THE EFFECT OF BETA-ADRENERGIC RECEPTOR ANTAGONISTS ON THE TEMPORAL ACCOMMODATIVE RESPONSE

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Doctor of Philosophy

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SUMMARY

In this thesis a modified Canon IR optometer was used to record static and continuous responses of accommodation during sustained visual tasks. The instrument was assessed with regard to the ocular exit pupil used, its frequency response and noise levels. Experimental work concerned essentially the temporal characteristcs and neurological basis of the accommodative mechanism.

In the absence of visual stimuli, the accommodative system assumes a resting or tonic accommodative (TA) position, which may be modified by periods of sustained fixation. The rate of regression from a near task to TA in darkness has exhibited differences between regression rates for emmetropes (EMMs) compared with late-onset myopes (LOMs). The rate of accommodative regression from a task set at 3D above TA was examined for a group of 10 EMMs and 10 LOMs for 3 conditions: saline, timolol and betaxolol. Timolol retarded the regression to TA for a sub-group of EMMs. The patterns of regression for the remaining emmetropes mirrored that for the LOMs, the drugs showing no difference in rate of regression compared with the saline condition. This provides support for the conjecture that LOMs and certain EMMs appear to be deficient in a sympathetic inhibitory component to the ciliary muscle which may attenuate adaptational changes in tonus and which leave them susceptible to the development of LOM.

It is well established that the steady-state accommodative response is characterised by temporal changes in lens power having 2 dominant frequency components: a low frequency component (LFC: < 0.6Hz) and a high frequency component (HFC: 1.0-2.2Hz). This thesis investigates various aspects of these microfluctuations of accommodation.

The HFC of accommodative fluctuations was shown to be present in central and peripheral lens zones, although the magnitude of the rms of accommodative microfluctuations was found to be reduced in the lens periphery. These findings concur with the proposal that the lens capsule acts as a force distributor, transmitting the tension from the zonules evenly over the whole of the lens surface.

An investigation into the correlation between arterial pulse and the HFC of accommodative fluctuations showed that the peak frequency of the HFC was governed by the arterial pulse frequency. It was proposed that the microfluctuations comprised a combination of neurological control (LFC) and physiological variations (HFC).

The effect of timolol maleate on the steady-state accommodative response for a group of 10 emmetropes showed that timolol reduced significantly the rms of accommodative microfluctuations in treated but not untreated eyes. Consequently, the effect was considered to be locally, rather than systemically induced.

The influence of the sympathetic system on within-task measurements of accommodation was examined by recording the accommodative response of 3 subjects to a sinusoidally moving target at 6 temporal frequencies from 0.05Hz to 0.5Hz for 3 drug conditions: saline, timolol and betaxolol. Timolol caused a reduced gain for frequencies below 0.3Hz whereas betaxolol reduced accommodative gain for all frequencies. It was proposed that the results for timolol were consistent with temporal response characteristics of sympathetic innervation of the ciliary muscle whereas the betaxolol results were thought to be a manifestation of fatigue resulting from the CNS depressant effect of the drug.

Key words: ocular accommodation, accommodative microfluctuations, ciliary muscle, beta-receptor antagonism, tonic accommodation, infra-red optometry.

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GENERAL INTRODUCTION

Modern day western society has created a social and economic environment which poses frequent demands upon the human visual system in the form of sustained periods of close work. The ocular consequences of such intense near activity have been widely examined and reports abound of a tendency to myopia with increased near visual demand. Consequently a great deal of speculation exists concerning a possible link between the accommodation system and the development of myopia. Whereas no mechanism linking near work with the development of myopia has been identified, it is well established that certain tasks can induce *latent* changes in the accommodative state. It has been proposed that the susceptibility to such latent accommodative changes, termed accommodative hysteresis, may be a pre-cursor to the development of myopia during adulthood, after the cessation of body growth, which has no clear hereditary basis (Ebenholtz, 1983). Recent pharmacological work has directed attention to the importance of the sympathetic system in attenuating adaptational changes in ciliary muscle tone following a near task (Gilmartin and Bullimore, 1987).

Of interest in this thesis therefore is the neurological basis of the accommodative mechanism, the neurological control of the nominally steady-state accommodation response and the temporal characteristics of both these aspects of accommodation. The following summary describes chronologically the progress through the work.

Instrumentation: the Canon R1 infra-red optometer

A Canon R1 infra-red optometer converted to enable continuous measurements of accommodation (Pugh and Winn, 1988, 1989) was used to measure accommodative responses for all experiments reported in this thesis. The instrument offers a number of advantages over a newly-designed laboratory-based instrument, such as ease of alignment and calibration, video monitoring of fixation, pupil independence above 3.8mm and the capability of being switched rapidly from its normal static mode of operation to its converted mode for continuous measurements of accommodation.

Continuous-recording infra-red optometers are invariably pupil area dependent and recordings are frequently plagued by artefacts from pupillary miosis and eye movements. An early methodological consideration was therefore to investigate the pupil area used by the Canon optometer in its normal and converted modes of operation. Although the manufacturer of the Canon R1 recommended a pupil larger than 2.9mm for consistent static measurements of accommodation, it was not clear whether this minimum value referred to the ocular entrance or exit pupil. Furthermore, when the Canon was used in its continuous mode of operation, it was essential to determine the extent of the exit pupil area required by the optometer to give an accurate representation of the accommodative response. The minimum pupil area necessary for artefact-free recordings of accommodation was determined using a model and human eyes. Further assessment of the performance of the optometer was made by measuring its sensitivity, frequency response and noise levels.

Autonomic control of accommodation

There is overwhelming pharmacological, physiological and anatomical evidence to support the autonomic control of accommodation being primarily due to the parasympathetic system. The importance of the sympathetic system during sustained and dioptrically demanding visual tasks is, however becoming increasingly acknowledged. Previous work using a Canon IR optometer in a quasi-static fashion has demonstrated that the magnitude of the sympathetic input to the ciliary muscle has a positive correlation with accommodative demand (Gilmartin and Bullimore, 1987). This relationship is further investigated in this thesis using an improved technique for continuous recordings of accommodation which has been used to assess pre-task, post-task and within-task accommodative performance.

Beta-adrenergic inhibition during sustained near tasks

Previous work has examined the effect of topical instillation of the non-selective beta-adrenergic receptor blocking drug timolol maleate 0.5% and a saline control on the accommodative regression patterns following a near task to pre-task tonic accommodation (TA) levels measured in darkness (Gilmartin and Bullimore, 1987). These authors were

able to deduce from this work the characteristics of the sympathetic input to the ciliary muscle during the task. It appeared that for individuals whose pre-task TAs were >0.75D, beta-receptor antagonism significantly retarded regression patterns from the near task to tonic accommodation in darkness.

The modified Canon optometer provides an opportunity to analyse further the relevance of beta-inhibition during tasks of high accommodative demand. An optometer which is capable of measuring accommodation continuously allows a more comprehensive representation into the immediate response to open-loop conditions following a near task than is possible with the Canon in its normal static mode of operation. Initial experimental considerations concerned a modification of the work of Gilmartin and Bullimore and included a comparison between the effect of a non-selective beta-receptor blocking agent, timolol maleate 0.5% with a β_1 selective drug, betaxolol HCl 0.5% on the regression patterns of accommodation from a near task to tonic accommodation levels in darkness. Betaxolol serves as a more appropriate control than saline, as its ocular hypotensive mechanism of action is likely to emulate that of timolol and produce   little, if any, effect on the beta$_2$-receptors in ciliary smooth muscle.

Steady-state ocular accommodation

The experimental work described above on the temporal characteristics of accommodation led to the measurement of steady-state accommodation as it appeared the microfluctuations of accommodation could be modified by drug treatment. Analysis of the temporal characteristics of the nominally steady-state accommodation has been made since the late 1950's, when sensitive infra-red optometers were devised which were capable of measuring small amplitude changes in accommodative power. Since this time, a number of investigators have recorded and analysed the microfluctuations, but controversy still exists as to the function, if any, of the dominant frequency components of the fluctuations. Whereas some authors propose that the high frequency fluctuations provide an odd-error cue to the accommodative control system in order to guide the initial response (Fincham, 1951; Smithline, 1974), others dispute such a role, proposing that

they are a manifestation of noise within the accommodative plant (Charman, 1983; Charman and Heron, 1988; Kotulak and Schor, 1986b).

The high frequency components of accommodative microfluctuations

A major part of this thesis concerned the examination of the dominant frequency components of the microfluctuations, particularly the high frequency components (HFCs). Charman and Heron (1988) proposed that the HFCs were a manifestation of noise in the accommodative plant. Their proposal was based on the Foucault knife-edge shadow patterns of Berny (1969) and Berny and Slansky (1970) who found that there were greater wavefront aberrations in the periphery of the lens at the points of attachment of the zonules. The proposal offered an explanation for the pupil area dependence of the HFCs evident in the work of Campbell and Westheimer (1959): accommodation measurements made with a 1mm pupil gave little evidence of a high frequency component (evident with a 7mm pupil) but an increased low frequency component was found.

Mathematical studies of the forces acting upon the crystalline lens during accommodation have concluded that the lens capsule acts as a force distributor, transmitting the zonular tension changes over the whole of the lens surface (Koretz and Handleman, 1982; 1983). It might be expected given this analysis that the frequency characteristics of accommodative fluctuations would remain constant over the entire lens surface. Consequently, a study was made to examine the characteristics of the fluctuations for different zones of the crystalline lens. To enable an adequate area of crystalline lens to be visible, a mydriatic drug was used so that 5 separate regions could be examined.

Role of the '2 Hz' component

The inter-subject variation (1.0-2.2Hz) present in the HFC of accommodative microfluctuations has not been fully accounted for by many authors and it has frequently

been nominally termed the *2 Hz* component. A functional role in providing an odd-error[*] directional cue to the accommodative control process is unlikely, as the peak frequency location for the HFC would not be expected to exhibit such marked variation. An examination of the raw data of recordings of accommodative fluctuations from previous work referred to above on the nature of the components in different zones of the crystalline lens revealed that the fast frequency oscillations appeared to possess an obvious rhythmic quality, similar in frequency to the well-documented recordings of the intraocular pressure (IOP) pulse.

Further, a number of the experimental subjects from the previous investigation had high resting pulses of over 90 beats/minute and it was noted that the peak frequency of the HFC of these subjects were often in the 1.5Hz region. These observations led to the investigation in Chapter 7 which examined the correlation between arterial pulse and the HFCs of accommodation. A highly significant correlation was found between the frequency of the arterial pulse and the peak frequency of the HFC.

The effect of exercise on HFCs

Further confirmation that the HFCs were significantly correlated with arterial pulse was possible by examining the effect of a change in pulse rate on the location of the HFCs. Consequently, the effect of exercise on the HFC location was investigated in a group of healthy subjects. The pulse rate and accommodation response were measured concurrently following a period of exercise and the change in pulse rate with recovery from exercise was then correlated with the peak frequency of the HFC.

Verification that the Canon measures accommodative microfluctuations

The amplitude of the HFCs are small, of the order 0.1D and thus it was important to determine that these changes originated in the crystalline lens and were not due to eye

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[*] Odd error: Cues to the accommodative system that have magnitude and directional properties are said to provide an odd-error cue. If the cue merely has magnitude and not sign information, it is known as an even-error cue (e.g. pure optical blur)

movements or pulsatile blood volume changes in the macula. Consequently, unilateral aphakic subjects were examined and an analysis of recordings of eye movements and accommodation made from the normal eye could be compared with recordings from the contralateral aphakic eye. No peak frequency corresponding with that of arterial pulse was found in the aphakic eye.

Changes in intra-ocular pressure and accommodative microfluctuations
Having examined the effect of a change in frequency of the accommodative HFCs induced by exercise, an appropriate extension to this work was to examine the nature of the fluctuations of accommodation under conditions of reduced intraocular pressure (IOP). It was reasoned that if the mechanisms by which arterial pulse induced the HFC were intra-ocular, changes in choroidal blood flow and IOP pulse were likely to be involved: the former inducing pulsatile changes in ciliary ring diameter from blood volume variations in ciliary body, the latter producing anterior lens surface curvature changes from resistance variations from the intraocular fluid.

The beta-adrenergic receptor antagonist timolol maleate was employed topically to determine the consequence of lowered IOP on the *magnitude* of the microfluctuations of accommodation. Recent research has demonstrated that topical timolol maleate 0.5% caused a reduction in the amplitude of the IOP pulse (Colloton and Perkins, 1986; Langham, 1990), the effect being attributed to a vasoconstriction of the choroidal blood supply (Colloton and Perkins, 1986). Further, timolol is known to cause a significant reduction in arterial pulse rate of between 6-10 beats/minute (Cinotti *et al*, 1985). The location and magnitude of the HFCs would therefore be expected to change following treatment with timolol. The effect of timolol on the magnitude and location of the HFCs was investigated and it was proposed that the method could provide a preliminary non-invasive means of examining the effect of topical beta-blockers on the eye.

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The effect of beta-adrenergic antagonists on the accommodative response to sinusoidal modulations of stimulus vergence

A recent report suggested that topical timolol maleate affects the accommodative response to rapid changes in vergence (Weber *et al*, 1989). These authors show that the response time during a rapid change in fixation from near-to-far is not affected by beta-adrenergic blockade, as it merely depends upon the elasticity of the choroid. Conversely, an accommodative change in the opposite direction requires ciliary muscle effort involving parasympathetic input, which showed a significantly reduced response time following treatment with timolol. The authors propose that the inhibitory action of timolol on the sympathetic system contributes to the faster response time from far-to-near.

This research programme commenced with the examination of the consequences of beta-inhibition during a near visual task by observing *post-task* accommodation regression patterns. Few studies have directed attention to the nature of autonomic events occurring during a task. The paucity of work in this area may be due to optical constraints as the changes induced by beta-antagonism are exceedingly small and may be masked by ocular depth-of-focus. The concluding chapter examines the nature of the autonomic input to the ciliary muscle *during* a task, by concentrating on temporal characteristics of autonomic innervation.

In the concluding experimental chapter, the accommodative gain to a sinusoidally moving target was examined for 6 temporal frequencies of target movement before and after topical instillation of timolol maleate 0.5%. The ß$_1$ selective agent betaxolol was again employed as a control in addition to saline.

CHAPTER 1

ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF ACCOMMODATION

1.1 - ANATOMY OF THE ACCOMMODATIVE MECHANISM

1.1A - The crystalline lens and zonules

The human crystalline lens is a bi-convex transparent structure, 9-10mm in diameter and suspended by the zonules between the iris and vitreous body. Its axial thickness varies with a change in accommodation and increasing age: in the latter case from about 3.5mm at birth, increasing to 5.0mm in extreme old age (Wolff, 1976). The increase in thickness with age is due to a growth process with new lens fibres being added continuously, giving the lens a layered texture (Weale, 1963; 1979; Wolff, 1976). Such a structure results in a reduction in light transmission from reflection and scattering at each layer which tends to increase with age (Sasaki *et al*, 1980). There is a variation in refractive index across the lens: the nucleus has the highest refractive power (~1.41) and the outer cortical layers possess the lowest (~1.38) (Nakao *et al*, 1969), giving the lens a gradient index (Marchand, 1978). Recent work has shown that the refractive index of the lens undergoes changes during childhood, decreasing from ~1.442 for 7 year-old children to ~1.436 at the age of 12 years (Mutti, Zadnik and Adams, 1991). Further, it appears that lens thickness decreases during this age range by ~0.11mm (Zadnik, Mutti and Adams, 1991). The lens may be divided into three main sections:

1) *The capsule* : the elastic capsule forms an envelope around the entire lens. Its thickness varies over the lens surface, being thickest on the anterior and posterior equatorial regions and thinnest at the posterior pole (Fincham, 1929). The capsule thickens and its elasticity decreases with advancing years (Fisher, 1969a).

2) *The epithelium* : situated at the anterior lens surface under the capsule, it is composed of a layer of cells which is arranged in columns near the equator where the epithelial cells elongate and are transformed into lens fibres (Wolff, 1976).

3)   *The lens fibres* : the fibres constitute the major bulk of the lens and   are

constantly being reproduced throughout life, older fibres being situated within the

lens substance, closest to the nucleus of the lens, the most recent fibres forming

the lens cortex (Wolff, 1976).
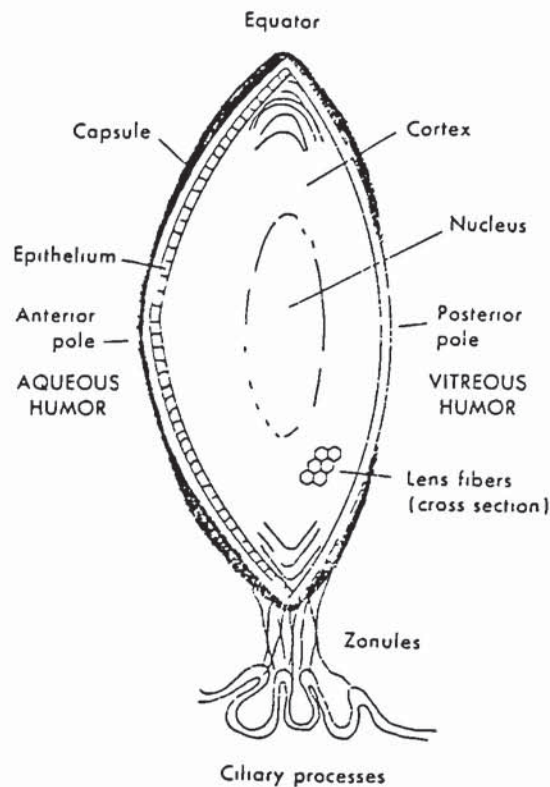
Figure 1.1: Diagram of crystalline lens and zonular apparatus illustrating the variation in capsular thickness

across the lens surfaces (redrawn after Adler, 1987).

The zonular apparatus

The crystalline lens is held in position by a number of delicate fibres which arise mainly

from the non-pigmented epithelium of the pars plana and partly from the ciliary processes

(Hogan, Alvarado and Weddell, 1971). The zonules project anteriorly, fuse with the pars

plana and anterior vitreous and are inserted in bundles into the capsule around the equator

of the lens (Raviola, 1977; Streeton, 1982). On contraction, the ciliary muscle moves

forward and inward, reducing the tension on the zonules, allowing the anterior lens

curvature to increase. The zonular fibres have Young's Modulus of elasticity of 3.5×10^5 Nm^{-1}, which is 10 times less extensile than the capsule and which shows no change in its extensile properties up to the age of 45 years (Fisher, 1986).

1.1B - Anatomy of the choroid

The importance of the choroid has been subject to conjecture by many workers studying myopia development. Its importance lies in its inherent elasticity which is thought to contribute to axial length elongation in myopia (Van Alphen, 1961; 1986). The choroid is a highly vascular connective tissue layer which lies between the sclera and retina. It is composed of 4 main layers: the suprachoroid, the stroma , the choriocapillaris and Bruch's membrane. The choroid provides a nutritive and supportive structure for the retina (Wolff, 1976; Davson, 1990).

Figure 1.2 : Diagrammatical representation of anatomy of the anterior segment of the eye illustrating the ciliary body, ciliary muscle, lens and suspensory apparatus. (From: The Human Eye in Anatomical transparencies. Bausch and Lomb press, Rochester, New York, 1945).

Choroidal blood supply

The blood supply of the choroid is via 15-20 short posterior ciliary arteries, 2 long posterior ciliary arteries and the anterior ciliary arteries. The short posterior ciliary arteries enter the eye at the optic nerve and pass forward in the choroidal stroma forming branches which supply the choriocapillaris. The latter structure is supplied by the anterior ciliary arteries and long posterior ciliaries at the equator. Venules from the choriocapillaris anastomose to form the vortex veins which are situated behind the equator (Wolff, 1976). The structure of the choroid is such that blood flows through its capillaries at an exceptionally high rate, the choroidal vascular system providing ~85% of the total ocular blood supply (Alm and Bill, 1973).

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Figure 1.3: Diagrammatical representation of the arterial supply and venous drainage of the choroid, ciliary body and iris (After Snell and Lemp, 1989).

1.1C - The ciliary body

The ciliary body lies posterior to the iris as a ring of highly vascular tissue comprising the ciliary muscle and processes (Figure 1.4). The ciliary body starts at the ora serrata where the choroid terminates. It is 5-6mm long, roughly triangular in shape, with its base facing

the iris. The inner surface comprises an anterior relatively flat surface known as the pars plana, and a posterior portion, known as the pars plicata, characterised by 70-80 vascular finger-like processes which project into the posterior chamber (Wolff, 1976).

Figure 1.4: Oblique section through the ciliary body (After Wolff, 1976)

Innervation of the ciliary body

The ciliary body is innervated by the long and short ciliary nerves. The long ciliary nerves are branches of the nasociliary nerve, which is derived from the ophthalmic division of the trigeminal nerve (Wolff, 1976). The initiation of a change in accommodative power is governed by the nature of the retinal image. Information is relayed from the retina to the calcarine (striate) cortex (area 17), then on to the peristriate cortex (area 19) and area 22. The efferent pathway from area 19 leads to the internal corticotectal tract to the hypothalamus and thereafter to the Edinger-Westphal nuclei where the parasympathetic fibres relay information via the third cranial or oculomotor nerve. The impulses resulting in accommodation are linked with those for convergence and pupillary constriction and arise from discrete cell groups in the oculomotor nucleus (Lowenstein, 1956). An examination of the mid-brain of the macaque monkey confirmed that the near triad was a cortical phenomenon which was modified at a lower level in the pre-tectum of the mid-brain (Jampel, 1959).

The oculomotor fibres are said to synapse in the ciliary ganglion (Behr, 1924; Kuntz, 1929; Ruskell and Griffiths, 1979), although this has been disputed (Westheimer and

Blair, 1973). More recent evidence supports the presence of a synapse in the ciliary ganglion (Ruskell, 1990). Thereafter the parasympathetic fibres enter the globe via the short ciliary nerves and the impulse is transmitted by the release of acetylcholine which acts on the post-synaptic muscarinic receptors of the ciliary smooth muscle (Duke-Elder, 1971). Figure 1.5 illustrates the nervous supply to the eyeball.

Figure 1.5: Autonomic innervation of the human eye :

a) parasympathetic route   b) sympathetic route

(From Bartlett and Jaanus, 1989)

1.1D - The ciliary muscle

The ciliary muscle comprises a ring of smooth muscle which follows the triangular contour of the ciliary body. The muscle is composed of longitudinal fibres, radial fibres and circular fibres, although this classification has been revised to describe the radial and circular fibres arrangement as being a meshwork of intermingling fibres (Hogan, Alvarado and Weddell, 1971). During accommodation, all the ciliary muscle fibres contract as a unit and pull the ciliary body forward and inward, releasing the tension on the suspensory ligaments (Snell and Lemp, 1989).

There is considerable evidence that the autonomic control of the ciliary muscle is via the parasympathetic nervous system, mediated by the action of acetylcholine on muscarinic receptors and that excitation initiates positive accommodation. There is mounting evidence for the importance of the sympathetic input to the ciliary muscle during sustained visual tasks, governed by the action of noradrenaline on inhibitory beta-adrenergic receptors, thus initiating negative accommodation (for review see Gilmartin, 1986).

According to Linksz (1958) the earliest reference to the possibility of a dual innervation of the ciliary muscle was by Von Graefe who, in 1855 suggested that "the choroid, like the iris, must have a double innervation, oculomotor on one side, sympathetic on the other". At the same time, Helmholtz dismissed the dual innervation theory on the basis that the muscle fibres of the ciliary body were too intertwined to allow such an innervation to be effective.

The earliest pharmacological evidence for sympathetic innervation of the ciliary muscle was made by Jessop (1886) following the observation that cocaine produced ciliary muscle relaxation after topical instillation into the human eye. Physiological evidence for the sympathetic component of accommodation was provided by many workers (e.g. Cogan, 1937; Olmsted and Morgan, 1941; Mohney *et al*, 1942). Cogan's work included observations on humans with Horner's syndrome, whereas the other workers based their

observations on animal nerve stimulation experiments. The hyperopic shifts induced by sympathetic stimulation were thought to be possibly due to the vasoconstriction of the ciliary body, inducing a greater tension on the ciliary zonular fibres, thereby flattening the lens. A number of workers supported the idea that vascular factors were important in inducing hyperopic shifts (e.g. Morgan, 1944; Fleming, 1957; Fleming and Hall, 1959).

Törnqvist (1966) clarified the role of the sympathetic system in accommodation and dismissed the importance of the vasoconstrictive element. His work involved sympathetic nerve stimulation in cynomolgus monkey (*macaca irus*) and he demonstrated that the hyperopic shift induced by sympathetic nerve stimulation could not be reversed by alpha-antagonistic drugs, despite the drug's reversing effect on ciliary volume (i.e ciliary volume increased after alpha-antagonism, but the hyperopic shift in refraction remained). Törnqvist concluded that beta-receptors in ciliary smooth muscle were responsible for distance accommodation and that the effects induced by stimulation of these receptors were inhibitory in nature. A comprehensive review of the role of the sympathetic system in accommodation is given by Gilmartin, (1986).

Temporal nature of sympathetic response

Tornqvist (1966) observed that the magnitude and time course of sympathetic activity was related to the prevailing level of parasympathetic activity. An increased level of parasympathetic tone induced pharmacologically and electrically resulted in an increased level of sympathetic inhibition, amounting to 1.5D at most, and took as long as 40s to show a maximal response. In contrast, the parasympathetic stimulation took only 1-2s to take effect. A similar magnitude of sympathetic inhibition recorded on monkey have subsequently been observed in humans. Support for the findings of Törnqvist (1966) was given by Hurwitz *et al* (1972a,b), who used vervet monkeys and stimulated the oculomotor nerve electrically in the mid-brain to investigate the change in ciliary muscle activity in conjunction with adrenergic agonist and antagonist drugs. They found that beta-inhibitory effects were only significant when the background parasympathetic activity reached -4D or more.

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1.2 - RECEPTORS OF THE ADRENERGIC SYSTEM

The main sympathetic catecholamine for the adrenergic system is noradrenaline (Von Euler, 1946). There are 4 types of receptors for noradrenaline, two classes of alpha-receptors, known as $alpha_1$ and $alpha_2$, and two beta-receptor classes: $beta_1$ and $beta_2$. This classification is based on the actions of agonist and antagonist drugs (Lands *et al*, 1967).

$alpha_1$: activation of post-synaptic $alpha_1$ receptors causes contraction of smooth muscle in blood vessels, dilator pupillae, sphincters of intestine. An exception is the relaxation of smooth muscle of the intestine.

$alpha_2$: These receptors are located presynaptically on terminals of sympathetic nerves, mediating inhibition of transmitter release. They are also in CNS and some are located postsynaptically in the periphery.

$beta_1$: These receptors predominate in heart and adipose tissue. Stimulation causes an increase in heart rate and an increased force of contraction.

$beta_2$: These receptors predominate in lung, liver and vascular smooth muscle. Activation causes a relaxation of the bronchioles. They are also present in ciliary muscle and ciliary processes (Wax and Molinoff, 1987)

Table 1.1 summarises the effect of noradrenaline on various ocular tissue.

Effector organ	Receptor type	Action on stimulation
Sphincter pupillae	alpha and beta	probably relaxation (i.e. pupillary dilation)
Dilator pupillae	mainly $alpha_1$	pupillary dilation
ciliary muscle	mainly $beta_2$	relaxation of accommodation
ciliary muscle	some $alpha_1$	inhibition
eyelid (Müller's muscle)	$alpha_1$	widening of palpebral aperture

Table 1.1: Summary of receptor classification and stimulatory effect of ocular adrenergic system.

1.2i - *In vitro* examination of receptor classification of ocular adrenergic system

The classification of receptors in ciliary muscle, ciliary body and iris are primarily based on results from experiments on animal tissue. Studies on rabbit ciliary processes have shown a predominance of beta$_2$ receptors (Bromberg, Gregory and Sears, 1980; Neufeld *et al*, 1978). Van Alphen *et al*, (1965) observed the effects of a range of adrenergic blocking agents on the dissected strips of cat, rabbit and monkey ciliary muscle.They measured muscle tension and concluded that alpha- and beta-receptors were present in cat ciliary muscle, but that beta-receptors predominated. In rabbit there was an alpha-receptor predominance, whereas in monkey, he found only beta-receptors.

Investigation of dissected human ciliary, sphincter and dilator muscles were carried out on enucleated eyes by Kern (1970). His findings revealed mainly alpha-receptors in dilator pupillae, a combination of alpha- and beta- inhibitory receptors in sphincter pupillae and beta-receptors in ciliary muscle, which were inhibitory in nature. This work was later confirmed by Van Alphen (1976) who investigated dissected strips of human ciliary muscle from eyebank eyes.

Recent experiments on humans have largely involved using ciliary muscle excised shortly after death (e.g. Lograno and Reibaldi, 1986; Wax and Molinoff, 1987). Wax and Molinoff examined receptors from the iris-ciliary body. Following treatment with a number of beta-adrenergic antagonist drugs they were able to determine the proportion of beta$_1$ and beta$_2$ subtypes in ciliary muscle and ciliary body. They concluded that 90% of the receptors in the iris-ciliary body of humans were of the beta$_2$ subtype. This work is supported by others (Lograno and Reibaldi, 1986; Zetterström and Hahnenberger, 1988).

The investigation by Zetterström and Hahnenberger into the pharmacological characteristics of human ciliary muscle involved examining strips of circular and meridional portions of ciliary muscle from excised tissue. The effects of a number of alpha- and beta-selective and non-selective adrenergic blocking drugs were examined.

They concluded that human ciliary muscle contains $beta_2$ and also $alpha_1$ receptors, both being inhibitory.

Meesmann(1952) examined the effect of sympathomimetic drugs on the enucleated eye and found a relaxation of accommodation. Lograno and Reibaldi (1986) carried out pharmacological tests on excised human ciliary muscle. In conjunction with other workers (e.g Nathanson, 1980; 1981), they were able to demonstrate using adrenergic agonists and antagonists that only $beta_2$ adrenoceptors were present in ciliary muscle. In contrast to the findings of Zetterström and Hahnenberger (1988), they concluded that alpha receptors were not present in ciliary muscle, as no ciliary muscle contraction was evident when treatment with phenylephrine, an alpha-receptor agonist, followed the $beta_2$ blockade induced by propranolol.

1.2ii - Anatomical evidence for the existence of sympathetic fibres in ciliary muscle

A number of workers identified sympathetic nerve fibres from histological animal preparations (Mohney *et al*, 1942; Wolter, 1953). More recently, Ruskell, (1973) studied cynomolgus and rhesus monkey ciliary muscle and concluded that as a mean of ~1% (range 0-2.5%) of nerve fibres were sympathetic, there was little evidence for the control of ciliary muscle function being significantly affected by the sympathetic system, although ciliary muscle function was not measured.

1.2iii - *In vivo* evidence for alpha- and beta-receptors in ciliary muscle

Phenylephrine HCl is an $alpha_1$ adrenoceptor agonist which, after topical instillation has been shown to decrease the amplitude of accommodation (Garner *et al*, 1983; Zetterström, 1988; Rosenfield *et al*, 1990), whereas the alpha-antagonist drug thymoxamine causes an increase in accommodative amplitude (Zetterström, 1988). No change in tonic accommodation (TA: see section 2.4) has been demonstrated with the above alpha-receptor agents. The consensus is that the vasoconstrictive effect of alpha-agonist agents causes a decrease in volume of the ciliary body with a consequent increase in zonular tension which results in a flattening of the anterior lens curvature and a

reduction in accommodative amplitude. It is possible however that the effect is mediated by a direct action on alpha$_1$ adrenoceptors in the ciliary muscle.

1.2iv - *In vivo* experimental work on receptor classification in humans

Experimental work involving pharmacological agents to determine the effects on ocular adrenergic receptors in humans have observed the effect of alpha- and beta-adrenergic drugs on a number of aspects of acommodation: a reduction in the *amplitude of accommodation* with the alpha agonist phenylephrine HCl has been reported (Gilmartin, Hogan and Thompson, 1984), an exponential reduction being evident with increasing concentrations of the drug - up to 3D with 1 drop of the 10% concentration (Zetterström, 1984; 1988); whereas no difference between measurements of *tonic accommodation* for 2 drug conditions: phenylephrine 2.5% and thymoxamine 0.5% compared with saline has been reported (Rosenfield *et al*, 1990). The effect of the beta-receptor antagonist timolol maleate on TA has shown conflicting results: a myopic increase in *TA* has been reported (Gilmartin, Hogan and Thompson, 1984; Zetterström, 1988) whereas no change in TA measurements with timolol has also been evident (Bullimore and Gilmartin, 1987a; Gilmartin and Bullimore, 1987). *Refractive error* : an increase of ~0.32D in myopia with phenylephrine, attributed to pupillary dilation (Zetterström, 1988); *pupil diameter* : a decrease with thymoxamine, an increase with phenylephrine (Gilmartin, Hogan and Thompson, 1984; Zetterström, 1988; Rosenfield *et al*, 1990), but no change with timolol (Gilmartin, Hogan and Thompson, 1984; Rosenfield *et al*, 1990).

Summary

A number of pharmacological studies have demonstrated the preponderance of beta$_2$ sympathetic receptors on ciliary smooth muscle. Consequently, beta-adrenoceptor antagonism of ciliary smooth muscle will occur with non-selective beta$_1$ and beta$_2$ antagonists such as timolol maleate but there will be a minimal, if any effect with the cardioselective[†] beta$_1$ blocking drug betaxolol. The latter drug would therefore act as an

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[†] Cardioselective: This term is used to denote the beta$_1$ affinity for a particular adrenergic drug, as beta$_1$ receptors predominate in the heart

appropriate control as both timolol and betaxolol will lower IOP through beta-activity thought to occur primarily in the ciliary processes (Zimmerman *et al*, 1977; Jones and Maurice, 1966; Yablonski *et al*, 1978; Coakes and Brubaker, 1978; Brubaker, Nagataki and Bourne, 1982; Reiss and Brubaker, 1983). Further analysis of the mode of action and effects of timolol maleate and betaxolol HCl will be made in the following section.

1.3 ADRENERGIC ANTAGONIST DRUGS

1.3A Timolol Maleate

Timolol is a non-selective beta-adrenergic receptor blocking drug, which, following topical instillation into the eye, competes with catecholamines such as noradrenaline for occupancy of beta-adrenergic receptor sites. First introduced in 1977 as an effective ocular hypotensive agent in the treatment of glaucoma, it produces a significant reduction in IOP - by an average of around 8-9mmHg for the 0.5% concentration which lasts for ~24 hours (Zimmerman and Kaufman, 1977a; Radius, Diamond and Pollack, 1978; Boger *et al*, 1978). The reduction in IOP is evident in the contralateral untreated eye, although to a lesser degree, thereby confirming that the drug produces a significant systemic effect (Zimmerman and Kaufman, 1977b; Radius, Diamond and Pollack, 1978; Grunwald, 1986).

Mechanism of action

The mechanism of action of topically applied timolol is largely unknown. Its major initial effect is thought to be due to its direct action on the secreting epithelia (Neufeld, 1979). It reduces aqueous production by about 30% (O'Donnell, 1984). The drug has little effect on outflow facility (Sonntag, Brindley and Shields, 1978; Zimmerman *et al*, 1977; Robinson and Kaufman, 1990). Fluorometric studies in human eyes have demonstrated topical instillation of beta-adrenergic antagonists reduce aqueous humour formation (Jones and Maurice, 1966; Yablonski *et al*, 1978; Coakes and Brubaker, 1978; Brubaker, Nagataki and Bourne, 1982), whereas topical instillation of adrenaline, an alpha- and beta-agonist, augments aqueous humour formation (Townsend and Brubaker,

1980). The latter effect is blocked by pre-treatment with timolol (Higgins and Brubaker, 1980; Thomas and Epstein, 1981). This effect is thought to be due to the interference of timolol with the agonist effect of adrenaline on outflow, and that timolol has a greater affinity for beta-receptors than adrenaline (Neufeld and Page, 1977; Neufeld, 1979).

Adrenaline has been observed to cause an increase in the facility of outflow though its $beta_2$ activity, as a combination of adrenaline and the $beta_1$ antagonist betaxolol has been demonstrated to reduce IOP to a greater extent than a combination of adrenaline and timolol (Allen and Epstein, 1986).

Measurements of aqueous humour flow in cynomolgus monkey, using fluorescein-labelled dextran following injection of timolol 0.1% into the posterior chamber, have demonstrated a 36% reduction in aqueous humour formation (Miichi and Nagataki, 1983). The effect of timolol 0.1%, 0.5% and 1% on aqueous flow in adult owl monkeys confirms a dose-related reduction. The 0.1% concentration did not produce a consensual effect, whereas the higher concentrations produced a dose-related bilateral effect (Bartels, 1988).

Ocular Penetration of timolol and rate of decay

The concentration of timolol 0.5% in human aqueous humour over a period of 7 hours following topical instillation into the eye has been found to decay exponentially in human eyes (Phillips *et al*, 1981). Results from albino rabbit experiments have shown that timolol does not remain bound at the receptors of the ciliary processes, which would be necessary to cause the prolonged decrease in aqueous humour formation evident in humans (Bartels *et al*, 1980). It is thought that timolol may bind to human pigment in the ciliary processes, allowing a slow-release of drug which prolongs its beta-blocking activity (Bartels, Liu and Neufeld, 1983).

Timolol and retinal blood flow

Timolol has been found to increase retinal blood flow by around 13% (Grunwald, 1986; Grunwald, 1990), an effect occurring in normal and ocular hypertensive eyes, which has

been attributed to an equivalent increase in perfusion pressure[#]. This conclusion is based on the finding of an increase in blood flow of ~13% and an increase in perfusion pressure of ~12% following timolol treatment. Venous diameter appears to be unaffected by timolol treatment (Grunwald, 1986; Martin and Rabineau, 1989) but a 4.1% *decrease* in arterial vessel diameter in treated eyes following instillation of timolol over a week has been demonstrated (Martin and Rabineau, 1989). No vasoconstriction was found in the untreated eye, leading to the conclusion that the retinal artery constriction was a local effect.

Timolol and choroidal blood flow

Non-invasive measurements of human choroidal blood flow are not possible at present, although tentative steps to measure choroidal blood flow using indocyanine green choroidal angiograms have been made in an attempt to counteract difficulties in measurements due to the presence of retinal and choroidal pigment and retinal vasculature (Flower and Klein, 1990). Assessments of human choroidal blood flow are usually based on measurements of the intra-ocular pressure pulse amplitude (e.g.Colloton and Perkins, 1986; Perkins, 1981; Langham, 1990). The assumption is that the ocular pulse amplitude reflects the changes in intraocular volume with each cardiac cycle (Silver *et al*, 1989). As the choroid supplies the eye with around 80% of its blood supply (Friedman, 1965; Bill, 1981), any change in amplitude of IOP pulse will mirror accurately changes in the choroidal vasculature.

The effect of topical timolol 0.25% on the pulsatile blood flow shows a decrease of 25% in humans within 1-2 hours (Langham, 1990). In support of this, a drop of 0.5% timolol

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Perfusion pressure
Blood flow though the eye is dependent on 3 factors:
1) the difference between the pressure in the arteries entering the eye and the pressure in the veins leaving it,
2) the resistance of the blood vessels,
3) the viscosity of blood.
Assuming a constant blood viscosity, the following relationship holds:
$$\text{Blood flow} = \frac{(Pa - Pv)}{R}$$
where Pa the pressure in the arteries entering the eye, Pv is the pressure in the veins, and R is the vascular resistance. The difference between Pa and Pv is the perfusion pressure.

applied topically in humans has caused a significant reduction in IOP pulse amplitude in treated eyes, but not in untreated eyes (Colloton and Perkins, 1986). Conversely, a reduction has been demonstrated to orally administered, but not topically instilled timolol (Grajewski, Ferrari-Dileo and Anderson, 1990).

Cardiovascular and respiratory effects of timolol

The effect of topical timolol on heart rate appears to show some variability (Munroe, Rundone and Kersher, 1985) and the effect is dose-dependent (Zimmerman and Kaufman, 1977a). The range of reduction in heart rate varies from 1-10 beats/minute (Berry, Van Buskirk and Shields, 1984; Cinotti *et al*, 1985). Topically applied 0.5% timolol induces a reduction in both resting and exercise heart rates even when there is an undetectable amount of timolol in plasma (Leier, Baker and Weber, 1986).

The β_2 blocking effect of timolol causes a constriction of the bronchioles in the lungs, with consequent serious implications for asthmatic sufferers (Zimmerman, Baumann and Hetherington, 1983; Van Buskirk, 1980; Prince and Carliner, 1984).

Ocular pigment and absorption of timolol

Heavily pigmented irides appear to exhibit a slower reaction to timolol, but once present, the ocular hypotensive effect may have a longer duration of action (Araie *et al*, 1982; Salminen and Urtti, 1984; Salminen, Imre and Huupponen, 1985; Menon *et al*, 1989). Consequently, an examination of the ocular consequences of timolol should involve the classification of the subject's iris pigmentation density, such as the iris pigmentation classification proposed by Seddon *et al*, (1990).

Timolol and accommodation dynamics

Timolol appears to alter the rate of accommodative response to a change in target location from far-to-near but not in the reverse direction (Weber, Tuinenburg and Van Der Heijde, 1989). The results are based on measurements of lens thickness using slit-lamp photographs. Weber and his associates concluded that their findings may be due to the sympathetic blocking activity of timolol in which the change of fixation from far-to-near

involves the unopposed action of the parasympathetic nervous system on the ciliary muscle. The unchanged time constant in the reverse fixational direction may be due to the relaxation of the ciliary muscle alone, with no input from the sympathetic system being evident, as the ciliary muscle change is primarily due to relaxation rather than an active input by the ciliary muscle to flatten the lens (Weber, Tuinenburg and Van Der Heijde, 1989). This work will be investigated further in an examination of the effect of timolol and betaxolol on the accommodative response to sinusoidally moving targets described in Chapter 10.

1.3B: Betaxolol Hydrochloride

Betaxolol HCl is a $beta_1$ adrenergic receptor blocking drug first introduced in 1979 as an ocular hypotensive agent. The main advantages of betaxolol lie in its relative cardioselectivity (β_1 activity): asthmatic patients are less likely to incur pulmonary problems induced by β_2 receptor blockade in the lung with a β_1 selective drug. A comparison of its ocular hypotensive effect with timolol has shown that although betaxolol produces an effective drop in IOP, the magnitude of reduction is marginally less than that induced by timolol (Vogel *et al*, 1989) and is of the order ~3-4mmHg for the 0.5% solution (Doughty, 1987; Berry, Van Buskirk and Shields, 1984; Allen and Epstein, 1986; Feghali and Kaufman, 1985). Conversely, an equivalent fall in IOP with timolol and betaxolol has also been reported (Levy,Boone and Ellis, 1985).

Mechanism of action

Betaxolol has been shown to suppress aqueous humour formation, producing a suppression of aqueous humour inflow of $32 \pm 13\%$ with no change in outflow facility (Reiss and Brubaker, 1983). However the precise mechanism of action for IOP reduction by which beta-antagonists such as timolol and betaxolol elicit this effect remains to be elucidated. The receptors which have been identified in ciliary processes, the main site of aqueous production are primarily $beta_2$ (75-90%) (Lesar, 1987). Nevertheless, despite its $beta_1$ selectivity, betaxolol 0.5% instilled topically in rabbit eyes has been found to block $beta_2$ receptors (Polansky and Alvarado, 1985). There is a suggestion that the reduction

in aqueous humour formation with beta-antagonists may be a consequence of a decrease in blood flow to the iris root and ciliary body (Watanabe and Chiou, 1983).

Cardiovascular effects

Betaxolol does not appear to affect arterial pulse rate or blood pressure significantly (Berrospi and Leibowitz, 1982; Stewart, Kimbrough and Ward, 1986), although a fall in arterial pulse rate of around 2 beats/minute has been reported (Berry, Van Buskirk and Shields, 1984). Although the drug is considered $beta_1$ selective, its $beta_1$ activity is said to be around 60% of the $beta_1$ activity of timolol (Mai Phan *et al*, 1987).

1.3C   Beta-blocking drugs and vasoconstriction

Neither betaxolol nor timolol is said to possess *intrinsic sympathomimetic activity*.§ It is documented however, that beta blocking drugs generally increase the sensitivity of vasoconstrictive alpha-receptors. A high level of beta-antagonism in plasma may lead to an alpha-sympathomimetic induced vasoconstriction in the orbital vessels (Thulesius and Gjöres, 1972; Waal-Manning, 1976).

There is some evidence for a constrictive effect on ocular vasculature with timolol, based on measurements of the IOP pulse amplitude (Colloton and Perkins, 1986; Langham, 1990). Timolol 0.5% has been found to reduce significantly the amplitude of the IOP pulse in treated but not untreated eyes, for which a constriction of the choroidal vasculature has been held responsible (Colloton and Perkins, 1986). Recent work supports a reduction in the amplitude of the IOP pulse by timolol (Langham, 1990; Grajewski *et al*, 1990), while experimental work on non-pigmented rabbits has demonstrated a localised vasoconstrictive effect induced by timolol, betaxolol and phenylephrine on the ciliary vasculature (Van Buskirk, Bacon and Fahrenbach, 1990).

The documented relationship between magnitude of the IOP pulse and absolute values of IOP is equivocal: whereas some suggest a positive correlation with IOP (Davanger, 1964;

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§ Intrinisic sympathomimetic activity (ISA)
A drug is said to possess ISA when it is a partial agonist in addition to having its primary antagonistic effect.

Hørven, 1970), others concluded that a negative correlation exists (Langham and To'mey, 1978). Further, it is purported that within the normal range of IOP, there is no change in the amplitude of the IOP pulse with changes in IOP (Perkins, 1981). The confusion may be linked with the differences between measuring techniques, and means of inducing raised IOP experimentally. Colloton and Perkins (1986) reasoned that the reduction in the pulse amplitude induced by timolol in their experiment could not be wholly due to the reduction in IOP level, implying that a positive correlation exists between IOP and pulse amplitude. The ocular pulse is a consequence of the pulsatile flow of blood through the intraocular arteries, primarily of the choroidal arteries, as the proportion of choroidal vessels exceeds the retinal vessels by a factor of 25 to 1 (Ulrich and Ulrich, 1985; Alm and Bill, 1973). Experimental support exists for the choroidal vasculature being primarily responsible for the IOP pulse: simultaneous recordings of retinal and choroidal blood flow in cynomolgus monkey showed that when an incremental change in IOP is induced artificially, there was a simultaneous decrease in choroidal blood flow. Further, at certain elevated IOPs, the primary contribution to the IOP pulse was from the retinal circulation (Ulrich and Ulrich, 1985). The IOP pulse does not possess a simple pressure-volume relationship with the intraocular system: it is also influenced by systemic changes in vascular pressure (Chopp et al, 1983).

1.3D Nervous control of blood flow

The retina appears to be devoid of the abundance of autonomic nervous supply that has been shown by histologic studies to be present in the uvea. Sympathetic nerves innervating the central retinal artery terminate at the level of the lamina cribrosa. In contrast, all uveal vascular beds are innervated by the adrenergic system (Laties, 1967) and the parasympathetic system (Ruskell, 1971). More recently, beta-receptor binding sites have been demonstrated in the retinal vasculature (Ferrari-Dileo, 1988).

The sympathetic system is thought to play an active role in the autoregulation of retinal blood flow when any change in perfusion pressure is counteracted to maintain a steady retinal flow (Bill, Linder and Linder, 1977). Sympathetic stimulation is known to decrease uveal blood flow in animals, while retinal blood flow remains unaffected (Alm,

1977; Bill, 1962a). This work is supported by measurements of ocular pulse amplitudes (PA) following sympathetic nerve stimulation. The PA, which is primarily derived from the uveal blood flow, has been seen to reduce as a result of sympathetic nerve stimulation (Langham and Rosenthal, 1966).

The role of the parasympathetic system remains equivocal. Vascular parasympathetic nerves have been located in the ciliary processes (Uusitalo and Palkama, 1971) and in the choroid (Ruskell, 1971). Oculomotor stimulation causes no effective change on choroidal or retinal blood flow (Stjernschantz, Alm and Bill, 1977; Alm and Törnquist, 1985). Estimations made of the net pulsatile blood flow in the human eye have been found to be 600µl per minute (Silver *et al*, 1989).

1.3E Summary

Timolol maleate is a potent non-selective beta adrenergic antagonist which is capable of reducing the IOP by significant amounts in both treated and untreated eyes. There is tentative evidence to suggest the drug has a vasoconstrictive effect on the ocular vasculature. Although the beta$_1$ selective agent betaxolol may be considered a viable control for accommodation experiments, as it is likely to lower IOP by a similar mode, no drug may be considered totally specific in its receptor action. Some beta$_2$ activity may exist following sufficient topical instillation of betaxolol, evidence for which has been reported following treatment with betaxolol (Harris, Greenstein and Boom, 1986; Elena *et al*, 1987).

The use of beta-blocking drugs in the experimental protocol for assessing the mechanism of accommodation requires that attention be given to the effects of the drugs on the choroidal vasculature. The situation is further complicated by the systemic effects induced by such agents which may affect factors such as arousal state, respiration, heart rate and other complex physiological bodily functions. Experimental work involving the use of beta adrenergic antagonists is described in Chapters 6 , 9 and 10.

CHAPTER 2

CHARACTERISTICS OF THE ACCOMMODATION RESPONSE

2.1 - THE MECHANISM OF ACCOMMODATION

2.1A - Experimental work on the accommodative mechanism

The ciliary body, processes and muscle are highly specialised structures which have profound effects not only on the accommodative mechanism, but also on the regulation of intraocular pressure: ciliary muscle contraction decreases outflow resistance to aqueous humour and is known to decrease IOP by up to 4mmHg (Coleman and Trokel, 1969; Armaly and Rubin, 1961) through a facilitation of outflow by a mechanical effect on the trabecular meshwork. Recent evidence suggests that the constriction of the pupil (induced by the potent drug carbachol) contributes substantially (~40%) to the total accommodative power available in monkeys (Crawford, Kaufman and Bito, 1990), although the magnitude of the effect is unknown in humans.

Traditional views of the mechanism underlying accommodation are based upon the relaxation theory of Helmholtz (1855): ciliary body contraction results in a reduction in the tension on the zonules, allowing the lens to be moulded by the highly elastic capsule to a more curved structure, thereby increasing the refractive power of the lens. Fincham (1937) supported the Helmholtz theory, although he disputed some elements concerning the lens elasticity. Fincham argued that the lens substance was plastic and that during accommodation, the conoid shape of the anterior lens surface was due to the difference in thickness of the capsule. This was disputed by Brown (1973) using slit-lamp photographic techniques. He concluded that the conoid anterior lens surface was due to the difference in the moulding ability between the nucleus and cortex: the nucleus expanding and moulding the surrounding cortex. The most marked cone-shaped lens surface was observed in a 29-year-old subject, where the nucleus formed a small area centrally; the least conoid shape was in a 11-year-old subject where the nucleus occupied a major portion of the lens, thereby moulding the cortex more generally (Brown, 1973).

Capsular elasticity and age

In a series of experiments, Fisher (1969a; 1969b; 1971) examined the elasticity of the capsule and lens and observed the anterior lens profile. He calculated Young's modulus of elasticity for the capsule as a function of age and found that a decrease from 6×10^7 to 1.5×10^7 dynes/cm^2 occurs from youth to old age (Fisher, 1971). In contrast to the proposal that on accommodation, the anterior lens surface assumes a conoid curvature (Fincham, 1937; Brown, 1973), Fisher concluded from examination of the lens profiles that the anterior surface of the lens becomes elliptical in shape.

Brown (1973) using slit-lamp photography, confirmed earlier observations by Fincham (1937) that the posterior pole moves backwards during accommodation. The magnitude of backward movement is less than the forward movement of the anterior surface with the anterior surface of the lens assuming a conoid shape.

The role of the vitreous in accommodation

There is no consensus regarding the role of the vitreous humour during accommodation. Coleman (1970) using anatomical and ultrasonography evidence, argued that the vitreous provides a supportive force which aids accommodation. The theory is refuted by gonioscopic evidence which demonstrates that during accommodation, the vitreous surface is bowed back at the periphery of the posterior lens surface and not moved forward in conjunction with the movement of the ciliary body. More recent work supports the proposal that the vitreous body is not necessary for accommodation, although it appears to aid in the accuracy of measurements of the near point of accommodation (Fisher, 1982). Further, it has been proposed that the vitreous may support the posterior lens surface during accommodation (Koretz and Handelman, 1982).

