

STUDIES ON THE EYE

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VOLUME I

## DECLARATION

In accordance with the statutes of the University of Edinburgh, I declare that the contribution of the author to the published research papers included in this thesis is categorised as follows:

- i. the research was performed entirely by the author, including preparation of the manuscript (papers 1,3,4,5,6,7,8,9,10,11,12,13,16,17,18,19,20,30,31,34).
- ii. the research was performed entirely by the author, and the manuscript was prepared with other(s), although the author was the major contributor (papers 2,14,15,31,32,33).
- iii. the research was performed in association with a research team. The author designed the studies, made a significant contribution to the performance of the studies, and was a major contributor to the preparation of the manuscript (papers 23,24,25,26,27,28,29,35).
- iv. the research was performed in association with a research team. The author made a significant contribution to the research study (papers 21,22).

Information from the following papers has been included, in part, in my Doctor of Medicine thesis: papers 1,2,3,4,5,6,7,8,9,10,11, 14,15,16,18).

Permission has been obtained from relevant publishers to include photocopies of published papers in the thesis.

Charles V Clark

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## ABSTRACT

This thesis comprises a series of studies on the eye, with particular reference to the pathogenesis of the primary glaucomas, and the complex effects of autonomic nerve function on the eye. The first section is devoted to studies on the primary glaucomas. The integrity of autonomic nerve function is investigated, and a significant prevalence of autonomic dysfunction - both systemic and ocular - is identified in each of the major categories of primary glaucoma. The association between diabetes mellitus and the primary glaucomas is defined by a series of prospective and retrospective studies. Diurnal variation in the dimensions of the anterior chamber is described, with shallowing of the anterior chamber in the evening, which is comparable to the diurnal variation in the onset of closed-angle glaucoma. Finally, factors predisposing to the development of posterior synechiae after glaucoma operations are assessed, and the potential application of mifepristone (RU486) as a peripheral blocker of dexamethasone and progesterone is evaluated.

The second section examines the relationship between autonomic nerve function and the eye, in conditions other than glaucoma. The effects of systemic autonomic nerve stimulation on the eye are assessed in a series of studies. In the anterior segment of the eye, the effects of systemic autonomic nerve stimulation on intraocular pressure are described in normal subjects and diabetic patients. In the posterior segment of the eye, the effects of systemic autonomic nerve stimulation on the retinal circulation are evaluated in normal subjects, demonstrating a significant association between systemic autonomic stimulation and retinal vessel calibre.

This response is shown to be reproducible, and the association between autonomic nerve stimulation and retinal vessel calibre is supported by the results of further studies on patients with diabetes, diabetic nephropathy, and cervical sympathectomy. Finally, in this section, the efficacy of autonomic nerve function in various conditions is described. A high prevalence of systemic autonomic neuropathy and ocular autonomic neuropathy is identified in patients with proliferative diabetic retinopathy, and ocular autonomic nerve function is defined in patients with progressive autonomic failure.

The third section comprises three miscellaneous papers, describing the association between diminished skin wrinkling and diabetes mellitus, not associated with other recognised complications of diabetes (retinopathy or autonomic neuropathy), the histopathology of extraocular muscle in congenital third nerve palsy, and the histopathology of carcinoid tumour in the lacrimal gland.

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## INTRODUCTION

A consecutive series of research papers are presented, summarising the results of studies on the eye, with particular reference to aetiological factors in the pathogenesis of the primary glaucomas, and the relationship between autonomic nerve function and the eye. These major areas of research are not mutually exclusive; on the contrary, a significant association is described between dysfunction of the autonomic nervous system and the primary glaucomas. The thesis has been divided into three sections: glaucoma, autonomic nerve function, and a final brief section of miscellaneous papers.

### Section I - Glaucoma

The primary glaucomas are a heterogeneous group of diseases with common characteristics: elevation of intraocular pressure, specific visual field defects, and cupping of the optic disc. Any or all of the aforementioned features may be present at a given examination. The aetiology of the primary glaucomas is multifactorial. In this context, the efficacy of autonomic nerve function in the primary glaucomas is described in a series of studies in section 1.1. This research has demonstrated a significant association between dysfunction of the autonomic nervous system and the primary glaucomas. Systemic autonomic neuropathy was present in a significant proportion of glaucoma patients, suggesting that the autonomic dysfunction was not exclusively localised to the eye. Utilising a series of autonomic function tests based upon cardiovascular reflexes - which are recognised to be indicative of generalised autonomic nerve function - systemic autonomic neuropathy was demonstrated in 58% of patients with closed-angle glaucoma (1,2). This prevalence level was determined by comparison with standard

normal limits for autonomic nerve function assessment. The previously-accepted limits for autonomic function were particularly relevant to a younger age range than that normally associated with glaucoma patients, and therefore the age-adjusted tolerance limits of cardiovascular autonomic function assessment for an elderly population were defined (3). When the results of the closed-angle glaucoma group were compared with age-adjusted tolerance limits - rather than arbitrarily-defined limits of normality - the prevalence of autonomic dysfunction decreased slightly to 50% (12). Systemic autonomic dysfunction was subsequently demonstrated in 42% of ocular hypertensive subjects (4,5) - with a significantly higher prevalence of autonomic dysfunction in narrow-angle ocular hypertensives (50%) than wide-angle subjects (34%) - and 37% of open-angle glaucoma patients (6).

Ocular autonomic integrity was determined by measurement of pupil cycle time - a screening test of the pupillary reflex arc - and the assessment of denervation hypersensitivity in the anterior segment of the eye. Significant impairment of the pupillary reflex arc was identified in patients with closed-angle glaucoma, with prolongation or absence of pupil cycling in 64% of subjects (7). Pupil responses to light were also significantly impaired in patients with ocular hypertension, with significantly-increased prevalence in narrow-angle ocular hypertensives compared with their wide-angle counterparts (8). Pupil cycle time was not assessed in patients with open-angle glaucoma, as the afferent limb of the pupil reflex is recognised to be abnormal in patients with open-angle glaucoma, and therefore no inferences may be drawn regarding the parasympathetic efferent limb of the reflex arc. Autonomic efficacy in the anterior segment of

the eye was further investigated by the assessment of denervation hypersensitivity in the anterior segment of primary glaucoma patients. 2.5% methacholine chloride and 0.5% phenylephrine hydrochloride were used for the assessment of parasympathetic and sympathetic denervation hypersensitivity of the iris respectively. Pupil constriction in response to 2.5% methacholine - indicative of parasympathetic denervation hypersensitivity - was significantly increased in each of the major categories of primary glaucoma (closed-angle glaucoma, open-angle glaucoma, and ocular hypertension), compared with age- and sex-matched control subjects (9,10). Similarly, pupil dilation in response to 0.5% phenylephrine was also significantly increased in all major categories of primary glaucoma (10,11).

The presence of ocular denervation hypersensitivity in each of the major categories of glaucoma implies that autonomic neuropathy is present in the anterior segment of these patients. The demonstration of significant ocular autonomic dysfunction in patients with primary glaucoma must be placed in perspective, as an association has been demonstrated between systemic autonomic dysfunction and all major categories of primary glaucoma. Autonomic neuropathy is not characteristically a localised disorder; evidence of ocular autonomic neuropathy in patients with a high prevalence of systemic autonomic dysfunction is therefore not unexpected. The prevalence of autonomic neuropathy seems to be directly related to the clinical category of glaucoma. The prevalence of autonomic neuropathy in closed-angle glaucoma patients was 50%, and the prevalence in ocular hypertensives was 42%, however when this group was subdivided by angle configuration into narrow-angle and

wide-angle categories, the prevalence in narrow-angle patients (50%) was significantly higher than in wide-angle subjects (34%). It is therefore apparent that the prevalence of autonomic dysfunction seems to be associated with the type of glaucoma; the prevalence in closed-angle glaucoma patients (50%) is identical to that of ocular hypertensives with narrow angles (50%), whilst the prevalence in open-angle glaucoma patients (37%) is similar to that in ocular hypertensives with wide-angles (34%).

Parasympathetic and sympathetic denervation hypersensitivity of the iris has been described in patients with closed-angle glaucoma, open-angle glaucoma, and ocular hypertension, and autonomic neuropathy has been suggested as a significant predisposing factor in the pathogenesis of raised intraocular pressure. The effects of autonomic neuropathy on the pathogenesis of glaucoma are probably dependent on the pre-existing anatomical configuration of the anterior chamber. In closed-angle glaucoma patients, the anterior chamber is characteristically shallow with narrow irido-corneal angles, and is therefore predisposed to angle closure. The importance of pupil block in angle closure is well-established; pupil block force is a posteriorly-directed vector, inhibiting the passage of aqueous from the posterior to the anterior chamber. Pupil block is maximal at mid-dilatation, the recognised pupil configuration during an acute episode of angle-closure. As previously explained, pupil diameter is directly controlled by the autonomic nervous system; parasympathetic and sympathetic neuropathy in the anterior segment would produce a mid-dilated pupil, the position of maximal pupil block. In eyes with narrow angles, increase in pupil block force may precipitate angle closure.

In patients with open-angle glaucoma and ocular hypertension, autonomic neuropathy may influence the development of raised intraocular pressure by a different mechanism. It has been proposed that autonomic dysfunction may increase intraocular pressure in subjects with ocular hypertension by impairment of aqueous outflow from the anterior chamber. Parasympathetic nerve stimulation increases facility of outflow by inducing ciliary muscle contraction on the scleral spur, thereby actively opening the trabecular meshwork and utilising the potential reserve outflow. In subjects with parasympathetic dysfunction, this mechanism will be impaired, and elevation of intraocular pressure may be precipitated.

A series of autonomic provocative tests were performed, demonstrating the effects of autonomic agonists on the dimensions of the anterior chamber (12). Patients presenting with closed-angle glaucoma were examined to assess the risk of angle closure developing in the fellow eye. Autonomic provocative tests were performed using topical pilocarpine - a parasympathetic agonist - and phenylephrine - a sympathetic agonist. Closed-angle glaucoma was demonstrated in 62% of fellow eyes. The pathogenesis of glaucoma is discussed, with particular reference to the significant association between systemic parasympathetic neuropathy and closed-angle glaucoma. As partial denervation enhances the sensitivity of a tissue to autonomic mediators - either endogenously released or exogenously applied - the hypothesis is proposed that the sensitivity of the pilocarpine-phenylephrine provocative test (93%) may be explained by autonomic dysfunction in the anterior segment of patients with closed-angle glaucoma, manifest by hypersensitive responses to autonomic agonists.

Variation in anterior chamber volume during the pilocarpine-phenylephrine provocative test was assessed; a significant decrease in the volume of the anterior chamber was demonstrated in eyes without a peripheral iridectomy during autonomic provocative testing (13). This is presumed to be a consequence of increased pupil block force, precipitating the development of a pressure differential across the iris-lens diaphragm, and therefore shallowing of the anterior chamber. When the pressure differential was neutralised by the creation of an alternative route for aqueous transfer from the posterior to the anterior chamber (via a peripheral iridectomy), the anterior chamber deepened in response to combined parasympathetic and sympathetic stimulation, and the volume of the anterior chamber is significantly increased.

The association between diabetes mellitus and the primary glaucomas is examined in a series of studies described in section 1.2. An association between diabetes and glaucoma has been recognised for many years, however this has not been accurately defined until comparatively recently. This association was shown to be specifically between narrow-angle categories of primary glaucoma and non-insulin dependent diabetes mellitus (14,15); the prevalence of diabetes mellitus in wide-angle categories of glaucoma was similar to that of the normal population. A significant association was also demonstrated between axial anterior chamber depth and abnormal glucose tolerance; axial anterior chamber depth was significantly correlated with both the probability of developing diabetes ( $r = -0.79$ ), and the 2-hour venous plasma glucose after 75-gram oral glucose tolerance test (15). The observation of an association between diabetes and glaucoma is not particularly surprising in the

context of a significant association between autonomic neuropathy and glaucoma, as diabetes mellitus is the commonest cause of autonomic neuropathy in the United Kingdom. This association was further investigated by retrospective and prospective studies. The prevalence of a family history of diabetes - specifically non-insulin dependent diabetes - was shown to be significantly increased in closed-angle glaucoma and ocular hypertensive patients, compared with an age- and sex-matched control group, although this was not present in open-angle glaucoma patients (16). The progression of impaired glucose tolerance to diabetes mellitus in patients with primary glaucoma was assessed by repeat 75-gram oral glucose tolerance test after one year; 16% of primary glaucoma patients with impaired glucose tolerance progressed to diabetes mellitus in a single year, compared with only 3% of the normal population, thereby further emphasising the association between diabetes mellitus and glaucoma (17). Examination of long-term glycaemic control by assessment of glycosylated haemoglobin demonstrated significantly-increased glycosylated haemoglobin in patients with primary glaucoma compared with an age- and sex-matched control group, although, once again, the association was specifically between narrow-angle categories of glaucoma and diabetes (18).

The effects of diurnal variation on glaucoma are examined in section 1.3. A significant physiological diurnal variation in the dimensions of the anterior chamber has been demonstrated, with significant shallowing of the anterior chamber in the evening compared with morning values. The shallowing was accentuated in the periphery of the anterior chamber; axial anterior chamber depth decreased by 2.1%, anterior chamber volume decreased by 5.7%, however

peripheral anterior chamber depth decreased by 21.1% (19). This is of particular significance to the development of closed-angle glaucoma, as the onset of closed-angle glaucoma demonstrates a similar diurnal variation, occurring mainly in the evening, with the inevitable implication that diurnal physiological shallowing of the anterior chamber may precipitate closed-angle glaucoma in anatomically-predisposed subjects (20).

Finally, there is a brief miscellaneous group of glaucoma research papers to complete section 1. An investigation to assess the distribution of posterior synechiae following glaucoma operations showed that posterior synechiae were either absent, or involved the pupil throughout 360 degrees. This potentially serious complication of glaucoma operations was exacerbated by the application of pilocarpine post-operatively, and the presence of a shallow anterior chamber (21).

A series of experiments were performed to determine whether topical mifepristone (RU486), a peripheral blocker of dexamethasone and progesterone, effected a decrease in intraocular pressure in the rabbit. Topical mifepristone was shown to significantly decrease rabbit intraocular pressure. There was also an anomalous decrease in intraocular pressure in response to topical dexamethasone, and it was therefore impossible to determine whether mifepristone exerted a protective effect against the potential elevation of intraocular pressure associated with application of topical steroids in the human eye (22).

## Section II - Autonomic nerve function

The effects of systemic autonomic nerve stimulation on the eye are described in section 2.1, which is subdivided into the effects on intraocular pressure (the anterior segment) in section 2.11, and the effects on the retinal circulation (the posterior segment) in section 2.12.

The intraocular pressure responses to 2 standard tests of autonomic nerve function were studied in normal subjects:

- i. The elevation of diastolic blood pressure provoked by sustained isometric muscle contraction, a response mediated by the sympathetic nervous system.
- ii. The heart-rate response to the Valsalva manoeuvre, a response mediated by the parasympathetic nervous system.

During sustained isometric exercise, the mean intraocular pressure significantly decreased, and remained significantly lower than baseline values for 5 minutes after discontinuing the test. During the Valsalva manoeuvre, the mean intraocular pressure increased, with a subsequent significant decrease in intraocular pressure during the recovery period. Possible mechanisms to explain these observations are discussed (23).

The intraocular pressure responses to equivalent systemic autonomic nerve stimulation were also evaluated in diabetic patients. The results demonstrated similar intraocular pressure responses to systemic autonomic stimulation in diabetics (with intact autonomic nerve function) as in normal subjects, suggesting that diabetes per se does not have a significant effect on the responses of aqueous

dynamics to systemic autonomic nerve stimulation (24).

The effects of systemic autonomic nerve stimulation on the retinal circulation are described in section 2.12. Controlled, reproducible stimulation of the autonomic nervous system may be achieved by sustained isometric muscle contraction, which provokes a well-established reflex elevation of diastolic blood pressure. The retinal vessel calibre responses to controlled stimulation of the autonomic nervous system were determined in normal subjects (25). Sympathetic nerve stimulation in response to sustained isometric handgrip at 33% of maximum voluntary contraction effected a mean retinal arteriolar constriction of 8.1% and mean retinal venule constriction of 3.7%, demonstrating a significant association between retinal vessel calibre and systemic autonomic stimulation. Reproducibility of retinal vessel responses to autonomic nerve stimulation was assessed, and the responses were shown to demonstrate statistically significant reproducibility (26). The responses of the retinal circulation to autonomic nerve stimulation were subsequently investigated in 2 separate groups of diabetic patients: with and without documented evidence of systemic autonomic neuropathy. The retinal vascular responses to systemic autonomic stimulation were significantly impaired in diabetic patients with autonomic neuropathy, compared to those with intact autonomic nerve function: retinal arteriolar constriction of 1.2% compared with 9.2%, and retinal venule constriction of 2.1% compared with 5.1% respectively (27). These results support the hypothesis of an association between autonomic neuropathy and failure of regulation of retinal blood flow. Complications of diabetes frequently demonstrate a coincidental natural history; an association was

demonstrated between nephropathy (microalbuminuria) and responses of the retinal circulation to autonomic stimulation (28). Retinal vessel responses were significantly decreased in patients with clinically significant microalbuminuria (albumin excretion rate  $> 10 \mu\text{g}/\text{min}$ ) compared with patients with no significant nephropathy (albumin excretion rate  $\leq 10 \mu\text{g}/\text{min}$ ): retinal arteriolar constriction of 0.1% compared with 6.9%, and retinal venule constriction of 1.0% compared with 4.2% respectively (28). The association between retinal vascular responses and systemic autonomic nerve stimulation was further supported by a study of patients with unilateral cervical sympathectomy. Retinal vascular reflexes were significantly impaired in the sympathectomised eye compared with the normal control eye: retinal arteriolar constriction of 4.6% compared with 7.1%, and retinal venule constriction of 1.5% compared with 4.9% respectively (29).

The efficacy of autonomic nerve function is examined in section 2.2. Systemic autonomic neuropathy was demonstrated in 75% of patients with proliferative diabetic retinopathy, compared with 5.2% of an age- and sex-matched control group (30). Ocular autonomic neuropathy was also significantly associated with proliferative diabetic retinopathy: pupillary reflexes were abnormal in 88.5% of patients, and ocular denervation hypersensitivity - involving either parasympathetic or sympathetic nerves - was present in 57% of subjects (31).

Ocular autonomic nerve function was assessed in patients with progressive autonomic failure. There were abnormalities of the pupillary reflex arc in all patients included in the study, and

ocular autonomic neuropathy was demonstrated in 75% of subjects. Denervation hypersensitivity of conjunctival vessels was demonstrated for the first time, supporting the concept of parasympathetic innervation to the conjunctival vessels, which had only previously been demonstrated in the animal model (32).

### Section III - Miscellaneous

The final section comprises three miscellaneous papers. Absence of skin wrinkling following sustained immersion of hands in water is shown to be a feature of diabetes mellitus, however this is not associated with other recognised complications of diabetes (retinopathy and autonomic neuropathy). (33)

The histopathology of extraocular muscle in congenital third nerve palsy is discussed (34). The paper describes the histopathological appearance of resected medial rectus muscle from a case of unilateral congenital third nerve palsy, and suggests that fibrous replacement of extraocular muscle may be associated with congenital denervation in some cases of third nerve palsy. This may explain the absence of evidence of aberrant regeneration in apparently peripheral nerve lesions, as this neurological sign requires the presence of an intact effector ie the extraocular musculature. The only definite conclusion which may be drawn from the evidence available to date is that congenital unilateral third nerve palsy is a diagnosis of exclusion; the location of the neurological lesion may be central or peripheral, and the anatomy of the denervated musculature may be grossly abnormal.

A carcinoid tumour in the lacrimal gland is described for the first time, a rare tumour which may either represent a metastasis from a previous mediastinal primary, or a second primary tumour (35). The possibility of divergent differentiation of ductal stem cells is discussed.

SECTION I

GLAUCOMA

1.1 AUTONOMIC NERVE FUNCTION IN THE PRIMARY GLAUCOMAS

PAPER 1

# Autonomic neuropathy in closed angle glaucoma

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## SUMMARY

A series of cardiovascular autonomic function tests were performed on 120 patients with a history of closed angle glaucoma and 75 age- and sex-matched control subjects. Systemic parasympathetic neuropathy was present in 58% of the angle-closure group compared with 6.8% of the control population. The implications are discussed.

## INTRODUCTION

Sequential changes in the dimensions of the anterior chamber are impossible to quantify during the genesis of a spontaneous attack of closed angle glaucoma. Deductions regarding pathogenesis must therefore be derived from models of experimental angle-closure – the rationale of provocative testing<sup>19</sup>. The propensity of the anterior chamber to show rapid and transient fluctuations in dimension has been clearly demonstrated<sup>20</sup>. Closure of the anterior chamber angle is by definition a dynamic process. The relative contribution of anterior translational movement of the iris lens diaphragm<sup>22</sup> and peripheral iris bombe<sup>4</sup> remains a source of debate, however the basic aetiological factor common to both mechanisms is pupil block<sup>17,18</sup> itself a manifestation of autonomic activity in the anterior segment. Pupil block force has been shown to be maximal if the pupil is fixed in mid-dilatation as a result of relative sympathetic and parasympathetic activity. Summation of diametrically opposed forces subsequent to isometric contraction of the iris musculature produces a posteriorly-directed vector. Impedance of aqueous flow from the posterior to the anterior chamber results in the development of a pressure differential across the iris-lens diaphragm. In a biological system capable of marked variation, changes in the dimensions of the anterior chamber necessarily follow: for example, the volume of the anterior chamber decreases by 16% in the fellow eye of a patient with closed angle glaucoma during the course of a provocative test with pilocarpine and phenylephrine<sup>3</sup>.

The prevalence of systemic autonomic neuropathy in patients with a history of closed angle glaucoma was assessed for the following reasons:

1. Pupil block is a significant predisposing factor in the pathogenesis of angle-closure<sup>21</sup>.
2. Diabetes mellitus, a metabolic disorder significantly associated with closed angle glaucoma<sup>23,24</sup> is the commonest cause of autonomic neuropathy in this country.

Autonomic insufficiency has an insidious onset which is impossible to identify accurately due to the compensatory mechanisms inherent within the autonomic nervous system. Until comparatively recently, tests of autonomic function have been difficult to interpret and

virtually impossible to quantify<sup>11</sup>. During the past 12 years, a series of simple, non-invasive tests based upon cardiovascular reflexes have been developed, permitting accurate, objective measurement of autonomic nerve function<sup>1,6,8,15,20</sup>. As in all reflex assessments, this depends upon a standardized input stimulus coupled with the measurement of the subject's output reaction. Results are based on blood-pressure and heart-rate responses to a variety of stimuli. A necessary corollary is that detected abnormalities cannot be localized to either the afferent, internuncial, or efferent components of the reflex. Evidence to date suggest that these tests also reflect damage elsewhere in the autonomic nervous system<sup>7</sup>.

## PATIENTS AND METHODS

One hundred and twenty patients with a history of closed-angle glaucoma (mean age  $66.8 \pm 10.0$  years) and 75 age- and sex-matched control subjects (mean age  $68.2 \pm 10.2$  years) were included in the study. The control population consisted of hospital staff and patients attending the casualty department who were subsequently determined to have either a short-term (3-5 days), self-limiting condition, or no detectable abnormality. Subjects known to have medical disorders predisposing to autonomic nerve dysfunction, or taking medication with effects on the autonomic nervous system, were excluded from the control group. Patients with a history of closed angle glaucoma on medication with autonomic effects were similarly excluded.

Five tests of autonomic integrity were employed (Table I). Determination of normal sinus rhythm is an essential prerequisite to autonomic assessment.

Table I Cardiovascular autonomic function tests

1. <i>Parasympathetic function</i>
i. Valsalva manoeuvre
ii. Heart-rate variation during deep breathing
iii. Immediate heart-rate response to standing
iv. Immediate heart-rate response to lying
2. <i>Sympathetic function</i>
Blood-pressure response to standing

### 1 *Parasympathetic nerve function*

i. *Valsalva manoeuvre*. Standardized Valsalva manoeuvre is performed by the subject blowing into a mouthpiece connected to a modified sphygmomanometer and maintaining a pressure of 40 mmHg (5.3 kPa) for 15 sec. A continuous electrocardiogram is recorded, commencing 20 sec prior to the manoeuvre and terminating 25 sec after the manoeuvre. The Valsalva ratio is the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the test. These are measured directly from the electrocardiogram, and the final ratio is the mean of three consecutive assessments. There are four discrete phases in the heart-rate and blood-pressure responses to this test. The heart-rate initially decreases for 2-3 sec (phase 1), then gradually increases in response to the reduced venous return and consequently decreased blood-pressure (phase 2).

There is a further increase in tachycardia on release of intrathoracic pressure as the subsequent rise in pulmonary venous capacitance precipitates a further fall in cardiac output (phase 3). This is followed by bradycardia in phase 4, a baroreflex response to increased cardiac output occurring during a period of raised peripheral vascular resistance.

ii. *Heart-rate variation during deep breathing*. This reflex depends upon an intact parasympathetic nerve supply; it is not influenced by beta-blockade, but is abolished by the systemic administration of atropine. The most convenient technique is breathing at 6 deep breaths per min, with a continuous electrocardiogram recorded during the test. In normal subjects a relative tachycardia occurs during inspiration, with a relative bradycardia during

expiration. Maximum and minimum R-R intervals are measured and expressed as beats per min. Six measured cycles are calculated and the final result is the mean of the differences between maximum and minimum heart-rates.

iii. *Immediate heart-rate response to standing.* During alteration in posture from lying to standing a characteristic cardiovascular reflex response occurs under vagal control. This consists of an initial tachycardia, maximal at about the 15th beat after standing, followed by a relative bradycardia around the 30th beat.

The patient rests supine for approximately 3 min prior to the test, then is requested to stand unaided. Once again, an electrocardiogram is recorded from 20 beats prior to the manoeuvre until 40 beats after standing. The R-R intervals are measured to determine the shortest around the 15th beat and longest at about beat 30, and the result expressed as the 30:15 ratio.

iv. *Immediate heart-rate response to lying.* Shortening of the R-R interval occurs during the 3rd-4th beat after commencing the manoeuvre, followed by a gradual increase in R-R interval. The initial decrease in R-R interval is abolished by systemic atropine but is unaffected by propranolol, thus indicating a reflex mediated by relative parasympathetic inhibition. Subjects were requested to stand for 2 min then lie down unaided. Heart-rate was recorded by electrocardiography, and the results calculated as the ratio of the longest R-R interval during the 5 beats before lying to the shortest R-R interval during the 10 beats after lying down (S:L ratio).

## 2 Sympathetic nerve function

### Blood-pressure response to standing.

Several cardiovascular reflexes are initiated by change in posture from the supine to the standing position. Gravitational pooling of blood in the lower extremities precipitates a fall in blood-pressure. The intact baroreflex arc rapidly reverses this tendency, effecting peripheral and splanchnic vasoconstriction via sympathetic efferent nerves.

After 3 minutes lying supine on an examination couch, the patient's blood-pressure is measured with a sphygmomanometer, then again immediately after standing upright. The difference between the systolic pressure lying and standing is the postural change in blood-pressure.

Assessments were undertaken on a single-blind basis; 893 tests were performed on 195 subjects (average 4.58 per subject). Acceptable limits of normality, determined by previous observers, are shown in Table II. The patients were then classified into four discrete categories on the basis of the results: normal; early parasympathetic damage if one abnormal parasympathetic result; definite parasympathetic neuropathy if two or more tests of parasympathetic function abnormal; parasympathetic plus sympathetic neuropathy if abnormal results are obtained in both groups.

Significance was determined by Student's unpaired *t*-test.

Table II Assessment criteria in cardiovascular autonomic function tests

	Abnormal
<i>1. Parasympathetic function</i>	
i. Valsalva ratio	≤ 1.10
ii. Heart-rate variation during deep breathing	≤ 10.00 beats/min
iii. 30:15 ratio	≤ 1.00
iv. S:L ratio	≤ 1.07
<i>2. Sympathetic function</i>	
Blood-pressure response to standing	≥ 30.0 mmHg

## RESULTS

Eight patients and one member of the control group were excluded from analysis of electrocardiographic data due to cardiac arrhythmias, listed in Table III. The results of cardiovascular autonomic function assessment in 112 patients with closed angle glaucoma and 74 age- and sex-matched control subjects are shown in Table IV. There were no significant differences between the two groups in assessment of Valsalva ratio ( $p < 0.05$ ) or postural hypotension ( $p < 0.05$ ). Significant differences were however observed in comparisons of heart-rate variation during deep breathing ( $p < 0.001$ ), 30:15 ratio ( $p < 0.001$ ) and S:L ratio ( $p < 0.01$ ).

