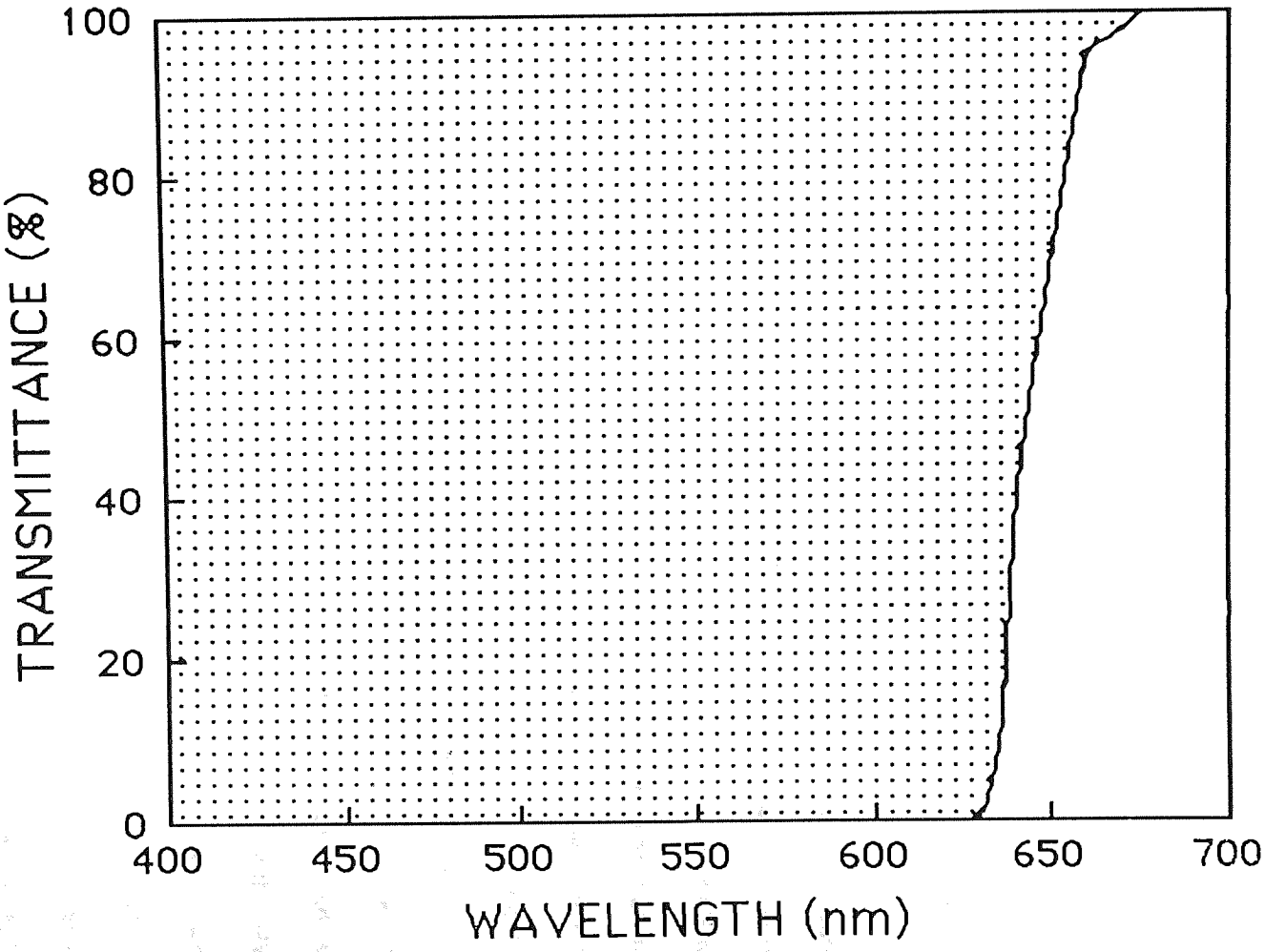



Figure 5.4. Percentage transmittance as a function of wavelength for the Schott RG 645 background filter employed for the assessment of macular pigment absorption. Transmitted wavelengths are represented by the unshaded area of the graph. Wavelengths above 630nm are transmitted and 50% transmission is achieved at a wavelength of approximately 645nm.

auxiliary lamp housings and by inserting a Schott RG645 filter (Schott Glaswerke, Mainz, Germany) in front of each of the three light sources. The transmission characteristics of this filter were considered to be suitable for adaptation of the LWS pathway (Adams, personal communication, 1991) and are detailed in Figure 5.4. A 25Hz flicker wheel was positioned between the stimulus bulb and the aperture plate of the HFA. A relay coil allowed the flicker wheel to be reset when not in use thereby ensuring an uninterrupted stimulus light path. The technique for the assessment of macular pigment absorption is described in full in Chapter 6.

5.2.4. Considerations in the choice of background for blue-on-yellow perimetry.

The choice of filters for blue-on-yellow perimetry was based on those of Johnson and co-workers (1989a, 1991, 1993a and b; Johnson, personal communication, 1990). The yellow adapting background was produced by inserting a Schott OG530 filter (Schott Glaswerke, Mainz, Germany) into each of the auxiliary lamp housings. The transmission characteristics of this filter were considered to be suitable for adaptation of the MWS and LWS pathways and are detailed in Figure 5.5. An adaptation level greater than that employed by Johnson and co-workers (1989a, 1991, 1993a and b) was selected in the light of criticism from other studies which asserted that a broad band stimulus filter did not ensure the same degree of SWS pathway isolation as a narrowband filter (Sample and Weinreb, 1990; Weinreb and Sample, 1991). An increase in background luminance has been demonstrated to result in an increased magnitude of MWS and LWS pathway adaptation (Yeh et al, 1989). The detection of a broadband blue stimulus by the MWS pathway using a higher adaptation level would therefore be suppressed (Adams, personal communication, 1992). As a result, an adaptation level of 330 $cdm^{-2}$ was chosen taking into account the requirements of a viable dynamic range ie the increase in background luminance from 202 $cdm^{-2}$ (Johnson et al, 1989a, 1991, 1993a and b) to 330 $cdm^{-2}$ resulted in a 0.20 log unit depression of sensitivity, which was nullified by the 0.20 log unit increase in measurement range due to the concave mirror. Consequently, the dynamic range was equivalent to that of Johnson and co-workers (1989a, 1991, 1993a and b). In addition, rod function has been demonstrated for adaptation levels of up to 300

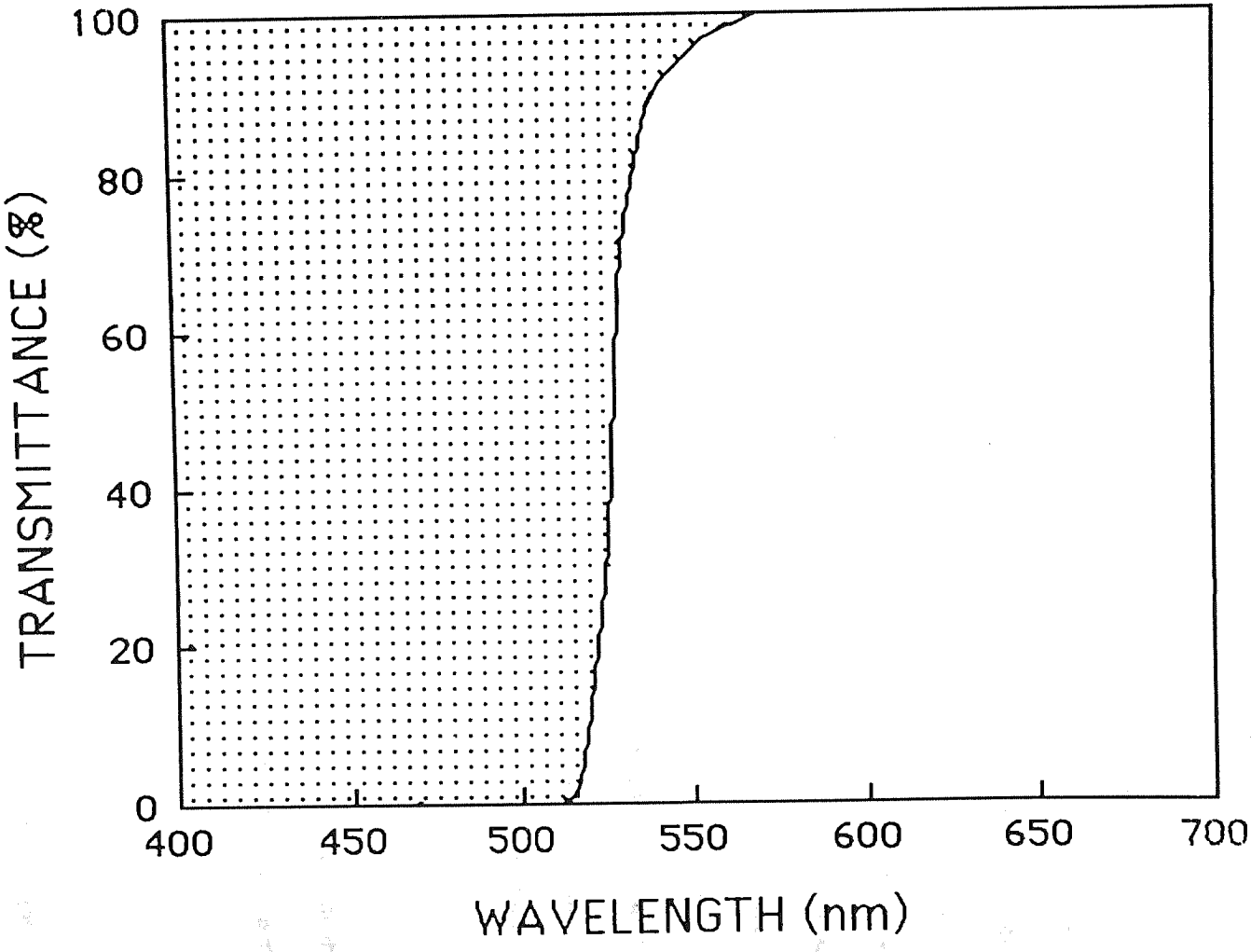



Figure 5.5. Percentage transmittance as a function of wavelength for the Schott OG 530 background filter employed for blue-on-yellow perimetry. Transmitted wavelengths are represented by the unshaded area of the graph. Wavelengths above 515nm are transmitted and 50% transmission is achieved at a wavelength of approximately 530nm.

$cdm^{-2}$. The 330 $cdm^{-2}$ yellow background was found to be accepted without discomfort by the majority of individuals who participated in the study.

5.2.5. Determination of spectral sensitivity.

Spectral sensitivity was determined, using the HFA in conjunction with the parameters previously selected for blue-on-yellow perimetry (ie a 330$cdm^{-2}$ yellow background and a stimulus of 1.724° angular subtense and of 200msec duration), for one randomly selected eye of each of 14 normal young subjects (6 males and 8 females: mean age 24.40yrs, SD 2.84). Inclusion and exclusion criteria were as those for the young subjects described in Chapter 3. In additon, all subjects were normal trichromats and had been extensively trained in the psychophysical techniques to be employed. Natural pupils were used through out (mean diameter 3.63mm, SD 0.48) and the distance refractive correction was employed. Sensitivity was assessed three times for 12 narrowband stimuli (410nm to 605nm, HPW 9nm to 11nm) at 9 locations along the 45° and 225° meridians (0°, 5.6°, 9.9°, 15.5° and 21.2°) using a custom threshold program. The order of stimulus filter was randomised. In addition, absorption due to the ocular media and macular pigment was assessed on two separate occasions in order to correct the SWS pathway spectral sensitivity function for the attenuation by the pre-receptoral filters. In total, a maximum of six 45 minute visits were required from each subject.

The decibel notation displayed on the HFA screen was recalculated to account for the attenuation of the stimulus luminance due to the introduction of each stimulus filter using the equation:

$$dB = k + 10 \log {}^{L}/_{\Delta L}$$

where dB is sensitivity measured in decibels, k is a constant dependent upon the state of retinal adaptation, L is the background luminance and $\Delta L$ is the threshold (L and $\Delta L$ are measured in apostilbs).

When L is 31.5asb and $\Delta L$ is 10,000asb (ie default parameters of the HFA)

Then

$$dB = 40 - 10 \log \Delta L$$

Say, the printout of the HFA is 15dB derived using a 530nm narrowband filter with a maximum stimulus luminance of 413.4asb.

Then $15 = 40 - 10 \log \Delta L_{theor}$

$\Delta L_{theor} = \log^{-1} 2.50 = 316.22asb$

The HFA does not account, however, for the attenuation caused by the 530nm narrowband stimulus filter.

| | | |
|---|---|---|
| Maximum $\Delta L$ of HFA in default mode | = 10000asb | = 4.00 log units |
| Maximum $\Delta L$ of HFA with 530nm filter | = 413.4asb | = 2.62 log units |

Therefore, attenuation due to the 530nm narrowband filter, $\Delta L_{atten}$

$= 4.00 - 2.62$

$= 1.38$ log units

| | | |
|---|---|---|
| The true threshold value, $\Delta L$ | $= \Delta L_{theor} - \Delta L_{atten}$ | |
| | $= 2.50 - 1.38$ | = 1.12 log units |
| ie | | = 13.18asb |

The threshold value derived for each individual filter was normalized relative to the stimulus luminance of the narrowband filter which provided a maximum dynamic range, that is 570nm, and the results were expressed in log units.

| | |
|---|---|
| Maximum $\Delta L$ of 570nm filter | = 422.0asb |
| Maximum $\Delta L$ of 530nm filter | = 413.4asb |

The threshold of the 530nm narrowband filter normalized relative to the 570nm filter

$= {}^{422.0}/_{413.4} \times 13.18$

$= 13.45$asb

| | | |
|---|---|---|
| and the normalized sensitivity | $= \text{Log } ({}^{1036.7}/_{13.45})$ | = 1.88 log units |

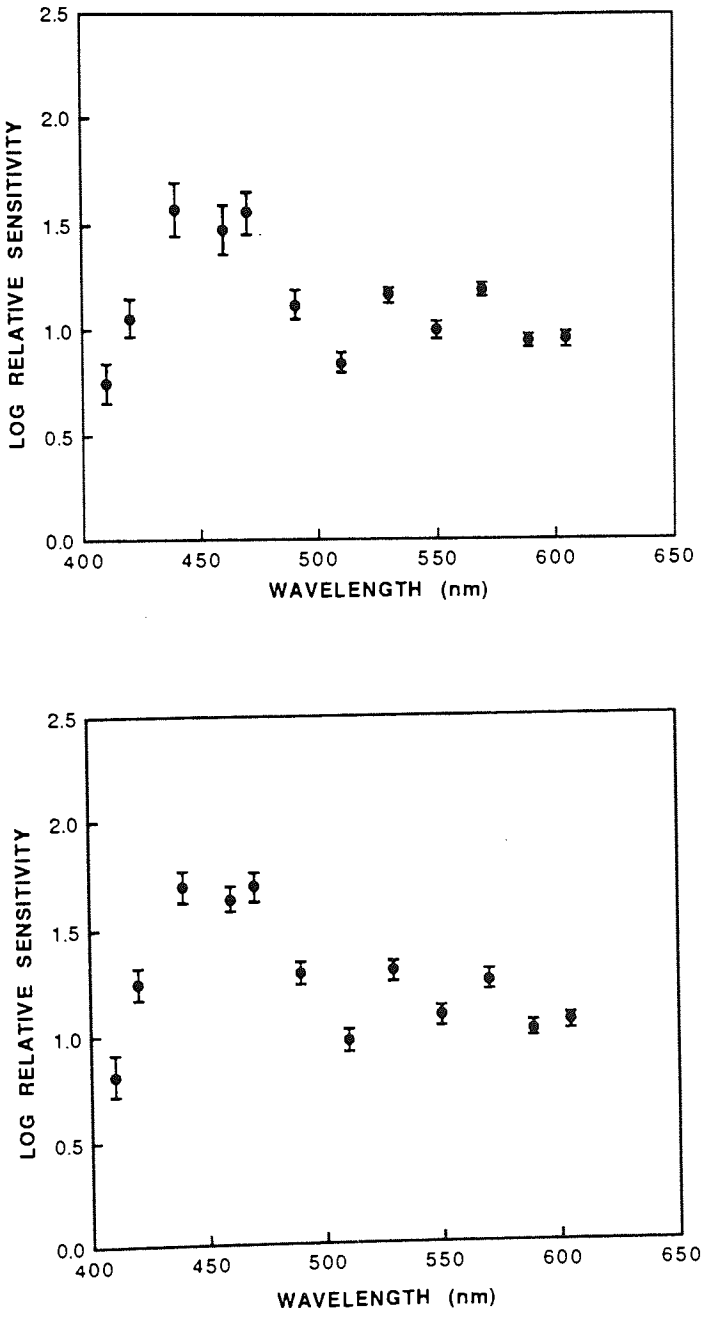



Figure 5.6. Group mean increment threshold spectral sensitivity function corrected for pre-receptoral absorption on a 330cdm$^{-2}$ yellow background at 21.2° (top) and 15.5° (bottom) eccentricity along the 45° meridian. The error bars represent ±1 standard error of the mean.

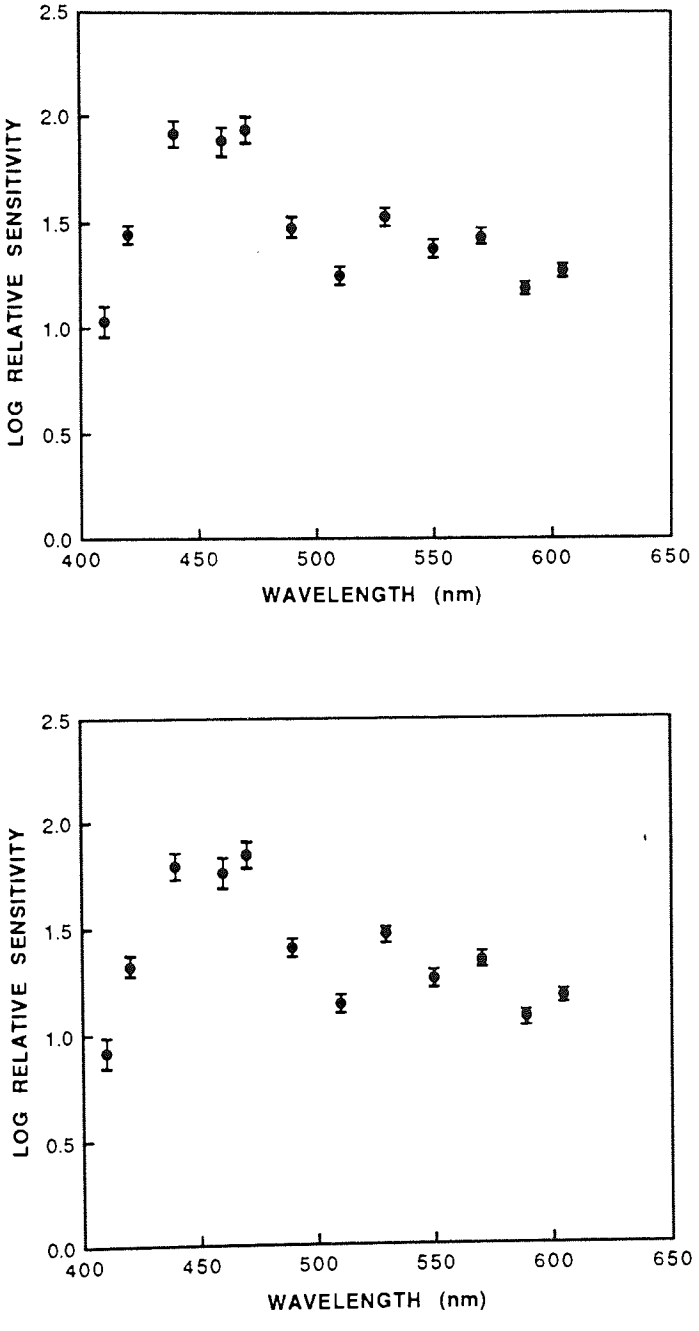



Figure 5.7. Group mean increment threshold spectral sensitivity function corrected for pre-receptoral absorption on a 330cdm$^{-2}$ yellow background at 9.9° (top) and 5.6° (bottom) eccentricity along the 45° meridian. The error bars represent ±1 standard error of the mean.

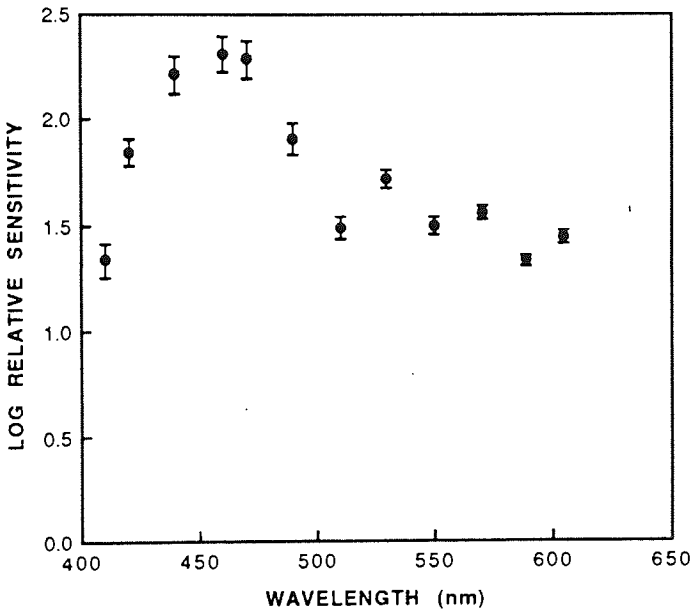



Figure 5.8. Group mean increment threshold spectral sensitivity function corrected for pre-receptoral absorption on a 330cdm$^{-2}$ yellow background at the fovea. The error bars represent ±1 standard error of the mean.

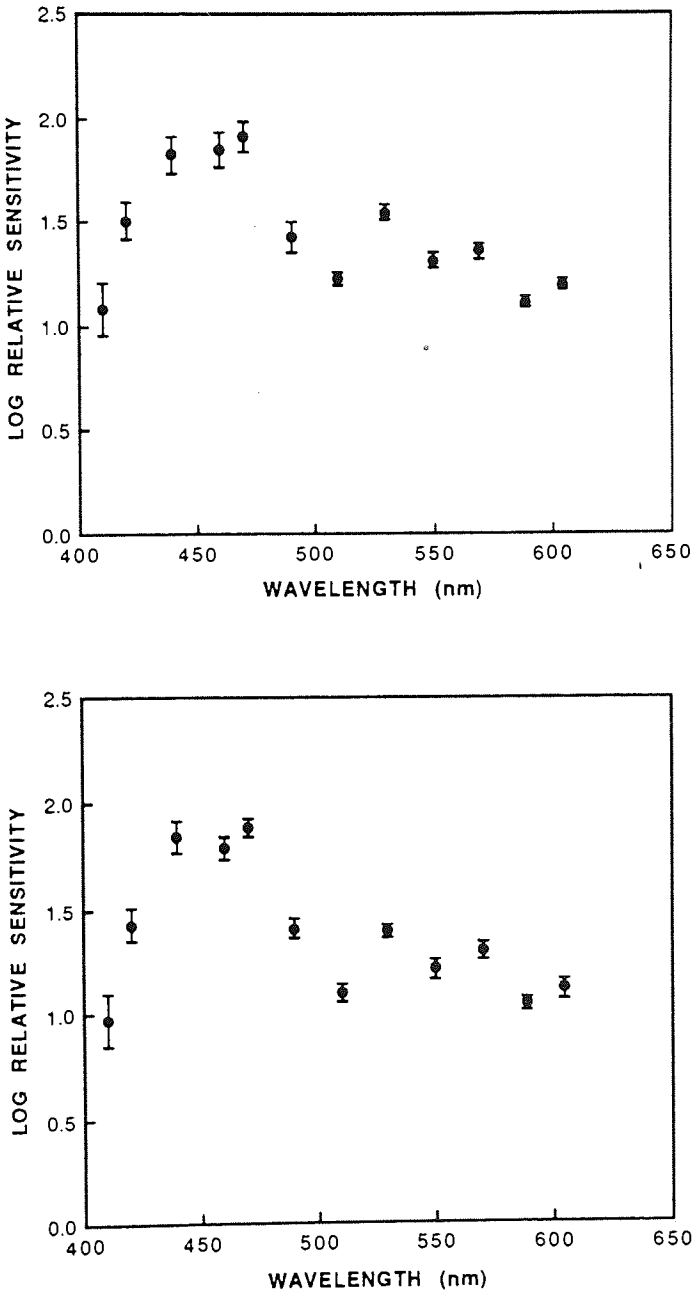



Figure 5.9. Group mean increment threshold spectral sensitivity function corrected for pre-receptoral absorption on a 330cdm$^{-2}$ yellow background at 5.6° (top) and 9.9° (bottom) eccentricity along the 225° meridian. The error bars represent ±1 standard error of the mean.

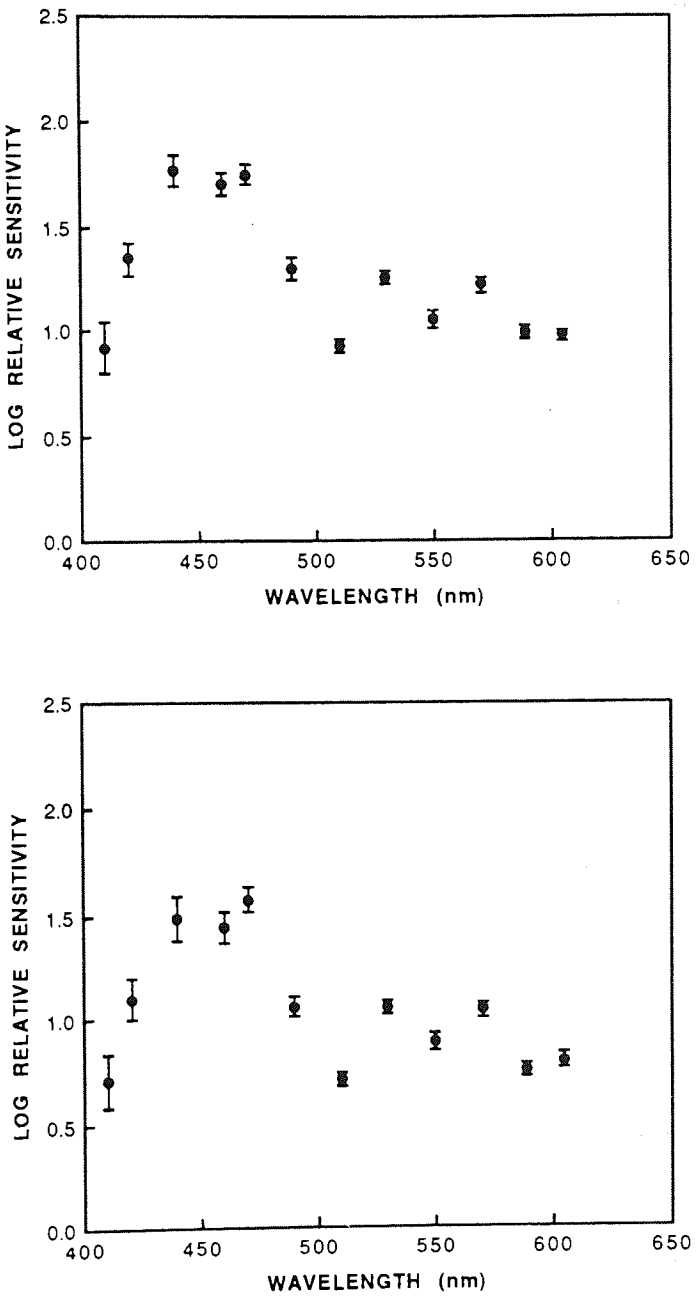



Figure 5.10. Group mean increment threshold spectral sensitivity function corrected for pre-receptoral absorption on a 330cdm$^{-2}$ yellow background at 15.5° (top) and 21.2° (bottom) eccentricity along the 225° meridian. The error bars represent ±1 standard error of the mean.