Mathematical analysis of the forces acting during accommodation

The mechanism of accommodation has been further examined by Koretz and Handelman (1982; 1983). These authors re-analysed slit lamp photographs amassed by Brown (1973) of an 11-year-old human crystalline lens and used an analysis based on deriving the mathematical expressions for the stresses and strains exerted on the anterior lens

surface during accommodation. They concluded that the forces transmitted through the zonular fibres act on the capsule at the site of zonular attachment and analysis of the forces acting upon the lens surface suggested that there was a uniform spread of the resulting stresses over the whole of the anterior lens surface. The implication is that the lens capsule acts as a force distributor during the act of accommodation. The lens material is therefore not moulded into different shapes by the capsule, but the organisation of the underlying lens fibres is altered in a manner which is thought to involve the redistribution of a small portion of lens cytoplasm in each fibre (Koretz, Handelman and Phelps-Brown, 1984).

The relevance of the work of Koretz and colleagues will be discussed in Chapter 7 when the frequency characteristics of accommodative microfluctuations will be examined in different regions of the crystalline lens.

2.2 - THE STIMULUS TO ACCOMMODATION

It is well established that the stimuli to accommodation are derived from a number of sources (Fincham, 1951; Campbell and Westheimer, 1959; Toates, 1972). These stimuli may be divided into optical and non-optical categories, where the former instigates a change in accommodation as a consequence of an alteration in retinal image composition and the latter results in a change in accommodative response which is independent of the retinal image. The primary stimulus to accommodation is generally agreed to be defocus blur (Phillips and Stark, 1977) but in addition, retinal blur can result from various aberrations of the eye known as Seidel aberrations: e.g diffraction, chromatic aberration, spherical aberration and astigmatism (Fry, 1955). Non-optical stimuli include: apparent size (Alpern, 1958a; Kruger and Pola, 1986; 1987; 1989), relative brightness (Toates, 1972), perceived stimulus distance (Hofstetter, 1942; Ittelson and Ames, 1950; Johnson, 1976; Rosenfield *et al*, 1990; Rosenfield and Gilmartin, 1990), cognitive demand (Kruger, 1980; Malmstrom *et al*, 1980; Bullimore and Gilmartin, 1987a; 1987b). In summary, there is a complex and subtle integration of optical and non-optical factors involved in the instigation of a change in accommodative response.

2.2A - Optical factors

i) *Retinal blur*

Blur has been considered an inadequate stimulus to the accommodative mechanism for two main reasons: 1) it is essentially even-error in nature 2) the retinal image is equivalent to that obtained when a target is defocused and when no accommodative response is said to occur (Fincham, 1951). Therefore further cues would appear to be required in order effect an adequate refractive change to a change in target vergence (Fincham, 1937, 1951; Toates, 1972). Many investigators have demonstrated that the accommodative mechanism operates with 50% errors when deprived of other cues (Stark and Takahashi, 1965; Troelstra *et al*, 1964).

Phillips and Stark (1977) compared the accommodative response to target and defocus blur in a variety of open and closed loop situations and found, contrary to the findings of Fincham (1951) who used a less sensitive static technique, that the eye made focusing attempts amounting to 1D to accommodate onto a blurred target. It was concluded that target and defocus blur were equivalent stimuli to the accommodation mechanism (Phillips and Stark, 1977).

ii) - *Astigmatism*

Campbell and Westheimer (1959) found that when a 1D cylinder was presented to an eye in which spherical aberration and chromatic aberration have been eliminated, the accommodative response was correct, whereas the response was in error without the induced astigmatism. They concluded that astigmatism could act as an effective cue to the accommodative system.

iii) - *Chromatic Aberration*

The ocular chromatic aberration amounts to ~2.5D for an eye which is emmetropic for 578nm over a wavelength range from ~400 to 750nm, shorter wavelengths of light being focused more anteriorly than longer wavelengths (Wald and Griffin, 1947; Bedford and Wyszecki, 1957; Charman and Jennings, 1976). Fincham (1951) promoted the idea that the eye could utilise the chromatic aberration to determine the light vergence at the retina.

The difference in coloured fringes at the retinal level could be used as accommodative cues, the hyperopic eye having a red fringe of a white point of light whereas a hyperopic eye would have a blue fringe, due to the short wavelengths focusing more anteriorly than the longer wavelengths. In Fincham's experiment, 60% of his subjects responded erroneously when deprived of the chromatic aberration using a monochromatic light source. These findings were in agreement with those of Campbell and Westheimer, (1959), who found that chromatic aberration was of some use in producing an accommodative cue for some people, but this was not evident for all.

Kruger & Pola (1986) found that the addition of chromatic aberration to blur increased the gain of the accommodative response and reduced the phase lag. They also found that some individuals appeared to be more dependent on chromatic aberration as an accommodative cue than others. The relative importance of blur, chromatic aberration and size was investigated in a procedure which allowed firstly only blur, then blur in combination with chromatic aberration and finally with blur, chromatic aberration and size present (Kruger and Pola, 1986; 1987). The results showed that the accommodative response was enhanced when defocus blur was supplemented by chromatic aberration and size changes. These findings oppose those of Stark and Takahashi, (1965), and Troelstra *et al* (1964), who concluded that chromatic aberration and other ocular aberrations such as spherical aberration, astigmatism and microfluctuations of accommodation are of minimal importance in guiding the accommodative response.

Charman and Tucker (1978a) observed the effect of the lack of chromatic aberration on the monocular steady-state accommodation using targets of different colours and found that observers responded with the same velocity and accuracy for different coloured targets. These authors found that the response of their observers could be improved with training. For untrained observers, the response tended to be inconsistent and it is suggested that a lack of training caused the reduced response accuracy for Campbell and Westheimer's subjects when deprived of the chromatic aberration cue (Charman and Tucker, 1978a).

The importance of training in visual experiments was documented by Provine and Enoch (1975), who examined the role of voluntary aspect of accommodation to a demanding task both with and without a visual stimulus. The authors discovered that following a period of intense training, subjects were able to perform highly demanding accommodative tasks on command even in darkness. They concluded that the initiation of the response was of a voluntary nature, but the final endpoint was tuned via the accommodative feedback mechanism (Provine and Enoch, 1975).

The inability to accommodate onto isoluminant red-green targets tends to contradict the proposal that chromatic aberration provides a cue to the accommodative mechanism (Wolfe and Owens, 1981; Switkes, Bradley and Schor, 1990). When the accommodative response to an isoluminant red-green sinusoid and an isochromatic luminance sinusoid of the same spatial frequency and contrast are compared, the accommodation system is unable to accommodate onto the former, but makes accurate responses to the latter (Switkes, Bradley and Schor, 1990). A model of the accommodation system based on the magnocellular LGN-striate-MT pathway which is sensitive to luminance stimuli and mediates motion perception has been considered, but rejected on the basis that the accommodation system is primarily affected by defocus blur, which will maximally affect the high frequency-sensitive cells in the parvocellular LGN-striate-V2-V4 pathway (Switkes, Bradley and Schor, 1990). The relative roles played by luminance and colour contrast in the mechanism of contour definition remain unclear.

Recent work has provided support for the importance of chromatic aberration as an accommodative cue (Kruger *et al*, 1991). It appears that when observers track a sinusoidally moving target, the deprivation or reversal of chromatic aberration appears to reduce accommodative gain or severely disrupt the accommodative response respectively.

iv) - Spherical Aberration

Campbell and Westheimer (1959) suggested that spherical aberration does play a role in guiding the accommodative response. In their experiment, a monochromatic light source was used as a target and a fixed pupil carefully centred over the eye. The subject

responded with reduced accuracy without spherical aberration and it was deduced that the spherical aberration provided a cue to the accommodative control mechanism. These findings were refuted by Charman and Jennings (1979) on the basis that the annular pupils used by Campbell effected an increase in the depth-of-focus of the eye, which could account for the increased variability of accommodative response obtained when spherical aberration was eliminated.

2.2B - Non-optical factors

i) - Target size and apparent distance

Campbell & Westheimer (1959) found that when blur and size were placed in conflict, the size cue over-rode that of blur. More recently, it has been demonstrated that when size is the sole cue available, it can present a powerful stimulus to the accommodative system and when combined with blur, although the gain of the response is unchanged, there is a significant reduction in phase lag, as depicted in the figure below (Kruger and Pola, 1985).
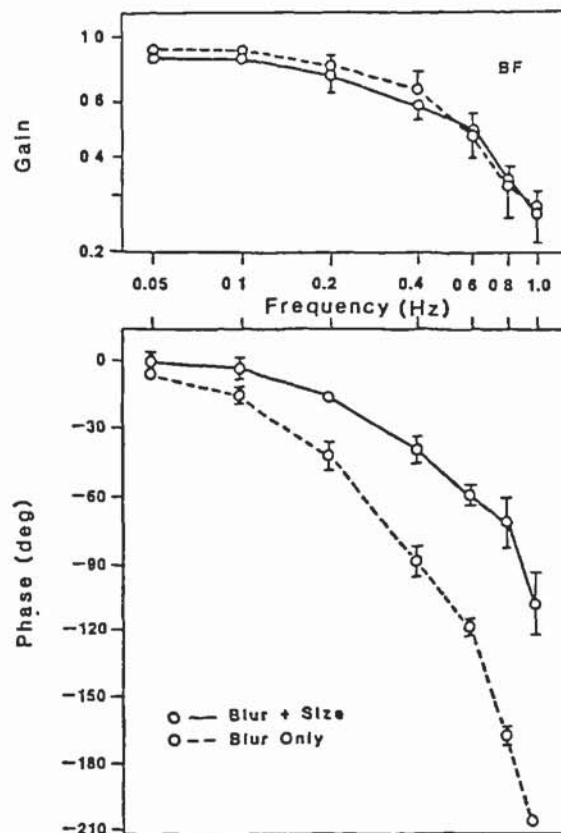
Figure 2.1. Gain and phase plots of accommodation as a function of frequency of target motion for one subject for 2 stimulus conditions: blur and size combined and blur on its own. When size is added to blur, there is a dramatic reduction in phase lag. Error bars show ±1 S.D (From Kruger and Pola, 1985).

Size cues appear to be effective when depth cues are present and when objects are in motion or the objects of regard vary from one distance to another (Kruger and Pola, 1985). Other workers have concluded that size has no influence on the accommodative response (Alpern, 1958a; Morgan, 1968; Hennessey *et al*, 1976), or a minimal influence (Ittelson and Ames, 1950). More recently, size has been shown to be an ineffective stimulus at low temporal frequencies (< 0.1Hz) but at higher temporal frequencies, it presented a powerful cue causing an increase in both the gain and phase of the accommodative response (Kruger and Pola, 1989). The implication is that at low temporal frequencies, the accommodation system has time to utilise the negative feedback system and respond correctly to blur despite the presence of a size conflict. At higher frequencies, the system is unable to respond to the information from the feedback system and size as a cue becomes more important (Kruger and Pola, 1989).

Changing size has been postulated to be linked with the perception of changing depth (Kruger and Pola, 1987). It appeared that the accommodation response for those subjects who perceived a target merely changing size and remaining stationary was substantially reduced or even absent, while those subjects who perceived targets moving in depth responded significantly to the sinusoidally varying target size.

McLin, Schor and Kruger (1988) examined the accommodative and vergence responses to a 'looming' Maltese cross target, i.e. one which varied sinusoidally in size and appeared to approach and recede. These authors examined the accommodative convergence/accommodation (AC/A) ratio or convergent accommodation/convergence (CA/C) ratios with accommodation or vergence loops opened respectively. Changing size altered the vergence and accommodative responses. Furthermore, they found that the vergence response matched the AC/A ratio induced by blur-driven accommodation, but the accommodative response differed from the CA/C ratio. The conclusions were that changing size directly stimulated accommodation while vergence was indirectly stimulated by the AC/A crosslink.

The importance of perceived distance, or the proximal effect as a cue to the accommodative system is supported by Rosenfield and Gilmartin (1990). These authors have shown that proximally induced accommodation (PIA) has a potent effect on open-loop measures of accommodation which amounts to 0.6D of accommodative response for each dioptre of stimulus vergence. They conjecture that PIA may be responsible for a significant input to the accommodative mechanism during the closed-loop accommodative response, although the proposal merits further clarification, as the proximal component of the closed-loop response was based on open-loop measurements of accommodation for 2 target vergences. Such assumptions on closed-loop accommodation from open-loop data may not be appropriate. Further support for the potentially potent influence of PIA on the aggregate accommodative response was demonstrated recently (Rosenfield and Ciuffreda, 1990). These authors found a PIA/stimulus demand ratio of ~0.4D/D for passive (listening to music) and active (counting backwards in sevens) mental states.

ii) - Cognitive effects

The effects of increased mental effort or cognitive demand on the accommodative response has resulted in a number of conflicting proposals. Kruger (1980) observed a mean increase of 0.28D in accommodative response when subjects were requested to change from passively reading numbers to actively adding them. Conversely, Malmstrom and Randle (1984) reported a reduction in accommodative response when subjects were requested to perform a counting task while viewing sinusoidally moving targets. Further, significant individual variations in response with the introduction of a cognitive element to a near task has been documented (Bullimore and Gilmartin, 1988). A significant interaction between cognitive demand and PIA has been demonstrated recently for a proportion of subjects (4 out of a total of 12) in an experiment designed to examine the influence of 2 levels of cognitive demand (listening to music and actively counting numbers) on proximally induced accommodation (Rosenfield and Ciuffreda, 1990).

2.3 - THE ACCOMMODATIVE RESPONSE

The accommodative response rarely matches the demand of the stimulus, but shows an over-accommodation or an accommodative 'lead' for targets beyond ~2 metres and an

under-accommodation, or an accommodative 'lag' for targets nearer than 1-2 metres (Westheimer, 1966). Figure 7 illustrates the phenomenon, first evinced by Morgan (1944) and later by a number of authors (Nadell and Knoll, 1956; Heath, 1956; Krueger, 1973; Charman and Tucker, 1977). The cross-over point, where there is no steady-state error between stimulus and response is thought to correspond to the tonic resting point of accommodation (TA: see section 2.4), although it has been proposed that the TA level represents a balance of previous accommodative stimuli (Tan and O'Leary, 1986).
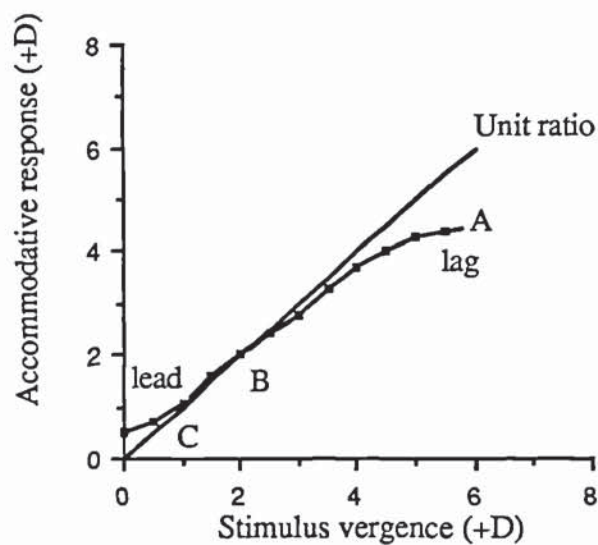
Figure 2.2: Accommodation response as a function of target vergence illustrating the tendency for an accommodative 'lead' for stimuli distal to the tonic resting position (TA) and a lag for stimuli which are proximal to TA. A linear portion where stimulus and response vary proportionately lies between the lag and lead portions of the curve (After Morgan, 1944). The response region from A to B has been proposed to be the parasympathetic range, the region B to C the sympathetic range while A to C represents the amplitude of accommodation (Toates, 1972; Charman, 1982)

It appears that the linear portion of the response/stimulus curve is affected by a number of target and subject characteristics, such as target luminance (Nadell and Knoll, 1956; Johnson, 1976); amblyopia (Wood and Tomlinson, 1975); central scotomas (Otto and Safra, 1974); spatial frequency (Charman and Tucker, 1977; 1978b; Charman and Heron, 1979; Bour, 1981; Tucker and Charman, 1987); blurred objects (Heath, 1956; Korge and Krueger, 1984); increased depth-of-focus (Ripps et al, 1962; Hennessy et al,

1976; Ward and Charman, 1985) age (Hamasaki, Ong and Marg, 1956; Simonelli, 1983); refractive error (McBrien and Millodot, 1986a,b).

Charman (1986) examined the slope of the linear portion of the stimulus/response curve under various conditions of luminance, spatial frequency, contrast, visual acuity and pupil size. He derived an equation relating the minimum angle of resolution (MAR) with the slope (m) of the linear part of the curve:

$$|m| = 1 - C \text{ (MAR)}$$

Using data from a number of workers, Charman concluded that the constant C may have a value which lies between ~0.1 and 0.5 min^{-1}. Subsequent experimental work has quantified C for one set of experimental conditions as being ~0.17 min^{-1} (Bullimore and Gilmartin, 1987c).

2.3A - Temporal response

When a target changes vergence, the accommodation remains unchanged for around 0.3-0.4s after which the response changes to match the new accommodative demand (Campbell and Westheimer, 1960; Phillips, Shirachi and Stark, 1972; Smithline, 1974; Tucker and Charman, 1979). The delay before the onset of a response is known as the reaction time or latency. The time taken to reach the new accommodative level is known as the response time which is of the order of 1s (Tucker and Charman, 1979; Heron and Winn, 1989). This experimental finding complies with electrical stimulation experiments on monkey demonstrating the time course of the stimulation of the parasympathetic system (Chapter 1).

2.3B - Frequency response of accommodation

The accommodative response to a sinusoidally varying target has been studied by a number of workers (Campbell and Westheimer, 1960; Stark, 1968; Kruger and Pola, 1985; 1986; 1987; 1989; Van der Wildt, Bouman and Van de Kraats, 1974; Malmstrom and Randle, 1984). The maximum frequency to which a documented accommodative response has been recorded was to target oscillation frequency of 2.8Hz over an amplitude of movement of 0.75D (Figure 2.3a), in which the phase lag of the

accommodative response was greater than 360° (Campbell, Robson and Westheimer, 1959). Figure 2.3b illustrates the change in accommodative amplitude for one subject over a range of frequencies showing a reduction in response amplitude as target frequency is increased (Campbell and Westheimer, 1960).
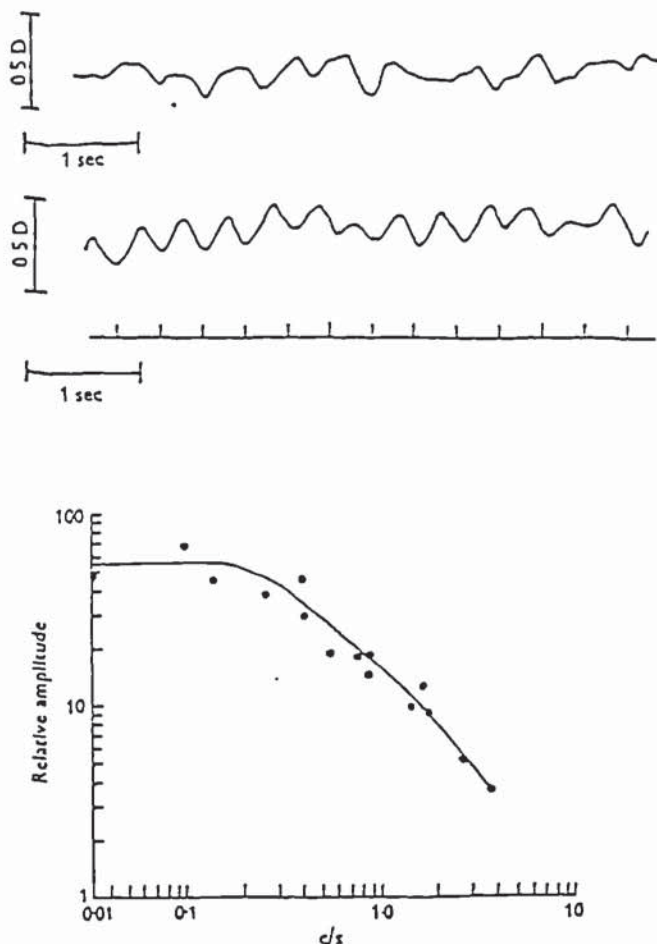
Figure 2.3a): Response to a target oscillating sinusoidally through 0.75D with a frequency of 2.8Hz (After Campbell, Robson and Westheimer, 1959). 2.3b) Graph illustrating the change in amplitude of accommodative response for a sinusoidally moving target moving over a 0.6D range at various frequencies (After Campbell and Westheimer, 1960)

A sinusoidally moving target allows a predictive element in the response, which is reflected in a reduction in latency and phase lag and an increase in gain (Phillips, Shirachi and Stark, 1972; Krishnan, Phillips and Stark, 1973; Van de Wildt, Bowman and Van der Kraats, 1974). An increase in mental activity during sinusoidal target tracking leads to accommodative fatigue: a decrease in gain and an increase of 6° in phase lag at a

frequency of 0.4Hz has been reported for a backwards-counting task executed during the tracking of a sine wave target (Malmstrom and Randle, 1984) (Figure 2.4).
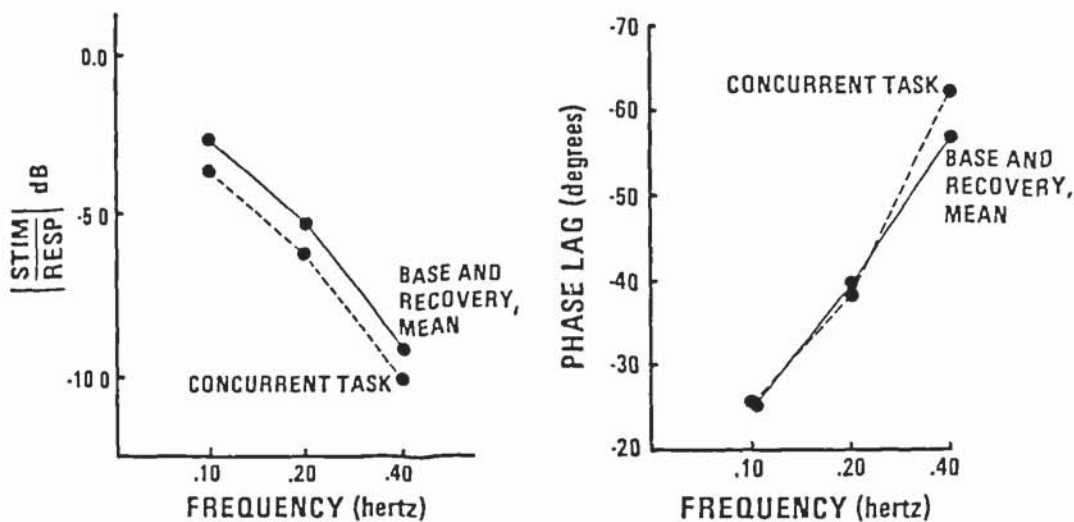
Figure 2.4: Bode plots showing effect of a mental task on: a) accommodative gain; b) phase lag of accommodation to a sinusoidally moving target at 3 temporal frequencies (After Malmstrom and Randle, 1984)

2.3C - Influence of spatial frequency on the accommodation response

The change in accommodative demand required to focus on a new object of regard was proposed to be initiated by the low spatial frequency components of the stimulus and refined by the higher spatial frequencies (Charman and Tucker, 1977; Charman and Heron, 1979), although the response was thought to be influenced by instructions given to subjects, a voluntary element being necessary for the fine-tuning effect induced by the higher spatial frequencies. This proposal has been disputed on the basis of the relative insensitivity of low spatial frequencies to blur. An alternative view has been proposed which is based on the eye's maximum contrast sensitivity to a spatial frequency of ~3 cpd (the 'contrast control' hypothesis): in the absence of the voluntary element, it is proposed

that the intermediate spatial frequencies are likely to play a significant role in guiding the initial accommodative response (Owens, 1980).

More recently, a 'gradient hypothesis' has been supported which proposes that the accommodative error decreases as the steepness of the contrast gradient increases, approaching that of a square-wave and therefore a maximally steep contrast gradient (Fujii, Kondo and Kasai, 1970; Ciuffreda, Dul and Fisher, 1987; Dul, Ciuffreda and Fisher, 1988). This alternative hypothesis was given recent support by the findings that an accommodative response was most accurate for targets formed from successive addition of higher-order odd harmonic sine components summed with the fundamental sinusoid (Dul, Ciuffreda and Fisher, 1988). An increase in accommodative error was obtained for single sinusoids, including that obtained with the 3 cpd sinusoid for which the eye is maximally sensitive. The removal of the intermediate spatial frequencies gave a reduced accommodative accuracy, thus refuting Charman and Tucker's fine-focus control hypothesis.

This hypothesis would explain the equivalent accuracy obtained for accommodation onto simple sinusoids of intermediate spatial frequencies to that obtained for complex gratings (Tucker and Charman, 1987; Ciuffreda, Dul and Fisher, 1987).

2.3D - Influence of temporal frequency

The accommodative response is degraded when a target is temporally modulated in contrast but the response becomes more accurate as the temporal frequency of the flickering stimulus is increased (Owens and Wolfe, 1985). Further, an increased variability of accommodation responses has been found with square-wave luminance flicker (Neary, 1989). A recent report has suggested that a flickering stimulus degrades the accommodative response accuracy even when contrast is always suprathreshold, especially for low spatial frequency stimuli (0.77-1.15 c/deg). The hypothesis is that the accommodation system is unable to utilise temporal cues from accommodative microfluctuations with flickering stimuli (Flitcroft, 1991).

2.4 - TONIC ACCOMMODATION

In the absence of visual stimuli the eye adopts a resting position known as the *dark focus* position and more recently by the term tonic accommodation (TA). This term was first adopted by Heath (1956) and more recently by Gilmartin, Hogan and Thompson (1984) and is appropriate as it relates to the endogenous tone of the ciliary muscle. The TA position is assumed when accommodation is open-loop such as in darkness, in an empty visual field, or with very small pupils when there is a large depth-of-focus. Empty field myopia is defined as the ocular position of focus in a completely featureless field, such as that experienced by pilots when flying through cloud or thick fog. The magnitude of empty field myopia is comparable to the TA level in darkness (Westheimer, 1957; Leibowitz and Owens, 1975a) and is of the order of 0.5-2.0D (Heath, 1956).

Although originally thought to be due to aberrations of the eye (Rayleigh, 1883; Otero and Duran, 1941), it is now widely accepted that the autonomic nervous system is primarily responsible for the myopic tendency in refraction which is evident when the stimulus to the accommodation system is degraded substantially, or when the retinal image quality is not dependent on the accommodative effort. Ocular aberrations may provide a small dioptric input to the TA level, however.

Range of tonic accommodation values in the population

Tonic accommodation values vary appreciably within the pre-presbyopic population. Recent pharmacological work provides evidence that the range of TA in the population is due to differences in parasympathetic tonic levels (Gilmartin and Hogan , 1985).

Mean values of TA for the general population differ according to the method of measurement, laser optometers giving higher (i.e. more myopic) mean values and larger standard deviations than those obtained with IR optometers. The differences between laser and IR optometer measurements are thought to be due to a cognitive demand on the accommodative system when actively judging the direction of movement of the laser speckles (Johnson, Post and Tsuetaki, 1984; Rosenfield, 1989). The difference in measurements of TA between intruments may be minimal however (mean TA of 1.75D

for the IR optometer; 1.70D for the laser optometer), when the presentation time for the laser speckles is within the accommodation reaction time of 360ms (Campbell and Westheimer, 1960) and the chromatic aberration difference between intruments and calibration are accounted for (Bullimore, Gilmartin and Hogan, 1986).

Rosenfield (1989) has demonstrated that the laser optometer may be vulnerable to a number of extraneous influences: measurements of TA comparing IR with laser revealed significant hysteresis effects with the laser but not with the IR optometer following an 8 min near vision task. The difference between measurements of TA using a laser and IR optometer may be due to an input to accommodation from an increased retinal illumination provided by the laser (Schor and McLin, 1988). A hand-held optometer based on the polarized vernier optometer has been recently devised and shown to produce comparable results to both the laser and polarized vernier optometers (Jaschinski-Kruza, 1988).

Table 2.1 illustrates the different values for TA documented in the literature

Range of TA (D)	Mean (D)	Instrument
+0.60 to -1.10	-0.82	Purkinje Images (Campbell and Primrose, 1953)
+0.50 to -4.00	-1.52	laser (Leibowitz and Owens, 1978)
+0.50 to -4.00	-1.66	laser (Heron, Smith and Winn, 1981)
0.00 to -2.80	-0.71	polarized vernier optometer (Simonelli, 1983)
+0.32 to -4.19	-1.55	laser (Gilmartin, Hogan and Thompson, 1984)
+1.00 to -4.00	-1.10	IR (Johnson, Post and Tsuetaki, 1984)
+0.06 to -3.43	-1.70	laser (Bullimore, Gilmartin and Hogan, 1986)
+0.13 to -4.03	-1.75	IR (Bullimore, Gilmartin and Hogan, 1986)
+0.25 to -2.00	-1.07	near retinoscopy (Bullimore, Gilmartin and Hogan, 1986)

Table 2.1 : Various documented range and mean values of TA

2.4A - Role of the autonomic nervous system in determining the TA position

The role of the sympathetic nervous system in the accommodation of the eye has remained a subject of conjecture for some time. Helmholtz, whose theory of accommodation (Helmholtz, 1855), proposed that the ciliary muscle was activated by the parasympathetic system only, and that in the optically relaxed emmetropic eye, the least effort of accommodation would occur when the eye focused at optical infinity. A change of focus to near distances would then require stimulation of the parasympathetic system to induce ciliary muscle contraction. This theory implies that in the absence of a visual stimulus, the activity of the parasympathetic system is reduced to zero and the eye is focused at a position which corresponds with its far point.

An alternative theory on the resting focus of the eyes in darkness was first postulated by Luckeish and Moss (1937). They proposed that the eye's resting point was not necessarily at infinity, but at some intermediate distance, due to a dual innervation of the ciliary muscle by the parasympathetic and sympathetic systems. The resting point was therefore a balance between these two antagonistic systems. Leibowitz and Owens (1975b) examined the phenomenon of night myopia and using control experiments with phenylephrine HCl 10%, concluded that optical aberrations were not major contributory factors to the effect. These authors found that the magnitude of night, empty field and instrument myopia were highly correlated for an individual (Leibowitz and Owens, 1975a).

2.4B - Stability of TA measurements

Measurements of TA over a 1 year period have shown a minimal variation (Owens and Higgins, 1983). Similarly, values of TA appear to show little diurnal variation (Krumholtz, Fox and Ciuffreda, 1986; Heron, Smith and Winn, 1981; Miller, 1978), although an increase of 0.6D in TA at the end of the day has been reported (Amerson and Mershon, 1988). More recently, a diurnal variation of approximately 1.00D has been documented using a Hartinger optometer on 3 subjects who were measured over a 16 hour period (Kurtev, Stoimenova and Georgiev, 1990).

Many studies have reported that mental activity can influence the measurement of TA (Kruger, 1980; Bullimore and Gilmartin, 1987a; 1987b; Jaschinski-Kruza and Toenies, 1988; Rosenfield, 1989). The consensus is that enhanced mental effort may increase the accommodative response, an effect which may be apparent using a laser optometer when active judgement of the direction of motion of the speckles is required. The Hartinger optometer requires active participation by the subject to judge the precise vertical alignment of 2 bars, involving a degree of cognitive effort: it may be that the diurnal variation reported by Kurtev, Stoimenova and Georgiev, (1990) reflected the inherent variation in subjective assessment and/or cognitive demand of the task.

2.4C - TA and Refractive Error

There is evidence that late onset myopes (LOMs: those who develop myopia after the age of 15 years, when it is thought that hereditary refractive error is stabilised) have lower values of TA than emmetropes (Maddock *et al*, 1981; Smith, 1983; Bullimore and Gilmartin, 1987b; McBrien and Millodot, 1987), although this is disputed (Simonelli, 1983; Ramsdale, 1985). Further, it has been found that EMMs also have lower TA values than hyperopes (Maddock *et al*, 1981; McBrien and Millodot, 1987a; 1988). It is unclear why TA values in LOMs should be relatively more hyperopic than those values for other refractive groups, although a weak sympathetic component in myopes may be responsible not only for a more remote TA position but that this condition might render an eye myopic in the absence of biometric changes from normal. The proposal was based on a reduced range of sympathetic response on the stimulus/response curve, which would adversely affect the vision of distant objects (Charman, 1982).

2.4D - Hysteresis effects

Hysteresis is the term given to the inward shift in TA following a near task, or the outward shift in TA following a period of fixation at distance. The term hysteresis in the context of accommodation was first employed by Ebenholtz (1983), who found that following an 8 minute period of fixation at the near point of accommodation, an inward shift of 0.34D in the level of TA was produced and an outward shift of 0.21D was

evident following fixation at distance. A similar effect has been found by a number of authors (Tan and O'Leary, 1986; Ebenholtz and Zander, 1987; Schor, Johnson and Post, 1984). The hysteresis effect shows evidence of consensuality (Fisher, Ciuffreda and Hammer, 1987): a monocular task producing a positive change in TA position in the non-fixating eye, although these findings are contrary to those of Wolf and Owens (1983). The magnitude of the hysteresis is similar for monocular and binocular tasks (Fisher, Ciuffreda and Bird, 1988; Rosenfield and Gilmartin, 1988a).

It appears that when a Hartinger optometer is used as a measuring instrument, the decay of hysteresis is dependent on the accommodative demand and duration of the task: the hysteresis effect may be eliminated within 3 minutes following a 45 minute reading task at a 5D vergence (Wolf, Ciuffreda and Jacobs, 1987). Recent measurements of TA following varying task durations from 0.25 to 8 minutes have indicated that the task duration has no effect on either the magnitude or the duration of the hysteretic after-effect (Fisher, Ciuffreda and Bird, 1990).

Using an IR optometer, for near tasks of short duration (<2 min), the hysteresis effect, if any is apparent, appears to dissipate within a few seconds, whereas a 30 minute adaptation period has shown an average increase of 0.5D in resting focus to a 6D stimulus (Schor, Johnson and Post, 1984). This hysteresis effect resisted depletion within the normal 2-15s rate evident for short-term adaptation whereas measurements of tonic vergence after the same adaptation period showed no evidence of hysteresis effects (Schor, Johnson and Post, 1984). The implication is that tonic after effects of the *accommodative* system to stimuli of short duration are small, longer periods of adaptation being required by the *fusional vergence* system to prism. Recent work supports the view that the tonic vergence and accommodative systems have independent adaptive time constants (Owens and Wolf-Kelly, 1987; Fisher, Ciuffreda and Bird, 1990).

The rate of onset of adaptation to a near vision stimulus has received attention recently: the proposal was that differences may exist between the fast reflex accommodation and

slow adaptive component of accommodation in LOMs and EMMs, the LOMs exhibiting a slower onset of adaptive accommodation leading to an increased dependency on the reflex component to maintain the accommodative response. It was conjectured that myopia might develop as a consequence of poor adaptive accommodation in an effort to reduce the stress induced by an increased demand on reflex accommodation (Rosenfield and Gilmartin, 1989). Short tasks of 15s, 30 and 45s were performed after which lights were extinguished and the regression of accommodation measured with an IR optometer over the following 90s period for 10 EMMs and 10 LOMs. No significant difference in adaptation between refractive groups was found, although adaptational effects were demonstrated for a task as short as 15s.

Hysteresis and Refractive Error

No clear relationship between refractive error and susceptibility to accommodative hysteresis has been reported using a Hartinger optometer to measure TA following a 10 minute task set at the near point of accommodation, although there was a trend for larger tonic after-effects in the high myopes than other refractive groups (Fisher, Ciuffreda and Levine, 1987).

Evidence for a differential hysteresis effect for LOMs compared with other refractive groups has been reported using a Canon IR optometer, LOMs exhibiting greater adaptive shifts in TA following near tasks than emmetropes or hyperopes (McBrien and Millodot, 1988; Gilmartin and Bullimore, 1991). Further, the imposition of a mental task during a period of near fixation promotes a greater hysteresis effect in LOMs compared with EMMs (Bullimore and Gilmartin, 1987b). This provides evidence for the greater susceptibility of LOMs to myopic shifts in TA which may be a precursor to further refractive changes.

Gilmartin and Bullimore (1987) have demonstrated that a visual task which requires a high accommodative effort (and therefore a substantial parasympathetic input to the ciliary muscle) is supplemented by an inhibitory sympathetic contribution. These authors used the non-selective beta-receptor antagonist drug timolol maleate to gain information

on the role played by the sympathetic system during a demanding near visual task. By examining the post-task accommodation regression rate from the task set at a vergence of 5D, it was evident that beta-antagonism had occurred during the task. A comparison between the timolol and no-drug condition for the post-task accommodation regression rate revealed a significantly increased rate of regression for a subset of subjects whose TA levels were greater than 0.75D (Gilmartin and Bullimore, 1987).

The implication is that individuals whose TA values are <0.75D may lack a sympathetic facility which promotes refixation at distant objects following intense periods of close work by attenuating the magnitude and duration of post-task positive shifts in TA. Furthermore, it is suggested that those emmetropes with low TA levels (<0.75D) may be more susceptible to the development of myopia as they appear to lack the sympathetic inhibition necessary to allow hysteresis effects to be rapidly eliminated following intense periods of close work (Gilmartin and Bullimore, 1987).

An extension of this work has demonstrated that LOMs appear to show significant differences in the rate of regression to TA following tasks set at 3D and 5D compared with emmetropes (Gilmartin and Bullimore, 1991). Significant differences in post-task regression patterns were evident between the 2 refractive groups: emmetropes regressing to tonic levels at a significantly faster rate following the imposition of dark-room conditions. In contrast to the work of McBrien and Millodot (1988) the authors found that initial positive shifts in TA for LOMs decayed within the 1-minute post-task period and propose that the differences in post-task regression patterns evident between the refractive groups may be due to the characteristics of the autonomic innervation to the ciliary muscle maintaining the within-task accommodative response (Gilmartin and Bullimore, 1991).

2.5 - Conclusions

It is evident that further work is required to clarify the role of the sympathetic nervous system during sustained near visual tasks and to examine whether there exists a difference between the sympathetic facility to the ciliary muscle for various refractive

groups, in particular the late-onset or adult myopic group whose refractive error is more likely to be environmentally than genetically determined. Examination of post-task regression patterns have so far been studied using static (McBrien and Millodot, 1987a; 1988) or quasi-static recording techniques (Gilmartin and Bullimore, 1987; Gilmartin and Bullimore, 1991). Using a continuous recording optometer will enhance further our understanding of the nature of the sympathetic innervation to the ciliary muscle during near tasks.

2.6 - ACCOMMODATION AND MYOPIA

Whereas there is no consensus regarding the basis for myopia development, there is increasing awareness that accommodation plays a major role in the development of the type of myopia which emerges relatively late in life (≥ 15 years) and which is associated with prolonged and habitual close work (Goldschmidt, 1968; McBrien and Barnes, 1984; Grosvenor, 1987; Gilmartin and Bullimore, 1987; 1991) now classified as late-onset myopia (LOM) or adult-onset myopia.

Childhood-onset myopia is primarily the result of axial elongation of the globe which includes an increased anterior chamber depth, an increased posterior chamber depth and a steeper cornea compared with the equivalent measurements in the age-matched emmetropic eye (Grosvenor and Scott, 1991). Classical studies have led to the conclusion that the axial elongation is arrested by the age of 13 years (Sorsby, *et al*, 1961; Sorsby and Leary, 1969). More recently, the age of cessation of childhood myopia has been quantified as 15.25 years in females and 16 years in males and has shown a high correlation with the age of growth cessation (Goss and Winkler, 1983).

2.6A - Heredity vs environmental influences

Studies on monozygotic twins are convincing in that workers who have studied twins separated at birth and with markedly different patterns of near work have concluded that heredity is the primary influence on the development of myopia, as the course of the myopia progression is the same, although the authors do not rule out completely the

effect of an environmental factor (Jancke and Holste, 1941; Sorsby, Sheridan and Leary, 1963; Juel-Nielson, 1965). A review of the major theories of emmetropia and ametropia is given by McBrien and Barnes, (1984) and will be briefly summarised:

2.6B - Theories of refractive error development

i) - Biological-statistical theory

Early observations by Steiger in 1913 inferred that the distribution of refractive errors was normal and that the refractive errors seen were a manifestation of a free association of the different components of refraction. Steiger regarded myopias of up to -7D as being within the range of a normal refractive error distribution. He based his assumption on measurements of corneal curvature which he found were normally distributed. Further work established that the curve of refractive error distribution was leptokurtotic for the emmetropic region, and skewed towards myopia. This cast doubt on Steiger's free association theory.

Sorsby (1967) postulated that there existed a mechanism which involved the four major components in ocular power: axial length, corneal power, lens power and anterior chamber depth. The correlation of these 4 components led to emmetropia by a particular mechanism, the failure of which would lead to correlation ametropia. He further divided ametropia into component ametropia, whereby a component (usually axial length) was very different from the value of the component in emmetropia. His studies led him to believe that the refractive errors were purely genetically determined.

ii) - Emmetropization.

Evidence in the literature points to a mechanism known as emmetropization, which controls the eventual refractive error of the eye, as it is clear that post-natal development of the eye tends to lead to emmetropia (Steiger, 1913; Slataper, 1950). Further, a normal distribution curve for refractive error would tend to predict less emmetropia than is present in the population (Wibaut, 1925; Sorsby et al, 1961).

66

O'Leary and Millodot (1979) examined the refractive error of human ptotic eyes and found that these eyes were significantly more myopic than the fellow normal eyes, although there was no prevalence of amblyopia in the ptotic eyes. The authors concluded that myopia may result from light deprivation as a consequence of a partial or complete physical obstruction to the eye during development, rather than reduced pattern vision. This conclusion is contrary to that made by Rabin, Van Sluyters and Malach (1981), who examined the refractive errors in humans who suffered from a variety of ocular anomalies. They concluded that normal visual stimulation was a necessary factor for emmetropization to occur.

Recent work examining the refractive development of subjects with congenital achromatopsia has provided evidence for the importance of normal retinal cone function in the emmetropization process (Evans, Fielder and Mayer, 1989). These authors found that the subjects with congenital achromatopsia were typically hyperopic with high astigmatism and they proposed that normal retinal cones play an important role in the feedback control of ocular refraction.

iii) - Use-abuse theory

The originator of this theory is thought to be Cohn (1886), who proposed that myopia could be the result of prolonged near work. Young and his colleagues have studied monkeys and Eskimos, and found that in primates, it was found that up to 75% of refractive errors could be environmentally induced. Adult animals raised in open-field conditions had few refractive error problems, whereas up to 75% developed myopic changes when housed in laboratories with restricted visual fields of 18" in front of the eyes. The refractive errors induced were of the order of -1.5D (Young, 1967). This work was supported by that of Rose, Yinon and Belkin (1974) who compared the refractive errors of street with caged cats. A high percentage (87.5%) of street cats were hypermetropic whereas 68.2% of the caged animals were myopic. Axial lengths were equivalent in both groups however.

The Eskimo population exhibited a substantially increased incidence of myopia (58%) in children born after the second World War. An increased amount of near work and TV watching were factors thought responsible (Young and Leary, 1972; Young *et al*, 1973) although a change in dietary habits could also have been a contributory factor.

Young's theory of ametropia development is based on the proposal that accommodation produces an increase in vitreous chamber pressure, which leads to an increased vitreous chamber depth. Experiments on monkeys showed that an increase in vitreous chamber pressure of 6-7mmHg followed the onset of accommodation (Young, 1975), although the transducer used to measure posterior chamber pressure is likely to have caused an imbalance, leading to erroneous measurements. Young claimed that his 'environmental stresses' theory would be sufficient to explain the development of refractive errors from low hypermetropia to emmetropia, and myopia up to -8.00D.

A number of animal experiments have concluded that myopia may be induced by excessive and prolonged accommodative demands or restricted visual fields (Young, 1975; Wilson and Sherman, 1976; Wallman, Turkel and Trachtman, 1978; Walman, Adams and Trachtman, 1981). The mechanism whereby an increase in accommodation leads to an increase in scleral stretch to induce an enlarged posterior chamber depth is unclear, as it is known that a decrease in intra-ocular pressure occurs with an increased accommodative demand (Armaly and Burian, 1958; Armaly and Jepson, 1962; Armaly and Rubin, 1961). Coleman, (1970) however, suggested that during accommodation, there was an increase in pressure gradient between the anterior and posterior chambers, with higher pressures being present in the vitreous chamber.

2.6C - Conclusions

There remains a great deal of controversy over why myopia develops in adulthood. The evidence of myopia development following demanding visual tasks such as intensive VDU work or abnormally lengthy and demanding near visual tasks such as microscopy would seem to suggest that environmental influences cannot be ignored. The literature abounds with suggested methods for arresting the progression of myopia, including

treatment with contact lenses, bifocals or cycloplegic drugs. The two latter treatments are based on the assumption that excessive or sustained accommodation leads to increases in myopia. There is no conclusive evidence to suggest that any of the treatments are successful in mitigating the progression of the myopic refractive error.

Young (1981) proposed that excessive near work induced a tonic change in the ciliary muscle which resulted in an accommodated state being prolonged, which could represent itself clinically as pseudomyopia. Following this stage, Young postulated that there was an increase in vitreous chamber pressure as a direct result of the increased ciliary muscle tonus which promoted axial length elongation and myopia. Further, Van Alphen (1961; 1986) has proposed a theory relating increased ciliary muscle tonus with axial length elongation and will be discussed further in Chapter 6. If the accommodative mechanism is involved in myopia development in adults, the means by which this increased accommodative tone is translated to axial elongation of the globe remains a subject of conjecture. The autonomic control of accommodation and its relevance in the development of myopia of the adult-onset type will be examined in Chapter 6.

CHAPTER 3

MICROFLUCTUATIONS OF ACCOMMODATION

3.1 Introduction

When the pre-presbyopic eye fixates a stationary near target the power of the lens is known to change rapidly and continuously. The first observation of this fluctuating activity using an infra-red optometer was by Collins (1937). Using his newly designed electronic refractionometer, he observed that the indicator light on the cathode ray tube screen of his device seemed to have 'a curious pulsating movement'. He estimated that the dioptric change was of the order of 0.5D, with a minimum frequency of around 1Hz.

Further investigation of this observation was not made until the 1950's with the advent of an ophthalmoscopic technique (Arnulf, Dupuy and Flamant, 1951a; 1955) which gave an estimated amplitude for the fluctuations of approximately 0.1D. Accurate measurements of these small changes in ocular power were not possible until an objective infra-red recording instrument with an adequate time resolution was devised by Campbell and Robson (1959). Analysis of recordings using this novel instrument revealed temporal frequencies in the accommodative response which ranged up to 5 Hz and with 7mm pupils, a dominant '2Hz' component was apparent which exhibited inter-subject variability within the range 1.0-2.2Hz (Figures 3.1 and 3.2).
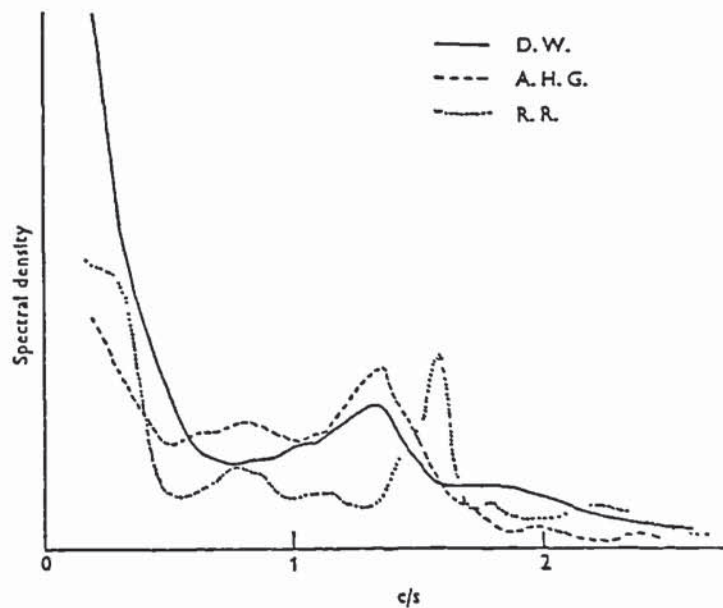
Figure 3.1: Power spectra for different subjects illustrating the inter-subject variability of the so-called '2Hz' component (After Campbell, Robson and Westheimer, 1959).

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The fluctuations were found to disappear under cycloplegia and were minimal at distance, indicating that their origin was likely to be accommodative (Campbell, Robson and Westheimer, 1959).
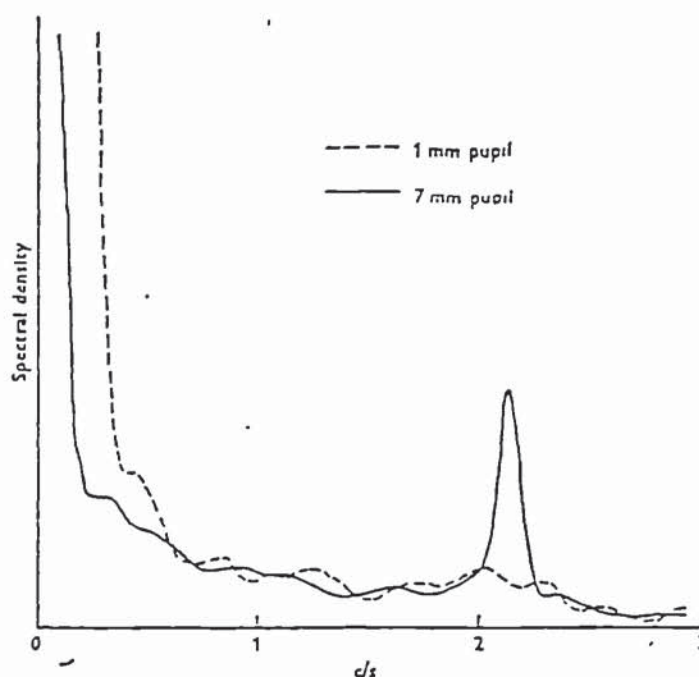
Figure 3.2: Power spectrum plot of accommodative microfluctuations showing effect of pupil size on the dominant frequency components (After Campbell, Robson and Westheimer, 1959).

3.1A - Effect of target vergence on microfluctuations

Many authors have noted that the profile of the power spectrum of the microfluctuations of accommodation changed with vergence (Denieul, 1982; Johnson, Post and Tsuetaki, 1984; Kotulak and Schor, 1986a). This aspect was first systematically investigated by Arnulf and Dupuy (1960) who concluded that the magnitude of the fluctuations was positively correlated with stimulus vergence. Confirmation of the finding was given by Denieul (1982) who reported a four-fold increase in the root-mean-square (rms) value of the response as stimulus vergence was increased from distance to near. A similar proportional increase in magnitude for the nominal '2 Hz' component from a vergence of -1D (0.02D mean to peak) to -4D (0.08D mean to peak) was observed by Kotulak and Schor (1986a). A minimum response was not observed for target vergences positioned at the tonic resting level of accommodation, indicating that a neural origin for this component of the fluctuations was unlikely.

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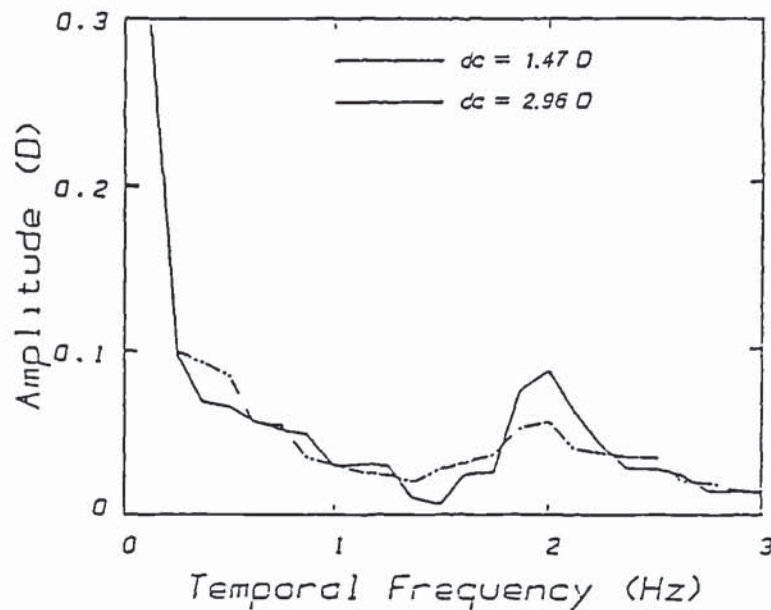
Figure 3.3: Power spectra showing effect of vergence on the magnitude of the '2Hz' component. Solid line: 4D target vergence, broken line: 1D vergence (After Kotulak and Schor, 1986a).