Classification of autonomic status is shown in Table V.

Table III Cardiac arrhythmias necessitating exclusion from study

	Angle-closure group	Control group
Atrial fibrillation	5	1
Sick sinus syndrome	2	
Pulsus bigeminus	1	

Table IV Results of cardiovascular autonomic function assessment in 112 patients with closed angle glaucoma and 74 age- and sex-matched control subjects

	Angle-closure group	Control group	Significance
<i>1. Parasympathetic function</i>			
i. Heart-rate variation during deep breathing (beats/min)	11.87 ± 0.73	17.85 ± 0.90	$p < 0.001$
ii. Immediate heart-rate response to standing (30:15 ratio)	1.11 ± 0.01	1.17 ± 0.01	$p < 0.001$
iii. Immediate heart-rate response to lying (S:L ratio)	1.15 ± 0.01	1.20 ± 0.01	$p < 0.01$
iv. Valsalva ratio	1.41 ± 0.03	1.49 ± 0.04	$p > 0.05$
<i>2. Sympathetic function</i>			
Decrease in systolic blood-pressure on standing (mmHg)	11.11 ± 1.22	8.12 ± 1.50	$p > 0.05$

(Group mean values ± SEM)

Table V Classification of autonomic status

	Normal	Early parasympathetic neuropathy	Definite parasympathetic neuropathy	Parasympathetic plus sympathetic neuropathy
Angle-closure group (n = 112)	47 (42%)	36 (32.1%)	18 (16.1%)	11 (9.8%)
Control group (n = 74)	69 (93.2%)	4 (5.4%)	0	1 (1.4%)

## DISCUSSION

The utilization of cardiovascular reflexes to define systemic autonomic function provides an accurate, quantifiable measurement of a nervous system previously virtually impossible to isolate. Heart-rate is determined at all times by the balance between sympathetic and parasympathetic influences<sup>12,16,25</sup>. The relative importance of each component during characteristic cardiovascular reflexes has been elucidated by selective pharmacological autonomic blockade.

Heart-rate variation during deep breathing is effected by the vagus nerve. Although a complex interaction of reflexes is responsible, respiration is considered the most important stimulus. Stretch receptors in the lungs are a principle source of afferent impulses, mediating reflex inhibition of the cardioinhibitory centre in the medulla oblongata<sup>10</sup>. Pharmacological evidence has shown that the immediate heart-rate response to standing results from a decrease in vagal efferent impulses, during the first 10–15 beats after standing, followed by increased vagal discharge at about beat 25–30. A minor component of the initial tachycardia is under the control of the sympathetic nervous system.

Short periods of muscular exertion are characterized by an initial withdrawal of vagus activity prior to increased vagal tone<sup>2,9,14</sup>. This has been postulated as the underlying mechanism in the immediate heart-rate response to lying, a hypothesis subsequently supported by standard pharmacological blockade permitting isolation of the components of the autonomic nervous system. Results have indicated that the sympathetic nervous system is the principle mediator only in the later stages of the reflex. The physiological principles underlying heart-rate changes during the Valsalva manoeuvre, and blood-pressure response to standing, have been adequately explained in the introductory text.

Although each test may be used individually, the application of all five provides a more detailed measure of systemic autonomic nerve function. The tests are accurate, reliable, non-invasive, and directed specifically towards the clinical situation.

The marked prevalence of diabetes mellitus and impaired glucose tolerance in patients with closed angle glaucoma assumes a greater significance when one realises that 20–40% of all diabetics have documented evidence of autonomic nerve dysfunction, according to recent large series<sup>5,13</sup>. In diabetes, autonomic neuropathy follows a characteristic course, with parasympathetic dysfunction occurring prior to sympathetic damage. Present evidence suggests a similar trend in patients with closed angle glaucoma.

The essential event precipitating irido-corneal contact is postulated to be a change in parasympathetic activity<sup>21</sup>. The presence of systemic parasympathetic neuropathy in 58% of patients with closed angle glaucoma supports this hypothesis. A corollary is that closed angle glaucoma may not be an isolated ocular event, but rather a manifestation of systemic disease.

## CONCLUSIONS

The application of autonomic function tests, based upon cardiovascular reflexes, has demonstrated a marked prevalence of parasympathetic neuropathy in patients with closed angle glaucoma, compared with an age- and sex-matched control population. Pupil block, a significant predisposing factor in the pathogenesis of angle-closure, is effected by relative autonomic activity in the anterior segment. The exact significance of systemic autonomic neuropathy remains to be elucidated, however a causal relationship seems probable.

## ACKNOWLEDGEMENTS

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PAPER 2

## The Prevalence of Autonomic Neuropathy in Glaucoma

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At its inception closed angle glaucoma is an acute event which requires, as a causal explanation, an equally sudden change within the anterior segment. The most prevalent view<sup>1,2</sup> suggests that the magnitude of the pupil block force is the proximate cause and, the various experimental models available, manipulate the pupil block force in an attempt to create an acute attack. Because a change within the anterior segment is necessary there are two possible approaches, either the pupil block force can be increased or, it can be decreased.

Historically, a decrease in the pupil block force has been the preferred model and this decrease is achieved by parasympathetic inhibition, either pharmacologically (mydriatic tests—tropicamide) or, physiologically (dark room test). These methods have been shown to be unreliable<sup>3,4</sup> with no predictive value and, furthermore, there is experimental evidence to doubt their validity. To suppose that dark room and mydriatic tests are models of closed angle glaucoma it must be assumed that pupil dilatation is one of the mechanisms that can produce acute closed angle glaucoma. Mapstone<sup>5</sup> tested this assumption by looking at patients who had presented with a *unilateral* closed angle glaucoma. The fellow (unaffected) eye was provoked using a combination of pilocarpine and phenylephrine.<sup>6</sup> If the test was positive (that is a pressure increase of 8 mm Hg or more, together with closure of at least 90 per cent of the angle and a reduction in outflow facility), it was reversed using a combination of Thymoxamine and indentation with a Zeiss gonioscope. At least one week later the same eye was dilated with a parasympatholytic drug (Tropicamide 1 per

cent) and, not one of 24 eyes investigated developed glaucoma in the dilated position. Neither was closed angle glaucoma produced as the pupil moved down, past mid-dilatation to miosis. From these results it necessarily follows that pupil dilatation may, occasionally, produce a closed angle glaucoma but, it is so uncommon in eyes at great risk, that it cannot be regarded as a model of primary acute closed angle glaucoma.

The other side of the coin, increasing the pupil block force, is most readily achieved by simultaneously instilling pilocarpine and phenylephrine. In a positive test the anterior chamber volume decreases by about 20 per cent, the iris lens diaphragm moves forwards and, the iris becomes apposed to cornea and trabecular meshwork producing an acute closed angle glaucoma.

If this test is used in different samples of eyes then peculiar results are obtained. In a sample of 117 normal eyes (without glaucoma or ocular hypertension) no eye developed an acute attack. In 54 eyes, selected because they had narrow angles only, 2 (4 per cent) developed closed angle glaucoma. If, now, the same test is done in eyes with narrow angles *and* ocular hypertension the number of positives increases to 26 per cent (12 of 47). Finally, in fellow eyes (the other eye having presented with spontaneous closed angle glaucoma) the proportion positive is 61 per cent (154 of 253 eyes). There is therefore some characteristic of anterior segments in—particularly—fellow eyes which makes them respond to a pilocarpine and phenylephrine provocative test with some vigour. It cannot be just the anatomical dimensions of the anterior segment for the reason that eyes, selected because of a narrow angle and shallow anterior chamber, rarely developed a

positive response. One possible hypothesis advances the notion that these susceptible anterior segments respond in an unusual fashion to autonomic mediators. The remainder of this paper is concerned with that possibility.

There is no compelling reason for asserting that there is an increased prevalence of diabetes in open angle glaucoma,<sup>7</sup> despite claims to the contrary.<sup>8</sup> There is however no published data concerning the prevalence of diabetes in closed angle glaucoma. Mapstone and Clark<sup>9</sup> following the diagnostic criteria suggested by the WHO (1980), looked at the prevalence of diabetes/impaired glucose tolerance in 316 patients with either open angle glaucoma, closed angle glaucoma or ocular hypertension. The patients were divided into three groups: those with open angle glaucoma or ocular hypertension and wide angles, those with open angle glaucoma or ocular hypertension and narrow angles and, those with closed angle glaucoma. The Table records the results and shows that there was a preponderance of diabetes/impaired glucose tolerance in patients with narrow angles—no matter whether the clinical diagnosis was open angle glaucoma, closed angle glaucoma or ocular hypertension. If the proportion of patients with *narrow* angle eyes,

Table I Group statistics

	Wide angle	Narrow angle	Closed angle
Number	109	101	106
Age:			
Mean	65.1	67.7	67.0
SD	8.3	8.6	9.5
ACD:			
Mean	2.61	2.01	1.87
SD	0.34	0.27	0.28
Diabetes*	9 (2)	17 (8)	20 (4)
IGT	11	11	21
Male/Female	45/64	35/66	32/74

\* The number in brackets equals known diabetics.  
 SD = Standard deviation.  
 ACD = Anterior chamber depth.  
 IGT = Impaired glucose tolerance.

who developed an abnormal response to an oral glucose load, was compared with the proportion in patients with *wide* angle eyes, then there was a highly significant difference between the two ( $\chi^2 = 12.12, p = 0.0005$ ). The anterior chamber depth of each patient was also known and, if the clinical diagnosis was ignored and, the probability of demonstrating an abnormal glucose tolerance test response plotted against anterior chamber depth, then the result is as shown in Fig. 1. There was a highly significant negative linear correlation

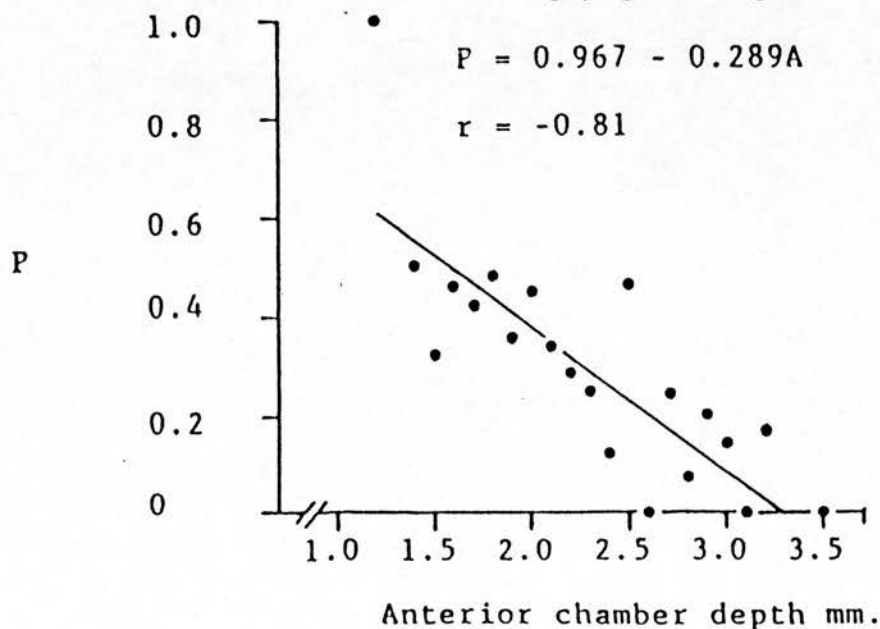


Fig. 1.

between the probability of an abnormal response and anterior chamber depth ( $r = -0.81, p < 0.001$ ). Furthermore, there was no significant difference between the proportion of eyes with narrow angles, who developed an abnormal response, and the proportion in eyes with closed angle glaucoma. There does therefore appear to be an association between diabetes/impaired glucose tolerance and primary glaucoma/ocular hypertension but, the association is not with the disease, rather, it is the anatomical dimensions of the anterior segment of the eye.

One of the consequences of diabetes in man may be an autonomic neuropathy,<sup>11</sup> it is a multi-system disease capable of producing widespread signs and symptoms involving the cardiovascular, respiratory, gastrointestinal and urogenital systems together with involvement of sweat mechanisms and temperature control. Since its first description the literature has become voluminous and, during the past decade or so, attention has been directed to the diagnosis of this entity using simple, non-invasive bedside tests.<sup>11,12,13,14</sup> All of the commonly used tests utilise cardiovascular reflexes and, if an abnormality is demonstrated, it is inferred that other parts of the autonomic nervous system are involved too. Each test depends upon a stimulus contrived by the clinician, this in turn is processed by the central nervous system; and, the reflex response measured—either a change in heart rate or blood pressure.

Five tests are used routinely, in three of which the effect upon heart rate is measured and, in the other two, a change in blood pressure. If an abnormality is found in any one of the three tests which monitor heart rate (response to a Valsalva manoeuvre, to deep breathing and to a positional change from lying to standing) then a neuropathy involving the parasympathetic supply to the heart is inferred.<sup>15</sup> Conversely, if an abnormality is found in the blood pressure response to the remaining two tests (postural fall in blood pressure in response to standing, blood pressure response to a sustained hand grip) then a neuropathy involving the sympathetic innervation to blood pressure control mechanisms is inferred. Sufficient experience has now been obtained with these tests to indicate

that autonomic neuropathy is more widespread in diabetics than symptoms would suggest,<sup>15</sup> with parasympathetic tests being more commonly abnormal than those involving the sympathetic.

Clark and Mapstone<sup>16</sup> applied five tests of autonomic function (Valsalva ratio, heart rate variation during deep breathing, immediate heart rate response to standing, immediate heart rate response to lying and change in systolic blood pressure on standing) to 112 patients who had presented with primary acute closed angle glaucoma and to 74 age and sex matched controls. The results are recorded in Tables II and III. From these results it is clear that patients who have developed closed angle glaucoma also demonstrate a very high prevalence of autonomic neuropathy, 58 per cent in the glaucoma group, 7 per cent in the control— $\chi^2 = 25.7, p < 0.001$ .

The relevance of these findings to the aetiology of narrow angle glaucoma derives from the consequences of an interruption in the autonomic nerve supply to a tissue. Two diseases with which ophthalmologists are familiar are Horner's and Adies syndromes. Both are characterised by autonomic denervation and both demonstrate a supersensitivity to exogenously applied or endogenously released autonomic mediators. So, by extension, the obvious question is—do the anterior segments of patients with diabetes also exhibit a denervation supersensitivity to autonomic drugs?

Gunderson<sup>17</sup> showed that the pupil of long term diabetics showed an absence of hippus together with small pupils and abnormalities of the light reflex. Findings which were confirmed by Smith *et al.*<sup>18</sup> who also demonstrated that the pupillary abnormalities were accompanied by signs of systemic autonomic neuropathy. In 1974 Sigsbee *et al.*<sup>19</sup> demonstrated in diabetics, a pupillary sensitivity to topical methacholine which varied directly with the degree of peripheral neuropathy. Hayashi and Ishikawa<sup>20</sup> investigated the response of diabetics with varying degrees of retinopathy to a number of different drugs, including methacholine and adrenaline. They concluded that their results signified a denervation supersensitivity to both sympathetic and

**Table II** Results of Cardiovascular Autonomic Function Assessment in 112 Patients with Angle-Closure Glaucoma and 74 Age- and Sex-Matched Control Subjects (Group mean values  $\pm$  SEM)

	Angle-closure group	Control group	Significance
<i>1. Parasympathetic function</i>			
i. Valsalva ratio	1.41 $\pm$ 0.03	1.49 $\pm$ 0.04	p > 0.05
ii. Heart-rate variation during deep breathing (beats/minute)	11.87 $\pm$ 0.73	17.85 $\pm$ 0.90	p < 0.001
iii. Immediate heart-rate response to standing (30:15 ratio)	1.11 $\pm$ 0.01	1.17 $\pm$ 0.01	p < 0.001
iv. Immediate heart-rate response to lying (S:L ratio)	1.15 $\pm$ 0.01	1.20 $\pm$ 0.01	p < 0.01
<i>2. Sympathetic function</i>			
Decrease in systolic blood-pressure on standing (mm Hg)	11.11 $\pm$ 1.22	8.12 $\pm$ 1.50	p > 0.05

**Table III** Classification of Autonomic Status

	Normal	Early parasympathetic neuropathy	Definite parasympathetic neuropathy	Parasympathetic plus sympathetic neuropathy
Angle-closure group (n = 112)	47 (42%)	36 (32.1%)	18 (16.1%)	11 (9.8%)
Control group (n = 74)	69 (93.2%)	4 (5.4%)	0	1 (1.4%)

parasympathetic agonist, with the sympathetic component more frequently involved. The evidence therefore seems compelling that the diabetic pupil is partly denervated and shows a supersensitivity to the action of exogenously applied autonomic agonists.

The reason why the fellow eye shows a 60

per cent positive response to topically applied pilocarpine and phenylephrine may, in part, be explained by the presence of a denervation supersensitivity. A necessary consequence is that narrow angle glaucoma is a presenting symptom of Type 2 diabetes—in fact a sick eye within a sick body.

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PAPER 3

AGE-ADJUSTED NORMAL TOLERANCE LIMITS FOR CARDIOVASCULAR AUTONOMIC FUNCTION  
ASSESSMENT IN THE ELDERLY

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## SUMMARY

Autonomic nerve function was assessed in 85 normal subjects (mean age  $66.1 \pm 10.2$  years) by a series of standard tests based upon cardiovascular reflexes. Age-adjusted normal tolerance intervals were established for each test. The clinical application of autonomic function assessment in the elderly is discussed, with particular reference to patients with diabetes mellitus, ocular hypertension, and primary glaucoma, which represent a significant proportion of the aged population.

## INTRODUCTION

Autonomic nerve function is postulated to decline with age; postural hypotension, reflecting impairment of the sympathetic nervous system, is significantly related to age (1), and recent evidence has suggested a similar progressive impairment of parasympathetic nerve function (2). Evaluation of autonomic efficacy is an important clinical test in two major categories within the elderly population: in diabetes mellitus, the commonest cause of autonomic neuropathy in this country (3), and in subjects with ocular hypertension, present in 9% of the population (4). Diabetes mellitus is estimated to affect 6% of all adults in Europe and the USA, the prevalence of diabetes (known or occult) rising to 16% in those aged 65 and over (5). Autonomic function is an important prognostic indicator in these patients; 50% of diabetic patients with cardiovascular autonomic dysfunction and symptoms of autonomic failure have a life expectancy of less than three years (6). In ocular hypertension, parasympathetic neuropathy is present in 42% of subjects (mean age  $66.0 \pm 9.5$  years) compared with 3% of an age- and sex-matched control group (7).

Autonomic insufficiency has an insidious onset, which is impossible to identify accurately due to the compensatory mechanisms inherent within the autonomic nervous system. Until comparatively recently, tests of autonomic nerve function have been difficult to interpret and virtually impossible to quantify. The recent development of non-invasive autonomic assessment, based upon cardiovascular reflexes, permits accurate, objective and reproducible measurement of autonomic function (8,9). As in all reflex assessments, this

depends upon a standardised input stimulus, coupled with measurement of the subject's output reaction. Results are based on blood pressure and heart-rate responses to a variety of stimuli. A necessary corollary is that detected abnormalities cannot be localised to either the afferent, internuncial, or efferent components of the reflex. There is considerable evidence that autonomic assessment by cardiovascular reflex responses correlates well with generalised autonomic function (10). Five autonomic function tests were used to assess systemic autonomic status. Although each test has been used individually to give a measure of autonomic function, assessment based upon a series of complementary tests has been advocated by Ewing and Clarke (1982) to preclude misleading deductions from single tests (9). This provides a comprehensive assessment of both sympathetic and parasympathetic function. The present study establishes effective tolerance limits of cardiovascular autonomic nerve function in older age categories.

## PATIENTS AND METHODS

After informed consent had been obtained, cardiovascular autonomic function was assessed in 85 'normal' subjects (mean age  $66.1 \pm 10.2$  years); these were attending for refraction, or had been referred by an optician for an ophthalmological opinion. No detectable abnormality was present in all subjects, following comprehensive ocular assessment. As attendance for routine refraction in an older age group, with progressively-increasing presbyopia, is normal, this represents a self-selected control sample with no subjective bias.

A detailed past history was obtained from each subject. Subjects known to have medical disorders predisposing to autonomic nerve dysfunction or taking medication with effects on the autonomic nervous system were excluded from the study. Systematic general medical examination was then performed, with emphasis on:

- i. Cardiovascular system: to exclude subjects with cardiovascular pathology; valvular disorders, such as mitral stenosis and congestive cardiac failure, are particularly relevant as these may adversely affect cardiovascular autonomic reflexes.
- ii. Central and peripheral nervous system: with assessment of sensory and motor somatic nerves, and cerebellar function.

Subjects with significant cardiovascular or neurological abnormalities were excluded from autonomic function assessment; this included any form of 'stroke' or cardiovascular accident, which may effectively negate cardiovascular reflexes.

Five tests of autonomic integrity were employed. Determination of normal sinus rhythm is an essential prerequisite to cardiovascular autonomic nerve function assessment.

A. Parasympathetic nerve function

i. Valsalva manoeuvre

A standardised Valsalva manoeuvre was performed by the subject blowing into a mouthpiece connected to a modified sphygmomanometer and maintaining a pressure of 40 mmHg (5.3 kPa) for 15 seconds. A continuous electrocardiogram was recorded, commencing 20 seconds prior to the manoeuvre and terminating 25 seconds after the manoeuvre. The subjects were seated during the test, and rested for at least 2 minutes between consecutive assessments. The Valsalva ratio is the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the test. These were measured directly from the electrocardiogram, and the final ratio was the mean of three consecutive assessments. There are four phases in the heart-rate responses to this test:

Phase 1: initial relative bradycardia for 2-3 seconds

Phase 2: gradually-increasing tachycardia

Phase 3: increased tachycardia for 2-3 seconds on release of intrathoracic pressure

Phase 4: bradycardia

The Valsalva ratio represents the ratio of the longest R-R interval in phase 4 divided by the shortest R-R interval in phase 2.

ii. Heart-rate variation during deep breathing

The subject was seated quietly at rest for 3 minutes prior to the test, then requested to breathe deeply at a rate of approximately 6 breaths per minute (5 seconds inspiration, 5 seconds expiration) whilst a continuous electrocardiogram was recorded. In normal subjects, a relative tachycardia occurs during inspiration, with a relative bradycardia in expiration. Maximum and minimum R-R intervals were measured directly from the electrocardiogram using an ECG ruler, and expressed as beats per minute. 6 consecutive measured cycles were calculated, and the final result was the mean of the differences between maximum and minimum heart-rates.

iii. Immediate heart-rate response to standing

During alteration in posture from lying to standing a characteristic cardiovascular reflex response occurs under vagal control. This consists of an initial increase in heart-rate, maximal at about the 15th beat after standing, followed by a relative bradycardia around the 30th beat. The subject rested supine for approximately 3 minutes prior to the test, then was requested to stand unaided. An electrocardiogram was recorded from 20 beats prior to the manoeuvre until 40 beats after standing. The R-R intervals were measured to determine the shortest around the 15th beat and longest at about beat 30, and the result expressed as the 30:15 ratio.

iv. Immediate heart-rate response to lying

Shortening of the R-R interval occurs during the 3rd-4th beat after

commencing the manoeuvre, followed by a gradual increase in R-R interval. Subjects were requested to stand for 2 minutes, then lie down unaided. Heart-rate was recorded by continuous electrocardiography from 20 beats prior to the manoeuvre until 20 beats after lying down. The results were calculated as the ratio of the longest R-R interval during the 5 beats before lying to the shortest R-R interval during the 10 beats after lying down, and the result expressed as the standing:lying ratio (S:L ratio).

#### B. Sympathetic nerve function

##### Systolic blood pressure response to standing

After 5 minutes lying supine on an examination couch, the subject's blood pressure was measured using a cuff sphygmomanometer, then again immediately after standing upright. The difference between the systolic pressure lying and standing is the postural change in blood pressure.

## RESULTS

Age-adjusted normal tolerance intervals for cardiovascular autonomic function tests were calculated by the following method. The results of each test of cardiovascular autonomic nerve function in 85 normal subjects were assessed for dependence on age by regression analysis. The data were fitted according to various mathematical models using the computer programme SPSSx on an IBM 4341 computer to obtain a normal distribution after adjustment for age, thus permitting determination of the 'normal' range. Logarithms of the data were used to derive a tolerance interval for the following reasons:

- i. Logarithms (after adjusting for age) are more nearly normally distributed than original readings, thus reducing skewness.
- ii. Tolerance limits on  $y = \log(x)$ , after age-adjustment, must always give positive values of  $x$  after transforming back to the original units, as  $e^y$  or  $10^y$  are always positive.

Plots of the logarithmic values on age were linear, allowing the 2.5th, 5th, 95th, and 97.5th percentiles to be calculated by linear regression analysis:

$$r_s = \frac{y - (a + bx)}{s_{y|x}}$$

$r_s$  = standardised residual

$s_{y|x}$  = residual standard deviation

A log normal distribution was obtained for the results of each of the cardiovascular autonomic function tests, except systolic blood pressure response to standing; as postural changes in blood pressure may include negative values, a logarithmic distribution

could not be described and thus a distribution based upon natural values was described. Tolerance limits were calculated from the log normal distribution (after adjusting for age) for all variables except systolic blood pressure response to standing; the latter was calculated from natural values.

i. In variables which did not depend significantly on age, tolerance limits were obtained by:

mean  $\pm$  1.67 SD (for 90% limits)

mean  $\pm$  2.00 SD (for 95% limits)

The values 1.67 and 2.00 were obtained from percentiles of  $t$  at 60 degrees of freedom.

ii. In variables which depended significantly on age, tolerance limits were obtained by:

a. Linear regression of  $\log_{10}(\text{variable})$ , or of systolic blood pressure response to standing untransformed, was performed on age to give:

$$\hat{y} = a + bx$$

$$\text{Residual} = y - \hat{y}$$

b. Tolerance limits from:

$$y \pm 1.67 \times s_{y|x} \quad (\text{for 90\% limits})$$

$$y \pm 2.00 \times s_{y|x} \quad (\text{for 95\% limits})$$

where  $s_{y|x}$  is the residual standard deviation after regression.

Translating back from the transformation yields the 'normal range' for each of the cardiovascular autonomic function tests.

A. Parasympathetic nerve function

i. Valsalva ratio

$\log_{10}$ (Valsalva ratio) was shown to depend significantly on age.

Linear regression analysis was calculated from:

$$RLVR = (\log_{10}VR - (0.43359 - 0.00409 \times \text{age}))/0.06960$$

$$RLVR = \text{standardised residual } \log_{10}VR$$

Tolerance limits (at the 2.5th, 5th, 95th, and 97.5th percentiles) are shown in figure 1.

ii. Heart-rate variation during deep breathing

$\log_{10}$ (heart-rate variation during deep breathing) was shown to depend significantly on age. Linear regression analysis was calculated from:

$$RLHRV = (\log_{10}HRV - (1.49598 - 0.00397 \times \text{age}))/0.16415$$

$$RLHRV = \text{standardised residual } \log_{10}(HRV)$$

Tolerance limits (at the 2.5th, 5th, 95th, and 97.5th percentiles) are shown in figure 2.

iii. 30:15 ratio

$\log_{10}$ (30:15 ratio) did not depend significantly on age. Linear regression analysis was calculated from:

$$RL30:15 \text{ ratio} = (\log_{10}30:15 \text{ ratio} - (0.08869 - 0.00031 \times \text{age}))/0.03751$$

$$RL30:15 \text{ ratio} = \text{standardised residual } \log_{10}(30:15 \text{ ratio})$$

Tolerance limits (at the 2.5th, 5th, 95th, and 97.5th percentiles) are shown in figure 3.

iv. Standing:lying ratio

$\log_{10}$ (S:L ratio) did not depend significantly on age. Linear

regression analysis was calculated from:

$$\text{RLS:L ratio} = (\log_{10} \text{S:L ratio} - (0.08535 - 0.00008 \times \text{age})) / 0.03191$$

$$\text{RLS:L ratio} = \text{standardised residual } \log_{10}(\text{S:L ratio})$$

Tolerance limits (at the 2.5th, 5th, 95th, and 97.5th percentiles) are shown in figure 4.

#### B. Sympathetic nerve function

Systolic blood pressure response to standing

Systolic blood pressure response to standing was shown to depend significantly on age. Linear regression analysis was calculated from:

$$\text{RPH} = (\text{PH} - (-6.12798 + 0.21258 \times \text{age})) / 12.56912$$

PH = postural hypotension (or systolic blood pressure response to standing)

RPH = standardised residual (postural hypotension)

Tolerance limits (at the 2.5th, 5th, 95th, and 97.5th percentiles) are shown in figure 5.