The effective maximum stimulus luminance for each filter and appropriate background was calibrated using an LMT L1003 photometer (LMT Lichtmesstechnik GMBH Berlin, Germany).

Group mean spectral sensitivity functions corrected for pre-receptoral absorption for each eccentricity are shown in Figures 5.6 to 5.10. As expected, the mechanisms mediating detection of wavelengths greater than 500nm were saturated, whilst the sensitivity of the SWS pathway was relatively enhanced. In addition, the SWS pathway spectral sensitivity function exhibited peak wavelengths at 440nm, 460nm or 470nm. As a result, a stimulus wavelength of 460nm was selected for blue-on-yellow perimetry since a 440nm filter would reduce the measurement range, whilst a 470nm filter would reduce the magnitude of SWS pathway isolation (Figures 5.6 to 5.10).

5.2.6. Quantification of SWS pathway isolation.

The magnitude of SWS pathway isolation was determined by assessing threshold versus intensity functions (TVI) (Stiles, 1959 and 1964; Stockman and Mollon, 1986; Pugh and Kirk, 1986). The technique assesses rod and cone function by varying the background luminance over a wide range of intensities and the wavelength characteristics of the background and stimulus can be manipulated to reveal a particular cone type. Under the conditions utilized for blue-on-yellow perimetry, blue cone (SWS pathway, $\pi_1$) function is determined.

TVI functions were measured with the HFA in conjunction with a 1.724°, 200msec stimulus for one randomly selected eye of each of 10 young subjects (4 males and 6 females: mean age 24.40yrs, SD 2.87). Inclusion and exclusion criteria were the same as those employed for the determination of spectral sensitivity. The pupil was fixed and dilated (mean diameter 6.80mm, SD 0.62) for each subject with one drop of 1% Tropicamide instilled in to the lower conjunctival sac (puncta closed). A second drop of 1% Tropicamide was instilled where necessary to ensure a fixed pupil and a steady state of cycloplegia. A near addition compatible with the magnitude of residual accommodation

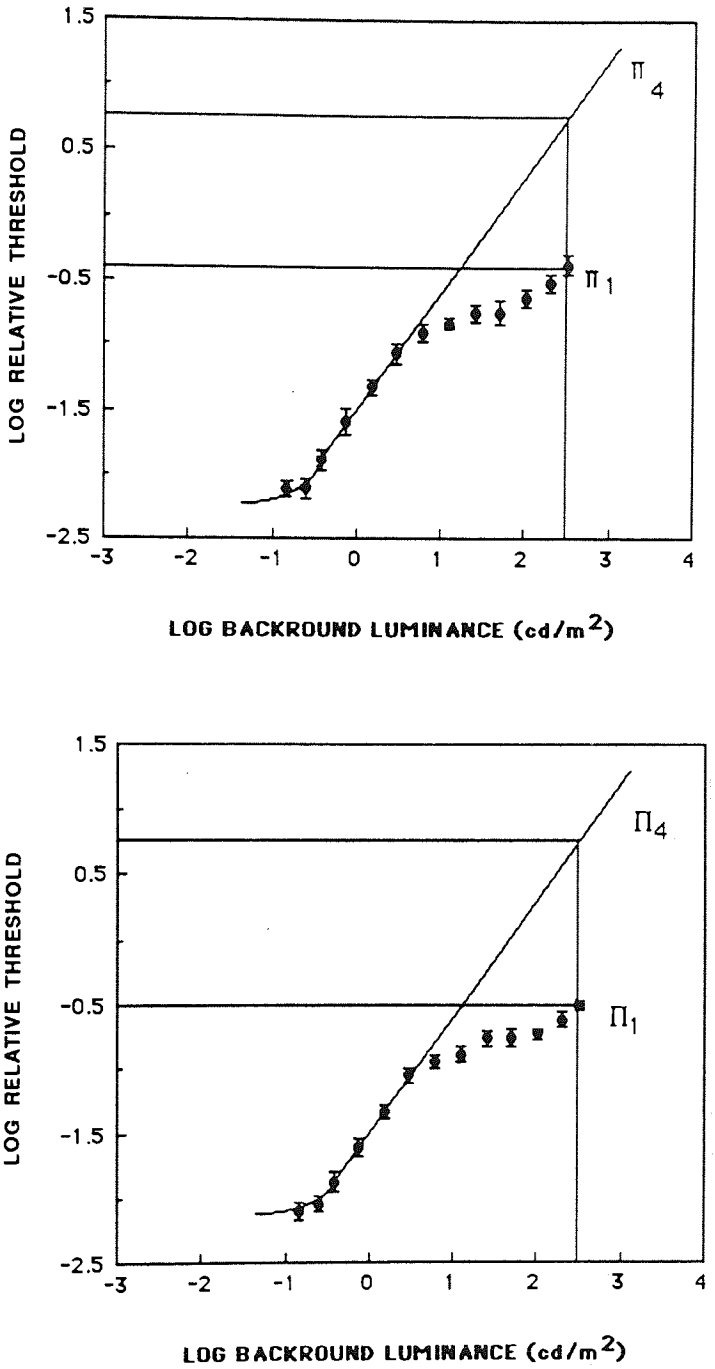



Figure 5.11. Group mean threshold versus intensity function for a 460nm narrowband stimulus at 21.2° (top) and 15.5° (bottom) eccentricity along the 45° meridian. The error bars represent ±1 standard error of the mean. The predicted sensitivity of the $\Pi_4$ mechanism is shown by the extrapolated diagonal line. The difference in threshold between the $\Pi_1$ and $\Pi_4$ mechanisms at 330cdm$^{-2}$ (ie vertical line) represents the magnitude of SWS pathway isolation.

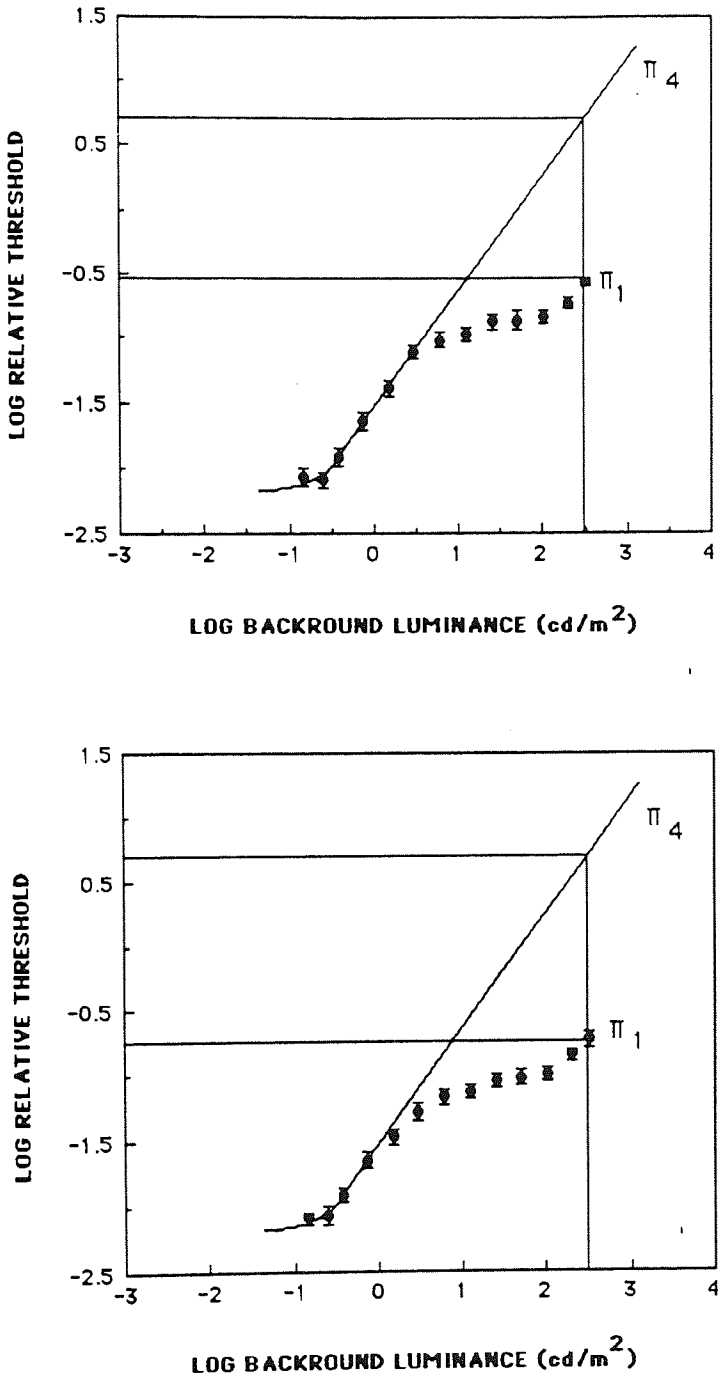



Figure 5.12. Group mean threshold versus intensity function for a 460nm narrowband stimulus at 9.9° (top) and 5.6° (bottom) eccentricity along the 45° meridian. The error bars represent ±1 standard error of the mean. The predicted sensitivity of the $\Pi_4$ mechanism is shown by the extrapolated diagonal line. The difference in threshold between the $\Pi_1$ and $\Pi_4$ mechanisms at 330cdm$^{-2}$ (ie vertical line) represents the magnitude of SWS pathway isolation.

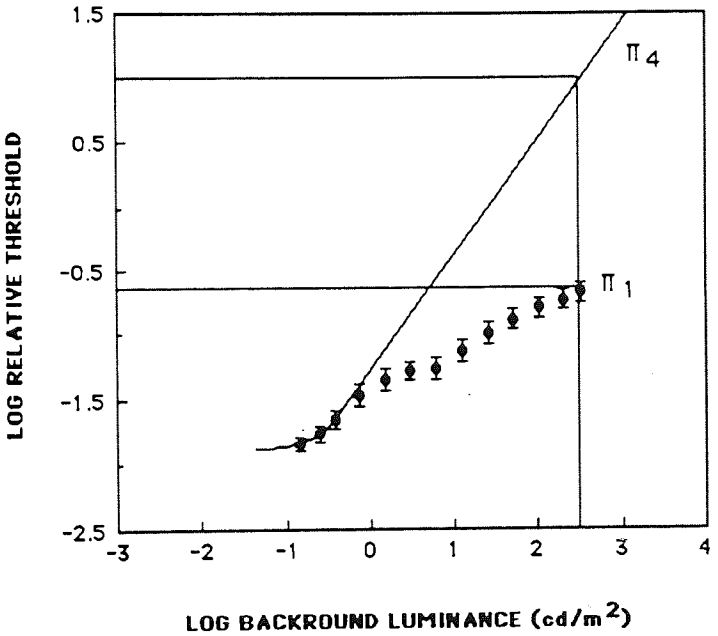



Figure 5.13. Group mean threshold versus intensity function for a 460nm narrowband stimulus at the fovea. The error bars represent ±1 standard error of the mean. The predicted sensitivity of the $\Pi_4$ mechanism is shown by the extrapolated diagonal line. The difference in threshold between the $\Pi_1$ and $\Pi_4$ mechanisms at 330cdm$^{-2}$ (ie vertical line) represents the magnitude of SWS pathway isolation.

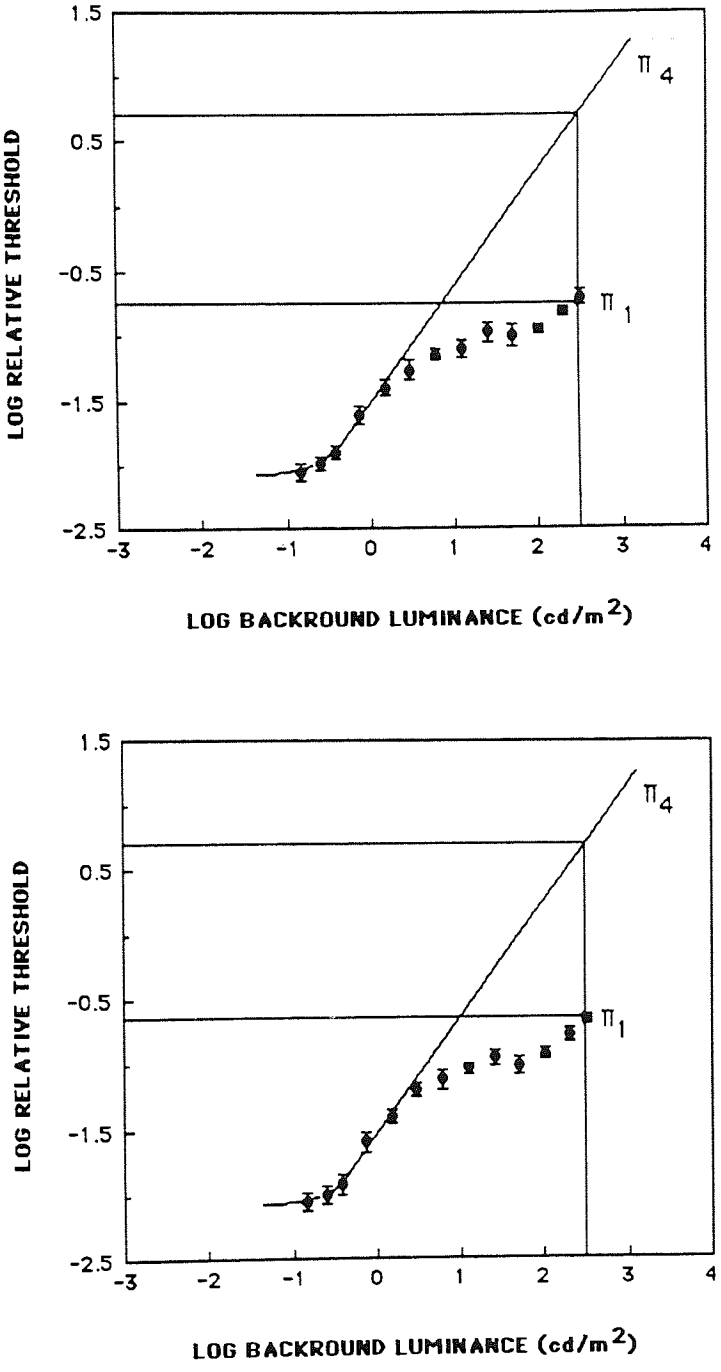



Figure 5.14. Group mean threshold versus intensity function for a 460nm narrowband stimulus at 5.6° (top) and 9.9° (bottom) eccentricity along the 225° meridian. The error bars represent ±1 standard error of the mean. The predicted sensitivity of the $\Pi_4$ mechanism is shown by the extrapolated diagonal line. The difference in threshold between the $\Pi_1$ and $\Pi_4$ mechanisms at 330cdm$^{-2}$ (ie vertical line) represents the magnitude of SWS pathway isolation.

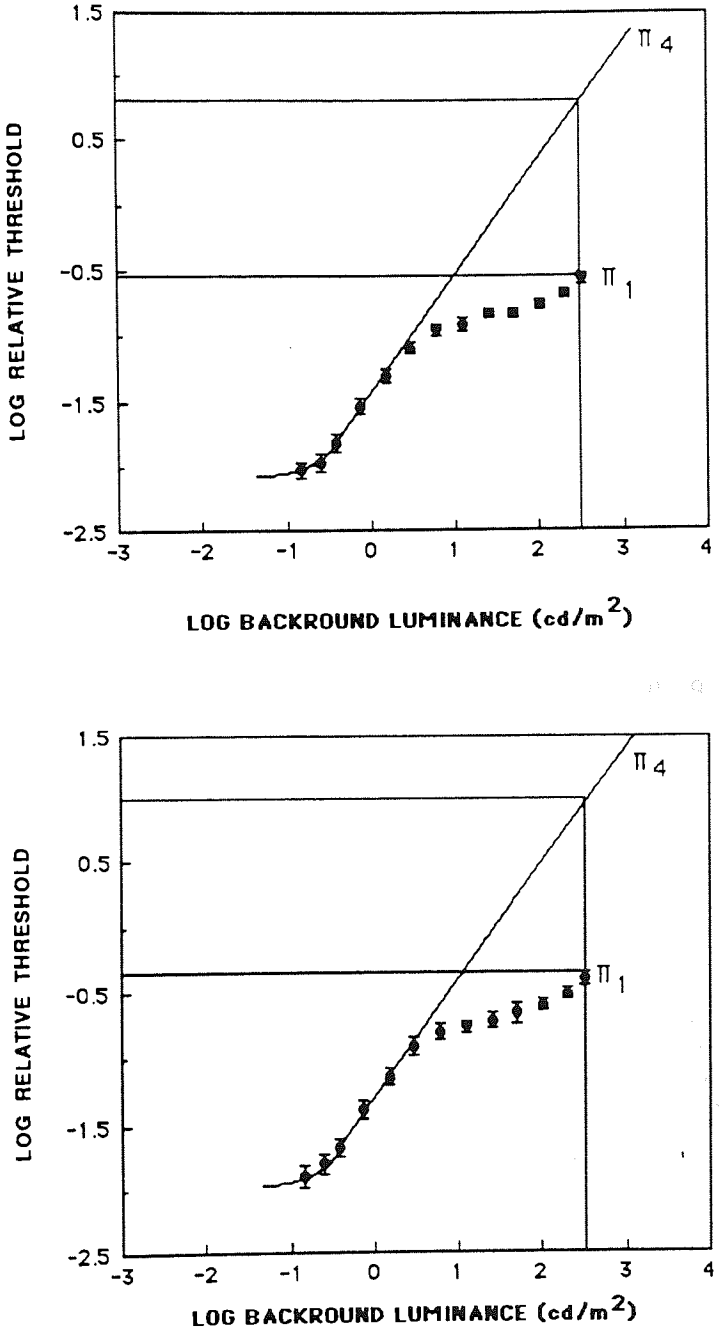



Figure 5.15. Group mean threshold versus intensity function for a 460nm narrowband stimulus at 15.5° (top) and 21.2° (bottom) eccentricity along the 225° meridian. The error bars represent ±1 standard error of the mean. The predicted sensitivity of the $\Pi_4$ mechanism is shown by the extrapolated diagonal line. The difference in threshold between the $\Pi_1$ and $\Pi_4$ mechanisms at 330cdm$^{-2}$ (ie vertical line) represents the magnitude of SWS pathway isolation.

| Eccentricity (degrees) | Mean SWS isolation (log units) | Standard deviation (log units) |
|---|---|---|
| +21.2° | 1.4 | 0.23 |
| +15.5° | 1.4 | 0.11 |
| +9.9° | 1.4 | 0.12 |
| +5.6° | 1.5 | 0.19 |
| 0° | 1.7 | 0.26 |
| -5.6° | 1.5 | 0.19 |
| -9.9° | 1.3 | 0.11 |
| -15.5° | 1.3 | 0.13 |
| -21.2° | 1.2 | 0.15 |

Table. 5.3. The magnitude and the standard deviation of SWS isolation for 9 stimulus locations along the 45° and 225° meridians (0°, 5.6°, 9.9°, 15.5° and 21.2°). A positive eccentricity corresponds to the 45° meridian and a negative eccentricity corresponds to the 225° meridian.

was used for the viewing distance of 33cm together with the distance refractive correction. The procedure was commenced approximately 15 minutes after instillation. Sensitivity was assessed three times at each of thirteen background luminances (range 0.15 $cdm^{-2}$ to 330 $cdm^{-2}$) using a 460nm (HPW 9nm) stimulus filter at the same locations as for the determination of spectral sensitivity. The background luminance was varied using a Farnell (Farnell Instruments Ltd, Wetherby, Yorkshire, UK) variable voltage transformer. The order of background luminance was randomised. It was acknowledged that variation in the colour temperature of the yellow background would influence the magnitude of isolation at photopic background luminances. A maximum of four 45 minute visits were required from each subject.

Group mean TVI functions for each eccentricity are shown in Figures 5.11 to 5.15. A Stiles template was fitted to the data and extrapolated to predict the threshold of the underlying cone mechanism (ie $\pi_4$). The vertical line corresponds to the background luminance employed for blue-on-yellow perimetry, whilst the lower and upper horizontal lines indicate the log threshold of the $\pi_1$ (SWS pathway) and $\pi_4$ (MWS pathway) mechanisms respectively at 330 $cdm^{-2}$. The difference in threshold between the $\pi_1$ and $\pi_4$ mechanisms represents the magnitude of SWS pathway isolation. As expected, isolation of the SWS pathway was achieved at all stimulus locations. The mean magnitude of SWS isolation was approximately 1.4 log units (range 1.2 log units to 1.7 log units) (Table 5.3.). The higher standard deviation of the foveal SWS isolation value (Table 5.3.) can be explained by the between subject variation in macular pigment absorption.

## 5.3. Discussion.

Sample and Weinreb (1990) achieved an additional 0.7-0.8 log units of dynamic range by increasing the voltage supply to the HFA stimulus bulb from 9.5 volts to 13 volts. A consequence of the increase in voltage supply is a significant reduction in the life of the stimulus bulb from approximately 1117 operating hours to 17 hours. In addition, this modification may compromise the calibration of the HFA . Calibration is undertaken at the

default 9.5 volt supply by the adjustment of a neutral density filter which ensures that despite ageing of the stimulus bulb the default maximum stimulus intensity is maintained at 10,000asb. The output of the stimulus bulb at the higher voltage cannot be guaranteed, however, by the calibration carried out at 9.5 volts ie the stimulus bulb output may be attenuated at 13 volts due to the effects of ageing but satisfactory calibration may still be achieved at 9.5 volts by the appropriate adjustment of the neutral density filter.

The employment of a 330 $cdm^{-2}$ background luminance will result in a smaller pupil size than that obtained at lower adaptation levels. A reduction in pupil size increases the lenticular pathlength and therefore might be expected to accentuate the magnitude of ocular media absorption (Weale, 1961; Mellerio, 1987; Weale, 1991). The influence of pupil size is small, however, in relation to the magnitude of ocular media absorption (Sample et al, 1988a; Werner, 1982). Indeed, a 4mm reduction in pupil diameter increased mean ocular media absorption at 460nm by approximately 0.1 log units in a group of 80 year old subjects (Weale, 1991).

The comparison of the magnitude of SWS pathway isolation with other studies is difficult since different background and stimulus combinations have been utilized. Johnson and co-workers (1988b) gained 1.1 log units of isolation using a 202 $cdm^{-2}$ background luminance and a relatively broadband blue stimulus filter (ie OCLI blue dichroic). In addition, Sample and co-workers (1993a) claimed 1.5 log units of SWS pathway isolation using a background luminance of 89 $cdm^{-2}$ and narrowband 440nm stimulus filter, although the method employed to derive this figure was not clear.

In summary, the modification of the HFA achieved an increase in measurement range of 0.2 log units, whilst providing a realistic bulb life and ensuring correct calibration of the instrument. A background luminance of 330 $cdm^{-2}$ was selected to permit an equivalent dynamic range to that of other studies (Johnson et al, 1989a; Sample and Weinreb, 1990) and to increase the magnitude of MWS and LWS pathway adaptation (Yeh et al, 1989).

Threshold versus intensity functions in conjunction with a 460nm narrowband stimulus filter showed that approximately 1.4 log units of SWS pathway isolation was gained.

# CHAPTER 6. THE INFLUENCE OF OCULAR MEDIA AND MACULAR PIGMENT ABSORPTION ON THE BLUE-ON-YELLOW VISUAL FIELD.

## 6.1. Introduction.

The recognised sources of pre-receptoral absorption are the components of the ocular media, primarily the crystalline lens and the macular pigment.

### 6.1.1. The crystalline lens.

The crystalline lens consists of a single cell type in various stages of cyto-differentiation (Marshall, 1985). The cellular contents of the lens are enclosed within a basement membrane termed the capsule. A single layer of epithelial cells separates the anterior capsule from the lens fibres. Each fibre arches over the equator of the lens to meet fibres from the opposite side at the lens sutures. The outer fibres comprise the lens cortex, while the inner fibres make up the lens nucleus. The fibres of the nucleus can be distinguished from those of the cortex by an absence of nuclei and organelles and by a reduced metabolic rate (Marshall, 1985; Bron et al, 1993). The lens fibres are deposited in a series of "onion-skin" layers from the equatorial germinative epithelial cells. All the cells of the lens are retained throughout life (Marshall, 1985). As each new fibre is formed, older fibres are displaced towards the lens nucleus and are reduced in volume, a process described as compaction (Bron et al, 1993). The sagittal width of the human lens at birth is approximately 4mm. This value remains constant during the first 20 years of life, while the lens grows equatorially, but increases at a rate of approximately 29μm per year after this age (Brown and Tripathi, 1974).

Metabolic energy at cellular level is derived from glucose which enters the lens from the aqueous by active transport (Giles and Harris, 1959). Amino acids may also provide an energy source (Trayhurn and van Heyningen, 1973). The metabolism of the cortex is essentially anaerobic, whilst that of the epithelium is aerobic (Kinoshita et al, 1961; Kinoshita, 1965). The epithelium and the superficial posterior cortical cells are major sites

of ionic pumping which regulate the osmotic and pH balance within the lens (Duncan, 1969; Gorthy et al, 1980; Iwata, 1985; Williams et al, 1992).

Crystallins comprise ninety percent of the lens protein (Weale, 1963; van Heyningen, 1972). The lens crystallins exhibit a short range molecular order similar to that of glass. This short range molecular order is responsible for the transparency of individual lens fibres (Delaye and Tardieu, 1983) and is also partly responsible for the high refractive index of the lens. In addition, lens transparency is also achieved by an orderly arrangement of the lens fibres, an absence of organelles within the fibres, the displacement of lens nuclei away from the optic axis, small extracellular spaces and thin fibre membranes (Yorio and Bentley, 1976; Bron et al, 1993). The normal young human lens has a transparency of 90% for wavelengths of light between 500nm and 1000nm (Lerman and Borkman, 1976). Diffuse aggregation of the crystallins will result in a generalized loss of lens transparency, whilst disruption of the lens fibre organization and integrity, expansion of the extracellular space and focal aggregation of lens proteins will result in a total loss of transparency, ie a lens opacity.

6.1.2. The macular pigment.

The macular pigment is comprised of a number of yellow non-bleaching carotenoid compounds primarily the xanthophylls lutein and zeaxanthin which are present in roughly equal proportions (Wald, 1949; Snodderly et al, 1984a; Bone et al, 1985; Bone et al, 1988; Handelman et al, 1988). It is concentrated in the receptor axon (Henle fiber) layer and, to a lesser extent, in the inner plexiform layer of the retina (Snodderly et al, 1984a).

Both lutein and zeaxanthin posses an elongated molecular structure (Isler, 1971; Bone and Landrum, 1984; Bone et al, 1992) and therefore exhibit dichroism, ie the absorption of polarized light depends upon the angle of incidence relative to the axis of the molecule (Bone and Landrum, 1984). In addition, a proportion of the lutein and zeaxanthin molecules are thought to be arranged in a non-random manner within the bilipid components of the receptor axon membranes such that the molecular axes are aligned

tangentially with respect to concentric circles about the fovea (Bone and Landrum, 1984; Bone et al, 1992). The dichroic properties and non-random arrangement of the macular pigment result in the entoptic phenomenon of Haidinger's Brushes.

The topographical distribution of the macular pigment exhibits a peak value at the fovea with an exponential decline to negligible pigmentation at eccentricities from 2° to 5.5° (Ruddock, 1972; Stabell and Stabell, 1980; Williams et al, 1981a; Viénot, 1983; Pease and Adams, 1983; Snodderly et al, 1984a and b; Moreland and Bhatt, 1984; Werner, Donnelly and Kliegel, 1987; Bone et al, 1988; Kilbride et al, 1989; Abadi and Cox, 1992). This distribution may be explained by the preferential uptake of zeaxanthin by the cones and, to a lesser extent, of lutein by the rods (Bone et al, 1988).