More recently, Miege and Denieul (1988) demonstrated that the microfluctuations exhibited maximum activity between -1D to -4D and minimum activity at the near and far points. The changes in tension exerted by the zonule on the lens for varying levels of accommodative demand were held responsible for the variations that were apparent. The magnitude of change reported within these studies may be related to the use of different recording techniques and the presence of inter-subject variability. A comprehensive review and discussion as to a possible role for the microfluctuations in the control of the accommodation response is given by Charman and Heron (1988).

3.1B - Correlation of accommodative fluctuations between the two eyes

Campbell (1960) was the first to study the correlation of the microfluctuations of accommodation between the two eyes. By using a double IR recording optometer, he found that simultaneous recordings of the accommodation fluctuations from the two eyes were practically identical for the three subjects examined (Figure 3.4). A small difference in the high frequencies was attributed to noise levels in the optometer. Campbell concluded that the origin of the microfluctuations of accommodation was at the level at which the two oculomotor nerves were binocularly functional.
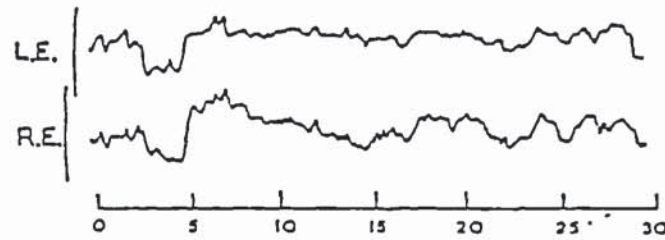
Figure 3.4: Binocular recordings of accommodative microfluctuations illustrating the common pattern exhibited for the two eyes (After Campbell, 1960).

A study of accommodative microfluctuations in Adie's syndrome has reported a reduction in magnitude of the HFC in the affected eye compared with the contralateral healthy eye (Ukai and Ishikawa, 1989). These authors concluded that the origin of the HFC was likely to be at no more peripheral a location than the ciliary ganglion, the origin of the Adie's defect.

3.1C - Accommodative fluctuations and visual acuity

The resolution of high spatial frequency targets appears to be affected by the components of microfluctuations of accommodation (Raymond, Lindblat and Leibowitz, 1983). In a study using a laser optometer, subjects were required to view a high spatial frequency grating and comment on the visibility of the grating during a 60s period. They found that the visibility of the grating was dependent on the viewing distance. The intermittent nature of the visibility of the target was due to the accommodative instabilities, as viewing under cycloplegia resulted in their complete elimination. Maximum visibility was found to correspond to a distance closer than the tonic accommodation level, and was age related.

Millodot (1968) examined the distance visual acuity of subjects under monochromatic and white light following cycloplegia. He reported improved acuities under monochromatic conditions but not in white light when the microfluctuations were eliminated by cycloplegia. The results were interpreted to suggest that the fluctuations

could be detectable under certain conditions and so could be of potential use to the accommodative control system.

3.1D - Effect of target luminance on accommodative microfluctuations

It appears that at low levels of target luminance, the accommodative response is characterised by large amplitude slow frequency drifts (< 0.5Hz). An accommodative origin for these drifts has been demonstrated by instilling a cycloplegic agent which eliminates them (Alpern, 1958b; Johnson, Post and Tsuetaki, 1984). Alpern (1958b) proposed a role for the slow frequency components in maintaining an accurate accommodative response. He thought that the increased magnitude of drift at low retinal illuminances (<10 trolands) was a consequence of an effort to locate the intensity difference threshold. Similarly, when target *contrast* is low, the accommodative response is dominated by instability oscillations of low temporal frequency (Denieul and Corno, 1986).

3.1E - Significance of the microfluctuations

There is controversy over whether the fluctuations have any functional role in the accommodative control system, or whether they are simply noise in the accommodative plant. A number of bio-engineers have described the accommodative system in terms of control theory (e.g Toates, 1970; Hung and Ciuffreda, 1988). The accommodative system is considered a closed-loop feedback control system in which retinal blur is an even-error signal: one which has magnitude but not directional information. The fluctuations of accommodation have been thought by some to provide this odd-error directional information (Alpern, 1958b; Fender, 1964; Smithline, 1974), although this has been disputed by evidence based on the inability of the eye under restricted monocular viewing conditions to respond to changes in target movement in the correct direction for more than 50% of the time (Troelstra *et al*, 1964; Stark and Takahashi, 1965; Stark 1968; Phillips and Stark, 1977; Bour, 1981).

The initial guiding cue could only be accomplished by the high frequency components (HFCs: 1.0-2.2Hz), as the low frequency components (LFCs: <0.6Hz) are too slow to

provide the necessary feedback within the accommodation reaction time of 0.36s, the response time being 0.6s (Campbell and Westheimer, 1960). Any functional role for the LFCs is thought to be linked with the maintenance of an accurate accommodative level (Charman, 1983; Charman and Heron, 1988). Unlike the HFCs, the LFCs appear to change in a manner consistent with depth-of-focus considerations: their magnitude showing a negative correlation with pupil size and being large enough to significantly affect the retinal image quality.

3.1F - Detectability of accommodative microfluctuations

An early consideration was to determine whether the eye could perceive such small changes in dioptric level. In an experiment in which a subject's pupil was homatropinized and a fixed 3mm pupil centred over it, Campbell and Westheimer (1958) found that it was possible to detect a change in focus equivalent to the eye's depth-of-focus, amounting to 0.2D. This dioptric value was virtually equivalent to the maximum amplitude of the accommodation microfluctuations. More recent experimental work supports this finding and has led to the conclusion that the fluctuations could provide directional cues to the accommodation system (Winn et al, 1989a). Moreover the accommodation system is capable of responding to changes in dioptric vergence of around 0.1D (Ludlam et al, 1968; Kotulak and Schor, 1986a), the magnitude of which is below that of the threshold for perception of 0.18D for a temporally moving target at 1Hz (Kotulak and Schor, 1986a). More recently, a role for the '2Hz' oscillations has been proposed by Miege and Denieul (1988), who suggested that this component, rather than guiding the initial response, is probably linked with maintaining an accurate accommodative level. This view is substantiated by their finding of a maximal accommodative response (i.e.minimum focusing error) corresponding to position found when a maximum amplitude of the '2Hz' oscillations was apparent.

3.1G - Origin of microfluctuations

i) - Neural

Experiments on amblyopic eyes have led some authors to suspect a neural origin for the accommodative microfluctuations. (Ukai, Ishii and Ishikawa, 1986; Winn et al, 1987).

Low frequency drifts have been found to be more common in amblyopic eyes compared with the fellow normal eyes. A study on the examination of microfluctuations of accommodation in the condition 'Adie's syndrome', revealed that the fast component of the lens oscillations was reduced in affected eyes, implying an origin for the fast component at no more peripheral a location than the ciliary ganglion, the origin of the 'Adie's' defect (Ukai and Ishikawa, 1989).

Kotulak and Schor (1986b) devised a mathematical model for the error detector of the human visual system. They postulated that the high frequency components of the microfluctuations of accommodation (i.e. the '2Hz' region) could provide both directional and magnitude information to the accommodative error detector, thus giving support to the theory that the lens fluctuations may be utilized in the accommodative control system.

ii) - Plant noise

Kotulak and Schor (1986a) found that the mean accommodative level was correlated with the amplitude of the '2Hz' component of the microfluctuations. Contrary to the findings of Bour (1981), who found a local minimum amplitude for the microfluctuations of accommodation at a vergence of around 2-3D, Kotulak and Schor reported no such minimum around the TA position for the '2Hz' component. These authors proposed that the fast component is likely to be a consequence of the mechanical and elastic properties of the lens.

Stark, Takahashi and Zames (1965), simulated the accommodation system using a computerized model and concluded that the high frequency component of the fluctuations in the accommodative mechanism (i.e. the '2Hz' component) was due to feedback instability. This study was criticized by Hung, Semmlow and Ciuffreda (1982), who suggested that too small an accommodative latency value (0.1s instead of 0.3s), led them to this erroneous conclusion. A latency of 0.3s would have resulted in an instability oscillation in agreement with other authors, i.e. a value of 0.45Hz, not '2Hz'.

Charman and Heron (1988), suggested that the fast oscillations might originate from the mechanical and elastic properties of the lens. This proposal was based on the Foucault knife-edge pictures of Berny (1969) and Berny and Slansky (1970). In these photographs, the radial grooves and other irregularities in the lens were clearly visible. The figures ascribe the largest fluctuations in wavefront to the peripheral portion of the lens, thereby explaining the pupil size dependence of the oscillations. A large pupil gives rise to an increase in high frequency oscillations, as the peripheral portion of the lens is exposed. The implication is that the slow components could conceivably be utilized in some form of accommodative control process, whereas the fast oscillations were probably attributed to plant noise.

3.2 - Conclusions

Whereas it is generally thought that the fast frequency oscillations are more likely to be the consequence of noise in the accommodative plant than being part of an odd-error feedback control system, the origin of the noise is unknown. The evidence based on the photographs of Berny and Slansky (1970) indicates that a difference in capsule thickness and profile gives rise to varying proportions of frequencies over central and peripheral lens zones, the faster frequencies (i.e ~2Hz) being more evident in the periphery than the central lens areas.

Koretz and Handelman (1982; 1983) have examined slit lamp photographs of human lenses and devised mathematical equations of the forces acting upon the lens during accommodation. The implications are that the capsule evenly distributes the force from the zonules over the whole of the lens surface. This may not be compatible with a proposal which designates varying proportions of the dominant frequencies of fluctuations for peripheral compared with central lens zones. Further clarification of the nature of the frequencies of fluctuations over the crystalline lens surface for different lens zones is required.

CHAPTER 4

METHODS AND INSTRUMENTATION

4.1 - MEASUREMENT OF ACCOMMODATION

4.1A - Introduction: Infra-red optometers

The design of infra-red (IR) instrumentation for the objective measurement of refraction was pioneered by Collins (1937) whose refractionometer provided the basis for many of the more recent instruments developed for research and clinical measurement purposes. In addition to incorporating IR light into the instrument, Collins' optometer introduced two further features which provided a major advance on previous designs:

1) The quality of the retinal image was assessed by allowing it to be projected onto a corresponding negative mask so that the maximum light transmission occurred when the quality of the retinal image was optimal.

2) The signal from the retinal image was enhanced by optical chopping, which produced an alternating current, whereas light from extraneous sources produced a steady current in the photodetector.

A comprehensive review of the Collins instrument is given by Charman (1976).

In general, IR optometers have two main advantages over other objective optometers such as the Hartinger optometer (Carl Zeiss Jena) or the time-consuming purkinje image photography technique which analyses the 3rd purkinje image:

1) The measuring beam is invisible to the subject and therefore accommodation may be more easily controlled as it is not influenced by the measuring technique.

2) The absence of a bright target avoids pupillary constriction which eliminates the tendency for accommodative changes induced by a change in depth-of-focus (Hennessy *et al*, 1976; Ward and Charman, 1985).

Currently available commercial IR optometers are based on one of three design principles:

1 - Grating focus principle

This technique is the most common employed in modern optometers. A grating target, illuminated by IR light is imaged on the retina of the subject. A photocell detects the

intensity of the IR image reflected back by the retina, after passing through a mask which consists of parallel bars. The intensity of the IR light increases as optimum retinal image focus is approached. This principle was first utilised in Collins' refractometer (Collins, 1937) and later reproduced in instruments such as the Canon *Autoref R1* and also in the *Dioptron Ultima*.

2 - Retinoscopy

The design of the Ophthalmetron (Bausch and Lomb) is based on the principle of retinoscopy. IR light enters the eye from the main light source of the instrument via an IR filter, a lens and semi-reflecting mirror arrangement and a rotating chopper drum which produces a moving patch of light on the subject's retina. A detector lens views the reflex and there are 2 photocells which are linked to a phase discriminator which identifies the direction of movement of the light across the photocells. The output from the phase discriminator determines the position of the detector lens and photocell assembly to a position coincident with the subject's retina. In this position, the photocells are simultaneously illuminated by the patch of light. This optometer has been modified successfully (Safir, Knoll and Mohrman, 1970) to enable a continuous measurement of accommodation and used by a number of workers in the study of accommodation dynamics (Schor, Johnson and Post, 1984; Johnson, Post and Tsuetaki, 1984; Kotulak and Schor, 1986a;c).

3 - Scheiner disc principle

Cornsweet and Crane (1970) developed a novel way of measuring accommodation dynamics. They devised an IR servo-driven optometer, based on the Scheiner disc principle. An accurate assessment of the instrument's resolution is not available. However, an optometer which is mechanically servo-driven invariably introduces a response time-lag, which can reduce the accuracy of the instrument. The Scheiner disc principle is incorporated in the objective '6600 Autorefractor'. Instead of 2 pin-holes, two light sources are used, which are displaced from the optical axis of the illuminating system. The superimposition of two light images of the target produces a sphero-

cylindrical refraction. The principle is also utilised in Charman and Heron's *simple infrared optometer* (Charman and Heron, 1975) and in the binocular *twin channel* IR optometer designed by Heron *et al* (1989).

4.1B - The Canon Autoref R-1 infra-red optometer

The Canon Autoref R-1 (Canon Europa) was introduced in 1981 to measure static refraction in a clinical environment. It is an IR optometer operating on the principle of grating focus (Matsumura *et al*, 1983). There are numerous advantages in the design of the instrument: it allows an easy method of alignment and an effective means of checking fixation by way of an IR video monitor; it provides an open binocular field of view thus minimising instrument myopia (Hennessy, 1975). The accuracy of the instrument has been demonstrated by a number of workers, (Matsumura *et al*, 1983; McBrien and Millodot, 1985) and the manufacturers claim that reliable readings can be obtained over a ±15.0D sphere and ±7.00 cylinder range of refractive errors, in 1° steps of 0.12D.

Mode of operation

Focusing lenses are moved along the axis of the instrument and the position corresponding to the least blurred state and maximum output for the 3 photodetectors is computed along 3 meridians, each separated by 60°. The spherical and astigmatic components of the refractive error are calculated within a measuring sweep of 0.2s using $sine^2$ equations which relate to the circle of least confusion for each of the 3 lenses (see Matsumura *et al* 1983).

For pupil diameters greater than the manufacturer's specified minimum of 2.9mm, the instrument has the advantage of being pupil independent in its static mode of operation, as it relies upon the *location* rather than the magnitude of the 3 peak photodetector outputs. Figure 4.1 illustrates the output from each of the three photodetectors, showing the peak positions which relate to the position of optimal focus.

Channel 1

Channel 2

Channel 3

0.2V/div

Time = 50ms/div

Rx error: -0.75/-1.00 x 8
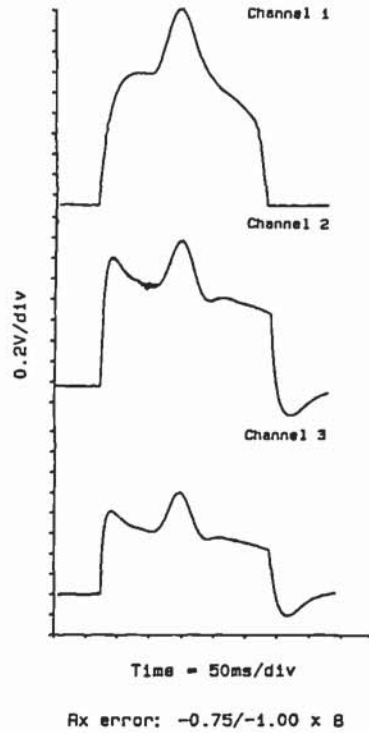
Figure 4.1: Signals from the three photodetectors as the Canon autorefractor performs one sweep in 'single-shot' mode.

Locating the position of maximum output for the 3 photodetectors becomes difficult when the pupil diameter reduces to below 2.9mm. The instrument reading becomes increasingly astigmatic as the pupil diameter diminishes to this limit, until finally, the instrument is unable to determine the position of the peak and calculate the refractive error. The effect of a gradually diminishing pupil diameter and the corresponding refractive error computation is illustrated for one meridian in Figure 4.2.
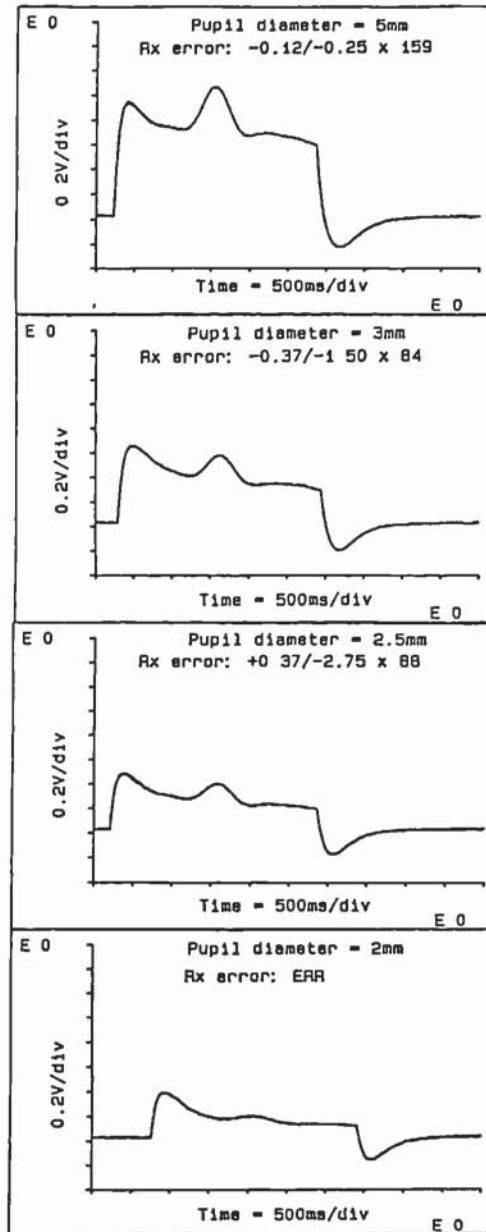
Figure 4.2: Effect of a change in pupil diameter on photodetector output. As the pupil diameter decreases, the gradients relating to the peak become increasingly flatter, hence the peak becomes harder to locate, until a point is reached with a 2mm pupil when no peak is located and an error ("ERR") reading is obtained.

4.1C - The modified Canon Optometer

The method of modifying the Canon R1 optometer by Pugh and Winn (1988) involved changing the principle of operation from a single-swept mode of operation to one which measured a single photodetector output to give an indication of the magnitude of defocus. Consequently, unlike measurements made using the Canon in its normal static mode of operation, the signals collected by the photodetectors for continuous measurements were amplitude-dependent. Conversion of the optometer involved disabling the lens drive mechanism and developing a method whereby the lens carriage could be manually positioned. The signals from each of the photodetectors were processed and these were then fed into a digital storage oscilloscope via an analogue output and thereafter connected to an on-line computer (Epson PCe-XT clone) through an IEEE-488 interface. Further details of the modification may be obtained by referring to Pugh and Winn (1988; 1989).

The output from one of the photodetectors undergoing a sweep in the measurement of the refractive error of the model eye is illustrated in Figure 4.3.
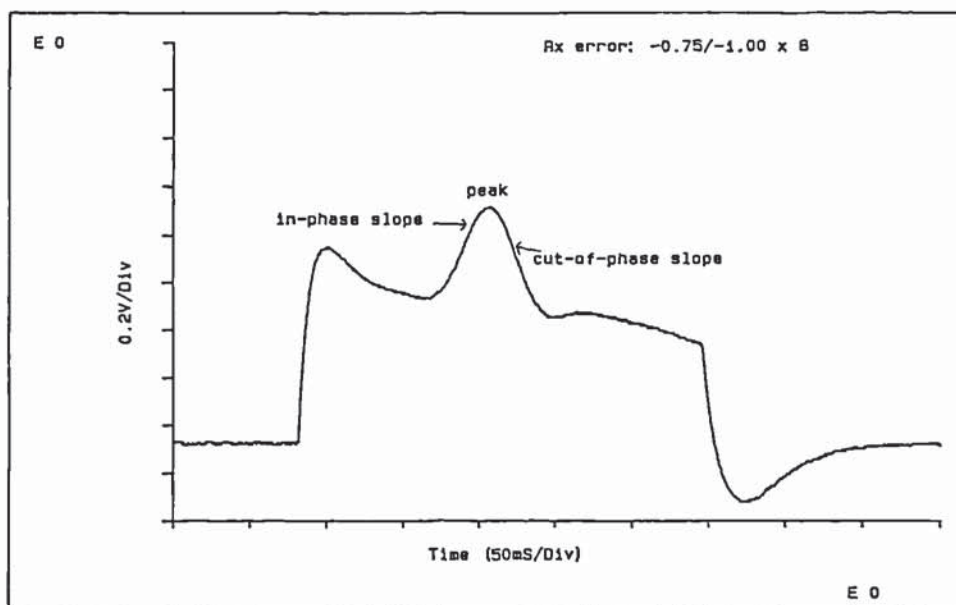
Figure 4.3: Output of one photodetector showing peak and slopes for a model eye with a refractive error equivalent to -0.75/-1.00 x 8

Pugh and Winn (1988) constructed a model eye to verify that the instrument in its modified form, was capable of measuring accommodation dynamics. The model eye

consisted of 2 lenses, a -2D lens positioned anteriorly and the second +20D lens situated 12 mm behind it and a loudspeaker cone upon which was attached a white card which acted as a movable 'retina' (see Figure 4.4). The use of a loudspeaker gave the advantage of allowing movement in a horizontal axis only. The axial length (i.e. the distance between the +20D lens and the 'retina') could be varied to produce different refractive errors using a frequency generator.
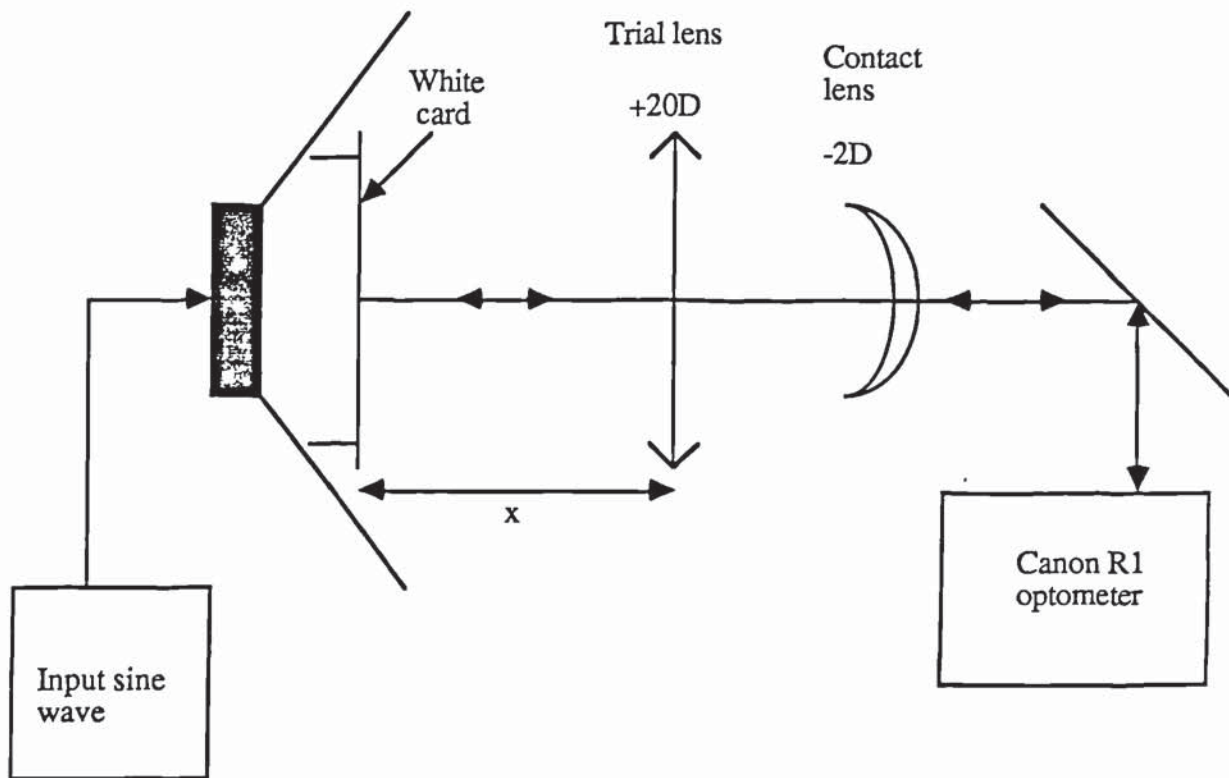
Figure 4.4: Schematic diagram of model eye. Distance 'x' was altered when a change in refractive error of the model eye was required.

For continuous measurements, the lens carriage could be positioned manually with the aid of an adjusting wheel to give one of 3 resulting waveforms: positioning the lens on the positive slope gave an 'in-phase' signal; on the negative slope, an 'out-of-phase' signal was produced, whereas if the lens carriage was placed such that the output from the photodetector was a maximum, an optically rectified signal was obtained. These 3 options are illustrated in Figure 4.5.
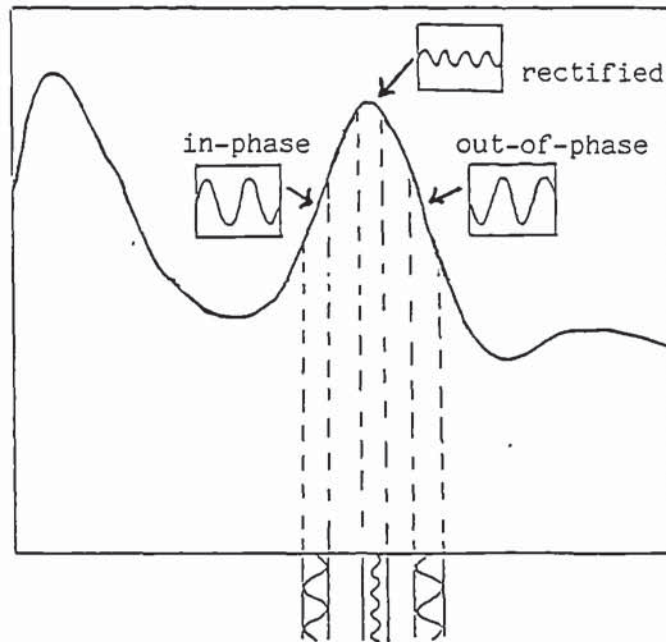
Figure 4.5: Diagrammatical representation of in-phase, out-of-phase and rectified signals from a single photodetector output.

Pugh and Winn (1988) verified that the Canon was capable of measuring changes in accommodation by using their model eye in which the 'retina' was driven sinusoidally at 2Hz by a frequency generator and the Canon switched to continuous mode. The position of the lens carriage was altered to give maximum output from one of the photodetectors. At this point, the resulting waveform was rectified, in that any change in position of the 'retina' about the maximum point resulted in a reduction in signal output (see Figure 4.6a). By adjusting the position of the lens carriage so that a 'defocused' signal was achieved, the waveform obtained was either in-phase or out-of-phase with the input signal, depending on the direction of defocus. Positioning the lens on the positive slope of the peak gave an in-phase waveform, and an out-of-phase waveform was obtained from the negative slope (see Figure 4.6b and 4.6c). By demonstrating the correct phase

relationship on both sides of the slope the authors were able to provide evidence for the instrument's ability to detect *defocus* , and not merely IR amplitude changes. The same phase relationship was successfully demonstrated on a human eye (Pugh and Winn, 1988) (see Figure 4.7).
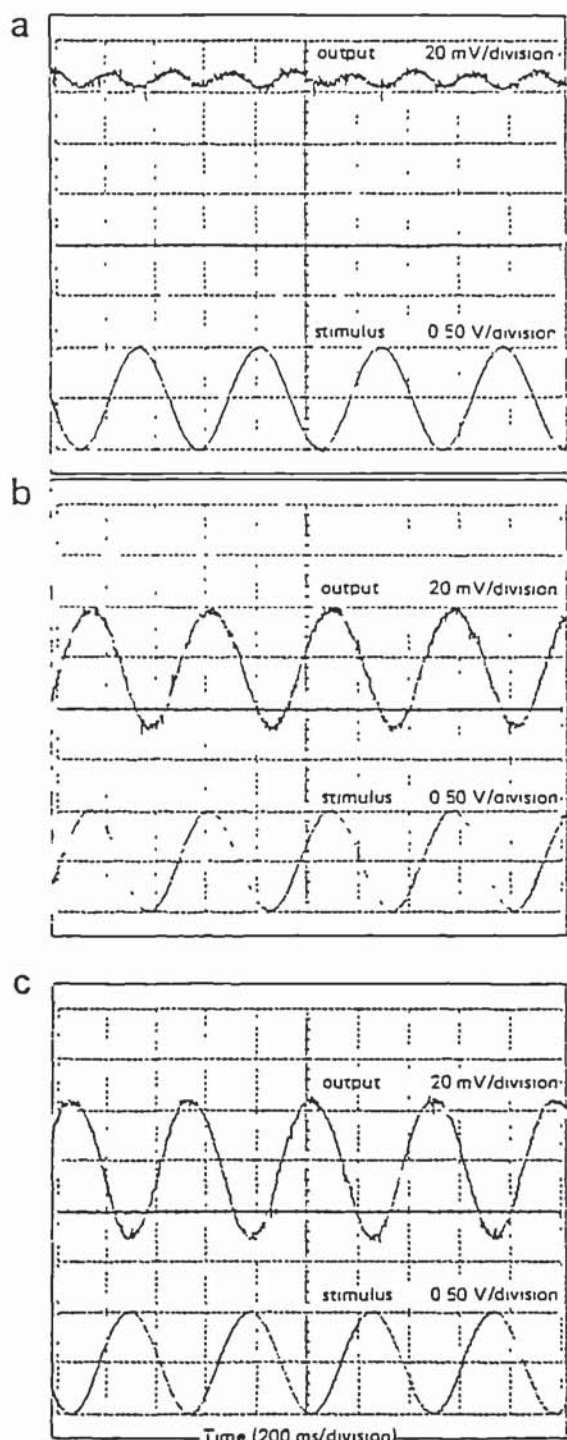
Figure 4.6a: Illustration of an optically rectified signal achieved by adjusting the wheel to the give a maximum output

4.6b Output signal is in-phase on the positive slope

4.6c Output signal is out-of-phase on the negative slope

(After Pugh and Winn, 1989)

86
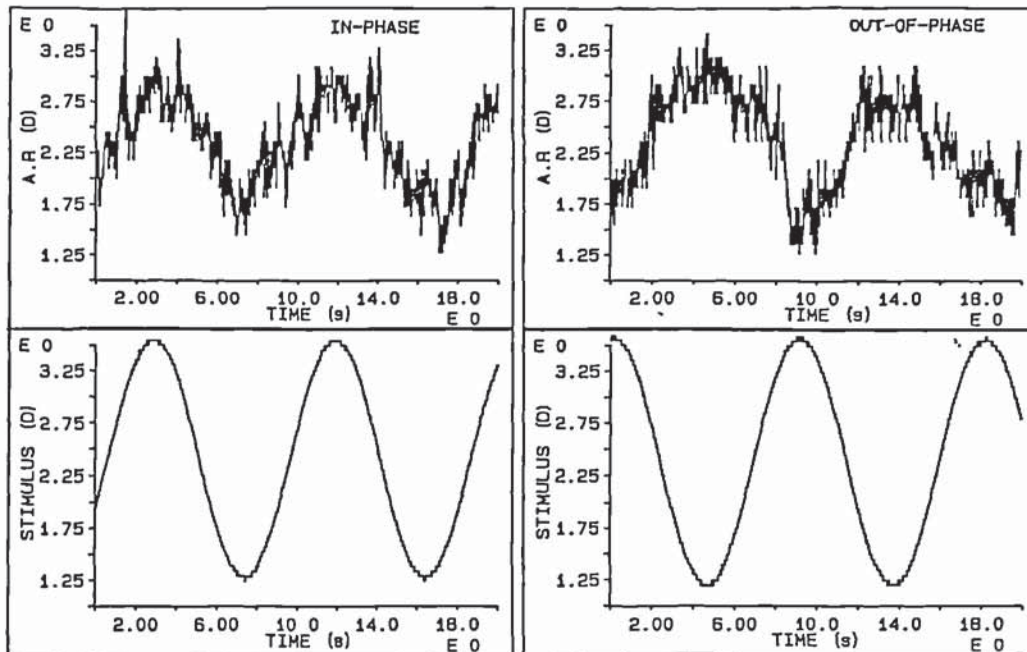
Figure 4.7: Response of Canon to human accommodative changes to a sinusoidally moving target over a dioptric range of 2.25D at a temporal frequency of 0.2Hz: a) adjusted to the positive slope of the peak b) adjusted to the negative slope of the peak. A.R = accommodative response.

Linearity for continuous measurements

The linearity of the Canon in continuous mode was determined by Pugh and Winn (1988) by oscillating the model eye at a frequency of 2Hz. This frequency was chosen in order to simulate the high frequency region of accommodative microfluctuations. The peak-to-peak amplitude measured 1.04mm, which gave a dioptric measurement of 0.72D. The peak-to-peak output was measured for varying degrees of defocus, and the sensitivity as a function of defocus was deduced. Figure 4.8 illustrates a graph of defocus measured from the peak against sensitivity, showing a maximum sensitivity of 98mV/D.
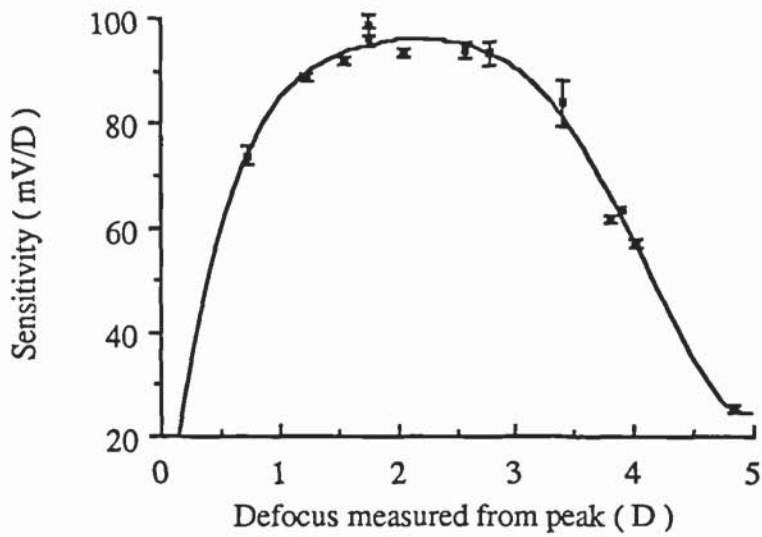
Figure 4.8: Graph of sensitivity versus degree of defocus on negative slope of the peak. The error bars indicate one standard error (From Pugh and Winn, 1988)

To evaluate the linearity and working range of the system, the graph of sensitivity against defocus was plotted. An equation was fitted to the curve and was integrated to give a graph of output voltage versus degree of defocus (Figure 4.9).
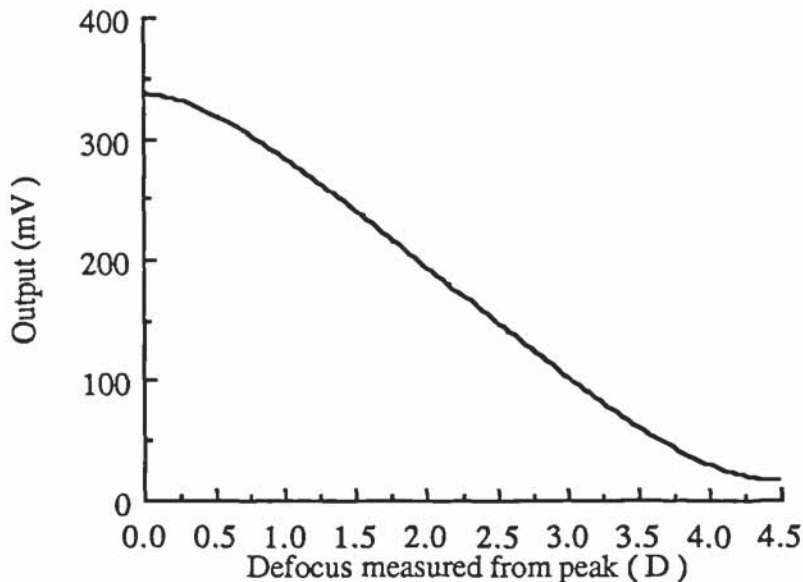
Figure 4.9: Graph of output voltage versus degree of defocus (negative slope) (From Pugh and Winn, 1988)

Calculations based upon this figure give a 2.8% non-linearity over a range of 0.8-3.8D and a 0.7% non-linearity over the range 2-3D. These results were obtained from measurements made from the negative slope of the peak to ensure that defocus changes

were measured and not spurious IR amplitude effects. Similar results for linearity were obtained from the positive slope (Pugh and Winn, 1988).

Summary

The Canon IR optometer has been converted to enable continuous measurements of accommodation. The linearity of the instrument and its feasability to record the human accommodation response has been evaluated using model and human eyes (Pugh and Winn, 1988). Further work is required to assess other aspects of the instrument such as its frequency response, noise levels and ocular exit pupil required for consistent recordings in continuous mode and these will be described in the following chapter.

CHAPTER 5

EXPERIMENTAL WORK ON THE CANON R1

5.1 Assessment of the Canon's sensitivity for measurements made in continuous mode using a static measuring technique

To establish the dioptric range over which the Canon optometer measures precisely when used in its continuous mode of operation, the model eye was used (Figure 4.4) and the latency to the peak position for a large range of static refractive errors noted. The various refractive errors were achieved by changing the power of the contact lens on the model eye and also by altering its axial length. A graph depicting the results is shown in Figure 5.1, which illustrates that the sensitivity of the instrument does not change over its static working range.
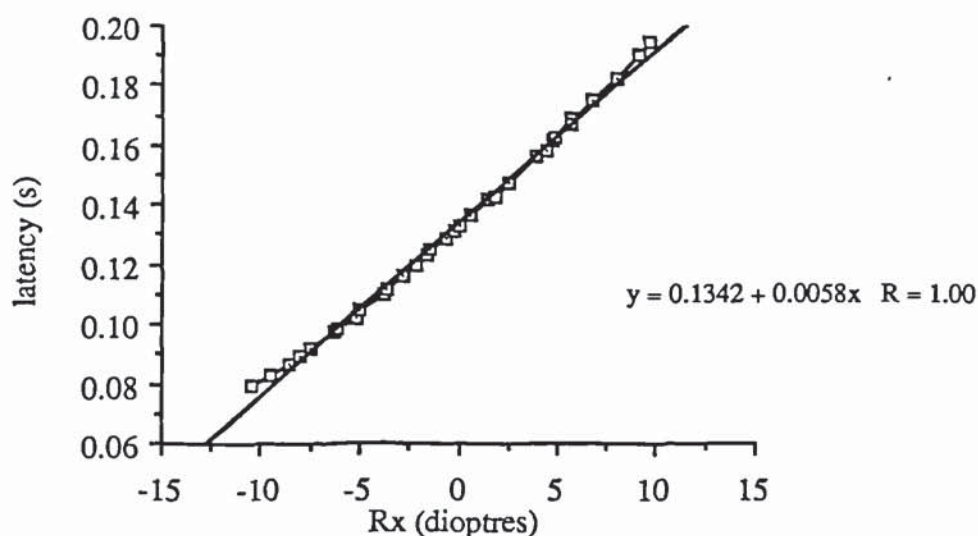
Figure 5.1 Graph showing the linearity of the Canon when measuring in its static mode

An investigation into the Canon's sensitivity when measuring a human eye has produced an instrument sensitivity of 12mV/D (Pugh and Winn, 1988). In this case, the subject was required to view a sinusoidally moving target through a +5D Badal lens over a 1.12D range. The static response to the extreme and mid-stimulus positions were noted and an accommodative response of 0.83D was found for the 1.12D range. The apparent reduced sensitivity for the human eye compared with a model eye is in part due to the

latter's greater reflectivity. The inherent variations induced by eye movements and pupillary diameter variations are further causes for the sensitivity reduction obtained when measurements are made on human eyes compared with the model eye.

5.2 - Noise level of Canon R1 Optometer

The model eye was mounted in front of the Canon R1 in order to assess the noise level of the instrument. To simulate the reflectance of a human eye, a neutral density filter was fixed in front of the model eye to give the same IR level as that obtained from a human eye. A low temporal frequency square wave was generated and recorded on the oscilloscope, and refractive errors at the extreme points were noted. By this procedure the drive voltage could be related to dioptric values. The Canon was then switched to continuous mode, and five 10s recordings of the signal from the optometer were made on the immobile model eye. Power spectrum analysis was performed on each 10s run, and the 5 runs were integrated to increase confidence (10 degrees of freedom). Figure 5.2 illustrates the power spectrum of the noise level of the optometer using a model eye compared with a typical power spectrum of accommodative microfluctuations of subject GB viewing a target at a -4D vergence. The root mean square (rms) fluctuations were 0.02D on the in-phase side and 0.015D on the out-of-phase side. The rms from a human eye when viewing a stationary target is ~0.2D and therefore the noise level of the optometer is an order of magnitude smaller than the variability in the human response to a stationary target. In Figure 5.3, the integrated power spectra obtained from the responses of a human aphakic eye (aged 22 years) to a 4D target vergence may be seen compared with the data obtained from subject GB (aged 21 years). A detailed examination of the response of an aphakic eye compared with a fellow normal eye will be made in Chapter 8 (pps. 129-142).
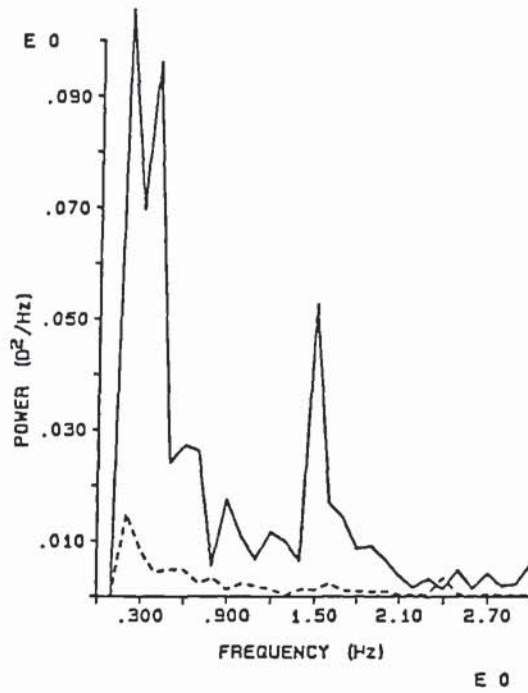
Figure 5.2: Power spectrum of noise level obtained with a model eye on the Canon optometer compared with the power spectrum of accommodative microfluctuations of a subject viewing a near target at a -4D.
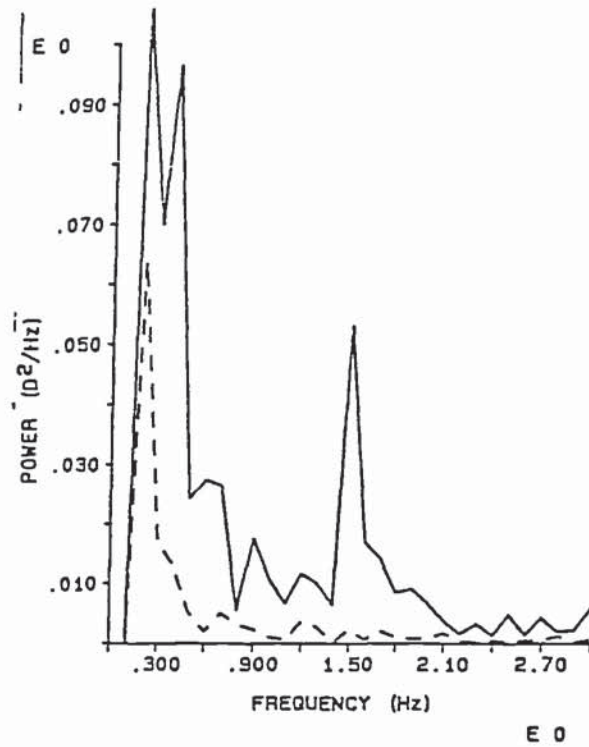
Figure 5.3: Power spectrum of aphakic eye's response to a target at a -4D vergence compared with that of a normal eye.

5.3 - Frequency response of the Canon Optometer

To evaluate the frequency response of the optometer, the'retina' of the model eye was oscillated at a number of temporal frequencies over the range 0.2-15Hz. Five 10s traces were recorded at each frequency over a 1D range and the gain of the system calculated. A Bode plot showing the frequency vs gain may be seen in Figure 5.4, which illustrates that the response of the Canon is flat over the range 0.1-15Hz. This range encompasses all frequencies of interest in the study of accommodation dynamics (Denieul, 1982; Winn *et al*, 1989a). Responses to frequencies above 15Hz were not recorded as the model eye became unstable.
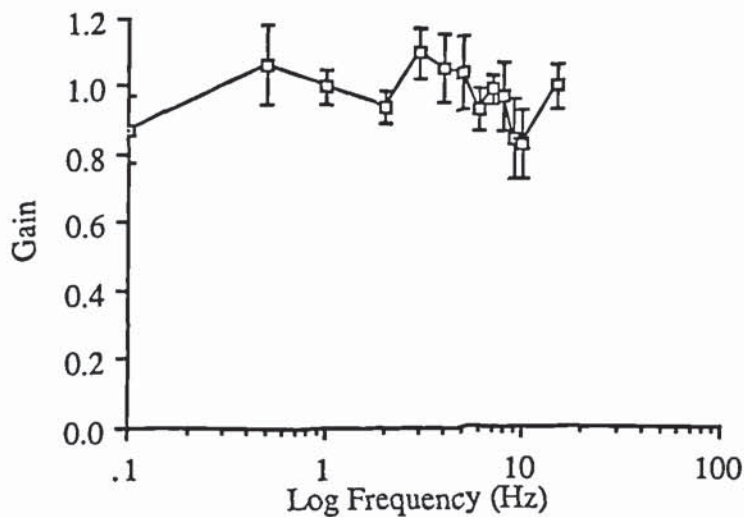
Figure 5 4: Bode plot illustrating the frequency response of the system. Error bars show 1 SEM.

5.4 - Calibration of the Optometer

In order to convert the output from the oscilloscope into dioptric measurements, it is necessary to perform a calibration procedure. This includes recording in static mode the accommodative response to a step change in vergence, followed by the recording of the response to an identical step change with the Canon switched to its continuous mode. The number of points on the oscilloscope screen may be converted into dioptres using a simple mathematical calculation, as illustrated below.
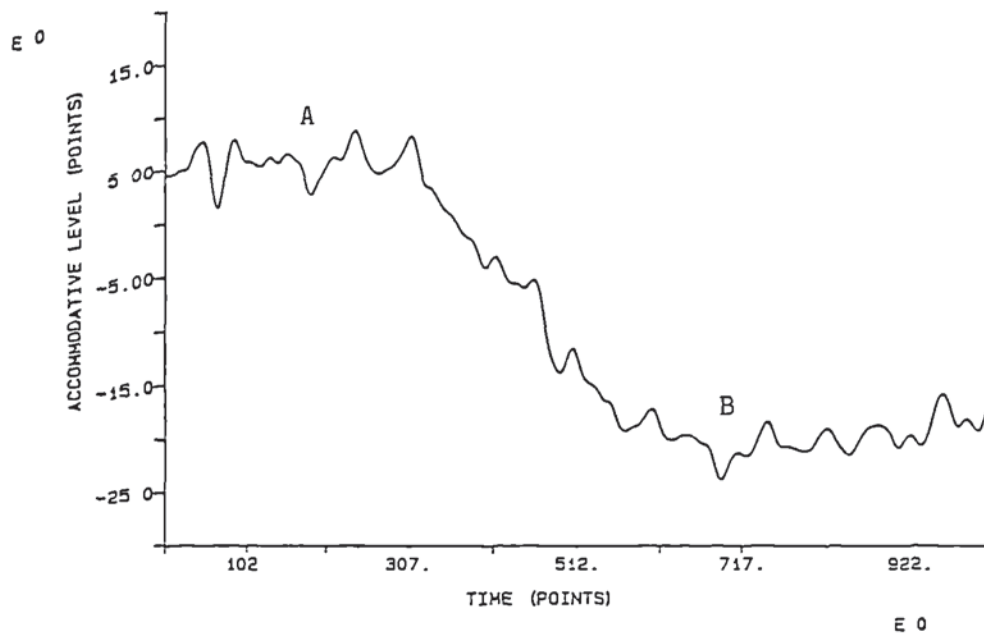
Figure 5.5: Calibration step in continuous mode: change from A to B may be converted from points into dioptres using the dioptric values obtained during static measurements.

Mean dioptric value§ at vergence corresponding to A shown above	4.08D
Mean dioptric value at vergence corresponding to B shown above	1.97D
Dioptric difference from A to B as measured in static mode	2.11D
Difference in points from A to B	33.0
Number of points per dioptre	15.6

5.5 - The effect of pupil diameter on static and dynamic measurements of accommodation using an IR optometer.

The alpha-adrenergic agonist drug phenylephrine HCl 2.5% is frequently used to dilate the pupil during recordings of accommodation dynamics, particularly when subjects are required to view a near target when pupillary miosis can induce artefacts on IR recordings (e.g.Kotulak and Schor, 1986a; Winn *et al*, 1987) although this drug is known to decrease the amplitude of accommodation by ~1-2D (Mordi, Lyle and Mousa, 1986;

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§ The mean dioptric value of the refraction was calculated by adding the spherical component to half the value of the cylindrical component

Doughty *et al*, 1988; Rosenfield *et al*, 1990). In addition, the drug may have an effect on the microfluctuations of accommodation, and preliminary evidence has shown that there is a reduction in the rms of the fluctuations, although the form of the power spectra appears unchanged (Heron *et al*, 1989). Furthermore, there exists the possibility of complications with the use of phenylephrine HCl. These include the risk of systemic side effects, the possible need for a counteracting miotic drug and the necessity for ethical approval prior to its use.

It is necessary therefore, to examine the effect of pupil diameter on the output signal of the Canon photodetector using model and human eyes and to determine the minimum ocular exit pupil diameter necessary for accurate measurements of accommodation dynamics. The necessity for a mydriatic drug may then be assessed before accommodation recordings are made.

5.5A - Investigation of the effect of pupil diameter on a model eye using a single-shot measuring technique.