## DISCUSSION

The utilisation of cardiovascular reflexes to define systemic autonomic function provides an accurate, reproducible, and quantifiable measurement of a nervous system previously virtually impossible to isolate. Heart-rate is determined at all times by the balance between sympathetic and parasympathetic influences; the relative importance of each component during characteristic cardiovascular reflexes has been determined by selective pharmacological autonomic blockade (11,12).

Heart-rate variation during deep breathing, in the form of the E:I ratio, has been examined by Smith (13), and Wieling et al have proposed normal tolerance intervals for maximum:minimum heart-rate differences during deep breathing (14) - although the latter study had an upper age limit of 65 years. Recently, an age-related normal range for Valsalva ratio has been described (15), however reference values for other parameters of autonomic nerve function are applicable to a younger age category. Tolerance limits for the results of each of the five tests of cardiovascular autonomic function (at age 65 years) are shown in table 1. Valsalva ratio, heart-rate variation during deep breathing, and systolic blood pressure response to standing were significantly correlated with age; consequently, tolerance limits based on the lower 5th percentile are shown in those categories relative to the mean age of the control group. If the tolerance limits of autonomic function assessment for these elderly subjects are compared with those advocated for younger age categories, remarkable similarities are apparent. In the following

list, the tolerance limits of the present study are compared with established diagnostic criteria of abnormality in a younger age range (9): Valsalva ratio, 1.13 cf 1.10; heart-rate variation during deep breathing (beats/minute), 9.2 cf 10.0; 30:15 ratio, 1.01 cf 1.00; S:L ratio, 1.06 cf 1.07; decrease in systolic blood pressure on standing (mmHg), 29.4 cf 30.0. The assessment of cardiovascular autonomic nerve function is thus equally possible in the elderly population; verification of tolerance limits, based on the lower 5th percentile, permits reasonable inferences from subsequent comparisons with 'normal' values.

The importance of autonomic function assessment in the clinical management of diabetes mellitus is well-established. Autonomic neuropathy occurs as a secondary complication of diabetes, in contrast to the primary glaucomas, where autonomic neuropathy is postulated to be a significant predisposing factor in the pathogenesis of both ocular hypertension and closed-angle glaucoma - diseases primarily of the aged; recent studies have shown a mean age of  $66.0 \pm 9.5$  years in ocular hypertension (7), and  $66.5 \pm 10.1$  years in closed-angle glaucoma (17). Reference tolerance limits for autonomic nerve function in the elderly are therefore essential; the present study has established effective tolerance limits for cardiovascular autonomic function assessment, permitting clinical determination of autonomic dysfunction in the age category particularly predisposed to this disorder.

## ACKNOWLEDGEMENT

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Figure 1

AGE-ADJUSTED NORMAL TOLERANCE INTERVALS FOR VALSALVA RATIO

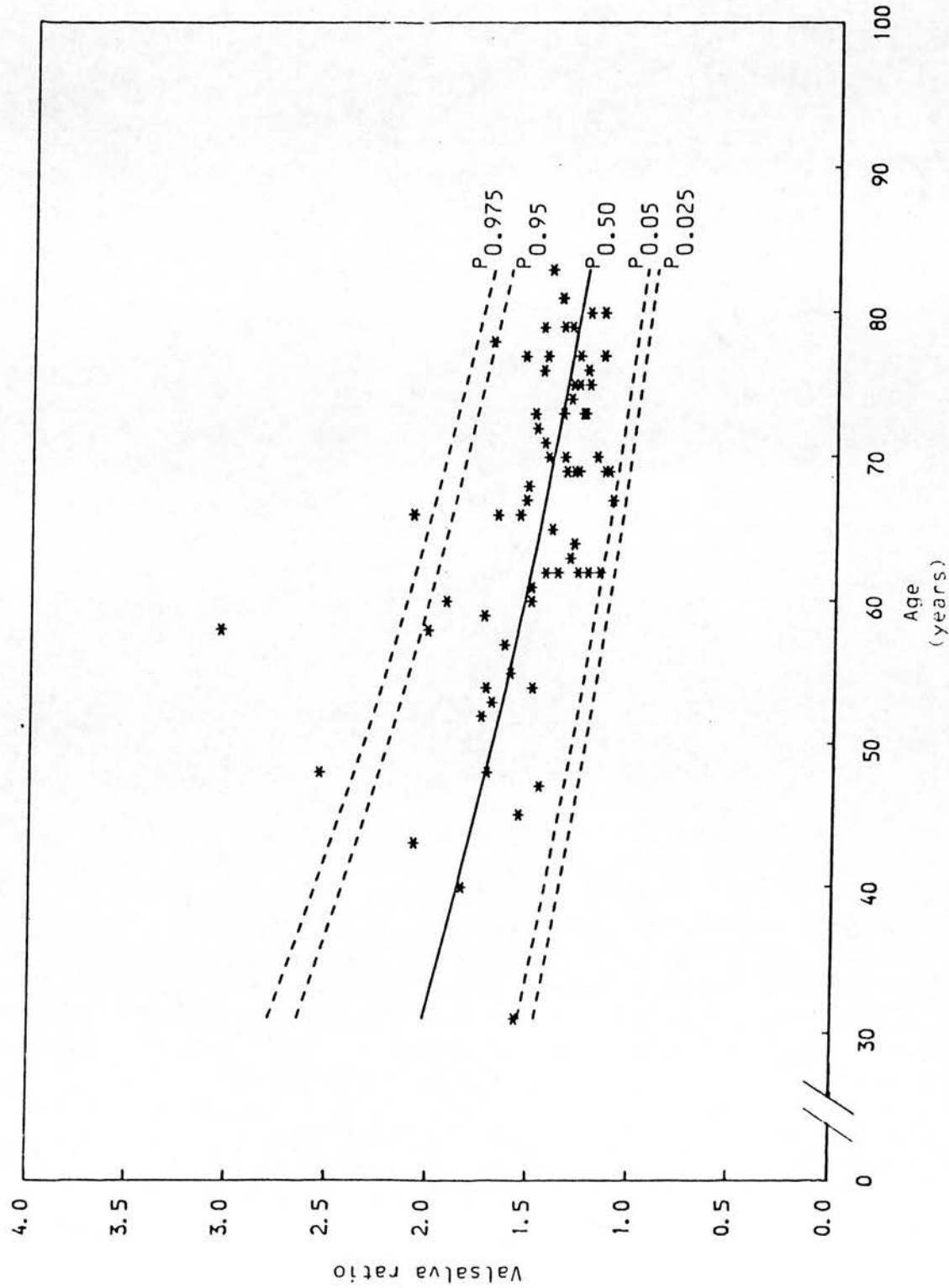


Figure 2

AGE-ADJUSTED NORMAL TOLERANCE INTERVALS FOR HEART-RATE VARIATION DURING DEEP BREATHING

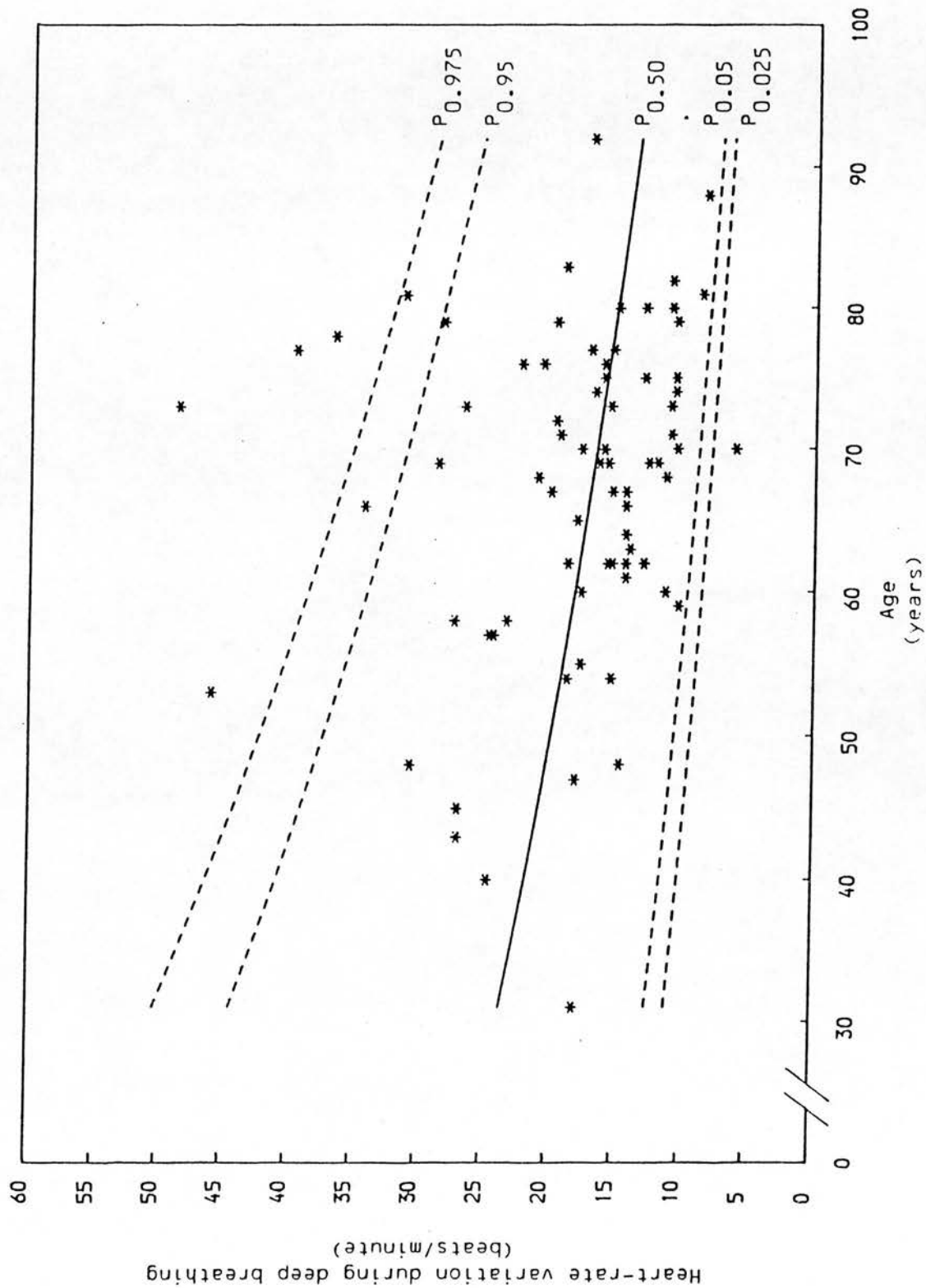


Figure 3

AGE-ADJUSTED NORMAL TOLERANCE INTERVALS FOR 30:15 RATIO

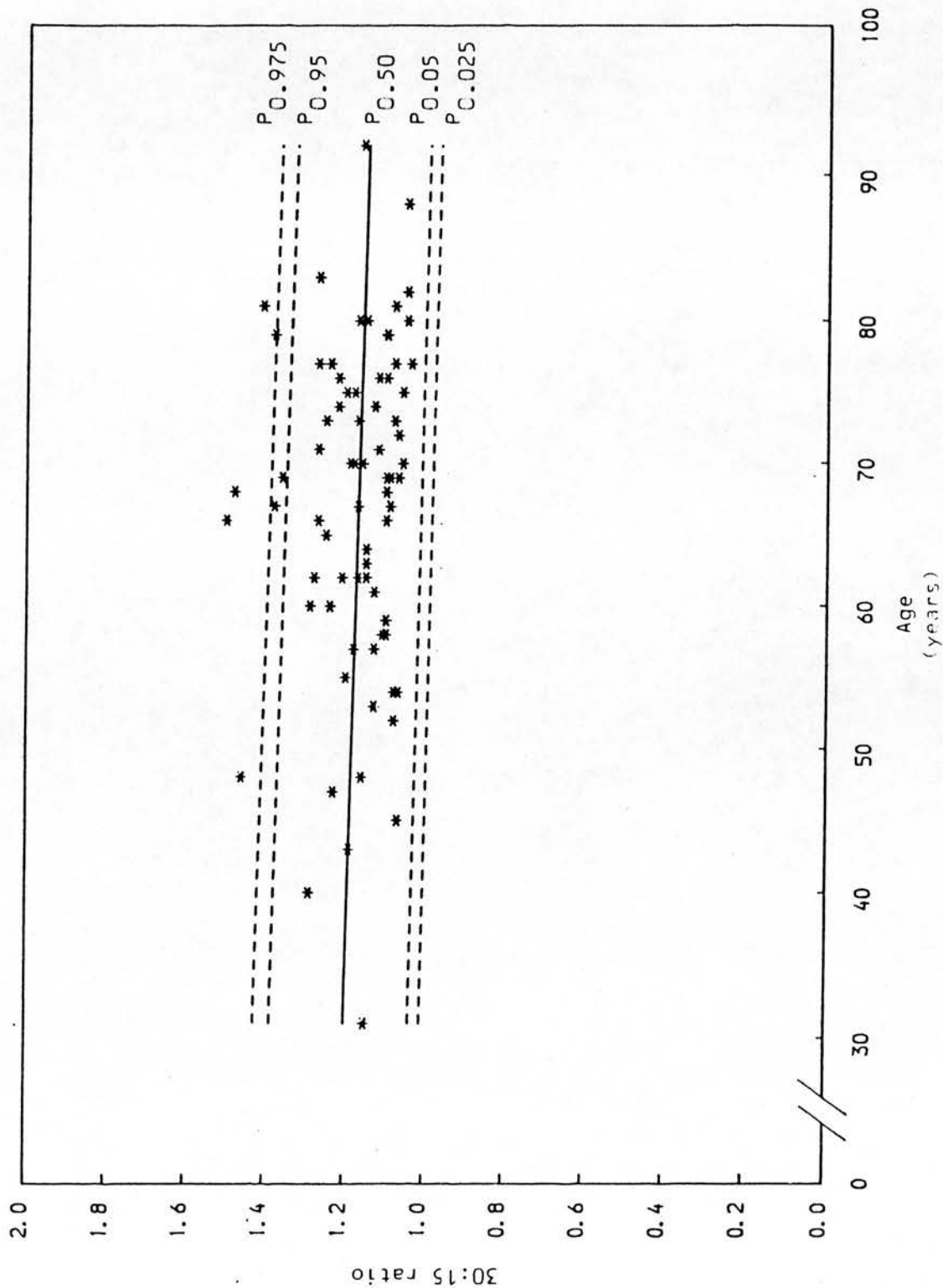


Figure 4

AGE-ADJUSTED NORMAL TOLERANCE INTERVALS FOR S:L RATIO

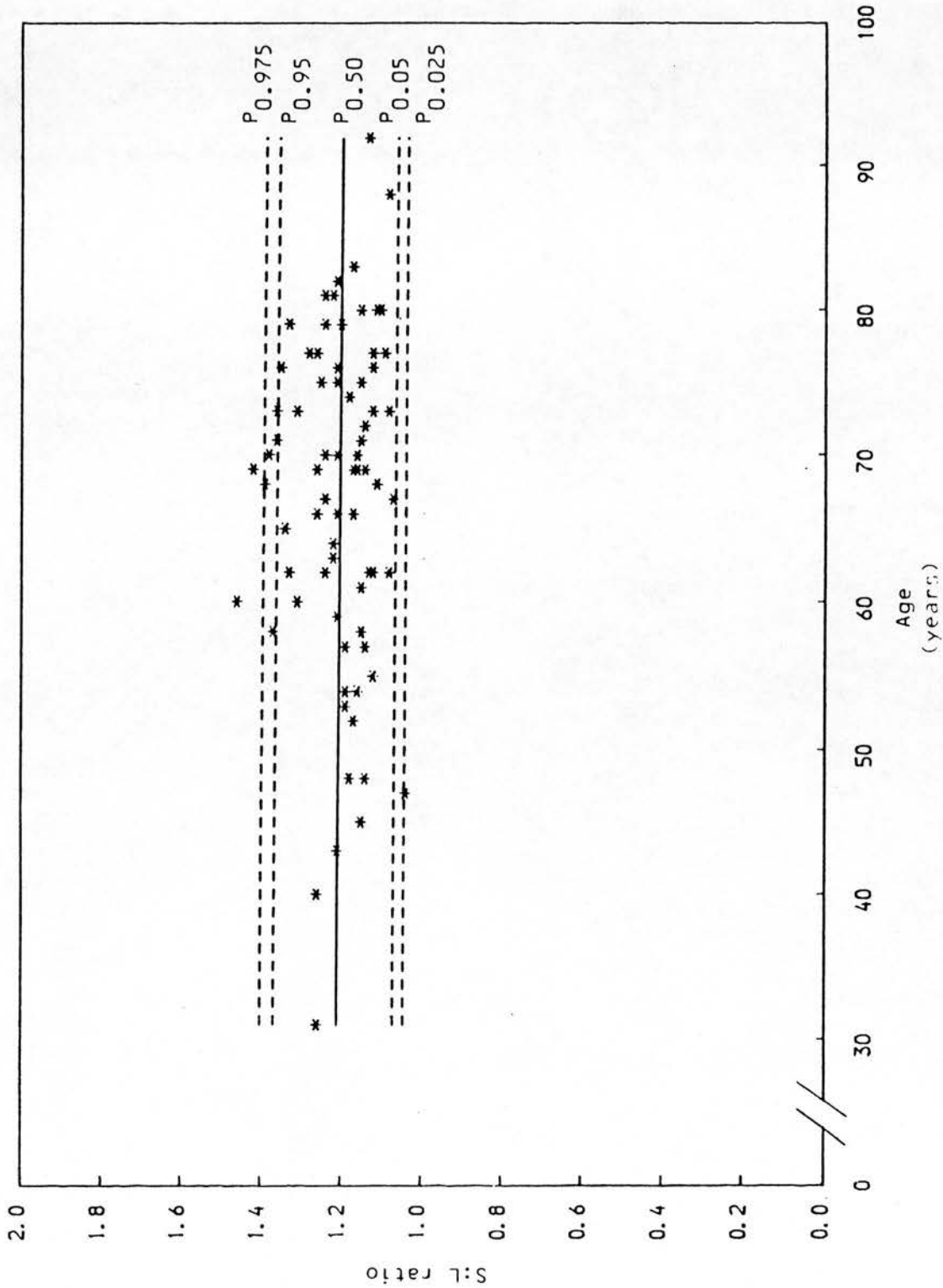


Figure 5  
 AGE-ADJUSTED NORMAL TOLERANCE INTERVALS FOR SYSTOLIC BLOOD PRESSURE  
 RESPONSE TO STANDING

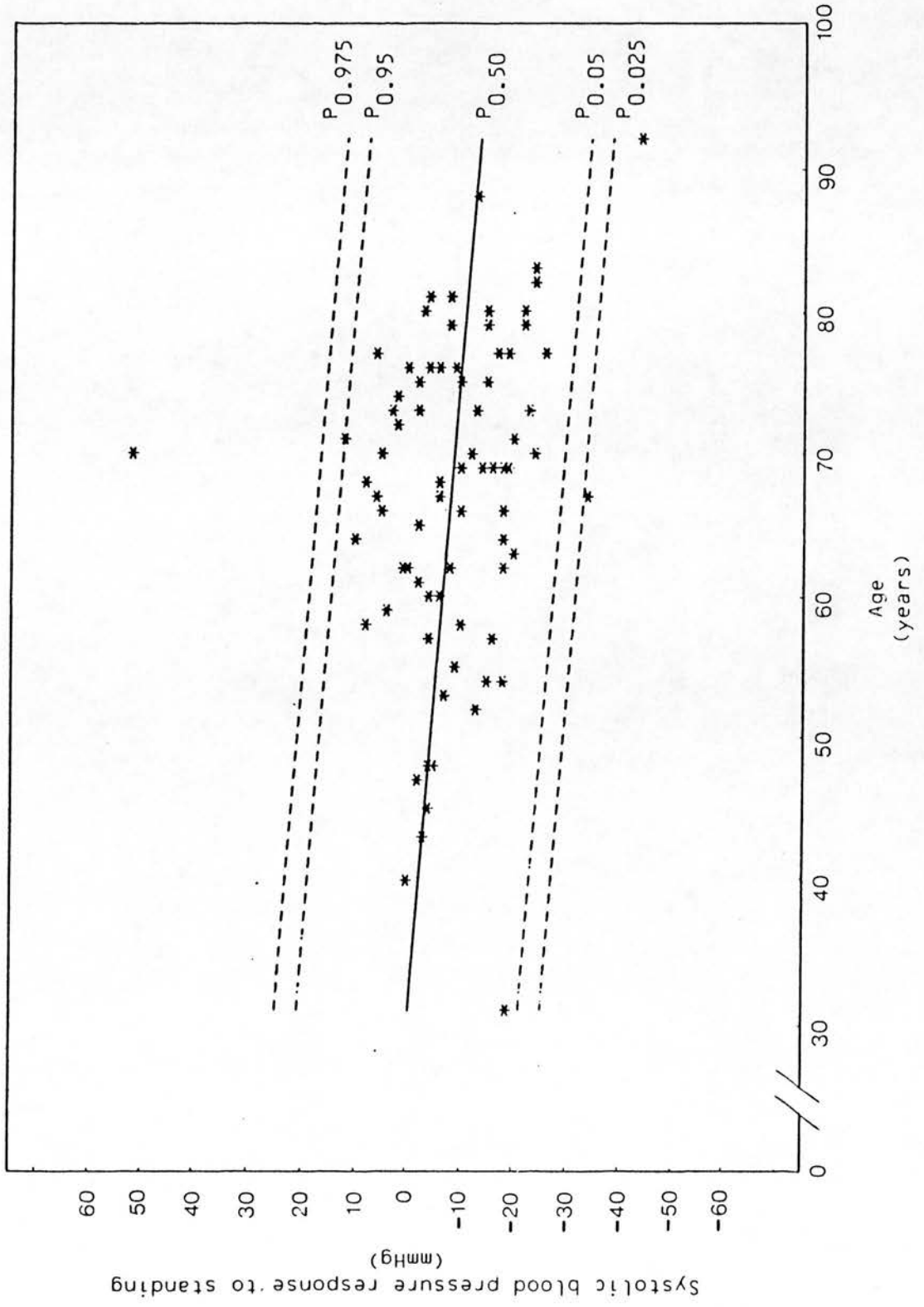


Table 1

AGE-ADJUSTED NORMAL TOLERANCE LIMITS (AT AGE 65 YEARS), DEFINED BY THE LOWER 5th PERCENTILE, FOR CARDIOVASCULAR AUTONOMIC FUNCTION TESTS

	Abnormal
<u>Parasympathetic function</u>	
i. Valsalva ratio	< 1.13
ii. Heart-rate variation during deep breathing (beats/minute)	< 9.20
iii. 30:15 ratio	< 1.01
iv. S:L ratio	< 1.06
<u>Sympathetic function</u>	
Decrease in systolic blood pressure on standing (mmHg)	> 29.38

PAPER 4

### Discussion

Antigen-induced inhibition of leucocyte migration has been widely accepted as an in-vitro correlate of cellular immunity. There is much evidence that cell-mediated immunity to gluten may be responsible for mucosal lesions in coeliac disease. Ferguson et al<sup>4</sup> have suggested that there are lymphocytes which are sensitised to  $\alpha$ -gliadin in untreated coeliac mucosa, and upon exposure to gliadin they release an increased amount of LIF. Consequently,  $\alpha$ -gliadin and its different fragments show an inhibitory effect on leucocyte migration in coeliac patients, though this effect seems to vary in degree depending on the presence or absence of gluten in the diet.<sup>7,8,13,14</sup> Ashkenazi et al,<sup>8</sup> for example, have found that "removal of gluten from the patient's diet for a year or more leads to conversion of a LIF-positive response to a negative one in about 50% of patients", and that "subsequent challenge with gluten can reconvert the negative response to a positive one". Since 12 of our patients had been on a gliadin-free diet for 6–12 months when first tested, and the other 12, after being on a gliadin-free diet for a year, had been taking a normal diet for only a short period, the moderately low percentage (37.5%) of gliadin-sensitive patients is consistent with the data of Ashkenazi et al<sup>8</sup> and other works.<sup>5,7,13,14</sup>

The exciting result of this study is that in all gliadin-sensitive patients, irrespective of their dietary status, naloxone reversed the effect of gliadin on leucocyte migration. These data, together with the gliadin-like effect of morphine on leucocyte migration, strongly suggest that opioid-like receptors on the sensitised lymphocytes might mediate the gliadin effect. Attempts to correlate the opioid-

like activities of different isolated  $\alpha$ -gliadin fragments with their effects on leucocyte migration in patients with coeliac disease are being undertaken.

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### AUTONOMIC NEUROPATHY IN OCULAR HYPERTENSION

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**Summary** By means of a series of cardiovascular autonomic function tests, systemic parasympathetic neuropathy was demonstrated in 41.8% of 189 patients with ocular hypertension and in 2.6% of 76 controls. Parasympathetic neuropathy was significantly more common in patients with narrow-angle hypertension than in those with wide-angle hypertension. Raised intraocular pressure may be a manifestation of systemic disease rather than an exclusively ocular phenomenon.

### Introduction

INTERMITTENT partial angle closure has been proposed as a factor in the pathogenesis of primary ocular hypertension; during provocation testing with guttae pilocarpine and phenylephrine, 40% of patients with ocular hypertension exhibited partial angle closure, with complete angle closure (ie, overt closed-angle glaucoma) in a further 6%.<sup>1</sup> The essential anterior-segment event precipitating iridocorneal contact, and therefore angle closure, is thought to be a change in parasympathetic tone.<sup>2</sup> This is supported by the demonstration of systemic parasympathetic neuropathy in 58% of patients with closed-angle glaucoma.<sup>3</sup>

The development of non-invasive tests based on cardiovascular reflexes has allowed accurate measurement of systemic autonomic nerve function.<sup>4–8</sup> The assessments are based on blood-pressure and heart-rate responses to a variety

of standardised stimuli. Cardiovascular autonomic reflexes probably reflect generalised autonomic nerve function.<sup>9</sup>

### Patients and Methods

189 patients with ocular hypertension (mean age 66.0±9.5 years) and 76 control subjects matched for age and sex (mean age 67.1±11.5 years) took part in the study. 90 had narrow iridocorneal angles and 99 had wide angles; angle assessment was made according to the Shaffer angle-grading system.<sup>10</sup> The control subjects were hospital-staff and patients attending the casualty department who were subsequently found to have no detectable abnormality. Subjects known to have medical disorders predisposing to autonomic nerve dysfunction or taking medication with effects on the autonomic nervous system were excluded.

Normal sinus rhythm was confirmed before assessment of cardiovascular autonomic function. The subjects' status was not revealed at the time of assessment.

### Tests of Parasympathetic Nerve Function

**Valsalva manoeuvre.**—The subject is asked to blow into a mouth-piece connected to a modified sphygmomanometer and to maintain a pressure of 40 mm Hg for 15 s. A continuous electrocardiogram is recorded, starting 20 s before the manoeuvre and ending 25 s after termination. The Valsalva ratio is the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the test. These are measured directly from the electrocardiogram, and the final ratio is taken as the mean of three consecutive assessments. There are four discrete phases in the heart-rate and blood-pressure responses to this test. Heart rate slows initially (phase 1) but then speeds up in response to reduced venous return and the resulting fall in blood-pressure (phase 2). Acute release of intrathoracic pressure on termination of the manoeuvre causes increased tachycardia as the subsequent rise in pulmonary venous capacitance precipitates a further fall in cardiac output (phase 3). This is followed by bradycardia in phase 4, a baroreflex response to increased cardiac output

TABLE I—CARDIOVASCULAR AUTONOMIC FUNCTION IN PATIENTS WITH OCULAR HYPERTENSION AND CONTROL SUBJECTS ( $\pm$ SEM)

	Ocular hypertension group (n = 189)	Control group (n = 76)	Significance
<i>Parasympathetic function:</i>			
Heart-rate variation during deep breathing (beats/min)	13.13 $\pm$ 0.55	18.32 $\pm$ 0.92	p<0.01
30:15 ratio	1.13 $\pm$ 0.01	1.17 $\pm$ 0.01	p<0.01
S:L ratio	1.19 $\pm$ 0.01	1.21 $\pm$ 0.01	p>0.05
Valsalva ratio	1.41 $\pm$ 0.02	1.49 $\pm$ 0.04	p>0.05
<i>Sympathetic function:</i>			
Fall in systolic BP on standing (mm Hg)	11.14 $\pm$ 0.98	8.14 $\pm$ 1.48	p>0.05

occurring during a period of raised peripheral vascular resistance.

*Heart-rate variation during deep breathing.*—Respiratory sinus arrhythmia is most conveniently assessed by means of continuous electrocardiographic recording of heart rate during deep breathing, at a rate of approximately 6 breaths per minute. In normal subjects a relative tachycardia occurs during inspiration and a relative bradycardia in expiration. Maximum and minimum R-R intervals are measured and expressed as beats per minute. The final result is the mean of the differences between maximum and minimum heart-rates over 6 measured cycles. This reflex depends on an intact parasympathetic nerve supply.