6.1.3. Light absorption and light scatter.

A distinction should be made between the terms light absorption and light scatter since the two phenomena occur concurrently as a result of reduced optical transmittance (Norren and Vos, 1974). Absorption is proportional to the inverse of optical transmittance. Indeed, any psychophysical procedure designed primarily to estimate light absorption will be influenced to a lesser degree by light scatter and vice versa (Norren and Vos, 1974). Absorption refers to the assimilation of light energy by pigments, whilst scatter refers to the redirection of light energy (Hemenger, 1982). In relation to blue-on-yellow perimetry, absorption can be anticipated to be the more important attenuating factor since intraocular light scatter is known to depend minimally on wavelength (Vos and Bouman, 1959; Wooten and Geri, 1987).

6.1.4. Ocular media absorption.

Ocular media absorption exhibits an exponential increase with light of shorter wavelength (Ludvigh and McCarthy, 1938; Geeraets et al, 1960; Boettner and Wolter, 1962; Cooper and Robson, 1969; Norren and Vos, 1974; Wyszecki and Stiles, 1982) and either a linear (Said and Weale, 1959; Mellerio, 1971; Werner and Wooten, 1980; Werner, 1982; Weale, 1988; Savage et al, 1993) or a biphasic increase (Coren and Girgus, 1972;

Zigman, 1978; Pokorny et al, 1987; Sample et al, 1988a; Johnson et al, 1988b) with increase in age. In addition, ocular media absorption has been reported to vary by approximately 1 log unit (relative to 400nm) between subjects of the same age (Coren and Girgus, 1972; Norren and Vos, 1974; Werner and Wooten, 1980; Werner, 1982; Pokorny et al, 1987; Sample et al, 1988a; Johnson et al, 1988b). Light absorption attributable to the cornea and vitreous is minimal (Wyszecki and Stiles, 1982; Weale, 1991; Savage et al, 1993) and the increase in ocular media absorption with increase in age is thought to occur primarily within the nucleus of the crystalline lens (Weale, 1991). Indeed, ocular media absorption may have some functional role by reducing chromatic aberration and acting as a filter for damaging short wavelength light (Marshall et al, 1983).

6.1.5. Macular pigment absorption.

The absorption spectra of the macular pigment exhibits a peak optical density at approximately 460nm, a negligible absorption for wavelengths greater than 560nm and shows a variation in the peak optical density between individuals of the same age of approximately 1 log unit (De Vries et al, 1953; Naylor and Stanworth, 1954; Brown and Wald,1963; Wyszecki and Stiles, 1982; Pease and Adams, 1983; Snodderly et al, 1984a; Bone et al, 1985; Pease et al, 1987; Werner et al, 1987; Bone et al, 1988; Handelman et al, 1988; Bone et al, 1992). It does not vary systematically with age (Ruddock, 1965b; Bone and Sparrock, 1971; Yasuma et al, 1981; Pease et al, 1987; Werner et al 1987; Bone et al, 1988). Theories relating to the function of the macular pigment include: the reduction of chromatic aberration and glare (Walls and Judd, 1933; Wald, 1967; Rodieck, 1973; Reading and Weale, 1974; Nussbaum et al, 1981; Snodderly et al, 1984a), the passive protection of the retina by the absorption of damaging short wavelength light (Lawwill et al, 1977; Ham et al, 1976; Ham et al, 1979; Sperling et al, 1980; Nussbaum et al, 1981; Haegerstrom-Portnoy, 1988) and the active protection of retinal tissues by the inactivation of cytotoxic free radicals or singlet oxygen atoms produced by photoreceptor light absorption (Feeney and Berman, 1976; Krinsky, 1976; Krinsky, 1979; Nussbaum et al, 1981; Kirschfeld, 1982; Bone and Landrum, 1984; Haegerstrom-Portnoy, 1988).

6.1.6. Aim of the study.

The influence of the macular pigment on the blue-on-yellow visual field has not been investigated. Previous psychophysical studies of macular pigment absorption have employed a 1° diameter stimulus and a Maxwellian view system (Pease and Adams, 1983; Pease et al, 1987; Werner et al, 1987). The estimation of macular pigment is dependent upon the optical density at the edge of the area of stimulation rather than the average of the area stimulated (Werner et al, 1987; Bone et al, 1992). It is necessary, therefore, to assess macular pigment absorption under similar conditions to those of blue-on-yellow perimetry. Such information is essential if blue-on-yellow perimetry is to be of value in the detection of macular disease.

A clinical procedure for the estimation of ocular media absorption based upon the difference in scotopic sensitivity between two narrowband spectral stimuli which are equally absorbed by rhodopsin is well established (Sample et al, 1988a; Sample et al, 1989; Johnson et al, 1988b; Johnson et al, 1989b). Using this procedure, a large variation in optical density between normal subjects at any given age of approximately one log unit (relative to 400nm) has been found (Sample et al, 1988a; Johnson et al, 1988b).

The reliability of a test procedure is defined as the consistency of results between two separate measurements of a given variable (Elliott and Bullimore, 1993). Reliability is determined by the interaction of two components; a within-test component that occurs at each of the first and second measurements and a between-test component. The within- and between-test components can vary independently of each other. The within-test component is reflected by the magnitude of the standard deviation (or standard error) of the mean of a series of measurements at a given session, whilst reliability (ie the resultant of the within-test component of the first and second sessions and the between-test component) is reflected by the coefficient of repeatability (COR). The COR describes the 95% confidence limits for any discrepancy between test and retest data (Bland and Altman, 1986; Reeves et al, 1987). For normally distributed data, the COR is 1.96 multiplied by the standard deviation of the discrepancy. A low COR represents a

measurement procedure of high reliability. The COR can also be employed to determine the significance of change in performance at follow-up (Reeves et al, 1987).

The extent to which the reported variation in macular pigment absorption is due to true between-subject variation or to poor reliability of the test procedure is unknown. Similarly, the variation in ocular media absorption can also be attributed to either true between-subject variation or to poor reliability of the test procedure. Such information is important if either of these two procedures are to be utilized clinically.

The primary aim of the study, therefore, was to determine measures of both macular pigment and ocular media absorption using procedures suitable for application with the HFA and to relate these findings to the blue-on-yellow visual field. The secondary aims of the study were to determine: (1) the relationships between macular pigment absorption and age and between ocular media absorption and age; and (2) the test-retest reliability of the macular pigment and ocular media absorption procedures.

## 6.2. Materials and methods.

### 6.2.1. Assessment of ocular media absorption.

Non-invasive techniques for the estimation of ocular media absorption are well documented and include: the deviation of individual colour matches from averaged colour matching data (Ruddock, 1965a; Coren and Girgus, 1972); measurement of the deviation of scotopic spectral sensitivity from the absorption spectrum of rhodopsin (Norren and Vos, 1974; Sample et al, 1988a; Sample et al, 1989; Johnson et al, 1989b; Savage et al, 1993); and measurement of the relative intensities of the 3rd and / or 4th Purkinje images for varying wavelengths of light (Said and Weale, 1959; Zeimer and Noth, 1984; Johnson et al, 1993c).

Ocular media absorption was assessed by measuring scotopic thresholds for 410nm and 560nm narrowband stimuli (Norren and Vos, 1974; Sample et al, 1988a; Sample et al, 1989; Johnson et al, 1988b; Johnson et al, 1989b). These wavelengths are equally absorbed by rhodopsin and any difference in scotopic sensitivity can therefore be attributed to absorption by the ocular media. This technique assumes that the absorption of light by rhodopsin and the absorption of light per unit pathlength of the crystalline lens (Mellerio, 1971) both remain constant throughout life. The technique was employed since it is the currently accepted method for assessing ocular media absorption using the HFA (Sample et al, 1988a; Sample et al, 1989; Johnson et al, 1988b; Johnson et al, 1989b).

The sample comprised 68 normal subjects (range 20-80 yrs: 36 males and 32 females) with a minimum of 10 subjects per decade. All subjects were normal trichromats (as assessed by the Farnsworth D15 test), were experienced perimetric observers with normal central fields (HFA Programs 30-2 and 10-2) and had been previously extensively trained in the psychophysical techniques employed. Inclusion criteria included a distance refractive error of equal to or less than ±3.00 dioptres sphere with ±3.00 dioptres cylinder, a visual acuity of 6/9 or better, no lenticular opacity present by slit lamp examination and retinoscopy, normal fundi and an intra-ocular pressure of less than 21 mmHg. Exclusion criteria were the same as those employed in the study of physiological statokinetic dissociation described in Chapter 3. One eye of each subject was selected randomly for the study. The distance refractive correction, together with the appropriate near addition, was used to correct for a viewing distance of 33 cm. Natural pupils were used for all tests.

The apparatus for the assessment of ocular media absorption is described in full in 5.2.2. Subjects were dark adapted for 30 minutes. A Goldmann size V (1.724°) 100msec stimulus presented from above threshold was employed. Using a custom threshold program, stimuli were separately presented three times each for a 410nm (half point band width, HPW 11nm) and a 560nm (HPW 9nm) filter at 15.6° eccentricity (to avoid the macular pigment) along the 45°, 135°, 225° and 315° meridians. The order of presentation

of the 410nm and 560nm stimuli was randomized. Three successive stable sensitivity values for each filter were required to ensure constancy of adaptation. If a progressive change in sensitivity was detected then further dark adaptation was undertaken before recommencing the test.

Individual ocular media absorption at 410nm was calculated using the equation of Norren and Vos (1974):

$$OD_{med} = 0.96\ (^{X}/_{0.90})$$

where $OD_{med}$ is the individual ocular media absorption at 410nm, 0.96 is the average or "standard observer" ocular media absorption at 410nm, X is the measured difference in sensitivity to the 410nm and 560nm stimuli and 0.90 is the average or "standard observer" difference in ocular media absorption between 410nm and 560nm. Ocular media absorption was expressed as the mean of the four eccentricities tested.

The test-retest data for ocular media absorption were obtained for a subsample of 16 of the 68 subjects (10 up to 30 years of age; 6 above 60 years of age) with an interval of seven days between the two visits.

6.2.2. Assessment of macular pigment absorption.

Non-invasive techniques for the estimation of macular pigment absorption are also well documented. Those which are appropriate for clinical application include: imaging fundus reflectometry (Norren and Tiemeijer, 1986; Kilbride et al, 1989); comparison of the difference in a colour match at the fovea and parafovea (Ruddock, 1963; Moreland and Bhatt, 1984); comparison of the difference in the spectral sensitivity at the fovea and parafovea (Pease and Adams, 1983; Pease et al, 1987; Werner et al, 1987; Hammond and Fuld, 1992); and measurement of the brightness match between a polarized stimulus and an unpolarized surround (Bone et al, 1992).

Macular pigment absorption was assessed by separately measuring MWS pathway sensitivity to 460nm and 570nm narrowband stimuli at the fovea and at eccentricities of 5.5° and 8°. The difference in sensitivities recorded between the fovea and 8° eccentricity and between 5.5° and 8° eccentricity for the 460nm stimulus relative to a value of zero at 570nm can be attributed to absorption by the macular pigment (Pease and Adams, 1983; Pease et al, 1987; Werner et al, 1987). The technique assumes that in the normal eye MWS cone spectral sensitivity does not vary within 8° eccentricity (except for the influence of the macular pigment), that the macular pigment is absent at 8° eccentricity (Moreland and Bhatt, 1984; Snodderly et al, 1984a and b; Werner et al, 1987; Bone et al, 1988; Kilbride et al, 1989) and that the macular pigment spectrum exhibits a peak absorption at 460nm and negligible absorption for wavelengths greater than 560nm (Brown and Wald, 1963; Wyszecki and Stiles, 1982; Snodderly et al, 1984a; Bone et al, 1985; Pease et al, 1987; Werner et al, 1987; Bone et al, 1988; Handelman et al, 1988; Bone et al, 1992).

Forty-six of the 68 subjects (age range 20-80 yrs: 22 males and 24 females) were able to perform the macular pigment absorption procedure. The number of subjects per decade were: all 15 up to 30 yrs; 8 out of 10 between 31-40yrs; 6 out of 10 between 41-50yrs; 6 out of 10 between 51-60yrs; 7 out of 10 between 61-70yrs; and 4 out of 13 between 71-80yrs. The attrition of subjects for the assessment of macular pigment absorption was due to an inability to detect a flickering stimulus which can be explained by the reduction in temporal sensitivity with increasing age (McFarland et al, 1958).

The apparatus for the assessment of macular pigment absorption is described in full in 5.2.3. Subjects were adapted to the red field for 3 to 4 minutes to achieve LWS pathway saturation. Using a custom threshold program, a Goldmann size V stimulus flickering at 25 Hz of 1300msecs duration was separately presented three times from below threshold for both a 460nm (HPW 9nm) and a 570nm (HPW 9nm) filter at each of 3 eccentricities (0°, 5.5° and 8°) along the 45°, 135°, 225° and 315° meridians. The order of presentation of the 460nm and 570nm stimuli was randomised. The 25Hz flicker excluded detection of

the stimulus by the rods and by the blue cones (Brindley et al, 1966; Eisner and MacLeod, 1980) and the subjects task was to respond to the flickering stimulus. The 1300msec stimulus duration reduced Troxler fading.

Individual macular pigment absorption at 460nm was calculated using the equation:

$$OD_{mac} = (\log S_{p460} - \log S_{f460}) + (\log S_{f570} - \log S_{p570})$$

where $OD_{mac}$ is the individual macular pigment optical density at 460nm, $\log S_{p460}$ and $\log S_{f460}$ are the measured 460nm sensitivities at 8° and at the fovea (or 5.5°) respectively and $\log S_{f570}$ and $\log S_{p570}$ are the measured 570nm sensitivities at the fovea (or 5.5°) and at 8° respectively. The data were represented as the mean of the three repetitions for each wavelength at each eccentricity.

The test-retest data for macular pigment absorption were obtained from the same 16 subjects as those recruited for the test-retest data of ocular media absorption with an interval of seven days between the two visits. The 16 subjects utilized for the test-retest data were recruited from the 46 subjects that were able to perform both the ocular media and the macular pigment absorption procedures. It was acknowledged that this could have biased the results since better performing subjects were utilized.

6.2.3. Assessment of blue-on-yellow perimetry.

A 460nm narrowband (HPW 9nm) stimulus filter in conjunction with a 330cdm$^{-2}$ yellow background, as detailed in Chapter 5, was utilized for blue-on-yellow perimetry. A Goldmann size V, 200msec stimulus, presented from below threshold was employed. Using a custom threshold program, stimuli were presented three times at each of 5 eccentricities (0°, 5.5°, 10°, 15.5° and 21°) along the 45° and 225° meridians. The mean of the three repeats was taken as threshold at each location.

The assessments of ocular media absorption, macular pigment absorption and blue-on-yellow perimetry were carried out on separate days. The order of assessment was varied

between individuals and each visit including rest periods lasted a maximum of 50 minutes. All tests for a given subject were carried out within a maximum period of three weeks.

## 6.3. Results.

Ocular media absorption relative to 410nm as a function of age for the 68 subjects is shown in Figure 6.1. The data exhibited a between-subject variation of approximately 0.8 to 0.9 log units at any given age. The relationship between ocular media absorption and age was best represented ($R^2$ 65.2%) by an increasing exponential equation of the form $y = 0.02e^{0.50x} + 1.82$, where y is lenticular absorption in log units and x is age in years. Ocular media absorption increased by approximately one log unit between the ages of 20 and 80 years.

The test-retest data of the 16 subjects for ocular media absorption relative to 410nm, expressed in terms of the difference in ocular media absorption between the two visits as a function of the mean value recorded at the two visits, is shown in Figure 6.2. The repeated measures were within ±0.10 log units for 11 subjects and approximately ±0.20 log units for all subjects. The COR for ocular media absorption relative to 410nm was ±0.20 log units.

Foveal macular pigment absorption relative to 460nm as a function of age for the 46 subjects is shown in Figure 6.3. The data exhibited a slight negative slope with increase in age ($r = -0.003$), which was not statistically significant (two-tailed *t*-test, $p>0.05$). The group mean foveal macular pigment absorption value relative to 460nm was found to be 0.40 log units (SE 0.03), which was significantly different from zero ($t=11.8$, $p<0.001$). Individual foveal macular pigment absorption values varied between -0.01 and 0.84 log units (Figure 6.4.). The group mean macular pigment absorption at 5.5° eccentricity was negligible for all four meridians ie 0.00 log units (SE 0.03) along the 45° meridian, -0.03 log units (SE 0.03) along the 135° meridian, -0.03 log units (SE 0.03) along the 225° meridian and 0.00 log units (SE 0.03) along the 315° meridian. Although the majority of values were above

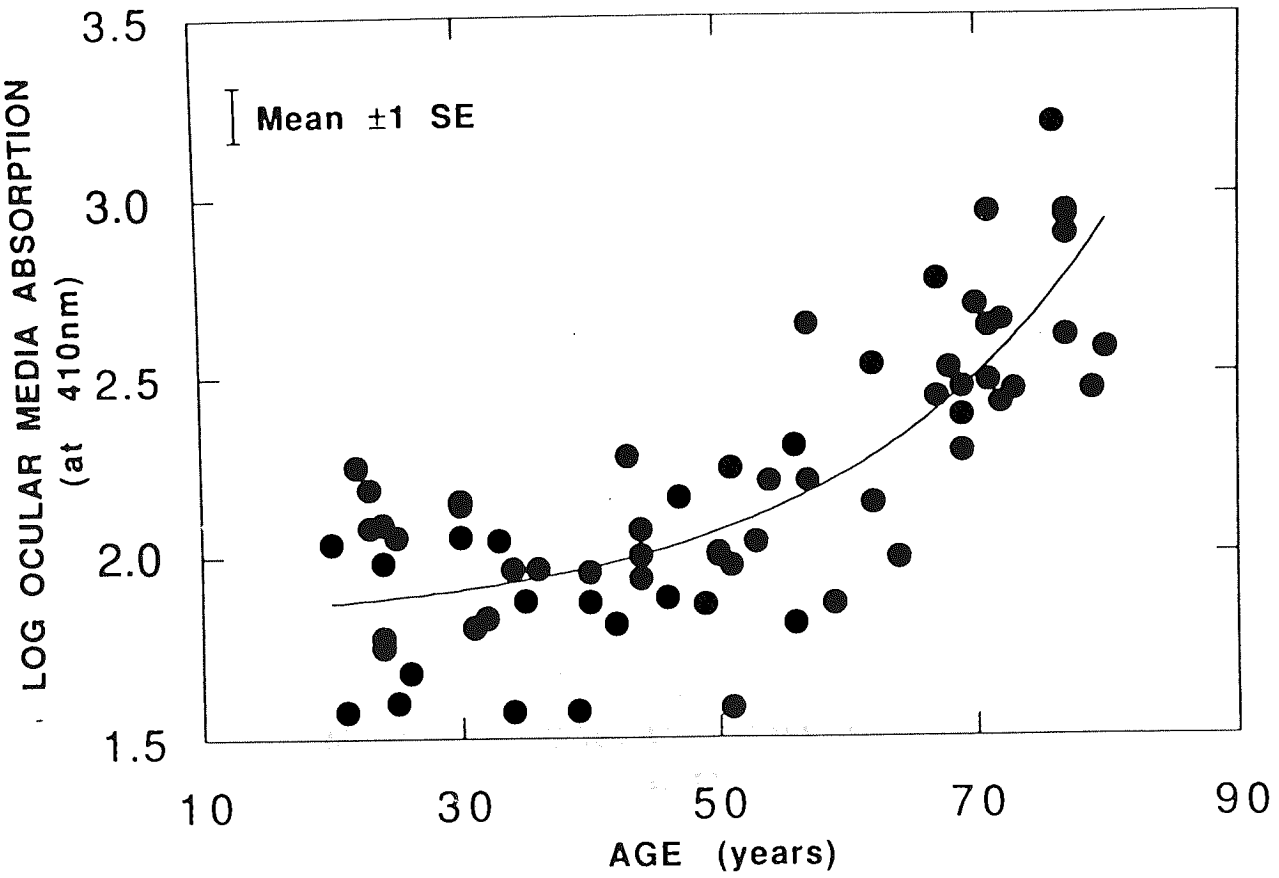



Figure 6.1. Log ocular media absorption at 410nm as a function of age for the 68 normal observers (age range 20-80 yrs).

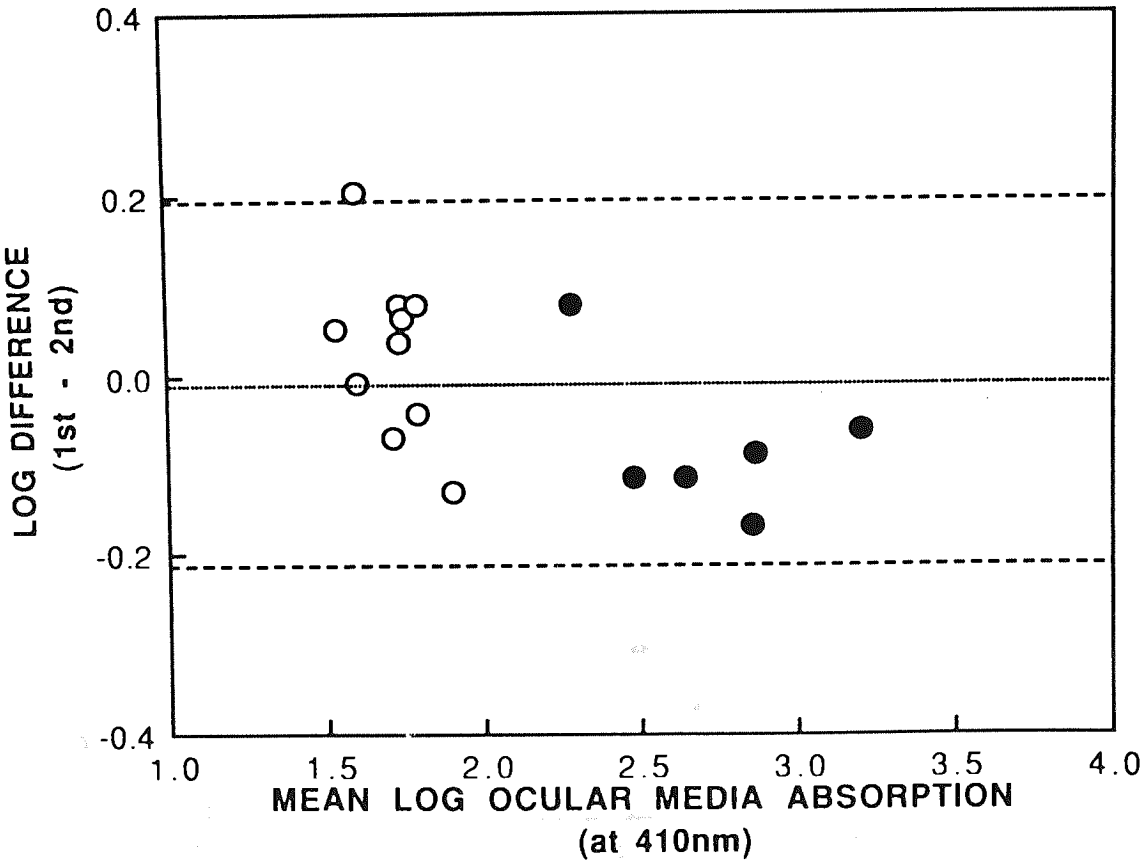



Figure 6.2. The difference in log ocular media absorption at 410nm between the test and retest values (interval 7 days) as a function of the mean of the two values, for 10 young observers (open circles) and 6 elderly observers (closed circles). The mean and 2 SDs of the differences are shown for reference.

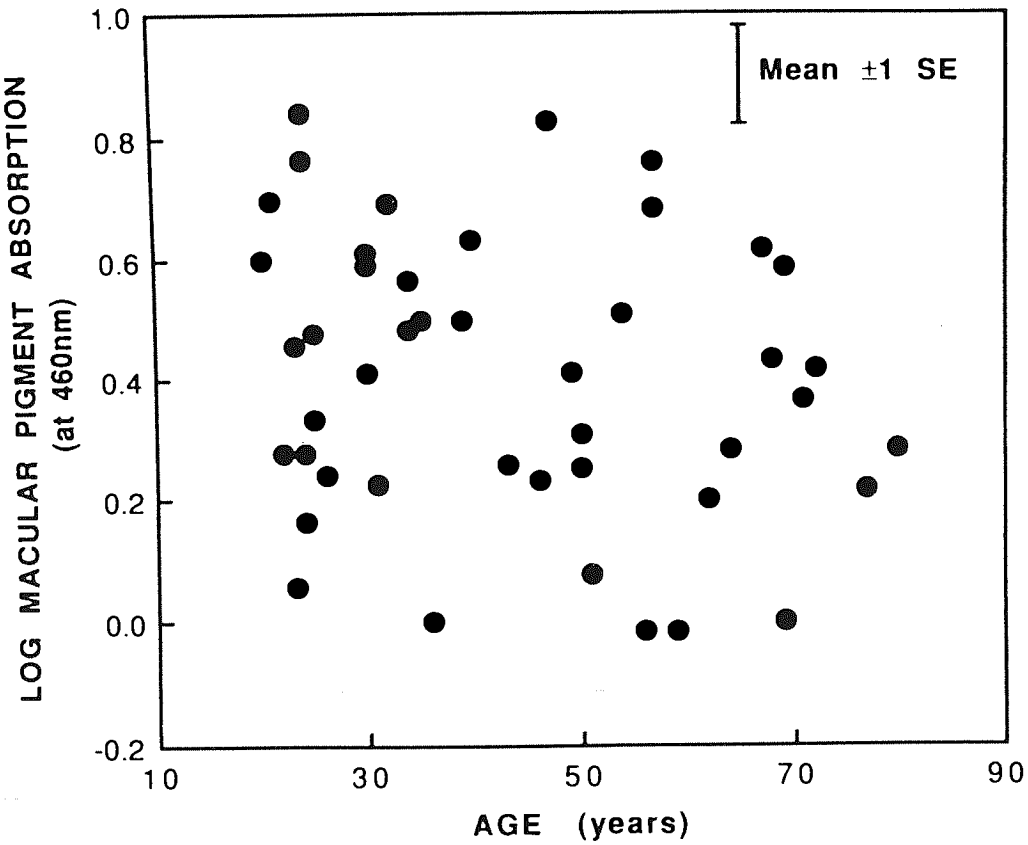



Figure 6.3. Log foveal macular pigment absorption at 460nm as a function of age for the 46 normal observers (age range 20-80 yrs).

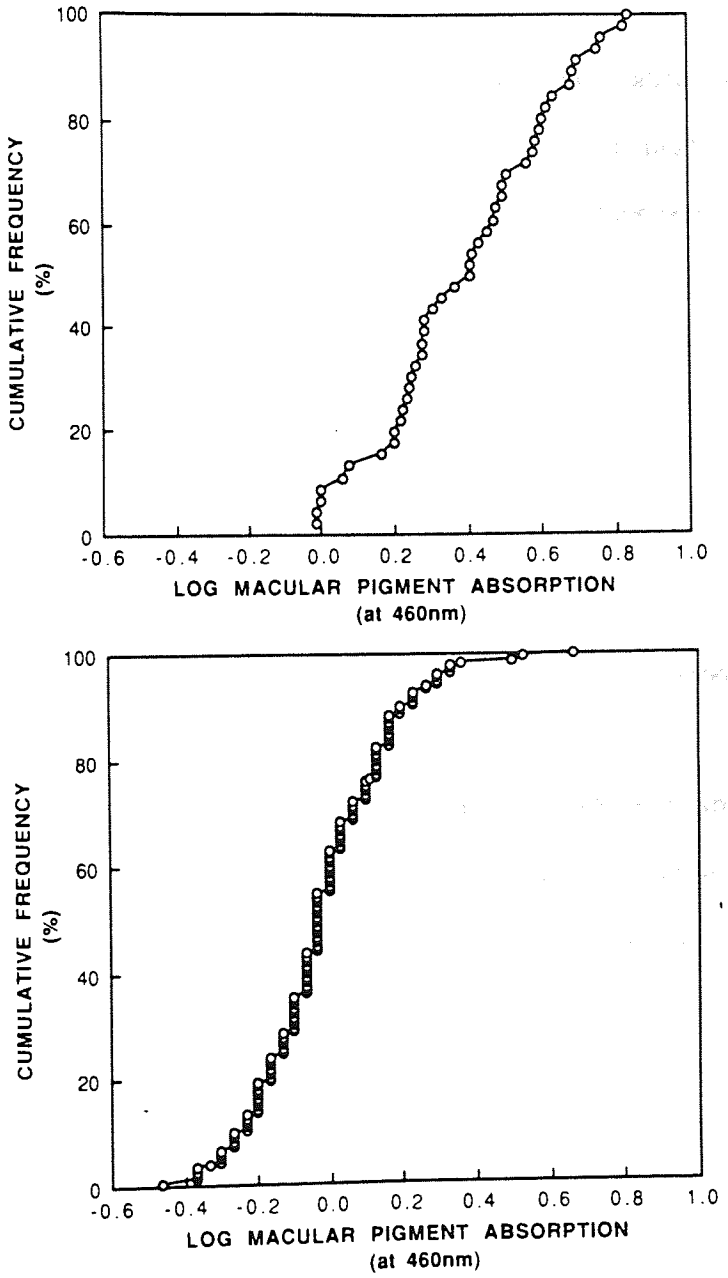



Figure 6.4. Cumulative frequency curves of individual macular pigment absorption values at the fovea (top) and at 5.5° eccentricity pooled for all four meridians (bottom).

zero, individual macular pigment absorption values at 5.5° varied between -0.5 to +0.7 log units (Figure 6.4.). There were no differences in the macular pigment absorption between the four meridians.