To evaluate the effect of pupil diameter on continuous measurements using a swept technique, the profile of the single sweep was examined for varying pupil diameters on a model eye. The quantitative effect of pupil diameter was assessed by measuring the gradient on both sides of the peak for 9 pupil diameters ranging from 2mm to 9mm. Figure 5.6 illustrates the method used to calculate the gradient on the negative slope of a sweep. The gradient was calculated over the range illustrated from point A to point B for each pupil diameter. A graph of slope against pupil diameter is illustrated in Figure 5.7. A scaling process was required to enable a comparison of the y-values, which involved dividing these values by the mean of the y values for pupil diameters greater than or equal to 5mm.
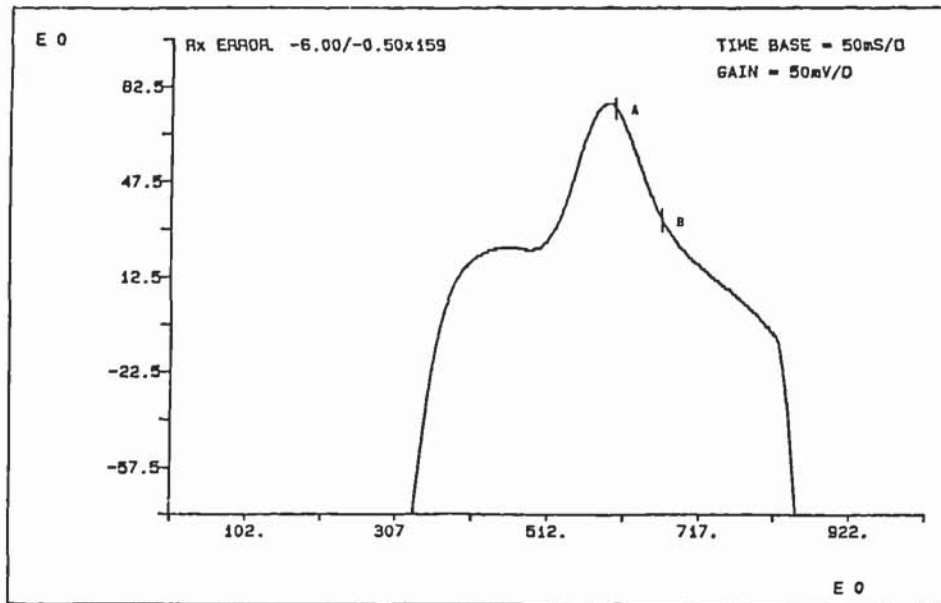
Figure 5.6: Illustration of method used to calculate the gradient for the negative slope of a single sweep.
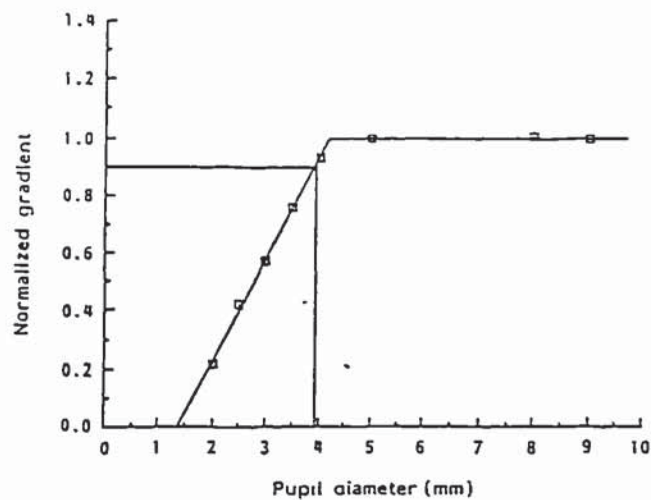
Figure 5.7: The effect of pupil diameter on the output of the optometer using a model eye: variation in the negative gradient with pupil diameter for static recording (After Winn *et al*, 1989b)

A 10% reduction in signal relative to the nominal maximum output level was used to define the pupil diameter limit below which the performance of the instrument in continuous mode was unacceptable. An examination of Figure 5.7 illustrates that the gradient is independent of pupil diameter when greater than approximately 4mm in diameter.

The maximum output level occurred for pupil diameters of 5mm and a mean of the output for this pupil diameter was used in a calculation to determine the pupil size which gave an output of 90% of this value. The results show that the minimum pupil diameter for the positive slope is 3.82mm and for the negative slope, 3.9mm. It may therefore be concluded that the output from the optometer is independent of pupils > 3.9mm in diameter in the case of the model eye.

5.5B - The effect of pupil diameter on dynamic measurements of accommodation

Having determined the minimum pupil diameter necessary for constant output during continuous measurements using a *static* technique, a similar procedure was carried out during continuous measurement on a *dynamic* model eye. In this case, the retina of the model eye was driven sinusoidally at 1Hz with a dioptric amplitude of 0.75D. The negative slope of the peak was located for a single channel, ensuring that any change in output was due to a change in focus and not due to variations in infra-red signal amplitude. The rms of 5 runs of sinusoidal output signal were recorded for each pupil diameter. Again a 10% reduction in the rms value of the output for a constant stimulus was taken as a criterion for artefact-free recording. Figure 5.8 illustrates that the minimum pupil diameter for this condition is 3.8mm.
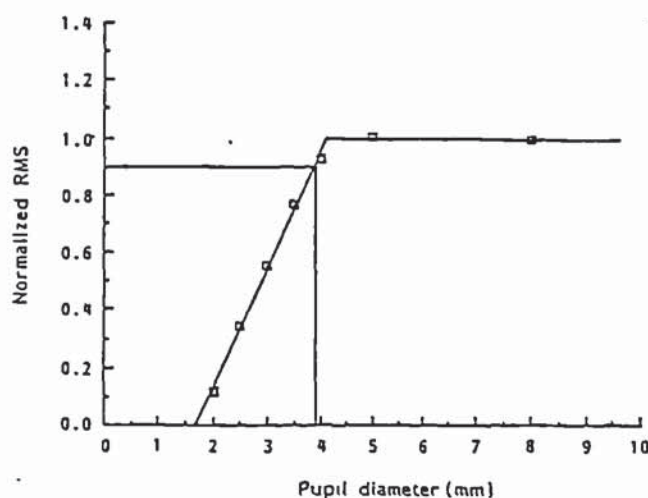
Figure 5.8: The effect of pupil diameter on the output of the optometer using a model eye: variations in the rms value for dynamic recording (After Winn *et al*, 1989b)

The manufacturer's minimum pupil recommendation for accurate static readings is 2.9mm. In order to clarify whether this was the stipulation for the entrance or exit pupil of the eye, it was necessary to determine the diameter of the incident beam. By aligning the Canon optometer on a narrow slit and photodiode, the incident beam measured 0.7mm at the corneal apex, indicating that it was the ocular *exit* pupil which provided the 2.9mm limiting aperture.

The Canon R1 therefore requires an ocular exit pupil of 3.8mm for pupil independent operation, i.e. the output profile for a single photodetector is constant for pupils diameters greater than 3.8mm

5.6 - Performance of the Canon on a human observer.

In order to examine the limit of pupil diameter on a human eye, it was necessary to dilate the pupil with 2 drops of the alpha-receptor agonist phenylephrine HCl 10%, preceded by a drop of 0.4% benoxinate HCl to minimise reflex tearing and facilitate absorption of phenylephrine. The mydriasis was required in order to produce a static pupil as under normal conditions, pupillary hippus would prevent accuracy in assessments of pupil diameter. Pupil mydriasis was achieved within 20 minutes and subsequently reduced by the instillation of the alpha-antagonist thymoxamine HCl 0.5%. Static single shots were taken at discrete intervals following the mydriatic instillation, and pupil diameters were noted. A similar procedure after the instillation of thymoxamine was followed. Further miosis was obtained by shining a torch light into the eye not under test, to enable greater constriction via the consensual pupil reaction.

The method used to calculate the minimum pupil size for constant output was identical to that used for the model eye (section 5.5A). The calculated slopes (positive and negative) over the range of pupil diameters were plotted and the results showed that a 10% reduction in gradient occurred at a pupil diameter of 3.7mm for the positive slope and 3.51mm for the negative slope (Figure 5.9).
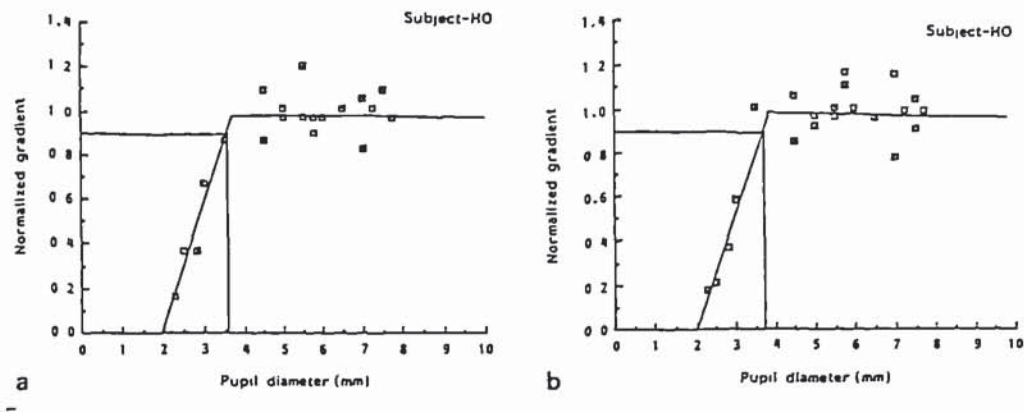
Figure 5.9: The effect of pupil diameter on the output of the optometer using a human eye. (a) Variation in the positive gradient with pupil diameter for static recording. (b) Variations in the negative gradient with pupil diameter for static recording (After Winn *et al*, 1989b)

In order to compare the model eye exit pupil with that of the human eye, a correction factor for the magnification effect of the cornea on the pupil must be applied. The real pupil is 1.12 times smaller than the apparent pupil (Alexandris, 1985). The real pupil is therefore ~3.3mm.

The data indicate that the optometer utilises a pupil area of constant diameter for measuring IR light in the case of model and human eyes. The exit pupil limit of 3.9mm above which the instrument is pupil independent indicates that the modified Canon optometer provides a viable opportunity to record accommodation dynamics on a human eye without the need for a mydriatic drug.

5.7 - The Hamamatsu C3160 Percept Scope

In order to monitor eye movements, a Hamamatsu C3160 Percept Scope was incorporated into the experimental apparatus. The Hamamatsu Percept Scope utilises the first Purkinje image reflected from the cornea of the subject to monitor eye movements. Simultaneous recordings of accommodation and eye movements may be made using the experimental set-up which is illustrated schematically in Figure 5.10.

MODIFIED AUTO-REF

visible

target

IR

Refraction

IR camera

Digital storage oscilloscope

PC

Percept scope

IEEE 488 bus

monitor
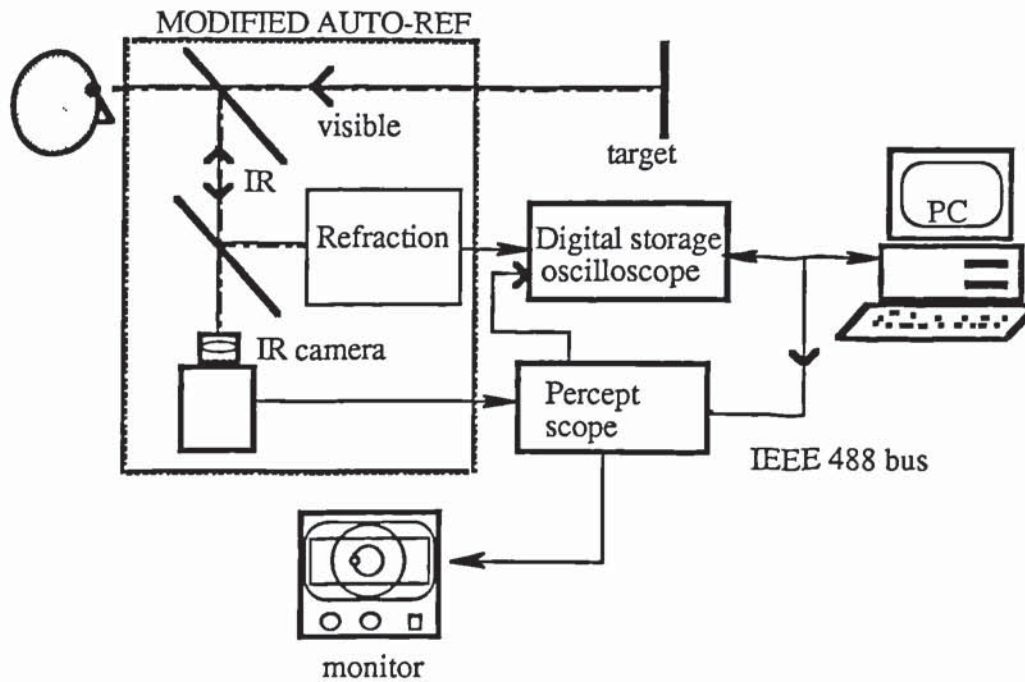
Figure 5.10: Schematic diagram of laboratory equipment[§]

5.8 - Eye movement artefacts during accommodation recordings

When measurements of temporal changes in accommodation are made using continuous recording techniques, it is evident that measurements are susceptible to artefacts induced by the subject's eye and head movements. The Canon optometer has the advantage of an IR TV monitor which may be used to verify that fixation during recordings is steady. To minimise artefacts induced by head movements during the accommodation recordings, the head rest supplied with the Canon was bolted to the wall of the laboratory with a metal strip. In addition, dental bites[#] were made for each subject which were fixed to a ball and socket joint attached to the chin rest. The wax bites were designed to create an oral seal which permitted swallowing and so minimise discomfort for the subject during recordings. Head movements were further restricted by means of a velcro tape which could be secured around the subject's head.

It was essential, however to determine an experimental limit for eye movements in order that the output of the Canon optometer was representative of accommodative changes and not merely due to changes in IR levels from spurious or rhythmic (e.g.microsaccadic) eye movements. In order to determine the tolerance limit for eye movements, measurements

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of the accommodation response with the Canon in continuous mode were made while a subject viewed a tangent scale mounted on a wall at 3m. The Hamamatsu percept scope was adjusted to monitor the position of the first Purkinje image produced by the alignment system of the Canon so that the subject's horizontal and vertical eye movements could be assessed. The subject viewed a central fixation spot, then changed fixation in 1 degree steps, and the change in position of the output from the Hamamatsu eye tracker on the oscilloscope screen was recorded. By monitoring the accommodation response, it was apparent that a steady accommodative level could be achieved for eye movements of less than 1 degree in magnitude. In addition, a model eye was used to calibrate the eye tracker which gave a value of 6 pixels per degree of movement. It was concluded that eye movements less than 1 degree in magnitude did not affect the output of the optometer.

5.9 - Summary.

The Canon Auto Ref R1 has been modified to provide an accurate means of measuring accommodation dynamics with relatively simple and speedy setting-up procedures. It is an instrument which is easy to align and operate, has the benefit of an open field-of-view, and can be easily switched from recording static to dynamic accommodation. Further it has a uniform frequency response up to 10Hz in its dynamic mode, which covers all frequencies attributed to accommodation and its sensitivity and resolution are appropriate to record the microfluctuations of accommodation. Given these advantages over previous continuous recording instruments therefore, the modified Canon is an ideal instrument to investigate temporal changes in the accommodative response.

Supporting publication

Winn B, Pugh JR, Gilmartin B and Owens H (1989b) The effect of pupil size on static and dynamic measurements of accommodation using an IR optometer. *Ophthal Physiol Opt* 9, 277-283.

CHAPTER 6

THE CHARACTERISTICS OF CILIARY MUSCLE INNERVATION IN EMMETROPIA AND LATE-ONSET MYOPIA

6.1 INTRODUCTION

In Chapter 2, the proposals of a number of investigators regarding the significant role that accommodation is likely to play in the development of late-onset myopia (LOM) were discussed. Previous studies based on measurements of amplitude of accommodation (Fledelius, 1981; McBrien and Millodot, 1986a) the accommodation stimulus/response function (McBrien and Millodot, 1986b; Bullimore and Gilmartin, 1987); the response accommodative convergence/accommodation (AC/A) and convergent accommodation/convergence (CA/C) ratios (Rosenfield and Gilmartin, 1987a,b; 1988b); tonic accommodation (TA) (Maddock *et al*, 1981; Bullimore and Gilmartin, 1987a,b; McBrien and Millodot, 1987a; 1988) and measurements of accommodative regression from a near task to pre-task TA (Gilmartin and Bullimore, 1987) have provided support for the proposal that there are differences in the characteristics of the accommodative mechanism between emmetropes (EMMs) and LOMs.

Latent changes in accommodative state known as accommodative hysteresis are an accepted characteristic consequence of sustained near visual tasks (Ebenholtz, 1983, 1991; Ehrlich, 1987; Fisher, Ciuffreda and Levine, 1987; McBrien and Millodot, 1988; Gilmartin and Bullimore, 1987), although the time course of the decay of hysteresis is a matter of conjecture and appears to be influenced significantly by the method of measurement. The hysteresis effects are presumed to be a manifestation of the adaptation of accommodation to the dioptric demand of the task. The method used to assess such adaptational effects is often based on measurements of accommodation in the absence of visual stimuli when the accommodative loop is opened in darkness (Ebenholtz, 1983; 1991; Gilmartin and Bullimore, 1987; 1991; McBrien and Millodot, 1987a; Rosenfield and Gilmartin, 1988a).

A number of studies have reported that LOMs appear to have lower tonic accommodation (TA) levels than EMMs (Bullimore and Gilmartin, 1987a;b; Bullimore *et al*, 1988; McBrien and Millodot, 1987a; 1988), which support the proposal that LOMs have a weak sympathetic activity range (Charman, 1982). Furthermore, it has been documented that LOMs exhibit a tendency for positive shifts in TA following prolonged near visual tasks which resist depletion for periods of up to 15 minutes following the imposition of dark room conditions (McBrien and Millodot, 1988), although there is no consensus regarding the time course for the depletion of the hysteresis effect. It appears that for short-term adaptation (<2 minutes) using an IR optometer, a negligible hysteresis effect is apparent which decays within 15s, whereas after a 30 minute adaptation period to a 6D stimulus, an increase of ~0.5D is maintained beyond the 15s decay period (Schor, Johnson and Post, 1984). Support for the above findings following short-term adaptation for emmetropic and myopic groups is given by Rosenfield and Gilmartin (1989), who found that for task durations up to 45s, accommodation regressed to pre-task TA within 40s of the imposition of dark room conditions. Significantly longer decay rates of accommodative hysteresis have been reported using laser optometers (e.g. Ebenholtz, 1983; 1991; Rosenfield, 1989).

Recent work has examined the nature of accommodative adaptation for a group of emmetropes who performed a 10 minute counting task set at vergences of -0.3D and -5D (Gilmartin and Bullimore, 1987). These authors used the non-selective beta-adrenergic receptor blocking drug timolol maleate and a saline control to compare the accommodative regression patterns to TA for the no-drug condition with those obtained when the beta-receptors in ciliary muscle were blocked. The results showed that the post-task TA regressed to baseline levels within 60s for the 15 emmetropes examined. Further, timolol retarded the rate of regression to TA for the emmetropes with pre-task TA $\geq$ 0.75D but only for the task set at -5D. It was concluded that sympathetic innervation of the ciliary muscle is augmented by concurrent parasympathetic activity and that emmetropes with low tonic levels may be more susceptible to post-task hysteresis effects following tasks with high levels of accommodative demand (Gilmartin and Bullimore, 1987). It was conjectured that the hysteresis effects may be a consequence of a weakened sympathetic

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facility in those subjects with TA levels below 0.75D and that these effects could act as a precursor to the physiological processes which lead to the development of posterior vitreous chamber elongation evident in myopia.

Further support for the above findings has been documented recently in an extension of the above work which examined a population of LOMs in addition to EMMs (Gilmartin and Bullimore, 1991). Following a similar experimental protocol as that for their earlier experiment, but without the use of drugs, Gilmartin and Bullimore found that the accommodative regression patterns to pre-task TA following the cessation of a near task were significantly slower for LOMs compared with EMMs and the difference in regression rates between the two refractive groups showed a positive correlation with task vergence. It was proposed that the rate of accommodative regression to TA represented an index of the characteristics of the innervation to the ciliary muscle present during the task: for certain emmetropes this may consist of a depletion of both parasympathetic and sympathetic inputs whereas for LOMs it may be representative of a decay of the parasympathetic input only.

The aim of this experiment is to extend the work of Gilmartin and Bullimore (1987; 1991) who used a quasi-static method of measurement, by examining further the regression patterns of accommodation following a 3 minute near task for a group of EMMs and LOMs using continuous recordings of accommodation. The advantage of such continuous recordings include the ability to analyse with greater precision, due to an increased sampling rate compared with the quasi-static method adopted by Gilmartin and Bullimore (1987, 1991) and the ability to record the accommodative response during the initial 5s period in darkness, which was lost in previous work, due to the necessity to realign the optometer during that time.

It has been established by pharmacological means that beta$_2$ adrenergic receptors predominate in ciliary smooth muscle (Lograno and Reibaldi, 1986; Wax and Molinoff, 1987; Zetterström and Hahnenberger, 1988; Van Alphen, Kern and Robinette, 1965; Van Alphen, 1976). Inhibition of the sympathetic component to the ciliary muscle will

therefore occur with beta antagonists such as timolol maleate which blocks both beta1 and beta2 receptors and only minimally, if at all, with cardioselective beta1 antagonists such as betaxolol HCl. Both agents will induce ocular hypotensive effects through beta activity at other ocular sites, thus betaxolol may be used as a control agent. In this experiment therefore, the receptors to the ciliary muscle will be blocked by the instillation of timolol and the control condition will include the use of betaxolol in addition to saline, as the former agent will act as a more appropriate control than the latter. The use of saline as a control condition provides the advantage of a comparison with previous work.

In this experiment, the Canon optometer (Chapter 4: Methods and Instrumentation, pps. 78-89) was used to record the accommodation responses continuously for a 3 minute period during a near visual task set at -3D above tonic levels and for a period of 80s following the imposition of dark room conditions. Ten EMMs and 10 LOMs participated in a double-blind protocol between timolol, betaxolol and saline.

6.2 METHOD

10 emmetropes (EMMs: 5 male, 5 female, mean age $\pm$ 1 S.D. $= 21.1 \pm 1.1$ years) and 10 LOMs (6 male, 4 female, mean age $\pm$ 1 S.D. $= 21.3 \pm 1.1$ years), all of whom were optometry students from Aston University, participated in the study. The subjects were aged between 19 and 31 years and following a full explanation of experimental procedures which had been approved by ethical committee, all signed a consent form prior to taking part in the study. The emmetropic subjects had refractive errors varying within the range of plano to +0.50D spherical equivalent (mean 0.15DS) with a maximum of 0.5D of astigmatism. The myopic subjects selected for the study had all developed their refractive error after the age of 15 years (mean age-of-onset 17.9$\pm$ 2.2 years), the range of refractive error being -1.25 to -3.25 dioptres best sphere (mean = -2.05 $\pm$ DS) again with a maximum of 0.5D of astigmatism (see Appendix I.1, p209). All subjects (including EMMs) were fitted with an appropriately powered ultrathin soft contact lens (*Acuvue*, Johnson and Johnson or *O4 series* Bausch and Lomb lenses) ensuring visual acuities of at least 6/5 and good initial comfort. The contact lenses were inserted at least 20 minutes prior to the commencement of recordings to allow sufficient time for

adaptation to the lenses. All subjects had iris pigmentation which was approximately equivalent to colour standard A (Seddon *et al*, 1990) and all had normal binocular vision. Ultrasonography (A-scan ultrasound) and keratometry measurements were taken for all subjects.

A modified Canon R1 infra-red optometer was used to measure the monocular accommodation response and a sampling rate of 10Hz was selected for a single meridian. Pre-task TA was measured following a 3 minute period in darkness to allow any pre-experimental effects on tonic levels to dissipate. Ten measurements of TA were then taken over the next 3 minutes using the Canon in its normal 'static' mode of operation. These readings were averaged to give a pre-task estimate of TA. Following completion of TA recordings, 3 measurements of IOP were recorded from both eyes using a *Digilab* pneumatonometer (Model 30D, Cambridge, Mass.), the eyes having been anaesthetised with 2 drops of 0.4% benoxinate HCl. Arterial pulse rate over a 15s period was measured from the wrist and by this means it was often possible to verify the systemic absorption of timolol, which is known to reduce arterial pulse by up to $10b.min^{-i}$ (Cinotti *et al*, 1985). A precision micropipette was then used to instill into the eye to be measured, 60µl (2 x 30µl drops) of either saline, timolol or betaxolol, following a double-blind protocol. There followed a period of 45 minutes before measurements of accommodation were resumed in order to allow an adequate period of time for the drug to take effect (Gilmartin, Hogan and Thompson, 1984).

Static TA measurements were again taken after the 45 minute break to ensure that the tonic level was unaffected by the drug. The Canon optometer was then switched to its continuous mode of operation and a calibration step recorded (see Methods and Instrumentation, Chapter 4). Subjects were requested to concentrate on the centre of a high contrast Maltese cross and letter target which was located at a vergence of -3D above the subject's TA position for a period of 3 minutes before the lights were extinguished. A small dim green fixation spot, located at 1m which had been shown to be an effective method of opening the accommodative loop (see Appendix I.2, p209), acted as a guide and helped maintain steady fixation in darkness. Accommodation was measured

continuously during the task and for a period of 80s after the task. A wash-out period of at least 4 days was allowed between drug trials.

6.3 RESULTS

The biometric measurements for the 10 emmetropic and 10 myopic subjects are depicted in histogram form in Figure 6.1 and the measurements are summarised in Table 6.1. It can be seen that there is a general trend for both axial lengths and vitreous chamber depths to be increased in the myopic eyes, although these differences reached statistical significance for the left eyes only (Student's t-test: axial length: $t = 3.09$, d.f = 17, $p = 0.007$; Vitreous chamber depth: $t = 2.54$, d.f = 17, $p = 0.02$). The mean refractive errors for the left eyes were marginally more myopic than those of the right (R: -1.86 ± 1.0; L: -2.40 ± 0.8DS). There was no significant difference between mean values of corneal curvature (K) or lens thickness for the 2 refractive groups (see Appendix 1.3 - 1.4, pps. 203-204).
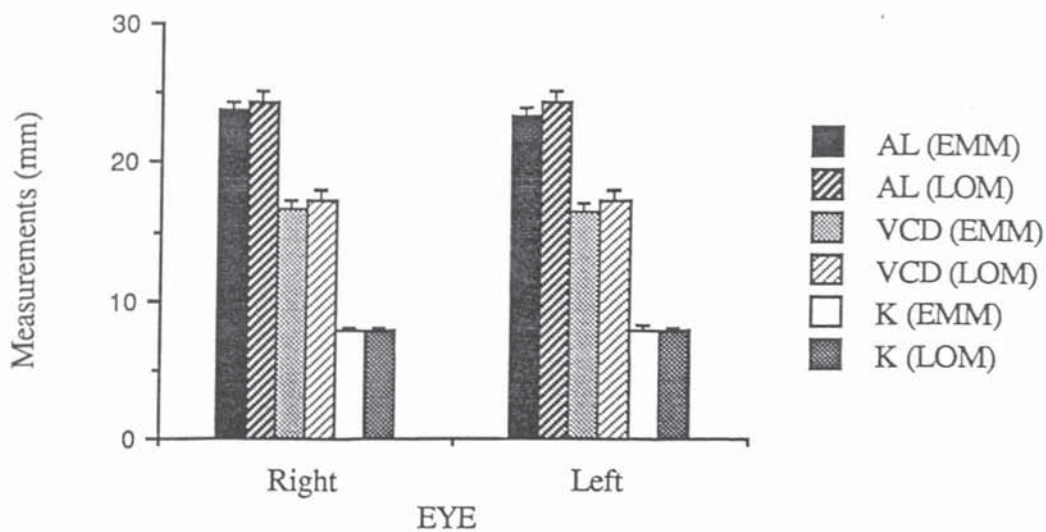
Figure 6.1: Histogram illustrating the biometric measurements for both emmetropes and myopes. AL = axial length; VCD = vitreous chamber depth; K (EMM) = mean keratometry readings for emmetropic subjects; K (LOM) = mean keratometry readings for myopic subjects. Error bars indicate 1 standard deviation.

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Biometric measurement	EMMs (mm)	LOMs (mm)
Axial length (R)	23.60 ± 0.5	24.28 ± 0.8
Axial length (L)	23.32 ± 0.6	24.35 ± 0.8
VCD (R)	16.46 ± 0.6	17.24 ± 0.8
VCD (L)	16.33 ± 0.6	17.25 ± 0.8
Mean K (R)	7.88 ± 0.2	7.83 ± 0.2
Mean K (L)	7.86 ± 0.2	7.85 ± 0.2
Lens (R)	3.50 ± 0.2	3.59 ± 0.2
Lens (L)	3.53 ± 0.2	3.61 ± 0.2
ACD (R)	3.67 ± 0.1	3.43 ± 0.2
ACD (L)	3.40 ± 0.2	3.49 ± 0.2

Table 6.1: Summary of mean values (± 1 S.D) for the biometric measurements for the 2 refractive groups. All measurements are in mm.

Table 6.2 summarises the dioptric values for TA and within-task accommodative responses for both refractive groups under all 3 drug conditions (see Appendix 1.5 and 1.6, p211). It may be seen that there was no significant difference between TA, or within-task measurements for the different drug treatments.

	Emmetropes		Late-onset myopes	
Drug condition	TA (D)	Within task response (D)	TA (D)	Within task response (D)
saline	-0.96 ± 0.3	-3.75 ± 0.4	-0.80 ± 0.5	-3.86 ± 0.4
timolol	-0.89 ± 0.2	-3.88 ± 0.2	-0.81 ± 0.5	-3.92 ± 0.4
betaxolol	-0.95 ± 0.4	-4.00 ± 0.5	-0.86 ± 0.5	-3.98 ± 0.4

Table 6.2: Details of TA and accommodative response (mean ± 1 S.D.) for saline and drug conditions for the 2 refractive groups.

Figure 6.2 illustrates the effect of timolol and betaxolol on the treated eyes for the two refractive groups. The data illustrate that timolol has a marginally greater reduction in IOP than betaxolol which supports the documented hypotensive effect of the drugs.
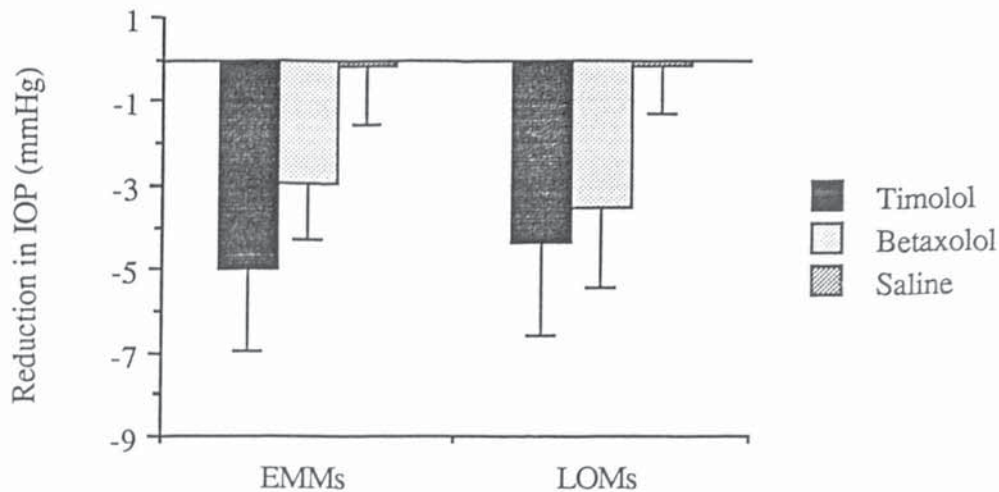
Figure 6.2: Histogram illustrating the reduction in IOP ~1 hour post-instllation induced by timolol and betaxolol for the 2 refractive groups. The saline data is also illustrated. Error bars indicate 1 S.D.

Post-task regression of accommodation

The composite plots of accommodative regression to baseline TA levels are illustrated in Figure 6.3 and 6.4 for the EMMs and LOMs respectively. The data are smoothed at 2Hz to illustrate the general form of the regression. Task accommodation levels have been normalized at 3D, so OD represents the tonic resting level of accommodation. The vertical dotted line represents the point at which the lights were extinguished. When the raw data is collapsed about the mid-point of each successive 10s period and the mean used to compute standard errors of the mean (sems), the dioptric value corresponding to 2 sems was of the order of 0.25D (see Appendix I.8, p214 for graphical illustration). The sems were of the same order for all experimental treatments and to simplify illustration of the data they have been omitted. The data for the myopic group for the betaxolol condition shows that there has been no significant effect on regression patterns. A similar regression pattern may be observed for the timolol condition for this refractive group.
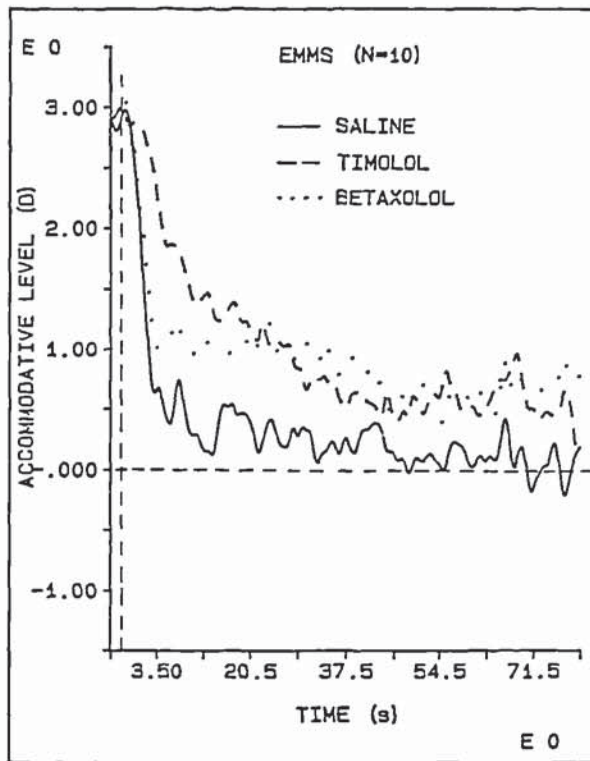
Figure 6.3: Regression plot of accommodation from a near task to TA for the group of EMMs (N=10)
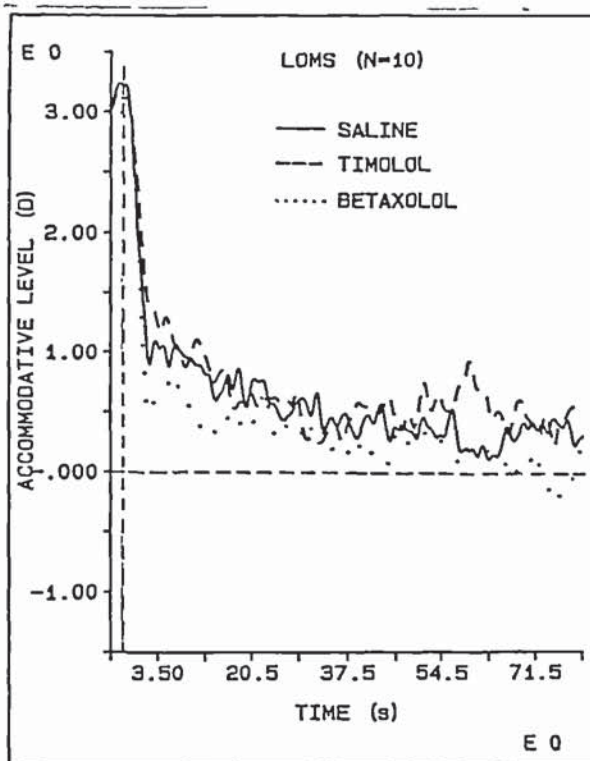
Figure 6.4: Accommodation regression plots from a near task to TA for the group of LOMS (N=10)

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Figure 6.3 illustrates the saline data for the group of 10 emmetropes: there is again a rapid regression to baseline levels which is also evident for the betaxolol data. In contrast, the data for timolol shows a distinctly slower regression pattern and a positive shift.

In Figure 6.5 and 6.6 the emmetropic group has been divided into 2 groups as an inspection of the individual data for the emmetropes revealed that the positive shift with timolol occurred only for 4 of the emmetropes: Figure 6.5 illustrates the regression patterns for the emmetropes who showed a slower regression response following timolol treatment whereas Figure 6.6 shows the regression patterns for the remaining 6 emmetropes whose responses were similar to those for the myopic subjects i.e. there was no significant difference between drug trials. In addition, there was a positive shift in TA at the end of the 80s period, indicating a persistence of post-task tonus and no evidence of within-task sympathetic inhibition.

The effects of timolol and betaxolol on the IOP of the emmetropic subjects are illustrated in table 6.2. The group of emmetropes has been divided into two groups: those showing a timolol shift and those without a positive shift. There was no significant difference between the reduction in IOP for the emmetropes with a timolol shift compared with those emmetropes without an effect with timolol.
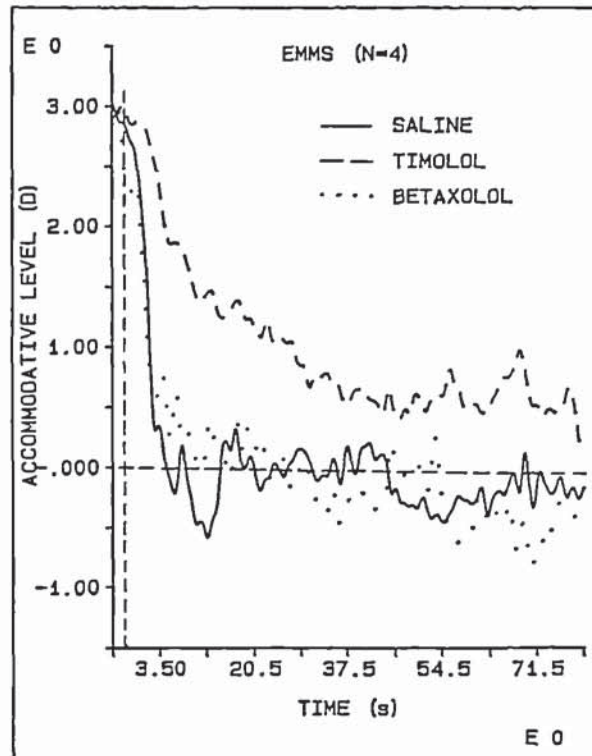
Figure 6.5: Accommodation regression plots for those emmetropes showing a positive shift and retarded rate of regression with timolol
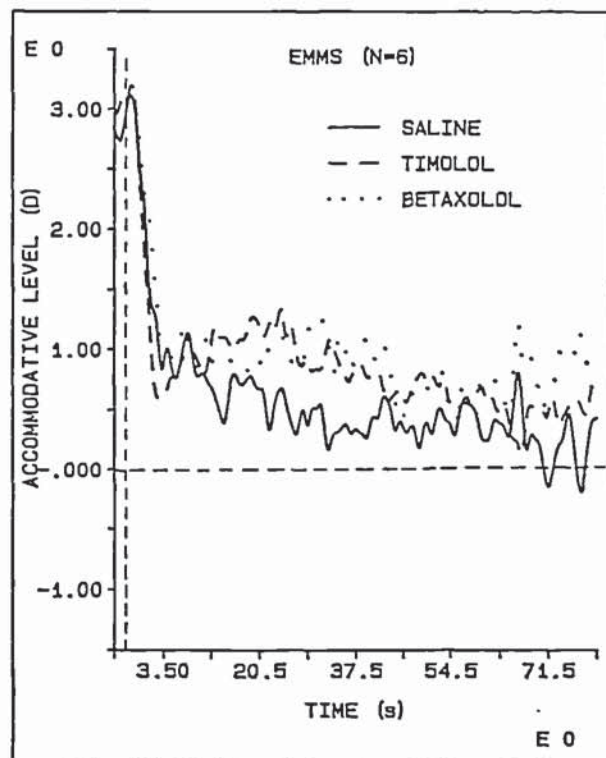
Figure 6.6: Accommodation regression plots for those emmetropes with no change in regression rate following timolol treatment

	Timolol treatment		Betaxolol treatment	
Subjects	IOP reduction (t) (mmHg)	IOP reduction (u) (mmHg)	IOP reduction (t) (mmHg)	IOP reduction (u) (mmHg)
With timolol shift (N = 4)	5.23±2.0	2.85±1.7	3.03±2.0	1.43±1.3
Without shift (N = 6)	5.23±2.1	2.33±2.2	2.78±0.8	1.88±1.0
All EMMs (N = 10)	5.23±1.9	2.54±1.9	2.88±1.3	1.70±1.0
All LOMs (N = 10)	4.34±2.2	2.66±1.7	3.51±1.9	1.80±2.1

Table 6.3: The effect of timolol and betaxolol on the treated (t) and untreated (u) eyes of the 2 refractive groups. The emmetropes have been subdivided into 2 groups: those who showed a positive shift in accommodative regression following timolol treatment and those with no accommodative shift. The numerical values illustrate the mean ± 1 S.D.

In Figures 6.7 and 6.8 the regression patterns for the emmetropic subjects AW and BE are illustrated over a 40s[#] period. IOP reduced by 3.2mmHg for subject AW and by 7mmHg for subject BE following timolol treatment. For subject AW, there is an obvious retardation in the accommodation regression pattern for the timolol condition compared with the saline and betaxolol conditions. In contrast, subject BE shows no such difference between the 3 drug conditions although there was an obvious positive shift in accommodation for all 3 conditions following cessation of the task. Subject BE's response pattern for the timolol conditions is similar to those depicted in Figure 6.3 for the LOMs in that timolol treatment did not produce a change in the accommodation regression pattern from the near task to TA. His response pattern was unique, however, as the accommodative level held at a higher level (~1.5D) for a longer period of time (~30s) compared with the other subjects. It is deduced from the regression patterns therefore, that subject BE has a deficit in within-task sympathetic inhibition and a retention of ciliary tone.

[#] The data were chopped at 40s for these two subjects as there was a tendency for increased artefacts from blinks and eye movements after this time.
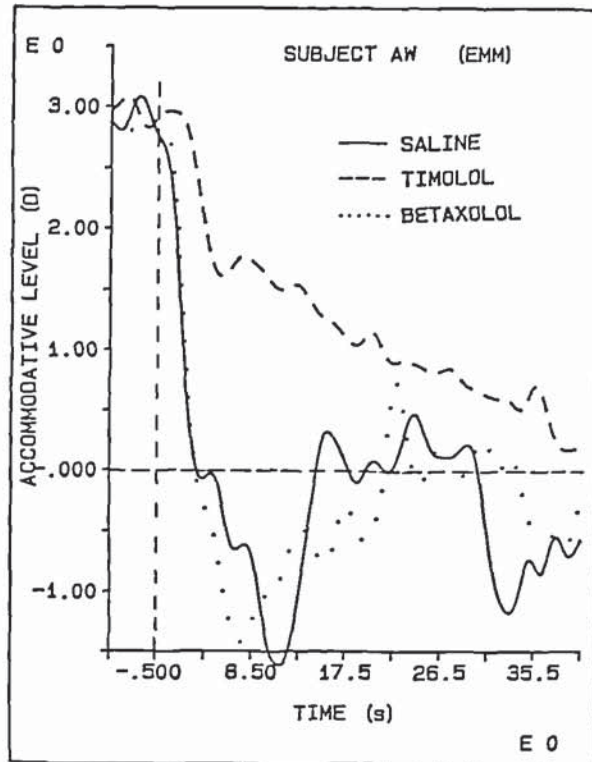
Figure 6.7: Regression of accommodation for subject AW from task to TA for the 3 drug conditions illustrating a retardation of regression for the timolol condition
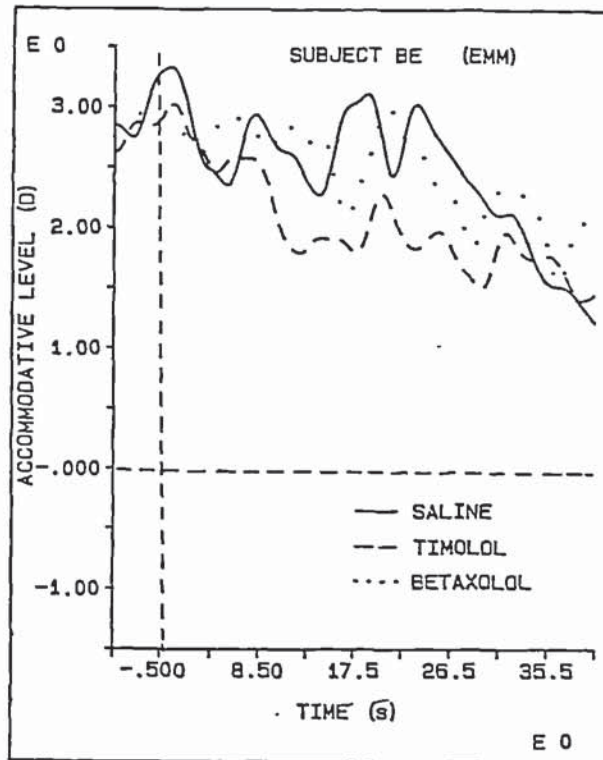
Figure 6.8: Regression of accommodation for subject BE from task to TA for the 3 drug conditions, illustrating no significant difference between the rates of regression for any of the drug conditions.

6.4 DISCUSSION

It is evident from the composite accommodative regression plot over the 80s period for the group of 4 emmetropes who showed an effect with timolol (Figure 6.5) that these regression patterns were significantly slower for the timolol condition compared with those for saline and betaxolol. The implication is that for these 4 emmetropic subjects, post-task adaptational effects are prolonged when the sympathetic system is blocked with timolol and that under normal conditions, the sympathetic system is active during a near task, providing an inhibitory component to the ciliary muscle. These results support the previous findings of Gilmartin and Bullimore (1987), that timolol significantly alters the rate of regression to baseline TAs for certain emmetropic subjects. The present results also concur with the proposal that the function of the sympathetic system is to attenuate hysteresis effects which may occur as a result of demanding and prolonged near visual tasks (Gilmartin and Bullimore, 1987; 1991).

None of the 10 LOMs who were examined showed a significant positive shift with timolol: the 3 drug conditions produced similar rates of regression of accommodation to baseline TA measures (Figure 6.3). It appears then that these subjects lacked an inhibitory sympathetic input to the ciliary muscle during the task, as blocking the sympathetic system with timolol had no obvious effect on the accommodative regression patterns following the imposition of dark room conditions.

It is deduced that the emmetropes whose accommodative regression patterns were similar to those of the myopic group also appear to possess a deficit in the inhibitory sympathetic input to the ciliary muscle. If such a deficit represents one of the factors which predispose individuals to the developments of LOM then these emmetropes may be susceptible to the development of myopia.

The biometric measurements in this study provide tentative support for previous work which has indicated that axial length and vitreous chamber depth is increased in LOM and that keratometry readings are comparable for both refractive groups (McBrien and Millodot, 1987b). Lens thickness for the subjects in this study appeared to be comparable

for the two refractive groups: this contradicts evidence that lens thickness is decreased in LOM compared with emmetropia (McBrien and Millodot, 1988) but concurs with the findings of Gilmartin, Bullimore and Royston (1991).

Recent work showing no significant difference between the ocular biometric measurements in early- and late-onset myopes for equivalent refractive errors (Grosvenor and Scott, 1991) has indicated that the results of experimental work examining the mechanisms involved in the progression of vitreous chamber elongation on the latter, more easily accessible group of subjects may reasonably be applied to early-onset myopes. Problems incurred from ethical approval of the examination of young children can therefore be averted.

The susceptibility to LOM is a complex issue and it is likely that a number of factors are involved. The influence of heredity is unclear: it remains equivocal whether the comparability in refractive errors between siblings is due to environmental influences (Young et al, 1969), genetic factors (Hegmann, Mash and Spivey, 1974) or both (Alsbirk, 1979). It is evident that an increase in the number of subjects examined in this study is required before definitive conclusions may be drawn regarding the deficiency of an inhibitory sympathetic facility in the susceptibility to LOM. Moreover, a longitudinal study to examine the refractive and biometric changes in a group of young emmetropes, preferably from a non-academic population is also required, to enhance our understanding of the mechanisms involved in the development of LOM. Further, an examination of other refractive groups including hyperopes, early-onset myopes and astigmats would be of interest.

Van Alphen (1961) proposed a theory of emmetropization, based on the data of Stenström (1946). He carried out a statistical evaluation of the components of refraction, and showed that 3 components may account for the 10 simple correlations between the 5 optical elements of the eye. Van Alphen deduced that the influence of IOP on scleral stretch was of paramount importance in the development of refractive errors. In emmetropia, the controlling mechanism responsible for counter-balancing stretch was

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choroidal tension, which was governed by ciliary muscle tonus. Consequently, a loss of ciliary muscle tone would cause scleral expansion. He proposed that the retina would project information to the Edinger-Westphal nucleus concerning the degree of stretch and the activity would be adjusted as part of a feedback control mechanism. Any disruption to the feedback loop would interfere with emmetropization. In a later study Van Alphen (1986) found further support for the importance of ciliary muscle tonus in the emmetropization process. He artificially inflated human eyes to 14 mmHg and caused axial elongation of the globe, rather than radial expansion. The elongation was shown to be the result of ciliary muscle stretch, the pars plana region of the choroid stretching after the ciliary muscle. The degree of choroidal stretch behind the equator was found to be minimal.

A number of animal experiments have concluded that myopia may be induced by excessive and prolonged accommodative demands or restricted visual fields (Young, 1975; Wilson and Sherman, 1976; Wallman, Turkel and Trachtman, 1978; Wallman, Adams and Trachtman, 1981) although the mechanism whereby an increase in accommodation leads to an increase in scleral stretch to induce an enlarged posterior chamber depth remains unidentified. It is well established that a *decrease* in intra-ocular pressure occurs with an increased accommodative demand (Armaly and Burian, 1958; Armaly and Jepson, 1962; Armaly and Rubin, 1961). Consequently, an increased accommodative demand would appear to counteract scleral stretch. Coleman, (1970) however, suggested that during accommodation, there was an increase in pressure gradient between the anterior and posterior chambers, with higher pressures being present in the vitreous chamber.

In conclusion, the mechanisms involved in the process whereby accommodative hysteresis effects are translated into biometric alterations in the eye are obscure: the proposal that ciliary and choroidal smooth muscle tonus, resistance to IOP and scleral stretch are somehow involved (Van Alphen, 1961; 1986) remains to be proven. Nevertheless, the deficit of sympathetic supply to the ciliary muscle which is deduced from the results in this study and from previous work (Gilmartin and Bullimore, 1987)

may be one further element involved in the multifactorial susceptibility to the development of LOM.

Refereed Papers Published in Conference Proceedings

Gilmartin B, Winn B, Owens H and Pugh JR (1990) Aspects of ciliary muscle innervation in late-onset myopia. Fourth International Conference on Myopia, The XXVI International Congress of Ophthalmology, Singapore, 119-128.

Refereed Published Abstracts of Conference Proceedings

Gilmartin B, Winn B, Pugh JR and Owens H (1989) Ciliary muscle innervation and predisposition to late-onset myopia (Poster).American Academy of Optometry Meeting, December 1989, New Orleans, USA. *Optom Vis Sci* 66, 217P.

CHAPTER 7
THE FREQUENCY CHARACTERISTICS OF ACCOMMODATIVE MICROFLUCTUATIONS FOR CENTRAL AND PERIPHERAL ZONES OF THE HUMAN CRYSTALLINE LENS

7.1 INTRODUCTION

In Chapter 3, a brief overview of the literature pertaining to the characteristics of the temporal fluctuations in the steady-state human ocular accommodation response was given. The two dominant frequency components: low frequency components (LFC < 0.6Hz) and high frequency components (HFC 1.0-2.2Hz) were separately discussed and it was concluded that no consensus regarding the origin and possible functional role for the microfluctuations in ocular accommodation exists.

Whereas a number of authors have suggested that the microfluctuations may provide a useful means of providing directional information to the accommodation control mechanism (Alpern, 1958b; Fender, 1964; Fincham, 1951; Smithline, 1974), others dispute such a role, on the basis that for 50% of the time, the accommodation system is in error when other monocular cues are eliminated under experimental conditions (Stark, 1968; Stark and Takahashi, 1965). The initial accommodative response to a change in stimulus vergence is therefore random when the accommodation system is deprived of its normal distance cues.

The magnitude of the separate components of accommodative microfluctuations appear to show pupil area dependence: the HFCs having a positive correlation with pupil size, the reverse being the case for the LFCs (Campbell, Robson and Westheimer, 1959; Campbell, 1960). This finding has fuelled speculation that the LFCs may have a role in the accommodation control system for monitoring and maintaining retinal image contrast during steady-state accommodation, larger magnitudes of fluctuation being required to cover larger depths-of-focus. In contrast, the HFCs are unlikely to contribute directly to the accommodative control process, as the magnitude of the HFCs reduces with small pupils when depth-of-focus is large. It has been suggested that the HFCs are a

manifestation of 'noise' in the accommodative plant (Charman, 1983; Charman and Heron, 1988), a proposal which is based on the Foucault knife-edge shadow patterns of Berny (1969) and Berny and Slansky (1970). These patterns depict greater wavefront aberrations at the peripheral portions of the lens at the point of attachment of the zonules, which offers an explanation for the pupil area dependence of the HFCs: the 'resonance' at the peripheral lens areas being responsible for the increased magnitude of the HFC with a 7mm pupil (Charman, 1983; Charman and Heron, 1988).

Contrary to the latter proposals, a mathematical analysis of the forces acting on the surfaces of the crystalline lens during a change of accommodative state have been examined and the results interpreted in a manner which describes these forces as being *uniformly* transmitted over the whole of the anterior lens surface (Chapter 2: Koretz and Handelman, 1982; 1983; Koretz, Handelman and Phelps-Brown, 1984). On this basis, the frequency characteristics over central and peripheral lens zones should be essentially the same, although differences in the magnitude of the response could still exist between the centre and periphery of the lens.