*Immediate heart-rate response to standing.*—Change in posture from lying to standing evokes a characteristic cardiovascular reflex response under vagal control; an initial tachycardia, maximum at about the 15th beat after standing, is followed by a relative bradycardia around the 30th beat. The patient rests supine for approximately 3 min before the test, then stands unaided. Heart-rate changes are recorded by continuous electrocardiography from 20 beats before the manoeuvre until 40 beats after standing. The R-R intervals are measured to determine the shortest (around the 15th beat) and longest (at about beat 30), and the result is expressed as the 30:15 ratio.

*Immediate heart-rate response to lying.*—The subject stands for 2 min then lies down unaided, while a continuous electrocardiogram is recorded. An initial shortening of the R-R interval, representing a relative tachycardia, occurs 3–4 beats after lying down and is followed by a gradual lengthening of the R-R interval. The results are expressed as the ratio of the longest R-R interval during the 5 beats before lying down to the shortest R-R interval during the 10 beats after lying down (S:L ratio).

#### Tests of Sympathetic Nerve Function

Several cardiovascular reflexes are initiated by change in posture from the supine to the standing position. A fall in blood-pressure is precipitated by gravitational pooling of blood in the lower extremities. The intact baroreflex arc rapidly reverses this tendency, effecting peripheral and splanchnic vasoconstriction via sympathetic efferent nerves. The patient's blood-pressure is measured after 3 min resting supine on an examination couch, then again immediately after standing. The difference between the systolic pressure lying and standing is the postural change in blood-pressure.

TABLE II—CARDIOVASCULAR AUTONOMIC FUNCTION IN NARROW AND WIDE ANGLE OCULAR HYPERTENSION (MEAN $\pm$ SEM)

	Narrow angles	Wide angles
<i>Parasympathetic function:</i>		
Heart-rate variation during deep breathing (beats/min)	11.57 $\pm$ 0.74*	14.54 $\pm$ 0.77*
30:15 ratio	1.12 $\pm$ 0.01	1.13 $\pm$ 0.01
S:L ratio	1.17 $\pm$ 0.01	1.20 $\pm$ 0.01
Valsalva ratio	1.36 $\pm$ 0.03	1.45 $\pm$ 0.03
<i>Sympathetic function:</i>		
Fall in systolic blood-pressure on standing (mm Hg)	11.53 $\pm$ 1.43	10.77 $\pm$ 1.36

\*Significance of difference narrow angles *v* wide angles, p<0.01.

#### Statistical Analysis

The significance of differences between the control group and the ocular-hypertension group was assessed with Student's unpaired *t* test. Dunnett's multiple comparison procedure<sup>11</sup> was applied to the levels of significance thus obtained, to avoid inaccuracy from multiple comparisons with a control. Dunnett's tables extend only to a maximum joint confidence coefficient of 99%, and every value of p<0.01 will be included within this category.

#### Results

1304 tests were done on 265 subjects. Abnormal values, determined by previous observers, are as follows:

##### Cardiovascular Autonomic Function Tests: Abnormal Values

<i>Parasympathetic function</i>	
Valsalva ratio	<1.10
Heart-rate variation during deep breathing	<10.0 beats/min
30:15 ratio	<1.00
S:L ratio	<1.07
<i>Sympathetic function</i>	
Blood-pressure fall on standing	>30.0 mm Hg

According to these criteria, the subjects fell into three categories: normal, parasympathetic nerve dysfunction, and parasympathetic plus sympathetic nerve dysfunction.

The results of cardiovascular autonomic function assessment in 189 patients with ocular hypertension and 76 control subjects are shown in table I. There were no significant differences between the two groups in Valsalva ratio (p>0.05), S:L ratio (p>0.05), or postural hypotension (p>0.05). However, the two groups differed significantly in heart-rate variation during deep breathing (p<0.01) and 30:15 ratio (p<0.01).

Patients with narrow iridocorneal angles showed a higher prevalence of systemic autonomic dysfunction than those with wide angles (table II). Patients with wide-angle ocular hypertension differed significantly from controls in heart-rate variation during deep breathing (p<0.01) and in 30:15 ratio (p<0.05) only. In patients with narrow-angle ocular hypertension, on the other hand, the results of all parasympathetic function tests were significantly lower than in controls (heart-rate variation during deep breathing, p<0.01; 30:15 ratio, p<0.01; S:L ratio, p<0.05; Valsalva ratio, p<0.05).

Heart-rate variation during deep breathing was significantly less in patients with narrow angles than in those with wide angles (p<0.01).

The autonomic status of patients and controls is summarised in table III. Overall, 50% of patients with narrow-angle ocular hypertension showed parasympathetic nerve dysfunction, compared with 34.3% of patients with wide angles (p<0.05).

#### Discussion

Tests of cardiovascular reflexes give a sensitive and accurate measurement of autonomic function. As these tests are simple and non-invasive and have no adverse effects, they are eminently suited to clinical application. Any of the tests

TABLE III—AUTONOMIC STATUS OF PATIENTS AND CONTROLS

	Normal	Parasympathetic nerve dysfunction only	Parasympathetic plus sympathetic nerve dysfunction
<i>Control subjects</i> (n = 76)	74 (97.4%)	2 (2.6%)	0
<i>Ocular hypertensives:</i>			
All (n = 189)	110 (58.2%)	64 (33.9%)	15 (7.9%)
OHNA (n = 90)	45 (50.0%)	35 (38.9%)	10 (11.1%)
OHWA (n = 99)	65 (65.7%)	29 (29.3%)	5 (5.0%)

can be used alone, but use of all five tests gives more information. The individual tests become abnormal at different stages in the disease process, and when used together they provide a measure of the degree of autonomic nerve dysfunction. Parasympathetic function is present if one or more of the results is abnormal.

That angle closure is not restricted to closed-angle glaucoma is of fundamental importance in determining the aetiology of primary glaucomas; a degree of angle closure develops in 46% of patients with ocular hypertension during the course of a provocation test with pilocarpine and phenylephrine. Comparisons between closed-angle glaucoma and ocular hypertension reveal several common characteristics. Although parasympathetic dysfunction is present in only 2-6% of a control group, the high prevalences in closed-angle glaucoma (58%) and ocular hypertension (42%) imply aetiological similarities. The probability that angle closure will develop during autonomic provocation in patients with ocular hypertension is related to angular configuration, with increased frequency in narrow-angle subjects; similarly, the prevalence of parasympathetic dysfunction is significantly higher in patients with narrow angles (50%) than in those with wide angles (34.3%).

In addition, diabetes mellitus is associated with both closed-angle glaucoma and ocular hypertension<sup>12</sup>—an association of particular significance in this context, since 20-40% of all diabetics have documented evidence of autonomic dysfunction.<sup>13,14</sup> In diabetes, autonomic neuropathy follows a characteristic course, with parasympathetic dysfunction appearing before sympathetic damage; a similar trend is seen in patients with closed-angle glaucoma and ocular hypertension.<sup>3</sup>

Autonomic effects on aqueous dynamics are of central importance in the determination of intraocular pressure. The medications most often prescribed in the treatment of glaucoma—pilocarpine, timolol, guanethidine, and adrenaline—act primarily through manipulation of the autonomic nervous system in the anterior segment. The demonstration of parasympathetic neuropathy in 42% of patients with ocular hypertension suggests that elevation of intraocular pressure is not an exclusively ocular phenomenon but may be a manifestation of systemic disease.

We thank Nurse C. Owen for technical assistance and Dr D. J. Ewing, of the University of Edinburgh, for advice. C. V. C. is in receipt of the R. D. Lawrence research fellowship from the British Diabetic Association.

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## Reviews of Books

### Recent Advances in Tropical Medicine

Number 1. Edited by H. M. Gilles, University of Liverpool. Edinburgh: Churchill Livingstone. 1984. Pp 353. £32.

It is 25 years since the last *Recent Advances in Tropical Medicine*. In this time the Western World has begun to wake up to its responsibilities in the Third World, the World Bank/WHO/UNDP has launched its Special Programme in research and training in tropical disease, scientists in immunology and molecular biology have turned their attention to parasites, and the pharmaceutical industry has turned in a few successes. All this at a time of increasing poverty and exploding population. As transport and communications have improved smallpox has disappeared, and cholera has returned to Europe; as the forests have been pushed back new diseases have come to light; as vigilance has waned malaria has resurged, more deadly than before; and as the desert has grown famine has spread. These are exciting and challenging times for medicine and science in the tropics. How can a slim book encompass all that has happened?

It cannot; and the editor has done very well to focus on selected subjects where progress has been made, and so produce a manageable book. The six Special Programme diseases are covered—malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy. There are also accounts of soil-transmitted helminths, Asian flukes, and diarrhoeal diseases. The book closes with chapters on immunodiagnosis, molecular biochemical characterisation of parasites, and pharmacokinetics of tropical drugs. Some of the chapters are written by more than one author, so that experimental and epidemiological advances are expertly covered as well as clinical advances. The team is good and writes well and the book has been published speedily.

The inclusion of advances in experimental research gives this volume a completeness and interest that standard tomes tend to lack. It shows that progress has been patchy—eg, in chemotherapy for leprosy but not for onchocerciasis, in control of schistosomiasis but not of malaria. The muddy pool of tropical diarrhoea becomes more clear and the expectations of molecular biology for diagnosis and immunisation are spelt out. Every multi-author book suffers from some inconsistency. In this one there are differences in presentation of the chapters, so that some are literally recent advances concisely presented, while others are up-to-date descriptions of a condition or a general review of a subject. Either way, the facts are here and the book should appeal to clinicians and the new breed of "tropical" scientists.

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ANTHONY BRYCESON

### Bereavement

*Reactions, Consequences, and Care*. Edited by Marian Osterweis and Frederic Solomon, Institute of Medicine, National Academy of Sciences, Washington, DC, and Morris Green, Indiana University School of Medicine, Indianapolis. Washington, DC: National Academy Press. Chichester: John Wiley and Sons. 1984. Pp 312. £22.50 (paperback).

A book written by a committee is in danger of being either a series of very extended minutes or a hotchpotch of chapters by different members, disparate in approach and style and marred by inevitable overlaps and gaps. This book has cleverly avoided both these difficulties and makes good and compelling reading. The committee in question was set up to study the health consequences of the stress of bereavement, at the request of the Office of Prevention of the National Institute of Mental Health in the USA. It was mandated to address three questions: what is known about the health consequences of bereavement; what further research would be important and promising; and whether there are preventive interventions that should either be widely adopted or further tested to evaluate their efficacy. The writers have fulfilled this mandate well, both in breadth and in depth, sifting through much evidence to ascertain what has already been established and to find gaps in knowledge that must be filled before soundly based policies can be

PAPER 5

THE PREVALENCE OF AUTONOMIC NEUROPATHY IN THE PRIMARY GLAUCOMAS

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## SUMMARY

The results of systemic autonomic nerve function studies in patients with closed-angle glaucoma and ocular hypertension are reviewed. Autonomic neuropathy has been demonstrated in 58% of patients with closed-angle glaucoma and 42% of ocular hypertensive subjects, with significantly increased prevalence in ocular hypertensives with narrow irido-corneal angles. The implications are discussed, with particular reference to the pathogenesis of raised intraocular pressure.

## KEY WORDS

Closed-angle glaucoma, ocular hypertension, autonomic neuropathy, pupil block

## INTRODUCTION

The essential anterior segment event precipitating irido-corneal contact, and therefore angle-closure, is postulated to be a change in autonomic activity in the anterior segment of the eye - with particular emphasis on parasympathetic tone (1). The depth of the anterior chamber is not a static dimension, and may show rapid and transient changes (2); alterations in depth are directly related to the pupil block force (3,4), itself a manifestation of autonomic activity in the anterior segment of the eye. In 1931, Curran suggested that angle-closure occurred as a secondary event, following anterior translational movement of the iris-lens diaphragm (5). The importance of pupil block in angle-closure is well-established (6,7,8,9), however the mechanism remained little known until comparatively recently. In 1968, Mapstone resolved pupil block force into three separate components (3):

- i. Force due to contraction of the sphincter muscle
- ii. Force due to contraction of the dilator muscle
- iii. Modulus of elasticity of the iris stroma

Pupil block force is thus a posteriorly-directed vector, the direction and magnitude determined by the relative contribution of the three contributing elements. (Figure 1) The importance lies in the *relative* contribution of each separate force. Independent component forces are not of equal potential magnitude; the sphincter muscle, when maximally-stimulated, may develop twice the power of the maximally-stimulated dilator muscle (10). The magnitude of pupil block force has been calculated, and shown to be maximal if the pupil is fixed in mid-dilatation as a result of relative parasympathetic

and sympathetic activity (11). The position of the iris-lens diaphragm at equilibrium is determined by the production of aqueous humour, the facility of outflow, and the degree of pupil block. (Figure 2) The vector force, representing the resolution of the constituent elements of pupil block, increases iris-lens apposition. In eyes without a peripheral iridectomy, aqueous flow from the site of production (ciliary processes) to that of escape (trabecular meshwork and uveoscleral route) can only occur via the pupil; increased pupillary block thus results in decreased aqueous flow from the posterior to the anterior chamber. As facility of outflow remains unaltered, impedance of aqueous flow via the pupil results in the development of a pressure differential across the iris-lens diaphragm, with increasing pressure in the posterior chamber (effected by continuing aqueous production with impaired outflow from the posterior chamber to the anterior chamber) and decreasing pressure in the anterior chamber (continuing outflow with impaired inflow). In a biological system capable of significant variation, changes in the dimensions of the anterior chamber are an inevitable consequence (3,4), with shallowing of the anterior chamber. Anterior translational movement of the iris-lens diaphragm facilitates irido-corneal contact and thus subsequent angle-closure: if the anterior chamber shallows by 0.2 mm, the distance between peripheral iris and cornea decreases by 0.08 mm; if the anterior chamber shallows by 0.33 mm, the irido-corneal gap narrows by 0.12 mm (4). Irido-corneal separation in eyes with narrow angles is only approximately 0.15 mm (1), and therefore relatively minor anterior displacement of the iris-lens diaphragm may cause disproportionate decreases in the irido-corneal interval, with eventual irido-corneal contact. As pupil block force is a direct manifestation of

autonomic activity in the anterior segment of the eye, it is essential to review the efficacy of autonomic nerve function in patients with primary glaucoma.

#### SYSTEMIC AUTONOMIC NERVE FUNCTION

The recent introduction of non-invasive tests based upon cardiovascular reflexes has permitted accurate and objective assessment of systemic autonomic nerve function for the first time (12,13,14,15,16,). (Table 1) Results are based on blood-pressure and heart-rate responses to a variety of standardised stimuli, and current evidence suggests that these tests reflect generalised autonomic nerve function (17). The following tests are employed in the assessment of systemic autonomic nerve function:

##### 1. Parasympathetic nerve function

###### *Heart-rate variation during deep breathing*

Respiratory sinus arrhythmia occurs in normal subjects, with a relative tachycardia during inspiration and a relative bradycardia during expiration. This is conveniently measured by electrocardiographic recording of heart-rate variation during deep breathing. The final result is the difference between maximum and minimum heart-rates, measured directly from the electrocardiogram, over a one-minute period.

###### *Immediate heart-rate response to standing*

A characteristic cardiovascular reflex occurs during alteration in posture from lying to standing. An initial tachycardia occurs at

about the 15th beat after standing, followed by a relative bradycardia around the 30th beat. R-R intervals are measured (from a continuous electrocardiogram) at these respective points, and the result expressed as the 30:15 ratio.

#### *Immediate heart-rate response to lying*

During this manoeuvre, a relative tachycardia occurs approximately 3-4 beats after lying down, followed by a gradual bradycardia. Heart-rate changes are recorded by continuous electrocardiography, and the 'S:L ratio' is the ratio of the longest R-R interval during the 5 beats before lying down to the shortest R-R interval during the 10 beats after commencing the manoeuvre.

#### *Valsalva manoeuvre*

A continuous electrocardiogram is recorded during the performance of a standardised Valsalva manoeuvre. The subject is requested to blow into the mouthpiece of a modified sphygmomanometer and maintain a pressure of 40 mmHg for 15 seconds. The Valsalva ratio is the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the test.

## 2. Sympathetic nerve function

#### *Systolic blood pressure response to standing*

Change in posture from the supine to the standing position precipitates gravitational pooling of blood in the lower extremities. Maintenance of blood-pressure during this manoeuvre is effected by peripheral and splanchnic vasoconstriction via sympathetic efferent

nerves. The patient's blood pressure is measured after 3 minutes resting supine, then immediately upon standing upright. The postural change in blood pressure is the difference between the systolic pressure lying and standing.

#### AUTONOMIC NERVE FUNCTION IN GLAUCOMA

##### Closed-angle glaucoma

Mapstone and Clark (1985) assessed the systemic autonomic nerve function of 112 patients with closed-angle glaucoma and 74 age- and sex-matched control subjects (18). 893 autonomic function tests were performed on 196 subjects (average 4.56 tests per subject). Results of 3 tests of autonomic nerve function were significantly lower in closed-angle glaucoma patients than control subjects: heart-rate variation during deep breathing ( $p < 0.001$ ), 30:15 ratio ( $p < 0.001$ ) and S:L ratio ( $p < 0.01$ ). Systemic parasympathetic dysfunction was present in 58% of closed-angle glaucoma patients, compared with 6.8% of the control group.

##### Ocular hypertension

Systemic autonomic nerve function was assessed in 189 patients with ocular hypertension and 76 age- and sex-matched control subjects by Clark and Mapstone in 1985 (19). Ocular hypertensive patients were subdivided by irido-corneal angle configuration into wide-angle and narrow-angle categories, according to the Shaffer angle-grading classification (20). 90 ocular hypertensives had narrow angles, with wide angles in 99 subjects. 1304 autonomic function tests were performed on 265 subjects. The results were subjected to Dunnett's

multiple comparison procedure (21), to prevent inaccuracy from multiple comparisons with a control; it should be noted that Dunnett's tables have a maximum joint confidence coefficient of 99% and therefore every significance level of  $p < 0.01$  will be included in this category.

There were significantly different results of systemic autonomic nerve function between narrow-angle and wide-angle subjects with ocular hypertension. A higher prevalence of systemic autonomic dysfunction was present in patients with narrow irido-corneal angles than in those with wide angles. Results of heart-rate variation during deep breathing ( $p < 0.01$ ) and 30:15 ratio ( $p < 0.05$ ) were significantly lower in wide-angle ocular hypertensive patients than control subjects. However in ocular hypertensive patients with narrow irido-corneal angles, results of all parasympathetic function tests were significantly lower than the comparable control group: heart-rate variation during deep breathing ( $p < 0.01$ ), 30:15 ratio ( $p < 0.01$ ), S:L ratio ( $p < 0.05$ ), and Valsalva ratio ( $p < 0.05$ ). Parasympathetic nerve dysfunction was present in 50% of ocular hypertensive patients with narrow angles, compared with 34.3% of those with wide angles ( $p < 0.05$ ). Sympathetic nerve dysfunction was present in 11.1% of narrow-angle ocular hypertensives, and only 5% of wide-angle subjects. In comparison, parasympathetic nerve dysfunction was present in only 2.6% of the comparable control group, and sympathetic dysfunction was not present in any member of the control group.

## DISCUSSION

The role of autonomic dysfunction in the aetiology of closed-angle glaucoma and ocular hypertension necessitates a brief reiteration of pathophysiological mechanisms in angle-closure. Closure of the irido-corneal angle in the anterior chamber is, by definition, a dynamic process. The relative contribution of anterior translational movement of the iris-lens diaphragm and peripheral iris bombe remains a source of debate, however the basic aetiological factor common to both mechanisms is pupil block, a direct result of relative parasympathetic and sympathetic activity in the anterior segment. Pupil block causes pressure inequalities between the posterior and anterior chambers, with consequent shallowing of the anterior chamber. Sphincter and dilator pupillae (the effectors of parasympathetic and sympathetic nerve stimulation) are not of equal potential magnitude; the maximally-stimulated sphincter muscle may develop twice the power of the maximally-stimulated dilator muscle (10). In consequence, parasympathetic tone has been proposed as the major determinant of pupil block (1). Impairment of parasympathetic nerve function effects a partial dilation of the pupil, thereby increasing pupil block. It has been shown that pupil block force is maximal at a pupil diameter of 3.8-4.2 mm, with exponential decrease in pupil block force as the pupil diameter either increases or decreases from this value. A concomitant denervation of sympathetic nerve function in the anterior segment would render the pupil relatively immobile; in the presence of a mid-dilated pupil, maximal pupil block would be sustained, with inevitable dimensional changes in the anterior chamber possibly terminating in overt angle-closure in patients with narrow angles.

Angle-closure is not exclusively restricted to patients with closed-angle glaucoma; this principle is of fundamental importance in the determination of common aetiological factors in the pathogenesis of the primary glaucomas. In ocular hypertension, autonomic provocation by simultaneous installation of guttae 2% pilocarpine and 10% phenylephrine produces significant partial closure of the anterior chamber angle, with consequent impairment of aqueous outflow, in 40% of subjects, with complete angle closure in a further 6%. Results are directly related to angular configuration, with angle-closure occurring during autonomic provocation in 88% of patients with grade 1 angles (Shaffer angle-grading), 69% of patients with grade 2 angles, and 11% of patients with grade 3 angles (22). Therefore angle-closure is not an all-or-none phenomenon; it is only when the angle is virtually completely closed that intraocular pressure rises precipitously, manifesting the characteristic signs of closed-angle glaucoma. Intermittent partial angle-closure produces intermittently raised intraocular pressure, with inevitable damage to outflow mechanisms; repeated episodes result in impaired facility of outflow, which also causes increased intraocular pressure, thus generating a self-perpetuating pathological cycle (22). The configuration of the anterior chamber angle is of marked importance; a narrow irido-corneal angle facilitates angle-closure by permitting a lesser anterior translational movement of the iris-lens diaphragm to effect angle-closure.

Having established this fundamental principle, one must determine the predisposition in certain individuals to develop the necessary change in autonomic activity precipitating angle-closure. Assessment of cardiovascular reflexes correlates closely with autonomic nerve

function in other systems (23), including the eye (24), and thus effectively provides an objective, quantifiable and reproducible measure of generalised autonomic nerve function. On this basis, the present results indicate that systemic autonomic dysfunction is significantly associated with closed-angle glaucoma and ocular hypertension; although autonomic dysfunction was associated with both wide-angle and narrow-angle categories of ocular hypertension, the prevalence was significantly higher in ocular hypertensive patients with narrow angles. Parasympathetic neuropathy comprised over 80% of the total autonomic dysfunction in these subjects; impairment of parasympathetic nerve function increases pupil block force, thereby increasing the probability of angle-closure, with potentially significant implications in the pathogenesis of closed-angle glaucoma and narrow-angle ocular hypertension.

In ocular hypertensive subjects with wide irido-corneal angles, autonomic dysfunction may influence the development of raised intraocular pressure by a different mechanism. It is recognised that parasympathetic nerve stimulation induces ciliary muscle contraction on the scleral spur, actively opening the trabecular meshwork and increasing the outflow of aqueous humour from the anterior chamber of the eye. In patients with autonomic neuropathy this mechanism will inevitably be impaired, and elevation of intraocular pressure in wide-angle ocular hypertensive subjects may therefore result from diminished aqueous outflow, a direct consequence of the inability to maximally utilise the potential reserve outflow facility (25).

The prevalence of parasympathetic neuropathy parallels that of

diabetes mellitus in patients with closed-angle glaucoma and in ocular hypertensive subjects with narrow angles (26). The similarity in the associations between diabetes mellitus/systemic autonomic neuropathy and narrow-angle categories of glaucoma are not surprising, as diabetes mellitus is the commonest cause of autonomic neuropathy in the United Kingdom (27).

Currently-proposed mechanisms of angle-closure are based on relative autonomic activity in the anterior segment of the eye. The prevalence of autonomic neuropathy in patients with closed-angle glaucoma and ocular hypertension provides a logical explanation for previous experimental observations of dynamic angle-closure during provocative testing.

LEGENDS

Figure 1

Pupil block

(Reproduced with permission, Documenta Ophthalmologica Proceedings Series)

Figure 2

Forces determining the position of the iris-lens diaphragm at equilibrium

(Reproduced with permission, Documenta Ophthalmologica Proceedings Series)

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Table 1

CARDIOVASCULAR AUTONOMIC FUNCTION TESTS

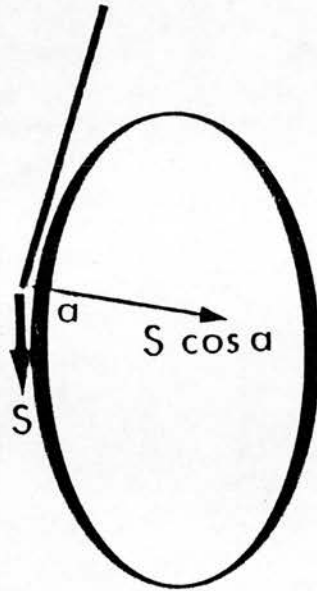
Parasympathetic nerve function

- i. Heart-rate variation during deep breathing
- ii. Immediate heart-rate response to standing
- iii. Immediate heart-rate response to lying
- iv. Valsalva manoeuvre

Sympathetic nerve function

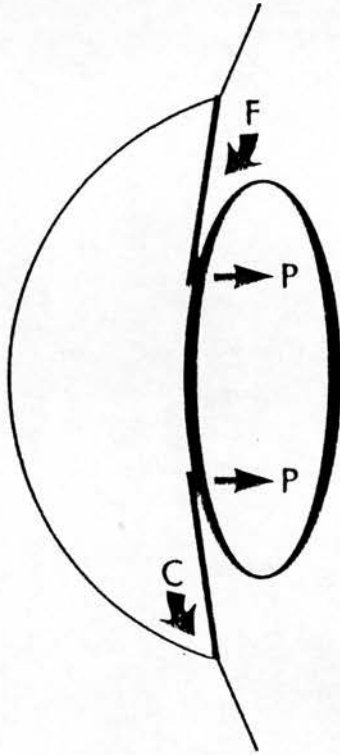
Systolic blood pressure response to standing

Figure 1



PUPIL BLOCK

Figure 2



P = Pupil block

F = Aqueous production

C = Facility of outflow

PAPER 6

## Systemic autonomic neuropathy in open-angle glaucoma

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**Abstract.** Systemic autonomic nerve function was assessed in 67 patients with open-angle glaucoma and 76 age- and sex-matched control subjects, using a series of well-established tests based upon cardiovascular reflex responses to standardised stimuli. Parasympathetic neuropathy was present in 37.3% of open-angle glaucoma patients compared with 2.6% of the control group. Demonstration of a significant association between autonomic neuropathy and primary glaucoma may provide a logical rationale for the efficacy of autonomic medication in glaucoma therapeutics; the prognostic implications are discussed.

### Introduction

Elevation of intraocular pressure secondary to reduced outflow of aqueous humour from the anterior chamber, ultimately leading to glaucomatous nerve fibre damage in open-angle glaucoma, is a well-recognised phenomenon, however the essential aetiological factor precipitating this pathological sequence of events remains unknown. The influence of the autonomic nervous system on aqueous dynamics is a major determinant of intraocular pressure; evidence of this is clearly demonstrated by the fact that medications in glaucoma therapy exert their effects via manipulation of the autonomic nervous system in the anterior segment of the eye, either as autonomic agonists (pilocarpine, adrenaline) or antagonists (timolol, guanethidine). Recent studies have shown a high prevalence of systemic autonomic dysfunction in patients with narrow-angle glaucoma (58%) and ocular hypertension (42%) (Mapstone and Clark, 1985; Clark and Mapstone, 1985); consequently, the hypothesis has been proposed that elevation of intraocular pressure is associated with systemic autonomic neuropathy. The rationale of the present study was therefore to assess autonomic function in patients with open-angle glaucoma, to determine their autonomic status.

Accurate evaluation of systemic autonomic nerve function is facilitated by a series of well-established tests based upon cardiovascular reflexes (Bellavere and Ewing, 1982; Ewing et al., 1985). Blood-pressure and heart-rate responses to standardised stimuli are recorded by electrocardiography, ensuring sensitive, quantifiable measurement of autonomic efficacy. A corollary is that cardiovascular autonomic function tests provide an accurate assessment of generalised autonomic nerve function (Campbell et al., 1977; Ewing et al., 1980).