The test-retest data of the 16 subjects for foveal macular pigment absorption relative to 460nm, expressed in terms of the difference in foveal macular pigment absorption between the two visits as a function of the mean value recorded at the two visits, is shown in Figure 6.5. The repeated measures for the foveal value were within ±0.10 log units for 11 subjects and within approximately ±0.20 log units for all subjects. The COR was ±0.28 log units at the fovea and ±0.27 log units at 5.5° eccentricity along the 45° meridian, ±0.31 log units along the 135° meridian, ±0.44 log units along the 225° meridian and ±0.36° log units along the 315° meridian.

The mean blue-on-yellow perimetric profile along the 45° and 225° meridians with and without correction for pre-receptoral absorption relative to 460nm for 42 subjects within three discrete age groups who completed all three test procedures is shown in Figure 6.6. The blue-on-yellow profile of the elderly group exhibited a lower sensitivity and a greater between-subject variation than that for the young and middle aged groups. The net effect of pre-receptoral absorption at the fovea relative to 460nm was in the region of 0.80 log units for all three age groups.

## 6.4. Discussion.

The exponential increase in ocular media absorption with age is in agreement with some studies (Coren and Girgus, 1972; Zigman, 1978; Pokorny et al, 1987; Sample et al, 1988a; Johnson et al, 1989b) but is contrary to the linear relationship described by others (Said and Weale, 1959; Mellerio, 1971; Werner and Wooten, 1980; Werner, 1982; Weale, 1988; Savage et al, 1993). A biphasic function has been attributed to the inclusion of subjects with cataract (Savage et al, 1993) or to possible changes of the macular pigment with age (Werner, 1982). Our results obtained from a sample without

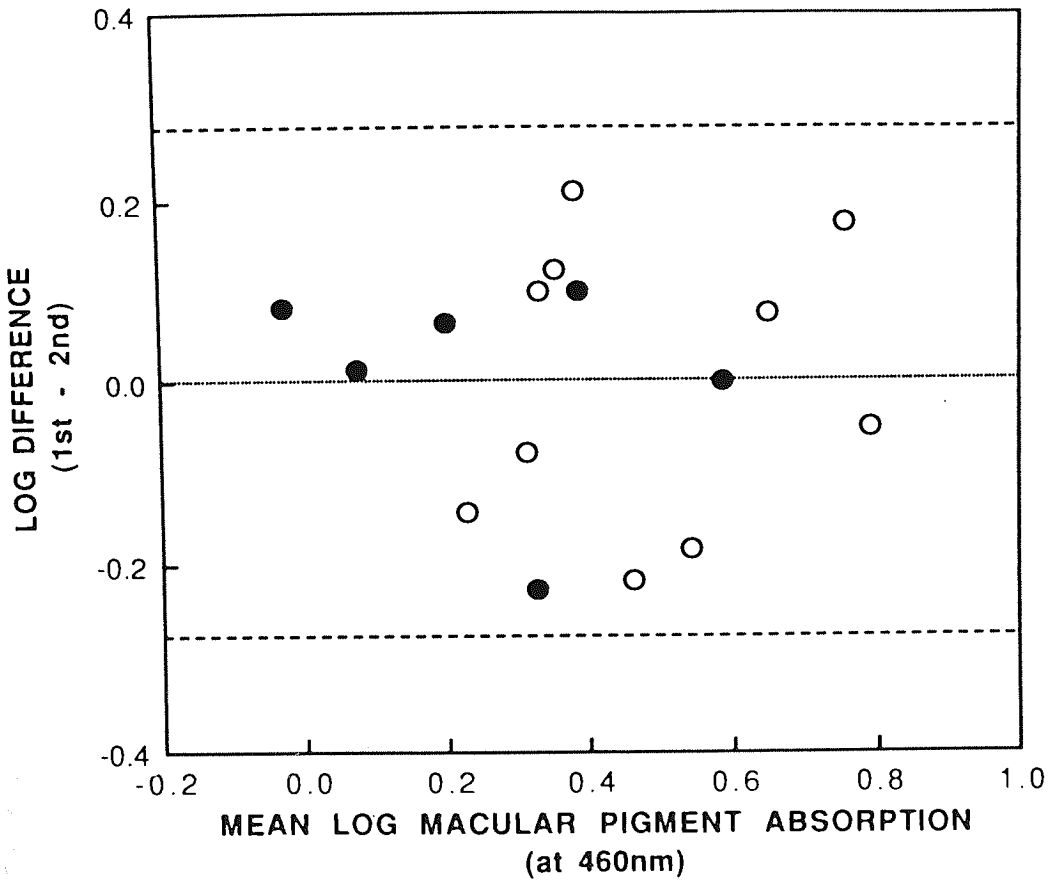



Figure 6.5. The difference in log foveal macular pigment absorption at 460nm between test and retest values (interval 7 days) as a function of the mean of the two values, for 10 young observers (open circles) and 6 elderly observers (closed circles). The mean and 2 SDs of the differences are shown for reference.

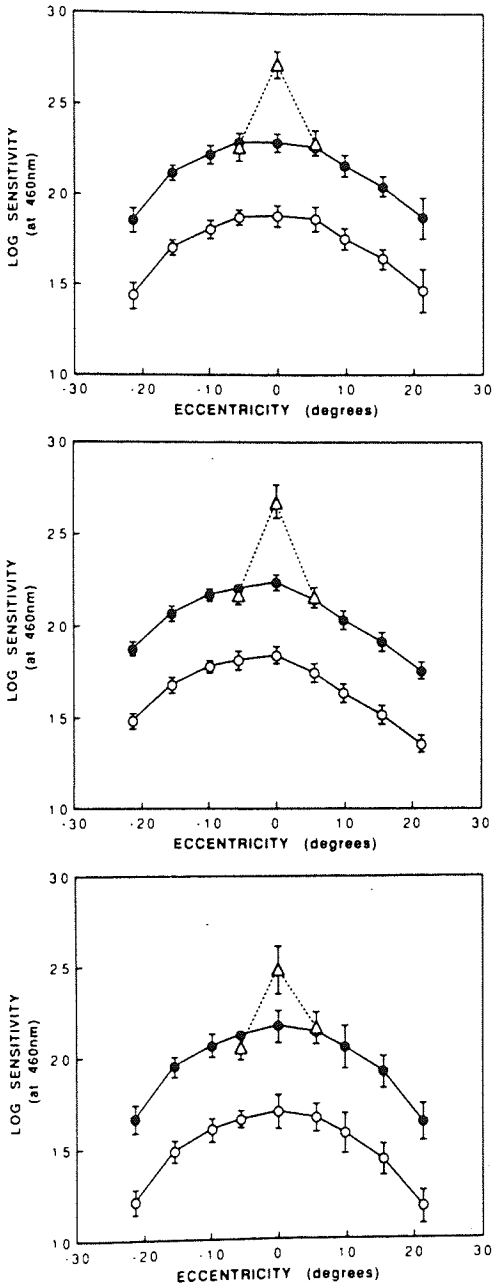



Figure 6.6. Group mean blue-on-yellow sensitivity profile (log units) along the 45° and 225° meridians relative to 460nm. Upper graph: 15 young subjects (mean age 24.66yrs, SD 3.01, range 20-30yrs). Middle graph: 14 middle-aged subjects (mean age 40.40yrs, SD 6.97, range 31-50yrs). Lower graph: 13 elderly subjects (mean age 61.20yrs, SD 6.01, range 51-69yrs). Open circles: uncorrected for pre-receptoral absorption. Closed circles: corrected for ocular media absorption. Open triangles: corrected for macular pigment absorption. A positive eccentricity indicates the 45° meridian and a negative eccentricity the 225° meridian. The error bars represent ±1 standard error of the mean.

lenticular opacity, however, would tend to exclude the former suggestion, whilst the lack of any systematic age dependency in the macular pigment data (Figure 6.3.) would tend to exclude the latter suggestion.

The increase in ocular media absorption with age can be explained by increased lens thickness and / or by increased lens pigmentation (Weale, 1963; Mellerio, 1972). Indeed, an increase in the sagittal width of the crystalline lens of normal subjects has been documented with increase in age (Brown and Tripathi, 1974; Sparrow et al, 1990). Furthermore, the process of lens yellowing which results in increased ocular media absorption is thought to occur as a result of the change in molecular size or the diffuse aggregation of lens crystallins (Benedek, 1971; Spector and Sigelman, 1974; Harding and Dilley, 1976; Bron et al, 1993). Such a process may occur as a result of the nonenzymatic glycosylation of lens crystallins (Lutze and Bresnick, 1991) and / or the accumulation of photodegredative products of molecules which absorb UV-A, eg tryptophan (Marshall, 1985).

The variation of ocular media absorption of 0.80 to 0.90 log units at any given age relative to 410nm is in broad agreement with previous findings (Coren and Girgus, 1972; Norren and Vos, 1974; Werner, 1982; Pokorny et al, 1987; Sample et al, 1988a; Johnson et al, 1989b; Sample et al 1991; Savage et al, 1993). Ocular media absorption exhibits an exponential rise in optical density with decrease in wavelength (Norren and Vos, 1974; Wyszecki and Stiles, 1982). The variation in ocular media absorption with age as a function of wavelength for the 68 observers is shown in Figure 6.7. The data were derived from the measurement made at 410nm and scaled relative to wavelength using the "standard observer" data of Norren and Vos (1974). A concomitant decrease in the spread of the data can be seen with increase in wavelength in addition to the expected reduction in the magnitude of ocular media absorption. Group mean ocular media absorption and 95% confidence limits calculated for each decade (minimum of 10 subjects per decade) for stimulus wavelengths from 400nm to 480nm are shown in Table 6.1. The data in Table 6.1 suggest that individual ocular media absorption values can be

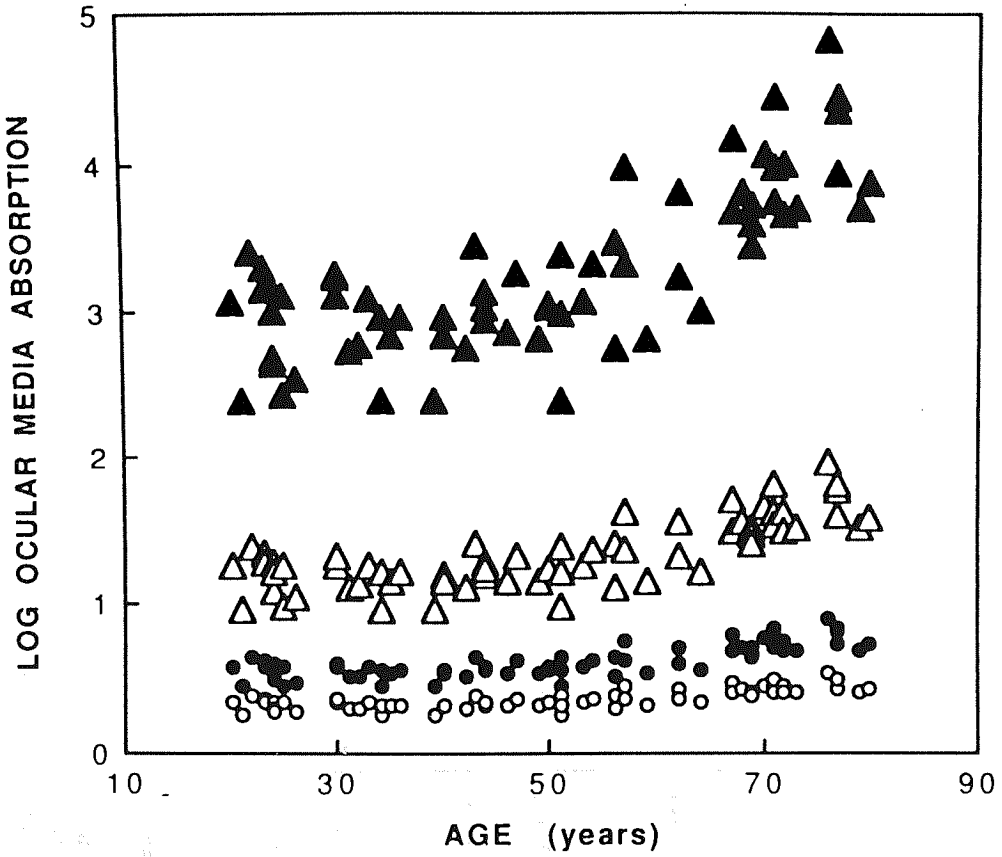



Figure 6.7. Log ocular media absorption against age as a function of wavelength for the 68 normal observers. (Closed triangles: 400nm. Open triangles: 420nm. Closed circles: 440nm. Open circles: 480nm). The values are derived from the measurement made at 410nm and scaled relative to wavelength using the "standard observer" data of Norren and Vos (1974).

| | 400nm | 420nm | 440nm | 460nm | 480nm |
|---|---|---|---|---|---|
| Up to 30yrs | 2.96 | 1.20 | 0.55 | 0.40 | 0.32 |
| (n=15) | (±0.67) | (±0.27) | (±0.12) | (±0.09) | (±0.07) |
| 31 - 40yrs | 2.78 | 1.13 | 0.51 | 0.38 | 0.30 |
| | (±0.48) | (±0.19) | (±0.09) | (±0.06) | (±0.05) |
| 41 - 50yrs | 3.02 | 1.22 | 0.56 | 0.41 | 0.33 |
| | (±0.42) | (±0.17) | (±0.07) | (±0.05) | (±0.04) |
| 51 - 60yrs | 3.15 | 1.28 | 0.58 | 0.43 | 0.34 |
| | (±0.89) | (±0.36) | (±0.16) | (±0.12) | (±0.09) |
| 61 - 70yrs | 3.65 | 1.48 | 0.68 | 0.50 | 0.40 |
| | (±0.70) | (±0.28) | (±0.13) | (±0.09) | (±0.07) |
| 71 -80yrs | 4.08 | 1.66 | 0.76 | 0.56 | 0.45 |
| (n=13) | (±0.75) | (±0.30) | (±0.14) | (±0.10) | (±0.08) |

Table 6.1. Group mean log ocular media absorption and 95% confidence limits in parentheses for stimulus wavelengths of 400nm, 420nm, 440nm, 460nm and 480nm as a function of age (10 subjects per decade unless otherwise indicated). The values are derived from the measurement made at 410nm and scaled relative to wavelength using the "standard observer" data of Norren and Vos (1974).

predicted with 95% confidence to within ± 0.12 log units for a 460nm narrowband stimulus. This would suggest that it is unnecessary to assess ocular media absorption in the non-cataractous eye when using a 460nm peak wavelength narrowband stimulus. The use of a 460nm stimulus, however, could be anticipated to reduce the degree of SWS isolation compared to a stimulus of shorter wavelength.

The test-retest reliability of the ocular media absorption procedure is influenced by the magnitude of the step sizes of the HFA thresholding algorithm, which in turn are governed by the maximum stimulus luminance permitted by the given narrowband filter. The narrowband filter with the larger step size of the two filters (ie the 560nm filter rather than the 410nm filter) determines the precision of measurement. The test-retest reliability of ocular media absorption (COR ±0.20 log units), can be compared with a final step size of 0.12 log units for the 560nm narrowband filter, with the range of ocular media absorption values encountered in the study (0.33 to 0.67 log units at 460nm) and with the magnitude of the normal short-term fluctuation (0.16 log units ±0.03) encountered for blue-on-yellow perimetry (Sample et al, 1993b). Furthermore, relative to the wavelength of the narrowband filter employed for blue-on-yellow perimetry (ie 460nm) the 95% test-retest confidence limits of ocular media absorption can be calculated from the data of Norren and Vos (1974) to be ±0.04 log units ie as wavelength increases, the magnitude of absorption decreases and consequently the measurement error decreases.

The measurement of ocular media absorption is influenced by the between-subject variation in pupil size (Weale, 1961; Mellerio, 1971; Mellerio, 1987; Weale, 1991). A reduction in pupil size increases the lenticular pathlength and therefore can be anticipated to increase the magnitude of ocular media absorption. The purpose of this study, however, was to describe the effective ocular media absorption since this is clinically more relevant. Consequently, natural pupils were employed in order to assess the combined influence of age-related changes in the ocular media and of senile miosis. In addition, the influence of pupil size is small in relation to the magnitude of ocular media absorption (Werner, 1982; Sample et al, 1988a) and reduces in importance with increase

in wavelength (Weale, 1991). Indeed, a 4mm reduction in apparent pupil diameter increased mean ocular media absorption relative to 460nm by approximately 0.1 log units in a group of 80 year old subjects (Weale, 1991). Furthermore, the results are confounded by the application of a scotopic measurement of ocular media absorption to a photopic measurement of blue-on-yellow sensitivity.

The group mean foveal macular pigment absorption of 0.40 log units (SE 0.03) is in close agreement with other findings (Werner et al, 1987; Wyszecki and Stiles, 1982; Vos, 1972) but is lower than that of a previous study (Pease et al, 1987) which, although employing a similar methodology, utilised a stimulus diameter of 1°. The measurement procedure, however, is dependent upon the optical density at the edge of the area of stimulation rather than the average of the area stimulated (Werner et al, 1987; Bone et al, 1992). A Goldmann size V stimulus of 1.724° diameter was employed in this study to be identical to that of blue-on-yellow perimetry (Johnson et al, 1989a; Sample and Weinreb, 1990; Weinreb and Sample, 1991; Johnson et al, 1991; Sample and Weinreb, 1992; Johnson et al, 1993a and b; Lewis et al, 1993; Sample et al, 1993a). The group mean foveal macular pigment absorption value at 460nm for a 1° stimulus was estimated from published data, describing the relationship between stimulus diameter and optical density (Werner et al, 1987; Bone et al, 1992), to be approximately 0.80 log units which is similar to that of Pease and co-workers (1987).

The group mean macular pigment absorption at 5.5° eccentricity is in agreement with previous studies which have reported negligible values at eccentricities from 2° to 5.5° (Ruddock, 1972; Stabell and Stabell, 1980; Williams et al, 1981a; Viénot, 1983; Pease and Adams, 1983; Moreland and Bhatt, 1984; Snodderly et al, 1984a and b; Werner et al, 1987; Kilbride et al, 1989; Bone et al, 1992; Abadi and Cox, 1992). The group mean standard error for macular pigment absorption foveally and at 5.5° eccentricity was 0.03 log units in each case. This value is minimal considering that a single absorption value is derived by the estimation of threshold for two different wavelengths at two different eccentricities. Some subjects exhibited values of macular pigment absorption at 5.5°

eccentricity greater than ±0.2 log units (Figure 6.4.). These findings, particularly negative absorption values, can largely be explained by the overlap of the size V stimulus onto areas of the retina influenced by macular pigment absorption and by eye movements despite the use of trained subjects and the constant monitoring of fixation with the video monitor of the HFA.

The precision of measurement of the macular pigment absorption procedure is also determined by the larger step size of the two filters utilized (ie the 570nm filter rather than the 460nm filter). The test-retest reliability of macular pigment absorption (COR ±0.28 log units foveally; ±0.35 log units at 5.5° eccentricity) can be compared with a final step size of 0.13 log units for the 570nm narrowband filter used to estimate macular pigment absorption and with the range of absorption values encountered at the fovea (-0.01 to 0.84 log units) and at 5.5° eccentricity (-0.46 to +0.66 log units). Both the foveal and 5.5° measures of test-retest reliability were greater than the magnitude of the normal short-term fluctuation (0.16 log units ±0.03) encountered for blue-on-yellow perimetry with HFA program 24-2 (Sample et al, 1993b).

The combined effect of ocular media and macular pigment absorption relative to 460 nm is to attenuate the blue-on-yellow visual field at the fovea by approximately 0.80 log units and elsewhere by 0.40 log units (Figure 6.6.). The absence of a marked influence of age on ocular media absorption relative to 460nm can be explained by a flattening in the exponential relationship between ocular media absorption and age with increase in wavelength (Figure 6.7.).

The variation in foveal macular pigment absorption for each subject as a function of ocular media absorption relative to 460nm is shown in Figure 6.8. The range of values for foveal macular pigment absorption was approximately 2.8 times greater than that due to the ocular media relative to a stimulus wavelength of 460nm. This finding is in agreement with a previous study (Kliegl et al, 1984). The disparity in the range of values between the two functions can be attributed in part to the greater measurement error associated with the

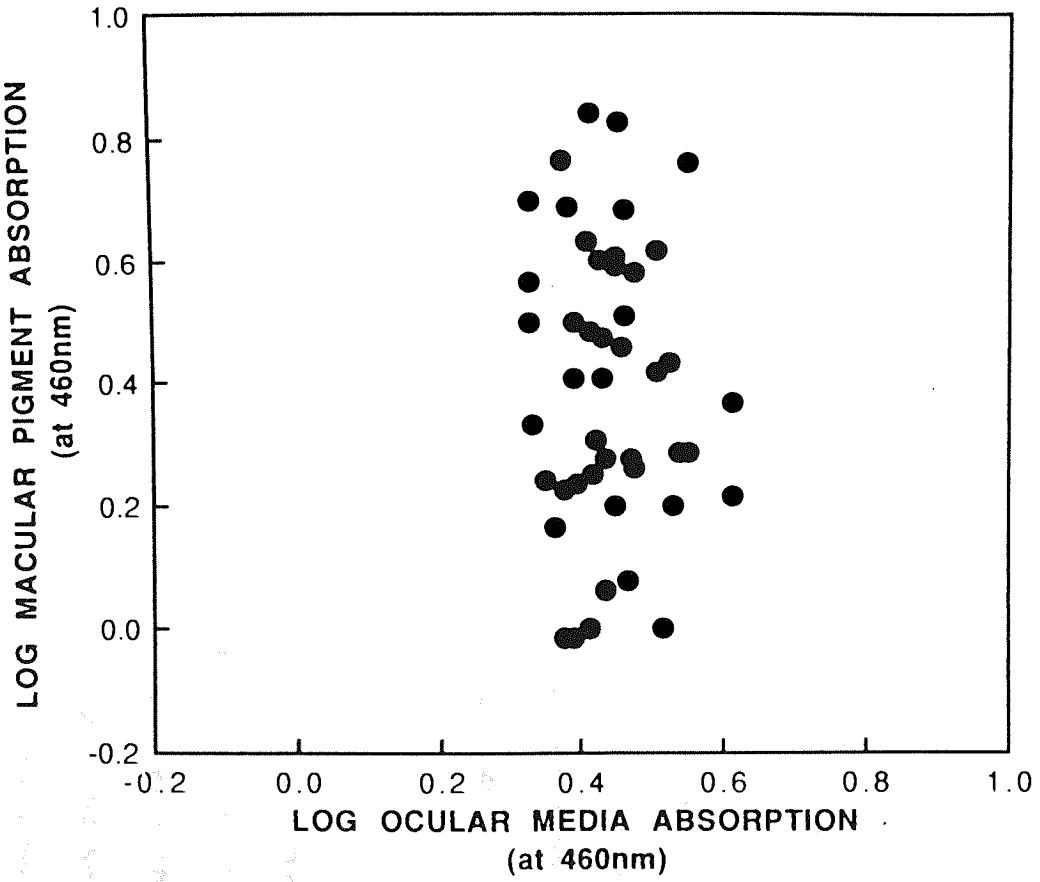



Figure 6.8. Log foveal macular pigment absorption at 460nm as a function of log ocular media absorption relative to 460nm. The ocular media absorption values at 460nm are derived from the measurement made at 410nm and scaled relative to wavelength using the "standard observer" data of Norren and Vos (1974).

assessment of macular pigment absorption and to the relationship of the peak absorption wavelengths of both the ocular media and the macular pigment relative to 460nm ie macular pigment absorption exhibits a maximum relative to 460nm, whilst the magnitude of ocular media absorption is relatively small relative to 460nm (Figure 6.7).

## 6.5. Conclusion.

Absorption by the ocular media and the macular pigment unquestionably attenuates the blue-on-yellow perimetric response. The need to assess ocular media absorption in the cataractous eye is undeniable regardless of the stimulus wavelength utilised for SWS isolation. However, when utilizing a narrowband stimulus of 460nm wavelength for blue-on-yellow perimetry, the assessment of ocular media absorption in the absence of cataract is clinically unnecessary due to the reduced between-subject variance, the absence of a marked age effect and good test-retest reliability. Indeed, a correction factor could be applied for any given age based upon group mean normal data. Conversely, the use of relatively longer wavelength blue stimuli will reduce the magnitude of the SWS isolation. This reduction, however, could be compensated by the employment of a higher background luminance.

The effective influence of macular pigment absorption on blue-on-yellow perimetry is limited to the fovea and out to approximately 4° to 5° eccentricity because of small fixational eye movements and the overlap of the size V stimulus. The combined effect of macular pigment absorption and small involuntary eye movements might be anticipated to result in an increased local short-term fluctuation for blue-on-yellow perimetry within the immediate macular region using a size V stimulus. The most profound effect of the macular pigment will be with HFA program 10-2, which has 30 stimulus locations within 5° eccentricity. Furthermore, the method employed to assess macular pigment absorption cannot be applied to the diseased macula because the technique is based on the underlying assumption that green cone spectral sensitivity is invariant within 8° eccentricity except for the influence of the macular pigment. The separation of the two

absorption components from the neural response using psychophysical techniques such as those described here is a complex and lengthy procedure which, until more rapid objective clinical techniques are developed, will continue to limit the application of blue-on-yellow perimetry.

# CHAPTER 7. BLUE-ON-YELLOW PERIMETRY FOR THE ASSESSMENT OF MACULAR SWS PATHWAY FUNCTION IN THE DIABETIC EYE.

## 7.1. Introduction.

The loss of visual acuity in diabetic retinopathy can be attributed to either diabetic maculopathy ie haemorrhages, exudates and retinal oedema within the macular region, or to proliferative diabetic retinopathy ie neovascularization leading to vitreous haemorrhage or traction retinal detachment (Bresnick, 1986). Indeed, diabetic maculopathy is the major cause of blindness in diabetics and occurs in approximately 10% of the diabetic population (Ghafour et al, 1983; Klein et al, 1984a). In addition, the duration of diabetes is a risk factor in the incidence and progression of diabetic retinopathy (Klein et al, 1988; Brinchmann-Hansen et al, 1992a). For patients with diabetes of 20 years or greater duration, the prevalence of diabetic maculopathy is approximately 25% (Klein et al, 1984b).