In order to compare the nature of the microfluctuations in peripheral lens areas with the centre, it was necessary to dilate the pupil with the alpha$_1$ adrenergic agonist phenylephrine HCl 10% to enable a sufficiently enlarged pupil for the measurement of 4 separate peripheral pupil zones. The Canon optometer was used to record continuously the accommodative response to a -4D target of 5 young emmetropic subjects. The results show that whereas the rms magnitude of accommodative fluctuations is reduced in peripheral lens areas compared with that in the centre, the fundamental frequency characteristics remain the same for all lens zones.

7.2 METHOD

Five emmetropic students, 2 male and 3 female (mean age 19.4 $\pm$ 1.6 years), all experienced observers, took part in the experiment. Informed consent was obtained from all subjects following a full explanation of experimental procedures. The subjects were required to view a high contrast (90%) Maltese cross target (luminance 40 cd.m^{-2}) located

at a vergence of -4D while the accommodation response was measured continuously with the Canon optometer.

In a previous investigation (see Chapter 4) it was demonstrated that the signal collected by the photodetector of the Canon optometer was unaffected by pupils > 3.52mm. To enable a comparison of the microfluctuation activity between central and peripheral lens zones, it was necessary to dilate the subjects' pupils with 2 drops of phenylephrine HCl 10%. A drop of the topical anaesthetic 0.4% benoxinate HCl preceded the instillation of the mydriatic in order to minimise reflex tearing and blinking and to facilitate absorption of the mydriatic drug through the corneal epithelium. It is known that phenylephrine even in its 2.5% concentration, causes a reduction in accommodative amplitude of ~1D (Mordi, Lyle and Mousa, 1986; Rosenfield *et al*, 1990; Zetterström, 1984) but sufficient accommodation is retained in young subjects to maintain steady fixation on a target at a vergence of -4D. A maximum pupil diameter of 8.5mm (measured from the 8.2x magnified image from the video output of the Canon) was attained following mydriasis with phenylephrine. This diameter was insufficient to allow completely separate zones of around 3.5mm diameter to be examined. An overlap of 17.9%[*] was obtained with measurements in 5 separate lens zones: central, superior, nasal, temporal and inferior (see Figure 7.1).

A calibration procedure was carried out for each lens zone prior to continuous recordings. This comprised a recording of the static response to the target which was placed at 2 vergences: -4.00D and -2.50D for all 5 lens zones. The optometer was then switched to continuous mode and a calibration step repeated for each lens zone. By this method, it was possible to relate the voltage change in continuous mode to the dioptric change measured in static mode, thus providing a means of calibrating the dynamic accommodation response in absolute terms.

Following the calibration procedure, 5 accommodation signals, each of 10s duration were

[*] For mathematical calculation of percentage overlap , see appendix II, pps.217-221

recorded for each lens zone at a sampling rate of 102.4Hz. The data were smoothed with a high frequency cut of 10Hz and a power spectrum calculated for each trace. The 5 spectra were then integrated to give a final power spectrum for each of the 5 lens regions, each with 10 degrees of freedom and a frequency resolution of 0.1Hz.

Figure 7.1: Diagrammatical representation of 5 lens zones measured using the Canon, showing the approximate overlap between the central and peripheral zones (From Winn *et al*, 1990a)

7.3 RESULTS

Using power spectrum analysis, the frequency characteristics for each lens zone were compared. Figure 7.2 illustrates the power spectrum of subject DC for all lens zones which clearly indicates the dominant frequencies present in the accommodative response. The data for this subject is typical for the whole group of subjects. A low and high frequency component may be seen at 0.5Hz and 1.3Hz respectively for each of the lens zones, although the total power is reduced in each of the peripheral zones compared with the power manifest in the central lens area. For some of the subjects, the power in the superior zone appeared to be virtually equivalent to that in the central zone (see Appendix II.2, p219-220). This was the result of the encroachment of the upper lid over the superior portion of the cornea during the experiment, forcing a greater overlap between the central and superior zones.
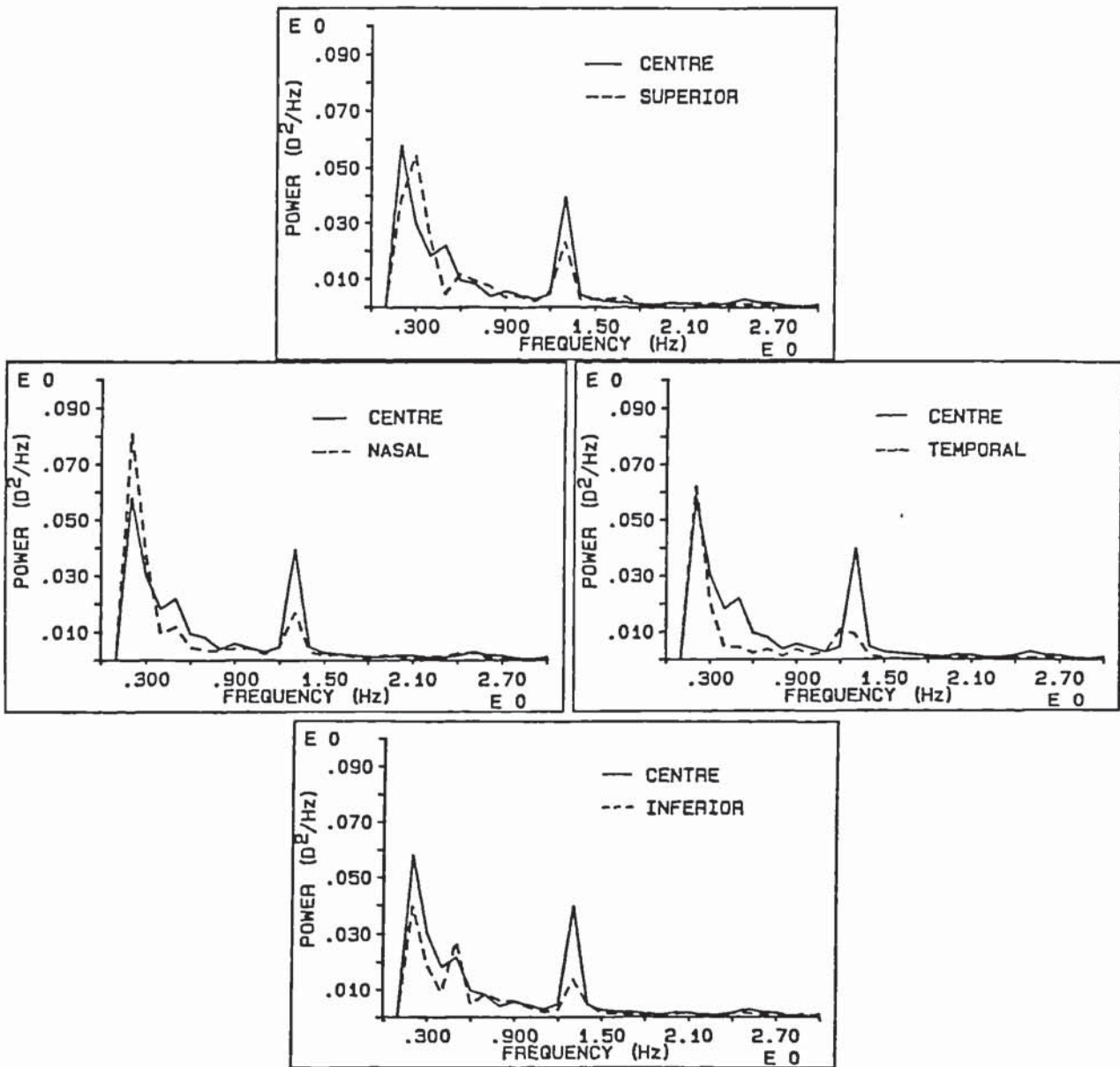
Figure 7.2: Power spectrum plot of accommodative microfluctuations for all lens zones for subject DC, showing the peak frequency for the LFC at 0.5Hz and that for the HFC at 1.3Hz.

Analysis of the data for subject DC whose power spectra of accommodative microfluctuations are shown in Figure 7.2 is given in the table below.

Lens zone	Total area (D²/Hz)	HF area (D²/Hz)	LF area (D²/Hz)
Centre	0.232	0.021	0.042
Inferior	0.159	0.009	0.028
Temporal	0.152	0.018	0.014
Nasal	0.218	0.013	0.029
Superior	0.118	0.009	0.029

Table 7.1: Measurements of total area, HF area and LF area under power spectra plots for each lens zone. The HF area includes 4 frequency bins which envelop the peak frequency of the HFC. The LF area is calculated from the area under 4 frequency bins from 0.3-0.6Hz.

The location of the high frequency peak exhibited some inter-subject variability (Figure 7.3), ranging from 1.2 to 1.8Hz for the 5 subjects examined over a number of trials (typically 25), whereas the within-subject HFC location did not vary during the experimental runs. In contrast, the low frequency peak showed little intersubject variability. These findings are consistent with those of other authors (Campbell, Robson and Westheimer, 1959; Kotulak and Schor, 1986a).

Table 7.2 summarises the positioning of the peak frequencies of the HFC and LFC for 5 subjects, illustrating the inter-subject variability in the peak frequency of the HFC.

Subject (M/F)	LFC peak frequency (Hz)	HFC peak frequency (Hz)
BE (M)	0.4	1.4
PI (M)	0.6	1.5
GB (F)	0.4	1.7
DC (M)	0.5	1.3
AM (F)	unclear	1.1

Table 7.2: Summary of peak frequency locations for the two dominant frequency components in the power spectra of the accommodative microfluctuations for 5 subjects.
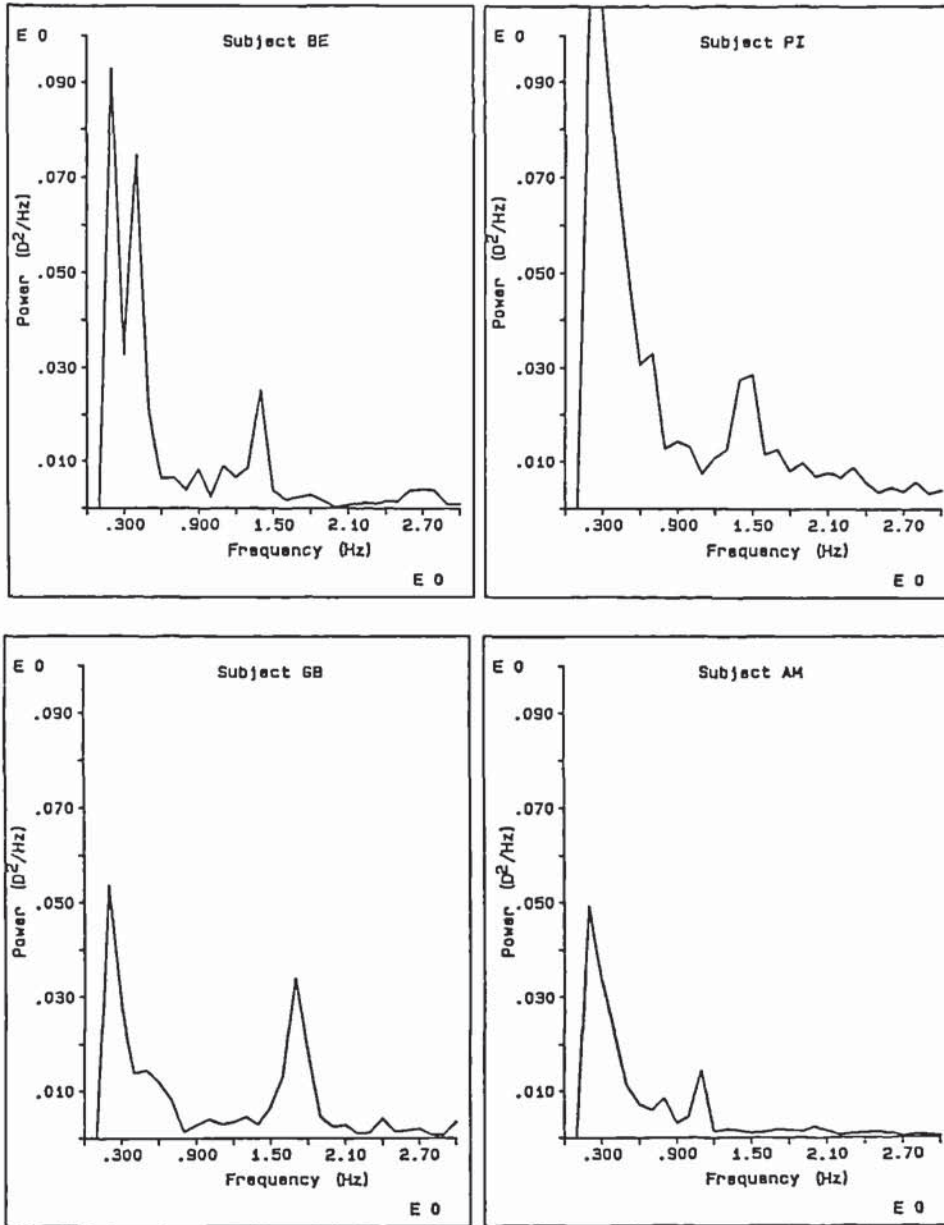
Figure 7.3: Power spectrum plot of accommodative microfluctuations of 4 subjects illustrating inter-subject variability of the peak frequency of the HFC

7.4 DISCUSSION

It is evident from the data that the HFCs of accommodative microfluctuations are present in central and peripheral lens areas and are not merely a manifestation of spurious oscillations that are restricted to the lens periphery. The findings comply with the mathematical modelling of the forces acting upon the human crystalline lens during accommodation as proposed by Koretz and Handelman (1982; 1983) and Koretz, Handelman and Phelps-Brown, (1984). These authors suggested that the capsule distributes the forces from the zonules evenly over the whole of the lens surface, allowing all portions of the lens to fluctuate as one body. The proposal by Charman (1983) and Charman and Heron (1988) suggests that 'resonance' from the peripheral areas of the lens and the zonular apparatus are responsible for the HFCs. While our findings appear to refute this proposal, further analysis of the individual data (see Appendix II.2, pps. 219-221) may lend support to it. Although the total power in a given peripheral lens area amounts to ~46% of an equivalent area in the centre, the total absolute power available in the peripheral lens areas is greater than that in the centre, assuming an ocular exit pupil diameter for the measuring optometer of 3.52mm. For pupil diameters of ≥ 6.5mm, the contribution from the periphery to the total rms power exceeds that in the centre (for calculation, see Appendix II.2, p 219-221).

Campbell, Robson and Westheimer (1959) reported that the HFCs were present only with 7mm pupils, noting that they disappeared in their subject with a ~1mm pin-hole pupil. An explanation for this effect may be based on the tendency of the eye to revert to its tonic resting position when placed in an 'open-loop' situation, as would have occurred with a 1mm pupil. It is well established that when the accommodative system is in an open-loop situation, the response is dominated by large, low temporal frequency drifts (Westheimer, 1957) which, in terms of data scaling, could have effectively swamped the HFC component.

The significance of the HFCs and LFCs in oculomotor control remains equivocal. It is unlikely that the fluctuations are involved in the directional guidance of the accommodative response to a step change in vergence, as for 50% of the time, when normal cues are

removed, the accommodative system is in error (Stark and Takahashi, 1965; Stark, 1968). Any functional role for the microfluctuations as an error-detector in the accommodative system is more likely to be linked with the maintenance of a steady-state response. It is now known that a proportion of the fluctuations will be perceivable, as they are capable of spanning the dead-band, or depth-of-focus (Winn *et al*, 1989a) and that it is possible to achieve an accommodative response to a change in target vergence of only 0.1D (Ludlam *et al*, 1968). It is therefore conceivable that the fluctuations have a role in the accommodative control system, although this work does not provide evidence for such a role.

The temporal nature of the accommodative reaction and response times of ~360ms and 1s respectively precludes the consideration of the LFCs in providing a cue to rapid step-changes in accommodation as they are too slow. The HFCs, however, may be fast enough to play a role in the accommodative feedback mechanism and thus provide the system with an odd-error directional cue.

The origin of the fluctuations is unclear: the HFCs exhibit a significant variation in peak frequency location between individuals, which may indicate an association with other physiological variations which instigate intraocular rhythmic variation. Although the LFCs are more static in their frequency location, initial experimental impressions suggest that they vary markedly in magnitude during accommodation recordings when experimental conditions remain constant. Further analysis of the variations in magnitude of the LFCs is required.

It is likely that the composite waveform of accommodative microfluctuations is derived from a combination of neurological control and localised plant noise although it is interesting to speculate whether the LFCs could also originate or at least be modified by certain physiological bodily changes. It is known, for example, that the IOP pulse is affected by complex intra- and extra-ocular changes in blood flow and respiratory variations (Cooper *et al*, 1979; Bain and Maurice, 1959); respiratory fluctuations in pupil noise have also been documented (Daum and Fry, 1981; Ohtsuka *et al*, 1988) and it is

feasible to imagine that similar complex forces could be transmitted to the crystalline lens through changes imposed on the choroidal vasculature. Further work will be described in the following chapters in an effort to establish the sites from which the main frequency components are derived.

Supporting publications

Winn B, Pugh JR, Gilmartin B and Owens H (1990a) The frequency characteristics of accommodative microfluctuations for central and peripheral zones of the human crystalline lens. *Vis Res* 30, 1093-1099.

Refereed Published Abstracts of Conference Proceedings

Winn B, Pugh JR, Gilmartin B and Owens H (1989) The frequency characteristics of accommodation microfluctuations for central and peripheral zones of the crystalline lens (Poster). Association for Research into Vision and Ophthalmology meeting, May 1989, Sarasota, Florida, USA. *Invest Ophthal Vis Sci (suppl)* 30, 135.

CHAPTER 8

THE INFLUENCE OF ARTERIAL PULSE ON STEADY-STATE ACCOMMODATION

8.1 - INTRODUCTION

Chapter 3 reported on a number of studies and reviews (e.g. Alpern, 1958b; Fender, 1964; Crane, 1966; Kotulak and Schor, 1986a,b; Charman and Heron, 1988) which have addressed the issue of whether a functional role exists for the accommodative microfluctuations. It remains unclear however, whether the accommodative microfluctuations provide directional information to the accommodation control system which obtains only even-error information from retinal image blur.

In addition to their functional significance, the *origin* of the accommodative microfluctuations continues to be a subject of conjecture: in this respect, the disappearance of the high frequency component with 1mm pupils (Campbell and Westheimer, 1960) has led to speculation that the HFC is a manifestation of 'plant noise' (Kotulak and Schor, 1986b), a consequence of increased exposure of the lens periphery (Charman, 1983; Charman and Heron, 1988). The latter proposal is supported by slit-lamp photographs depicting an increase in wavefront aberrations in peripheral lens areas (Berny, 1969; Berny and Slansky, 1970). Further speculation concerning HFCs and accommodation control is based on findings that they do not appear to be affected by changes in stimulus parameters (Denieul and Corno, 1986).

In contrast, the low frequency components appear to alter in a manner which is consistent with changes in depth-of-focus: with small pupils (1mm), they appear to increase in magnitude and with 7mm pupils, their magnitude decreases: these effects have provided support for the proposal that it is the low frequency components which may be under direct neurological control of the accommodative controller system.

It was reported in Chapter 7 (pps. 119-128) that the high frequency component activity is not merely confined to peripheral lens regions: it is also present in the central lens area. The

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significant inter-subject variation in the exact location of the peak frequency of the high frequency components and the relative stability within-subjects reported in this work led to the question of whether there was an association between the HFC of accommodative fluctuations and other physiological systems providing intraocular rhythmic variation.

The rhythmic variations in intraocular pressure of 2-3mmHg which occur in healthy eyes are known to be a manifestation of arterial pulse waves (Theil, 1928; Bynke and Schele, 1967; Buchanan and Williams, 1985). Further, rhythmic variations in axial length caused by arterial pulse waves have been observed in the human eye (Fercher et al, 1982), which induce pulsatile dioptric variations of ~ 0.01D.

It is possible therefore that the waveform of accommodation microfluctuations is derived from a combination of both neurological control and localised plant noise. The aim of this study was to determine whether the high frequency components of accommodative microfluctuations are correlated with intraocular rhythmic variation induced by arterial pulse.

8.2 - METHOD

Twenty young observers (mean age 25.3 years) served as subjects for the main part of the experiment. They were requested to observe a high contrast (90%) Maltese cross and letter target at a -4D vergence and the accommodation response was measured with the Canon optometer in continuous mode. Arterial pulse frequency was measured simultaneously with accommodation by a sensor-emitter photodiode arrangement (photo-plethysmograph) on the subject's right thumb. Power spectrum analysis (Pugh et al, 1987) was performed on the 5 runs of accommodation and pulse over each 10s recording period collected at a sampling rate of 102.4Hz. A correlation coefficient was calculated between the peak frequency of the HFC of accommodation and arterial pulse frequency.

In order to examine the effect of a change in arterial pulse frequency on the frequency location of the HFC, 3 subjects were requested to perform a period of acute exercise

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following an initial period of recordings as outlined above. Accommodation and arterial pulse recordings were made for up to 2 minutes post-exercise.

Thirdly, in order to confirm that the HFC recordings were lenticular in origin, two unilateral aphakic subjects (aged 21 years and 40 years) were examined. The response from the aphakic eye was recorded, the eye having been corrected with a soft contact lens of appropriate power to enable fixation on the near target and the response was compared with that from the normal, phakic eye. An attempt was made to verify further that the microfluctuations were lenticular in origin, by examining the ratio of Purkinje images I/IV. This procedure involved examining, frame by frame, the separation of the 2 Purkinje images recorded on video while the subject maintained steady fixation on the target. The separation of the 2 Purkinje images was measured with the aid of electronic calipers. The data is incorporated into Appendix III (pps. 223-224). Poor resolution due to the dimness of the Purkinje images led to inconclusive results using this method.

To examine the correlation between the peak frequency of the HFC and the IOP pulse frequency which is known to correlate with arterial pulse, the accommodation response of one subject was recorded from one eye, while simultaneously recording the IOP from the contralateral eye. The former recordings were made to the same experimental set-up described above for the 20 emmetropes used in the first part of the experiment, while the latter was measured with a Digilab pneumotonometer (Model 30D), modified to enable continuous recordings of IOP. The output from the tonometer was fed into the digital storage oscilloscope and both accommodation and IOP recordings were made over a 10s period. Ten repetitions of simultaneous recordings of accommodation and IOP were made.

Finally, as a preliminary study, the effect of a change in the frequency of respiration was examined for one subject. The subject was chosen for his excellent fixation ability and was instructed to fixate on the Maltese cross target located at -4D for 2 respiration frequencies: normal breathing and at a frequency of 0.7Hz. The 0.7Hz breathing rate was achieved with the aid of an auditory cue from a metronome.

For all parts of the experiment, pupil diameters greater than 3.8mm were used to ensure that the optometer output was pupil independent (see Methods, Chapter 5, pps. 98-99). Pupil dilation was induced by the instillation of 1 drop of the alpha$_1$ agonist sympathomimetic mydriatic 2.5% phenylephrine HCl for the 20 emmetropes used in the first part of the experiment. Eye movements were monitored with the Hamamatsu C3160 Percept Scope which was connected to the optometer's IR video output and subsequently interfaced via the digital storage oscilloscope.

8.3 - RESULTS

In Figure 8.1 the characteristic features of the power spectrum of accommodative microfluctuations are illustrated for subject GB. It may be seen that the dominant frequency components for this individual are located at 0.4Hz and 1.5Hz, the high frequency component location being evident from that frequency bin above 1.0Hz containing the maximum power. Examples of the simultaneous recordings of accommodation and pulse for an individual subject are given in Figures 8.2a and 8.2b respectively. The corresponding power spectra are given in Figures 8.3 which clearly show high frequency peaks located at 1.2Hz.
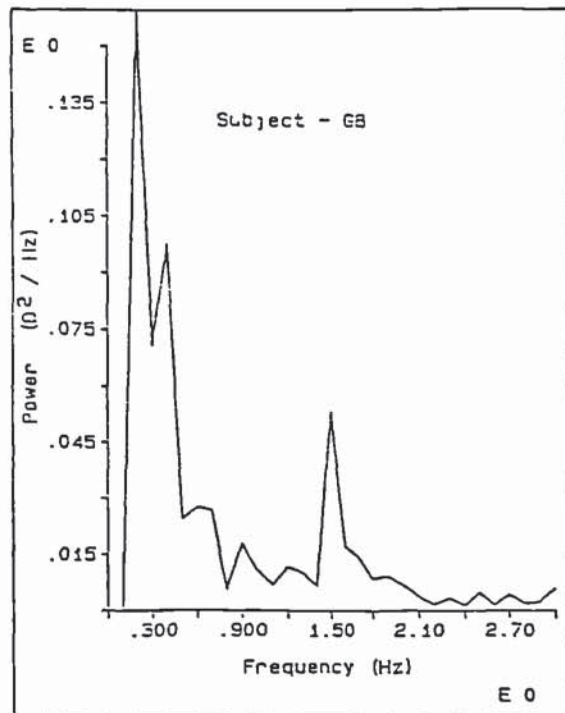
Figure 8.1: Power spectrum of accommodation microfluctuations for subject GB illustrating the characteristic low (0.5Hz) and high (1.5Hz) frequency components (From Winn *et al*, 1990b)
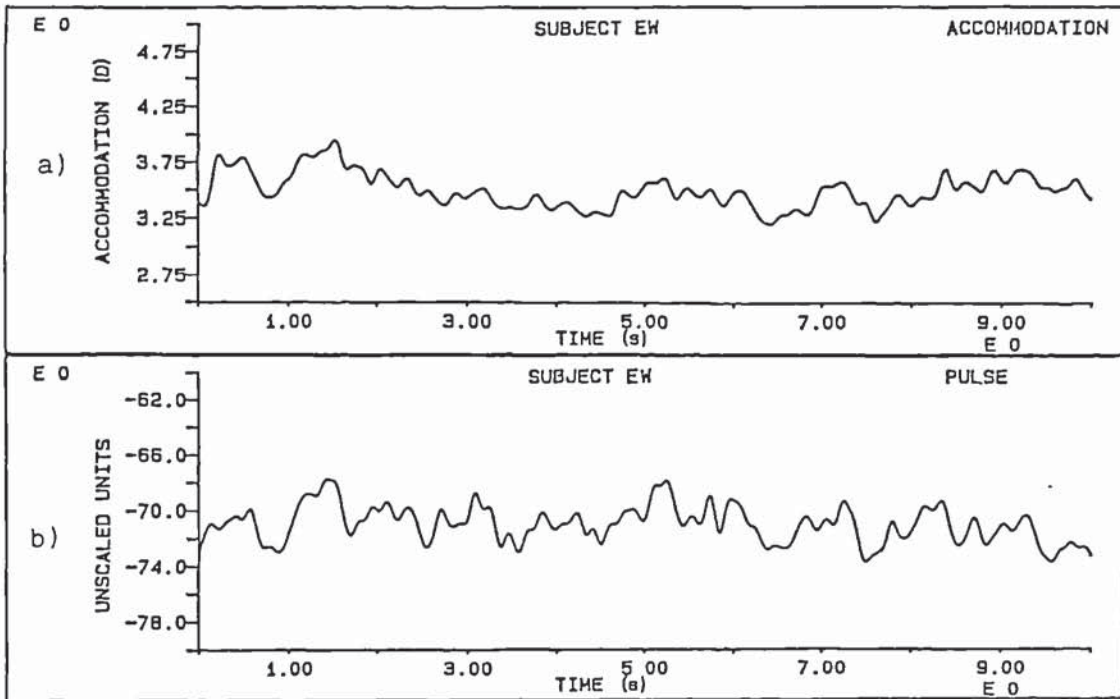
Figure 8.2

a) Plot of accommodation response to a stationary target at a vergence of -4D

b) Simultaneous recording of pulse from subject's thumb from an IR emitter-sensor combination
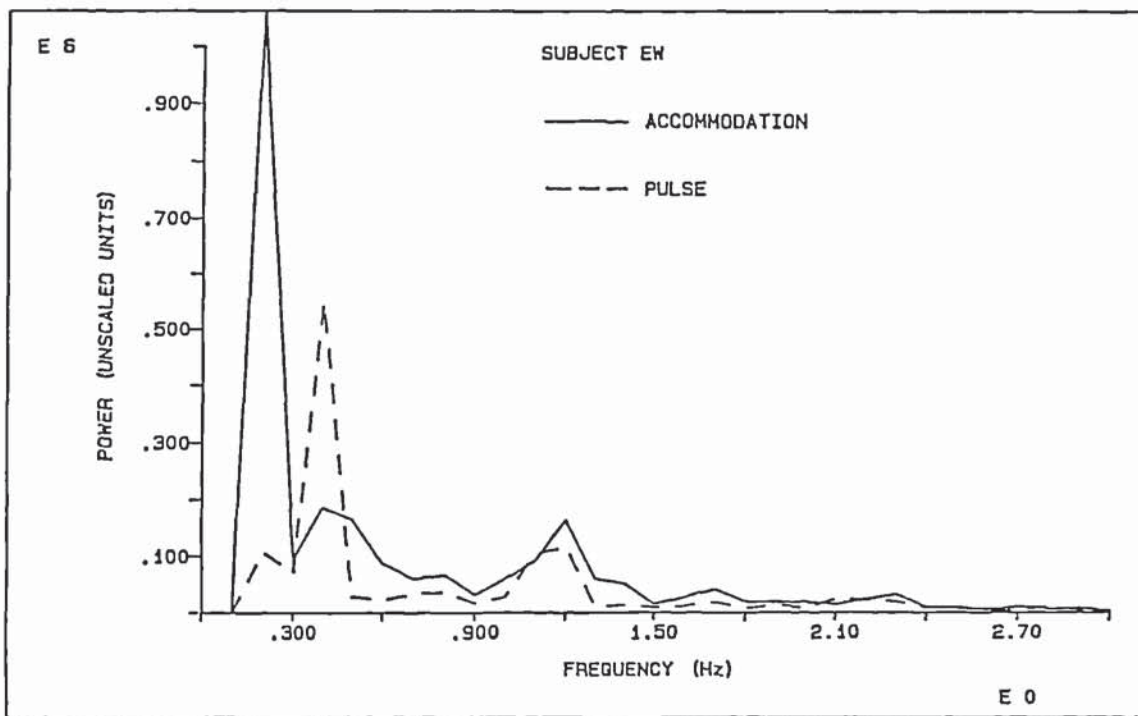
Figure 8.3: Power spectra of accommodation (solid line) and arterial pulse (dashed line) for subject EW

pertaining to traces of accommodation and pulse from Figure 8.2

Group data (Figure 8.4) for a total of 98 samples show a significant positive correlation between arterial pulse frequency and the peak frequency of the high frequency component ($r = 0.98$, $p<0.001$). (see Appendix III.1 and III.2, pps.222 for raw data)

Correlation between HFC and AP (N=98)

$y = 0.106 + 0.9236x$ $R = 0.98$
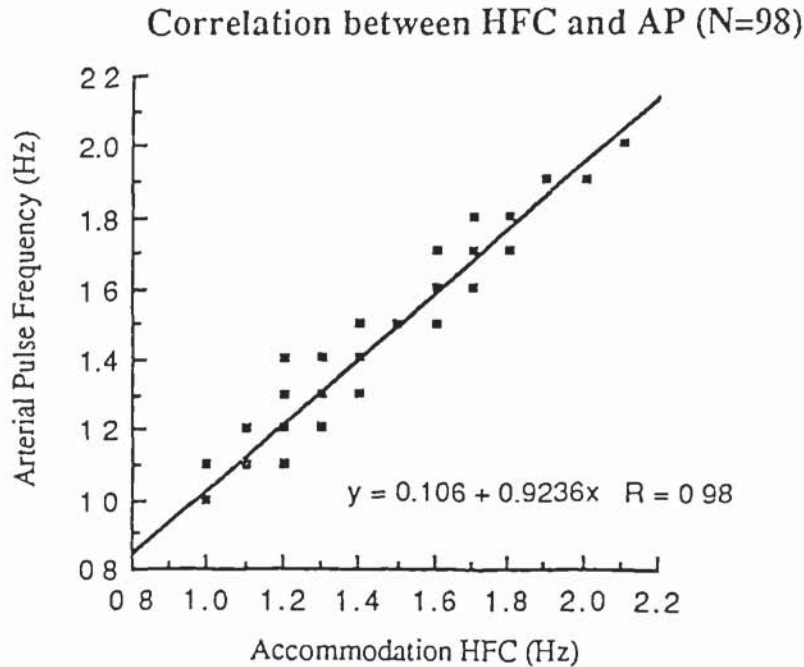
Figure 8.4 Correlation between arterial pulse frequency and the dominant high frequency component of accommodation for group data (98 samples). The frequency resolution was 0.1Hz for each response and is responsible for the quantization of the data. There is considerable overlap of individual data points.

Figure 8.5 illustrates the mean datapoints for each of the 20 subjects in the experiment which shows more clearly the correlation between arterial pulse and the peak frequency of the HFC for each subject.

Arterial pulse values for the group of subjects in the experiment ranged from 1.0-2.0Hz (60-120 b.min^{-1}). The range may at first appear to include unusually high values for arterial pulse, but may be explained by the relatively stressful experimental conditions: the requirement to observe the target steadily, without blinking, for periods of 10s; the need for a dental bite and head restraint; the raised room temperature in the laboratory especially towards the end of the recording session.

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Correlation between HFC and AP (N=20)

$y = 0.0604 + 0.9516x \quad R = 0.99$
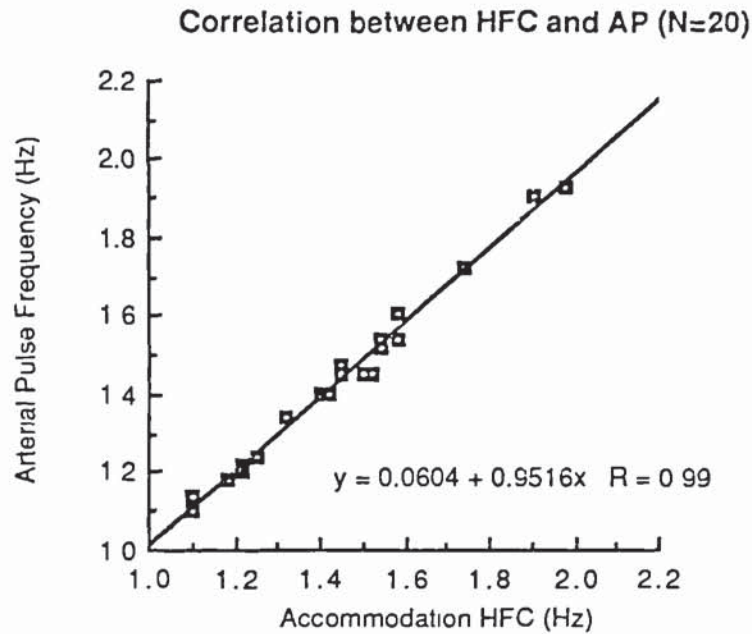
Figure 8.5: Correlation between arterial pulse frequency and the dominant high frequency component of accommodation for group data (N=20). The data fall within the quantization limit of 0.1Hz. (From Winn *et al*, 1990b)

Data for the 3 subjects who were involved in acute exercise show that the correlation between arterial pulse and the peak frequency of the HFC was retained during the recovery phase (Figure 8.6). Furthermore, although the relationship between arterial pulse and the high frequency component of accommodation was demonstrable in the sound eyes of the unilateral aphakics, it was absent from the affected eyes. Figure 8.7 illustrates the power spectra from both the normal and aphakic eyes of subject PH. This subject was aged 40 years, and it is interesting to note that the power spectrum of accommodation from the sound eye demonstrates a noticeable reduction in the magnitude of the HFC of microfluctuations compared with the power specrum from subject GB illustrated in Figure 8.1. It is no different in magnitude from the HFC component in the sound eye of the 22 year old unilateral aphakic illustrated in Figure 8.8, however. In both aphakic cases, the high frequency peak present in the sound eye is absent from the aphakic eye.

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Recovery from Exercise (subject - VP)
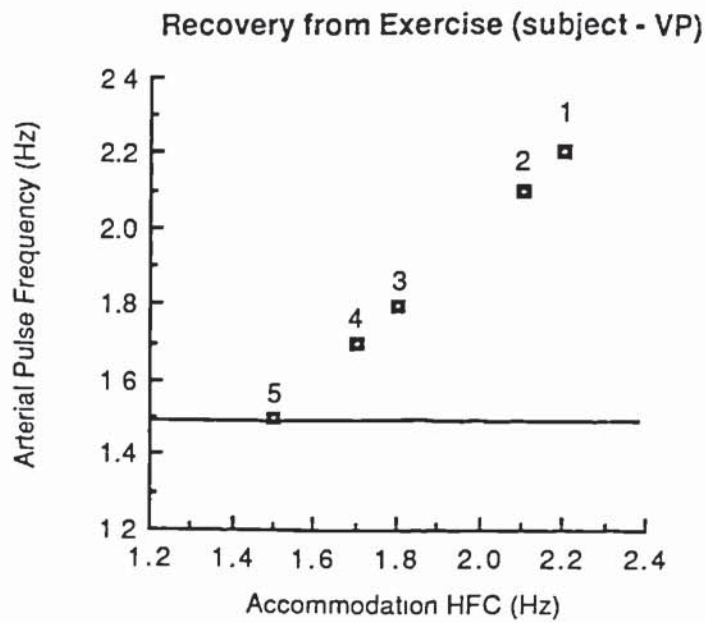
Figure 8.6: Correlation between arterial pulse frequency and the high frequency component of accommodation for the recovery phase (sequence 1-5) of exercise-induced changes in pulse. The subject was a 21 year old female whose base-line pulse was 1.5Hz under the experimental conditions (From Winn *et al*, 1990b).

Figure 8.9a illustrates the raw data of accommodation from one eye of subject DS and the simultaneous recording of IOP from the contralateral eye is given in Figure 8.9b. It may be observed that similarities in the waveforms exist even on gross inspection. Power spectra of accommodation and IOP are given in Figures 8.10 which illustrate that the peak frequencies at 1.2Hz occur for both accommodation and IOP.
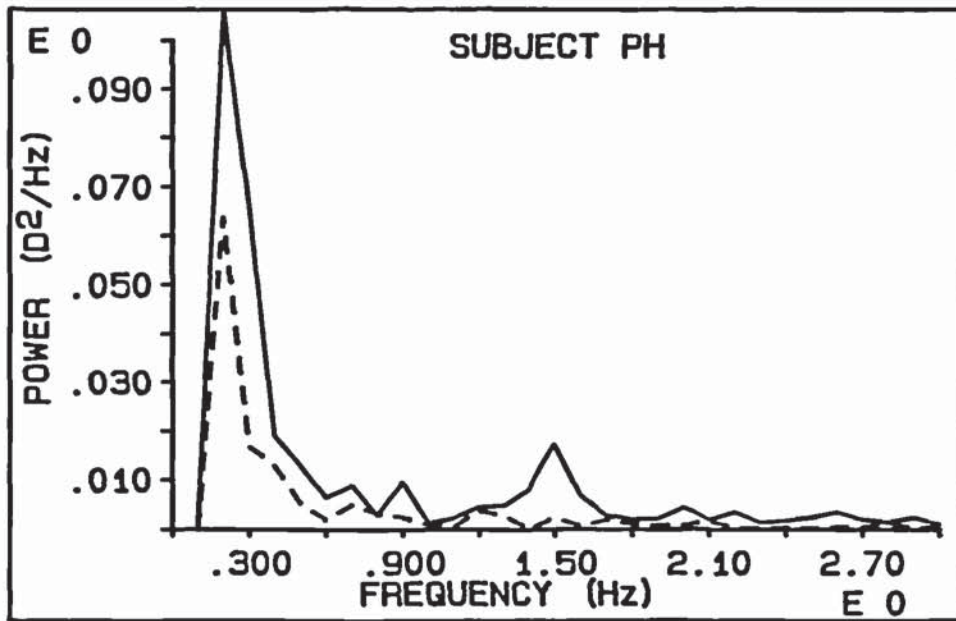
Figure 8.7: Power spectrum of accommodative microfluctuations. Solid line is the power spectrum from the sound eye of a unilateral aphakic aged 40; dashed line is that from the aphakic eye
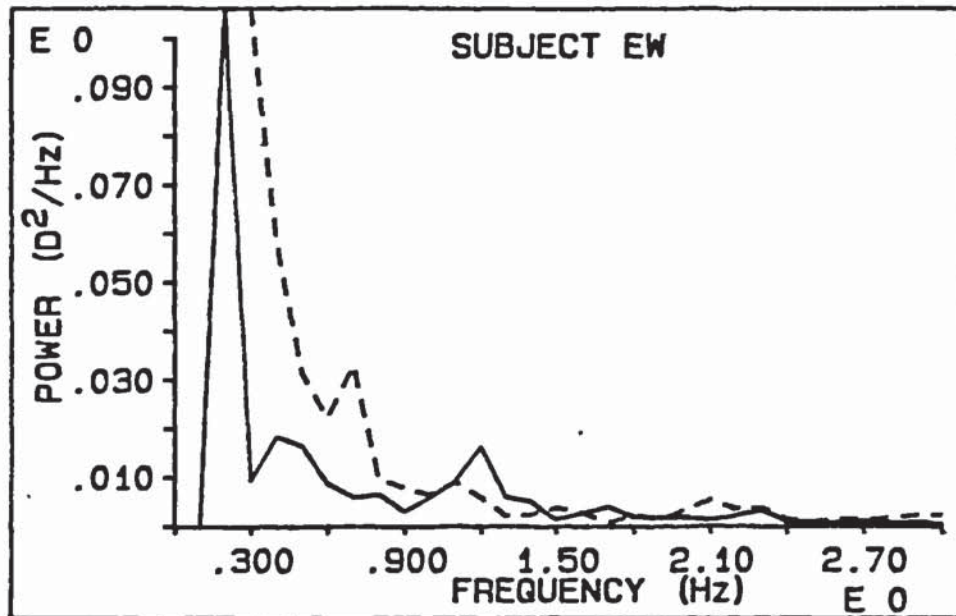
Figure 8.8: Power spectrum of accommodative microfluctuations from subject EW, unilateral aphakic, aged 22 years. Solid line, power spectrum from sound eye; dashed line, power spectrum from aphakic eye.

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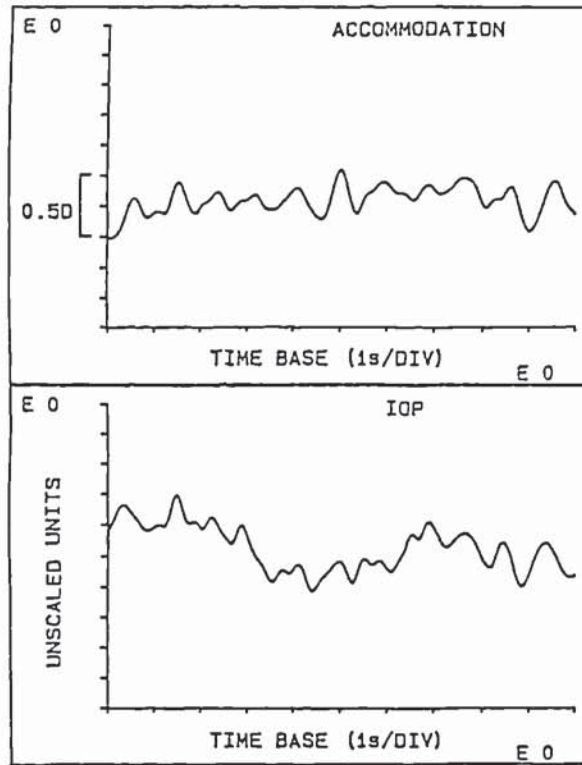
Figure 8.9: a) Continuous recording of accommodation from right eye of subject DS viewing a target at a vergence of -4D. b) Continuous recording of IOP from left eye of subject DS. Accommodation and IOP were recorded simultaneously.
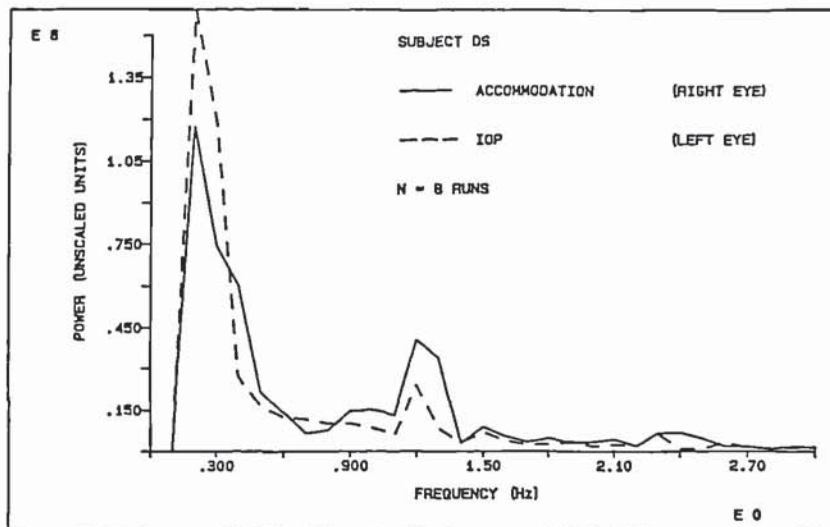
Figure 8.10: Power spectra of accommodation (solid line) and IOP (dashed line) for subject DS. Raw data are given in the previous figure.

The accommodative power spectra for subject BE whose response was measured while breathing at normal and then at an increased temporal frequency are given in Figure 8.11. An examination of this figure reveals that the peak frequency of the LFC at 0.4Hz appears

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to have reduced in magnitude for the increased breathing rate condition. Further, there is an additional peak at 0.7Hz which corresponds with the increased respiration rate.
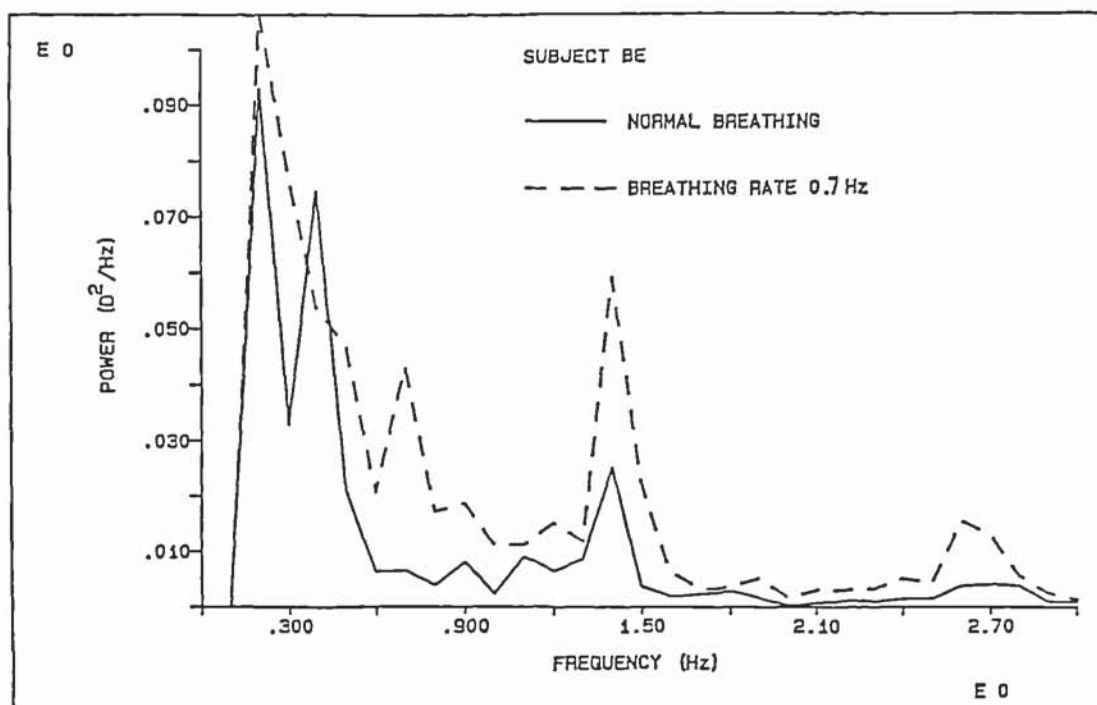
Figure 8.11: Power spectrum of accommodative microfluctuations for subject BE to a target located at a vergence of -4D. Solid line: normal breathing; dashed line, breathing rate 0.7Hz.

8.4 - DISCUSSION

It is evident that the high frequency component of accommodative microfluctuations is a consequence of the physiological variations induced by arterial pulse and is not under direct sensory control of the accommodative mechanism. This finding is in agreement with computer-derived models of the accommodation system, which have indicated that the accommodative response will be enhanced with a frequency oscillation 0.45Hz (Hung, Semmlow and Ciuffreda, 1982). It appears therefore that the aggregate waveform of the nominally steady-state accommodative response is composed of a low frequency component of unknown origin but which is likely to be neurologically driven and a physiologically derived high frequency component.

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It is unclear whether a functional role for accommodative fluctuations exists, although their ability to provide an odd-error signal to aid directional changes in response to step-type stimulation is questionable, as under restricted monocular viewing conditions, there is a even chance of an accommodative response in the wrong direction (Stark, 1968; Stark and Takahashi, 1964, Chapter 3). Previous studies have been unable to demonstrate systematic variations in the magnitude of high frequency components with changes in stimulus characteristics. Further, although the low frequency fluctuations alter consistently with changes in stimulus parameters, they are too slow to provide an odd-error signal to achieve the appropriate temporal response.

It is possible that the high frequency components may influence or be an integral part of a contrast-detection mechanism even though it is not under its direct control. It may be speculated that if such a system exists, the magnitude of the low frequency component, assuming it is neurologically-controlled, will be affected by the systemically-modulated high frequency component. It is possible, therefore, that a substantial increase in the magnitude of the high frequency components may occur during exercise or stress resulting in symptoms of blur as a direct result of the temporary ineptitude of the controller mechanism.

It is interesting to examine the difference in magnitudes of the accommodative microfluctuations between the 2 unilateral aphakics and other normal subjects. The power spectrum for the older subject (subject PH: Figure 8.7) shows a marked reduction in total power for the normal eye compared with that of a younger subject (subject GB: Figure 8.1). It is conceivable that the reduction in power of accommodative microfluctuations evident in the older subject could be a manifestation of capsular elasticity changes which are known to occur with age (Fisher, 1971). However, the magnitude of the HFC of accommodative microfluctuations in the other younger unilateral aphakic also appears to be relatively small compared with that of subject GB. Rather than a correlation between age and magnitude of HFC, it is conceivable that a correlation may exist between cardiac fitness and the HFC magnitude. In Chapter 7, the power spectra of accommodative microfluctuations were given for subject DC, a fitness enthusiast. An examination of Figure

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7.2 (p.123) for the central lens zone exhibits a peak HFC which is evidently greater in magnitude than those peak HFCs shown in Figure 7.3. It is evident that further work is required to determine whether the magnitude of the fluctuations of accommodation decreases as a function of age or increases in proportion to the volume of exercise taken or whether both these factors are important sources of variation in the magnitude of the HFC.

It must be noted that for the younger unilateral subject, the response from the aphakic eye exhibited large low temporal frequency drifts (Figure 8.8). The aphakic eye of this subject was amblyopic to 6/60 and fixation on the target was consequently poor, the power spectrum exhibiting peaks related to eye movements. The increased magnitude of the low temporal frequency component in the power spectrum of the amblyopic aphakic eye of this subject is consistent with the work of others (Ciuffreda, Kenyon and Stark, 1980) in that low frequency fixational drifts are more common in recordings from amblyopic eyes compared with those from fellow, normal eyes.

A number of workers have utilised the IOP pulse as a method of determination of the patency of the choroidal vasculature (see Chapter 2). The IOP pulse is known to be affected by a number of diseases, including glaucoma (Davanger, 1964; Lawrence and Schlegel, 1966), diabetes (Grunwald et al, 1986; Langham et al, 1989) and high myopia (Bynke and Schele, 1967; Avetisov and Savitskaya, 1977). The findings in this study could lead to an alternative non-invasive method of assessing the intra-ocular consequences of systemic diseases of a vacular nature (e.g. diabetes).

Whereas many authors have speculated about the likelihood of the LFC being an integral part of a controller mechanism which is used in maintaining the accuracy of the nominally steady-state accommodation response, it is possible that it is physiologically driven or at least modified by physiologically-derived variations. It is well established, for example, that the IOP pulse is affected by respiration and other vascular changes in the body (Coleman and Trokel, 1969; Daum and Fry, 1984; Silver et al, 1989) and it would be difficult to imagine that the microfluctuations of the lens are unaffected by such changes which can induce larger fluctuations in IOP than those induced by the arterial pulse

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(Coleman and Trokel, 1969). Furthermore, a frequency component at 0.4Hz has been demonstrated in ECG recordings from the heart, which appears to diminish in magnitude when the subject is required to perform a mental arithmetic task (Cerutti *et al*, 1988). Further work is required to determine the effect of physiological changes on the LFC of accommodative microfluctuations.