### Subjects and methods

After informed consent had been obtained, 67 patients with open-angle glaucoma (mean age  $68.6 \pm 8.5$  years) and 76 age- and sex-matched control subjects (mean age  $67.1 \pm 11.5$  years) were included in the study. The diagnosis of open-angle glaucoma was made according to established criteria (Hollings and Graham, 1966; Schwartz, 1982). The control group consisted of patients attending an ophthalmic casualty department, subsequently determined to have no detectable abnormality. Subjects taking medication with effects on the autonomic nervous system, or known to have medical disorders predisposing to autonomic nerve dysfunction, were excluded from the study. Ocular examination was performed on all subjects, as follows:

- i) Anterior segment assessment
  - a. biomicroscopic examination of cornea, anterior chamber, iris integrity, and lens
  - b. gonioscopy to assess angle configuration and exclude angle abnormalities
  - c. intraocular pressure by Goldmann applanation tonometry
- ii) Posterior segment assessment
  - a. direct ophthalmoscopy of optic disc, cup:disc ratio, macula and retinal vessels
  - b. indirect ophthalmoscopy to assess retinal periphery
  - c. visual field examination by Goldmann perimetry

Normal sinus rhythm was established in all subjects prior to assessment of cardiovascular autonomic nerve function. The study was performed on a single-blind basis, i.e. the status of each subject was not known to the examining ophthalmologist at the time of assessment. Five tests of autonomic function were performed on each subject, as follows:

#### A) Parasympathetic nerve function

##### i. Valsalva manoeuvre

A standardised Valsalva manoeuvre was performed by the subject blowing into a mouthpiece connected to a modified sphygmomanometer and maintaining a pressure of 40 mmHg for 15 seconds. A continuous electrocardiogram was recorded, commencing 20 seconds prior to the manoeuvre and terminating 25 seconds after the manoeuvre. The patients were seated during the test, and rested for at least 2 min between consecutive assessments. The Valsalva ratio is the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the test. These were measured directly from the electrocardiogram, and the final ratio was the mean of 3 consecutive assessments. The test is based upon the circulatory response to forced, controlled respiration against resistance. The responses are differentiated into 4 separate phases. The heart-rate decreases due to the initial rise in intrathoracic pressure (phase 1).

This is followed by a gradual increase in heart-rate in response to reduced venous return and the consequent decrease in blood-pressure (phase 2). The acute release of intrathoracic pressure upon termination of the manoeuvre precipitates increased tachycardia (phase 3). This is followed by bradycardia (phase 4), which represents a baro-reflex response to increased cardiac output during a period of raised peripheral vascular resistance. The Valsalva ratio is the ratio of the longest R-R interval in phase 4 divided by the shortest R-R interval in phase 2.

ii. Heart-rate variation during deep breathing

Parasympathetic nerve function may be evaluated by measurement of the heart-rate variation during deep breathing, utilising the principle of respiratory sinus arrhythmia. The subject was seated quietly at rest for 3 min prior to the test, then was requested to breathe deeply at a rate of approximately 6 breaths per minute (5 seconds inspiration, 5 seconds expiration) whilst a continuous electrocardiogram was recorded. In normal subjects, a relative tachycardia occurs during inspiration, with a relative bradycardia in expiration. Maximum and minimum R-R intervals were measured directly from the electrocardiogram and expressed as beats per minute using specific conversion tables. Six consecutive measured cycles were calculated, and the final result was the mean of the differences between maximum and minimum heart-rates.

iii. Immediate heart-rate response to standing

During alteration in posture from lying to standing a characteristic cardiovascular reflex response occurs under vagal control. This consists of an initial increase in heart-rate, maximal at about the 15th beat after standing, followed by a relative bradycardia around the 30th beat. The patient rested supine for approximately 3 min prior to the test, then was requested to stand unaided. An electrocardiogram was recorded from 20 beats prior to the manoeuvre until 40 beats after standing. The R-R intervals were measured to determine the shortest around the 15th beat and longest at about beat 30, and the result expressed as the 30:15 ratio.

iv. Immediate heart-rate response to lying

Shortening of the R-R interval occurs during the 3rd–4th beat after commencing the manoeuvre, followed by a gradual increase in R-R interval. Subjects were requested to stand for 2 minutes, then lie down unaided. Heart-rate was recorded by continuous electrocardiography from 20 beats prior to the manoeuvre until 40 beats after lying down. The results were calculated as the ratio of the longest R-R interval during the 5 beats before lying to the shortest R-R interval during the 10 beats after lying down, and the result expressed as the standing:lying ratio (S:L ratio).

## B) Sympathetic nerve function

## Systolic blood-pressure response to standing

Change in posture from the supine to the erect position evokes characteristic cardiovascular reflexes. Gravitational pooling of blood in the venous capacitance vessels of the lower extremities precipitates an immediate fall in venous return and consequently cardiac output. Homeostasis in the maintenance of systemic blood-pressure is effected by increased sympathetic efferent impulses; the resultant raised peripheral vascular resistance reverses the decrease in venous return, and in conjunction with direct chronotropic cardio-accelerator effects, preserves adequate cardiac output. The assessment is performed according to the following technique. The subject's blood-pressure was measured after 3 min resting supine on an examination couch, then again immediately after standing upright. The postural change in blood-pressure is the difference between the systolic pressure lying and standing.

## Results

The results of systemic autonomic nerve function assessment in 67 patients with open-angle glaucoma and 76 age- and sex-matched control subjects are shown in Table 1. In each test of autonomic function, comparisons were made between the results of the glaucoma group and the control group; significance was assessed by Student's unpaired *t* test. There were significant differences between the 2 groups in 3 of the 5 autonomic function tests: heart-rate variation during deep breathing ( $p < 0.001$ ), Valsalva ratio ( $p < 0.05$ ), and 30:15 ratio ( $p < 0.05$ ). In every test, results in the glaucoma patients were lower than the comparable control group.

Established normal tolerance limits for autonomic nerve function assessment (Bellavere and Ewing, 1982; Ewing et al., 1985) are shown in Table 2.

Table 1. Systemic autonomic nerve function assessment in 67 patients with primary open-angle glaucoma and 76 age- and sex-matched control subjects (Group mean values  $\pm$  SEM)

	Open-angle glaucoma group	Control group	Significance
<i>Parasympathetic nerve function</i>			
i. Heart-rate variation during deep breathing (beats/minute)	13.32 $\pm$ 0.83	18.32 $\pm$ 0.92	$p < 0.001$
ii. Valsalva ratio	1.38 $\pm$ 0.04	1.49 $\pm$ 0.04	$p < 0.05$
iii. 30:15 ratio	1.13 $\pm$ 0.01	1.17 $\pm$ 0.01	$p < 0.05$
iv. S:L ratio	1.18 $\pm$ 0.01	1.21 $\pm$ 0.01	$p > 0.05$
<i>Sympathetic nerve function</i>			
Decrease in systolic blood-pressure on standing (mmHg)	11.28 $\pm$ 1.21	8.14 $\pm$ 1.48	$p > 0.05$

Table 2. Normal tolerance limits for autonomic nerve function assessment

	Abnormal
<i>Parasympathetic nerve function</i>	
i. Heart-rate variation during deep breathing (beats/minute)	< 10.0
ii. Valsalva ratio	< 1.10
iii. 30:15 ratio	< 1.00
iv. S:L ratio	< 1.07
<i>Sympathetic nerve function</i>	
Decrease in systolic blood-pressure on standing (mmHg)	≥ 30.0

Table 3. Autonomic status of 67 patients with open-angle glaucoma and 76 age- and sex-matched control subjects

	Normal	Parasympathetic neuropathy	Sympathetic neuropathy	Parasympathetic plus sympathetic neuropathy
Control subjects (n = 76)	74 (97.4%)	2 (2.6%)	0	0
Open-angle glaucoma patients (n = 67)	38 (56.7%)	25 (37.3%)	4 (6.0%)	0

Autonomic dysfunction is defined by the presence of at least one abnormal autonomic function test. Subjects were classified into 4 categories on the basis of results: normal, parasympathetic neuropathy, sympathetic neuropathy and parasympathetic plus sympathetic neuropathy. Classification of autonomic status is shown in Table 3. Parasympathetic neuropathy was present in 37.3% of open-angle glaucoma patients compared with 2.6% of the control group. Sympathetic neuropathy was present in 6% of open-angle glaucoma patients compared with none of the control group. No subject in either category had combined dysfunction of parasympathetic and sympathetic nervous systems.

### Discussion

Until recently, tests of autonomic nerve function have been difficult to interpret and almost impossible to quantify; the development of tests based upon cardiovascular reflexes has revolutionised assessment of autonomic integrity. Their simplicity facilitates clinical application as they are totally non-invasive – without known side-effects – and the accuracy of sensitive cardiovascular monitoring by electrocardiography permits reproducible measurement of autonomic efficacy. Heart-rate represents a balance of

sympathetic and parasympathetic influences (Robinson et al., 1966; Levy, 1971); the relative importance of each component during cardiovascular reflexes has been determined by selective pharmacological autonomic blockade (Ewing, 1978; Bellavere and Ewing, 1982). As individual tests demonstrate abnormality at different stages in the progression of autonomic neuropathy, the utilisation of 5 tests enhances assessment of autonomic nerve function; parasympathetic dysfunction is present if at least one parasympathetic function test result is abnormal.

The results of the present study demonstrate a significant association between open-angle glaucoma and autonomic neuropathy, similar to that shown by other major categories of primary glaucoma; parasympathetic neuropathy is present in 58% of patients with narrow-angle glaucoma (Mapstone and Clark, 1985), 42% of ocular hypertensive subjects (Clark and Mapstone, 1985), and 37% of patients with open-angle glaucoma, compared with only 3% of a comparable age- and sex-matched control group. The demonstration of generalised autonomic damage in each of the major categories of primary glaucoma implies a common aetiological factor in pathogenesis; the individual degree of autonomic neuropathy may partially explain why certain individuals with ocular hypertension progress to overt glaucoma, whilst others do not. The efficacy of autonomic mediators in the treatment of glaucoma is understandable within a background of autonomic neuropathy; obviously, topical application of autonomic agonists and antagonists may provide the autonomic control of aqueous dynamics which is significantly impaired in a patient with autonomic neuropathy. This has important prognostic implications, as the likely response to therapy by autonomic agents may be predictable on the basis of a subject's autonomic status, with enhanced responses in subjects with autonomic insufficiency; results of studies currently in progress support this hypothesis. The degree of autonomic neuropathy may also explain the well-recognised inter-individual variation in response to medical therapy frequently shown by glaucoma patients.

Evidence of a significant association between autonomic neuropathy and the primary glaucomas — open-angle glaucoma, narrow-angle glaucoma, and ocular hypertension — suggests a common aetiological factor in pathogenesis, and may facilitate future research into glaucoma therapeutics by establishing a logical rationale for glaucoma management.

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PAPER 7

PUPIL CYCLE TIME IN PRIMARY CLOSED-ANGLE GLAUCOMA

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ABSTRACT

Pupil cycle time was measured in fellow eyes of 124 patients with closed-angle glaucoma and 70 age- and sex-matched control subjects. The duration of pupil cycle time was significantly prolonged in patients with closed-angle glaucoma; in addition, there was a significantly-increased prevalence of absent pupillary oscillation in these patients. The implications are discussed, with particular reference to the association between closed-angle glaucoma and systemic parasympathetic neuropathy.

## INTRODUCTION

Recent observations have demonstrated a significant association between autonomic neuropathy and closed-angle glaucoma; systemic parasympathetic neuropathy is present in 58% of patients with closed-angle glaucoma, compared with 6.8% of an age- and sex-matched control group (1). This has significant implications in the pathogenesis of closed-angle glaucoma. Closure of the irido-corneal angle is a dynamic process; the relative contribution of anterior translational movement of the iris-lens diaphragm (2) and peripheral iris bombe (3) remains a source of debate, however the basic aetiological factor common to both mechanisms is pupil block, a direct consequence of relative parasympathetic and sympathetic activity in the anterior segment. Pupillary dynamics represent an external manifestation of autonomic integrity in the anterior segment, which may be quantified by determination of the pupil cycle time. Pupil cycle time enables the integrity of the pupillary reflex arc to be accurately and objectively evaluated by a simple, non-invasive, clinically-orientated technique (4,5). Providing the ultimate effector, the iris musculature, is structurally normal with intact innervation, the pupil cycle time is dependent upon velocity of nerve conduction, synaptic delay, and the number of nerve impulses transmitted. A thin slit-beam focussed at the pupillary margin produces pupil oscillations which can be accurately timed with a stop-watch. The beam is positioned to just overlap the pupillary margin; light stimulating the retinal receptors initiates the pupil reflex, with subsequent constriction of the pupil. Elimination of afferent stimulation results in reflex dilation of the pupil, light re-enters the eye and a second cycle is initiated.

## PATIENTS AND METHODS

After informed consent had been obtained, pupil cycle time was measured in 124 patients with closed-angle glaucoma (mean age  $66.5 \pm 10.1$  years) and 70 age- and sex-matched control subjects (mean age  $66.2 \pm 10.1$  years). The control group consisted of hospital staff, and patients attending the casualty department who were subsequently determined to have no detectable abnormality. All subjects had a corrected visual acuity of  $\geq 6/9$  in each eye. A comprehensive past, present and family history was obtained from each subject. The present history included details regarding presentation, current treatment, visual acuity, and visual symptoms. A detailed general systemic enquiry and drug history was also documented. Past medical history specifically recorded ophthalmic disease, cardiovascular or neurological disorders, diabetes mellitus and other predisposing factors to autonomic dysfunction. Subjects known to have medical disorders predisposing to autonomic nerve dysfunction, or taking medication with effects on the autonomic nervous system, were excluded from the study.

Systemic general medical examination was performed; subjects with significant neurological abnormalities were excluded from assessment. Ocular examination was performed on all subjects, as follows:

- i. Anterior segment assessment
  - a. slit-lamp examination of cornea, anterior chamber, iris integrity/dynamics, and lens
  - b. gonioscopy by Zeiss 4-mirror gonioprism to determine angle configuration and exclude angle abnormalities
  - c. intraocular pressure by Goldmann applanation tonometry

- ii. Posterior segment assessment
  - a. direct ophthalmoscopy of optic disc, cup:disc ratio, retinal vessels and macula
  - b. indirect ophthalmoscopy, after pupillary dilation, to assess posterior pole and retinal periphery
  - c. visual field examination: by Goldmann perimetry

Pupil cycle time was measured 4 weeks after the initial ocular examination.

Eyes were excluded from assessment if there was a history of:

- i. eye operations. Only unoperated eyes were included in the study. In patients with closed-angle glaucoma, assessments were performed only in unoperated fellow eyes; eyes which had sustained closed-angle glaucoma were specifically excluded.
- ii. eye trauma.
- iii. current ophthalmic drug treatment. Only eyes not on treatment were included in the study.

After applying the exclusion criteria, pupil cycle time was measured in:

- i. Closed-angle glaucoma group: 118 eyes in 118 patients
- ii. Control group: 122 eyes in 70 subjects

Edge-light pupil cycle time was measured according to the following method. The patient was seated at the slit-lamp (Zeiss 30SL, Carl Zeiss, Welwyn Garden City, England) in a room with low, constant background illumination (20 lux), and requested to fixate straight ahead on an object at 6 metres. A 0.5 x 6 mm slit-beam was positioned horizontally and elevated until it just overlapped the margin of the pupil, then focussed on the iris-lens border. The pupil constricted, then reflexly dilated in response to iris blocking the light

and thus removing afferent stimulation. 30 consecutive pupillary cycles were timed using a stop-watch; the result divided by 30 is the duration of a single cycle of the pupillary reflex arc. The pupil cycle time was measured 4 times for each eye separately (ie 4 x 30-cycles) and the result averaged. The measurement of 30 cycles with subsequent division to determine the duration of a single cycle reduces subjective error in manual timing.

All assessments were performed on a single-blind basis.

## RESULTS

The results of pupil cycle time assessment in 124 patients with closed-angle glaucoma and 70 age- and sex-matched control subjects are described as follows:

- i. Pupil cycle time in patients with closed-angle glaucoma
- ii. Age-adjusted normal tolerance intervals for pupil cycle time
- iii. The prevalence of absent pupillary oscillation in patients with closed-angle glaucoma and the age- and sex-matched control group

i. Pupil cycle time in patients with closed-angle glaucoma

The results of pupil cycle time assessment in 124 patients with closed-angle glaucoma and 70 age- and sex-matched control subjects are shown in table 1. Sustained pupillary oscillation in response to edge-light stimulation was absent in a significant percentage of eyes examined; consequently, measurement of pupil cycle time was possible in a proportionately decreased number of eyes:

- i. Closed-angle glaucoma group: 64 eyes in 64 patients
- ii. Control group: 106 eyes in 61 subjects

Comparisons of mean pupil cycle time were made between the control group and patients with closed-angle glaucoma; significance was assessed by Student's unpaired t test. Pupil cycle time in fellow eyes of patients with closed-angle glaucoma was significantly higher than the control group ( $p < 0.001$ ).

ii. Age-adjusted normal tolerance intervals for pupil cycle time

The results of pupil cycle time (PCT) measurement in the age- and sex-matched control group were assessed for dependence on age by regression analysis. The data were fitted according to various mathematical models using the computer programme SPSSx on an IBM 4341 computer to obtain a normal distribution after

adjustment for age, thus permitting determination of tolerance intervals. Logarithms of the data were used to derive tolerance intervals, and a log normal distribution was obtained.  $\log_{10}(\text{PCT})$  did not depend significantly on age. Linear regression analysis, permitting determination of 2.5th, 5th, 95th, and 97.5th percentiles, was calculated from:

$$\text{RLPCT} = (\log_{10}\text{PCT} - (-0.02883 + 0.00019 \times \text{age}))/0.05469$$

assumed to have the standard Normal distribution.

$$\text{RLPCT} = \text{standardised residual } \log_{10}(\text{PCT})$$

The logarithms of the percentiles (allowing for regression on age), transformed back to natural values, with 2.5th, 5th, 95th, and 97.5th percentiles, are shown in figure 1. The age-adjusted normal tolerance limit, ie the upper 95th percentile of the log normal distribution after regression on age, was applied to the results obtained from patients with closed-angle glaucoma, to determine the proportion of eyes outwith the normal limit; results are shown in table 2.

iii. The prevalence of absent pupillary oscillation in patients with closed-angle glaucoma and the age- and sex-matched control group

Pupillary oscillation was absent in a significant proportion of eyes examined (table 3):

- a. Closed-angle glaucoma group: 54 eyes in 54 patients
- b. Control group: 16 eyes in 11 subjects

Comparisons were made between the prevalence of absent pupillary oscillation in the control group and patients with closed-angle glaucoma; significance was assessed by  $\chi^2$  test with Yates' correction. The prevalence of absent pupillary oscillation was significantly higher in patients with closed-angle glaucoma than the control group ( $p < 0.001$ ).

## DISCUSSION

Measurement of pupil cycle time accurately assesses the integrity of the pupillary reflex arc. The duration of the cycle is prolonged in older subjects;  $968 \pm 131$  ms in the present study (mean age  $66.2 \pm 10.1$  years) compared with  $822 \pm 69$  ms in subjects aged less than 50 years (4). 14.3% of eyes in control subjects were characterised by an absence of sustained pupillary oscillation in response to edge-light stimulation; consequently, definitive measurement of pupil cycle time was not possible. This phenomenon has not been reported in previous descriptions of pupil cycle time. The following 3 sub-groups are included within this category:

- i. initial pupil oscillation, rapidly diminishing in amplitude and velocity, with eventual pupil immobility prior to the completion of 120 cycles
- ii. irregular pupillary unrest or hippus, with minimal pupillary "fibrillating" oscillations which were impossible to quantify
- iii. relative pupillary immobility, interrupted at irregular intervals by segmental contractions of the sphincter pupillae.

Whether the lack of quantifiable movement results from subclinical sphincter innervational defects (6), increased conduction time in anterior optic pathways (6), or arteriosclerosis and deposition of hyaline in the iris stroma and muscles (7), remains speculative, however it is present in a significant proportion of control subjects.

In comparisons with the control group, pupil cycle time was significantly prolonged in fellow eyes of patients with closed-angle glaucoma. The prevalence of abnormal pupil cycle time, defined by the 95th percentile of the log normal distribution after regression on age, was significantly increased

in patients with closed-angle glaucoma (18.8%); the prevalence of absent pupillary oscillation in response to edge-light stimulation was also significantly higher in the closed-angle glaucoma group (45.6%).

Pupil cycle time assesses the integrity of the pupillary reflex arc as a discrete and indivisible unit; inferences to localise any defect within the reflex pathway revealed by prolongation of the pupil cycle time may only be made by supplementing the data with additional information relating to individual components of the pathway. There was no evidence of retinal nerve fibre bundle defects, following meticulous peripheral and central visual field assessment, in all eyes of control subjects and fellow eyes of patients with closed-angle glaucoma. Nerve fibre bundle defects characteristic of glaucoma may affect the afferent limb of the reflex arc; when afferent defects are not revealed by standard techniques, prolonged pupil cycle time may be attributed to defects in either the internuncial or efferent component of the arc by reasonable implication. Autonomic neuropathy is not characteristically a localised disorder; as systemic parasympathetic dysfunction is present in 58% of patients with closed-angle glaucoma (1,8), one may reasonably postulate co-existent parasympathetic dysfunction in the anterior segment of the eye. The essential anterior segment event precipitating irido-corneal contact - and therefore angle-closure - is postulated to be a change in autonomic activity - in particular, parasympathetic tone (9,10); the results of the present study support this concept. Evaluation of the pupillary reflex arc is equally possible in primary glaucoma patients on treatment with guttae 0.5% timolol maleate, as this drug has no measurable effect on the duration of the pupil cycle time (11).

One may conclude that the pupillary reflex arc is impaired in asymptomatic fellow eyes of patients with closed-angle glaucoma, with concomitant relative iris immobility manifesting absence of sustained pupillary oscillation in response to light.

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KEY WORDS

Pupil cycle time, closed-angle glaucoma, pupillary reflex, autonomic neuropathy

Table 1

RESULTS OF PUPIL CYCLE TIME ASSESSMENT IN 124 PATIENTS WITH CLOSED-ANGLE  
GLAUCOMA AND 70 AGE- AND SEX-MATCHED CONTROL SUBJECTS  
(Group mean values  $\pm$  SEM)

	Pupil cycle time (ms)
Control subjects (n=70)	970 $\pm$ 10
Closed-angle glaucoma patients (n=124)	1070 $\pm$ 20

Table 2

THE PREVALENCE OF ABNORMAL PUPIL CYCLE TIME, DEFINED BY THE AGE-ADJUSTED NORMAL TOLERANCE LIMIT AT THE UPPER 95th PERCENTILE, IN 124 PATIENTS WITH CLOSED-ANGLE GLAUCOMA AND 70 AGE- AND SEX-MATCHED CONTROL SUBJECTS

	Prevalence of abnormal PCT
Control subjects (n=70)	4.6%
Closed-angle glaucoma patients (n=124)	18.8%

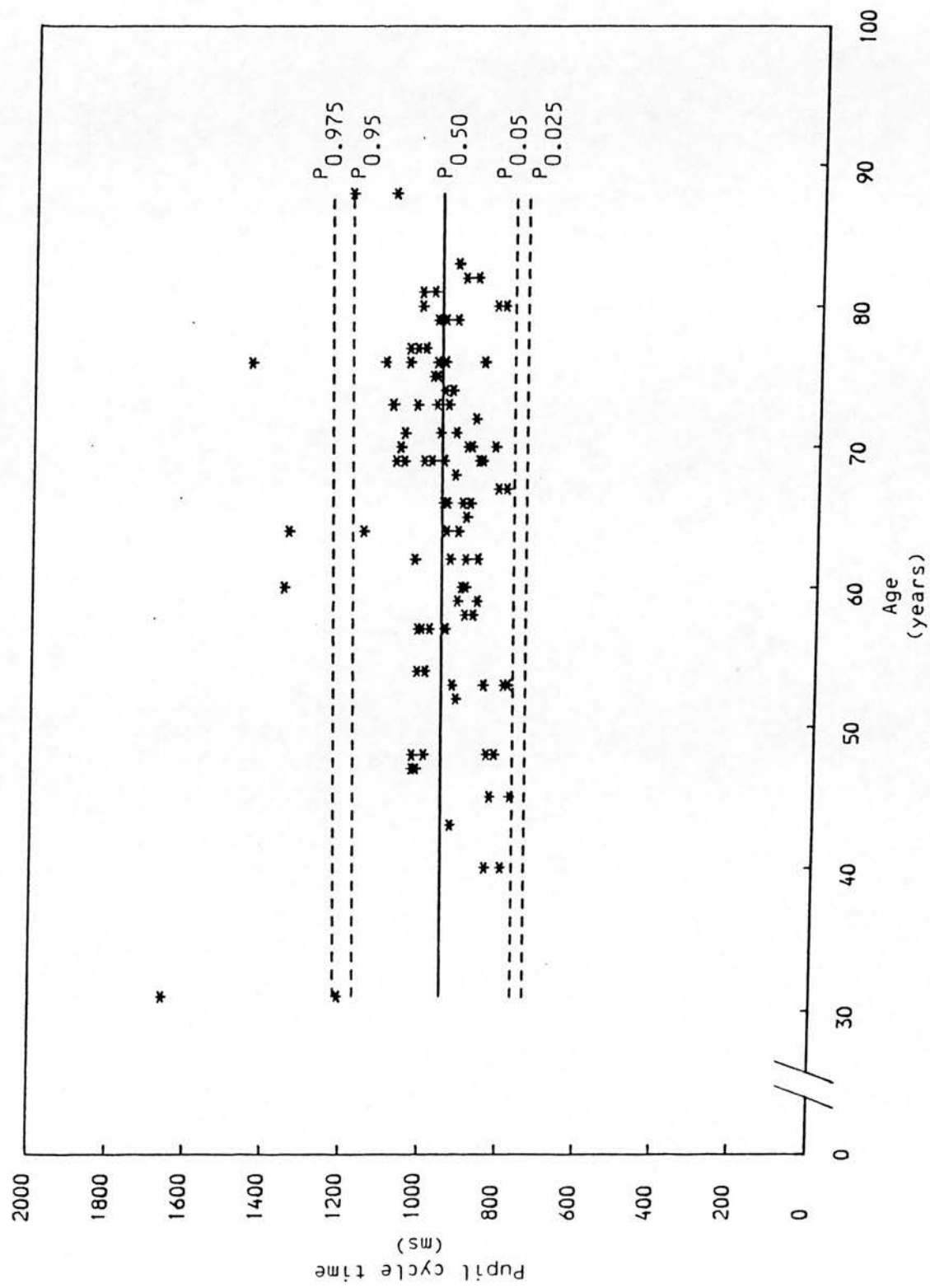
Table 3

THE PREVALENCE OF ABSENT PUPILLARY OSCILLATION IN 124 PATIENTS WITH  
CLOSED-ANGLE GLAUCOMA AND 70 AGE- AND SEX-MATCHED CONTROL SUBJECTS

	Prevalence of absent pupillary oscillation
Control subjects (n=70)	14.3%
Closed-angle glaucoma patients (n=124)	45.6%

Figure 1

AGE-ADJUSTED NORMAL TOLERANCE INTERVALS FOR PUPIL CYCLE TIME



PAPER 8

## Anterior segment autonomic dysfunction in ocular hypertension

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**Key words:** ocular hypertension, pupil cycle time, autonomic nerve function

**Abstract.** Autonomic nerve function in the anterior segment of the eye was assessed by measurement of the pupil cycle time in 189 patients with ocular hypertension and 70 age- and sex-matched control subjects. Parasympathetic dysfunction was significantly present in ocular hypertensive patients with narrow irido-corneal angles, though not in wide-angle subjects. The results are discussed, with particular reference to the accumulating evidence implicating autonomic dysfunction as a significant factor in the pathogenesis of the primary glaucomas.

### Introduction

That autonomic dysfunction may be part of primary glaucoma is suggested by the fact that production and outflow of aqueous humour in the anterior segment of the eye is therapeutically controlled by the application of topical autonomic drugs [1]; the hypothesis that elevation of intraocular pressure may signify dysfunction of the autonomic nervous system is supported by the demonstration of systemic parasympathetic neuropathy in 58% of patients with closed-angle glaucoma [2] and 42% of patients with ocular hypertension [3].

Recently, edge-light pupil cycle time was proposed as a quantifiable autonomic reflex [4], and it has been suggested that this test should be performed in patients with ocular hypertension to determine their ocular autonomic nerve function [5]. Pupil cycle time enables the integrity of the pupillary reflex arc to be accurately and objectively evaluated by a simple, non-invasive, clinically-orientated technique [6, 7]; in patients with normal iris musculature, pupil cycle time depends directly upon the number of nerve impulses transmitted, the velocity of nerve conduction, and the synaptic delay. A thin beam of light focussed at the pupillary margin induces oscillations of the pupil which may be accurately timed with a stop-watch. The beam is positioned to just overlap the inferior pupillary margin; light stimulation of retinal receptors initiates the pupil reflex, with constriction of the pupil, which in turn eliminates the afferent stimulation and induces a reflex dilation of the pupil, and light re-enters the eye and a second cycle commences.