### 7.1.1. The clinical classification of diabetic maculopathy.

The mechanism of diabetic maculopathy can be explained by retinal vascular hyperpermeability or by ischaemia (Stevens, 1981; Dodson and Gibson, 1991). The hyperpermeability maculopathies result from a breakdown in the blood-retinal barrier at the capillary endothelium (Wallow and Engerman, 1977), whilst ischaemic maculopathy results from vascular closure of the retinal capillaries and arterioles (Bresnick et al, 1976). In addition, the hyperpermeability maculopathies can be sub-divided into oedematous and exudative maculopathy. Oedematous maculopathy is characterized by macular oedema, whilst exudative maculopathy is characterized by the formation of lipid rings (Stevens, 1981). The classification of maculopathy into hyperpermeable and ischaemic causes, however, is difficult since a combination of the two mechanisms is frequently observed (Dodson and Gibson, 1991).

Diabetic macular oedema is the most common hyperpermeability maculopathy and presents as an area of slightly opaque thickened retina with cyst-like spaces at the fovea (cystoid macular oedema) (Stevens, 1981). The pattern of diabetic macular oedema can be focal or diffuse. Focal oedema is characterized by hard exudates and microaneurysms within the thickened area of retina. Diffuse oedema is characterized by an absence of exudates, fewer microaneurysms and many dilated capillaries (Bresnick, 1983). Exudative diabetic maculopathy, however, presents clinically as a yellow intraretinal or subretinal accumulation of lipoprotein centred on the macula (Toussaint, 1962) which clears with time to leave features such as crystalline plaques, fibrous nodules and pigmentary degeneration (Stevens, 1981). Prompt laser photo-coagulation can halt the deterioration in visual acuity due to diabetic macular oedema and exudative diabetic maculopathy (Patz et al, 1973; ETDRS, 1985 and 1991; Verougstraete, 1988; Clune et al, 1993).

Ischaemic diabetic maculopathy presents clinically as retinal nerve fibre layer infarcts (cotton wool spots or soft exudates), blot haemorrhages, diffuse opacification of the walls of retinal arterioles and areas of intraretinal microvascular abnormalities. Fluorescein angiography is generally undertaken to confirm the diagnosis of ischaemic diabetic maculopathy and to define areas of capillary nonperfusion. Ischaemic maculopathy responds poorly, however, to conventional laser photocoagulation and is currently regarded as "essentially untreatable" (Stevens, 1981).

7.1.2. The diabetic crystalline lens and ocular media absorption.

Increased thickening of the capsule (Laurent et al, 1981) and cortex (Huggert, 1953; Brown and Hungerford, 1982) results in a greater sagittal width of the diabetic crystalline lens when compared to that of normal subjects of the same age. Indeed, the annual increase in sagittal width is approximately 1.7 times greater in diabetics compared to normal subjects (Sparrow et al, 1990). The findings have been explained variously: an increased rate of lens growth, a swelling of the lens as a result of an increase in membrane permeability and / or deficient ion pumping, or a reduced rate of compaction (Bron et al, 1993). As a result of the increased thickness, the surface curvature of the diabetic

crystalline lens is also greater (Sparrow et al, 1990 and 1992). The two factors, combined, have been suggested as the mechanism for the increased incidence of myopia in diabetic patients (Fledelius, 1983, 1986 and 1987). In addition, the transient refractive changes associated with diabetes are generally thought to be due to changes in the refractive index of the crystalline lens (Duke-Elder, 1925; Marmor, 1973; Gwimup, 1976; Bron et al, 1993).

Various studies have demonstrated that the increases in ocular media absorption (Weale, 1982; van Best et al, 1985; Lutze and Bresnick, 1991) and in light scattering (Weiss et al, 1982; Bursell et al, 1989a and b) with increase in age are greater in diabetics compared to normals. The only psychophysical assessment of ocular media absorption in the diabetic eye is that of Lutze and Bresnick (1991) who measured scotopic thresholds to stimuli equally absorbed by rhodopsin. The technique is described in Chapter 6 and has also been utilized by Norren and Vos (1974), Sample and co-workers (1988a and 1989) and Johnson and co-workers (1988b and 1989b). Lutze and Bresnick (1991) measured the rate of increase of ocular media absorption with increase in age in a sample of 31 insulin-dependent type I diabetics and compared their findings with a sample of 50 normal subjects. The rate of increase in ocular media absorption with age in young, type I diabetic patients was similar to the rate of increase found in elderly normal subjects. It was suggested that the assessment of ocular media absorption may provide a measure of long-term glucose regulation in diabetic patients.

### 7.1.3. Disturbances of visual function in diabetes.

A number of investigative techniques, such as contrast sensitivity, dark adaptation, nyctometry, visual-evoked cortical potentials, electroretinography, hue discrimination, colour matching, chromatic adaptation and spectral sensitivity have demonstrated a loss of visual function in diabetic patients with minimal or no retinopathic abnormalities but with normal visual acuity. The most recent publications reporting abnormalities of contrast sensitivity in diabetic patients include Higgins and co-workers (1986), Trick and co-workers (1988) and Brinchmann-Hansen and co-workers (1993), whilst those reporting

abnormalities of dark adaptation and nyctometry include Frost-Larsen and co-workers (1989a and b, 1992), Brinchmann-Hansen and co-workers (1988, 1992b, 1993), Midena and co-workers (1990) and Greenstein and co-workers (1993). In addition, studies demonstrating abnormalities of visual-evoked cortical potentials and electroretinography in diabetic patients include Bresnick and co-workers (1985), Bresnick and Palta (1987), Brinchmann-Hansen and co-workers (1988 and 1992c), Frost-Larsen and co-workers (1989b) and Holopigian and co-workers (1992). Hue discrimination and colour matching abnormalities have been documented by Green and co-workers (1985), Bresnick and co-workers (1985), Roy and co-workers (1986), Mäntyjärvi (1987), Daley and co-workers (1987), Trick and co-workers (1988), Greenstein and co-workers (1990), Lagerlöf (1991), Birch and co-workers (1991), Hardy and co-workers (1992) and Brinchmann-Hansen and co-workers (1993). Chromatic adaptation and spectral sensitivity abnormalities have been described by Adams and co-workers (1987a and b), Greenstein and co-workers (1989a, b and c, 1990), Terasaki and co-workers (1990), Schefrin and co-workers (1991) and Greenstein and co-workers (1992).

The results of visual function studies are equivocal; some studies have reported a correlation between the magnitude of the sensory loss and the degree of retinopathy (Begg and Lakowski, 1980; Bresnick et al, 1985; Adams et al, 1987a; Greenstein et al, 1990; Brinchmann-Hansen et al, 1992b, c and 1993) while others have failed to show any relationship (Moloney and Drury,1982; Hardy et al, 1992; Brinchmann-Hansen et al, 1993). Similarly, some studies have demonstrated a correlation between the magnitude of sensory loss and the duration of diabetes (Trick et al, 1988; Brinchmann-Hansen et al, 1992c) while others have failed to demonstrate any such relationship (Roy et al, 1986; Greenstein et al, 1990; Hardy et al, 1992; Brinchmann-Hansen et al, 1992b and 1993).

In general, the results of visual function tests are considered to reflect neurosensory loss rather than vascular dysfunction since abnormal results have been obtained from patients with minimal or no retinopathic changes (Bresnick, 1986; Hardy et al, 1992; Greenstein et al, 1993; Brinchmann-Hansen et al, 1993). The neurosensory loss may occur at any site

along the visual pathway as a consequence of the general systemic and local metabolic abnormalities of diabetes. Indeed, visual function tests are believed to provide information additional to that obtained from ophthalmoscopy, retinal photography and fluorescein angiography (Bresnick, 1986; Hardy et al, 1992; Greenstein et al, 1993; Brinchmann-Hansen et al, 1993).

### 7.1.4. Aim of the study.

The majority of studies of the effects of diabetes on colour vision have failed to consider the influence of pre-receptoral absorption on the outcome of the results and this may explain the absence of any relationship between the magnitude of the colour vision loss and the degree of diabetic retinopathy. Furthermore, visual function tests have generally provided little information about the topographic characteristics of the neurosensory loss in diabetes since foveal presentation and / or relatively large stimuli have been employed. Indeed, only one clinical study has utilized blue-on-yellow perimetry to study the effects of diabetic retinopathy on SWS pathway sensitivity (Lutze et al, 1989). Lutze and co-workers (1989) compared blue-on-yellow perimetry to conventional "white-on-white" perimetry in 5 diabetic patients and in 5 normal subjects using program 30-2 and stimulus size V. The reduction in blue-on-yellow sensitivity, after correction for ocular media absorption, did not correlate with the grade or the retinal location of the lesion (as assessed by fluorescein angiography) or with the results of conventional perimetry.

The aim of the study, therefore, was to: (1) compare the magnitude of ocular media absorption in diabetics with that of normal subjects; and (2) to undertake a pilot study to investigate the utility of blue-on-yellow perimetry in the assessment of macular function in diabetic patients.

## 7.2. Materials and methods.

### 7.2.1. Sample.

The sample comprised 68 normal subjects (range 20-80 yrs: 36 males and 32 females) with a minimum of 10 normal subjects per decade and 27 diabetic patients (range 19-72yrs: 15 males and 12 females). The normal subjects had previously been examined for ocular media and macular pigment absorption as described in Chapter 6. One eye of each volunteer was selected randomly for the study. Inclusion criteria for the diabetic patients comprised a distance refractive error of equal to or less than ±4.00 dioptres sphere and ±3.00 dioptres cylinder, a visual acuity of 6/9 or better, an absence of lenticular opacity and an intraocular pressure of less than 21 mmHg. Exclusion criteria comprised a positive family history of glaucoma in a first degree relative, use of any topical eye treatment, systemic medication with known CNS effects, neurological and psychiatric illness and the use of contact lenses. Furthermore, all of the diabetic patients had normal red-green hue discrimination (Ishihara 24 plates edition, Kanahara and Co, Tokyo, Japan).

Type I and II patients with diabetes of varying duration including insulin dependent and non-insulin dependent individuals were recruited with a wide range of retinopathic changes to determine any relationship between the magnitude of SWS pathway sensitivity loss and the degree of retinopathy. In addition, diabetic patients taking oral hypoglycaemic agents were included in the study since these agents have been suggested to adversely influence colour vision (Lyle, 1974). Furthermore, diabetic patients who had undergone photocoagulation therapy were recruited to assess whether blue-on-yellow perimetry was sensitive to severe retinal damage, ie to provide "end-point controls".

Volunteers attended for psychophysical assessment over a total of four appointments each of approximately 60 minutes duration and carried out on four separate days. Conventional visual field examination using HFA programs 30-2 and 10-2 and stimulus size III was undertaken at the initial appointment. The non-standard perimetry was carried

out at the remaining three appointments. All visits were undertaken within a maximum period of 4 weeks. Frequent rest periods were given during each session. Training in the psychophysical tests to be employed was undertaken prior to data collection.

The diabetic patients attended for a fifth appointment to undergo a comprehensive ophthalmological examination that included colour stereo photography of the retina (Topcon TRL50VT fundus camera; four stereo photographs covering 35° eccentricity from the fovea). The fundus photographs were evaluated independently of the results of the psychophysical tests. Blood glucose was measured at the end of every visit using a Reflolux-S meter (Boehringer Mannheim GmbH, Germany) in the 23 diabetic patients that routinely carried out self-assessment. No measurement was recorded for the remaining 4 diabetic patients. In addition, glycosylated haemoglobin ($HbA_1$) was recorded for each diabetic patient based on a single value taken within ±3 months of the perimetric and psychophysical examinations. The clinical characteristics of the 27 diabetic patients are illustrated in Table 7.1.

7.2.2. Perimetry.

Four stimulus and background conditions were employed; a white stimulus on a $10cdm^{-2}$ white background (ie low white-on-white); a white stimulus on a $360cdm^{-2}$ white background (ie high white-on-white); a yellow stimulus (Schott OG530) on a $330cdm^{-2}$ yellow background (ie yellow-on-yellow); and a blue stimulus (OCLI blue dichroic; Figure 7.1.) on a $330cdm^{-2}$ yellow background (ie blue-on-yellow). The slightly higher luminance of the high white background when compared to the yellow background can be explained by the attenuation of the Schott OG530 filter.

A custom program of approximately four minutes duration comprising 13 stimulus locations within 10° eccentricity of the fovea was utilized in conjunction with stimulus size V for all four perimetry conditions (Figure 7.2.). The custom program was repeated three times for each condition. The order of presentation of the four conditions was randomized between individuals across the three appointments. The refraction of each diabetic

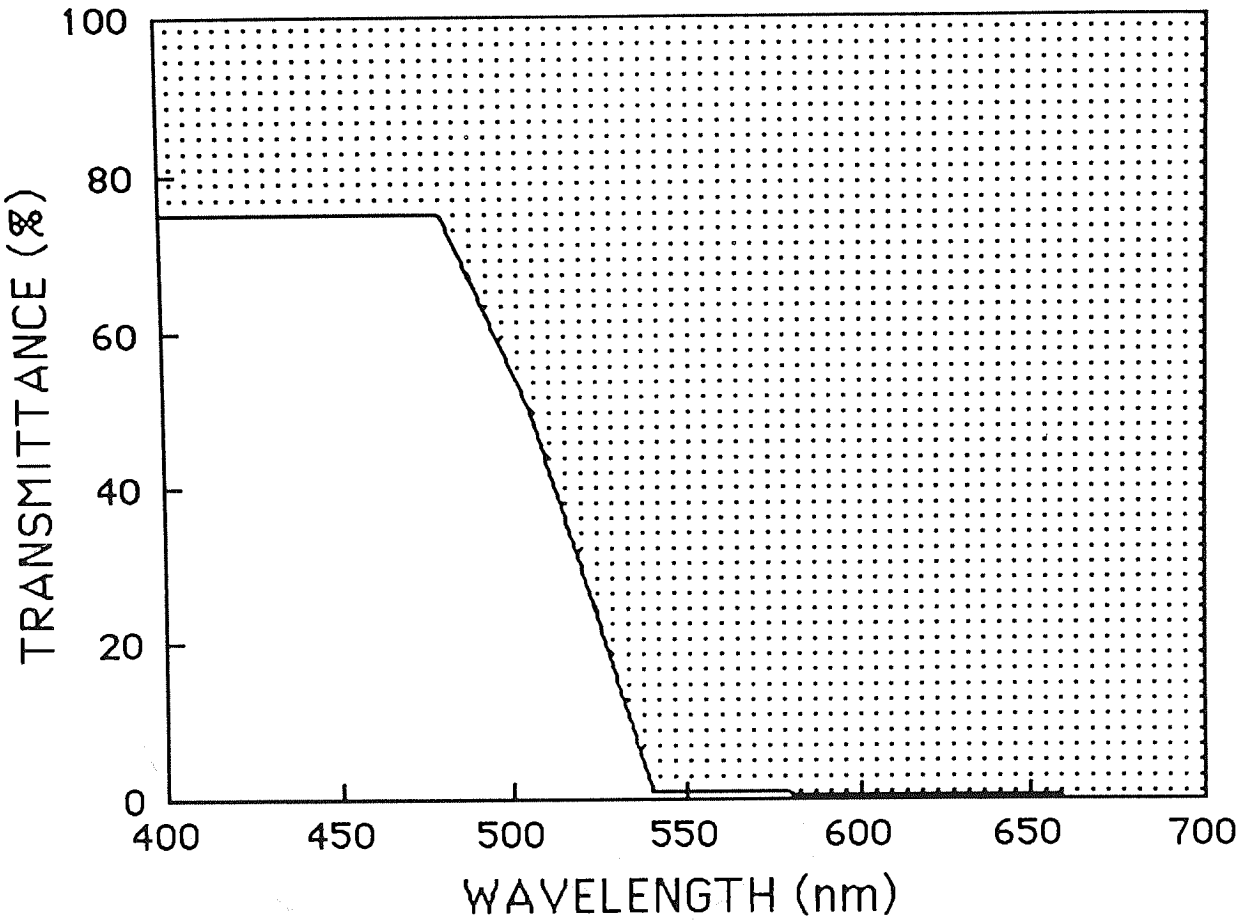



Figure 7.1. Percentage transmittance as a function of wavelength for the OCLI blue dichroic stimulus filter employed for blue-on-yellow perimetry. Transmitted wavelengths are represented by the unshaded area of the graph. Wavelengths below 480nm are transmitted and the transmission is reduced to 50% at a wavelength of approximately 505nm.

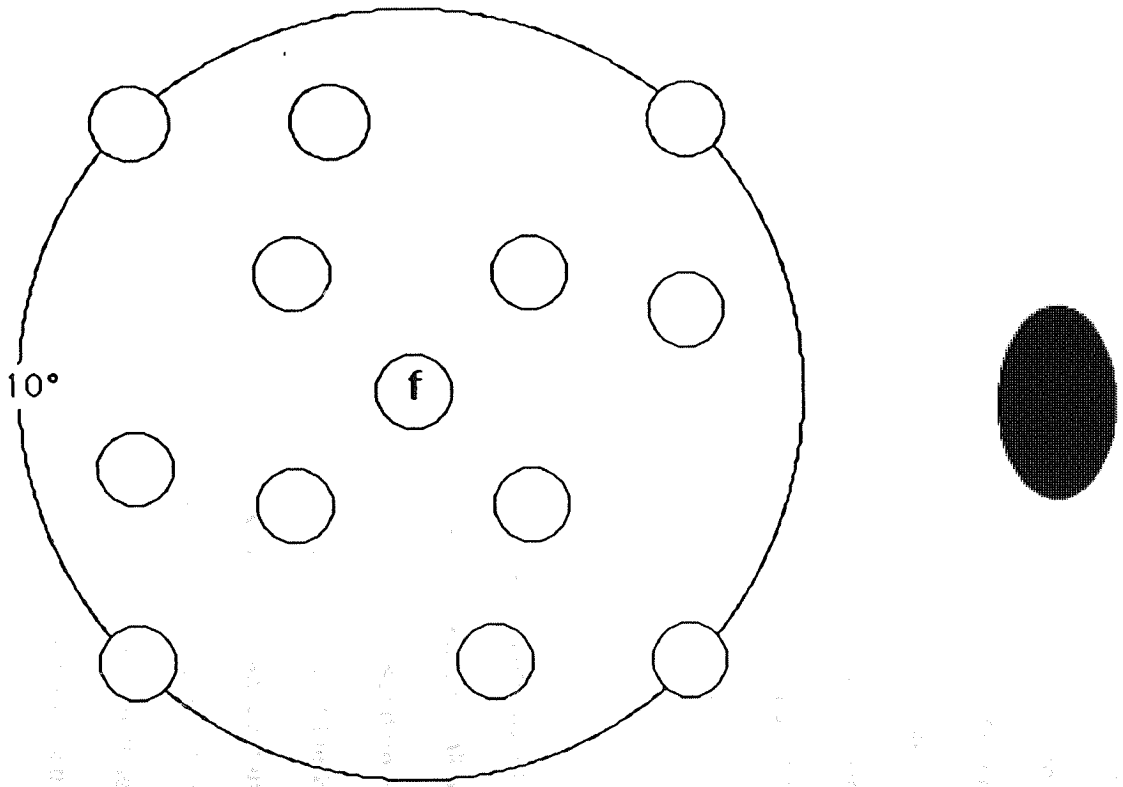



Figure 7.2. Scale diagram of the 13 point custom program illustrating the degree of retinal cover of the size V stimuli (right eye shown).

patient was checked and adjusted when necessary at each visit. The distance refractive correction, together with the appropriate near addition, was used to correct for a viewing distance of 33 cm. Natural pupils were used for all tests.

The low white-on-white condition permitted comparison of the blue-on-yellow perimetry with the adaptation level of conventional perimetry. The high white-on-white and yellow-on-yellow conditions acted as controls for the blue-on-yellow perimetry since both assessed the LWS / MWS pathway. In addition, the yellow-on-yellow response was less affected by pre-receptoral absorption of shorter wavelengths. An OCLI blue dichroic stimulus filter was employed for blue-on-yellow perimetry rather than the 460nm narrowband stimulus filter utilized in the study of pre-receptoral absorption (Chapter 6) since the broader spectral transmission (Figure 7.1.) permitted a greater measurement range of 2.94 log units. This filter had previously been shown to provide 1.1 log units of isolation in conjunction with a 202cdm$^{-2}$ yellow background (Johnson et al, 1988b).

### 7.2.3. Pre-receptoral absorption.

The blue-on-yellow perimetry results were corrected for ocular media and macular pigment absorption. The normal data for ocular media absorption was based upon all 68 normal subjects, whilst the normal data for macular pigment absorption was based on 46 of the 68 normal subjects who managed to carry out the test (Chapter 6). All of the 27 diabetic patients completed the ocular media absorption procedure. The macular pigment absorption technique assumes a normal spectral sensitivity and consequently could not be applied to the diabetic patients. The results of blue-on-yellow perimetry for those normal subjects unable to complete the macular pigment absorption procedure and all the diabetic patients were therefore corrected for macular pigment absorption using the group mean foveal value derived in Chapter 6 of 0.40 log units relative to a 460nm narrowband filter.

The values of ocular media and macular pigment absorption were derived relative to narrowband stimuli of 410nm and 460nm respectively. The OCLI blue dichroic stimulus

filter utilized for the blue-on-yellow perimetry, however, has relatively broadband spectral transmission characteristics (Figure 7.1.). A significant proportion of light is transmitted by the OCLI blue dichroic filter at wavelengths longer than 410nm and at wavelengths either side of the peak absorption spectra of the macular pigment (ie 460nm). Consequently, the magnitude of ocular media and macular pigment absorption relative to the OCLI blue dichroic filter was reduced when compared to that assessed with narrowband filters. In addition, the between-subject variation attributable to the ocular media and macular pigment was also reduced as a result of using the OCLI blue dichroic filter. All ocular media and macular pigment absorption values were therefore adjusted to take into account the interaction of the transmittance characteristics of the OCLI blue dichroic filter and the absorption spectrum of the crystalline lens and the macular pigment respectively.

Resultant absorption values were derived for both the ocular media and the macular pigment at discrete wavelengths in 10nm steps over the visible spectrum using the equation:

$$\text{Resultant absorption} = \text{Transmittance}_{OCLI} \times \left({}^{Ab_{so}}/_{Ab_{peak}}\right)$$

where $\text{Transmittance}_{OCLI}$ is the percentage transmittance of the OCLI filter at a given wavelength, $Ab_{so}$ is the "standard observer" absorption value (log units) at the given wavelength and $Ab_{peak}$ is the "standard observer" peak absorption value (log units). The "standard observer" data for ocular media absorption was taken from Norren and Vos (1974), whilst that for the macular pigment was taken from Wyszecki and Stiles (1982). Conversion factors were derived for both the ocular media and macular pigment by summing the resultant absorption values for each discrete wavelength and dividing by the total number of wavelengths. A conversion factor of 0.39 was calculated to relate ocular media absorption for the OCLI blue dichroic filter to that derived relative to a 410nm narrowband filter, whilst a conversion factor of 0.66 related macular pigment absorption for the OCLI filter to that derived relative to a 460nm narrowband filter.

| Patient | Sex | Age (yrs) | Type | Duration (yrs) | Control | $HbA_1$ (%) | Blood glucose[1] (mmol / L) | Hypertension | Eye | Acuity | Retinopathy details |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 19 | I | 17 | Insulin | 4.6 | 1.9 / 13.5 /13.5 | No | LE | 6/5 | Background - 2 blot haemorrhages beyond 10°. |
| 2 | F | 22 | I | 13 | Insulin | 8.0 | 3.2 / 13.9 / 3.2 | No | RE | 6/4 | None. |
| 3 | M | 23 | I | 12 | Insulin | 6.4 | 11 / 13.2 / 11.1 | No | LE | 6/4 | None. |
| 4 | M | 24 | I | 14 | Insulin | 3.6 | 2.6 / 15.2 / 2.6 | No | RE | 6/4 | Background - exudates within 5° of fovea. |
| 5 | M | 29 | I | 15 | Insulin | 6.5 | 1.5 / 18.3 / 14.7 | No | LE | 6/5 | None. |
| 6 | M | 31 | I | 4 | Insulin | 7.0 | 5.0 / 14.5 / 7.1 | No | LE | 6/3 | None. |
| 7 | F | 33 | I | 22 | Insulin | 6.3 | 2.0 / 11.7 / 2.0 | No | RE | 6/5 | None. |
| 8 | M | 35 | I | 20 | Insulin | 5.5 | 1.9 / 6.6 / 4.7 | Yes | LE | 6/6 | Background - exudates and microaneurysms within 5° of fovea. |
| 9 | M | 38 | I | 22 | Insulin | 7.0 | 9.1 / 12.7 / 9.1 | No | RE | 6/3 | Background - exudates, cotton woll spots and microaneurysms within 5° of fovea. |
| 10 | M | 42 | I | 9 | Insulin | 5.9 | 4.7 / 15.8 / 10.4 | No | RE | 6/3 | None. |

Table 7.1. Clinical characteristics of the diabetic patients.

| Patient | Sex | Age (yrs) | Type | Duration (yrs) | Control | $HbA_1$ (%) | Blood glucose[1] (mmol / L) | Hypertension | Eye | Acuity | Retinopathy details |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | F | 44 | II | 12 | Insulin | 6.9 | Not available. | No | RE | 6/5 | Background - dot and blot haemorrhages within 5° of the fovea. |
| 12 | M | 45 | I | 17 | Insulin | 6.8 | 1.6 / 16.3 / 3.8 | No | RE | 6/5 | Pre-proliferative - cotton wool spots, nerve fibre layer and blot haemorrhages within 10° of fovea. |
| 13 | F | 45 | I | 20 | Insulin | 8.0 | 3.0 / 6.0 / 3.0 | No | RE | 6/5 | Pre-proliferative - exudates, microaneurysms and blot haemorrhages within 5° of fovea. |
| 14 | M | 49 | II | 3 | Oral | 4.9 | 3.8 / 5.8 / 3.8 | No | RE | 6/4 | Pre-proliferative - exudates, cotton wool spots, microaneurysms, nerve fibre layer haemorrhages and intra-retinal microvascular abnormalities within 5° of fovea. |

Table 7.1. (Continued).

| Patient | Sex | Age (yrs) | Type | Duration (yrs) | Control | $HbA_1$ (%) | Blood glucose[1] (mmol / L) | Hypertension | Eye | Acuity | Retinopathy details |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | M | 52 | II | 2 | Oral | 9.7 | 11 / 19.8 / 11 | No | RE | 6/4 | None. |
| 16 | F | 53 | II | 4 | Oral | 5.7 | 2.8 / 5.0 / 5.0 | No | LE | 6/5 | Drusen within 5° of fovea. |
| 17 | F | 54 | I | 10 | Insulin | 5.3 | 3.3 / 10.3 / 9.0 | No | RE | 6/5 | None. |
| 18 | F | 59 | II | 1.5 | Oral | 5.8 | 2.2 / 7.3 / 6.1 | No | LE | 6/5 | None. |
| 19 | M | 61 | II | 20 | Insulin | 5.7 | 2.3 / 10 / 10 | No | RE | 6/5 | None. |
| 20 | F | 61 | I | 32 | Insulin | 7.1 | 14 / 22.1 / 22.1 | No | RE | 6/5 | Background - haemorrhages. One dot haemorrhage within 5° of fovea. |
| 21 | F | 64 | II | 7 | Oral | 8.3 | 9.1 / 11.8 / 9.1 | Yes | RE | 6/6 | Background - exudates within 5° of fovea. Panretinal photocoagulation beyond 10° eccentricity. |
| 22 | M | 67 | II | 3 | Oral | 5.5 | 6.2 / 8.2 / 8.2 | Yes | LE | 6/4 | Background - exudates, microaneurysms and dot haemorrhages within 5° of fovea. |

Table 7.1. (Continued).

| Patient | Sex | Age (yrs) | Type | Duration (yrs) | Control | $HbA_1$ (%) | Blood glucose[1] (mmol / L) | Hypertension | Eye | Acuity | Retinopathy details |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | M | 68 | II | 11 | Oral | 6.4 | Not available. | No | LE | 6/9 | Background - exudates and microaneurysms within 5° of fovea. Atrophic macular degeneration. |
| 24 | F | 68 | II | 7 | Oral | 6.0 | Not available. | Yes | LE | 6/5 | Background - microaneurysms. One microaneurysm within 5° of fovea. |
| 25 | F | 68 | II | 1 | Oral | 5.4 | 6.4 / 9.1 / 9.1 | Yes | RE | 6/5 | None. |
| 26 | M | 69 | II | 9 | Oral | 5.2 | 4.6 / 8.4 / 7.5 | Yes | LE | 6/5 | Background - microaneurysms beyond 5° of fovea. |
| 27 | F | 72 | II | 18 | Oral | 4.9 | Not available. | Yes | RE | 6/8 | Background - microaneurysms and nerve fibre layer haemorrhages. Microaneurysms within 5° of fovea. |

[1] Lowest value recoded over the four visits / highest value recorded / value recorded at blue-on-yellow assessment.