Supporting publication

Winn B, Pugh JR, Gilmartin B and Owens H (1990b) Arterial pulse modulates steady-state accommodation. *Curr Eye Res* **9**, 971-975.

Refereed Published Abstracts of Conference Proceedings

Winn B, Pugh JR, Gilmartin B and Owens H (1990) Arterial pulse modulates temporal response characteristics of accommodation (Paper). Association for Research into Vision and Ophthalmology meeting, May 1990, Sarasota, Florida, USA. *Invest Ophthal Vis Sci (suppl)* **31**, 82.

Winn B, Pugh JR, Gilmartin B and Owens H (1990) Heart beat modulates the accommodation response. *Transactions of the 2nd International Congress of the British College of Ophthalmic Opticians. London*, **2**, 15

Winn B, Pugh JR, Gilmartin B and Owens H (1990) Arterial pulse modulates temporal response characteristics of accommodation (Poster). American Academy of Optometry Meeting, December 1990, Nashville, USA. *Optom Vis Sci* **67**, 94.

Owens H, Winn B, Gilmartin B and Pugh JR (1990) The influence of arterial blood flow on steady-state accommodation (Paper).Society of Experimental Optometry, July 1990, Birmingham.*Ophthal Physiol Opt* **10**, 412.

CHAPTER 9

THE EFFECT OF A TOPICAL BETA-ADRENERGIC RECEPTOR ANTAGONIST ON THE DYNAMICS OF STEADY-STATE ACCOMMODATION

9.1 INTRODUCTION

In the previous chapter, it was demonstrated that there is a significant correlation between the frequency of arterial pulse (AP) and the peak frequency of the HFC. These findings led to the proposal that the HFCs are not governed by an accommodative control system, although they may potentially be utilised in conjunction with the low frequency components (LFCs: < 0.5Hz) by a sensory detection system which monitors retinal image contrast during steady-state accommodation.

The mechanisms by which arterial pulse induces the HFC are likely to involve both rhythmic variations in choroidal blood flow and intraocular pressure (IOP) pulse: the former inducing changes in ciliary ring diameter from pulsatile blood volume changes in the ciliary body, the latter producing changes in effective lens power following small shifts in lens position or, with each drop in IOP, reduced resistance to inherent lens substance and capsule elasticity.

Topical instillation of the beta-adrenergic receptor antagonist timolol maleate has been shown to reduce significantly the magnitude of the IOP pulse (Colloton and Perkins, 1986; Langham, 1990; Grajewski, Ferrari-Dileo and Anderson, 1990; Yoshida *et al*, 1990), an effect which has been attributed to the vasoconstrictive action of the drug on the choroidal vasculature (Colloton and Perkins, 1986). Topical instillation of timolol can also induce significant peripheral and central systemic effects which could affect oculomotor function by either direct action on central control sites or by indirect action via its anxiolytic activity. These properties present an opportunity to investigate the feasibility of using of accommodative microfluctuations in general and HFCs in particular as non-invasive measures for investigating the consequences of local and systemic interference with intraocular function.

The effect of timolol maleate 0.5% on the frequency characteristics of accommodation microfluctuations was examined for direct measures on treated eyes and for consensual measures on untreated eyes: local effects of timolol will predominate in the former condition, systemic effects in the latter. In addition, it is well documented that topical timolol reduces arterial pulse rate by an average of 9 beats/min (Boger *et al*, 1978), an effect which will provide a further means of substantiating the findings in Chapter 8 that the arterial pulse governs the location of the HFC of accommodative microfluctuations.

9.2 METHODS

The Canon IR optometer was used to record continuously the monocular accommodation response over 10s time periods to a 90% contrast, Maltese cross and letter target (luminance 40 cd.m^{-2}) located at a vergence of -4D (25cm). A Hamamatsu C3160 Percept scope eye tracker recorded eye movements during the experiment to verify that fixation during recording was within the experimental limits of 1°. The outputs from the Canon optometer and Percept scope were displayed on a digital storage oscilloscope (Gould 1604) and transferred to an Epson PcE-XT clone computer via an IEEE-488 interface for subsequent analysis using *Asystant* Software. Ten accommodation runs, each of 10s duration, were collected at a sampling rate of 102.4Hz with care taken to eliminate any data containing eye movement or blink artefacts. The data were smoothed with a high frequency cut at 10Hz and power spectrum analysis was performed on each individual trace with a frequency resolution of 0.1Hz. A minimum of 8 accommodation power spectra were averaged for each experimental condition to improve the confidence limits (16 d.f.)[*].

A double-blind protocol between saline and timolol was employed. Measurements of IOP were made with a *Digilab* pneumatonometer; blood pressure measurements with a sphygmomanometer, and pulse rate noted by counting the brachial pulse beats over a 15s period.

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[*] The probability density function of a power spectrum obtained by averaging 'n' spectra is a X^2 distribution of order 2 (Pugh and Winn, 1987)

Data was collected before and 45 minutes following the instillation of saline or timolol. Informed consent from all subjects was given following a full explanation of all experimental procedures.

The experiment consisted of three sections:

Experiment 1:

The effect of unilateral instillation of 1 drop (30µl) of timolol maleate 0.5% following topical anaesthesia (with 2 drops of 0.4% benoxinate HCl) on the dynamics of the steady-state accommodation response was investigated in the treated eye of ten emmetropic subjects (5 male and 5 female), with an age range of 21-28 (mean 23.1 ±2.8) years. All subjects had lightly-pigmented irides equivalent to colour standard A in the recent classification proposed by Seddon *et al*, (1990).

Experiment 2:

The above experimental protocol was repeated on 4 subjects with additional recordings made on the *untreated* eyes to allow a comparison of local and systemic effects: the untreated eye thus indicates the ocular consequences of the systemic action of timolol.

The two recording sessions used in both experiments were separated by at least one week.

Experiment 3:

The effect of uniocular instillations of 2 drops of the cardioselective beta$_1$-adrenergic receptor blocking agent betaxolol HCl (Chapter 2, pps 40-41) on the rms of accommodative microfluctuations for both treated and untreated eyes was examined in one subject. The protocol described above was followed for this experimental part.

9.3 RESULTS

Experiment 1:

Following the instillation of timolol a mean reduction in IOP of 5.17±1.6 mmHg and 1.9±1.1 mmHg was observed for the treated and untreated eyes respectively. Group data

illustrating these changes in IOP are shown in Figure 9.1. These findings lend support to previous clinical studies which have demonstrated that the unilateral instillation of timolol reduces the IOP of the contralateral eye but to a lesser degree than that of the treated eye (Zimmerman and Kaufman, 1977a; Neufeld, 1979). In addition, systemic absorption of the drug caused the pulse rate to reduce by 6.2 ± 3.3 beats/minute but there was no significant change in blood pressure (see Appendix IV.3, p226)
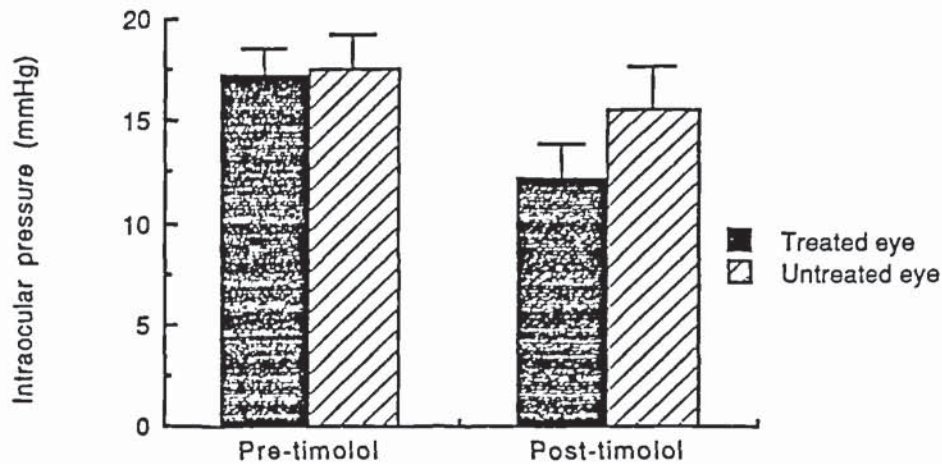
Figure 9.1: Group data illustrating the significant reduction in IOP induced by timolol on both the treated and untreated eyes. (Student's paired t-test: treated, $t=10.4$; $p< 0.01$; d.f = 9; untreated, $t=5.4$; $p<0.01$; d.f = 9) (From Owens *et al*, 1991)

Accommodative power spectra obtained from two subjects before and after the saline-timolol condition are shown in Figure 9.2 and are typical of the group used in the first experiment. The spectra show the characteristic low and high frequency components of accommodation and are consistent with previously reported work in both form and magnitude (Denieul, 1982; Kotulak and Schor, 1986c). The root-mean-square (rms) value of steady-state accommodation microfluctuations did not demonstrate any significant difference between trials for the saline-saline control condition but a significant reduction (Students paired t-test: $t=5.398$; $p<0.01$, df=9) in the rms value was induced by treatment with timolol (Table 9.1).(see Appendix IV).
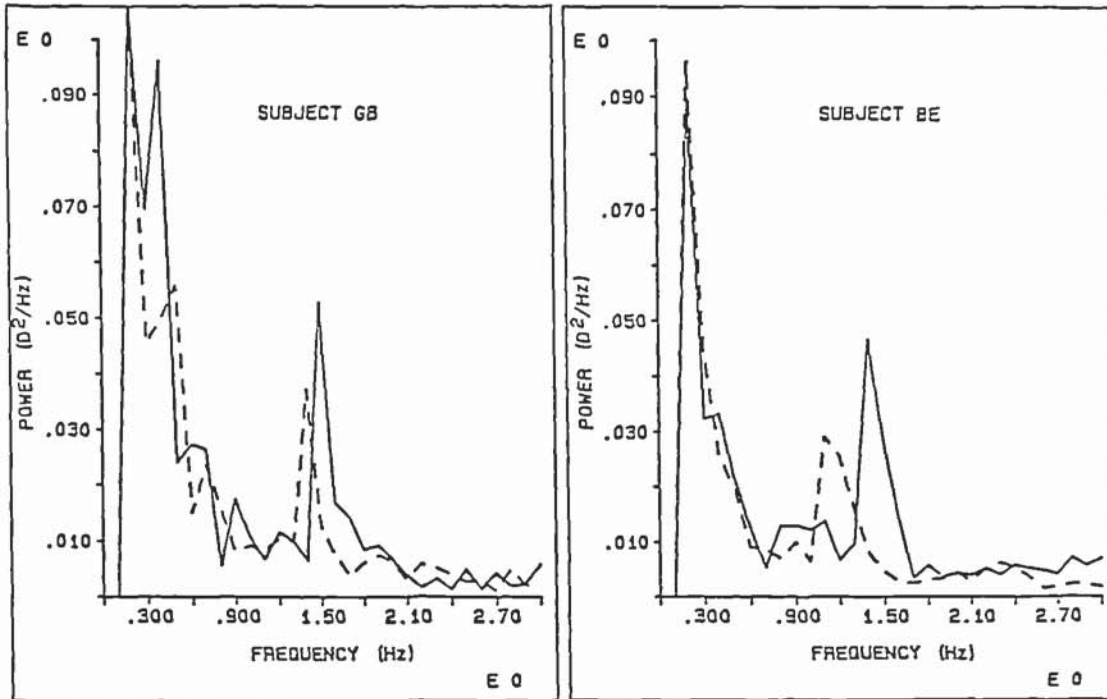
Figure 9.2: Power spectra with 16 degrees of freedom of the accommodative microfluctuations for 2 subjects illustrating the effect of timolol on the treated eyes. (Solid lines - pre-timolol; dashed lines - post-timolol). Note the overall reduction in power and the reduced frequency of the HFC following treatment with timolol (From Owens *et al*, 1991)

| Subject | PRE-TIMOLOL | | POST-TIMOLOL | |
	mean accom rms(D)	peak HFC (Hz)	mean accom rms(D)	peak HFC (Hz)
AM	0.18	1.3	0.14	1.1
BE	0.21	1.4	0.19	1.1
DC	0.23	1.3	0.21	1.1
FE	0.22	1.1	0.21	1.0
GB	0.27	1.5	0.23	1.4
JH	0.18	1.4	0.13	1.3
PI	0.27	1.5	0.18	1.4
TH	0.10	1.5	0.08	1.4
VH	0.17	1.5	0.12	1.4
VP	0.20	1.1	0.14	0.9
Mean	0.21	1.36	0.17	1.21
S.D.	±0.04	±0.15	±0.04	±0.19

Table 9.1: Mean data for the rms of accommodation microfluctuations and dominant HFC for all subjects used in experiment 1.

Individual data have been plotted for both the control and treatment conditions and are illustrated in figure 9.3. The data show a high level of correlation between the two trials

for both treatment conditions but the gradient of the slope (m=0.84) is reduced for the saline-timolol trial compared to the saline-saline control (m=0.95). The effect of the drug on the two principal frequency components of the accommodation response has also been plotted (figure 9.4a and 9.4b). Both the LFCs (0.3-0.6 Hz) and HFCs were significantly reduced in the treated eyes (Student's paired t-test: LFC; t=3.573; p<0.02; df=9; HFC; t=2.824; p<0.05; df=9). There appeared to be some inter-subject variability in the effect of timolol on the magnitude of the HFC. Individual power spectra for the 10 subjects are given in Appendix IV.4, (p227), from which it may be seen that whereas 5 subjects (BE, DC, GB, PI, VP) showed a manifest reduction in HFC area, no change was evident for the other 5 subjects. The experiment was repeated on 2 well-trained. subjects (BE and VP), the results for whom were consistent with earlier experimental runs.
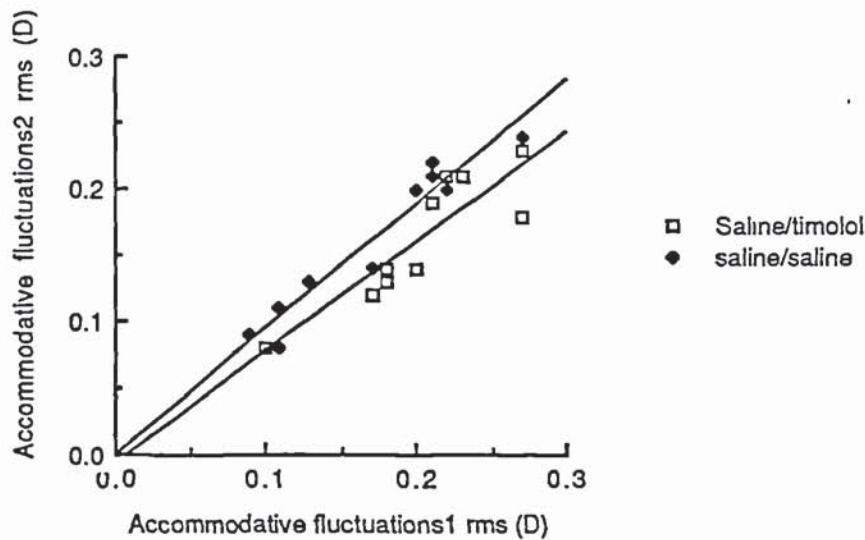
Figure 9.3: Individual rms data are shown for the control and treated conditions. Accommodative fluctuations 1 - pre-treatment trial; accommodative fluctuations 2 - post-treatment trial. The regression equation for the saline-saline trial was y=0.95x; R^2=0.92 and for the saline-timolol trial the equation was y=0.84x; R^2=0.77.
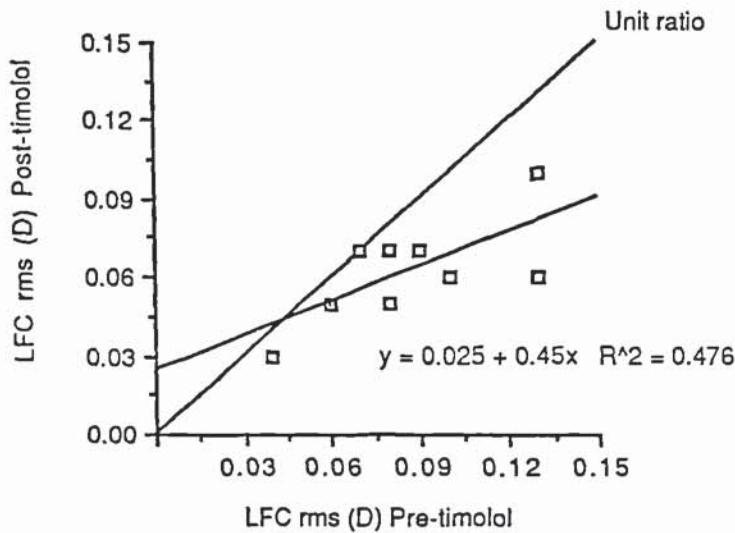
Figure 9.4a: Group data illustrating the effect of timolol on the LFC of accommodative microfluctuations. Typical SEMs were 0.012D with a range of 0.007-0.014D.
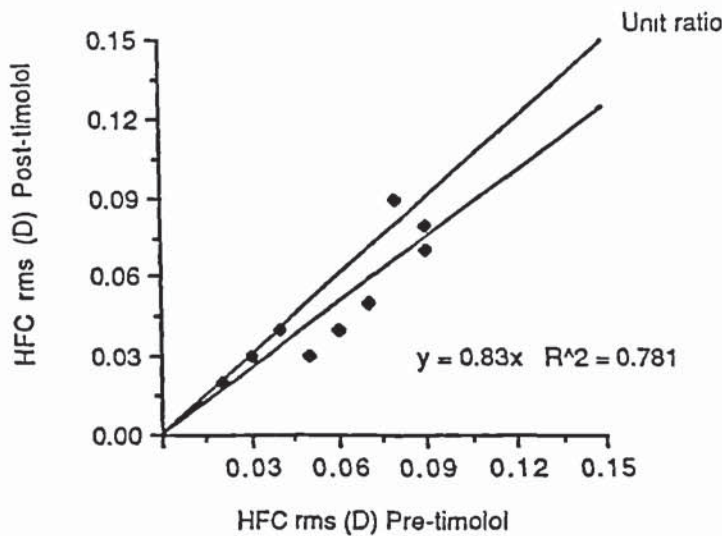
Figure 9.4b: Group data illustrating the effect of timolol on the HFC of accommodative microfluctuations. Typical SEMs were 0.005D with a range of 0.004-0.008D

Experiment 2:

Measurements of the accommodation fluctuations on both the treated and untreated eyes were made in this section of the experimental trial. The rms values for all treated eyes were significantly reduced as in the previous section but no significant change was observed in the contralateral untreated eyes (Table 9.2).

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	Pre-timolol			Post-timolol		
Subject	mean accom rms (D) (t)	mean accom rms(D) (u)	AP bm⁻¹ (Hz)	mean accom rms (D) (t)	mean accom rms (D) (u)	AP bm⁻¹ (Hz)
BE	0.22	0.19	66 (1.1)	0.19	0.18	60 (1.0)
DS	0.19	0.18	76 (1.3)	0.15	0.21	72 (1.2)
JH	0.18	0.23	78 (1.3)	0.13	0.21	72 (1.2)
VP	0.20	0.27	62 (1.0)	0.14	0.26	48 (0.8)

Table 9.2: Data for subjects in experiment 2 showing the rms values for both treated (t) and untreated (u) eyes before and after instillation of timolol. AP values are also provided pre- and post-treatment to demonstrate the systemic effect of the topically applied drug.

Power spectra which were calculated from recordings made on the treated and untreated eyes of subject VP are shown in figure 9.5 to allow comparison of local and systemic effects on the accommodation microfluctuations. The overall reduction in power observed in the treated eye compared to the consensual eye is principally the result of localised effects whereas the reduced frequency of the dominant HFC, which occurs in both eyes, is due to a change in the systemically modulated AP. This pattern of effects is typical of the sample used in this section of the experimental trial.

Systemic absorption of timolol produced a consistent shift in the location of the AP modulated HFC in both eyes but the change in magnitude of this component in the consensual eyes exhibited inter-subject variability. Normalised data are presented in histogram form (figure 9.6) to show the relative change in the rms values of the HFC for the treated and untreated eyes for all of the subjects used in this section of the study. No significant difference in the HFC magnitude was observed in 2 of the subjects (BE and DS) but the remaining 2 subjects exhibited a significant increase in HFC magnitude (subject JH: $t=3.069$, $p< 0.02$, $df=8$; subject VP $t=3.983$, $p<0.02$, $df=7$). The small subject sample used prevents any definitive conclusion to be drawn which could account for the presence of inter-subject variability in the consensual eye response.
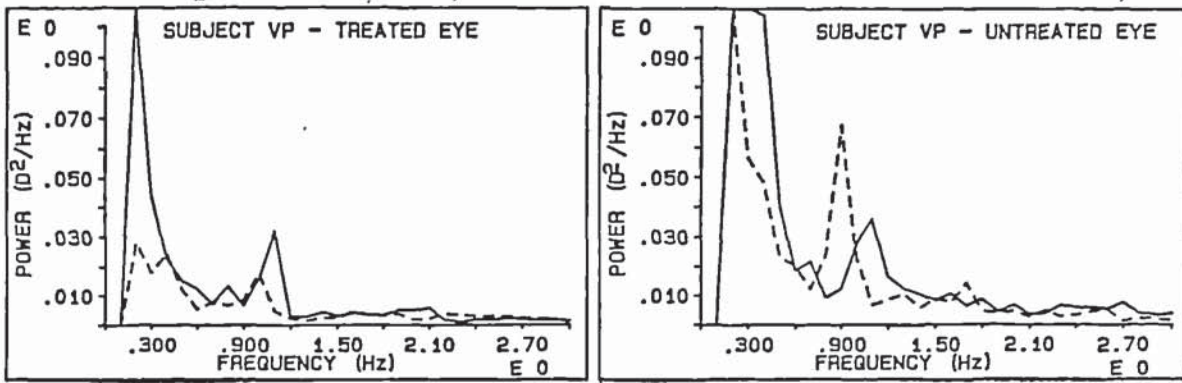
Figure 9.5 Power spectra of accommodative microfluctuations for subject VP for the treated and untreated eyes (Solid lines - pre-timolol; dashed lines - post-timolol). Note the overall reduction in power in the treated eye compared with the untreated eye and the reduced frequency of the HFC in both eyes (From Owens *et al*, 1991)
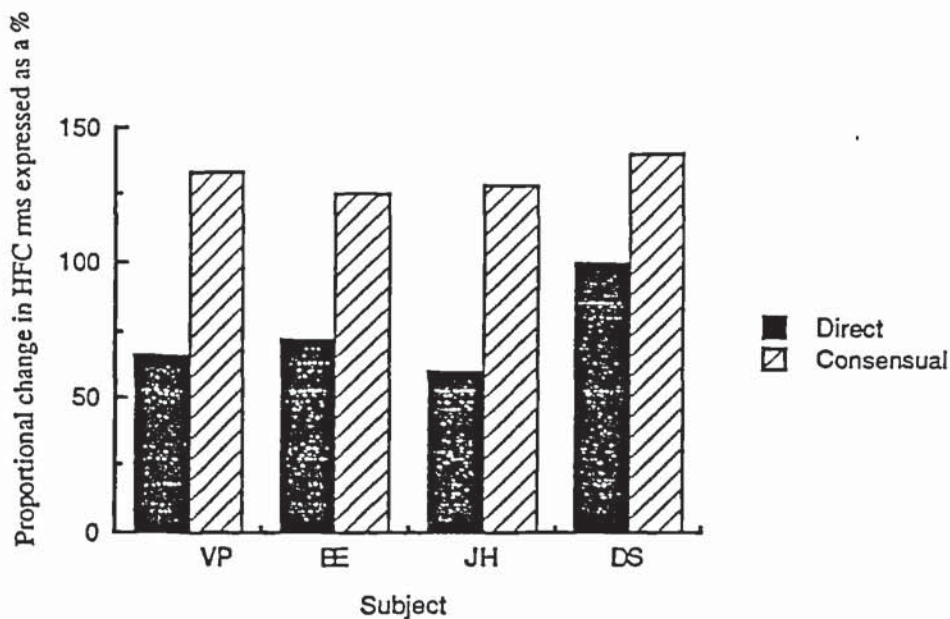
Figure 9.6: Histogram illustrating the percentage change in the HFCs of accommodative microfluctuations following instillation of timolol for both treated and untreated eyes.

Experiment 3:

Composite power spectrum plots of accommodative microfluctuations for the subject who was treated with betaxolol are illustrated in Figure 9.7a and 9.7b for treated (right) and untreated (left) eyes respectively. The effect of betaxolol on the rms of

accommodative microfluctuations is similar to that incurred following timolol treatment: there is a manifest reduction in rms in the treated eye but no reduction in the untreated eye. Table 9.3 summarises the effect of betaxolol on the IOP, blood pressure and arterial pulse rate of this subject.

	IOP (mmHg)	Blood Pressure (Systolic/ Diastolic) (mmHg)	Pulse rate (b.min⁻¹)
Pre-betaxolol	R 13.3±1.0 L 11.7±1.5	98/63	72
Post-betaxolol	R 11.5±0.6 L 13.7±1.2	100/58	72

Table 9.3: Effect of unilateral instillation on IOP, BP and arterial pulse of 2 drops of betaxolol on the right eye of subject NE
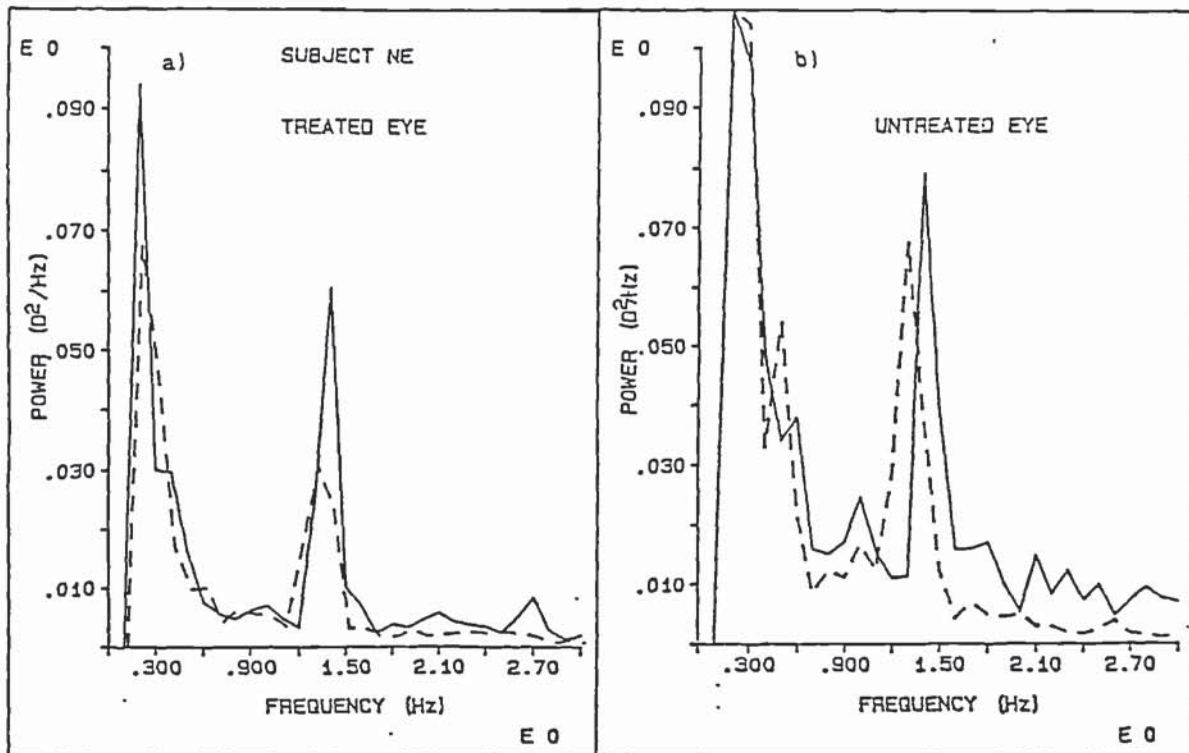
Figure 9.7: Effect of betaxolol HCl on the accommodative microfluctuations on a) treated eye b) untreated eyes of subject NE. The power spectrum pre-betaxolol is indicated by the solid line; post-betaxolol is indicated by the dashed line.

The change in the rms of accommodative microfluctuations for the treated and untreated eyes is given in the table below.

Eye	Pre-treatment rms (D)	Post treatment rms (D)
Right (treated)	0.20	0.17
Left (untreated)	0.28	0.29

Table 9.4: Effect of betaxolol on the rms of the treated and untreated eyes of subject NE

From Figure 9.7, it may be seen that the HFC peak frequency shows a marginal shift post-treatment by a maximum of ~1 frequency bin. The shift is equivalent to an arterial pulse shift of up to ~6b.min^{-1}, which supports the documented effect of betaxolol on the arterial pulse rate (Berry, Van Buskirk and Shields, 1984).

9.4 DISCUSSION

The results show that the frequency characteristics of accommodative microfluctuations are significantly modified by the local and systemic ocular effects following topical instillation of timolol maleate 0.5%. The systemically modulated reduction in pulse rate induced by timolol was found to correlate with the change in frequency of the HFC of accommodative fluctuations in both treated and untreated eyes and this lends further support to the findings reported in Chapter 8, that the HFCs are significantly correlated with arterial pulse.

Topical timolol significantly reduces the rms of accommodative microfluctuations in the treated eyes but not in the untreated eyes. The implication is that the effect is instigated by a local action of the drug on the treated eye, as a systemically modulated effect would be expected to affect both eyes to the same degree.

Timolol treatment caused a significant reduction in the rms value of the HFCs. This finding may be explained in terms of the purported effect of timolol on the choroidal vasculature. There is evidence that one drop of 0.5% timolol applied topically in humans causes a significant reduction in IOP pulse amplitude in treated eyes, but not in untreated

eyes, an effect which has been associated with a constriction of the choroidal vasculature (Colloton and Perkins, 1986). Further, measurements of IOP pulse amplitude have indicated that topical timolol 0.25% decreases blood flow by 25% in humans within 1-2 hours (Langham, 1990). Conversely, a reduction in pulse amplitude has been demonstrated to orally administered, but not topically instilled timolol (Grajewski, Ferrari-Dileo and Anderson, 1990).

If the HFCs are instigated by the pulsatile blood flow in the choroid, then the reduction in the rms of the HFCs with timolol treatment reported for the subjects in this work (see Appendix IV.4, p227) lends support to the proposal that the drug significantly reduces choroidal blood flow. The literature on the effect of timolol on ocular blood flow appears contradictory, however. While some authors report no concomitant change in blood flow with topical timolol treatment (Grajewski, Ferrari-Dileo and Anderson, 1990; Chiou, Girgis and Chiou, 1988), others report a reduction only with orally administered timolol (Grajewski, Ferrari-Dileo and Anderson, 1990) whereas an *increase* in *retinal* blood flow with topical treatment has been demonstrated in normal eyes (Grunwald, 1986). It may be conjectured that the contradictory evidence in the literature could be due to inter-subject differences in the effectivity of the drug in reducing choroidal blood flow, as found with the effect of timolol on the HFCs of accommodative microfluctuations reported in this work.

The effect of betaxolol on the rms of accommodative microfluctuations would appear to support the proposal that the reported reduction in rms evident in treated eyes is unlikely to be due to a localised beta$_2$ effect in the eye, as the drug betaxolol has little, if any, beta$_2$ effect. It is more likely that betaxolol also possesses the same vasoconstrictive properties as timolol. There is no documented evidence based on IOP pulse measurements to support this proposal, however. It has been conjectured that the mechanism of action of beta-blocking drugs such as timolol on the IOP may be the consequence of an alpha-mediated vasoconstriction of the blood vessels supplying the ciliary processes (Trope and Clark, 1982). It is feasible therefore to postulate that a vasoconstriction could also occur within the choroidal vasculature.

The reason for the increase in magnitude of HFCs in the contralateral untreated eye of subjects VP and JH is unclear, but it may be speculated that the reduction in IOP resulting from the consensual response to timolol would lower the intraocular resistance to changes either in the position or in the anterior curvature of the crystalline lens. The absence of vasoconstriction in the choroidal blood vessels in the untreated eye may allow the consequences of the change in resistance to become manifest as an increase in the magnitude of the HFC, whereas in the treated eye, the choroidal vasoconstriction effect swamps the resistance change effect and therefore the HFCs in the treated eyes will be reduced in magnitude. No definite conclusion may be drawn, however, as the subject numbers for the consensual action of timolol are small and the literature on the choroidal vascular effects of timolol is sparse and contradictory.

The inter-subject differences evident from the effect of timolol on the consensual eyes may represent individual differences in the systemic absorption of timolol, although there was no correlation between the magnitude of the consensual reduction in IOP and change in magnitude of HFC in the untreated eye. Evidently, the processes which dictate the magnitude of the arterial pulse and consequently the magnitude of the HFC of accommodative microfluctuations are complex and susceptible to numerous endogenous (e.g. systemic blood pressure) influences, which could not be measured during the experiment. Nevertheless, the possibility that the effect of timolol on the rms of accommodative microfluctuations is wholly associated with the well documented CNS stress-reducing properties of beta-blocking drugs may be discounted, as the response in the untreated eyes does not exhibit a reduction in rms.

It is interesting to speculate about the mechanism of action of timolol and its long-term effectivity. It is documented that some patients treated with timolol over an extended period become resistant to its ocular hypotensive effect, the IOP gradually increasing to previous high levels (Boger, 1979). It is feasible to imagine that a pumping mechanism exists which is linked to the pulsatile changes in the choroid which are transmitted via the zonules to the lens as accommodative microfluctuations. Such a mechanism could be

responsible for ensuring that aqueous flow is kept at a constant rate to maintain IOP at a tolerable level. If the pumping mechanism were disrupted by dampened pulsatile forces, then it is possible that the effectiveness of the pump could be weakened, leading to raised IOP. This proposed mechanism would provide an explanation of the ocular hypotensive effect of exercise (Lempert *et al*, 1967; Passo *et al*, 1989) and also why glaucoma rarely affects pre-presbyopic individuals. Further work is necessary to examine the effect of age and raised IOP on accommodative microfluctuations before such a mechanism is given credence.

The findings of this work indicate that measurement of microfluctuations has potential as a non-invasive method of assessing the effect of beta-adrenergic antagonists on the eye and of identifying a possible mechanism involved in the regulation of IOP.

Supporting publication

Owens H, Winn B, Gilmartin B and Pugh JR (1991) Effect of a topical beta-antagonist on the dynamics of steady-state accommodation. *Ophthal Physiol Opt* **11**, 99-104.

Refereed Papers published in Conference Proceedings

Owens H, Winn B, Gilmartin B and Pugh JR (1990) The effect of topical beta-adrenergic antagonists on the dynamics of steady-state accommodation. Non-invasive assessment of the visual system, Optical Society of America and American Academy of Optometry, Santa Fe, 88-91.

Refereed published abstracts in conference proceedings

Winn, B, Gilmartin B, Owens H and Pugh JR (1991) The effect of topical timolol maleate on accommodative microfluctuations (Poster) Association for Research into Vision and Ophthalmology meeting, May 1991, Sarasota, Florida, USA. *Invest Ophthal Vis Sci (suppl)* **32**, 759.

CHAPTER 10

THE EFFECT OF BETA-ADRENERGIC RECEPTOR ANTAGONISTS ON DYNAMIC MEASUREMENTS OF ACCOMMODATION

10.1 INTRODUCTION

It is now well established that the ciliary muscle receives a dual autonomic innervation: i.e. from both the parasympathetic and the sympathetic nervous systems (for review, see Gilmartin, 1986). Physiological and pharmacological evidence suggests that the time course of the sympathetic system is slow (Törnqvist, 1967; see Chapter 2, p31) and consequently it is likely to play a relatively minor role in the accommodative response to the normal visual environment which involves rapid changes of fixation from one object of regard to the next. In contrast, the rapid response time following nerve stimulation of the parasympathetic system (Törnqvist, 1967) correlates with the experimental findings on humans of Campbell and Westheimer (1960) that an accommodative response may be completed within 1 second.

Sympathetic innervation to the ciliary muscle involves beta-adrenergic receptors which are predominantly of the beta$_2$-subtype (Lograno and Reibaldi, 1986; Wax and Molinoff, 1987; Zetterström and Hahnenberger, 1986). Recent studies have utilised the beta-adrenergic receptor antagonist timolol maleate to examine the effect of blocking the adrenergic receptors in ciliary smooth muscle on various aspects of the accommodative mechanism (Gilmartin, Hogan and Thompson, 1984; Gilmartin and Bullimore, 1987; Rosenfield and Gilmartin, 1987a, 1987b, 1989; Owens *et al*, 1991).

The majority of studies involved in the assessment of autonomic function in human accommodation have involved measurements of open-loop accommodation. Such work has affirmed three further characteristics of the sympathetic input to the ciliary muscle: that it is inhibitory, relatively small in magnitude and augmented by concurrent parasympathetic activity (Gilmartin, Hogan and Thompson, 1984; Gilmartin and Bullimore, 1987; 1991; Rosenfield and Gilmartin, 1987a,b,1989). Considerations of the temporal nature of the sympathetic system and of evidence that augmentation occurs with

increased parasympathetic activity has led to the proposal that the main function of the sympathetic component to the ciliary muscle is related to prolonged near visual tasks of relatively high accommodative demand (Gilmartin and Bullimore, 1987; 1991). Consequently, there is considerable interest about the relationship between the autonomic nervous system and the development of late-onset myopia following intense periods of close work (see Chapter 2; pps 65-69).

Gilmartin and Bullimore (1987) have demonstrated that timolol maleate is effective in retarding the regression patterns of accommodation to pre-task tonic accommodation levels from a near task of relatively high accommodative demand for certain emmetropic individuals. It was deduced by these authors that some individuals may be deficient in a sympathetic facility which could predispose them to adaptational effects and possible near vision stress following prolonged periods of close work. A fuller account of this work is given in Chapter 2 (pps 63-64).and is examined further in Chapter 6 (pps 102-118). However, speculation concerning accommodative events which occur during the normal closed-loop situation from open-loop measurements may be of limited value.

Aspects of autonomic innervation of ciliary smooth muscle during *closed-loop* measurements of accommodation have inevitably led to difficulties in that the changes induced by the drugs are constrained by the depth-of-focus of the eye. Nevertheless, comparisons have been made between the response accommodative convergence (AC/A) ratio during a near task of 16 minutes' duration for saline and timolol treated eyes (Rosenfield and Gilmartin, 1987b). The results were equivocal but did reveal that a reduction in AC/A occurred during the first 4 minutes of a near task for the timolol condition, indicating direct involvement of the sympathetic innervation to the ciliary muscle during a prolonged near vision task. These results led to the proposal that following timolol treatment there was a reduced parasympathetic requirement to the ciliary muscle to maintain the accommodative response as a direct consequence of the blocked $beta_2$ receptors in ciliary smooth muscle.

Further evidence for a sympathetically mediated effect during a near vision task has been demonstrated in static closed-loop measurements of the accommodative response to 3 target vergences (Bullimore and Gilmartin, 1988). A group of emmetropes performed 2 types of task: passive (reading numbers) and active (adding numbers) at dioptric demands of -1D, -3D and -5D for saline and timolol conditions. Timolol induced a significant increase in accommodative response for the -5D task only. It was deduced that the imposition of mental effort increased the parasympathetic innervation and concurrently increased the sympathetic inhibitory component. Blocking this component with timolol caused a manifest increase in the parasympathetically mediated accommodative response.

Recent work has demonstrated that topical timolol maleate reduces the accommodative response time from far-to-near fixation but not for near-to-far for rapid step changes in stimulus vergence (Weber et al, 1989). The interpretation of the results by the authors led to the proposal that there was no sympathetic input to the ciliary muscle for visual tasks from near-to-far, the time constant which occurs in this direction being wholly a characteristic of the visco-elastic properties of the lens. This finding is supported by analysis of the accommodation reaction and response times obtained in the near-to-far direction compared with those in the reverse direction (Tucker and Charman, 1979; Heron and Winn, 1989). Conversely, in the far-to-near direction, beta-antagonism by timolol resulted in a reduced time constant, an effect which was concluded to be the result of the unopposed action of the parasympathetic supply to the ciliary muscle.

The aim of this experiment is to examine further the role of the sympathetic system during a task involving a change of stimulus vergence. In view of the optical constraints experienced by previous workers using pharmacological agents to assess within-task autonomic function in ciliary muscle, the approach adopted in this study was to concentrate on the temporal characteristics of ciliary muscle innervation. This section reports on the effect of beta-antagonist drugs on the accommodative response to sinusoidally modulated targets at 6 different temporal frequencies, ranging from 0.05Hz to 0.5Hz. Timolol maleate 0.5% was employed to antagonise the $beta_2$ receptors in the ciliary muscle, whereas the $beta_1$ selective agent betaxolol HCl 0.5% served as a control.

The ocular hypotensive mechanism of action of betaxolol is thought to emulate that of timolol but the former agent will have a minimal effect at most on $beta_2$ receptors in the ciliary muscle. Saline was also used a control condition and used to compare results with those from previous work, in a double-blind protocol.

The hypothesis is that for rapid changes in vergence, beta-receptor antagonism would not modify the accommodative response as it is likely to be mediated predominantly by the parasympathetic system. Conversely, low temporal frequency changes in target vergence might be susceptible to beta-receptor antagonism. Our results comply with the hypothesis for timolol-treated eyes but $beta_1$ antagonism with betaxolol produced an unexpected result: for this drug condition, there was a frequency independent reduction in accommodative gain.

10.2 METHOD

Three well-trained young observers (BE: 29 years; LP: 21 years; JH: 22 years) selected from the optometry department viewed monocularly through a Badal lens system a high contrast Maltese cross and letter target with a luminance of $40cd.m^{-2}$. The lens F2 (Figure 10.1) was moved sinusoidally over a range of 1.5D to produce vergence demands of -5D and -3.5D at 6 temporal frequencies ranging from 0.05Hz to 0.5Hz which were presented in a random order. A schematic representation of the optical set-up is given in Figure 10.1.
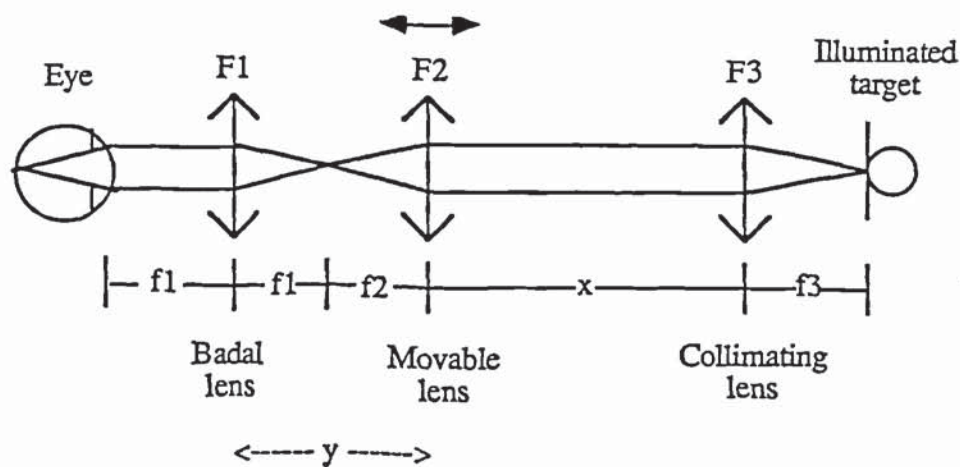
Figure 10.1: Schematic representation of optical set-up. Lens F2 was varied in position such that the separation (y) between F1 and F2 was within the range $f2 \leq y < (f1+f2)$. In the case shown above, the subect is exerting no accommodation.

A dental bite and forehead rest ensured minimal movement during recordings. All subjects were emmetropic with at least 6/6 vision in the tested eye and were chosen for their good fixational ability and previous training in experiments of this type. Following approval from the ethical committee, a full explanation of the experimental procedures was issued to the subjects who then gave their informed consent.

Continuous measurements of the accommodation response were made with the Canon optometer for a minimum of 5 cycles per frequency of target oscillation. Data acquisition over increased time periods, necessary for the lower temporal frequencies, was achieved by altering the time base on the oscilloscope. The accommodative response was calculated for each frequency by averaging the magnitudes of the responses over the trials and the gain calculated by dividing the average response by the actual dioptric value of the step. The experiment consisted of 2 parts: an initial experimental session when measurements of accommodation for all temporal frequencies were made for a no-drug condition, followed by a repetition of the experimental run 45 minutes after the instillation of one of the 3 drugs. A double-blind protocol was followed for the 3 drugs: timolol (1 drop: 30μl); betaxolol (2 drops: 60μl) and saline, which were instilled following a measurement of IOP. Two drops of benoxinate HCl were instilled prior to IOP measurements with a *Digilab* pneumotonometer. It was necessary to instil twice the dose of betaxolol compared with timolol as the latter is a more potent ocular hypotensive drug than the former (Stewart, Kimbrough and Ward, 1986). The subjects were encouraged to indicate whether they were tired and a break was given if the subject was fatigued. The average duration of each experimental measurements session was 1 hour.

In addition to measurements of IOP using a *Digilab* pneumotonometer, pulse rate was measured by counting the number of brachial pulse beats which occurred over 15s. Blood pressure was measured by sphygmomanometry. These measurements were made after each experimental run: i.e. 2 sets of measurements for each experimental session.

10.3 RESULTS

Table 10.1 Illustrates the average reduction in IOP for both treated and untreated eyes induced by the two adrenergic antagonist drugs. Pulse rate was reduced by 6.2 ± 1.4 beats per minute by timolol and 2.5 ± 1.6 beats per minute by betaxolol. This is consistent with the documented effects of the drugs on heart rate (Van Buskirk and Fraunfelder, 1984).

Eye	Mean IOP change with timolol ($\pm$1S.D) (mmHg)	Mean IOP change with betaxolol ($\pm$1S.D) (mmHg)	Mean IOP change for saline ($\pm$1S.D) (mmHg)
treated	2.2 ± 1.6	3.0 ± 0.5	0.7 ± 1.5
untreated	1.3 ± 0.4	1.4 ± 1.2	0.5 ± 0.9

Table 10.1: Summary of effect of timolol, betaxolol and saline treatments on the IOP of the treated and untreated eyes for the 3 subjects.

Figure 10.2 illustrates the ocular hypotensive effects of the 2 drugs on the individual subjects.
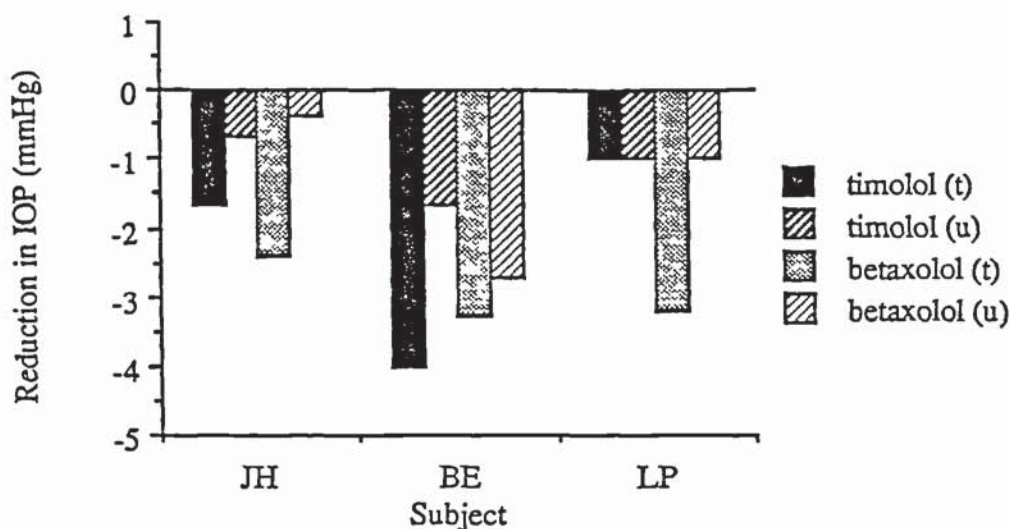
Figure 10.2: Histogram plot showing the effect of the two drugs on the treated (t) and untreated (u) eyes of the individual subjects

There was no significant change in blood pressure with either drug (Average systolic/diastolic measurements were $95\pm 5/ 70 \pm 3$ mmHg).

In keeping with previous studies, the accommodative gain reduced with higher temporal frequency target movement. This effect is illustrated in figure 10.3 for subject LP for 3 temporal frequencies.
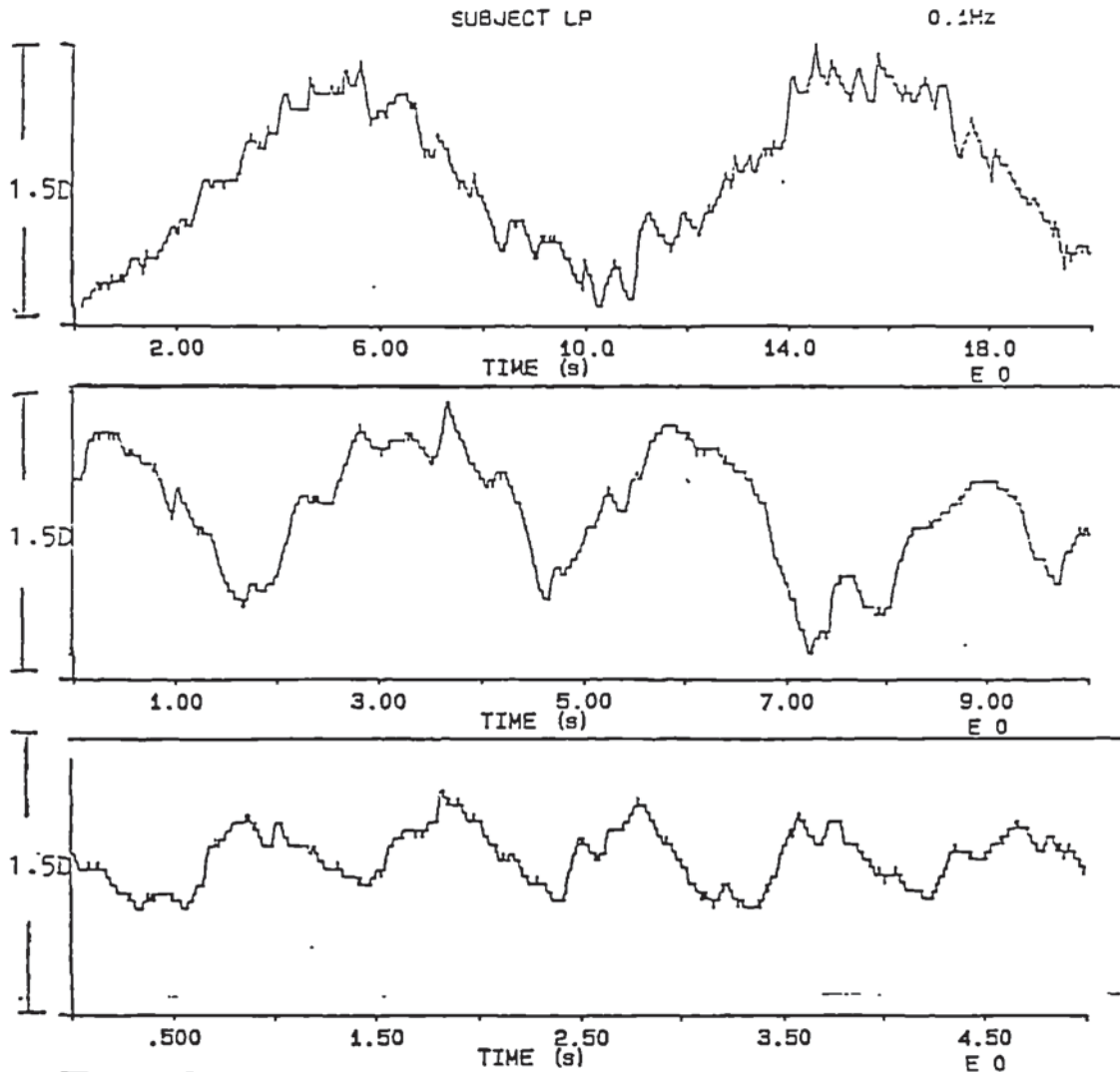
Figure 10.3: Accommodative gain for 3 temporal frequencies illustrating that as temporal frequency of target oscillation increases, accommodative gain decreases.