### Patients and methods

Pupil cycle time was measured in 189 patients with ocular hypertension (mean age  $66.0 \pm 9.5$  years) and 70 age- and sex-matched control subjects (mean age  $66.2 \pm 10.1$  years), after informed consent had been obtained. The criteria of Hollands and Graham (1966) were employed in the diagnosis of ocular hypertension [8]. Angle assessment was made according to the standard Shaffer classification [9]; 90 patients had narrow irido-corneal angles (mean age  $67.5 \pm 9.2$  years) and 99 had wide angles (mean age  $64.8 \pm 9.6$  years). The control group consisted of hospital staff, and patients attending the casualty department who were subsequently determined to have no detectable abnormality. All subjects in the control group had wide irido-corneal angles, and visual acuity of  $\geq 6/9$  in each eye.

A comprehensive present and past history was obtained from each subject, followed by systematic general medical examination and ocular examination. Eyes were excluded from assessment if there was a history of: i. ocular trauma; ii. ocular operations; iii. current ophthalmic drug treatment; iv. eye disease. Subjects were also excluded from assessment on the basis of the following criteria: i. on treatment with autonomic or somatic neurological effects; ii. a past history of: a. medical disorders predisposing to autonomic nerve dysfunction; b. neurological disease.

After applying the exclusion criteria, pupil cycle time was measured in: i. Control group: 122 eyes in 70 subjects; ii. Ocular hypertension (narrow angles): 165 eyes in 90 patients; iii. Ocular hypertension (wide angles): 183 eyes in 99 patients.

Edge-light pupil cycle time was measured according to the following method. The patient was seated at a slit-lamp (Zeiss 30SL, Carl Zeiss, Welwyn Garden City, England) in a sealed room with low, constant background illumination (20 lux), and requested to fixate straight ahead on a distant object at 6 metres. A  $0.5 \times 6$  mm slit-beam was positioned horizontally and elevated until it just overlapped the inferior margin of the pupil, then focussed on the iris-lens border. The pupil constricted, then reflexly dilated in response to removal of afferent stimulation by iris blocking the light. 30 consecutive pupil cycles were timed by stop-watch; the result divided by 30 is the duration of a single cycle of the pupillary reflex arc. The pupil cycle time was measured 4 times for each eye separately (ie  $4 \times 300$  cycles) and the result averaged. The measurement of 30 cycles with subsequent division to determine the duration of a single cycle reduces subjective error in manual timing.

All assessments were performed on a single-blind basis.

### Results

The results of pupil cycle time assessment in 189 patients with ocular hypertension and 70 age- and sex-matched control subjects are described as follows:

*Table 1.* Results of pupil cycle time assessment in 141 patients with ocular hypertension and 61 age- and sex-matched control subjects (Group mean values  $\pm$  Sem).

	Pupil cycle time (ms)
Control subjects (n = 61)	968 $\pm$ 12
Ocular hypertensive patients (n = 141)	
OHNA (n = 63)	1049 $\pm$ 11
OHWA (n = 78)	1008 $\pm$ 11

- i. Pupil cycle time in patients with ocular hypertension
- ii. Normal tolerance intervals for pupil cycle time
- iii. The prevalence of absent pupillary oscillation in patients with ocular hypertension and the age- and sex-matched control group

*i. Pupil cycle time in patients with ocular hypertension*

The results of pupil cycle time assessment in 141 patients with ocular hypertension and 61 age- and sex-matched control subjects are shown in Table 1. Pupillary oscillation was not sustained for 120 cycles (ie  $4 \times 30$ -cycles) in a significant percentage of eyes examined; consequently, measurement of pupil cycle time was possible in a decreased number of eyes: i. Control group: 106 eyes in 61 subjects; ii. Ocular hypertension (narrow angles): 107 eyes in 63 patients; iii. Ocular hypertension (wide angles): 151 eyes in 78 patients.

Comparisons of mean pupil cycle time were made between the control group and patients with OHNA and OHWA separately; significance was assessed by Student's unpaired t test, with Dunnett's correction for multiple comparisons with a control group (10). Dunnett's tables have a maximum joint confidence coefficient of 99%, and every value of  $p < 0.01$  is therefore included in this category. The actual p value plus the corrected p value ( $p'$ ) are quoted for significant results. Pupil cycle time in patients with OHNA was significantly higher than the control group ( $p < 0.001$ ;  $p' < 0.01$ ). Pupil cycle time in patients with OHWA was also significantly higher than the control group, however this was nonsignificant after allowing for multiple comparisons ( $p = 0.02$ ;  $p' > 0.05$ ).

*ii. Normal tolerance intervals for pupil cycle time*

The results of pupil cycle time measurement in the control group were assessed for dependence on age by regression analysis. Using the computer programme

*Table 2.* The prevalence of abnormal pupil cycle time, defined by the age-adjusted normal tolerance limit at the upper 95th percentile, in 141 patients with ocular hypertension and 61 age- and sex-matched control subjects.

	Prevalence of abnormal PCT
Control subjects (n = 61)	4.6%
Ocular hypertensive patients (n = 141)	
OHNA (n = 63)	17.1%
OHWA (n = 78)	9.3%

SPSSx on an IBM 4341 computer, the data were fitted according to various mathematical models to obtain a normal distribution after adjustment for age, thereby permitting determination of tolerance intervals. Logarithms of the data were used to derive tolerance intervals, and a log normal distribution was obtained.  $\log_{10}$  (PCT) was not significantly age-dependent. Linear regression analysis, permitting determination of 2.5th, 5th, 95th and 97.5th percentiles, was calculated from:  $RLPCT = (\log_{10} PCT - (-0.02883 + 0.00019 \times \text{age})) / 0.05469$ ;  $RLPCT = \text{standardised residual } \log_{10} PCT$ . The age-adjusted normal tolerance limit, arbitrarily set at the upper 95th percentile of the log normal distribution after regression on age, was applied to the results obtained from patients with OHNA and OHWA, to determine the proportion of eyes outwith the normal limit; results are shown in Table 2. These tolerance limits are used as a standard for comparison in all routine assessments of pupil cycle time in the Glaucoma Unit, Liverpool, and the Department of Ophthalmology, University of Edinburgh.

*iii. The prevalence of absent pupillary oscillation in patients with ocular hypertension and the age- and sex-matched control group*

Pupillary oscillation was not sustained in a significant proportion of eyes examined (Table 3): i. Control group: 16 eyes in 11 subjects; ii. Ocular hypertension (narrow angles): 58 eyes in 38 patients; iii. Ocular hypertension (wide angles): 32 eyes in 19 patients.

Comparisons were made between the prevalence of absent pupillary oscillation in the control group and patients with OHNA and OHWA separately; significance was assessed by  $\chi^2$  test with Yates' correction. To allow for multiple comparisons with a control group, significant p values were multiplied by the number of comparisons made to obtain a corrected p value ( $p'$ ); the actual p value plus the corrected p value are quoted for significant results. The prevalence of absent pupillary oscillation was significantly higher in patients

*Table 3.* The prevalence of absent pupillary oscillation in 189 patients with ocular hypertension and 70 age- and sex-matched control subjects.

	Prevalence of absent pupillary oscillation
Control subjects (n = 70)	14.3%
Ocular hypertensive patients (n = 189)	
OHNA (n = 90)	35.6%
OHWA (n = 99)	16.6%

with OHNA than the control group ( $p < 0.001$ ;  $p' < 0.001$ ). No significant differences were present between the prevalence of absent pupillary oscillation in the control group and patients with OHWA ( $p > 0.05$ ).

### Discussion

Pupil cycle time enables rapid, quantifiable assessment of the pupillary reflex arc, which may be easily performed by clinicians with the facilities of standard biomicroscopy. There are no possible side-effects and no expense is incurred. However it must be stressed that pupil cycle time assesses the pupillary reflex arc as a discrete and indivisible unit; localisation of defects within the reflex suggested by prolongation of pupil cycle time can only be made by supplementing the data with specific information relating to individual components of the pathway. In this context, preliminary ocular examination of all control subjects and ocular hypertensive patients included meticulous central and peripheral visual field assessment; no field defects were demonstrated in any subject included in the study. This precaution is essential in the interpretation of results, as retinal nerve fibre bundle defects characteristic of glaucoma may impair the afferent limb of the reflex arc [11]; when afferent defects have been excluded, within the limits of sensitivity for visual field tests in current use, prolonged pupil cycle time may be attributed to defects in either the internuncial or efferent components of the arc by reasonable implication. Visual field assessment is not 100% sensitive in the determination of afferent defects, however it represents a reasonable clinical estimation of the afferent limb.

The duration of pupil cycle time is prolonged in older subjects; a mean pupil time of  $822 \pm 69$  ms has been proposed for subjects aged  $< 50$  years [6], compared with a mean of  $968 \pm 131$  ms in the present study of subjects aged  $66.2 \pm 10.1$  years. Prolongation of pupil cycle time in older control subjects may represent fatigue within the reflex, 14% of eyes in control subjects demonstrated an absence of sustained pupillary oscillation in response to edge-light stimulation.

The proposal that prolongation of pupil cycle time is a sensitive measure of dysfunction in the efferent parasympathetic limb of the pupillary light reflex [4] is supported by the present results. Recent studies have confirmed that pupil cycle time is particularly sensitive to dysfunction in the parasympathetic efferent limb of the pupillary reflex arc [12]. As afferent defects were carefully excluded as far as possible, significant prolongation of the pupil cycle time in patients with ocular hypertension may be attributed to the efferent limb. There is considerable supportive evidence to suggest that this interpretation is correct; assessment of systemic autonomic function by tests based upon cardiovascular reflexes, in the same patients, demonstrated parasympathetic dysfunction in 42% of ocular hypertensives, with significantly higher prevalence in narrow-angle patients (50%) than wide-angle patients (34%) [3]. Prolongation of pupil cycle time in patients with diabetes mellitus has been shown to correlate well with evidence of autonomic neuropathy, determined by cardiovascular reflex assessment [12]. The results of this study imply parasympathetic dysfunction in the efferent limb of the pupillary reflex arc in ocular hypertensive patients with narrow irido-corneal angles; pupil cycle time was significantly prolonged compared with the age- and sex-matched control group ( $p < 0.001$ ), pupillary oscillation was absent in a significantly-increased proportion of subjects (36% cf 14%), and pupil cycle time was outwith the age-adjusted normal tolerance limit in 17% of patients compared with 5% of the control group. In comparison, anterior segment parasympathetic dysfunction is probably not present to a significant degree in ocular hypertensive patients with wide angles.

These results are in complete accord with current evidence suggesting autonomic dysfunction as a significant predisposing factor in the pathogenesis of some of the primary glaucomas. Intermittent angle-closure in the anterior segment of the eye—effected by changes in parasympathetic tone [13]—has been demonstrated in 46% of patients with ocular hypertension [14]. Closure of the angle in the anterior segment of the eye is a dynamic process, resulting from a combination of anterior translational movement of the iris-lens diaphragm [15] and peripheral iris bombe [16]; the basic aetiological factor common to both mechanisms is pupil block, a manifestation of relative parasympathetic and sympathetic activity in the anterior segment [17]. The probability of developing angle-closure during autonomic provocation is directly related to the configuration of the anterior chamber angle, with increased frequency as angle width decreases [14]; ocular parasympathetic dysfunction is specifically associated with narrow-angle ocular hypertension.

The results of the present study have demonstrated impairment of the pupillary reflex arc in ocular hypertensive patients with narrow angles, manifest by delay or absence of sustained pupillary oscillation in response to light, efferent parasympathetic dysfunction is implied. As systemic parasympathetic dysfunction is present in 50% of narrow-angle ocular hypertensive patients, the presence of ocular autonomic neuropathy in this category is not unexpected, providing further evidence in support of the association between ocular hypertension and dysfunction of the autonomic nervous system.

### Acknowledgements

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PAPER 9

PARASYMPATHETIC DENERVATION HYPERSENSITIVITY OF THE IRIS  
IN OCULAR HYPERTENSION

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## ABSTRACT

Seventy-eight ocular hypertensive patients and forty-seven age- and sex-matched control subjects were assessed for parasympathetic denervation hypersensitivity of the iris using topical application of 2.5% methacholine chloride solution. Constriction of the pupil in response to methacholine stimulation of the sphincter pupillae was significantly greater in the ocular hypertensive patients than the control group ( $p < 0.001$ ). The implications are discussed, with particular reference to the association between autonomic neuropathy and the primary glaucomas.

## KEY WORDS

Denervation hypersensitivity, ocular hypertension, autonomic neuropathy, primary glaucoma

## INTRODUCTION

Adrenoceptor density, determined by radioligand binding, is significantly increased at the postsynaptic receptor site in autonomic denervation hypersensitivity (1,2). This mechanism may be applied to the anterior segment of the eye, where pupillary diameter is directly controlled by the autonomic nervous system; parasympathetic nerves effect pupillary constriction via the sphincter pupillae, and sympathetic nerves effect pupillary dilation via the dilator pupillae. Pupillary diameter therefore represents an external manifestation of relative autonomic activity in the anterior segment of the eye. 2.5% methacholine is an effective determinant of parasympathetic denervation hypersensitivity; topical guttae 2.5% methacholine constricts Adie's tonic pupils, whilst normal pupils may not be affected by concentrations up to 15% (3). 2.5% methacholine was therefore used in the present study to determine the degree of parasympathetic denervation hypersensitivity in the anterior segment of patients with ocular hypertension.

## MATERIALS AND METHODS

After informed consent had been obtained, pupillary responses to guttae 2.5% methacholine chloride were assessed in 78 patients with ocular hypertension (mean age  $66.6 \pm 8.7$  years) and 47 age- and sex-matched control subjects (mean age  $67.0 \pm 11.1$  years). The control group consisted of hospital staff, and patients attending the casualty department who were subsequently determined to have no detectable ocular abnormality. Subjects known to have medical disorders predisposing to autonomic nerve dysfunction, or taking medication with effects on the autonomic nervous system, were excluded from the study. A comprehensive ocular examination was performed on all subjects. In particular, there was no evidence of visual field defects following dynamic and static Goldmann perimetry: dynamic perimetry with  $I_4, I_3, I_2$  isopters; static perimetry with  $I_3$  and  $I_2$  isopters; blind spot with  $I_3$  and  $I_2$  isopters. Intraocular pressures, by Goldmann applanation tonometry, were as follows (mean  $\pm$  SEM): control group  $16.6 \pm 0.2$  mmHg; ocular hypertensive patients  $25.2 \pm 0.2$  mmHg. Assessment of pupillary denervation hypersensitivity was performed four weeks after initial ocular examination. Eyes were excluded from assessment if there was a history of ocular operations, ocular trauma, or current ophthalmic drug treatment. No subject included in the study - either control or ocular hypertensive - had ever been treated with anti-glaucoma medication.

Pupil diameters were recorded photographically. Subjects' eyes were photographed between 9-11am under standard lighting conditions, with measured luminance of 20 apostilbs. The subject was instructed to rest his/her forehead against an ophthalmic head-rest, and a scale was positioned against the lower eyelid in the perpendicular plane of the iris. The subject fixated at 6 metres, then a photograph at x3 magnification was taken of both eyes together. One drop of 2.5% methacholine chloride solution was

placed in the conjunctival sac of the right eye. Forty-five minutes later, a second photograph was taken in a similar manner. The photographic slides were projected on to a white screen at 5 metres, producing a final magnification of x17. Horizontal pupillary diameters were measured to an accuracy of  $\pm 0.5$  mm, and corrected to actual values by comparison with relative magnification of the scale; this resulted in measurements of actual pupillary diameters to  $\pm 0.03$  mm.

$$2.5\% \text{ methacholine ratio} = \frac{\text{horiz. pupil diameter 45 min post-test}}{\text{horiz. pupil diameter pre-test}}$$

The concurrent assessment of an age- and sex-matched control group provided effective standards for comparison. One eye was tested in each subject, and all assessments were performed on a single-masked basis.

Diabetes mellitus is significantly associated with ocular hypertension (3), and may cause parasympathetic denervation hypersensitivity of the pupil (4). To determine the possible influence of diabetes on pupil function in ocular hypertension, the diabetic status of each subject was assessed by 75-gram oral glucose tolerance test according to the standard criteria of the National Diabetes Data Group (5). Subjects with known diabetes mellitus were excluded from oral glucose tolerance test.

## RESULTS

i. Age-adjusted normal tolerance intervals for 2.5% methacholine ratio 2.5% methacholine ratios in the control group were assessed for dependence on age by regression analysis(6). The data was fitted according to various mathematical models using the computer programme SPSSx on an IBM 4341 computer to obtain a normal distribution on age, thus permitting determination of tolerance intervals (7). Linear regression analysis was calculated from:

$$RLM_{2.5} = (\log_{10} M_{2.5} - (0.01756 - 0.00076 \times \text{age})) / 0.05241$$

$$RLM_{2.5} = \text{standardised residual } \log_{10}(\text{2.5\% methacholine ratio})$$

$\log_{10}(\text{2.5\% methacholine ratio})$  was shown to depend significantly on age ( $r = -0.40$ ;  $p < 0.001$ ). (Figure 1)

ii. Pupil responses to 2.5% methacholine chloride in ocular hypertension Comparisons were made between the results of the control group and patients with ocular hypertension; significance was assessed by Student's unpaired t test. 2.5% methacholine ratios (mean  $\pm$  SEM) were significantly lower in patients with ocular hypertension ( $0.87 \pm 0.01$ ) than the control group ( $0.94 \pm 0.01$ ) ( $p < 0.001$ ). Pupillary constriction resulting from methacholine stimulation of the sphincter pupillae in a patient with ocular hypertension is shown in figure 2.

iii. Diabetic status and denervation hypersensitivity

Diabetes mellitus was present in 17 patients with ocular hypertension (21.8%) and 3 control subjects (6.4%). There were no significant differences ( $p > 0.05$ ) in pupil responses to 2.5% methacholine between diabetic and non-diabetic subjects, in either the ocular hypertensive subjects or the control group.

## DISCUSSION

Neuropharmacological manipulations are effectively utilised in the localisation of defects in autonomic innervation of the iris musculature. Observations of hypersensitive reactions to topical cholinergic agonists in parasympathetic denervated irides (8) resulted in the use of dilute guttae methacholine as a pathognomonic test of pupillotonia (2), and subsequently to the definitive treatise on denervation hypersensitivity by Cannon and Rosenbluth in 1949 (9). However constriction of the pupil per se, in response to methacholine stimulation of the sphincter pupillae, may not be indicative of an increase in postsynaptic receptors; whilst previous descriptions have attributed the manifestations of denervation hypersensitivity to an increase in postsynaptic receptor numbers - without alteration in receptor affinity (1) - alternative explanations may be equally applicable. Thus although this test is of undisputed value in the clinical assessment of anterior segment denervation hypersensitivity, explanations of the observed effect remain speculative. This study has shown that pupil responses to 2.5% methacholine are significantly age-dependent in normal subjects, a fact not previously well-recognised, and therefore comparison with an age- and sex-matched control group is essential. Pupillary constriction following administration of topical 2.5% methacholine was significantly greater in patients with ocular hypertension than the control group ( $p < 0.001$ ), supporting the hypothesis of parasympathetic denervation hypersensitivity of the iris in patients with ocular hypertension. The presence of ocular autonomic neuropathy in these patients is not unexpected, as systemic parasympathetic dysfunction - demonstrated by tests based upon cardiovascular reflexes - is present in 42% of patients with ocular hypertension (10). Autonomic neuropathy is not characteristically a localised disorder; it is unlikely that significant autonomic neuropathy in the anterior segment of the

eye is restricted to the iris. Autonomic dysfunction may affect the outflow mechanism directly; parasympathetic nerve stimulation has been shown to increase facility of outflow by inducing ciliary muscle contraction on the scleral spur, thereby actively 'opening' the trabecular meshwork. In the presence of parasympathetic dysfunction, as in ocular hypertension, one may reasonably assume this mechanism to be impaired.

Effects of the autonomic nervous system are recognised to be of fundamental importance in the determination of intraocular pressure, forming the basis of treatment for primary glaucoma with topical application of autonomic agonists (pilocarpine, adrenaline) and antagonists (timolol, guanethidine). In this context, the demonstration of significant parasympathetic neuropathy in the anterior segment of patients with raised intraocular pressure is an interesting observation, the exact relevance of which remains to be determined.

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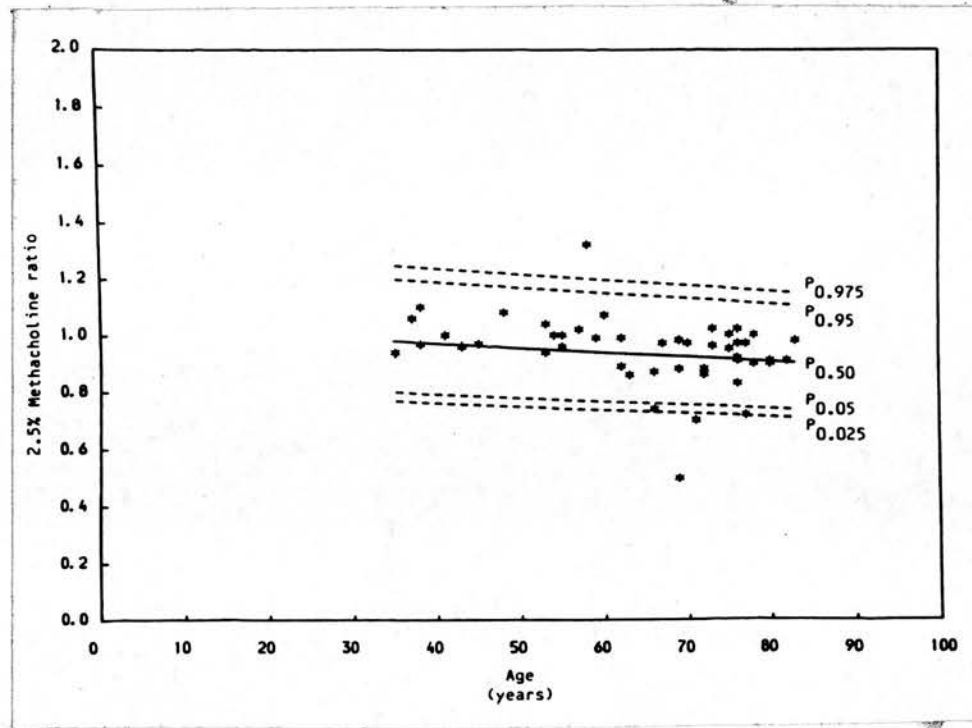
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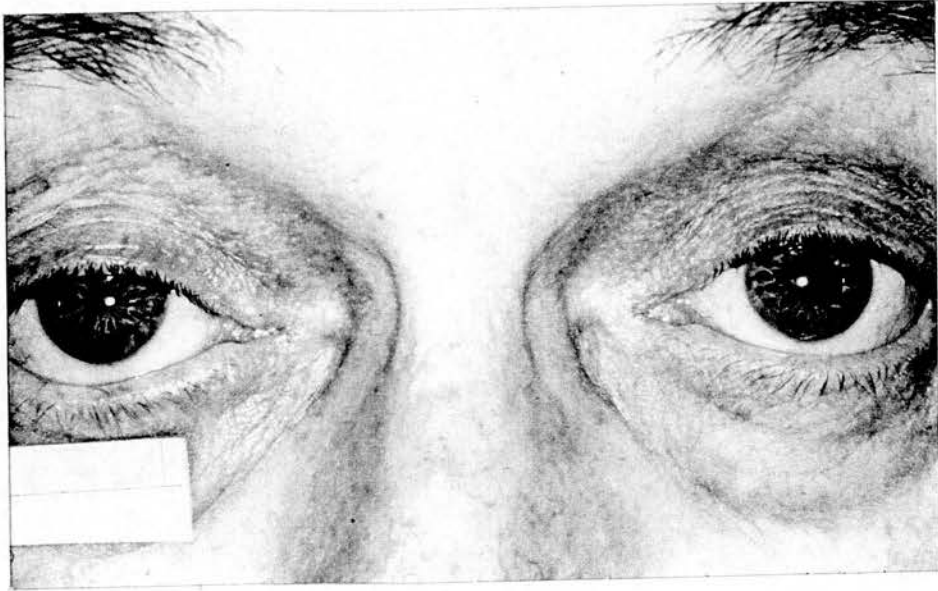
## Figure 1

Age-adjusted normal tolerance intervals for 2.5% methacholine ratio, with 2.5th, 5th, 95th, and 97.5th percentiles.

## Figure 2

Pupil constriction following instillation of 2.5% methacholine chloride solution into the right eye of a patient with ocular hypertension, demonstrating denervation hypersensitivity





PAPER 10

## Autonomic Denervation Hypersensitivity in the Primary Glaucomas

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### Summary

Autonomic denervation hypersensitivity of the iris was assessed in 44 patients with primary closed-angle glaucoma, 20 patients with primary open-angle glaucoma, and 40 age- and sex-matched control subjects. Significantly increased pupillary constriction in response to 2.5% methacholine chloride, indicating parasympathetic denervation hypersensitivity, was present in both closed-angle ( $p < 0.02$ ) and open-angle glaucoma patients ( $p < 0.001$ ), compared with the control group. Significantly increased pupillary dilatation in response to 0.5 per cent phenylephrine hydrochloride, indicating sympathetic denervation hypersensitivity of the iris, was also present in both closed-angle glaucoma ( $p < 0.01$ ) and open-angle glaucoma patients ( $p < 0.05$ ). The association between autonomic neuropathy and the primary glaucomas is discussed, with particular reference to the potential effects of autonomic dysfunction on aqueous dynamics.

Elevation of intraocular pressure in the primary glaucomas occurs as a consequence of impaired outflow of aqueous humour from the anterior chamber of the eye. The mechanism of obstruction to outflow forms the basis of categorisation in glaucoma: in closed-angle glaucoma the exit of aqueous from the anterior chamber is physically prevented by apposition of peripheral iris to cornea; in open-angle glaucoma the site of obstruction lies within the angle, probably the trabecular meshwork, and the entrance to the angle is not a primary contributing factor to the glaucomatous process. The pathological effects of raised intraocular pressure on the retinal nerve fibre layer are well established, however the aetiological factors precipitating the primary glaucomas have not been fully defined. Autonomic nerve function is a major determinant of intraocular pressure; glaucoma therapeutics are based upon manip-

ulation of the autonomic nervous system in the anterior segment of the eye. The efficacy of ocular autonomic nerve function can be inferred from the assessment of denervation hypersensitivity. In the presence of autonomic neuropathy, receptor density is significantly increased at the postsynaptic receptor site,<sup>1</sup> and may be detected by the measurement of exaggerated end-organ responses to specific autonomic agonists. The pupil provides an excellent model for the assessment of autonomic integrity in the eye; pupillary diameter represents a balance between parasympathetic and sympathetic activity in the anterior segment, and assessment of denervation hypersensitivity permits these components of the autonomic nervous system to be individually measured by a simple, non-invasive and accurate technique. Several pharmacological agents have been employed in the assessment of autonomic denervation

hypersensitivity;<sup>2,3,4</sup> the only prerequisite to the utilisation of any drug for this purpose is the preliminary determination of the normal response. Parasympathetic denervation hypersensitivity may be effectively assessed by topical application of 2.5% methacholine chloride,<sup>5,6</sup> and sympathetic denervation sensitivity is demonstrated by the pupillary effects of 0.5% phenylephrine hydrochloride;<sup>7</sup> normal age-adjusted tolerance intervals to both agents have recently been documented.<sup>6,7</sup>

The aim of this study was to assess autonomic nerve function in the anterior segment of the eye in patients with primary closed-angle glaucoma and primary open-angle glaucoma, by measurement of pupillary responses to pharmacological agents recognised to be indicative of autonomic denervation hypersensitivity.

#### Patients and Methods

After informed consent had been obtained, ocular autonomic nerve function was assessed in 44 patients with closed-angle glaucoma (mean age  $66.5 \pm 10.2$  years), 20 patients with open-angle glaucoma (mean age  $66.7 \pm 7.9$  years), and 40 age- and sex-matched control subjects (mean age  $65.3 \pm 12.7$  years). The diagnosis of open-angle glaucoma and closed-angle glaucoma was made according to established criteria.<sup>8,9,10</sup> The open-angle glaucoma group consisted of 20 consecutive new referrals to a glaucoma clinic, prior to the commencement of treatment. A comprehensive medical history was obtained from each subject, followed by systematic general medical and ocular examination; applanation tonometry was specifically not performed until after the assessment of denervation hypersensitivity. Eyes were excluded from assessment if there was a history of:

- (i) ocular operations: only unoperated eyes were included in the study. In patients with closed-angle glaucoma, assessments were performed only in unoperated fellow eyes. Eyes which had closed-angle glaucoma were specifically excluded.
- (ii) ocular trauma
- (iii) current ophthalmic drug treatment
- (iv) corneal disease
- (v) dry eyes

Subjects known to have medical disorders predisposing to autonomic nerve dysfunction, or taking medication with effects on the autonomic nervous system, were similarly excluded from the study.