Table 7.1. (Continued).

### 7.2.4. Statistical Analysis.

The mean sensitivity for each individual was calculated from the three repetitions for each of the four perimetry conditions. Similarly, mean ocular media absorption was calculated from three repetitions. Ninety-five per cent confidence limits were calculated for the range of mean sensitivity and ocular media absorption values exhibited by a minimum of 10 normal subjects within each decade. A best-fitting line was drawn through the 95% confidence limits to approximate the range of normal population values for the four perimetry conditions and for ocular media absorption. Similarly, 95% confidence limits based on three repeats of each stimulus condition were calculated for each diabetic patient. The results of a diabetic patient were considered to be abnormal if the 95% confidence limits for that patient lay outside those of the age-matched normal range.

## 7.3. Results.

### 7.3.1. Conventional visual field examination.

The visual fields of 5 of the diabetic patients as assessed with Program 30-2 were classified as either abnormal or borderline. Visual field defects as shown by conventional perimetry have been reported previously in diabetic patients and have been attributed to subclinical microangiopathy (Trick et al, 1990). Only one diabetic patient (21), however, who had undergone panretinal photocoagulation (Table 7.1.), produced an abnormal result with Program 10-2.

### 7.3.2. Ocular media absorption.

Ocular media absorption relative to 410nm for the normal subjects and diabetic patients as a function of age is shown in Figure 7.3. The 95% confidence limits (mean ± 2 SD) of every diabetic patient were found to lie above and outside those of the group mean normal data.

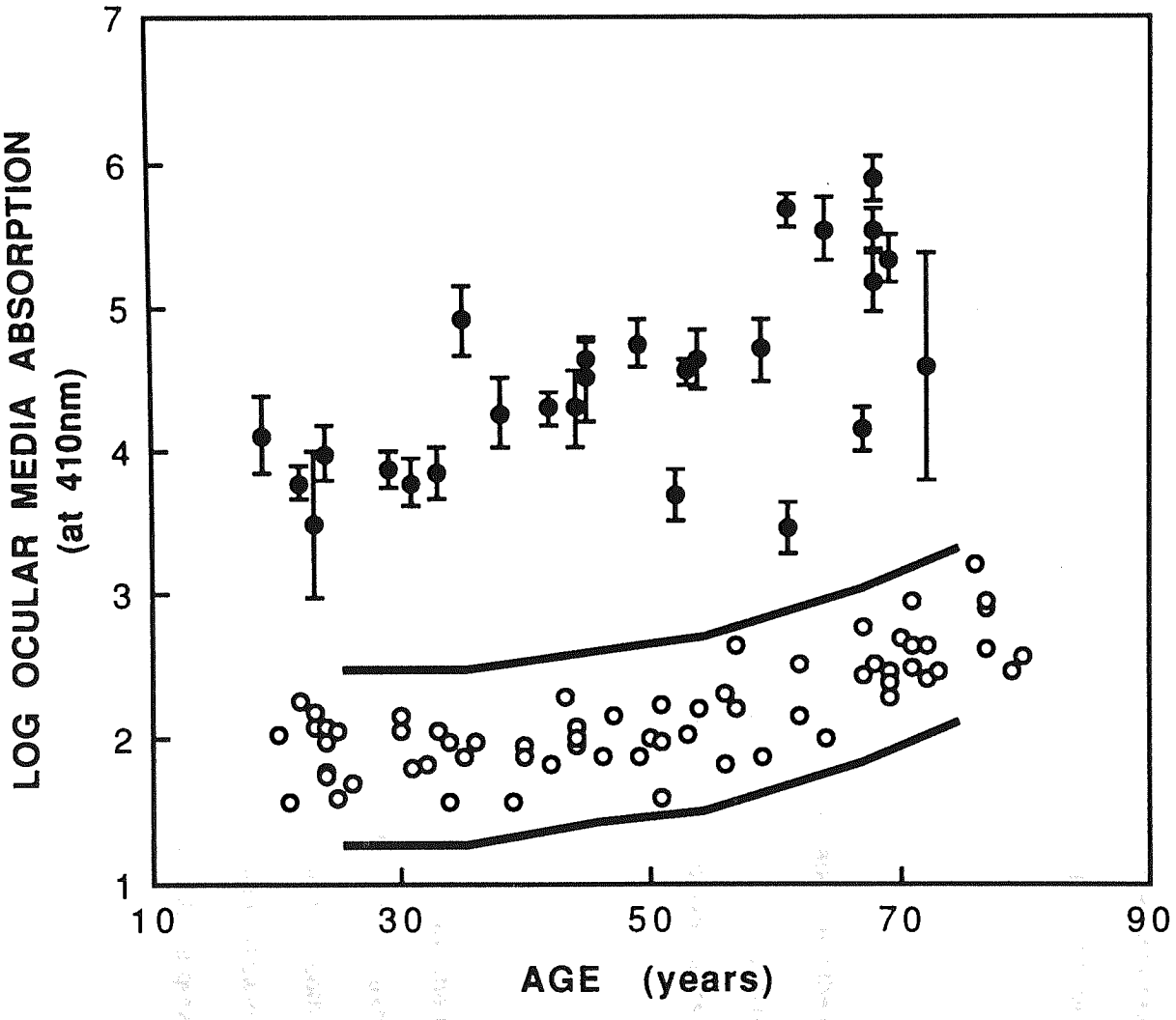



Figure 7.3. Log ocular media absorption at 410nm as a function of age for the diabetic patients (closed circles) and normal subjects (open circles). The error bars represent the 95% confidence limits (± 2 SDs) of the range of values exhibited by a given diabetic patient. The lines represent the approximated 95% range of normal population values.

7.3.3. Non-standard perimetry.

A summary of the results for all four perimetry conditions is shown in Table 7.2.

7.3.3.1. Low white-on-white.

Low white-on-white log relative mean sensitivity for each diabetic patient and the range of normal values is shown in Figure 7.4. Two diabetic patients (8 and 9) exhibited a reduced low white-on-white mean sensitivity but the 95% confidence limits of both patients overlapped the age-matched normal range. Diabetic 10 exhibited a wide standard deviation for the low white-on-white test. Careful inspection of the raw data revealed a progressive loss of sensitivity during the three repeats of the custom program for diabetic 10 which was attributed to fatigue.

7.3.2.2. High white-on-white.

High white-on-white log relative mean sensitivity for each diabetic patient and the range of normal values is shown in Figure 7.5. Two diabetic patients (14 and 21) exhibited a reduced high white-on-white mean sensitivity but the 95% confidence limits of both patients overlapped the age-matched normal range.

7.3.2.3. Yellow-on-yellow.

Yellow-on-yellow log relative mean sensitivity for each diabetic patient and the range of normal values is shown in Figure 7.6. Two diabetic patients (8 and 11) exhibited a reduced yellow-on-yellow mean sensitivity but the 95% confidence limits of both patients overlapped the age-matched normal range. Diabetic 3 exhibited a high yellow-on-yellow mean sensitivity. Careful inspection of the raw data revealed a high rate (ie greater than 33%) of false-positive responses for diabetic 3.

7.3.2.4. Blue-on-yellow.

Blue-on-yellow log relative mean sensitivity for each diabetic patient and the range of normal values is shown in Figure 7.7. The difference in the magnitude of sensitivity between the blue-on-yellow condition and the other perimetry conditions can be

| Patient number | Low white-on-white | High white-on-white | Yellow-on-yellow | Blue-on-yellow | Visual acuity | Retinopathy |
|---|---|---|---|---|---|---|
| 3 | N | N | (H) | (H) | 6/4 | None |
| 8 | L | N | L | N | 6/6 | Background |
| 9 | L | N | N | N | 6/3 | Background |
| 10 | (W) | N | N | N | 6/3 | None |
| 11 | N | N | L | A | 6/5 | Background |
| 12 | N | N | N | A | 6/5 | Pre-prolif |
| 14 | N | L | N | N | 6/4 | Pre-prolif |
| 15 | N | N | N | A | 6/4 | None |
| 17 | N | N | N | A | 6/5 | None |
| 21 | N | L | N | A | 6/6 | Background |
| 22 | N | N | N | L | 6/4 | Background |

Table 7.2. Summary of the mean sensitivity results of the diabetic patients for the four perimetry conditions. (N; normal mean sensitivity. L; low mean sensitivity but the 95% confidence limits overlap the age-matched normal range. H; high mean sensitivity but the 95% confidence limits overlap the age-matched normal range. W; wide standard deviation of the mean. A; abnormal mean sensitivity). Classifications in parenthesis indicate an artifactual reduction of sensitivity. Diabetic patients who exhibited normal mean sensitivities for all four perimetry conditions have been omitted. The visual acuity and retinal appearance of each diabetic patient are also shown (None; no retinopathy. Background; background diabetic retinopathy. Pre-prolif: pre-proliferative diabetic retinopathy).

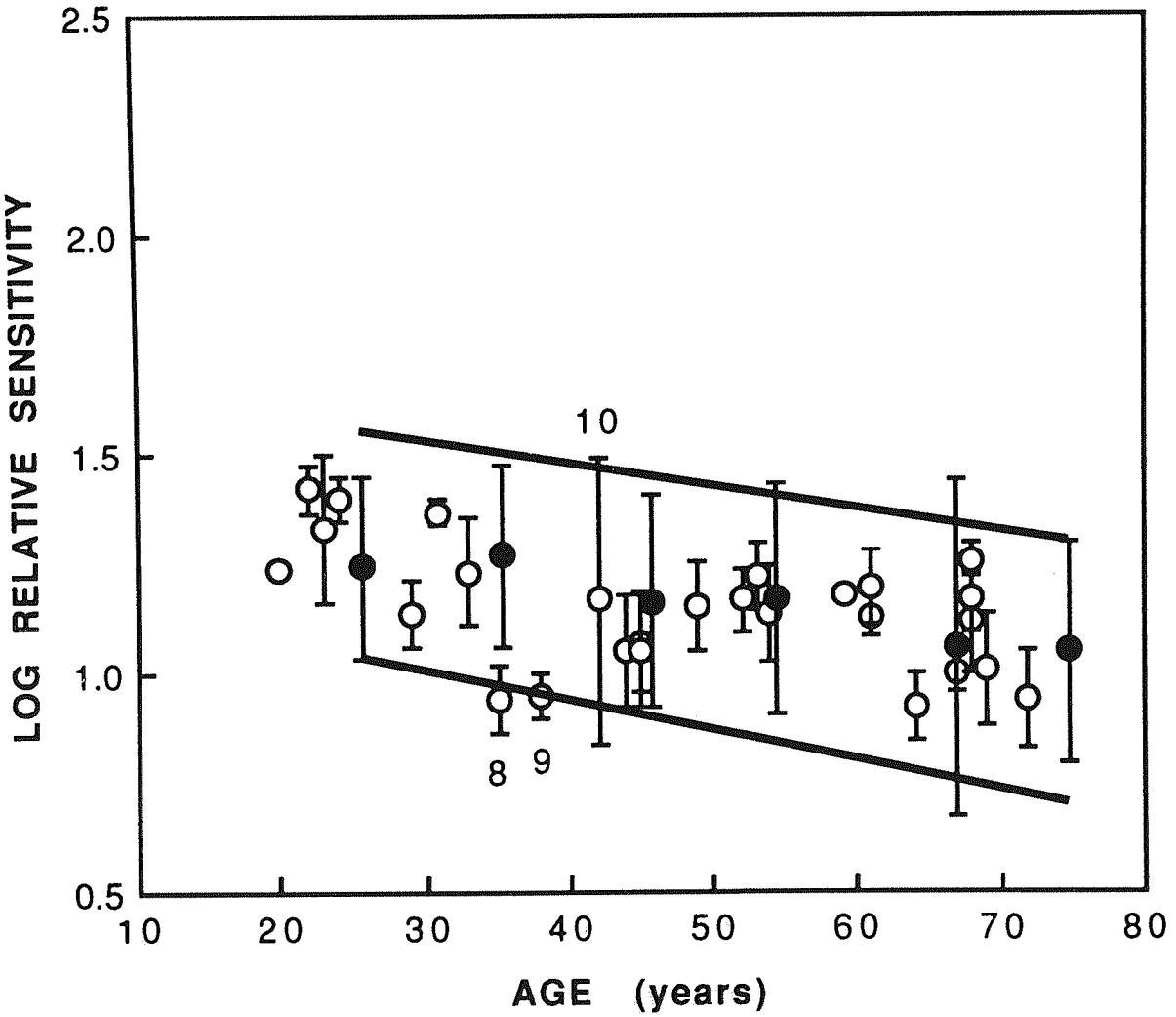



Figure 7.4. Low white-on-white log relative mean sensitivity and 95% confidence limits (± 2 SDs) for the diabetic patients (open circles) as a function of age. The closed circles represent the mean values and 95% confidence limits (± 2 SDs) of the normal subjects within each decade. The lines represent the approximated 95% range of normal population values.

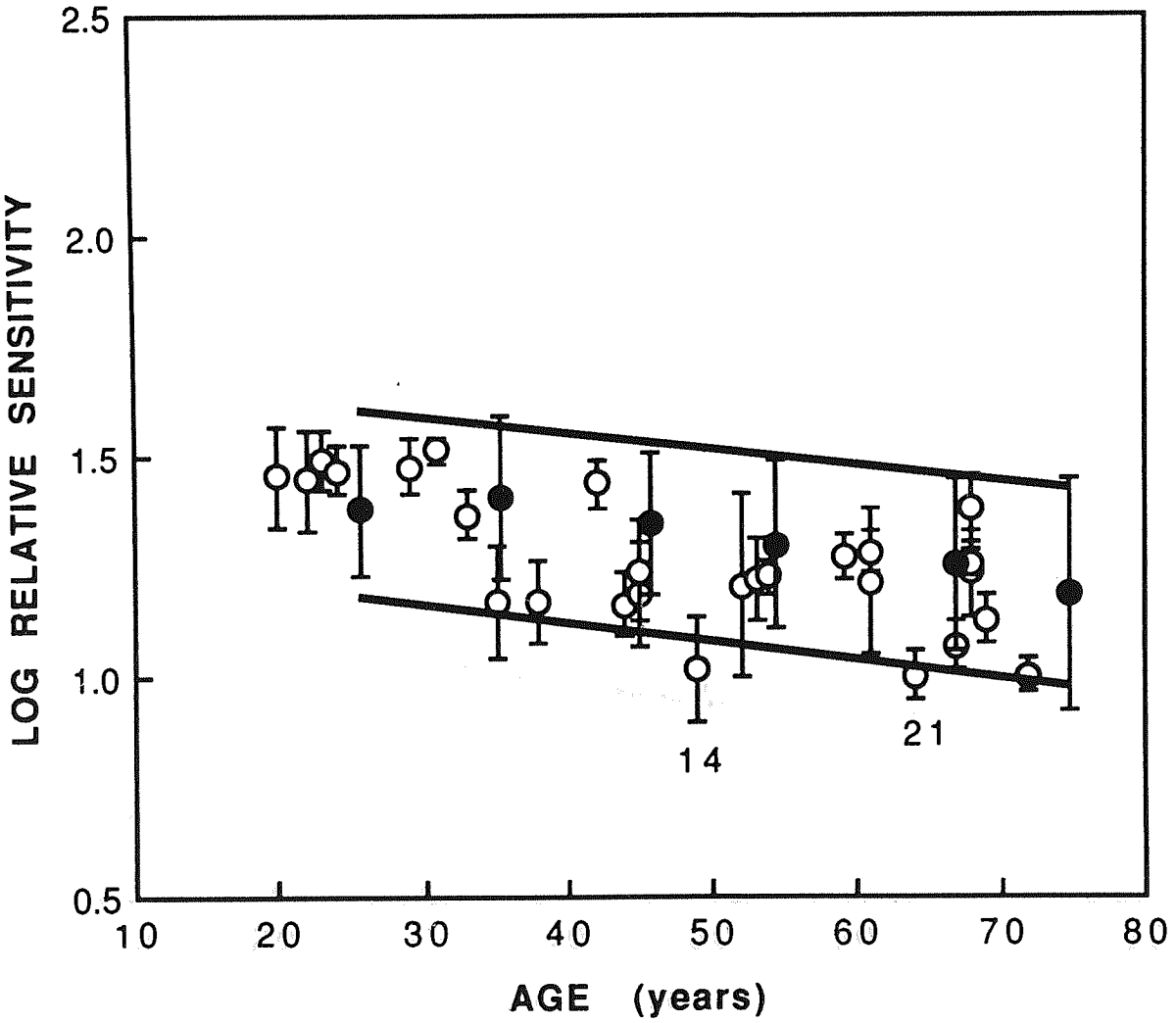



Figure 7.5. High white-on-white log relative mean sensitivity and 95% confidence limits (± 2 SDs) for the diabetic patients (open circles) as a function of age. The closed circles represent the mean values and 95% confidence limits (± 2 SDs) of the normal subjects within each decade. The lines represent the approximated 95% range of normal population values.

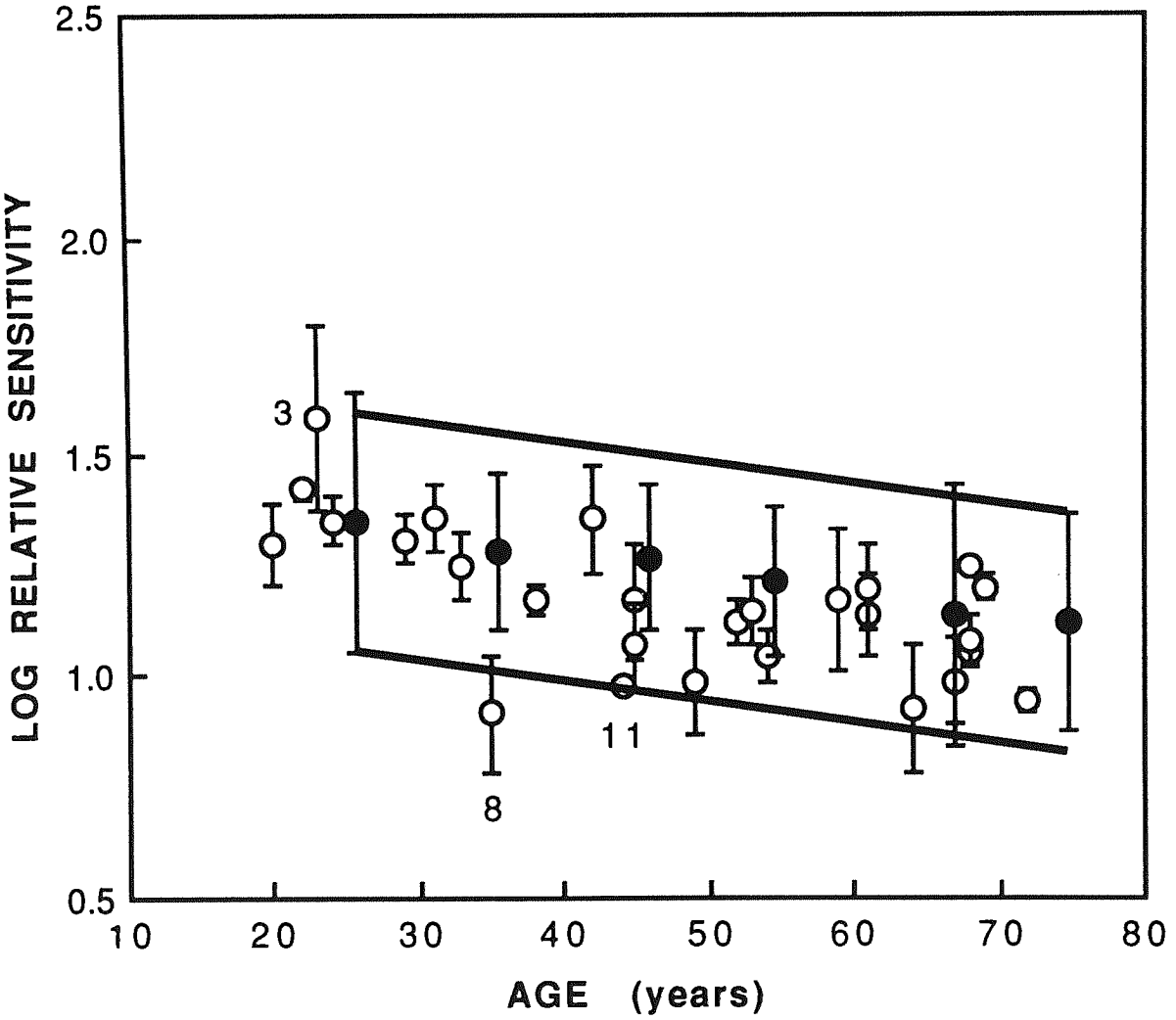



Figure 7.6. Yellow-on-yellow log relative mean sensitivity and 95% confidence limits (± 2 SDs) for the diabetic patients (open circles) as a function of age. The closed circles represent the mean values and 95% confidence limits (± 2 SDs) of the normal subjects within each decade. The lines represent the approximated 95% range of normal population values.

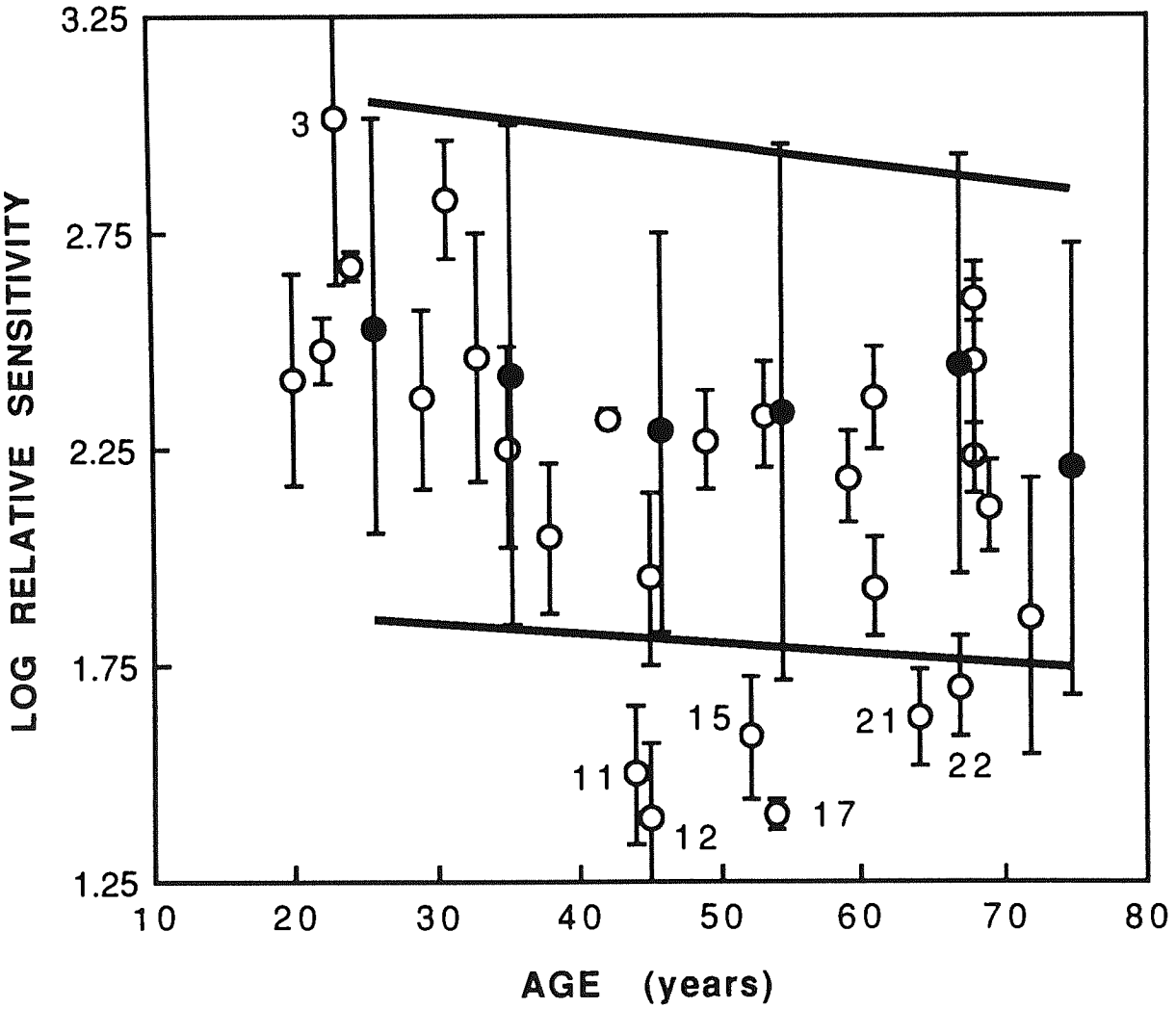



Figure 7.7. Blue-on-yellow log relative mean sensitivity and 95% confidence limits (± 2 SDs) for the diabetic patients (open circles) as a function of age. The closed circles represent the mean values and 95% confidence limits (± 2 SDs) of the normal subjects within each decade. The lines represent the approximated 95% range of normal population values.

explained in part by the unique adaptation properties of the SWS cones (Stiles, 1959). Five diabetic patients (11, 12, 15, 17 and 21) exhibited a reduced blue-on-yellow mean sensitivity that was significantly lower than the age-matched normal range ($p \leq 0.05$). Another diabetic patient (22) exhibited a reduced blue-on-yellow mean sensitivity but the 95% confidence limits of this patient overlapped the age-matched normal range. Diabetic 3 exhibited a high blue-on-yellow mean sensitivity which was again attributable to a high rate (ie greater than 33%) of false-positive responses.

The characteristics of the blue-on-yellow sensitivity loss exhibited by diabetic patients 11, 12, 15, 17 and 21 were assessed using cumulative frequency graphs (Bebié et al, 1989) of the pointwise sensitivity values of the 13 point custom program.

Diabetic 11 was a 44 year old female and a Type II insulin dependent diabetic of 12 years duration (Table 7.1.). Retinal photography revealed background diabetic retinopathy comprising dot and blot haemorrhages within approximately 5° of the fovea. She exhibited an abnormal blue-on-yellow mean sensitivity and a low yellow-on-yellow mean sensitivity, whilst the results for the low white-on-white and high white-on-white conditions were found to be within normal limits (Table 7.2.). The cumulative frequency graph of the pointwise blue-on-yellow results of diabetic 11 is shown in Figure 7.8. A diffuse loss of blue-on-yellow sensitivity was exhibited. The blue-on-yellow sensitivity loss was confirmed when the test was repeated on a second occasion (Figure 7.8.).

Diabetic 12 was a 45 year old male and a Type I insulin dependent diabetic of 17 years duration (Table 7.1.). Retinal photography revealed pre-proliferative diabetic retinopathy comprising cotton wool spots, nerve fibre layer haemorrhages and blot haemorrhages within approximately 10° of the fovea. He exhibited an abnormal blue-on-yellow mean sensitivity, whilst low white-on-white, high white-on-white and yellow-on-yellow mean sensitivities were found to be normal (Table 7.2.). The cumulative frequency graph of the pointwise blue-on-yellow results of diabetic 12 is shown in Figure 7.9. A diffuse loss of blue-on-yellow sensitivity was exhibited.