This result was typical for the 3 subjects used in this study, although it must be noted that accommodative gain appeared to improve with successive experimental trials, suggesting that training improved the magnitude of the response at higher temporal frequencies. This is consistent with a previous report that training increases the velocity of the accommodative response to sinusoidally moving targets with a concurrent increase in gain and reduction in phase-lag (Randle and Murphy, 1974). In view of this, later experimental trials necessitated

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an increase in temporal frequency of target motion above 0.5Hz for subject JH in order to confirm a reduction in accommodative gain with increased temporal frequency.

Figure 10.4 are accommodative bode plots comparing the saline with the timolol condition for the individual subjects used in the experiment. It may be seen that the timolol condition reduces the gain for the lower frequencies for the 3 subjects, although there is some inter-subject variation in the frequency above which the gains for timolol and saline concur. For subject BE, timolol treatment induced a gain deficit up to a temporal frequency of 0.3Hz compared with the saline condition, whereas for subject LP, the difference is minimal beyond 0.2Hz. For subject JH, the difference in gain is only apparent for the two slowest frequencies measured (0.05 and 0.1Hz). Interestingly, the reduction in IOP with timolol was greatest for subject BE (~4mmHg) compared with ~1.5mmHg for the other two subjects.

A 2-way ANOVA showed that the reduction in accommodative gain was highly significant for both drug, frequency and the interaction between drug and frequency for all subjects for the timolol condition (Subject LP: Frequency: $F = 37.461$; $P = 0.0001$; Drug $F = 13.169$; $P < 0.001$; Interaction $F = 3.785$; $P = 0.057$. Subject JH: Frequency: $F = 13.26$; $P < 0.001$; Drug $F = 22.78$; $P < 0.001$; Interaction $F = 6.92$; $P < 0.001$. Subject BE: Frequency: $F = 4.44$; $P < 0.005$; Drug $F = 28.08$; $P < 0.001$; Interaction $F = 1.3$; $P = 0.279$)

In contrast, the data for betaxolol did not show a frequency dependence. For all 3 subjects, there was a reduction in accommodative gain across all frequencies which was highly significant for all subjects. (Subject LP: Frequency: $F = 17.45$; $P < 0.001$; Drug $F = 47.38$; $P < 0.001$; Interaction $F = 1.65$; $P = 0.165$. Subject JH: Frequency: $F = 26.741$; $P < 0.001$; Drug $F = 134.78$; $P < 0.001$; Interaction $F = 1.365$; $P = 0.2542$. Subject BE: Frequency: $F = 14.052$; $P < 0.001$; Drug $F = 55.44$ $P < 0.001$; Interaction $F = 0.848$; $P = 0.523$). (See Appendix V.1, pps. 228-230).
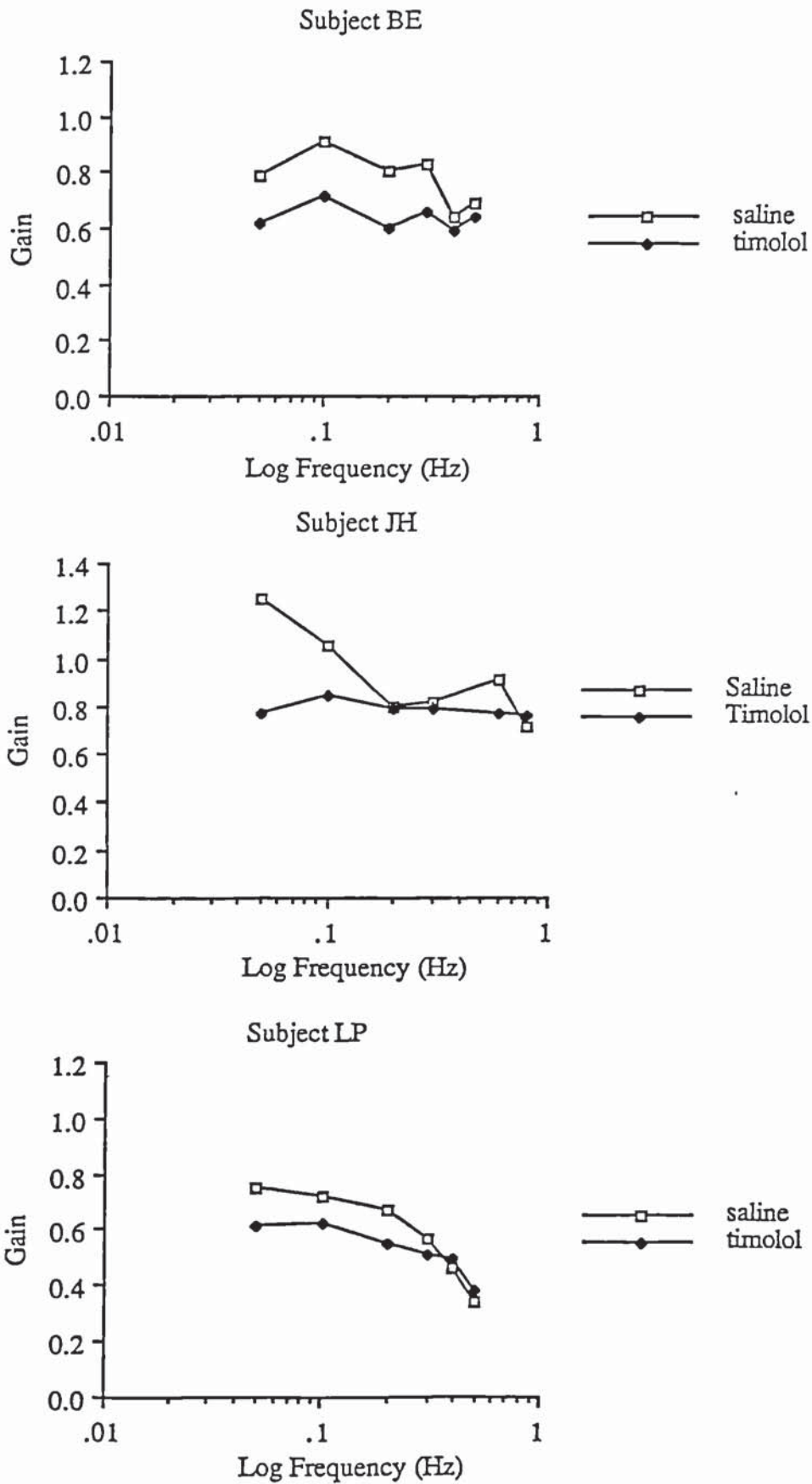
Figure 10.4: Bode plots for the 3 subjects illustrating the accommodative gain for saline and timolol conditions

for all temporal frequencies measured.

Samples of individual accommodative responses for 3 frequencies are given in Figure 10.5 below, which illustrate the accommodative response to 3 temporal frequencies of target motion: 0.1Hz, 0.3Hz and 0.8Hz for subject JH for the 3 drug conditions.
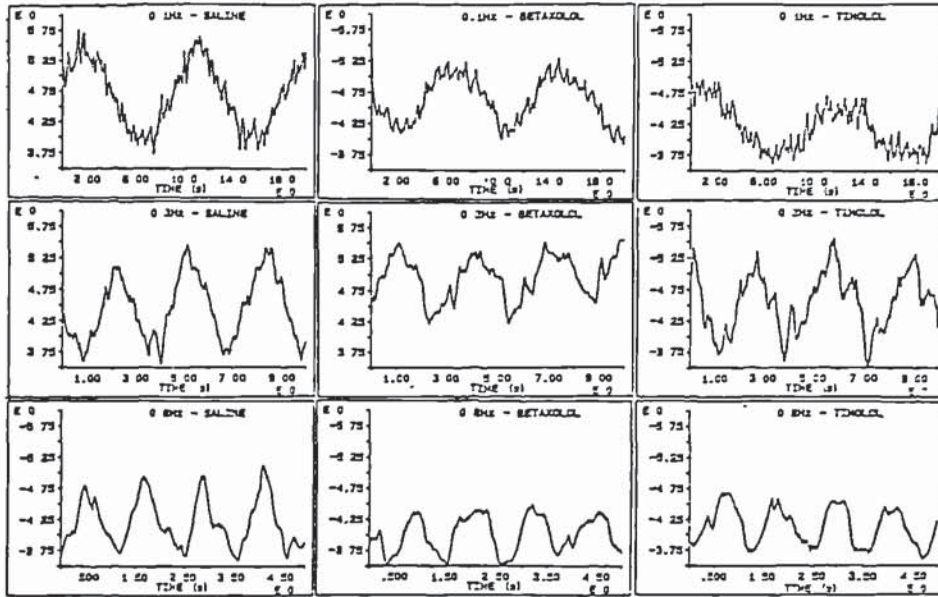
Figure 10.5: Accommodative responses to 3 temporal frequencies for the 3 drug conditions for subject JH

It may be seen that timolol reduces the accommodative gain to the 0.1Hz frequency only, whereas betaxolol reduces gain for the 3 temporal frequencies shown. The bode plots for the 3 subjects comparing saline with betaxolol are illustrated in Figure 10.6. Subject BE's responses at 0.3Hz appears to show an increased gain for this frequency compared with gain for the lower temporal frequencies for both saline and betaxolol condition. The reason for this increased gain is unkown. The reduction in gain for all subjects under betaxolol treatment is given in histogram form in Figure 10.7.
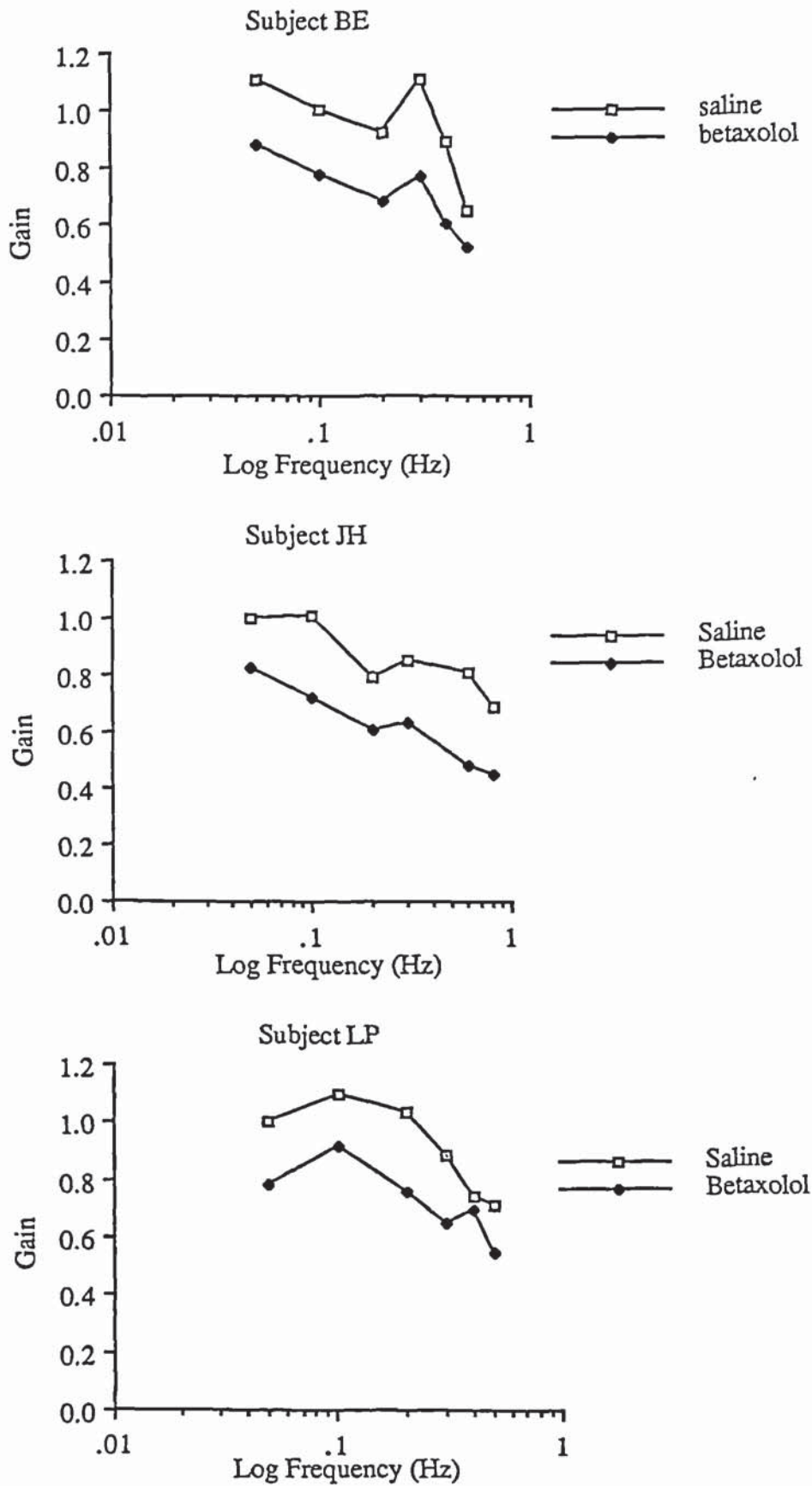
Figure 10.6: Bode plots for the 3 subjects illustrating the accommodative gain for saline and betaxolol conditions for all temporal frequencies measured. (see Figure 10.7 for equivalent histogram plots).

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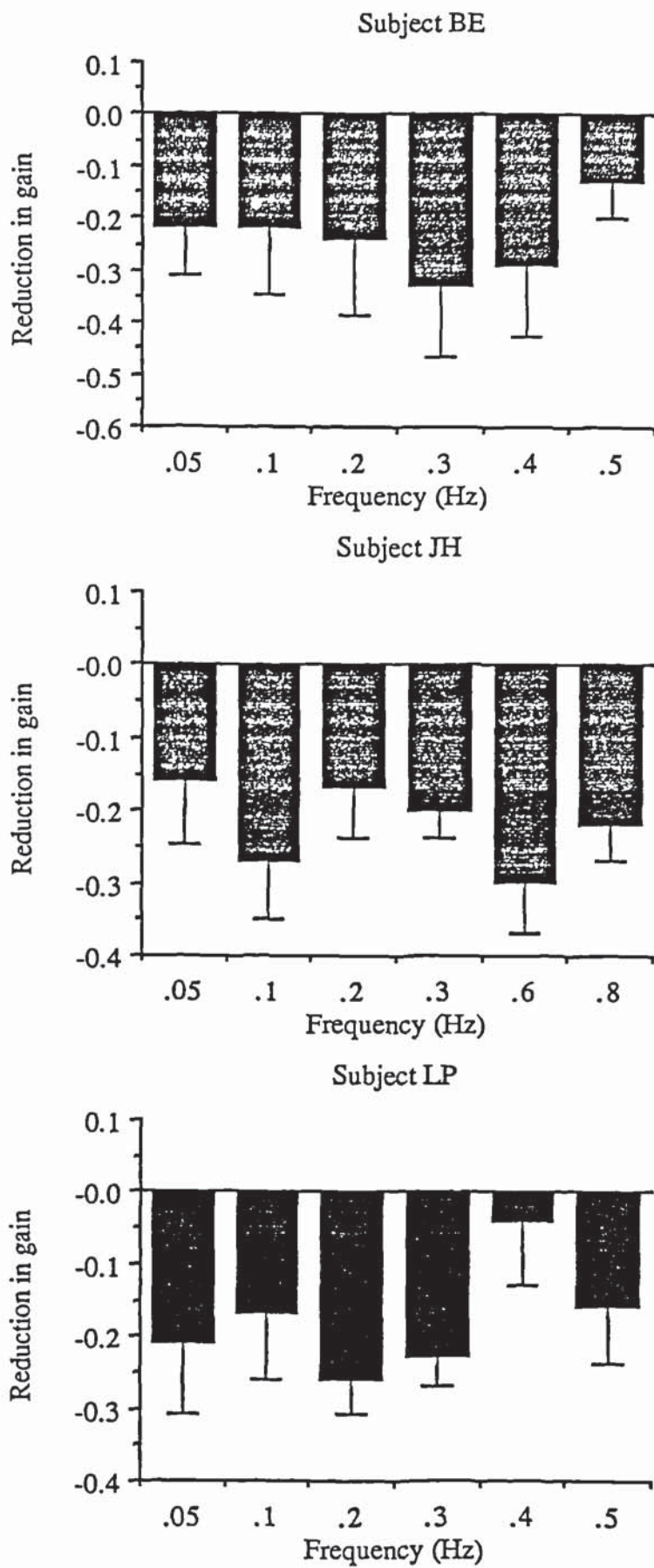
Figure 10.7: Histogram plots showing the reduction in gain across all frequencies for the 3 subjects. Error bars represent 1 S.D.

Analysis of the rate of change of the accommodative responses for the 3 subjects from far-to-near and *vice-versa* were equivocal: for subject BE there was a tendency for the slope to be decreased in the near-to-far direction, indicating a slower velocity, but there was no change in the reverse direction (Figure 10.8). The retarded velocity from near-to-far was evident for temporal frequencies up to 0.3Hz, although significant changes were only manifest for the 0.2Hz frequency (Students paired t-test: $t = 3.376$; $p < 0.05$; $df = 5$). Conversely, for subject LP, there was an increased velocity of response in the far-to-near direction for temporal frequencies up to 0.2Hz, but this tendency just failed to reach significance at the 5% level. There was no significant change in velocity of response for subject JH in either direction.

For the betaxolol condition, 2 of the 3 subjects showed evidence of a significantly reduced velocity of response for both directions of target motion which reached significance at the 3% level. The third subject showed no significant difference in response velocity with betaxolol.
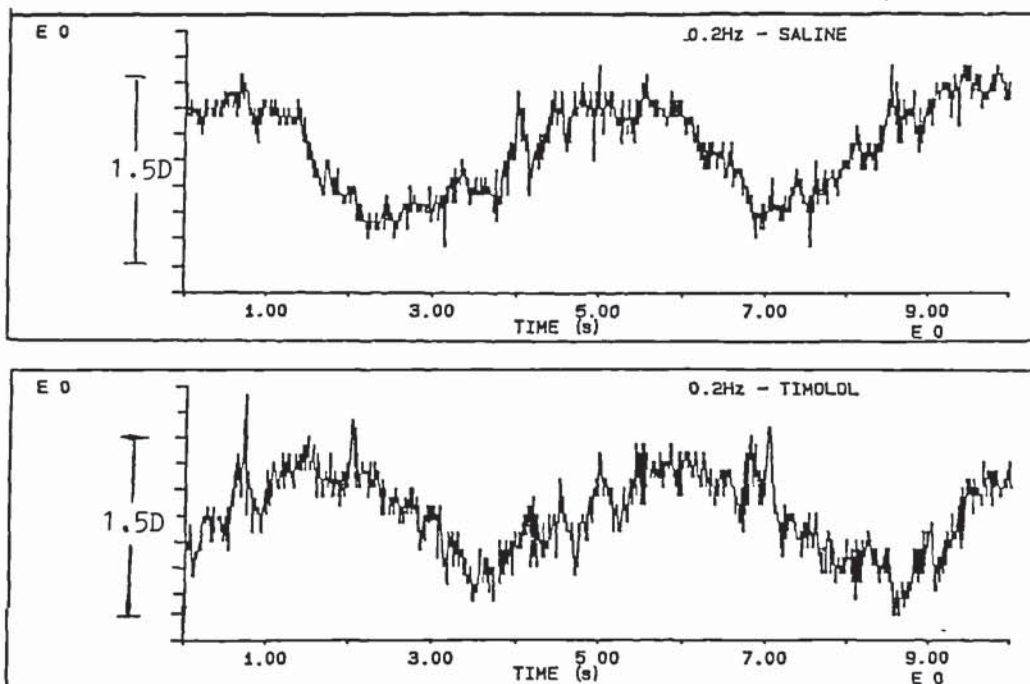
Figure 10.8: Accommodative response to a 0.2Hz target motion for subject BE. Note that there is evidence of a saw-tooth response prior for the saline condition, the gradient being flatter from far-to-near than *vice-vera*. The response following timolol treatment shows that the gradients are similar in both directions.

10.4   DISCUSSION

The results suggest that timolol reduces the accommodative gain to a moving target but shows a frequency dependence. For rapid changes in vergence, timolol treatment does not modify accommodative gain but for slowly moving targets (< 0.2Hz), over the dioptric range measured (i.e ~1.5D), timolol treatment significantly reduces the magnitude of the accommodative response. The implication is that the sympathetic system may not influence accommodative responses to rapid changes in stimulus vergence. This is consistent with the work of Törnqvist (1967) concerning the temporal nature of the sympathetic innervation to the ciliary muscle, that it is a slow system, requiring from 20 to 40s for the onset of the sympathetic response and a similar time constant for decay to occur.

In contrast, betaxolol treatment reduced the accommodative gain for all temporal frequencies. The difference exhibited in accommodative gain between that of saline and betaxolol was of the order of ~0.2-0.3. It should be noted that the average accommodative range measured was $1.7 \pm 0.3D$ and that the dioptric equivalent to the magnitude of gain reduction equates to approximately 0.4D. It is possible that the change in gain could be the manifestation of a reduction in magnitude of the accommodative microfluctuations, as the gain reduction evident with betaxolol treatment approaches the maximum rms of the microfluctuations of ~ 0.3D. It has been demonstrated that timolol reduces significantly the rms of accommodative microfluctuations (Chapter 9, pps. 143-156). Preliminary results using betaxolol would indicate that this drug produces a similar reduction in magnitude of the accommodative microfluctuations (Chapter 9, pps. 151-152). Whereas this may offer an explanation for the effect apparent with betaxolol, the frequency dependence of the effect with timolol on this basis remains to be explained.

A further possible explanation for the betaxolol-mediated result may be linked with the effect of beta-blocking drugs on the CNS. It is well documented that such agents have an anxiolytic side-effect, reducing tremor and inducing fatigue (Beresford and Hill, 1986; Lader, 1988; Tyrer, 1988). Furthermore, lethargy is known to reduce accommodative gain for sinusoidally moving targets (Malmstrom *et al*, 1981). Whereas it is impossible to assess the concentration of the drug absorbed systemically, it is possible that the increased dosage

of betaxolol compared with timolol may have been sufficient to induce the necessary amount of drowsiness to reduce the accommodative gain. In this respect, the increased lipophilicity of betaxolol compared with timolol (Lesar, 1987) is of interest, as it is documented that a drug with a high degree of lipophilicity enters the blood/cerebrospinal fluid/brain compartments with relative ease and can reach the brain within minutes (Myers *et al*, 1975).

Recent work which observed the effect of sinusoidal changes in target vergence on pupillary responses has shown that target alignment can significantly affect the pupillary component of the near response (Stakenburg, 1991; Phillips *et al*, 1991). Stakenburg showed that whereas there appeared to be a vergence-dependent pupillary response to a sinusoidally moving target over a dioptric vergence of -2.5D, when care was taken to align the target system as accurately as possible, no correlated pupillary changes in diameter occurred, even though vergence changes were evident, which the author presumed were accommodation-driven. Phillips *et al* (1991) examined further this effect and measured simultaneously the accommodation response and pupillary changes in diameter. Their results supported the work of Stakenburg: when target alignment was improved by using a laser beam to align the lens and target system, no pupillary fluctuations corresponding to the frequency of sinusoidal target motion were evident.

In the present study, although care was taken to align the individual experimental lenses in the set-up for each subject, it is possible that cues to accommodation were present from an imperfectly-aligned target system. Whereas this is a possible criticism in the experimental design, any misalignment for the no-drug conditions would also have been present for the drug condition which followed 45 minutes later. The change in gain evident for the drug condition could not therefore be attributed to a change in target alignment. It is possible, however, that the drug could modify the response to accommodative cues from vergence cues as a consequence of target system misalignment.

Experimental work on animals has indicated that there are beta-adrenergic receptors in the lens fibres of chicks (Ireland and Maisel, 1987; Ireland and Jacks, 1989) and the lens

epithelium of rabbit eyes (Elena *et al*, 1987). In chick eyes, the receptors are predominantly of the beta$_1$ subtype, the population of which decreases toward the older nuclear portion of the lens (Ireland and Jacks, 1989), whereas in rabbit, there is a preponderance of beta$_2$ receptors (Elena *et al*, 1987). Although no study has identified such beta-adrenergic receptors in human crystalline lenses, it remains a possibility that they do exist and therefore may be susceptible to adrenergic drug effects. Consequently, it may be speculated that the discrepancy between the results for timolol and betaxolol in this study may be a result of a difference between the direct action of the drugs on receptors in the crystalline lens, particularly if the human lens emulates that of the rabbit with respect to its beta-receptor population.

The results presented in this study differ from those by Weber, Tiunenberg and Van der Heijde (1989), who looked at rapid changes in stimulus vergence only. This study provides preliminary evidence that it is the temporal nature of the sympathetic system which governs the magnitude of the accommodative response to low temporal frequency changes in target vergence. Rapid changes in vergence are likely to involve only the parasympathetic input to the accommodative response. Further work is required to examine the effect of betaxolol on the accommodative gain to sinusoidally moving targets by measuring the response from the contralateral untreated eye. In this manner, the contamination of results from a local drug-induced reduction in rms of the accommodative microfluctuations may be minimised.

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CHAPTER 11

CONCLUSIONS AND PROPOSALS FOR FUTURE WORK

11.1 REVIEW OF EXPERIMENTAL RESULTS

The converted Canon R1 optometer has been employed to examine a number of aspects of the temporal accommodation response. An outline of the contributions made by the current programme of research is given below.

1. The converted Canon optometer was shown to require a minimum pupillary diameter of 3.52mm for artefact-free continuous recordings of accommodation (Chapter 5, pps. 98-99). Accommodation recordings from many subjects are therefore possible without the need of a mydriatic drug to dilate the pupil, as providing the illumination is maintained at a fairly low level (~40cd.m^{-2} for experimental work in this thesis), pupillary diameter in many cases is ~4mm.

2. Accommodation regression from a 3 minute near task located at a vergence of -3D above pre-task TA recorded with the Canon optometer followed a retarded time course over the initial 10s period for a sub-group of emmetropes after treatment with topical timolol. The remaining emmetropes and all late-onset myopes followed a regression pattern which was not altered by beta-receptor antagonism (see Chapter 6, pps. 102-118). It was proposed that those emmetropes showing retarded time courses following timolol treatment were likely to possess a sympathetic facility which would operate during a near vision task to attenuate post-task adaptational changes in ciliary muscle tone which could counteract the development of LOM. Conversely, those emmetropic subjects whose regression patterns showed no difference following timolol are likely to be deficient in the sympathetic inhibitory component and post-task adaptational changes were more likely to occur, leading to the possibility of the development of LOM.

3. The HFC of accommodation microfluctuations have been shown to be present in central areas of the crystalline lens in addition to the peripheral regions (see Chapter

7, pps. 119-128). This finding supports the proposals of Koretz and Handelman (1982, 1983) that the capsule of the lens disperses evenly the fluctuating activity conveyed upon it to the underlying lens. The magnitude of the fluctuations in the centre is greater per unit area than in peripheral lens areas, but as the of the lens periphery exceeds that in the centre, there is more power available in the periphery.

4. A highly significant correlation has been demonstrated between the HFC of accommodative microfluctuations and arterial pulse frequency (see Chapter 8, pps. 129-142). This finding has implications for accommodative control theory in that the HFC has been shown to be physiologically derived and therefore is not under direct sensory control of the oculomotor system. Any neurologically derived component is likely to be located in the low frequency end of the power spectrum, the function of which is probably related to the maintenance of a steady-state accommodation response. Although not neurologically driven, the HFC could potentially be incorporated into the control mechanism, such that a substantial increase in the magnitude of the HFC could temporarily disturb the controller mechanism, leading to the detection of blur.

5. Topical instillation of timolol maleate reduces the rms of accommodation microfluctuations in treated but not untreated eyes (see Chapter 9 pps. 143-156). It was proposed that the lack of change in rms in contralateral untreated eyes was evidence for the effect in treated eyes to be locally induced and not mediated by the well documented anxiolytic effect of beta-blocking drugs. Comparisons were drawn from data on IOP pulse, in which a vasoconstriction of the choroidal vasculature was proposed to be responsible for the reduction in pulse amplitude achieved with topical timolol (Colloton and Perkins, 1986). Preliminary data on 1 subject for the effect of betaxolol HCl on the rms of accommodative microfluctuations produced a similar result: the rms of the fluctuations were reduced solely in the treated eye.

6. Topical timolol reduces the accommodative gain to a sinusoidally moving target for low temporal frequencies (<0.3Hz) but not for higher temporal frequencies over an accommodative vergence range of 1.5D. Betaxolol treatment appears to reduce accommodative gain for all temporal frequencies measured (see Chapter 10 pps. 157-172). The results for timolol were attributed to the temporal nature of the sympathetic system, whereas the findings for betaxolol were inconclusive. It was proposed that fatigue from the CNS depressant effect of the drug could have been responsible for the gain reduction over all frequencies measured.

11.2 - PROPOSALS FOR FUTURE WORK

11.2A - Accommodative regression to TA following near tasks

It has recently been documented that early-onset myopes (EOMs) are no different from late-onset myopes (LOMs) with respect to ocular biometric changes (Grosvenor and Scott, 1991). The posterior chamber depth is significantly longer in myopes, regardless of the age-of-onset of the refractive anomaly. The experiment reported in Chapter 6 which examined the regression rates to tonic levels in darkness following a 3 minute near task was performed on LOMs and emmetropes (EMMs) from which it was demonstrated that the rate of regression of accommodation from a near task to TA for certain EMMs differed from LOMs following timolol treatment. The results led to the proposal that all LOMs and some EMMs are likely to be deficient in a sympathetic facility which may predispose them to changes in ciliary muscle tonus and increased posterior chamber depth.

Work which has demonstrated no significant difference between the biometric changes in early-onset and late-onset myopia would indicate that further work in this area is justified, as the results from the more easily accessible group of LOMs may be extrapolated to EOMs. In addition, the work could be extended to examine the post-task regression patterns of accommodation in other refractive groups, including hyperopes and astigmats. Further, a comparison of results from a non-academic population for different refractive groups would be useful.

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An additional study on those individuals with autonomic dysfunction such as Horner's Syndrome would be of interest, although it is likely that the inherent pupillary miosis would present a problem for artefact-free accommodation signals from the Canon optometer.

11.2B Accommodative microfluctuations

The work documented in Chapter 8 (pps. 130-142) provided evidence that the peak frequency of the dominant HFC of accommodative microfluctuations was highly correlated with the frequency of the arterial pulse. It was proposed that the dominant components of the accommodative microfluctuations comprised the LFCs which were likely to be involved in accommodative control in the maintenance of the steady-state response and the HFCs which were evidently a manifestation of arterial pulse. Further work is required to determine whether other rhythmic bodily variations contribute to the LFC of accommodative microfluctuations. A number of accommodation recordings during the nominally steady-state response were made in Chapter 8 during which it was evident that the LFC showed marked variations in magnitude despite constant stimulus conditions. It would seem reasonable to expect a controlling mechanism located at a particular frequency to be relatively constant in magnitude given unchanging experimental conditions. The magnitude of the variation in LFC between the frequency range 0.3-0.6Hz even in very well trained subjects was of the order of ~0.05D.

The IOP pulse is known to be affected by respiration (Coleman and Trokel, 1969; Silver *et al*, 1989). It would be interesting to discover whether the LFCs of accommodative microfluctuations are affected or modified by changing respiration rates. Preliminary data on one subject was given in Chapter 7 in which a subject's breathing rate of 0.7Hz was regulated by an auditory cue from a Metronome. The power spectrum exhibited the usual LFC at 0.4Hz but it appeared to be reduced in magnitude. Further work is required to test the significance of this change in magnitude, with attention being paid to careful monitoring and elimination of artefacts from head and eye movements during rapid breathing. A unilateral aphakic might be used again to test the significance of head

movements during rapid breathing rates. In addition, a more accurate method of examining the arterial pulse wave, by way of an ECG recording would be interesting so that a cross-correlation between the cardiac waveform and the waveform of accommodative microfluctuations may be performed.

Data on simultaneous recordings of IOP from one eye and accommodation in the other eye were given in Chapter 8. It would be interesting to observe the effect of ocular antihypertensive drugs such as timolol on simultaneous recordings of IOP and accommodation.

11.2Bi   The effect of betaxolol on accommodative microfluctuations
Timolol has been shown to reduce the magnitude of the rms of accommodative microfluctuations (Chapter 9, pps. 143-156). It was deduced that the effect was likely to be a consequence of a vasoconstriction of the choroidal vessels and not merely due the stress-reducing properties of the drug, as no reduction in rms was seen in the untreated eyes. The cardioselective $beta_1$ antagonist betaxolol has been used in a number of experiments on ocular accommodation (Chapters 6 and 10) where it was used as an experimental control against timolol. Whereas a number of studies have been made on the effect of timolol on the IOP pulse, there is no such documented study on the effect of betaxolol.

Initial experimental results which examined the effect of betaxolol on the steady-state accommodation were illustrated in Chapter 9, Figure 9.7. This figure depicted composite power spectrum plots of accommodative microfluctuations for a subject who viewed a stationary target at -4D vergence before and after betaxolol treatment ($2 \times 30\mu l$) in one eye. Accommodative power spectra were illustrated for both treated and untreated eyes. It was evident that the effect of betaxolol on accommodative microfluctuations was similar to that induced by timolol in that there is a significant reduction in rms in the treated eye but not in the untreated eye. It would be pertinent to examine further the effect of betaxolol on accommodative microfluctuations and to perform simultaneous measurements of IOP pulse on treated subjects, so that accepted methods of assessment

of choroidal patency based on IOP pulse amplitude may be compared with the method based on accommodative microfluctuations.

11.2Bii   Accommodative microfluctuations and refractive error

The magnitude of the IOP pulse has provided a means of assessing a number of ocular anomalies and diseases. For example, reduced pulse amplitudes have been seen in diabetic retinopathy (Grunwald *et al*, 1986; Langham *et al*, 1989); high myopia (Bynke and Schele, 1967; Avetisov and Savitskaya, 1977; Perkins, Edwards and Saxena, 1977; To'mey *et al*, 1981), and in cataractous eyes (Hopkins, Grebe and Langham, 1989).

In view of the reduction in IOP pulse amplitude with high myopia (>6.0DS), a comparison between the magnitudes of accommodative fluctuations for an anisometropic subject would be of interest. In Chapter 9, it was proposed that the magnitude of the HFC was affected by the choroidal vasculature and therefore a significantly more myopic eye might be expected to produce a reduced HFC magnitude compared with a fellow, more emmetropic eye. This finding would provide further support for the proposal that the reduction in HFC with timolol documented in Chapter 9 was due to choroidal vasoconstriction.

11.2C - Within-task examination of autonomic innervation to ciliary muscle

It was shown that the sympathetic supply to the ciliary muscle may not have a significant input to the accommodative response for rapid changes in stimulus vergence (Chapter 10). For low temporal frequency changes in vergence, it appeared that the sympathetic system contributed to the aggregate accommodative response as blocking the adrenergic receptors in ciliary smooth muscle diminished the magnitude of the response.

The surprising result following betaxolol treatment that accommodative gain was reduced for all frequencies measured, may be further clarified by assessing the accommodative response from the untreated eye. It appeared that the reduction in rms of accommodative

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micofluctuations with timolol and betaxolol occurred in the treated eye only. By measuring the accommodative gain in the untreated eye, the local effect of the drug may be eliminated and in this way it may be ascertained whether the reduction in rms of accommodative microfluctuations is responsible for the reduced accommodative gain, or whether it is a centrally-induced effect.

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APPENDICES

THE CHARACTERISTICS OF CILIARY MUSCLE INNERVATION IN EMMETROPIA AND LATE-ONSET MYOPIA

I.1 - Refractive error of the myopic subjects

The mean refractive error of all the LOMs are given in the table below. The cylindical value (where present) has been halved and added to the spherical component of the refractive error to give the mean value. Astigmatism did not exceed 0.75D in any case.

Subject	Mean Rx error (R)	Mean Rx error (L)
BW	-3.25	-3.25
CW	-0.87	-2.50
DB	-1.12	-0.87
EW	-2.87	-3.37
GH	-2.00	-2.67
JR	-2.00	-3.12
LP	-3.00	-2.37
MR	-0.25	-1.50
NF	-2.00	-2.62
SK	-1.25	-1 75
	1.86±1.0	-2.40±0.8

I.2 To evaluate the effectiveness of opening the accommodative loop using: 1) red fixation spot 2) green fixation spot 3) darkness

The fixation spots were located at 1m from the subject. Accommodation measurements were made with the Canon optometer in static mode.

Subject	Red fixation spot (D)	green fixation spot (D)	darkness (D)
BE	-1.31	-0.95	-0.92
CN	-1.28	-0.17	+0.14
CT	-0.82	-0.46	+0.15
DC	-0.97	-0.60	-0.60
JH	-1.30	-1.18	-1.32
LE	+0.64	+0.53	+0.10
LM	-2.33	-0.89	-1.21
PF	-1.08	-0.81	-0.92
RD	-1.09	-0.71	-0.48
JD	-1.15	-0.98	-1.62
Mean±1S.D.	-1.07±0.7	-0.62±0.5	-0.67±0.6

I.3 - Ocular Biometric measurements for the emmetropic subjects

AL = axial length
VCD = vitreous chamber depth
MEAN K = mean keratometry reading
LENS = lens thickness
ACD = anterior chamber depth

Keratometry measurements were made with a Topcon Keratometer. All other biometric measurements were made with an A-Scan Ultrasound measuring device. The eye to be measured was anaesthetised with 2 drops of 0.4% benoxinate HCl. The probe of the ultrasound device was sterilized with an ocusert wipe and measurements were then taken. Average measurements are shown. Typical standard deviations are given below. All measurement units are in mm.

Subject	AL (R)	AL (L)	VCD (R)	VCD (L)	K (R)	K (L)
AW	22.87	22.36	15.88	15.36	7.74	7.78
BE	23.31	23.30	15.98	16.11	7.81	7.79
FE	23.85	23.72	16.45	16.56		
JL	23.56	23.60	16.64	16.02	7.97	7.97
JR	24.43	24.13	17.48	17.27	8.14	8.19
LM	23.82	23.00	16.55	16.64		
NF	23.44	22.97	16.26	16.15	7.63	7.52
RS	24.31	24.15	17.32	17.24	8.10	8.09
VH	23.15	23.04	16.15	15.94	7.78	7.85
VP	23.24	22.95	15.93	16.04		
Mean	23.60	23.32	16.46	16.33	7.88	7.86
±1S.D	±0.5	±0.6	±0.6	±0.6	±0.2	±0.2

Subject	LENS (R)	LENS (L)	ACD (R)	ACD (L)
AW	3.64		3.60	3.02
BE	3.18	3.17	3.79	3.38
FE	3.63	3.47	3.56	3.38
JL	3.30	3.52		
JR	3.27	3.19	3.68	3.67
LM	3.84	3.78	3.75	3.50
NF	3.37	3.43	3.81	3.39
RS	3.63	3.65	3.36	3.26
VH	3.54	3.81	3.83	3.83
VP	3.63	3.72	3.67	3.18
Mean ± 1sd	3.50±0.2	3.53±0.2	3.67±0.1	3.4±0.2

I.4 - Ocular Biometric measurements for the myopic subjects

AL = axial length
VCD = vitreous chamber depth
MEAN K = mean keratometry reading
LENS = lens thickness
ACD = anterior chamber depth

All measurement units are in mm.

Subject	AL (R)	AL (L)	VCD (R)	VCD (L)	K (R)	K (L)
BW	24.96	25.20	17.78	17.50	8.08	8.08
CW	25.14	25.26	18.10	18.35	8.08	8.07
DB	23.93	23.46	16.66	16.25	7.68	7.82
EW	24.71	24.86	17.81	17.69	7.87	7.91
GH	23.41	23.44	16.46	16.72	7.59	7.66
JR	24.11	24.99	17.22	17.79	7.55	7.62
LP	24.32	24.07	17.18	16.59	8.03	7.96
MR	22.97	23.48	15.79	16.29	7.61	7.59
NF	24.81	24.58	18.09	18.04	7.80	7.83
SK	24.45	24.18	17.34	17.26	8.02	7.97

Mean±1sd 24.28±0.7   24.35±0.7   17.24±0.8   17.25±0.7   7.83±0.2   7.85±0.2

Subject	LENS (R)	LENS (L)	ACD (R)	ACD (L)
BW	4.02	3.99	3.16	3.71
CW	3.43	3.42	3.61	3.49
DB	3.73	3.77	3.54	3.44
EW	3.53	3.52	3.38	3.65
GH	3.56	3.51	3.40	3.22
JR	3.37	3.48	3.37	3.72
LP	3.89	3.93	3.25	3.55
MR	3.65	3.69	3.53	3.51
NF	3.36	3.32	3.36	3.21
SK	3.39	3.49	3.72	3.43
Mean±1sd	3.59±0.2	3.61±0.2	3.43±0.2	3.49±0.2

I.5 - Sample print-out of biometric measurements from one emmetropic subject using the A-scan Ultrasound device

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*    STOPZ INSTRUMENT CUMPANY *  *
*       COMPUSCAN OMEGA: V5.01     *
*                                  *
* DATE: 13 Jun 1990  TIME: 14:16 *
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         REVIEW MEASUREMENTS

         S.R.K. II Regression
                FORMULA

RIGHT EYE    PATIENT # RS

   K1                          0.00
   K2                          0.00
   Aconstant 1                 0.00
   Aconstant 2                 0.00
   Aconstant 3                 0.00
   Desired Postop Refraction  -1.00
   Adjustment was              0.00
   Velocity, normal            1550


      AXIAL  STD   ACD   PROBE   IOL
      LEN                COMER   POWER

 1   24.58  0.03  3.68  +++++  N
 2   24.75  0.01  3.65  +++++  N
 3   24.58  0.02  3.45  +++++  N
 4   24.20  0.07  3.23  +++++  N
 5   24.12  0.03  3.32  +++++  N
 6   24.15  0.03  3.32  +++++  N
 7   24.17  0.01  3.31  +++++  N
 8   24.12  0.00  3.23  +++++  N
 9   24.13  0.02  3.24  +++++  N
10   24.09  0.00  3.19  +++++  N


   AVERAGE AXIAL LENGTH        24.31
   STD OF AVG MEASUREMENT       0.24
   IOL USING ACONS  0.00       +++++
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*    STOPZ INSTRUMENT COMPANY + *
*       COMPUSCAN OMEGA: V5.01     *
*                                  *
* DATE: 13 Jun 1990  TIME: 14:16 *
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         REVIEW MEASUREMENTS

         S.R.K. II Regression
                FORMULA

RIGHT EYE    PATIENT #

   K1                          0.00
   K2                          0.00
   Aconstant 1                 0.00
   Aconstant 2                 0.00
   Aconstant 3                 0.00
   Desired Postop Refraction  -1.00
   Adjustment was              0.00
   Velocity, normal            1550


       ANTER   LENS   VIT
       DEPTH   THCK   DEPTH

 1     3.68    3.53   17.23   N
 2     3.65    3.63   17.47   N
 3     3.45    3.57   17.56   N
 4     3.23    3.63   17.47   N
 5     3.32    3.71   17.14   N
 6     3.32    3.61   17.23   N
 7     3.31    3.63   17.24   N
 8     3.23    3.61   17.28   N
 9     3.24    3.69   17.26   N
10     3.19    3.63   17.27   N

AVG:   3.36    3.63   17.32
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*    STOPZ INSTRUMENT COMPANY  *
*       COMPUSCAN OMEGA: V5.01     *
*                                  *
* DATE: 13 Jun 1990  TIME: 14:13 *
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         REVIEW MEASUREMENTS

         S.R.K. II Regression
                FORMULA

LEFT EYE    PATIENT # RS

   K1                          0.00
   K2                          0.00
   Aconstant 1                 0.00
   Aconstant 2                 0.00
   Aconstant 3                 0.00
   Desired Postop Refraction  -1.00
   Adjustment was              0.00
   Velocity, normal            1550


      AXIAL  STD   ACD   PROBE   IOL
      LEN                COMER   POWER

 1   24.42  0.02  3.43  +++++  N
 2   24.16  0.03  3.45  +++++  N
 3   24.43  0.06  3.53  +++++  N
 4   24.04  0.01  3.23  +++++  N
 5   23.95  0.00  3.17  +++++  N
 6   24.07  0.01  3.13  +++++  N
 7   24.17  0.02  3.13  +++++  N
 8   23.34  0.02  2.94  +++++  N
 9   23.73  0.01  2.95  +++++  N
10   24.49  0.03  3.43  +++++  N
11   24.54  0.02  3.48  +++++  N


   AVERAGE AXIAL LENGTH        24.15
   STD OF AVG MEASUREMENT       0.24
   IOL USING ACONS  0.00       +++++
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*    STOPZ INSTRUMENT COMPANY  *
*       COMPUSCAN OMEGA: V5.01     *
*                                  *
* DATE: 13 Jun 1990  TIME: 14:18 *
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         REVIEW MEASUREMENTS

         S.R.K. II Regression
                FORMULA

LEFT EYE    PATIENT #

   K1                          0.00
   K2                          0.00
   Aconstant 1                 0.00
   Aconstant 2                 0.00
   Aconstant 3                 0.00
   Desired Postop Refraction  -1.00
   Adjustment was              0.00
   Velocity, normal            1550


       ANTER   LENS   VIT
       DEPTH   THCK   DEPTH

 1     3.43    3.72   17.28   N
 2     3.45    3.68   17.11   N
 3     3.50    3.68   17.25   N
 4     3.23    3.67   17.15   N
 5     3.17    3.71   17.07   N
 6     3.22    3.53   17.23   N
 7     3.13    3.67   17.38   N
 8     2.94    3.64   17.26   N
 9     2.95    3.62   17.22   N
10     3.43    3.63   17.42   N
11     3.48    3.68   17.25   N