#### Autonomic Denervation Hypersensitivity

##### (i) *Parasympathetic nervous system*

Pupil diameters were recorded photographically between 9 and 11 am under standardised lighting conditions; the subject faced a surface with measured luminance of 20 apostilbs, whilst low, constant background illumination was maintained. The subjects were positioned on an ophthalmic head-rest, thereby effecting reproducible positions for photography. A scale was placed against the lower eyelid in the perpendicular plane of the iris, the subjects fixated at 6 metres, then a photograph at  $\times 3$  magnification was taken of both eyes together using a Nikon F camera with Medical Nikkor 120 mm f4 lens and Kodak Ektachrome Professional Film (ASA 200). One drop of 2.5% methacholine chloride solution was placed in the conjunctival sac of one eye, and one drop of sterile normal saline solution concurrently placed in the conjunctival sac of the contralateral eye. In open-angle glaucoma patients and control subjects the choice of the eye to be tested was selected randomly. In closed-angle glaucoma patients only fellow eyes were tested. Forty-five minutes later, a second pupil photograph was taken. Responses to 2.5% methacholine, if present, were of short duration; pupil diameters returned to normal within one and a half hours of instilling methacholine.

##### (ii) *Sympathetic nervous system*

Three days later, the assessment of sympathetic denervation hypersensitivity was performed using essentially the same technique, substituting 2.5% methacholine by 0.5% phenylephrine hydrochloride. Assessments were performed on the same eye in each subject.

##### (iii) *Pupil measurement*

The photographic slides were projected on to a white screen at five metres, and were magnified by a factor of 17. Horizontal pupil diameters were measured directly from the screen

to an accuracy of  $\pm 0.5$  mm, and were then corrected to actual values by comparison with relative magnification of the scale. Effectively, measurement of pupil diameter was accurate to within  $\pm 0.03$  mm.

Parasympathetic denervation hypersensitivity was expressed as the 2.5% methacholine ratio:

$$\frac{\text{horizontal pupil diameter 45 minutes post-test}}{\text{horizontal pupil diameter pre-test}}$$

Sympathetic denervation hypersensitivity was also determined by the ratio of the post- to pre-test horizontal pupil diameter, and expressed as the 0.5% phenylephrine ratio.

The concurrent assessment of an age- and sex-matched control group provided effective standards for comparison. All assessments were performed on a double-masked basis.

#### Statistical analysis

Comparisons were made between the results of the control group and both categories of primary glaucoma separately; significance was assessed by Student's unpaired *t* test. Dunnett's multiple comparison procedure was applied to the levels of significance thus obtained, to prevent incorrect conclusions from multiple comparisons with a control.<sup>11</sup> Results are expressed as mean  $\pm$  SEM.

#### Results

##### (i) Parasympathetic denervation hypersensitivity

Significantly increased pupillary constriction in response to 2.5% methacholine chloride, indicating parasympathetic denervation of the iris, was present in both closed-angle and open-angle glaucoma groups. 2.5% methacholine ratios were significantly lower in patients with closed-angle glaucoma ( $0.92 \pm 0.01$ ) than the control group ( $0.96 \pm 0.01$ ) ( $p < 0.02$ ). 2.5% methacholine ratios were also significantly lower in open-angle glaucoma patients ( $0.84 \pm 0.04$ ) than control subjects ( $p < 0.001$ ).

##### (ii) Sympathetic denervation hypersensitivity

Significantly increased pupillary dilatation in response to 0.5% phenylephrine, indicating sympathetic denervation hypersensitivity of

the iris, was also present in both major categories of primary glaucoma. 0.5% phenylephrine ratios were significantly higher in patients with closed-angle glaucoma ( $1.30 \pm 0.03$ ) ( $p < 0.01$ ) and open-angle glaucoma ( $1.30 \pm 0.08$ ) ( $p < 0.05$ ) than the control group ( $1.19 \pm 0.03$ ).

#### Discussion

The concept of denervation hypersensitivity originated in the early years of the 20th century; in 1904, Meltzer described paradoxical pupil dilatation in response to adrenaline,<sup>12</sup> and in 1905 Markus<sup>13</sup> and Anderson<sup>14</sup> separately noted sensitivity of the denervated pupil to cholinergic drugs. Sensitisation of the denervated pupillary sphincter to acetylcholine was confirmed by Shen and Cannon in 1936;<sup>15</sup> the principles of denervation hypersensitivity were initially proposed by Cannon in 1939<sup>16</sup> and subsequently confirmed in a definitive treatise by Cannon and Rosenbluth in 1949.<sup>17</sup>

Assessment of denervation hypersensitivity permits accurate and objective measurement of autonomic efficacy in the anterior segment of the eye. The results of the present study have demonstrated increased pupillary responses to minute quantities of parasympathetic and sympathetic agonists in both closed-angle and open-angle glaucoma patients, compared with an age- and sex-matched control group. Although the degree of pupillary constriction in response to 2.5% methacholine was significantly higher in open-angle glaucoma than in closed-angle glaucoma patients, this does not necessarily suggest a higher prevalence of neuropathy in open-angle glaucoma. Indirect assessment of nerve function by measurement of a tissue response is obviously dependent upon an intact effector—the iris musculature; in closed-angle glaucoma patients, fellow eyes may have sustained previous episodes of intermittent angle-closure, and up to 66% of fellow eyes may subsequently develop overt angle-closure.<sup>18,19</sup> Previous episodes of intermittent angle-closure may impair iris integrity, which is a prerequisite for the indirect assessment of autonomic denervation hypersensitivity in the anterior segment. The lesser degree of pupillary constriction demonstrated

in closed-angle glaucoma patients compared with their open-angle glaucoma counterparts may therefore reflect impaired iris function, rather than a lesser degree of autonomic neuropathy.

The presence of ocular denervation hypersensitivity in both major categories of primary glaucoma implies that autonomic neuropathy is present in the anterior segment of both open-angle and closed-angle glaucoma. The demonstration of significant ocular autonomic dysfunction in patients with open-angle and closed-angle glaucoma must be placed in perspective. An association has been demonstrated between systemic autonomic dysfunction and all major categories of primary glaucoma; systemic autonomic neuropathy may be presented in up to 58% of patients with closed-angle glaucoma,<sup>20</sup> 42% of ocular hypertensive subjects,<sup>21</sup> and 37% of open-angle glaucoma patients.<sup>22</sup> Autonomic neuropathy is not characteristically a localised disorder; evidence of ocular autonomic neuropathy in patients with a high prevalence of systemic autonomic dysfunction is therefore not unexpected. Although there is a significant association between autonomic neuropathy and the primary glaucomas, prevalence levels of the disorder seem to be directly related to the clinical category of glaucoma. The prevalence of autonomic neuropathy in 124 patients with primary closed-angle glaucoma (58%) was determined by comparison of results with standard normal values;<sup>20</sup> if the results are compared with age-adjusted normal tolerance limits for autonomic function tests<sup>23</sup>—a more rigorous parameter—the prevalence of systemic autonomic dysfunction in these patients decreases to 50%. The prevalence of autonomic neuropathy in 189 ocular hypertensive subjects was reported as 42%,<sup>21</sup> however when this group was subdivided by angle configuration into narrow-angle and wide-angle categories, the prevalence in narrow angle patients with ocular hypertension (50%) was significantly higher than in wide-range subjects (34%). It is therefore apparent that the prevalence of autonomic dysfunction seems to be associated with the type of glaucoma; the prevalence in closed-angle glaucoma patients (50%) is identical to that of ocular hypertensives with nar-

row angles (50%), whilst the prevalence in open-angle glaucoma patients (37%) is similar to that in ocular hypertensives with wide angles (34%).

Parasympathetic denervation hypersensitivity of the iris has previously been described in patients with ocular hypertension, and parasympathetic neuropathy has been suggested as a significant predisposing factor in the pathogenesis of raised intraocular pressure.<sup>6</sup> The effects of autonomic neuropathy on the pathogenesis of glaucoma are probably dependent upon the pre-existing anatomical configuration of the anterior chamber. In closed-angle glaucoma patients, the anterior chamber is characteristically shallow with narrow irido-corneal angles, and is therefore predisposed to angle-closure. The importance of pupil block in angle-closure is well established;<sup>24,25,26</sup> pupil block force is a posteriorly-directed vector, inhibiting the passage of aqueous from the posterior to the anterior chamber. Pupil block is maximal at mid-dilatation,<sup>27</sup> the recognised pupil configuration during an acute episode of angle-closure. As previously explained, pupil diameter is directly controlled by the autonomic nervous system; parasympathetic and sympathetic neuropathy in the anterior segment would produce a mid-dilated pupil, the position of maximal pupil block. In eyes with narrow angles, increase in pupil block force may precipitate angle-closure.

In patients with open-angle glaucoma and ocular hypertension, autonomic neuropathy may influence the development of raised intraocular pressure by a different mechanism. It has been proposed that autonomic dysfunction may increase intraocular pressure in subjects with ocular hypertension by impairment of aqueous outflow from the anterior chamber.<sup>6</sup> Parasympathetic nerve stimulation increases facility of outflow by inducing ciliary muscle contraction on the scleral spur, thereby actively opening the trabecular meshwork and utilising the potential reserve outflow. In subjects with parasympathetic dysfunction, this mechanism will be impaired, and elevation of intraocular pressure may be precipitated. Ocular hypertension may progress to overt glaucoma in a significant proportion of patients, and this

mechanism has subsequently been forwarded as an explanation for the effects of anterior segment parasympathetic neuropathy on the pathogenesis of open-angle glaucoma.<sup>28</sup>

Evidence of autonomic denervation hypersensitivity is considered a pathognomonic feature of autonomic neuropathy. Although the present study does not establish a temporal relationship between the development of autonomic neuropathy and the diagnosis of glaucoma, there are several significant features which suggest the probable sequence of events. A high prevalence of systemic autonomic neuropathy has been demonstrated in patients with closed-angle glaucoma and open-angle glaucoma; autonomic neuropathy is not characteristically a localised disorder, and ocular autonomic dysfunction almost certainly represents a feature of the generalised disorder. As one cannot postulate a mechanism whereby glaucoma may precipitate systemic autonomic neuropathy (although the converse is a feasible hypothesis), one may reasonably assume that autonomic dysfunction either precedes glaucoma, or develops concurrently as a manifestation of a similar primary aetiological process. This does not preclude the potential secondary effects of glaucoma on ocular autonomic integrity; elevation of intraocular pressure may compromise autonomic nerve function in the anterior segment of the eye, thereby exacerbating the primary process. Thus the ocular autonomic neuropathy demonstrated by the presence of significant autonomic denervation hypersensitivity is likely to represent the effects of both primary and secondary autonomic dysfunction. The aetiology of the primary glaucomas is multifactorial; present evidence suggests that autonomic dysfunction may be a significant predisposing factor, in association with many others.

The prevalence of autonomic nerve dysfunction in each of the major categories of primary glaucoma, and also in the potentially pre-glaucomatous diagnosis of ocular hypertension, inevitably suggests a common aetiological factor in pathogenesis. Evidence of an association between autonomic neuropathy and glaucoma does not establish a causal relationship, although there are several significant factors which support this hypoth-

esis. The pathogenesis of closed-angle glaucoma is dependent upon the pupil block force, which is directly controlled by the autonomic nervous system. In open-angle glaucoma, elevation of intraocular pressure occurs as a consequence of impaired aqueous outflow from the anterior chamber; as previously explained, aqueous outflow may be significantly compromised by parasympathetic neuropathy. Medical therapy in glaucoma is based upon manipulation of autonomic receptors in the anterior segment. The demonstration of significant autonomic neuropathy in the anterior segment of glaucoma patients provides a logical rationale for the efficacy of autonomic agents in the management of the disorder; therapy with autonomic agonists and antagonists may provide the autonomic control of aqueous dynamics which is inevitably impaired in a patient with autonomic neuropathy. As both parasympathetic and sympathetic pharmacological effects are specifically stimulated in the management of the primary glaucomas, one may reasonably postulate that both branches of the autonomic nervous system may be involved in the pathological process. It is significant that the same medications are effective in open-angle glaucoma and closed-angle glaucoma, although different anatomical mechanisms are involved in the genesis of both conditions, suggesting that although these conditions produce sufficiently elevated intraocular pressure to damage the retinal nerve fibre layer by different physical processes, a similar aetiological factor may be involved in the pathogenesis of both conditions.

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PAPER 11

SYMPATHETIC DENERVATION HYPERSENSITIVITY OF THE IRIS  
IN OCULAR HYPERTENSION

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Short title:            Sympathetic denervation in ocular hypertension

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## ABSTRACT

Sympathetic denervation hypersensitivity of the iris was assessed in 51 patients with ocular hypertension and 36 age- and sex-matched control subjects. Significantly increased pupillary dilatation in response to topically-applied 0.5% phenylephrine hydrochloride, suggesting sympathetic denervation hypersensitivity of the iris, was present in the ocular hypertensive group ( $p < 0.003$ ). The effects of autonomic nerve function on aqueous dynamics are reviewed, and the association between autonomic dysfunction and ocular hypertension is discussed.

## KEY WORDS

Denervation hypersensitivity, ocular hypertension, autonomic neuropathy, primary glaucoma

## INTRODUCTION

Ocular hypertension is defined as intraocular pressure  $\geq 21$  mmHg in the absence of glaucomatous visual field defects, abnormal mesoderm in the anterior chamber angle of the eye, and no history suggestive of angle-closure (Hollows and Graham, 1966). This ubiquitous condition affects up to 9% of the population (Hollows and Graham, 1966; Stromberg, 1962), of whom 10% eventually progress to primary glaucoma (David, Livingston and Luntz, 1977). The autonomic nervous system has a significant role in the control of intraocular pressure: sympathetic nerve function affects the production of aqueous in the ciliary processes and the outflow of aqueous from the anterior chamber (Sears and Neufeld, 1975), whilst parasympathetic nerve stimulation has significant effects primarily on aqueous outflow (Kaufman and Barany, 1975). As pupillary diameter is representative of relative autonomic activity in the anterior segment of the eye, the pupil may be effectively utilised in the assessment of ocular autonomic integrity. Autonomic neuropathy precipitates denervation hypersensitivity, effecting a significant increase in the density of postsynaptic autonomic receptors (U'Pritchard and Snyder, 1978). Various pharmacological agents have been employed in the assessment of ocular autonomic denervation hypersensitivity (Thompson and Mensher, 1971; Jaffe, 1950; Scheie, 1940); sympathetic denervation hypersensitivity may be measured by pupillary responses to topical 0.5% phenylephrine hydrochloride (Clark, 1988), and parasympathetic supersensitivity is effectively assessed by 2.5% methacholine chloride (Scheie and Adler, 1940; Clark and Mapstone, 1987). Recently, parasympathetic neuropathy has been demonstrated in the anterior segment of ocular hypertensive subjects, with

significantly-increased pupillary constriction in response to 2.5% methacholine chloride compared with age-matched normal subjects, suggesting parasympathetic denervation hypersensitivity of the iris (Clark and Mapstone, 1987).

The aim of this study was to assess the efficacy of sympathetic nerve function in the anterior segment of the eye in patients with ocular hypertension, by photographic measurement of pupillary responses to a sympathetic agonist recognised to be indicative of ocular sympathetic denervation hypersensitivity.

## PATIENTS AND METHODS

Ocular sympathetic nerve function was assessed in 51 patients with ocular hypertension (mean age  $66.6 \pm 8.0$  years) and 36 age- and sex-matched control subjects (mean age  $65.0 \pm 12.8$  years). The control group consisted of hospital staff, and patients attending an ophthalmic casualty department who were determined to have no detectable ocular abnormality. A comprehensive medical history was obtained from each subject, followed by systematic general medical and ocular examination. No subject had any medical disorder or were taking any medication known to interfere with autonomic function. Eyes were excluded from assessment if there was a history of ocular disease, ocular trauma, ocular operations, current ophthalmic drug treatment, corneal disease or dry eyes. No subject had received treatment with anti-glaucoma medication at any time. Intraocular pressures, assessed by Goldmann applanation tonometry, were as follows (mean  $\pm$  SEM): ocular hypertensive subjects  $25.4 \pm 0.2$  mmHg; control group  $16.5 \pm 0.2$  mmHg. There were no visual field defects present in any subject, assessed by repeated Goldmann perimetry: dynamic perimetry with  $I_4, I_3, I_2$  isopters; static perimetry with  $I_3$  and  $I_2$  isopters; blind spot with  $I_3$  and  $I_2$  isopters. Assessment of ocular sympathetic denervation hypersensitivity was performed at least four weeks after the ocular examination. Informed consent was obtained from all participants in the study.

Sympathetic denervation hypersensitivity of the iris was assessed by the following technique. Pupil diameters were recorded photographically between 9-11 am under standardised lighting conditions; each subject faced a surface with controlled luminance of

20 apostilbs whilst low, constant background illumination was maintained. The subject was instructed to rest his/her forehead against an ophthalmic head-rest, thereby effecting reproducible positions for pupil photography. A scale was positioned against the lower eyelid in the perpendicular plane of the iris, the subject was requested to fixate at 6 metres, then a photograph at x3 magnification was taken of both eyes together using a Nikon F camera with Medical Nikkor 120 mm f4 lens and Kodak Ektachrome professional film (ASA 200). One drop of 0.5% phenylephrine chloride solution was placed in the conjunctival sac of one eye, and one drop of sterile normal saline solution was concurrently placed in the conjunctival sac of the contralateral eye; the choice of eye to be tested was selected randomly. Forty-five minutes later, a second pupil photograph was taken under similar ambient lighting conditions.

The effect of 0.5% phenylephrine on pupil diameter was determined by projecting the photographic slides on to a white screen at a distance of 5 metres, thereby effecting a magnification of x17. Horizontal pupil diameters were measured directly from the screen to an accuracy of  $\pm 0.5$  mm, and corrected to actual values by comparison with relative magnification of the scale; actual pupil diameters were therefore accurate to within  $\pm 0.03$  mm. Sympathetic denervation hypersensitivity of the iris was expressed as the 0.5% phenylephrine ratio:

$$\frac{\text{horizontal pupil diameter 45 minutes post-test}}{\text{horizontal pupil diameter pre-test}}$$

All assessments were performed on a double-masked basis, with neither

the subject nor the examiner being aware which was the tested eye during the experimental procedure. The measurement of pupil diameters was also performed on a double-masked basis.

#### Statistical analysis

Comparisons were made between the results of the control group and subjects with ocular hypertension; significance was assessed by Student's unpaired t test and Mann-Whitney U test. Results are expressed as mean  $\pm$  SEM.

#### RESULTS

Pupil dilatation in response to 0.5% phenylephrine hydrochloride was significantly increased in patients with ocular hypertension, suggesting sympathetic denervation hypersensitivity of the iris. 0.5% phenylephrine ratios were significantly higher in patients with ocular hypertension ( $1.31 \pm 0.03$ ) than the age-matched control group ( $1.19 \pm 0.03$ ) ( $p < 0.003$ ).

Pupil dilatation resulting from phenylephrine stimulation of the dilator pupillae in a patient with ocular hypertension is shown in Figure 1.

## DISCUSSION

Intraocular pressure represents a balance between the formation of aqueous humour in the posterior chamber and its outflow from the anterior chamber. Aqueous humour is formed in the ciliary processes by diffusion, ultrafiltration and secretion (Potter, 1981), whilst outflow of aqueous occurs primarily via the trabecular meshwork and Schlemm's canal (90%), with the remaining 10% passing through the uveoscleral pathway (Bill and Phillips, 1971). The effects of autonomic nerve function on both aqueous production and outflow forms the basis of clinical management in the primary glaucomas, with autonomic agonists (pilocarpine, adrenaline) and antagonists (timolol, guanethidine), although the exact mechanisms of autonomic modulation of aqueous dynamics has not been determined. Stimulation of the parasympathetic nervous system induces ciliary muscle contraction on the scleral spur which opens the trabecular meshwork, thereby significantly increasing the facility of outflow and decreasing intraocular pressure (Kaufman and Barany, 1976). Significant cholinergic denervation hypersensitivity of the iris has been demonstrated in both ocular hypertension (Clark and Mapstone, 1987) and open-angle glaucoma (Jordan et al, 1988); impairment of aqueous outflow secondary to ocular parasympathetic neuropathy has been subsequently proposed as a significant predisposing factor in the pathogenesis of ocular hypertension and open-angle glaucoma.

Although drugs specifically manipulating sympathetic nerve function in the anterior segment of the eye have been used for over 50 years in the treatment of glaucoma (Hamburger, 1923), the mechanisms of action are still not fully understood. The effects of adrenaline (an

alpha- and beta-adrenergic agonist) on intraocular pressure seem to be dependant upon the duration of treatment, with a significant decrease in aqueous formation initially (Richards and Drance, 1967; Sears, 1976; Araie and Takase, 1981), followed by an increase in aqueous outflow after several months of continuous treatment (Sears, 1976). Paradoxically, beta-adrenergic blockade produces similar pressure-lowering effects; timolol, a beta<sub>1</sub> and beta<sub>2</sub> antagonist, decreases aqueous formation by up to 40% (Coakes and Brubaker, 1978). The anterior segment of the eye in humans is innervated with both sympathetic (Staflova, 1969) and parasympathetic nerves (Nathanson, 1981), with a relatively denser adrenergic innervation of ciliary processes - predominantly beta<sub>2</sub> receptors (Nathanson, 1981) - than of aqueous outflow pathways in the anterior chamber (Staflova, 1969).

Phenylephrine is a sympathomimetic amine which effects mydriasis by alpha-adrenoceptor stimulation of the dilator pupillae muscle (Turner, 1969), although phenylephrine has specifically no effects on intraocular pressure or aqueous flow (Lee and Brubaker, 1982). The results of the present study have demonstrated significantly-increased pupillary dilatation in patients with ocular hypertension in response to minute concentrations of topical phenylephrine, suggesting increased adrenoceptor density, and implying sympathetic denervation hypersensitivity of the iris. Evidence of sympathetic neuropathy in the anterior segment of ocular hypertensive subjects is not particularly surprising as parasympathetic denervation hypersensitivity of the iris has also been demonstrated in the same group of patients (Clark and Mapstone, 1987). Systemic autonomic dysfunction, assessed by tests based upon cardiovascular reflexes, has been demonstrated in up to 42% of ocular

hypertensive subjects (Clark and Mapstone, 1985), suggesting that the ocular autonomic neuropathy may represent another feature of the systemic disorder.

Effects of the autonomic nervous system are fundamental to the regulation of intraocular pressure. Evidence of significant autonomic neuropathy - with concomitant denervation hypersensitivity - in the anterior segment of ocular hypertensive subjects (Clark and Mapstone, 1987) and open-angle glaucoma patients (Jordan et al, 1988) may provide a logical explanation for the actions of autonomically-mediated drugs in glaucoma therapeutics; topical application of autonomic agonists and antagonists may replace the inevitably decreased levels of endogenous neurotransmitters, and may therefore provide the autonomic control of aqueous dynamics which is presumably impaired in ocular hypertensive and glaucoma patients with autonomic neuropathy.

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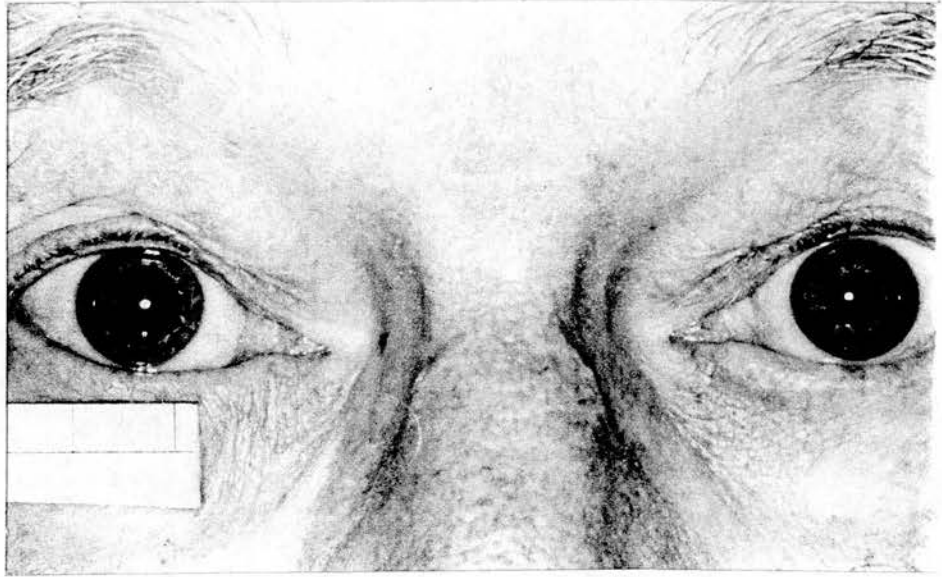
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LEGEND

Figure 1

Pupil dilatation following instillation of 0.5% phenylephrine hydrochloride solution into the right eye of a patient with ocular hypertension, demonstrating denervation hypersensitivity



PAPER 12

DENERVATION SUPERSENSITIVITY EFFECTS IN GLAUCOMA

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## ABSTRACT

202 consecutive patients presenting with closed-angle glaucoma were examined to assess the risk of angle-closure developing in the fellow eye. Autonomic provocative tests were performed using topical pilocarpine and phenylephrine. Closed-angle glaucoma was demonstrated in 62% of fellow eyes. The pathogenesis of angle-closure is discussed, with particular reference to the significant association between systemic parasympathetic neuropathy and closed-angle glaucoma. As partial denervation enhances the sensitivity of a tissue to autonomic mediators - either endogenously released or exogenously applied - the hypothesis is proposed that the sensitivity of the pilocarpine-phenylephrine provocative test (93%) may be explained by autonomic dysfunction in the anterior segment of patients with closed-angle glaucoma, manifest by hypersensitive responses to autonomic agonist drugs.

## INTRODUCTION

Anterior chamber depth is not a static dimension, and may show rapid and transient changes (1). Variation in depth is directly related to the pupil block force (2,3), a manifestation of autonomic activity in the anterior segment (Figure 1). Summation of diametrically-opposed forces subsequent to isometric contraction of the iris musculature produces the posteriorly-directed vector of pupil block, which is maximal at a pupil diameter of 3.8-4.2 mm (1). The only known method of maintaining pupil diameter at mid-dilation is to simultaneously maximally stimulate both parasympathetic and sympathetic nervous systems in the anterior segment, the basis of the pilocarpine-phenylephrine provocative test (4,5). The position of the iris-lens diaphragm at equilibrium is determined by the production of aqueous humour, the facility of outflow, and the degree of pupil block (Figure 2a). Pupil block and facility of outflow are significantly increased during the initial stages of the pilocarpine-phenylephrine provocative test. An inevitable consequence is that aqueous flow from the posterior to the anterior chamber is less than the rate of outflow from the anterior chamber; the resultant pressure differential effects forward movement of the iris-lens diaphragm with shallowing of the anterior chamber - thereby facilitating irido-corneal contact, the first stage of angle-closure.

The aim of the present study was to provoke fellow eyes of closed-angle glaucoma patients using the pilocarpine-phenylephrine provocative test, to determine the risk of closed-angle glaucoma

developing in the fellow eye, and to record changes in anterior segment dimensions during experimental angle-closure.

## PATIENTS AND METHODS

202 consecutive cases of closed-angle glaucoma (CAG) were included in the study. A pilocarpine—phenylephrine provocative test was performed on the fellow eye of each subject according to the following method.

### 1. Initial measurement of:

- a. Intraocular pressure - by Goldmann applanation tonometry
- b. Anterior chamber depth - by pachometry
- c. Irido-corneal angle assessment - by gonioscopy
- d. Facility of outflow - by tonography

One drop of 2% pilocarpine and 10% phenylephrine were placed in the lower fornix of the fellow eye.

### 2. One hour later

All measurements were repeated.

- a. If IOP increased by  $\geq 8$  mmHg, with total angle-closure, the test was positive and therefore terminated by guttae 0.5% thymoxamine and intravenous acetazolamide 500 mg.
- b. If IOP not increased by  $\geq 8$  mmHg, one drop of 2% pilocarpine and 10% phenylephrine were again placed in the lower fornix of the fellow eye.

### 3. Two hours later

All measurements were repeated.

- a. If IOP increased by  $\geq 8$  mmHg, with total angle-closure, the test was positive and therefore terminated by guttae 0.5% thymoxamine and intravenous acetazolamide 500 mg.
- b. If IOP not increased by  $\geq 8$  mmHg, the test was negative

and terminated by guttae 0.5% thymoxamine.