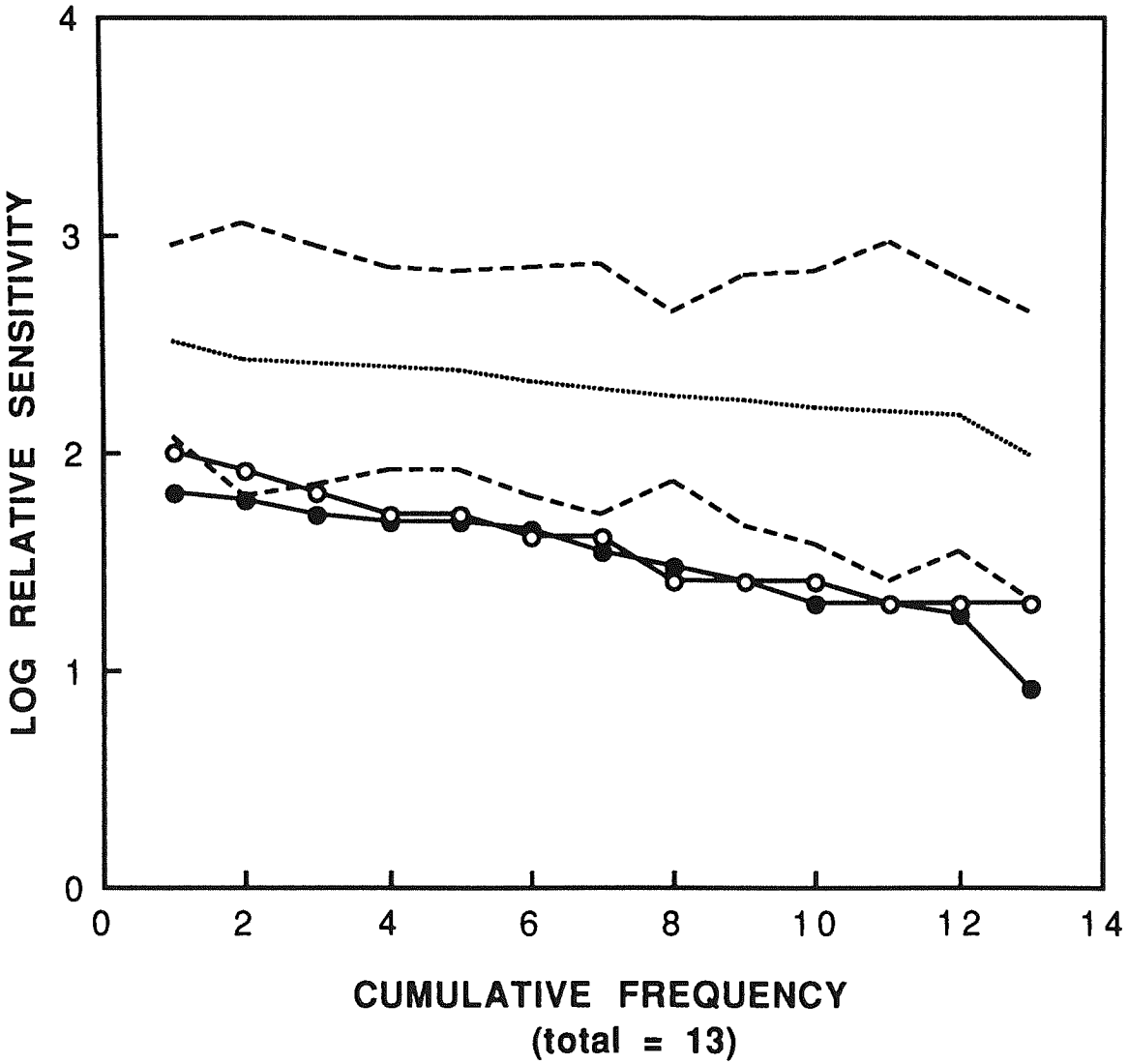



Figure 7.8. Cumulative frequency graph (Bebié curve) of the pointwise blue-on-yellow sensitivity values of the 13 point custom program (closed circles) for diabetic 11. The open circles represent blue-on-yellow sensitivity when repeated on a separate occasion. The middle dotted line represents the mean value of the normal subjects, whilst the upper and lower dashed lines represent the 95% confidence limits (± 2 SDs) of the range of normal values.

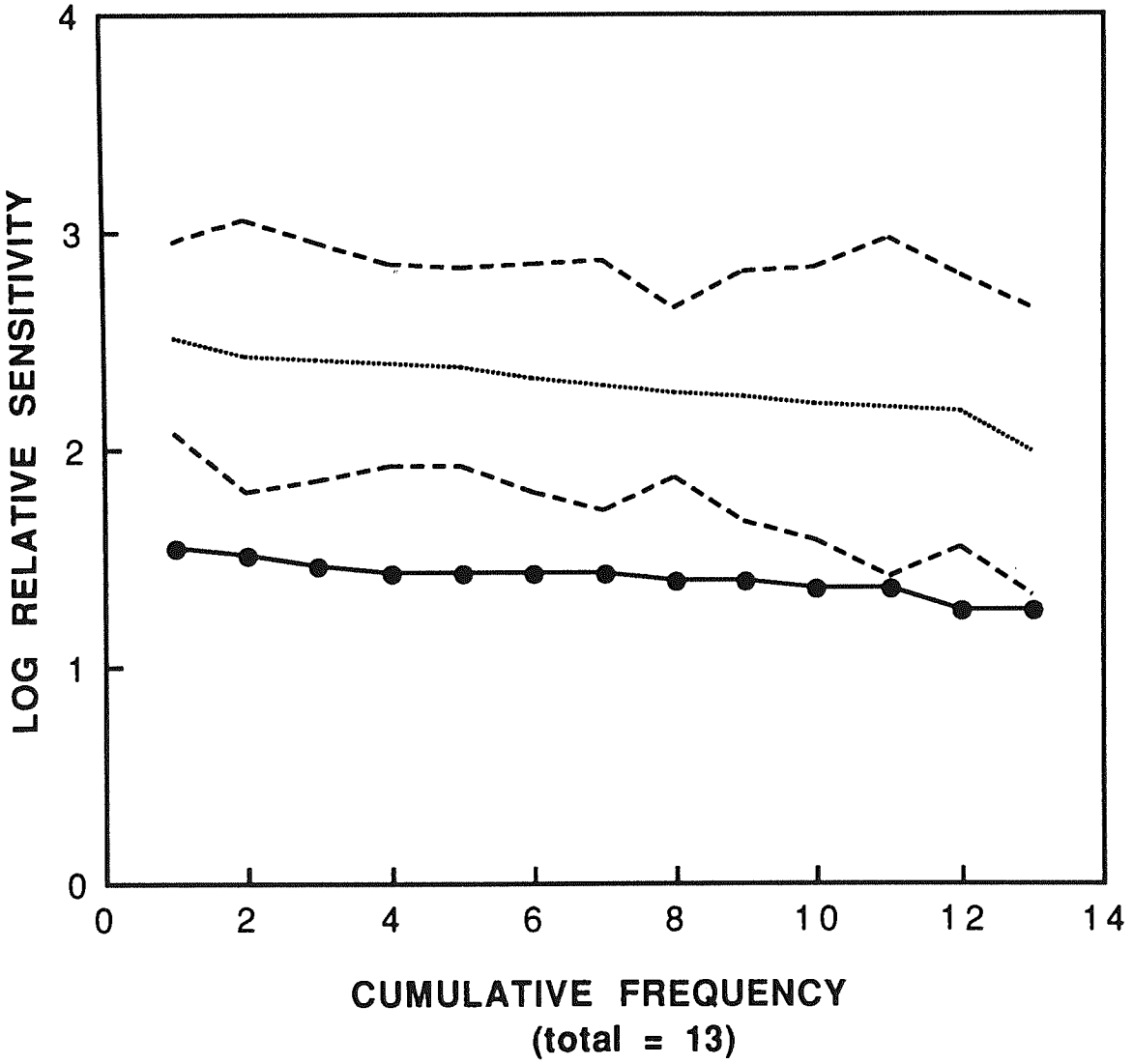



Figure 7.9. Cumulative frequency graph (Bebié curve) of the pointwise blue-on-yellow sensitivity values of the 13 point custom program (closed circles) for diabetic 12. The middle dotted line represents the mean value of the normal subjects, whilst the upper and lower dashed lines represent the 95% confidence limits (± 2 SDs) of the range of normal values.

Diabetic 15 was a 52 year old male and a Type II non-insulin dependent diabetic taking oral hypoglycaemic drugs of 2 years duration (Table 7.1.). Retinal photography revealed no signs of diabetic retinopathy. He exhibited an abnormal blue-on-yellow mean sensitivity, whilst low white-on-white, high white-on-white and yellow-on-yellow mean sensitivities were found to be normal (Table 7.2.). The cumulative frequency graph of the pointwise blue-on-yellow results of diabetic 15 is shown in Figure 7.10. A diffuse loss of blue-on-yellow sensitivity was exhibited. The blue-on-yellow pointwise sensitivity improved slightly when the test was repeated (Figure 7.10.) but blue-on-yellow mean sensitivity was still found to be abnormal. This between-examination improvement in sensitivity can be attributed to a residual learning effect despite the extensive training regime undertaken prior to data collection.

Diabetic 17 was a 54 year old female and a Type I insulin dependent diabetic of 10 years duration (Table 7.1.). Retinal photography revealed no signs of diabetic retinopathy. She exhibited an abnormal blue-on-yellow mean sensitivity, whilst low white-on-white, high white-on-white and yellow-on-yellow mean sensitivities were found to be normal (Table 7.2.). The cumulative frequency graph of the pointwise blue-on-yellow results of diabetic 17 is shown in Figure 7.11. A diffuse loss of blue-on-yellow sensitivity was exhibited. The blue-on-yellow sensitivity loss was confirmed when the test was repeated on a second occasion (Figure 7.11.).

Diabetic 21 was a 64 year old female and a Type II non-insulin dependent diabetic taking oral hypoglycaemic drugs of 7 years duration (Table 7.1.). Retinal photography revealed background diabetic retinopathy comprising exudates within approximately 5° of the fovea and panretinal photocoagulation beyond approximately 10° eccentricity. She exhibited an abnormal blue-on-yellow mean sensitivity and a low high white-on-white mean sensitivity, whilst the results for the low white-on-white and yellow-on-yellow conditions were found to be within normal limits (Table 7.2.). The cumulative frequency graph of the pointwise blue-on-yellow results of diabetic 21 is shown in Figure 7.12. A diffuse loss of blue-on-yellow sensitivity was exhibited.

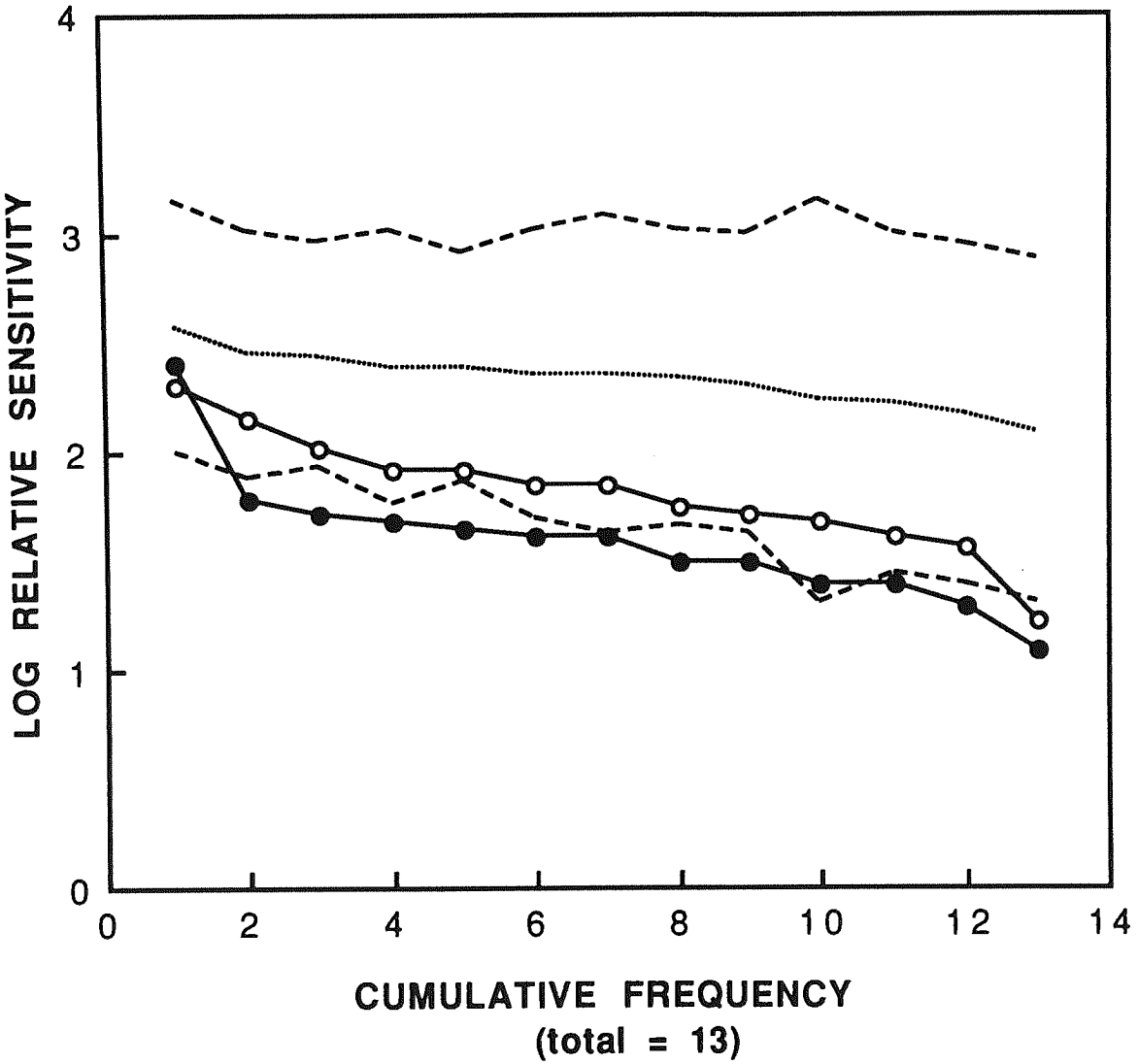



Figure 7.10. Cumulative frequency graph (Bebié curve) of the pointwise blue-on-yellow sensitivity values of the 13 point custom program (closed circles) for diabetic 15. The open circles represent blue-on-yellow sensitivity when repeated on a separate occasion. The middle dotted line represents the mean value of the normal subjects, whilst the upper and lower dashed lines represent the 95% confidence limits (± 2 SDs) of the range of normal values.

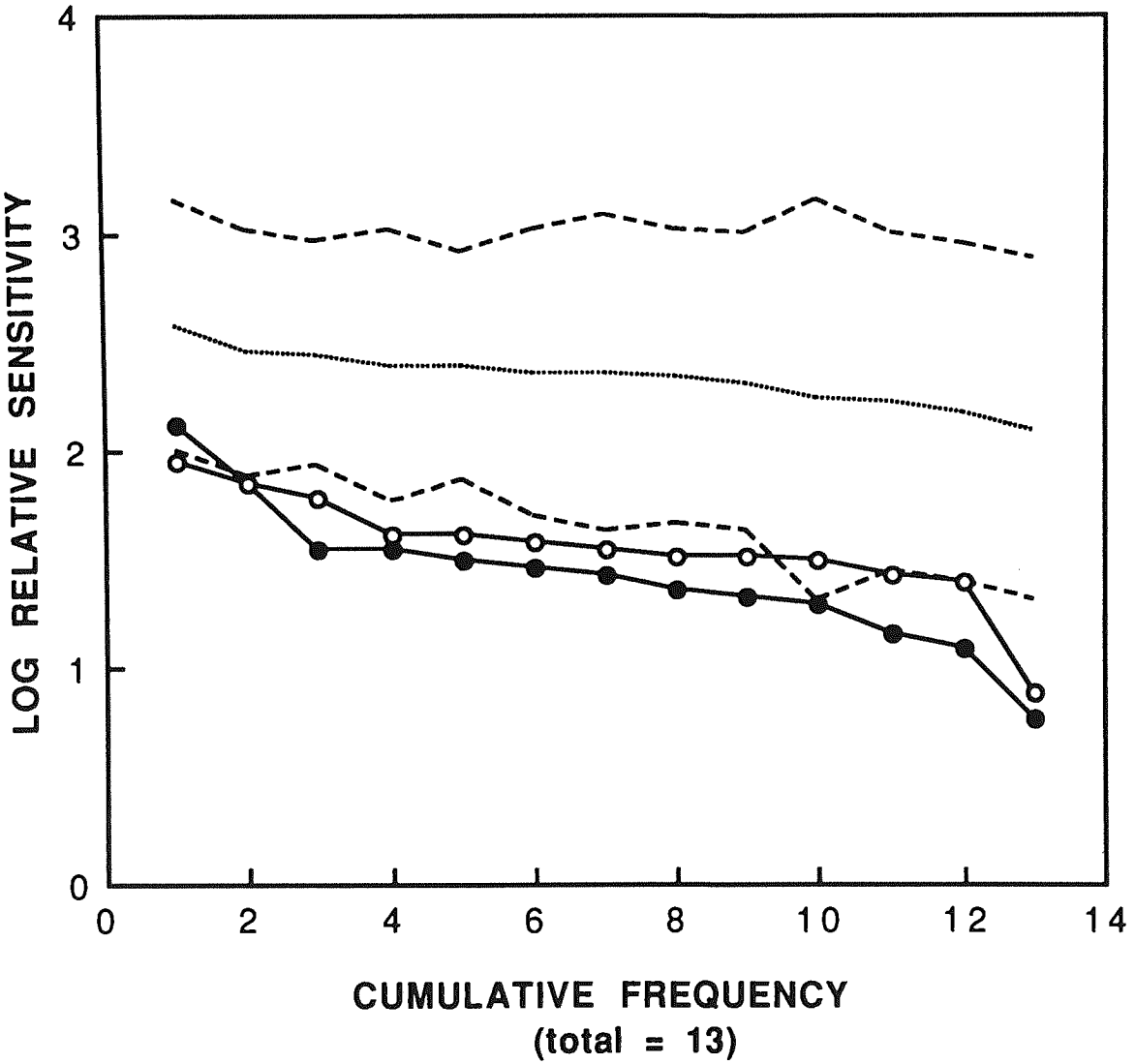



Figure 7.11. Cumulative frequency graph (Bebié curve) of the pointwise blue-on-yellow sensitivity values of the 13 point custom program (closed circles) for diabetic 17. The open circles represent blue-on-yellow sensitivity when repeated on a separate occasion. The middle dotted line represents the mean value of the normal subjects, whilst the upper and lower dashed lines represent the 95% confidence limits (± 2 SDs) of the range of normal values.

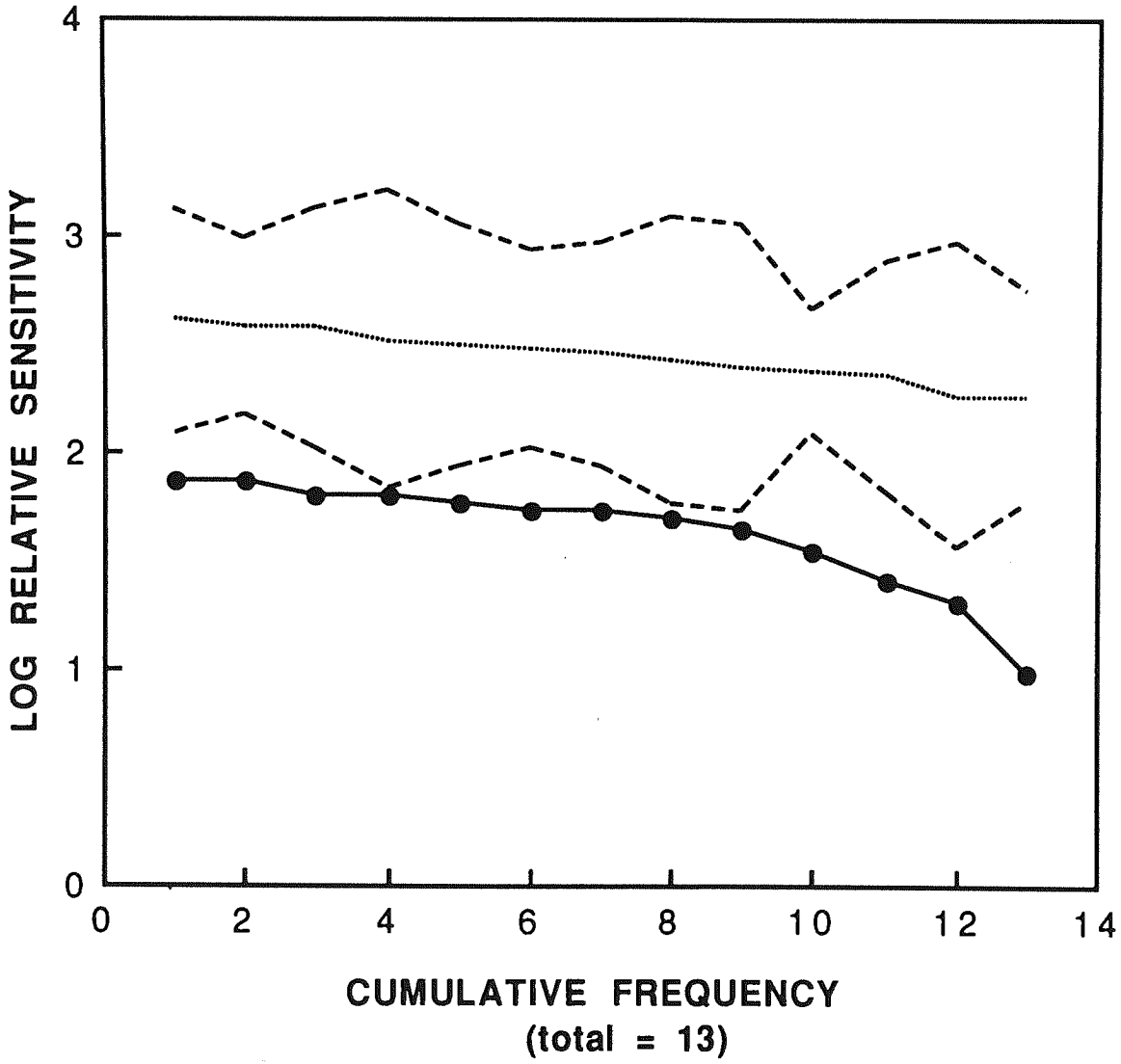



Figure 7.12. Cumulative frequency graph (Bebié curve) of the pointwise blue-on-yellow sensitivity values of the 13 point custom program (closed circles) for diabetic 21. The middle dotted line represents the mean value of the normal subjects, whilst the upper and lower dashed lines represent the 95% confidence limits (± 2 SDs) of the range of normal values.

The analysis showed that the reduction in blue-on-yellow sensitivity was diffuse rather than foveal which rendered a consideration of the spatial characteristics of the sensitivity loss unnecessary.

## 7.4. Discussion.

### 7.4.1. Ocular media absorption in the diabetic eye.

The greater magnitude of ocular media absorption for the diabetic patients compared to the normal subjects is in agreement with previous studies based upon objective (Weale, 1982; van Best et al, 1985) and upon psychophysical (Lutze and Bresnick, 1991) techniques. Indeed, it has been suggested that the estimation of ocular media absorption may provide a measure of the long-term control of glucose metabolism in diabetic patients (Lutze and Bresnick, 1991). The results of the current study show, however, that the magnitude of ocular media absorption is significantly increased in all diabetic patients irrespective of type, duration and control.

The elevated plasma glucose levels exhibited by diabetic patients have been hypothesized to result in the nonenzymatic glycosylation of lens crystallins and consequently to disturb the short range molecular order of the crystallins (Lutze and Bresnick, 1991). Such a process would lead to an increase of ocular media absorption. The increase in the sagittal width (Laurent et al, 1981; Huggert, 1953; Brown and Hungerford, 1982; Sparrow et al, 1990) and the refractive index (Marmor, 1973; Gwimup, 1976; Bron et al, 1993) of the diabetic crystalline lens may also explain the greater magnitude of ocular media absorption. The increase in ocular media absorption occurs at an early stage in the time course of the diabetic condition since diabetic patients of short duration (eg diabetic 25; 1yr duration) were found to have a significant increase in the magnitude of this function. It could be hypothesized that the initial disturbance of glucose metabolism results in a relatively abrupt increase in ocular media absorption which is a profound and subsequent feature of the diabetic eye.

The results also indicate that unless the attenuation of short wavelength light by the ocular media is considered in the diabetic eye any evaluation of the SWS pathway would result in an under estimation of sensitivity and consequently a loss of specificity of the colour vision test or psychophysical procedure.

7.4.2. Blue-on-yellow perimetry in diabetes.

An abnormal blue-on-yellow mean sensitivity was obtained in five diabetic (11, 12, 15, 17 and 21) patients who exhibited either low or normal results for the other three perimetry conditions (Table 7.2.). Conversely, a normal blue-on-yellow result was exhibited by three diabetic patients (8, 9 and 14) with low mean sensitivities to one or more of the other three perimetry conditions. These findings suggest either a limitation of the experimental design or that blue-on-yellow perimetry provides information of visual dysfunction in diabetic patients that is additional to and not always in agreement with that of conventional perimetry. Long-term follow-up is necessary, however, to determine the significance of SWS pathway sensitivity loss in the presence of normal white-on-white and MWS / LWS pathway sensitivity in the diabetic eye.

Of the 5 diabetic patients with an abnormal blue-on-yellow mean sensitivity, two patients (15 and 17) did not exhibit retinopathy as assessed by retinal photography. In both patients, the blue-on-yellow sensitivity loss was confirmed when the test was repeated on a separate occasion. The findings suggest that SWS pathway sensitivity loss can occur in the absence of retinopathic abnormalities. The lack of a relationship between the degree of retinopathy and blue-on-yellow sensitivity is in agreement with some studies which have assessed various visual functions (Moloney and Drury,1982; Hardy et al, 1992; Brinchmann-Hansen et al, 1993) but is contrary to the results of other studies (Begg and Lakowski, 1980; Bresnick et al, 1985; Adams et al, 1987a; Greenstein et al, 1990; Brinchmann-Hansen et al, 1992b, c and 1993). The interpretation of diabetic retinopathy as a neurosensory disorder rather than a condition limited to the retinal vasculature might explain the SWS pathway sensitivity loss in the absence of retinopathic abnormalities (Bresnick, 1986; Hardy et al, 1992; Greenstein et al, 1993; Brinchmann-Hansen et al,

1993). In addition, it is possible that microvascular abnormalities or retinal nonperfusion were missed in some diabetic patients since fluorescein angiography is the more appropriate procedure rather than retinal photography for the detection of early retinopathy (Greenstein et al, 1990). Furthermore, diabetic patients taking oral hypoglycaemic agents were included in the study. These drugs may adversely influence colour discrimination (Lyle, 1974) and this could provide an alternative explanation for the abnormal blue-on-yellow mean sensitivity of diabetic 15 (Table 7.1) who did not exhibit any retinopathy.

All of the diabetic patients with an abnormal blue-on-yellow mean sensitivity exhibited visual acuities of 6/5 or better. Conversely, the diabetic patient with the poorest visual acuity exhibited a normal mean sensitivity (diabetic 23; visual acuity 6/9) to all four perimetry conditions (Table 7.2.). From these limited results, visual acuity appears to be an insensitive measure of early diabetic visual dysfunction. Such a finding is consistent with the literature (Zwas et al, 1980; Adams, 1982; Zisman and Adams, 1982; Adams et al, 1987a; Greenstein et al, 1989a; Greenstein et al, 1990 and 1992).