AVG:   3.26    3.65   17.24
```

I.6 - Values of within-task accommodative response (W.T) and tonic accommodation (TA) for the 3 drug conditions for the emmetropic subjects

All measurements are in dioptres.
N.B. No correction for chromatic aberration and the -0.25DS over-minusing made by the Canon has been added to the tables below. An additional -0.55DS should be added to the readings to account for the above discrepancies

Subject	TA (S)	TA (T)	TA (B)	W.T (S)	W.T (T)	W.T (B)
AW	-0.32	-0.17		-3.59	-4.27	
BE	-0.50	-0.21	-0.43	-3.97	-3.77	-3.97
FE	-0.19	-0.41	-0.19	-3.94	-3.99	-3.96
JL	-0.53	-0.53	-0.54	-3.5	-3.90	-3.50
JR	-0.36	-0.28	-0.02	-4.56	-4.28	-4.69
LM	-0.49	-0.49	-0.94	-3.82	-3.82	-4.64
NF	0.26	-0.12	0.26	-3.45	-3.50	-3.45
RS	-0.53	-0.34	-0.70	-3.37	-3.87	-4.49
VH	-0.47	-0.56	-0.55	-3.25	-3.63	-3.36
VP	-0.92	-0.30	-0.52	-4.09	-3.80	-3.98
Mean	0.41	0.34	0.40	3.75	3.88	4.00
±1s.d	±0.3	±0.2	±0.4	±0.4	±0.2	±0.5

I.7 - Values of within-task accommodative response (W.T) and tonic accommodation (TA) for the 3 drug conditions for the myopic subjects

Subject	TA (S)	TA (T)	TA (B)	W.T (S)	W.T (T)	W.T (B)
BW	-0.14	-0.14		-3.80	-3.80	
CW	-0.32	-0.30	0.20	-3.82	-4.22	-4.33
DB	-0.17	-0.13	-0.05	-4.19	-3.28	-3.14
EW	-0.04	-0.04	-0.22	-3.75	-3.75	-4.21
GH	0.49	-0.57	-0.40	-3.43	-3.70	-4.07
JR	-0.38	-0.28	0.02	-4.56	-4.28	-4.69
LP	-0.77	-0.77	-0.56	-4.33	-4.38	-4.09
MR	-1.36	-1.09	-1.38	-3.99	-4.06	-3.86
NF	-0.13	0.35	0.17	-3.31	-4.22	-3.62
SK	0.36	0.36	-0.53	-3.46	-3.46	-3.88
Mean	-0.25	-0.26	-0.31	-3.86	-3.92	-3.98
±1s.d	±0.5	±0.5	±0.5	±0.4	±0.4	±0.4

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I.8 - Mean regression plot for the group of EMMs and LOMs. Error bars indicate 2 sems.
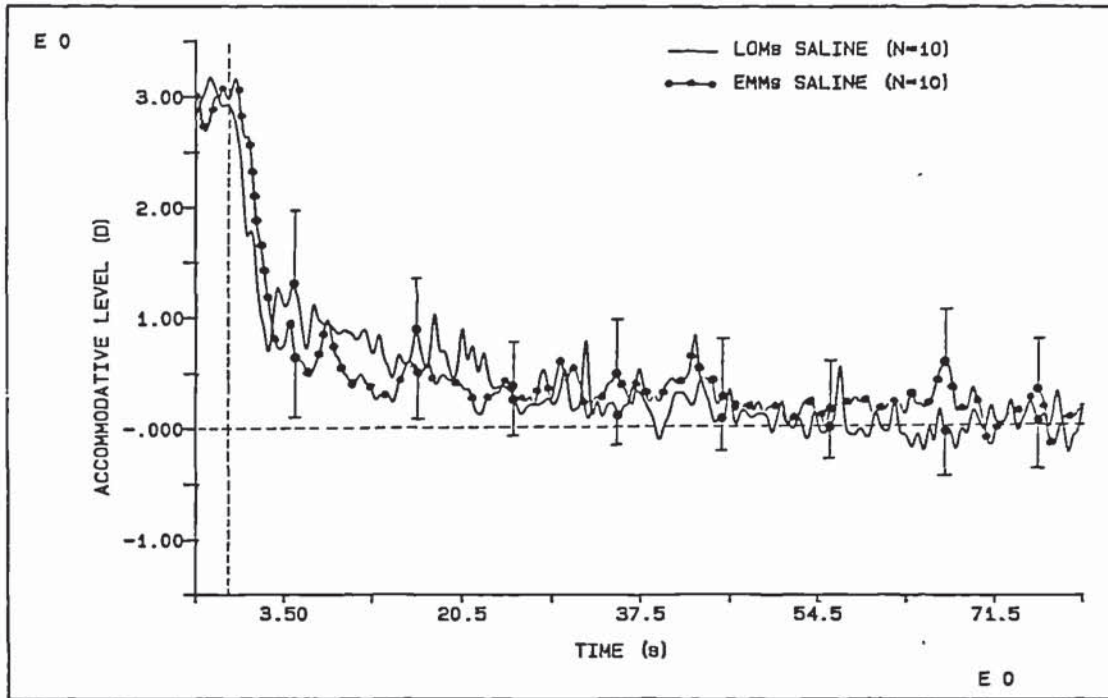
I.9 Individual regression plots of accommodation to TA

a) EMMs

b) LOMs

Solid line - saline
Dashed line - timolol
Dotted line - betaxolol

I.9b)

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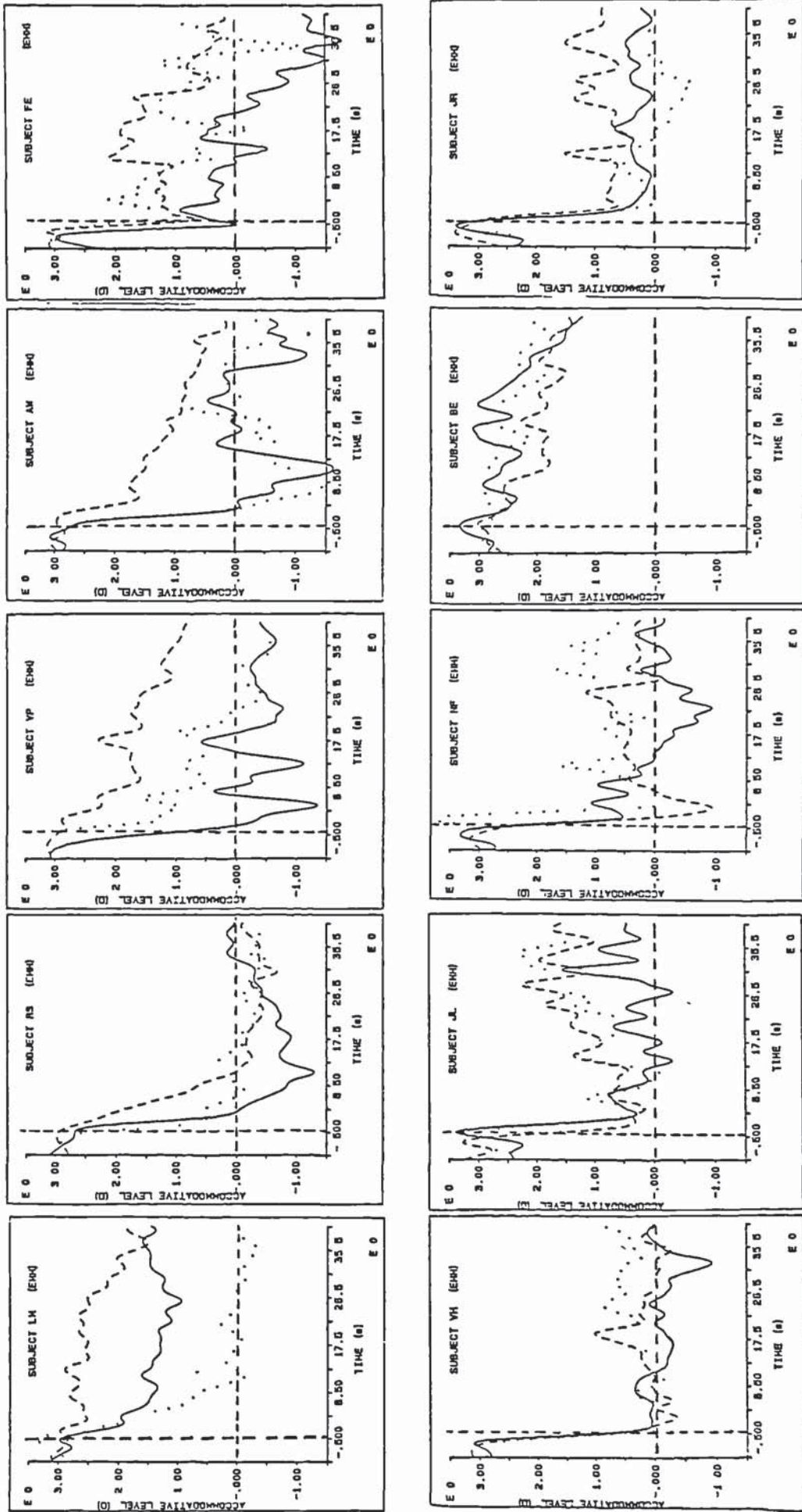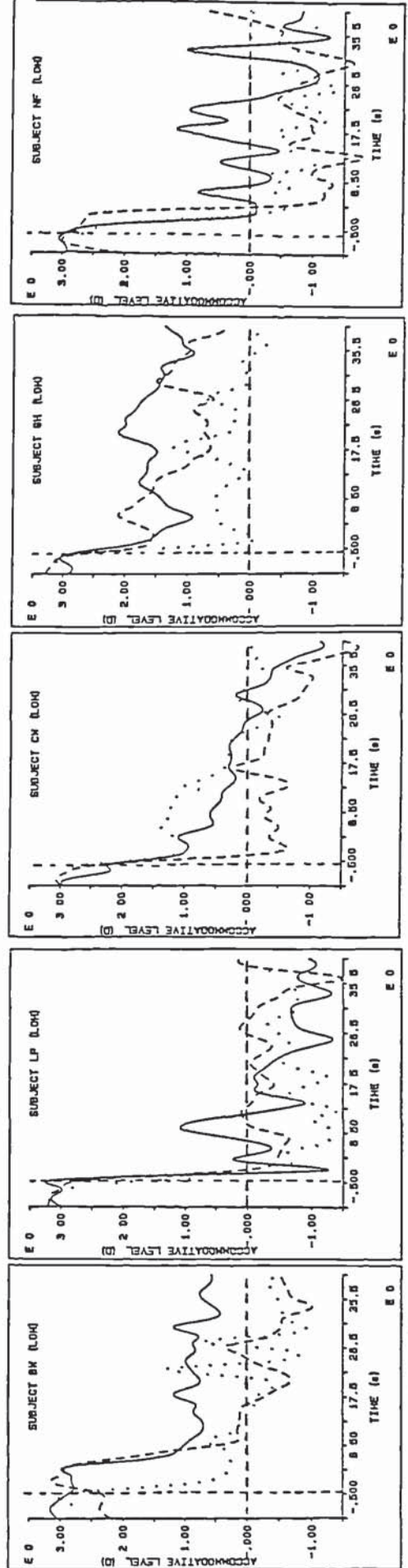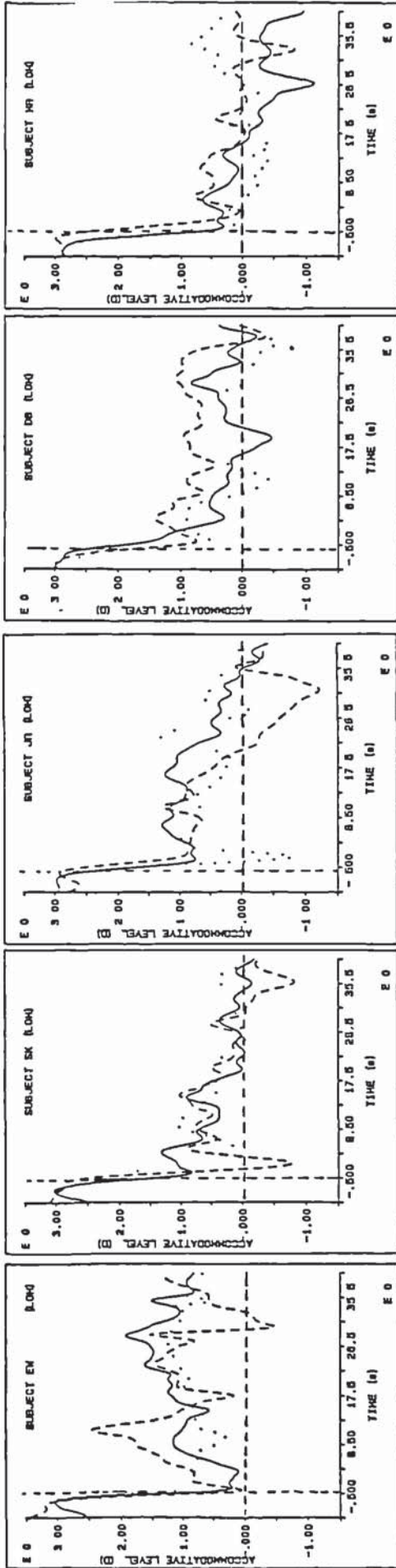
II.1 - Calculation of percentage overlap between central lens zone and peripheral zones
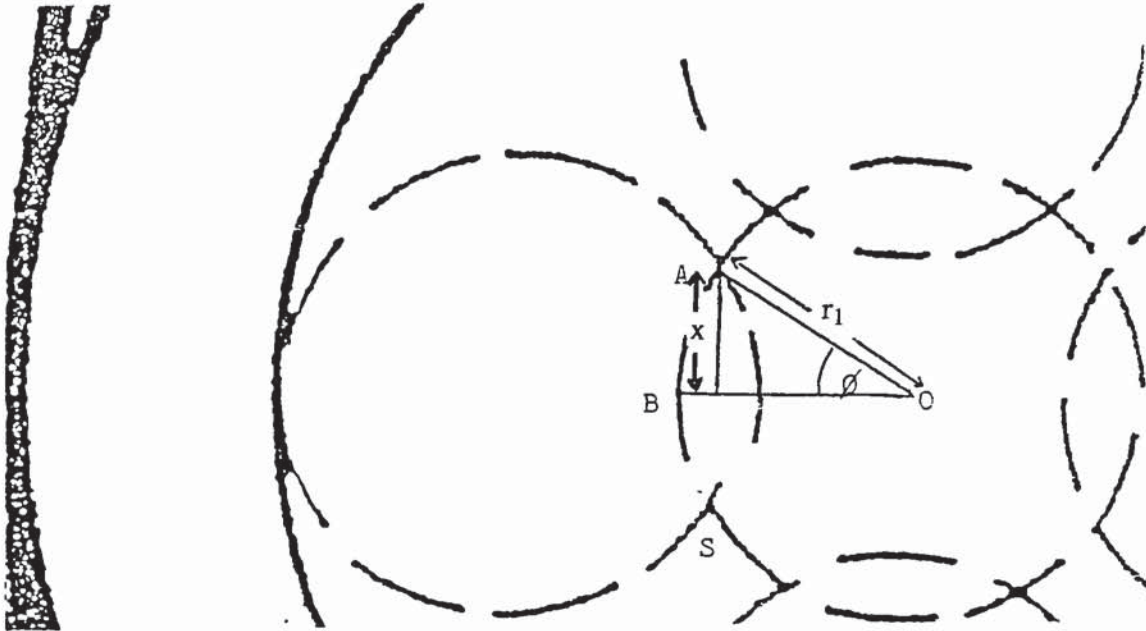
Figure II.1: Diagrammatical representation of overlap between the 4 peripheral lens zones measured and the central area.

Maximum pupil diameter attained with phenylephrine 10% mydriasis = 8.5mm

Maximum area utilised by Canon in continuous mode = 3.52mm

r_1 = 1.76mm

By Pythagoras' theorem:

$x^2 = 1.76^2 - 1.25^2$

$x^2 = 3.10 - 1.56$

$x^2 = 1.54$

$x = 1.24$

AS = 2x = 2.5

<u>Area of sector AOS</u>

$\cos \phi = 1.25/ 1.76$

$\phi = 44.75°$

$2\phi = 89.5° = 24.8\%$ of circle

Area of circle $= \pi r_1^2 = \pi (1.76)^2$	9.73 mm^2
Area of sector OAB = 23.5% of 9.73	2.42mm^2
Area of triangle OAB = 1/2 base x height	
0.5 x 2.6 x 1.19	1.55mm^2
Area of sector ASB = 2.29-1.55	0.87mm^2
Total overlap = 2 x ASB	1.74mm^2

Area of inner circle	9.73mm^2
Percentage overlap between zones	(1.74/9.73) 100
	17.9%
Area of central circle	9.73mm^2
Area of each peripheral zone = 82.1% of 9.73	7.99mm^2
4 x peripheral zones	31.96
Central zone	_9.73_ +
Total area measured	41.69mm^2

Area of outer circle $= \pi$ x 4.25^2	56.75
Less total area measured	41.69-
Unmeasured area	15.06 mm^2

Area of outer circle	56.75
Area of inner circle	_9.73_ -
Peripheral area	47.02mm^2

Therefore, unmeasured area is (15.06/47.02)100 = 32% of periphery or (15.06/33.0)100 = 45.6% of measured peripheral area.

II.2 - Power spectra of accommodative microfluctuations for 5 lens zones for subject NF
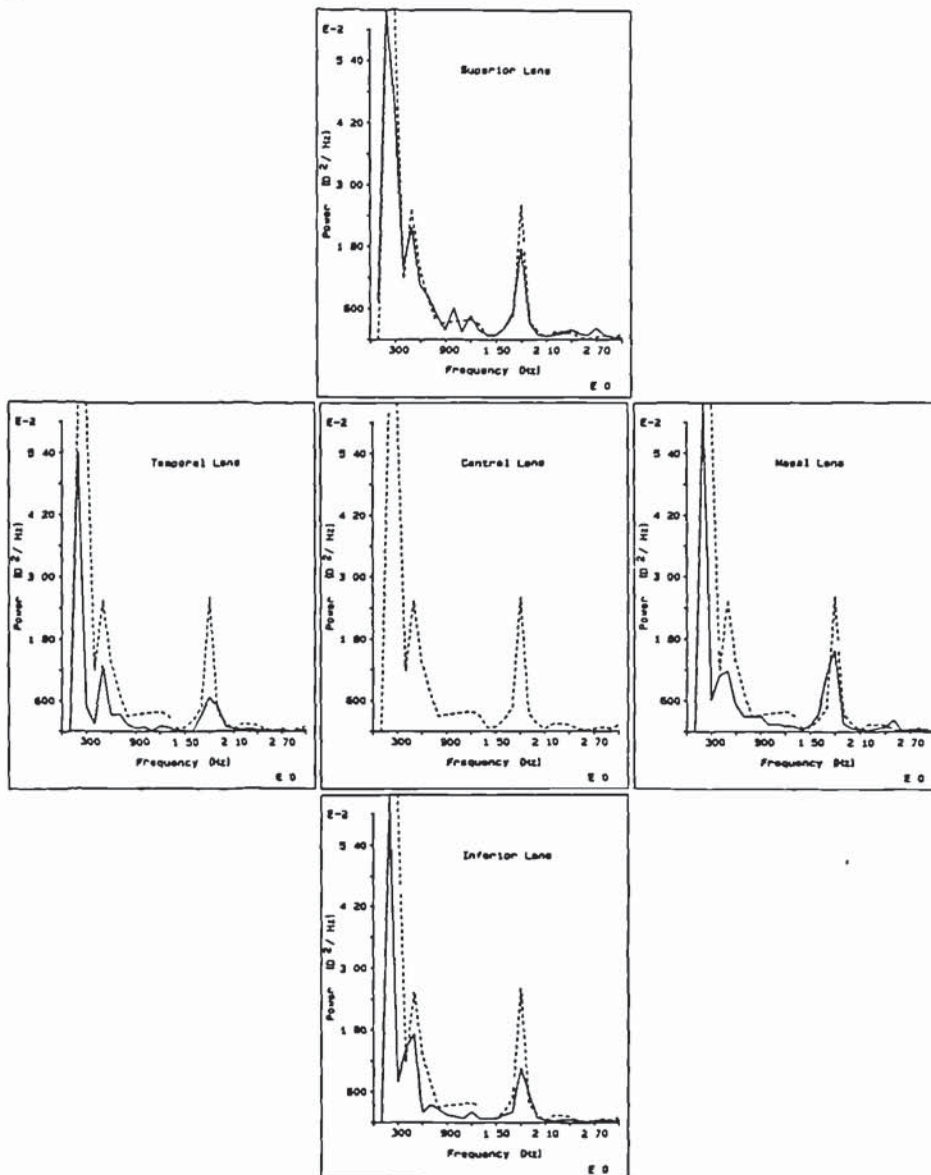
Figure II.2: Power spectra of accommodative microfluctuations illustrating the power in the central and peripheral lens zones (After Winn *et al*, 1990a)

II.3 - Measurements of area under the power specrum curve for each lens zone (Measurement units are unscaled except where specified)

Central zone	2726 units (0.32D)
superior	2633 (NB larger overlap with central zone due to upper lid droop)
nasal	1697
inferior	1586
temporal	1138

Average power measured in each peripheral zone based on nasal, inferior and temporal

zones	1474 (0.17D)
Assuming 17.9% overlap with central zone	
42.5% of 2726	487.9 (0.03D)
Remainder in each peripheral zone	986 (0.14D)
4 x peripheral zones	3944
42.5% unmeasured	1798+
total power in periphery	5742 (0.7D)

Area of 8.5mm pupil	56.75mm^2
Less central 3.5mm	9.73mm^2
Difference	47.02mm^2

Therefore for an area of 47.02mm^2, there are   units of power in the periphery (0.7D)

For each 1mm^2 there are 128.4 units of power in the periphery (0.015D)

Summary

For a pupil diameter of 3.52mm, there is 0.32D of power centrally, but only 0.15D of power for an equivalent area in the periphery. The peripheral power per unit area is 45.6% of the centre.

For a 3.52mm diameter pupil, total area = 9.73 mm^2 which is equivalent to 2726 units of power (0.32 D) centrally

pupil diameter (mm)	Total peripheral area (mm^2)	Total power (centre + periphery) (DS)
4.5	15.9-9.73 = 6.17	0.32 + 0.09 = 0.41
5.5	23.76-9.73 = 14.03	0.32 + 0.20 = 0.52
6.5	33.18-9.73 = 23.45	0.32 + 0.33 = 0.65
7.5	44.18-9.73 = 34.45	0.32 + 0.48 = 0.80
8.5	56.75-9.73 = 47.02	0.32 + 0.66 = 0.98

For 3.52mm diameter pupil, area = 9.73mm^2

1mm pupil is equivalent to 8.1% of the area for an 3.52mm pupil

8.1% of 0.32D = 0.026D

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HFC zone	HFC Power (Pts)	Total power (Pts)	HFC % of total
Central	448	2726	16.4%
Superior	378	2633	14.4%
Nasal	383	1697	22.6%
Inferior	229	1586	14.4%
Temporal	189	1138	16.6%

As the total power for a 1mm diameter pupil = 0.026D, power in the HFC will be ~16.4% of this = 0.004D

APPENDIX III

APPENDIX RELATING TO CHAPTER 8: THE INFLUENCE OF

ARTERIAL PULSE ON STEADY-STATE ACCOMMODATION

III.1: Peak frequency of the HFC of accommodative microfluctuation for 20 subjects. A.F = accommodation frequency (Hz) for the peak HFC

Subject	A.F	A.F	A.F	A.F	A.F
BE	1.1	1.0	1.1	1.1	1.1
MCD	1.1	1.6	1.5	1.4	1.6
RD	1.2	1.1	1.2	1.2	1.2
DC	1.2	1.1	1.2	1.2	1.2
JH	1.6	1.5	1.6	1.6	1.6
LM	1.3	1.2	1.4	1.3	1.4
NF	1.7	1.8	1.7	1.8	1.7
JP	1.5	1.5	1.5	1.6	1.6
LE	1.5	1.5	1.7	1.5	1.5
VP	1.5	1.1	1.4	1.4	1.5
DJ	1.3	1.6	1.3	1.4	1.5
PB	1.2	1.2	1.3	1.2	1.3
BW	1.6	1.6	1.6	1.6	1.5
JM	2.0	1.9	1.5	1.9	2.1
RB	1.0	1.0	1.2	1.1	1.2
CS	1.2	1.2	1.3	1.2	1.2
AW	1.9	1.9	1.9	1.9	1.9
LT	1.2	1.5	1.3	1.2	1.4
JD	1.2	1.4	1.1	1.6	1.2
HO	1.3	1.3	1.6	1.4	1.4

III.2: Frequency of arterial pulse (Hz)

Subject	Pulse frequency	Pulse frequency	Pulse frequency	Pulse frequency	Pulse frequency
BE	1.2	1.1	1.1	1.1	1.2
MCD	1.2	1.5	1.5	1.3	1.5
RD	1.2	1.1	1.2	1.2	1.2
DC	1.2	1.2	1.2	1.2	1.2
JH	1.6	1.5	1.6	1.7	1.6
LM	1.3	1.3	1.3	1.4	1.4
NF	1.7	1.7	1.7	1.8	1.7
JP	1.5	1.5	1.5	1.6	1.6
LE	1.5	1.5	1.6	1.5	1.5
VP	1.5	1.5	1.5	1.4	1.5
DJ	1.3	1.5	1.3	1.4	1.5
PB	1.2	1.2	1.3	1.2	1.2
BW	1.5	1.6	1.6	1.5	1.5
JM	1.9	1.9	1.8	1.9	2.0
RB	1.1	1.1	1.2	1.2	1.1
CS	1.2	1.2	1.3	1.2	1.2
AW	1.9	1.9	1.9	1.9	1.9
LT	1.6	1.5	1.5	1.4	1.4
JD	1.4	1.4	1.2	1.5	1.5
HO	1.3	1.3	1.6	1.4	1.4

III.3: Assessment of accommodative microfluctuations using the Purkinje Image technique.

The distance between the two 1st Purkinje images and the two IVth Purkinje images as measured with electronic calipers from a video monitor (Panasonic 6200 VTR) of recordings of the nominally steady-state accommodation are given below. The time resolution is given in hrs:mins:25 frames/s.

Time (hr/min/sec)	Purkinje I	Purkinje IV	Purkinje I/IV
1.36.20	37.45	23.63	1.585
1.36.23	37.39	23.51	1.59
1.37.01	37.31	23.72	1.573
1.37.07	37.57	23.61	1.591
1.37.10	37.45	23.46	1.596
1.37.13	37.54	23.95	1.567
1.37.16	37.46	23.81	1.573
1.37.19	37.58	23.60	1.592
1.37.22	37.44	23.82	1.572
1.38.00	37.54	23.54	1.595
1.38.03	37.23	23.65	1.573
1.38.06	37.52	23.56	1.593
1.38.09	37.34	23.49	1.589
1.38.12	37.29	23.76	1.569
1.38.15	37.64	23.65	1.592
1.38.18	37.70	23.61	1.597
1.38.21	37.47	24.18	1.549
1.38.24	37.52	23.38	1.605
1.39.02	37.60	23.59	1.594
1.39.05	37.60	23.87	1.575
1.39.08	37.46	23.60	1.587
1.39.11	37.43	23.92	1.565
1.39.14	37.27	23.74	1.569
1.39.17	37.82	23.51	1.609
1.39.20	37.56	24.14	1.556
1.39.23	37.18	23.56	1.578
1.40.01	37.23	23.36	1.594
1.40.04	37.33	23.87	1.564
1.40.07	37.43	24.17	1.549
2.27.03	37.82	23.35	1.619
2.27.06	37.99	24.08	1.578
2.27.09	37.73	24.72	1.526
2.27.12	38.33	24.71	1.551
2.27.15	38.29	24.63	1.555
2.27.18	37.84	24.79	1.526
2.27.21	37.72	24.84	1.519
2.27.24	37.54	24.15	1.554
2.28.02	38.05	24.42	1.558
2.28.05	38.00	24.00	1.583
2.28.08	37.86	24.00	1.578
2.28.11	37.73	24.17	1.561
2.28.14	37.57	24.69	1.522
2.28.17	37.60	24.20	1.554
2.28.20	37.61	24.54	1.533
2.28.23	37.55	24.21	1.551
2.29.01	38.05	24.20	1.572
2.29.04	37.66	24.66	1.527
2.29.07	37.84	23.82	1.589
2.29.10	37.94	23.81	1.593
2.29.13	37.79	24.32	1.554

Time resolution	Purkinje I	Purkinje IV	Purkinje I/IV
2.30.00	37.84	24.36	1.553
2.30.03	37.68	24.32	1.549
2.30.06	37.92	24.47	1.549
2.30.09	37.84	24.28	1.558
2.30.12	37.99	24.18	1.571
2.30.15	37.76	24.46	1.544
2.30.18	38.12	24.19	1.576
2.30.21	38.04	24.50	1.541
2.30.24	37.88	24.41	1.552
2.31.00	37.69	24.19	1.558
2.31.03	37.74	23.95	1.576
2.31.06	38.18	23.65	1.614
2.31.09	38.04	24.55	1.549
2.31.12	37.87	24.52	1.544
2.31.15	38.08	24.65	1.543
2.31.18	37.92	24.92	1.522
2.31.21	37.99	24.11	1.576
2.31.24	38.07	24.70	1.541
2.32.02	38.22	24.77	1.543
2.32.05	38.04	25.10	1.516
2.32.08	38.18	24.36	1.567
2.32.11	38.02	24.50	1.552
2.32.14	37.82	24.99	1.517
2.32.17	38.14	24.83	1.536
2.32.20	38.25	24.40	1.568
2.32.23	38.12	24.49	1.556
2.33.01	37.94	24.97	1.519
2.33.04	38.17	24.96	1.529
2.33.07	38.32	24.58	1.559
2.33.10	38.28	24.57	1.558
2.33.13	38.29	25.02	1.530
2.33.16	38.17	24.51	1.557
2.33.19	38.36	24.46	1.568
2.33.22	38.18	24.41	1.564
2.34.00	38.23	25.05	1.526
2.34.03	38.20	24.58	1.554
2.34.06	38.14	24.73	1.542
2.34.09	38.27	24.65	1.553
2.34.12	37.97	24.32	1.561
2.34.15	38.25	24.85	1.539
2.34.18	38.31	24.76	1.547
2.34.21	38.04	24.98	1.523
2.34.24	38.06	24.89	1.529
2.35.02	38.36	25.08	1.530
2.35.05	38.16	24.68	1.546
2.35.08	38.17	24.94	1.530

Summary
Analysis was repeated on 1 data set to determine the repeatability of measurements. Simultaneous recordings of accommodation were made with the optometer so that the power spectra using both methods could be compared. Results were inconsistent due to the poor resolution as a consequence of the poor quality of the Purkinje images.

APPENDIX RELATING TO CHAPTER 9: THE EFFECT OF A TOPICAL BETA-RECEPTOR ANTAGONIST ON THE DYNAMICS OF STEADY-STATE ACCOMMODATION

IV.1: Measurements of total area, HF area and LF area for saline and timolol conditions for all subjects in experiment 1. Measurement units are in D^2/Hz)

SALINE DATA

Subject	Total area	HFR (Hz)	HFR area	LFR (<0.5Hz)	LFR area (0.3-0.6Hz)
AM	0.340	1.1-1.4	0.011	0.241	0.070
BE	0.454	1.3-1.6	0.075	0.193	0.062
DC	0.533	1.1-1.4	0.061	0.314	0.085
FE	0.485	1.0-1.3	0.066	0.260	0.107
GB	0.719	1.4-1.7	0.079	0.471	0.160
JH	0.320	1.2-1.6	0.029	0.247	0.057
PI	0.733	1.3-1.6	0.051	0.424	0.169
TH	0.101	1.3-1.6	0.004	0.064	0.015
VH	0.288	1.3-1.6	0.018	0.163	0.040
VP	0.391	0.9-1.2	0.035	0.246	0.050

TIMOLOL DATA

Subject	Total area	HFR (Hz)	HFR area	LFR (<0.5Hz)	LFR area (0.3-0.6Hz)
AM	0.191	0.9-1.2	0.012	0.122	0.045
BE	0.373	1.0-1.3	0.050	0.199	0.055
DC	0.440	1.0-1.3	0.026	0.321	0.048
FE	0.436	0.9-1.2	0.075	0.214	0.042
GB	0.507	1.3-1.6	0.058	0.260	0.101
JH	0.178	1.2-1.6	0.034	0.096	0.030
PI	0.326	1.3-1.6	0.023	0.167	0.041
TH	0.068	1.2-1.5	0.005	0.037	0.008
VH	0.147	1.2-1.5	0.017	0.067	0.022
VP	0.196	0.8-1.1	0.020	0.087	0.043

IV.2: Measurements of rms (D), area under HFC and LFC (D²/Hz) of accommodative microfluctuations for saline (S) and timolol (T) conditions. Data for treated eyes (DIRECT DATA) and consensual untreated eyes are given for the 4 subjects in experiment 2 in Chapter 9 (pps)

DIRECT DATA (TREATED EYE)

Subject	RMS(S)	RMS(T)	AREA (S)	AREA (T)	HFR(S)	HFR(T)	LFR(S)	LFR(T)
VP	0.20	0.14	0.39	0.20	0.04	0.02	0.05	0.04
BE	0.22	0.19	0.50	0.38	0.05	0.03	0.04	0.08
JH	0.18	0.13	0.66	0.18	0.06	0.03	0.12	0.03
DS	0.26	0.23	0.68	0.52	0.11	0.10	0.08	0.08

CONSENSUAL DATA (UNTREATED EYE)

Subject	RMS(S)	RMS(T)	AREA (S)	AREA (T)	HFR(S)	HFR(T)	LFR(S)	LFR(T)
VP	0.19	0.18	0.36	0.33	0.03	0.05	0.10	0.04
BE	0.17	0.14	0.30	0.19	0.01	0.02	0.06	0.02
JH	0.23	0.21	0.53	0.44	0.08	0.08	0.06	0.04
DS	0.19	0.23	0.35	0.53	0.04	0.05	0.03	0.04

IV.3: Measurements of blood pressure (mmHg) using a sphygmomanometer.

Subject	Blood pressure (pre-timolol) (mmHg)	Blood pressure (post-timolol) (mmHg)
AM	110/78	110/78
BE	110/60	110/70
DC	130/90	120/80
FE	110/78	110/80
GB	110/80	102/70
JH	105/75	100/70
PI		
TH	130/68	125/70
VH		
VP	116/65	95/60

Mean blood pressure:

pre-timolol = 115.1±9.6/74±9.5 mmHg

post-timolol = 109.0±10.0/72.3±6.8 mmHg

IV.4 - Power spectra of accommodative microfluctuations for the 10 subjects used in the first part of the experiment in Chapter 9, to demonstrate the effect of topical timolol on the accommodative microfluctuations.
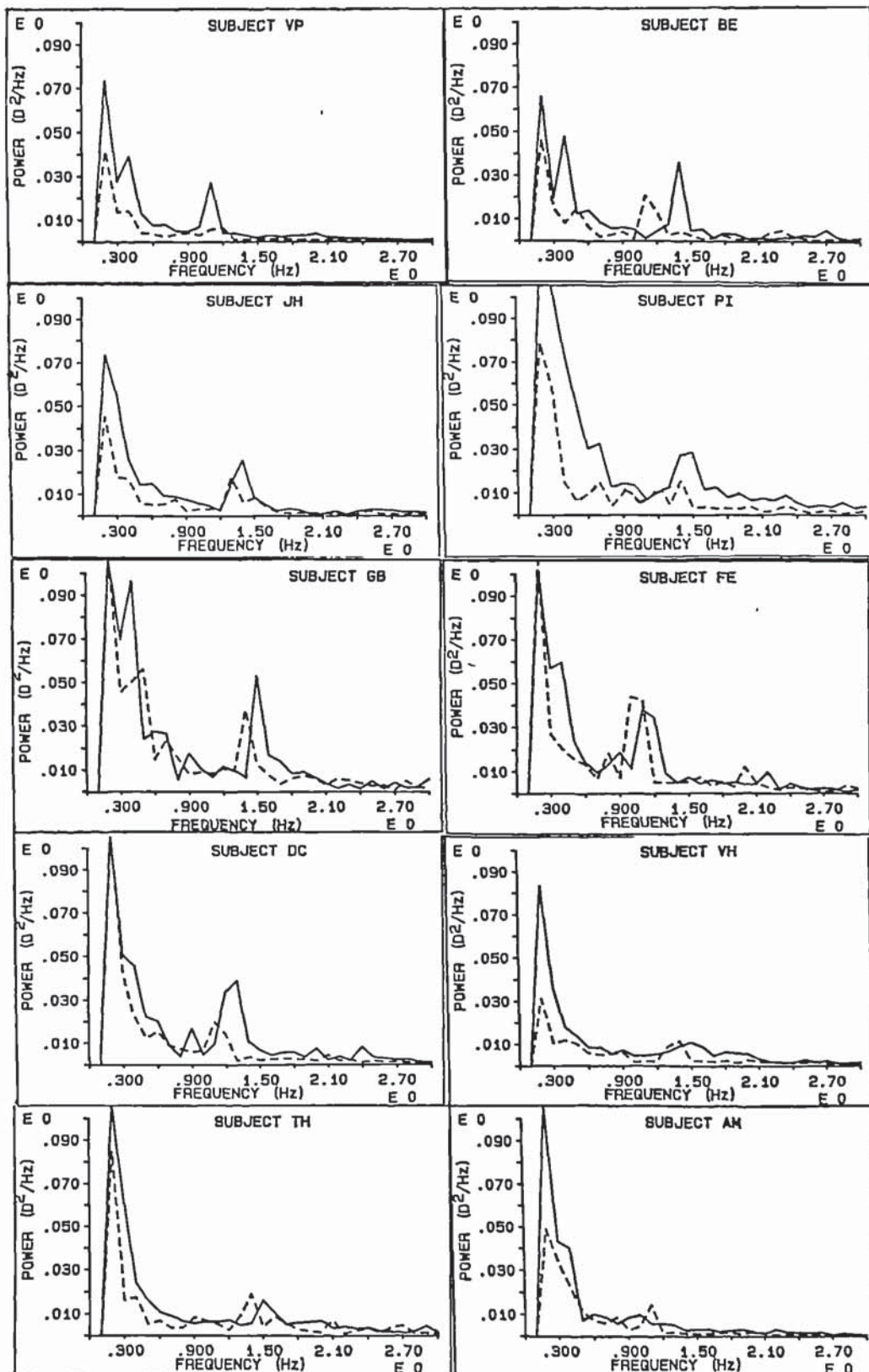
APPENDIX V
APPENDIX RELATING TO CHAPTER 10: THE EFFECT OF BETA-ADRENERGIC RECEPTOR ANTAGONISTS ON DYNAMIC MEASUREMENTS OF ACCOMMODATION

V.1: Measurements of accommodative gain for all frequencies recorded for the 3 drug conditions: subject BE

Frequency: 1 = 0.05 Hz; 2 = 0.1 Hz; 3 = 0.2 Hz; 4 = 0.3 Hz; 5 = 0.4 Hz; 6 = 0.5 Hz

	Frequency	Drug s/b	Gain s/b	Drug s/t	Gain (s/t)
1	1 000	saline	1.230	saline	670
2	1 000	saline	1 150	saline	860
3	1 000	saline	1 020	saline	750
4	1 000	saline	930	saline	800
5	1 000	saline	1 080	saline	850
6	2 000	saline	1 000	saline	8-0
7	2 000	saline	1 040	saline	980
8	2 000	saline	1 050	saline	850
9	2 000	saline	910	saline	950
10	2 000	saline	1 000	saline	940
11	3 000	saline	970	saline	950
12	3 000	saline	1 050	saline	850
13	3 000	saline	1 060	saline	620
14	3 000	saline	.700	saline	870
15	3 000	saline	810	saline	750
16	4 000	saline	1 150	saline	820
17	4 000	saline	1 020	saline	720
18	4 000	saline	1.020	saline	980
19	4 000	saline	1 110	saline	820
20	4 000	saline	1 210	saline	800
21	5 000	saline	1 010	saline	670
22	5 000	saline	850	saline	760
23	5 000	saline	920	saline	650
24	5 000	saline	380	saline	470
25	5 000	saline	800	saline	630
26	6 000	saline	960	saline	720
27	6 000	saline	.550	saline	.590
28	6 000	saline	.570	saline	710
29	6 000	saline	.560	saline	680
30	6 000	saline	610	saline	.750
31	1 000	betax	390	amolol	820
32	1 000	betax	860	amolol	.520
33	1 000	betax	880	amolol	.380
34	1.000	betax	750	amolol	820
35	1 000	betax	1 000	amolol	.540
36	2 000	betax	.850	amolol	.690
37	2.000	betax	.790	amolol	780
38	2 000	betax	960	amolol	840
39	2.000	betax	630	amolol	630
40	2 000	betax	690	amolol	630
41	3 000	betax	.730	amolol	670
42	3 000	betax	.590	amolol	.330
43	3 000	betax	.720	amolol	.550
44	3 000	betax	490	amolol	.530
45	3 000	betax	880	amolol	.730
46	4 000	betax	790	amolol	690
47	4 000	betax	850	amolol	.590
48	4 000	betax	950	amolol	.720
49	4 000	betax	.590	amolol	630
50	4 000	betax	680	amolol	660
51	5 000	betax	.780	amolol	670
52	5 000	betax	.590	amolol	.420
53	5 000	betax	.500	amolol	.560
54	5 000	betax	.430	amolol	.650
55	5 000	betax	.710	amolol	.670
56	6 000	betax	620	amolol	.620
57	6 000	betax	.560	amolol	.730
58	6 000	betax	460	amolol	670
59	6 000	betax	.450	amolol	.570
60	6 000	betax	.530	amolol	610

V.2: Measurements of accommodative gain for all frequencies recorded for the 3 drug conditions: subject JH
Frequency: 1 = 0.05 Hz; 2 = 0.1 Hz; 3 = 0.2 Hz; 4 = 0.3 Hz; 5 = 0.6 Hz; 6 = 0.8 Hz

	Drug 1	Fr (Hz)	Gain s/t	Drug 2	gain s/b
1	saline	1	1 300	saline	990
2	saline	1	1 250	saline	900
3	saline	1	1 200	saline	710
4	saline	1	1 400	saline	1 090
5	saline	1	.	saline	920
6	saline	2	970	saline	950
7	saline	2	110	saline	890
8	saline	2	980	saline	930
9	saline	2	110	saline	900
10	saline	2	110	saline	970
11	saline	3	730	saline	740
12	saline	3	770	saline	690
13	saline	3	740	saline	730
14	saline	3	800	saline	700
15	saline	3	980	saline	800
16	saline	4	930	saline	890
17	saline	4	880	saline	820
18	saline	4	740	saline	760
19	saline	4	800	saline	750
20	saline	4	740	saline	700
21	saline	5	810	saline	730
22	saline	5	810	saline	740
23	saline	5	760	saline	800
24	saline	5	660	saline	750
25	saline	5	1 030	saline	700
26	saline	6	870	saline	650
27	saline	6	680	saline	730
28	saline	6	.580	saline	620
29	saline	6	450	saline	.500
30	saline	6	420	saline	630
31	timolol	1	760	betax	690
32	timolol	1	800	betax	690
33	tim i l	1	900	betax	800
34	timolol	1	600	betax	720
35	timolol	1	.	betax	900
36	timolol	2	850	betax	780
37	timolol	2	6~0	betax	580
38	timolol	2	950	betax	600
39	timolol	2	940	betax	630
40	timolol	2	850	betax	690
41	timolol	3	630	betax	510
42	timolol	3	720	betax	650
43	timolol	3	900	betax	580
44	timolol	3	.530	betax	.580
45	timolol	3	600	betax	470
46	timolol	4	760	betax	610
47	timolol	4	700	betax	600
48	timolol	4	780	betax	600
49	timolol	4	920	betax	570
50	timolol	4	660	betax	510
51	timolol	5	6~0	betax	490
52	timolol	5	810	betax	.520
53	timolol	5	830	betax	430
54	timolol	5	660	betax	330
55	timolol	5	740	betax	450
56	timolol	6	660	betax	480
57	timolol	6	750	betax	410
58	timolol	6	880	betax	440
59	timolol	6	610	betax	.340
60	timolol	6	600	betax	400

V.3: Measurements of accommodative gain for all frequencies recorded for the 3 drug conditions: subject LP

Frequency: 1 = 0.05 Hz; 2 = 0.1 Hz; 3 = 0.2 Hz; 4 = 0.3 Hz; 5 = 0.4 Hz; 6 = 0.5 Hz

LP	DRUG	Fr(Hz)	Gain	Drug s/b	gain s/b
1	SALINE	1	730	saline	890
2	SALINE	1	810	saline	1 020
3	SALINE	1	650	saline	960
4	SALINE	1	680	saline	990
5	SALINE	1	880	saline	960
6	SALINE	2	780	saline	1 110
7	SALINE	2	750	saline	880
8	SALINE	2	650	saline	1.210
9	SALINE	2	780	saline	830
10	SALINE	2	630	saline	1 200
11	SALINE	3	760	saline	1 030
12	SALINE	3	700	saline	1 090
13	SALINE	3	640	saline	850
14	SALINE	3	660	saline	970
15	SALINE	3	590	saline	1 040
16	SALINE	4	510	saline	950
17	SALINE	4	560	saline	920
18	SALINE	4	490	saline	940
19	SALINE	4	610	saline	580
20	SALINE	4	620	saline	860
21	SALINE	5	450	saline	810
22	SALINE	5	520	saline	680
23	SALINE	5	420	saline	570
24	SALINE	5	420	saline	.700
25	SALINE	5	470	saline	790
26	SALINE	6	410	saline	770
27	SALINE	6	400	saline	750
28	SALINE	6	370	saline	630
29	SALINE	6	300	saline	630
30	SALINE	6	320	saline	620
31	TIMOL	1	610	betax	760
32	TIMOL	1	630	betax	830
33	TIMOL	1	540	betax	580
34	TIMOL	1	660	betax	740
35	TIMOL .	1	590	betax	840
36	TIMOL	2	650	betax	.930
37	TIMOL...	2	720	betax	1 000
38	TIMOL...	2	610	betax	870
39	TIMOL.	2	450	betax	740
40	TIMOL .	2	680	betax	870
41	TIMOL..	3	580	betax	750
42	TIMOL...	3	550	betax	.780
43	TIMOL...	3	540	betax	690
44	TIMOL	3	510	betax	750
45	TIMOL	3	550	betax	660
46	TIMOL...	4	540	betax	650
47	TIMOL...	4	570	betax	660
48	TIMOL	4	480	betax	640
49	TIMOL..	4	470	betax	580
50	TIMOL...	4	510	betax	580
51	TIMOL .	5	490	betax	780
52	TIMOL...	5	470	betax	740
53	TIMOL	5	430	betax	670
54	TIMOL...	5	490	betax	640
55	TIMOL .	5	590	betax	540
56	TIMOL	6	330	betax	.570
57	TIMOL.	6	430	betax	630
58	TIMOL	6	360	betax	430
59	TIMOL	6	390	betax	490
60	TIMOL .	6	400	betax	500

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V.4: Analysis of gradients of the accommodative responses for the 3 subjects

The gradients were calculated from the x and y co-ordinates of points along the accommodation response slopes (one near the peak of the response, the other near the trough) to the various frequencies illustrated below. No correction for the different time bases used for the different frequencies has been made.

i) Subject BE

Fr 0 1 S+	Fr 0 1 S-	Fr 0 1 T+	Fr 0 1 T-	Fr 0 2 S+	Fr 0.2 S-	Fr 0 2 T+	Fr 0 2 T-
0 13	0 07	0 08	0 07	0 06	0 14	0 1	0 09
0 14	0 08	0 12	0 08	0 07	0 09	0 05	0 07
0 08	0 1	0 06	0 12	0 04	0 09	0 03	0 07
0 08	0 15	0 12	0 11	0 06	0 11	0 06	0 06
0 09	0 1	0 1	0 08	0 05	0 09	0 07	0 06
0 12	0 17	0 07	0 06	0 08	0 17	0 08	0 06
0 06	0 15	0 13	0 11			0 06	0 09
0 1	0 1		0 06				0 03
0 06							
Fr 0.3 S+	Fr 0.3 S-	Fr 0.3 T+	Fr 0.3 T-	Fr 0 4 S+	Fr 0.4 S-	Fr 0 4 T+	Fr 0 4 T-
0 14	0 02	0 14	0 19	0 14	0 19	0 19	0 18
0 09	0 19	0 12	0 11	0 17	0 12	0 14	0 18
0 07	0 1	0 06	0 07	0 07	0 18	0 19	0.23
0 11	0 27	0 05	0 09	0.24	0 08	0 14	0 12
0 09	0 1	0 11	0 16	0 19	0 2	0.2	0 13
0 13	0 15	0 17	0 1	0 18	0 14	0 1	0 08
0 1	0 08	0 09	0 08	0 15	0 11	0 36	0 16
0 18	0.21	0 15	0 15	0 12	0.1	0 12	'0 12
0 16	0 19	0 11	0 13			0 06	0 14
	0 11					0 08	0 08
Fr 0 5 S+	Fr 0.5 S-	Fr 0.5 T+	Fr 0.5 T-				
0 17	0 15	0 17	0 16				
0 17	0 09	0 17	0.13				
0 19	0 11	0 19	0 07				
0 1	0 09	0 1	0 14				
0 13	0 16	0 13	0 13				
0 28	0 14	0 28					
0.22		0 22					

ii) Subject LP

Fr 0.1S+	Fr 0.1S-	Fr 0.1T+	Fr 0.1T-	Fr 0.3S+	Fr 0.3S-	Fr 0.3T+	Fr 0.3T-
0 14	0 1	0 24	0 11	0 23	0 3	0 27	0 27
0 1	0 14	0 18	0 11	0 23	0 28	0 33	0 33
0 15	0 13	0 13	0 16	0 29	0 28	0 23	0 23
0 08	0 14	0 16	0 13	0 28	0 31	0 44	0 44
0 07	0 11	0 12	0 13	0 26	0 28	0 3	0 3
0 16	0 11	0 12	0 15	0 25	0 2	0 32	0 32
0 1	0 16	0 1	0 14	0 25	0 2	0 29	0 29
0 16		0 18	0 13	0 39	0 6	0 27	0 27
0 08		0 11	0 13	0 27	0 31	0 28	0 28
			0 12	0 37	0 26	0 36	0 36
				0 22	0 25		
				0 19			

Fr 0 1S+	Fr 0 1S-	Fr 0 1B+	Fr 0 1B-	Fr 0.4S+	Fr 0.4S-	Fr 0 4B+	Fr 0.4B-
0 07	0 08	0 05	0 13	0 06	0 09	0 16	0 13
0 04	0 08	0 06	0 14	0 09	0 13	0 13	0 13
0 06	0 07	0 06	0 09	0 13	0 12	0 14	0 1
0 1	0 13	0 09	0 11	0 09	0 14	0 16	0 08
0 06	0 09	0 09	0 09	0 15	0 14	0 07	0 09
0 08	0 07	0 09	0 1	0 12	0 07	0 08	0 08
0 08	0 16	0 08	0 08	0 15	0 12	0 13	0 18
0 08	0 09	0 08	0 08	0 21	0 09	0 06	0 11
0 08	0 19		0 09	0 18	0 09	0 12	0 07
0 09				0 08	0 09	0 08	0 14
				0 06	0 14	18	0 14
				0 08	0 08	0 16	0 16
				0 09	0 1	0 08	0 11
				0 13	0 11		0 12
							0.04
							0 03

Fr 0 05 S+	Fr 0 05 S-	Fr 0.05 T+	Fr 0.05 T-	Fr 0 1 S+	Fr 0 1 S-	Fr 0 1 T+	Fr 0.1 T-
0 09	0 08	0 09	0 12	0 14	0 13	0 07	0 12
0 12	0 07	0 04	0 05	0 15	0 16	0 07	0 08
0 06	0 08	0 07	0 09	0 15	0 15	0 08	0 08
0 09	0 1	0 07	0 11	0 15	0 15	0 09	0 08
0 12	0 12	0 09	0 06	0 14	0 17	0 08	0 16
0 09	0 1	0 09	0 07	0 13	0 13	0 11	0 15
0 12	0 12	0 05	0 06	0 12	0 12	0 1	0 13
0 08	0 11	0 06	0 06	0 17	0 14	0 15	0 15
0 07	0 12			0 11	0 12	0 14	0 16
0 06	0 05			0 1	0 16	0 09	0 2
0 07	0 09			0 11	0 13	0 1	0 16
	0 07			0 1	0 13	0 08	0.13
	0 05			0 13	0 1	0 14	0 13
				0 12	0 13		0 11
				0 12	0 13		0 1
				0 15	0 16		0 11
				0 15	0 12		
				0 1			
				0 13			
				0 1			

Fr 0 3S+	Fr 0 3S-	Fr 0 3T+	Fr 0.3T-
0 17	0 29	0 22	0 2
0.2	0 19	0 3	0 22
0 16	0 17	0 25	0 21
0 33	0 22	0 11	0 21
0 2	0 23	0 15	0.2
0 15	0 26	0 16	0 15
0 25	0 19	0 21	0 16
0 2	0 3	0 14	0 12
0 2	0 17	0 14	0 28
0 19	0 19	0 18	0 19
0 28	0 32	0 15	0.12
0 19	0 18	0 2	0 13
0.2	0 26	0.13	0.15
0 23		0 21	0 13

Fr 0 3S+	Fr 0.3S-	Fr 0.3B+	Fr 0.3B-	Fr 0.8S+	Fr 0 8S-	Fr 0 8B+	Fr 0.8B-
0 43	0 19	0 29	0 18	0.29	0 17	0.18	0.16
0 34	0 28	0 23	0 2	0.27	0 17	0 19	0.2
0 26	0 25	0 2	0.1	0 32	0.23	0 19	0 17
0 34	0 23	0 19	0 18	0.29	0 32	0 1	0 19
0 18	0 18	0 11	0 22	0 31	0.35	0.21	0.1
0 27	0 16	0 24	0 18	0 16	0 25	0 1	0 11
0 22	0 19	0 23	0 14	0.23	0 31	0 28	0 12
0 26	0 21	0 15	0 22	0 19	0 29	0 19	0 19
0 27	0 29	0 21	0 18	0 17	0 23	0 13	0.11
0 18	0 22	0 14	0 24	0.29	0 19	0 18	0 18
0 22	0 22	0 21	0 18	0 3	0 25	0 1	
0 17	0.22	0 17	0 1	0 14			
		0 12	0 19				

APPENDIX VI

VI.1 - SUPPORTING PUBLICATIONS

VI.1.1   Winn B, Pugh JR, Gilmartin B and Owens H (1989) The effect of pupil size on static and dynamic measurements of accommodation using an infra-red optometer. *Ophthal Physiol Opt* 9: 277-283.

VI.1.2   Winn B, Pugh JR, Gilmartin B and Owens H (1990) The frequency characteristics of accommodative microfluctuations for central and peripheral zones of the human crystalline lens. *Vis Res* 30:1093-1099

VI.1.3   Winn B, Pugh JR, Gilmartin B and Owens H (1990) Arterial pulse modulates temporal response characteristics of accommodation. *Curr Eye Res* 9, 971-975.

VI.1.4   Owens H (1990) IOP- a review of physiological variations and pharmacological control.*The Optician* 199, 12-19.

VI.1.5   Owens H, Winn B, Gilmartin B and Pugh JR (1991) Effect of a topical beta-antagonist on the dynamics of steady-state accommodation. *Ophthal Physiol Opt* 11, 99-104.

VI.1.6   Gilmartin B, Bullimore MA, Rosenfield M, Winn B and Owens H (1991) Pharmacological effects on accommodative adaptation. *Optom Vis Sci* (in press)

VI.2 - Refereed Papers published in Conference Proceedings

VI.2.1   Owens H, Winn B, Gilmartin B and Pugh JR (1990) The effect of a topical beta-adrenergic antagonist on the dynamics of steady-state accommodation. Non-invasive assessment of the visual system, Optical Society of America and American Academy of Optometry, Santa Fe, 88-91.

VI.2.2   Gilmartin B, Winn B, Owens H and Pugh JR (1990) Aspects of ciliary muscle innervation in late-onset myopia. (Paper) Fourth International Conference on Myopia, The XXVI International Congress of Ophthalmology, Singapore, 119-128.

VI.3 - Refereed published abstracts of conference proceedings

VI.3.1 Winn B, Pugh JR, Gilmartin B and Owens H (1989) The frequency characteristics of accommodation microfluctuations for central and peripheral zones of the crystalline lens (Poster). Association for Research into Vision and Ophthalmology meeting, May 1989, Sarasota, Florida, USA. *Invest Ophthal Vis Sci (suppl)* 30, 135.

VI.3.2 Gilmartin B, Winn B, Pugh JR and Owens H (1989) Ciliary muscle innervation and predisposition to late-onset myopia (Poster). American Academy of Optometry Meeting, December 1989, New Orleans, USA. *Optom Vis Sci* 66, 216P.

VI.3.3 Gilmartin B, Winn B, Owens H and Pugh JR (1990) The effect of topical beta-adrenergic antagonists on the temporal response characteristics of ocular accommodation in humans (Paper) 9th International Congress for Eye Research, Helsinki, Finland, 96.

VI.3.4 Winn B, Pugh JR, Gilmartin B and Owens H (1990) Arterial pulse modulates steady-state ocular accommodation (Paper). Transactions of the 2nd International Congress of the British College of Ophthalmic Opticians. London, 15.

VI.3.5 Winn B, Pugh JR, Gilmartin B and Owens H (1990) Arterial pulse modulates steady-state ocular accommodation (Poster). Association for Research into Vision and Ophthalmology meeting, May 1990, Sarasota, Florida, USA. *Invest Ophthal Vis Sci (suppl)* 31, 82.

VI.3.6 Owens H, Winn B, Gilmartin B and Pugh JR (1990) The influence of arterial blood flow on steady-state accommodation (Paper). Society of Experimental Optometry, July 1990, Birmingham. *Ophthal Physiol Opt* 10, 412.

VI.3.7 Winn B, Pugh JR, Gilmartin B and Owens H (1990) The influence of non-ocular systems on steady-state accommodation (Paper). American Academy of Optometry Meeting, December 1990, Nashville, USA. *Optom Vis Sci* 67, 94-95.

VI.3.8 Owens H, Gilmartin B and Winn B.(1991) The effect of beta-receptor antagonists on the temporal accommodation response. (Paper) Applied Vision

Association Conference, April, 1991, UMIST, Manchester, *Ophthal Physiol Opt* **11**, (in press).

VI.3.9   Winn, B, Gilmartin B, Owens H and Pugh JR (1991) The effect of topical timolol maleate on accommodative microfluctuations (Poster) Association for Research into Vision and Ophthalmology meeting, May 1991, Sarasota, Florida, USA. *Invest Ophthal Vis Sci (suppl)* **32**, 759.

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