Undoubtedly, learning and fatigue will have an influence on the outcome of the results. The learning effect was minimized, however, by the training of volunteers in the psychophysical procedures to be employed prior to the data collection visit, whilst the fatigue effect was minimized by allowing frequent breaks within- and between-tests. In addition, learning and fatigue were minimized by repeating tests on a separate occasion if a progressive change of sensitivity was suspected and by randomizing the order in which the four perimetry conditions were presented. Furthermore, in order to determine any systematic improvement (ie learning) or deterioration (ie fatigue) in sensitivity over the 3 repeats of the custom program for the blue-on-yellow procedure, the mean sensitivity obtained for the first custom program was compared to that of the third custom program for each of the diabetic patients (Figure 7.13). The difference in mean sensitivity between the first and third custom program was within ±0.20 log units for 21 of the 27 diabetic patients. The COR for the repeatability of blue-on-yellow sensitivity was ±0.30 log units.

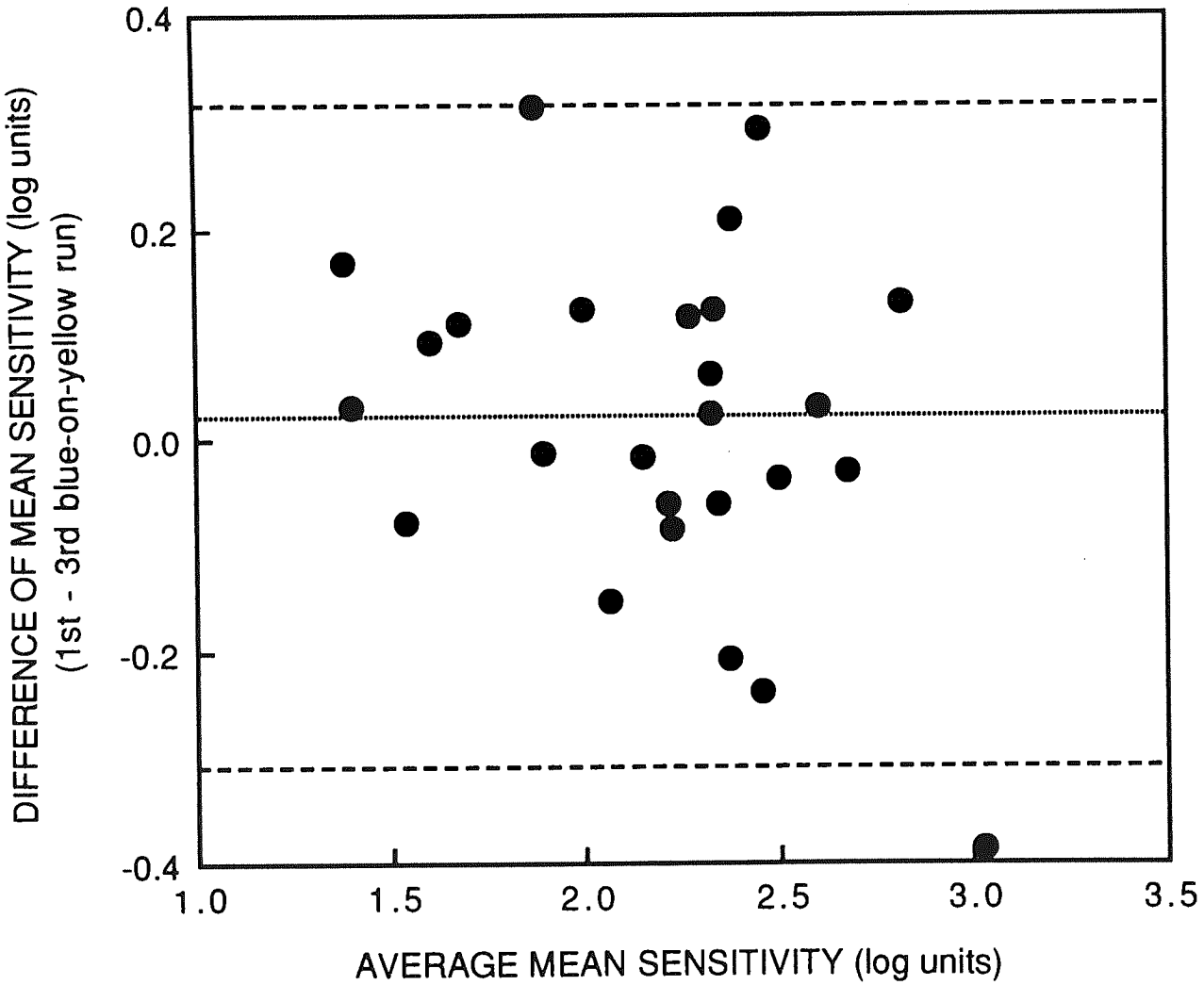



Figure 7.13. The difference in blue-on-yellow mean sensitivity between the first and third repeat of the custom program as a function of the mean value of the two repeats for the 27 diabetic patients. The mean and 2 SDs of the differences are shown for reference.

Fifteen patients exhibited a decrease in sensitivity between the two custom programs, whilst 12 patients exhibited an increase in sensitivity. The data shows no obvious sign of a systematic change in sensitivity and the effects of learning and fatigue were therefore considered to be minimal.

The number of subjects recruited for the normal database influences the position and spread of the 95% range of normal values. This has a major influence on the confidence with which the result of a given diabetic can be assigned as normal or otherwise. Indeed, the 61-70 year old normal subjects exhibited an unexpectedly high group mean blue-on-yellow mean sensitivity (Figure 7.7). The recruitment of a larger normal database might be anticipated to reduce the 61-70 year old group mean blue-on-yellow mean sensitivity. A larger normal database, however, would also narrow the 95% range of normal values.

Any error introduced as a result of estimating macular pigment absorption in the diabetic patients is minimal. The OCLI blue dichroic stimulus filter effectively reduces the influence of macular pigment absorption by a factor of 0.66. In addition, the position of stimuli within the custom program ensures that macular pigment absorption will only have a major influence on the foveal stimulus (assuming eye movements are within approximately 2° of fixation). As a result, an error in the estimation of foveal macular pigment absorption of 1.00 log unit relative to 460nm will result in an error of mean sensitivity of 0.05 log units when utilizing the OCLI blue dichroic filter.

### 7.4.3. SWS pathway vulnerability.

The findings suggests that the SWS pathway exhibits a greater vulnerability to the effects of the diabetic disease process. The increased vulnerability of the SWS pathway particularly in diabetes and glaucoma has been studied previously (Hood et al, 1984; Kalloniatis and Harwerth, 1989). Various theories have been hypothesized to explain the increased vulnerability of the SWS pathway. The SWS cones comprise between 2% (Walraven, 1974) to 13% (Marc and Sperling, 1977) of the total retinal cone population. The relative scarcity of SWS cones (Bowmaker and Dartnall, 1980; Williams et al, 1981b;

Mansfield et al, 1984) has been suggested to result in an increased susceptibility of the SWS pathway to the effects of disease processes (Mollon, 1982a). Hood and co-workers (1984) argued, however, that a scarcity of SWS cones does not necessarily result in a greater vulnerability.

Numerous studies have shown that the SWS cones are more susceptible to chemical (Marc and Sperling, 1977; de Monasterio et al, 1981) and light (Harwerth and Sperling, 1975; Sperling et al, 1980) induced damage than either the MWS or LWS cones. In addition, the appreciable contribution of the SWS cones to colour vision, despite their relative scarcity, suggests a neural amplification process unique to the SWS pathway. This neural amplification has been suggested to result in the greater spatial and longer temporal summation characteristics of the SWS pathway (Mollon, 1982b) and it may be that this mechanism is vulnerable to impairment as a result of disease (Sample et al, 1988c). Furthermore, signals from the SWS cones are confined to the B-Y colour opponent channel, unlike signals from the MWS and LWS cones which can be carried by the R-G and B-Y colour opponent channels and by the R+G non-opponent luminance channel. Consequently, a disease process that selectively effects only colour opponent channels will disproportionately impair SWS cone function (Mollon, 1982a).

Hood and co-workers (1984) hypothesized that SWS pathway vulnerability occurs as a result of an innate limitation of the SWS pathway response range. A psychophysical procedure, the "probe-flash paradigm", was employed in conjunction with appropriately coloured probe, flash and adapting fields to isolate the SWS and LWS pathways. The technique confirmed that the SWS pathway had a more limited response range than the LWS pathway. If retinal disease is assumed to decrease the response range of all pathways equally then increment threshold measurements of the SWS pathway will be affected relatively more than those of the LWS pathway.

Kalloniatis and Harwerth (1989) hypothesized that the differential adaptation properties of the three cone types explained SWS pathway vulnerability. The MWS and LWS pathways

adapt (ie reach Weber behaviour) at lower background intensities than the SWS pathway (Stiles, 1959; Yeh et al, 1989). If retinal disease is assumed to reduce the sensitivity of the three cone pathways equally then this would imply that both the test and field threshold should be elevated equally and therefore a 45° shift of the threshold-versus-intensity curve along the Weber line would result (assuming Weber behaviour). Kalloniatis and Harwerth (1989) predicted that the differential adaptation characteristics of the cone pathways would result in a selective increase of the SWS pathway threshold. Indeed, increment threshold spectral sensitivity functions derived from a series of threshold-versus-intensity curves of a rhesus monkey showed that both the SWS and MWS pathways were affected equally at low adapting levels. At the high adapting levels commonly used in clinical studies (ie 10,000 Td yellow), however, an apparent selective loss of sensitivity of the SWS pathway was found.

7.4.4. The characteristics of the sensitivity loss exhibited by diabetic patients.

The cumulative frequency graphs illustrate that the blue-on-yellow sensitivity loss exhibited by the 5 diabetic patients with abnormal results was of a diffuse type. Interestingly, in glaucomatous eyes a predominantly localized loss of blue-on-yellow sensitivity has been reported (Sample et al, 1993c). These findings indicate an overall reduction of SWS pathway sensitivity and are similar to those reported by Greenstein and co-workers (1993) who found a diffuse depression of rod sensitivity up to 30° from fixation in a sample of 18 diabetic patients with early, or an absence of, retinopathy. A reduction in the retinal sensitivity of diabetic patients with minimal retinopathic abnormalities has been attributed to either hypoxia or metabolic disturbances preceeding hypoxia (Bresnick, 1986; Hardy et al, 1992; Brinchmann-Hansen et al, 1993; Greenstein et al, 1993). Both of these mechanisms might be expected to result in a diffuse depression of retinal sensitivity (Greenstein et al, 1993). Indeed, the sensitivity of both the rods (Macaluso et al, 1992; Hirsch-Hoffmann and Niemeyer, 1992) and the blue cones (Schneck et al, 1991) have been suggested to be directly affected by the level of blood glucose. These sensitivity changes are thought to vary throughout the course of a day and to be reversible (Schneck et al, 1991).

## 7.5. Conclusion.

Ocular media absorption was found to be greater for all the diabetic patients in this study when compared to age-matched normal subjects. Indeed, diabetic patients of one year duration exhibited a significant increase in ocular media absorption which suggests that this phenomenon occurs at a relatively early stage in the time course of the diabetic condition.

Blue-on-yellow sensitivity was found to be abnormal in 5 diabetic patients with normal or low white-on-white and MWS / LWS pathway sensitivity. Blue-on-yellow perimetry, therefore, provides information on the visual function of the diabetic eye that is additional to and not always in agreement with measures of visual acuity and conventional perimetry and with the vascular integrity detailed by retinal photography. These findings may be explained by the interpretation of diabetic retinopathy as a neurosensory disorder that can affect any site along the visual pathway rather than a visible condition limited to the retina. In addition, the findings suggest a selective vulnerability of the SWS pathway to the diabetic disease process. A diffuse depression of sensitivity was a characteristic of the SWS pathway sensitivity loss. An overall reduction in retinal sensitivity was therefore indicated which can be attributed to either hypoxia or metabolic disturbances preceeding hypoxia.

# CHAPTER 8. GENERAL SUMMARY OF RESULTS AND CONCLUSIONS AND FUTURE WORK.

## 8.1. Summary of results and conclusions.

### 8.1.1. Physiological statokinetic dissociation.

The magnitude of retinal sensitivity exhibited by normal subjects was different between kinetic and static perimetry, a phenomenon termed physiological SKD. A greater sensitivity to kinetic stimuli presented at 4° per second was exhibited by all subjects. In general, the kinetic technique over-estimated static sensitivity by an average of 4.5dB. A minimal variation in the magnitude of physiological SKD was found both within- and between-subjects. Furthermore, the magnitude of physiological SKD was found to be largely independent of subject age, stimulus size, meridian and eccentricity.

Physiological SKD is a confounding factor in the quantitative comparison of static and kinetic perimetry. In addition, the presence of a physiological component should be considered in any study of SKD in visual pathway abnormality. That is, to document a disease related disturbance of SKD in a given individual, the magnitude of the abnormal SKD must fall outside the 95% confidence limits of physiological SKD. Furthermore, identical conditions must be employed for any comparison of static and kinetic sensitivity to be valid.

The hypothesis of successive lateral spatial summation as the underlying mechanism of physiological SKD (Greve, 1973) was questioned since the magnitude of this function was found to be independent of variation in stimulus size. This finding does not necessarily exclude successive lateral spatial summation as one of a number of underlying mechanisms of physiological SKD. Indeed, it may indicate a saturation point in terms of stimulus velocity and / or stimulus size at which further summation cannot occur.

8.1.2. Perimetric fatigue.

A progressive deterioration of the global indices MD and LV was found during the time course of the G1X program with the Octopus 1-2-3 both for normal subjects and for ocular hypertensive patients. The deterioration of MD was greater for the inferior hemifield and for the peripheral annulus, whilst that of LV was greater for the superior and nasal hemifields and for the peripheral annulus. In addition, a greater deterioration of SF for the nasal hemifield was found. In general, these changes were more pronounced for phase 2 and for the second eye and with increase in age. Furthermore, the introduction of breaks within the examination procedure failed to overcome the deterioration of sensitivity. The performances of the normal and ocular hypertensive groups were found to be almost indistinguishable.

The fatigue effect can be envisaged as a progressive overall depression and a concomitant change in the shape of the hill of vision. The results suggest a sinking, together with a steepening, of the hill of vision. The depression was found to be more marked in the inferior than in the superior field and more in the peripheral than in the central annulus but similar between the nasal and the temporal fields. The change in shape was more pronounced in the superior and nasal fields and in the peripheral annulus. The use of fatigue as a potential provocative diagnostic test for glaucoma can be discounted since there was a considerable overlap of results between the normal subjects and the ocular hypertensive patients.

If the conventional algorithms are to be utilized the confidence limits for the definition of abnormality should reflect the more pronounced effect of fatigue on the results from the second eye and therefore be different between the two eyes. The underlying mechanism of perimetric fatigue is unknown. The change in shape of the superior field might be associated with a progressive upper lid ptosis. Furthermore, the greater deterioration of sensitivity for the more peripheral visual field implicates the formation of a stabilized retinal image, which in turn is associated with the phenomena of Ganzfeld

blankout and / or Troxler fading. Psychological factors such as attention or vigilance may also influence retinal sensitivity.

8.1.3. SWS pathway spectral sensitivity and isolation.

A 330 $cdm^{-2}$ yellow background was chosen to maximize SWS pathway isolation when utilized in conjunction with a broad band blue stimulus filter for blue-on-yellow perimetry. Despite the relatively high background luminance, however, a measurement range comparable with that of other workers (Sample et al, 1993a; Johnson et al, 1993a and b) was achieved. A concave mirror was positioned behind the stimulus bulb of the HFA in order to image the source back on itself. A resultant increase in light output of 60% was attained.

Group mean spectral sensitivity functions, derived using the 330 $cdm^{-2}$ yellow background, demonstrated saturation of the mechanisms mediating the detection of wavelengths greater than 500nm within approximately 22° eccentricity. In addition, the SWS pathway spectral sensitivity functions varied both within- and between-subjects and were found to exhibit peak sensitivities at wavelengths of between 440nm and 470nm. After consideration of the conflicting requirements of the magnitude of SWS pathway isolation and of a viable measurement range, a stimulus wavelength of 460nm was selected for blue-on-yellow perimetry. That is, a 440nm stimulus filter would enhance SWS pathway isolation but reduce the measurement range, whilst a 470nm stimulus filter would enhance the measurement range but reduce the magnitude of SWS pathway isolation. Group mean threshold versus intensity functions derived for a 460nm narrowband stimulus demonstrated that isolation of the SWS pathway was achieved at all stimulus locations. The group mean magnitude of SWS pathway isolation was approximately 1.4 log units.

The modifications made to the HFA 640 ensured adequate SWS pathway isolation, whilst at the same time achieving a viable measurement range.

8.1.4. Pre-receptoral absorption.

Ocular media absorption exhibited an exponential increase with increase in age. Group mean ocular media absorption relative to 410nm increased by approximately one log unit between the ages of 20 and 80 years. In addition, a between-subject variation in ocular media absorption of approximately 0.80 to 0.90 log units at any given age was found. The COR for ocular media absorption relative to 410nm was found to be ±0.20 log units.

Foveal macular pigment absorption exhibited no systematic trend with age. The group mean macular pigment absorption value relative to 460nm was found to be 0.40 log units at the fovea and negligible at 5.5° eccentricity for all four meridians. Individual macular pigment absorption values varied between -0.01 and 0.84 log units at the fovea, whilst those at 5.5° eccentricity varied between -0.50 to 0.70 log units. The COR for macular pigment absorption relative to 460nm was found to be ±0.28 log units at the fovea and ±0.34 log units at 5.5° eccentricity.

The magnitude of ocular media absorption was demonstrated to reduce with increase in stimulus wavelength. Indeed, when utilizing a 460nm narrowband stimulus filter for blue-on-yellow perimetry, the assessment of ocular media absorption in the absence of cataract is clinically unnecessary. Furthermore, relative to a 460nm narrowband filter, the COR value for ocular media absorption was calculated to be ±0.04 log units. Therefore, by deriving ocular media absorption relative to a longer wavelength than 410nm the reliability of the test procedure was effectively improved.

The attenuation by the macular pigment of blue-on-yellow sensitivity extended out to approximately 4° to 5° eccentricity. Indeed, the finding of large macular pigment absorption values at 5.5° eccentricity in some individuals was explained by the overlap of the size V stimulus onto areas of the retina influenced by the macular pigment and by eye movements. Furthermore, the combined effect of macular pigment absorption and small involuntary eye movements can be predicted to increase the magnitude of local short-term fluctuation for blue-on-yellow perimetry within the immediate macular region.

8.1.5. Ocular media absorption and SWS pathway sensitivity in the diabetic eye.

The magnitude of ocular media absorption relative to 410nm for individual diabetic patients was significantly greater than that of the age-matched normal 95% confidence range irrespective of the type, duration and control of diabetes. Indeed, diabetic patients of relatively short duration were found to exhibit an increase in ocular media absorption.

An abnormal blue-on-yellow sensitivity was obtained in five diabetic patients who exhibited normal visual acuities and either a normal or a borderline mean sensitivity both to conventional white-on-white and MWS / LWS stimuli. In addition, two of these patients showed no signs of retinopathy. Furthermore, the blue-on-yellow sensitivity loss was characterized by a diffuse depression of sensitivity.

Failure to consider the attenuation of short wavelength light by the ocular media in the diabetic eye would result in an under estimation of blue-on-yellow sensitivity and a loss of specificity of the technique.

The findings suggest that blue-on-yellow perimetry provides information on the visual function of the diabetic eye that is additional to that of visual acuity, conventional perimetry and conventional retinal photographic documentation. Furthermore, the results indicate that the SWS pathway possesses a greater vulnerability to the diabetic disease process than the pathways responsible for the detection of white-on-white and yellow-on-yellow stimuli.

## 8.2. Future work.

The suggestions for future work result from the natural outcome of the study. That is, more questions instinctively arise as a consequence of an increased understanding of a subject. The suggestions also attempt to address some of the inadequacies and inconsistencies in the literature on the topics covered in the study and of perimetry as a whole.

### 8.2.1. Statokinetic dissociation.

The investigation of the underlying mechanisms of SKD both in normal subjects and in patients with visual pathway abnormalities is the logical progression of this area of research. This information should provide an insight into the processing of spatial and temporal vision and the mechanisms of disease processes. The precise control, however, of the temporal and spatial characteristics of stimuli and of subject variables such as reaction time is a pre-requisite of these studies. Techniques which exclude the influence of stimulus velocity, therefore, such as flicker perimetry or modulated sinusoidal wave gratings, should be exploited to elucidate the distinct characteristics of spatial and temporal sensitivity within a given individual (Plant, 1986; Plant and Wilkins, 1988; Osako et al, 1991b). In addition, the derivation of spatiotemporal threshold surfaces at various stimulus locations will emphasize differences of spatial and temporal sensitivity. Furthermore, by applying these techniques to various disease processes at defined anatomical locations along the visual pathway, it may be possible to localize the underlying mechanisms of SKD.

### 8.2.2. Perimetric fatigue.

The introduction of rapid test programs is a logical step for the advancement of automated perimetry. This goal can be achieved by either developing faster thresholding algorithms (Weber, 1991 and 1992) or by reducing the number of stimulus locations within the test program (de la Rosa et al, 1990 and 1992; Weber and Diestelhorst, 1992). It is important, however, that gains in efficiency (ie time) are not at the expense of the reliability (ie

accuracy) of the procedure. In particular, algorithms which adjust the thresholding step size according to the slope of a given individuals frequency-of-seeing curve appear to offer considerable gains in efficiency (Weber, 1991 and 1992).

An understanding of the mechanism of perimetric fatigue may result in the identification of the causative factors of this phenomenon. The Troxler effect and the formation of a stabilized retinal image have been implicated as possible factors, whilst the vigilance decrement and the process of habituation have also been hypothesized as contributors towards the fatigue effect. The development of test procedures which overcome such causative factors would seem to offer an alternative means of combating perimetric fatigue. Stabilized retinal images are suppressed by allowing freedom of eye movement across a visual field of varying contrast. In addition, attempts to make the perimetric examination enjoyable and challenging rather than tedious should counteract the vigilance decrement and the process of habituation.

### 8.2.3. Blue-on-yellow perimetry.

There is a pressing need to systematically examine the dependency of SWS pathway isolation on both the spectral transmission characteristics of the stimulus filter and the background luminance under the conditions of blue-on-yellow perimetry. That is, threshold versus intensity functions should be derived for stimuli of various peak wavelengths and band transmissions. This information can be used to determine stimulus conditions for blue-on-yellow perimetry which satisfy the conflicting requirements of SWS pathway isolation and the dynamic range of the instrument. Subsequently, the standardization of stimulus parameters for blue-on-yellow perimetry could then be undertaken.

### 8.2.4. Pre-receptoral absorption.

The adoption of blue-on-yellow perimetry as a routine clinical test will depend not only on a demonstrable increase in the sensitivity and specificity of the technique when compared to conventional perimetry, but also on the ease of application of the test. In

particular, the psychophysical procedure employed to assess ocular media absorption is time consuming. Objective (Johnson et al, 1993c) and statistical (Sample et al, 1993c) procedures have recently been proposed to overcome the necessity for the psychophysical assessment of ocular media absorption. Alternatively, the results of the current study suggest that the effects of ocular media absorption can be minimized in the normal eye by careful consideration of the wavelength characteristics of the stimulus employed for blue-on-yellow perimetry. Consequently, the relationship between ocular media absorption and stimulus wavelength should also be considered in the standardization of the stimulus parameters for blue-on-yellow perimetry.

The psychophysical assessment of macular pigment absorption is a lengthy and a complex procedure. The development of objective techniques for the quantification of macular pigment absorption is necessary if blue-on-yellow perimetry is to be employed in conjunction with macular programs such as program 10-2 of the HFA. Fundus reflectometry (Kilbride et al, 1989) may provide an objective and rapid estimation of macular pigment absorption. Alternatively, the influence of macular pigment absorption can be minimized by employing stimuli at 5° eccentricity or greater from the fovea and with spectral transmission characteristics that avoid the peak wavelength of the macular pigment absorption spectra.

8.2.5. Ocular media absorption and SWS pathway sensitivity in the diabetic eye.

The implications of an increased ocular media absorption in diabetic patients are uncertain. Indeed, the magnitude of ocular media absorption in a given diabetic patient has been suggested to be a measure of the long term control of glucose metabolism (Lutze and Bresnick, 1991). The results of the current study, however, indicate that ocular media absorption is significantly increased at an early stage of the diabetic disease process. Future work should examine the relationship between ocular media absorption, duration of diabetes and long term glucose control and, in particular, relate these findings to the reliability of the test procedure utilized to assess ocular media absorption. The

extent to which the increased magnitude of ocular media absorption is determined by the duration of diabetes and the control of glucose metabolism could then be evaluated.

The relevance of the SWS pathway sensitivity loss exhibited by the 5 diabetic patients described in Chapter 7 is unknown. Long-term follow-up of these patients is necessary to determine whether an SWS pathway sensitivity loss is indicative of future vascular dysfunction as indicated by reductions in visual acuity and conventional white-on-white perimetric sensitivity. In addition, future studies should employ larger numbers of normal subjects and diabetic patients to increase the statistical power of the results. Furthermore, fluorescein angiograms and grading of the severity and location of lesions is required to detect the earliest vascular changes and accurately relate SWS pathway sensitivity to the degree of retinopathy.

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APPENDICES.

A.1. Supporting publications.

This thesis is based on the following publications:

Hudson C and Wild JM: Assessment of physiologic statokinetic dissociation by automated perimetry. Investigative Ophthalmology and Visual Science 1992; 33: 3162 - 3168.

Hudson C, Wild JM, and O'Neill EC: Fatigue effects during a single session of automated static threshold perimetry. Investigative Ophthalmology and Visual Science. In press.

Hudson C, Wild JM and Archer-Hall JM: Maximizing the dynamic range of the Humphrey Field Analyzer for blue-on-yellow perimetry. Ophthalmic and Physiological Optics 1993; 13: 405-408.

Flanagan JG, Moss IM, Wild JM, Hudson C, Propokopich L, Whitaker DJ and O'Neill EC: Evaluation of Fastpac - a new strategy for threshold estimation with the Humphrey Field Analyzer. Graefe's Archive for Clinical and Experimental Ophthalmology. 1993; 231: 465-469.

Hudson C, Wild JM and Hussey MK: Physiological statokinetic dissociation (SKD) by automated perimetry. Noninvasive Assessment of the Visual System, Santa Fe, New Mexico, USA, Technical Digest 1992; 1: 2 - 5.

Hudson C and Wild JM: Increment threshold spectral sensitivity functions on coloured backgrounds: Implications for colour perimetry. Noninvasive Assessment of the Visual System, Monterey, California, USA, Technical Digest 1993; 3: 260 - 263.

Hudson C and Wild JM: The influence of pre-receptoral absorption on blue/yellow automated perimetry. Perimetry Update 1992-93, Proceedings of the Xth International Perimetric Society Meeting. Mills RP, editor. Amsterdam, New York, Kugler Publications. 1993: 451-457.

Hudson C, Wild JM, Searle AET and O'Neill EC: The magnitude and locus of perimetric fatigue in normals and OHTs. Perimetry Update 1992-93, Proceedings of the Xth International Perimetric Society Meeting. Mills RP, editor. Amsterdam, New York, Kugler Publications. 1993: 503-507.

Investigative Ophthalmology & Visual Science, Vol. 33, No. 11, October 1992


# Assessment of Physiologic Statokinetic Dissociation by Automated Perimetry

Chris Hudson and John M. Wild

Graefe's Arch Clin Exp Ophthalmol (1993) 231:465–469

Graefe's Archive
for Clinical and Experimental
Ophthalmology


# Evaluation of FASTPAC: a new strategy for threshold estimation with the Humphrey Field Analyser

John G. Flanagan[1], Ian D. Moss[2], John M. Wild[2], Chris Hudson[2], Lisa Prokopich[3], David Whitaker[2], Eamon C. O'Neill[4]

Technical Note

# Maximizing the dynamic range of the Humphrey Field Analyzer for blue-on-yellow perimetry

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# Fatigue Effects During a Single Session of Automated Static Threshold Perimetry

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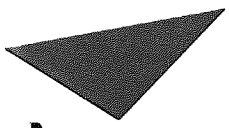

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