If the test was positive, a peripheral iridectomy was performed.

If the test was negative, a provocative test was repeated at yearly intervals for up to 10 years.

## RESULTS

The results were as follows:

1. Development of induced CAG (by pilocarpine-phenylephrine provocation) or spontaneous CAG in 202 fellow eyes
  - a. Positive provocative tests in 115 fellow eyes.  
104 tests were positive within 2 months of presentation.  
11 tests were initially negative, but became positive within 6 years of presentation.
  - b. Negative provocative tests in 58 fellow eyes.
  - c. Spontaneous CAG developed in 9 fellow eyes, despite negative provocative tests.
  - d. 20 patients lost to follow-up.
  
2. Intraocular pressure and facility of outflow during a positive provocative test  
Intraocular pressure and facility of outflow changes in 26 consecutive positive pilocarpine-phenylephrine provocative tests are shown in table 1. Three patterns of response are demonstrated:
  - a. Group 1  
In 12 eyes, provocative test positive within 1 hour; IOP significantly increased and facility of outflow significantly decreased.
  - b. Group 2  
In 7 eyes, provocative test positive within 2 hours. IOP increased and facility of outflow decreased marginally after first hour; IOP increased significantly and facility

of outflow decreased significantly after second hour of test.

- c. In 7 eyes, provocative test positive within 2 hours. IOP decreased and facility of outflow increased after first hour; IOP increased significantly and facility of outflow decreased significantly after second hour of test.

3. Anterior chamber depth during a positive provocative test  
Anterior chamber depth measurements in 10 consecutive fellow eyes during a positive provocative test, and reversal of changes during resolution of angle-closure, are shown in table 2. Anterior chamber depth significantly decreased during acute closed-angle glaucoma ( $t = 9.72, p < 0.001$ ); anterior chamber depth significantly increased during resolution of closed-angle glaucoma ( $t = 6.82, p < 0.001$ ).
4. Anterior chamber depth during a pilocarpine-phenylephrine provocative test in eyes with a peripheral iridectomy  
Anterior chamber depth measurements during a provocative test in 17 consecutive eyes with a peripheral iridectomy are shown in table 3. Anterior chamber depth significantly increased in eyes with a peripheral iridectomy during autonomic provocation ( $t = 3.81, p < 0.01$ ).

## DISCUSSION

Closed-angle glaucoma is demonstrable in 62% of fellow eyes within ten years of the initial event; 90% of acute attacks may be induced in the fellow eye within six months of presentation. Previous studies show a similar trend; if the fellow eye is treated conservatively, 45-70% eventually develop acute glaucoma (6,7). As the sensitivity of the pilocarpine-phenylephrine provocative test is 93%, and the predictive value of a negative test is 94%, a reasonable inference is that anterior segment events induced by pilocarpine-phenylephrine provocation simulate the pathogenesis of spontaneous closed-angle glaucoma.

Significant variation in the dimensions of the anterior chamber occurs during the course of a pilocarpine-phenylephrine provocative test. Simultaneous stimulation of parasympathetic and sympathetic nervous systems in the anterior segment effects maximal pupil block, thereby impeding aqueous flow from the posterior chamber to the anterior chamber. As facility of outflow is initially increased (an effect of pilocarpine-induced stimulation of the ciliary muscle opening the trabecular meshwork via the scleral spur), a pressure differential develops across the iris-lens diaphragm with inevitable shallowing of the anterior chamber. Anterior translational movement of the iris-lens diaphragm facilitates irido-corneal contact and subsequent angle-closure (Figure 2b).

Free transfer of aqueous between the posterior chamber and the

anterior chamber occurs in eyes with a patent peripheral iridectomy; as pressure is equalised across the iris-lens diaphragm by the iridectomy, displacement of the diaphragm is controlled exclusively by the posteriorly-directed vector of pupil block, and the depth of the anterior chamber increases as pupil block increases during autonomic provocation (Figure 2c).

The essential anterior segment event precipitating irido-corneal contact is postulated to be a change in parasympathetic tone (8); systemic parasympathetic neuropathy has been demonstrated in 58% of patients with closed-angle glaucoma (9). A consequence of partial denervation of a tissue is to enhance the sensitivity of the tissue to autonomic mediators - endogenously released or exogenously applied. Autonomically-denervated irides demonstrate adrenergic and cholinergic denervation supersensitivity to topically-applied autonomic agonists (10,11). The hypothesis is therefore proposed that the efficacy of the pilocarpine-phenylephrine provocative test may be explained by autonomic dysfunction in the anterior segment of patients with closed-angle glaucoma, manifest by hypersensitive responses to autonomic agonist drugs. Impairment of parasympathetic nerve function in the anterior segment causes partial dilation of the pupil; pupil block force increases, effecting anterior translational movement of the iris-lens diaphragm and thereby facilitating closure of the anterior chamber angle.

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Table 1

## INTRAOCULAR PRESSURE AND FACILITY OF OUTFLOW DURING A POSITIVE PROVOCATIVE TEST

(Group mean values  $\pm$  SEM)

	0 Hour		1 Hour		2 Hours	
	IOP	C	IOP	C	IOP	C
Group 1 (n=12)	16.0 $\pm$ 1.2	0.21 $\pm$ 0.02	35.1 $\pm$ 1.2	0.05 $\pm$ 0.01		
Group 2 (n=7)	14.9 $\pm$ 1.1	0.24 $\pm$ 0.06	16.6 $\pm$ 1.1	0.14 $\pm$ 0.04	40.0 $\pm$ 4.7	0.02 $\pm$ 0.01
Group 3 (n=7)	19.7 $\pm$ 2.0	0.17 $\pm$ 0.03	16.4 $\pm$ 1.3	0.27 $\pm$ 0.03	32.7 $\pm$ 3.3	0.02 $\pm$ 0.0

IOP = mmHg

C =  $\mu$ L/min/mmHg

Table 2

VARIATION IN ANTERIOR CHAMBER DEPTH DURING A POSITIVE PROVOCATIVE TEST  
(Group mean values  $\pm$  SEM)

	Variation in anterior chamber depth (mm)
Stage 1: Angle-closure (n=10)	-0.30 $\pm$ 0.04
Stage 2: Resolution of angle-closure (n=10)	+0.27 $\pm$ 0.04

Table 3

VARIATION IN ANTERIOR CHAMBER DEPTH DURING A PROVOCATIVE TEST  
IN EYES WITH A PERIPHERAL IRIDECTOMY  
(Group mean values  $\pm$  SEM)

	Variation in anterior chamber depth (mm)
Fellow eyes with peripheral iridectomy (n=17)	+0.18 $\pm$ 0.05

PAPER 13

## VARIATION IN ANTERIOR CHAMBER VOLUME DURING THE PILOCARPINE/PHENYLEPHRINE PROVOCATIVE TEST

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### ABSTRACT

Anterior chamber volume was measured by a photogrammetric technique during the course of a pilocarpine/phenylephrine provocative test. In eyes without a peripheral iridectomy, there was a significant decrease in the volume of the anterior chamber; if a peripheral iridectomy was present, anterior chamber volume significantly increased. The aetiology of dynamic changes in anterior chamber volume is discussed.

### INTRODUCTION

The depth of the anterior chamber of the eye is not a static dimension and may show rapid and transient changes (1). Such alterations in depth are directly related to the pupil block force (2,3), itself a manifestation of autonomic activity in the anterior segment (Fig. 1). Contraction of the pupil may be resolved into a series of component forces, the net effect summing to increased iris/lens apposition (4). Pupil block is maximal if the pupil is fixed, as a result of relative parasympathetic and sympathetic activity, in mid-dilatation with the sphincter muscle contracting strongly. The magnitude of pupil block force has been calculated and shown to be maximal at a pupillary diameter between 3.8 and 4.2 mm (1,5). The only known method of maintaining pupillary diameter at mid-dilatation is to simultaneously maximally stimulate both sympathetic and parasympathetic nervous systems in the anterior segment, the basis of the pilocarpine/phenylephrine provocative test (6,7). The component forces determining the position of the iris/lens diaphragm at equilibrium are the production of aqueous, the facility of outflow, and the degree of pupil block (Fig. 2a). Assuming a constant production of aqueous, both pupil block and facility of outflow are increased during the pilocarpine/phenylephrine provocative test. As aqueous flow from the posterior to anterior chamber is less than the rate of outflow from the anterior chamber (8), the resultant pressure differential results in forward movement of the iris/lens diaphragm and consequently

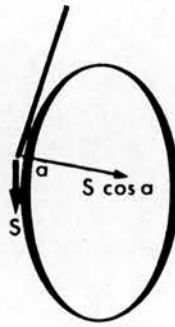
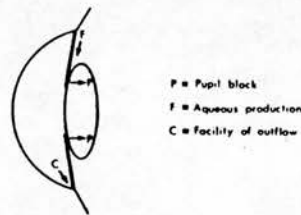


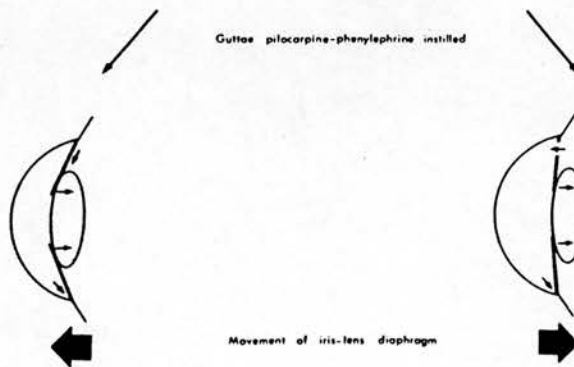
Fig. 1. Pupil block.

shallowing of the anterior chamber (Fig. 2b). the first stage of angle closure (i.e. iridocorneal contact) is thus facilitated (9,10). It has been clearly shown that axial anterior chamber depth may decrease significantly during provocative testing; however minimal changes in depth at the periphery of the



P = Pupil block  
 F = Aqueous production  
 C = Facility of outflow

(a) Forces determining the position of the iris-lens diaphragm



(b) Eyes without a peripheral iridectomy

(c) Eyes with a peripheral iridectomy

Fig. 2. Variation in anterior chamber volume during the pilocarpinephenylephrine provocative test.

anterior chamber are of much greater significance in the pathogenesis of angle closure (11,12). Reproducible documentation of this latter measurement is provided by the photogrammetric technique, in which the depth of the anterior chamber is measured at 0.5 mm intervals from the optic axis to the iridocorneal angle from a polaroid photograph, using a transparent optically-distorted curvilinear grid (13,14,15).

The presence of a peripheral iridectomy negates the effect of decreased aqueous flow via the pupil, and the vector force of pupil block without a pressure differential across the iris results in posterior displacement of the iris/lens diaphragm (Fig. 2c).

Rapid, accurate measurements of anterior chamber volume are thus possible during dynamic changes in the dimensions of the anterior chamber subsequent to autonomic provocation.

### PATIENTS AND METHODS

Patients were selected on the basis of the following criteria:

1. Acute closed-angle glaucoma in the contralateral eye
2. Ocular hypertension in association with narrow angles
3. Ocular hypertension in association with wide angles

Fifty-six patients were included in the study. A pilocarpine 2%/phenylephrine 10% provocative test was performed according to the standard method. In addition, anterior chamber depth and volume were measured using a Zeiss photo slit-lamp and Polaroid camera attachment. With the slit illuminator set at 55° and magnification  $\times 16$ , the slit was aligned vertically along the optic axis such that the upper border of the pupil and lower border of the cornea were visible. The photograph was taken ensuring maximum clarity of the iridocorneal angle. A transparent anterior chamber template was aligned with the posterior corneal curve, and the depth of the anterior chamber measured to an accuracy of 0.1 mm at 0.5 mm intervals from the optic axis. The depths were multiplied by an appropriate weighting factor and summated, resulting in the total anterior chamber volume.

The final experimental model involves two discrete stages:

1. Prior to provocation, the following baseline measurements were taken in both eyes:
  - i. Intraocular pressure
  - ii. Facility of outflow
  - iii. Depth and volume measurement of anterior chamber
  - iv. Gonioscopy

One drop of pilocarpine 2% and phenylephrine 10% instilled in one eye.

2. Two hours later all measurements were repeated. Test terminated with guttae thymoxamine 0.5% (plus acetazolamide 500 mg i.v. if necessary). The anterior chamber depth and volume were calculated from the photographs on a single-blind basis, i.e. the observer was not aware of details relating to each photograph at the time of measurement.

Significance was assessed by Student's paired and unpaired 't' tests, and Kruskal-Wallis one-way analysis of variance by ranks.

Table 1. Variation in anterior chamber volume during the pilocarpine 2%/phenylephrine 10% provocative test (Group mean values  $\pm$  SD)

	Volume of A/C before provocation ( $\mu$ l)	Volume of A/C 2 hours later ( $\mu$ l)	Change in volume of A/C ( $\mu$ l)	Significance
Pilocarpine 2%/phenylephrine 10% provocative test in eyes without a peripheral iridectomy				
All (n = 77)	98.31 $\pm$ 35.11	84.22 $\pm$ 32.41	14.09 $\pm$ 14.55	p < 0.001
Fellow eye of patients with closed-angle glaucoma (n = 15)	76.17 $\pm$ 10.94	61.15 $\pm$ 14.82	15.02 $\pm$ 13.37	p < 0.001
Ocular hypertension/narrow angles (n = 28)	77.68 $\pm$ 20.95	68.73 $\pm$ 21.13	8.95 $\pm$ 14.06	p < 0.01
Ocular hypertension/wide angles (n = 34)	125.09 $\pm$ 33.09	107.03 $\pm$ 30.77	18.06 $\pm$ 14.05	p < 0.001
Pilocarpine 2%/phenylephrine 10% provocative test in eyes with a peripheral iridectomy				
(n = 20)	92.93 $\pm$ 29.03	105.05 $\pm$ 28.46	12.12 $\pm$ 13.54	p < 0.001
Control group: eyes in which no drops were instilled				
(n = 12)	90.13 $\pm$ 27.01	89.26 $\pm$ 25.63	0.87 $\pm$ 3.98	p > 0.05

## RESULTS

### 1. *Provocative test in eyes without a peripheral iridectomy*

There was a significant decrease ( $p < 0.001$ ) in the volume of the anterior chamber during the test (Table 1). No significant differences ( $p > 0.05$ ) were shown in comparisons between each of the three subgroups.

### 2. *Provocative test in eyes with a peripheral iridectomy*

There was a significant increase ( $p < 0.001$ ) in the volume of the anterior chamber during the test (Table 1).

### 3. *Control group: eyes in which no drops were instilled*

This group exhibited no significant change in volume ( $p > 0.05$ ) during the 2 hour period between commencement and termination of provocation in the contralateral eye.

## DISCUSSION

Significant variation in the dimensions of the anterior chamber has been shown to occur during the course of a provocative test with pilocarpine and phenylephrine. The stimulation of both parasympathetic and sympathetic nervous systems in the anterior segment by the simultaneous administration of guttae pilocarpine and phenylephrine maintains the pupil in mid-dilatation by isometric contraction of the iris musculature, resulting in maximal pupil block. In eyes without a peripheral iridectomy, aqueous flow from the site of production (ciliary processes) to that of escape (trabecular meshwork and uveoscleral route) can only occur via the pupil. Increasing pupil block thus results in decreased aqueous flow from the posterior to the anterior chamber. The increased facility of outflow previously shown to occur in the early stages of a pilocarpine/phenylephrine provocative test (as a result of pilocarpine-induced contraction of the ciliary muscle opening trabecular meshwork via the scleral spur) produces shallowing of the anterior chamber as a direct consequence of the pressure differential across the iris/lens diaphragm.

The presence of a functioning peripheral iridectomy permits free transfer of aqueous. As no pressure difference exists between the posterior and anterior chambers, the direction and degree of displacement of the iris/lens diaphragm is controlled exclusively by the vector component of pupil block, i.e. posteriorly. The translational movement of the iris/lens diaphragm by autonomic provocation can only be explained on this basis.

Anterior chamber volume assessment by the photogrammetric technique permits accurate measurement of rapid changes in the dimensions of the anterior segment. The fact that significant changes in volume were observed in each of the three groups of patients examined suggests the possibility of a common aetiological factor. This is currently the basis of further investigation.

## CONCLUSIONS

This study has established the degree to which variation in the dimensions of the anterior chamber contribute to angle closure, providing photographic

evidence by an objective, reproducible, accurate technique. More significantly, quantification of changes in anterior chamber volume is possible in those cases in which angle closure does not occur and thus intraocular pressure remained unchanged. A negative provocative test merely indicates no significant increase in intraocular pressure; however significant changes in ocular dimensions may occur with consequent prognostic implications.

#### ACKNOWLEDGEMENTS

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## 1.2 DIABETES MELLITUS AND PRIMARY GLAUCOMA

PAPER 14

# Diabetes and glaucoma

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## SUMMARY

A relationship exists between the primary glaucomas and diabetes but not with the specific clinical diagnosis. The probability of a patient with either primary glaucoma or ocular hypertension demonstrating an abnormal response to an oral glucose tolerance test is significantly related to the depth of the anterior chamber. The possible mechanisms are discussed.

## INTRODUCTION

The notion that an association exists between diabetes and primary open angle glaucoma has been present for about a quarter of a century, but this idea has led to no real solution of the problem concerning the pathogenesis of the primary glaucomas in man. Furthermore, if the evidence is critically examined, then the objective observer must conclude that the thesis is far from proven.

Armstrong *et al*<sup>2</sup> reported that, in a group of unselected diabetics, the prevalence of open angle glaucoma was 40/1000 compared with a rate of 13/1000 in a control group. The other side of the coin – the prevalence of diabetes in patients with open angle glaucoma – is about 80/1000<sup>7,11</sup>. The significance and relevance of these findings is difficult to determine for the following reasons. In affluent societies published prevalence rates for diabetes are numerous but few allow age specific and sex comparisons to be made. Hamman<sup>8</sup> has taken this into account and constructed a table of age adjusted prevalence rates from various sources. This reveals wide variations from 8.4/1000 to 78/1000 in females and from 11.8/1000 to 113.4/1000 in males. In developing countries the rates are even more variable, from 3/1000 in a township in Zimbabwe to 344/1000 in a Micronesian population in the South Pacific<sup>17</sup>. So, while there may be an increased prevalence of open angle glaucoma in diabetes, there is no compelling reason for asserting that there is an increased prevalence of diabetes in open angle glaucoma. Any relationship that exists between diabetes and open angle glaucoma is not therefore as clear-cut as has been claimed<sup>5</sup>.

In patients with primary closed angle glaucoma the evidence is even less clear. Becker<sup>1</sup> wrote 'Angle closure glaucoma appears to be no more common in diabetic patients than in the general population'. This observation is confirmed by a population study<sup>11</sup> which found one patient with closed angle glaucoma in 533 diabetics. However, because there is a low prevalence of closed angle glaucoma in diabetes, it is not a necessary consequence that there is a low prevalence of diabetes in closed angle glaucoma. Neither is there any published evidence to show that the question has been investigated.

Armaly<sup>1</sup>, during the follow-up of a group of patients with ocular hypertension, discovered 4

who had developed field loss and all 4 demonstrated abnormal glucose tolerance test results. Wilensky *et al*<sup>16</sup> reported similar findings. Consequently it became accepted that a combination of diabetes and ocular hypertension represented an individual at particular risk.

Bankes<sup>3</sup>, using data obtained from the Bedford glaucoma survey, found that the intra-ocular pressure in diabetics and 'pre-diabetics' was no different from that in the general population. Becker however, recorded an increased mean intra-ocular pressure in diabetics with no retinopathy<sup>5</sup>. More recently Klein & Klein<sup>10</sup> investigated a population of 2103 diabetics in Wisconsin and, below age 30, the prevalence of ocular hypertension was 68/1000 in females and 59/1000 in males. Above age 30 the rates were 96/1000 and 73/1000 respectively - little different from the prevalence rates in the population at large<sup>9</sup>.

Bankes also looked at the rate of diabetes in ocular hypertension and recorded a figure of 16.6/1000<sup>3</sup>. So, again, any relationship that may exist between ocular hypertension and diabetes is unremarkable. This does not imply that a relationship is absent, for the reason that there may exist within a glaucomatous population subgroups in which there is a relationship but, because of the way in which the primary glaucomas are classified, any relationship is obscured.

#### THE DIAGNOSTIC DIFFICULTY

One of the major problems involved in evaluating any relationship between diabetes and glaucoma concerns the question of diabetes diagnosis. In North America the usual oral glucose load is 100 g whereas, in Europe, a 50 g load is preferred. The National Diabetes Data Group in 1979 placed emphasis upon a raised plasma fasting glucose concentration, the European Association for the Study of Diabetes however, based diagnosis upon blood glucose concentrations after an oral glucose load. In 1980 the WHO Expert Committee on Diabetes Mellitus made recommendations for diagnosis which were similar to those proposed by both European and North American study groups<sup>15</sup>. It proposed a standard glucose load of 75 g for adults with fasting and 2 h post-ingestion glucose values being of major diagnostic value. They also recognized two abnormal states, diabetes and impaired glucose tolerance, the latter state

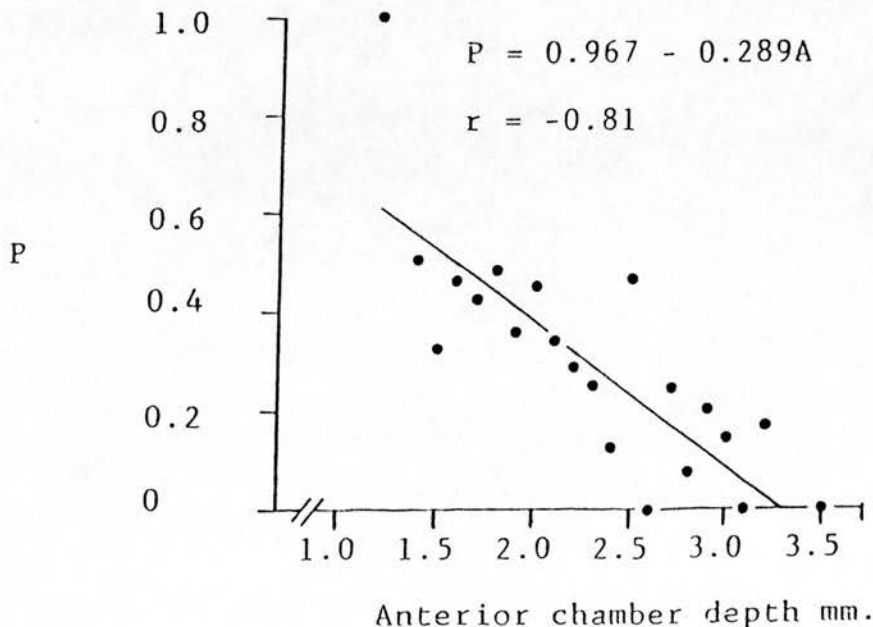


Figure 1. Glucose tolerance test response.

removing the dubious terms: latent, chemical, suspect, borderline and sub-clinical diabetes. If a fasting plasma value  $>8$  mmol/litre was found, that was classed as diabetic. If the 2 h venous plasma sample was  $>11$  mmol/litre that too was classed as diabetic. If the fasting level was  $>8$  mmol/litre, but the 2 h sample  $>8$  mmol/litre and,  $<11$  mmol/litre, then that response was classed as impaired glucose tolerance.

#### THE RELATIONSHIP BETWEEN ABNORMAL GLUCOSE METABOLISM AND THE PRIMARY GLAUCOMAS/OCULAR HYPERTENSION

Mapstone & Clark<sup>13</sup> following the criteria suggested by the WHO<sup>15</sup>, looked at the prevalence of diabetes/impaired glucose tolerance in 316 patients with open angle glaucoma, closed angle glaucoma or ocular hypertension. The patients were divided into three groups, those with open angle glaucoma or ocular hypertension and wide angles; those with open angle glaucoma or ocular hypertension and narrow angles and, those with closed angle glaucoma. The age patterns (Table I) of the three groups are similar and all demonstrate a preponderance of females. The proportion of abnormal responses to a glucose tolerance test, in the group with wide angle eyes (20 of 109), is less than in the groups with narrow angles (38 of 101) or closed angle glaucoma (41 of 106) (see Table I). Because eyes with closed angle glaucoma have narrow angles too, they can be combined with the narrow angle group as far as angle appearance is concerned. The proportion of patients within this larger narrow angle group, who developed an abnormal response to a glucose tolerance test (79 of 207), is significantly greater than the proportion in the group with wide angles (20 of 109) -  $\chi^2 = 12.12$ ,  $p = 0.0005$ .

The relationship can be made more explicit (Figure 1). If the clinical diagnosis is ignored and patients are classed according to their axial anterior chamber depth, the probability, at any one depth, of demonstrating an abnormal test response (P) to oral glucose, decreases in a linear fashion as the depth (A) increases. There is a significant negative linear correlation between these two variables:  $r = -0.81$ ,  $p < 0.001$ ; the equation of the regression line is  $P = 0.97 - 0.29A$ .

There does therefore appear to be an association between anterior chamber depth and the

Table I Group statistics

	Wide Angle	Narrow Angle	Closed Angle
Number	109	101	106
Age:			
Mean	65.1	67.7	67.0
SD	8.3	8.6	9.5
ACD:			
Mean	2.61	2.01	1.87
SD	0.34	0.27	0.28
Diabetes*	9 (2)	17 (8)	20 (4)
IGT	11	11	21
Male/Female	45/64	35/66	32/74

\*The number in brackets equals known diabetics.

SD = Standard deviation

ACD = Anterior chamber depth

IGT = Impaired glucose tolerance

probability of demonstrating an abnormality of glucose metabolism but what does this association mean? There are two main possibilities:

1. Diabetic lenses are thick<sup>6</sup>, therefore, if a patient has diabetes/impaired glucose tolerance then his anterior chambers are shallower than would otherwise be the case. Because closed angle glaucoma is most often associated with a shallow anterior chamber one inference is that the major determinant of whether or not an eye develops closed angle glaucoma is anterior chamber depth and, by implication, that all eyes with shallow anterior chambers are at equal risk. If, however, a fellow eye is provoked with pilocarpine and phenylephrine, about 66% develop a positive test response. If an eye has ocular hypertension and a shallow anterior chamber then the figure is about 25% but, if an eye has a shallow anterior chamber only (that is with no glaucomatous pathology or risk factor) then the figure drops to between 3–5%<sup>12</sup>. The necessary consequence is that while a shallow anterior chamber may be a necessary factor it is not sufficient, and some other factor or factors must be present too.

2. The second possibility concerns the mechanism of closed angle glaucoma in man. Most experimental models of closed angle glaucoma in man depend upon manipulating the autonomic nervous system. Those which simply dilate the pupil (dark room test, mydriatic test) rarely produce an acute closed angle glaucoma because no shallowing of the anterior chamber is produced. The model which produces the greatest shallowing is a combination of pilocarpine and phenylephrine and, as a result, peripheral iris comes into contact with cornea and trabecular meshwork. However, as indicated above, an eye which develops a positive test response must have something in addition to a shallow anterior chamber. Because the model manipulates the autonomic nervous system, one reasonable conclusion is that eyes which do develop a positive test have an abnormality of the autonomic system which makes that eye respond in an abnormal way to autonomic mediators, either endogenously released or topically applied. One of the characteristics of the diabetic is the frequent occurrence of an autonomic neuropathy which, in effect, produces a denervation supersensitivity to autonomic drugs. If therefore an autonomic neuropathy can be demonstrated in patients who have developed spontaneous closed angle glaucoma then this would be evidence in favour of an hypothesis that some narrow angle glaucoma is a consequence of autonomic disease within the anterior segment of the eye.

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PAPER 15

# CLINICAL RESEARCH

## Prevalence of diabetes in glaucoma

ROY MAPSTONE, CHARLES V CLARK

### Abstract

Oral glucose 75 g was given to 352 patients with chronic glaucoma, acute glaucoma, or ocular hypertension and 73 patients without glaucoma. The proportion of patients with shallow anterior chambers who showed an abnormal response was significantly greater than that in patients with deep anterior chambers and in the control group ( $p < 0.005$ ). The probability of developing an abnormal response to oral glucose tests increased as the depth of the anterior chamber decreased; these two variables showed a significant negative linear correlation ( $r = -0.79$ ,  $p < 0.001$ ). The high prevalence of autonomic dysfunction in patients with shallow anterior chambers and glaucoma may explain this association. Because of this, acute glaucoma should be regarded as a symptom of diabetes.

### Introduction

An association between diabetes, chronic (open angle) glaucoma, and ocular hypertension has been recognised for some years,<sup>1-3</sup> but acute (closed angle) glaucoma has a low prevalence in patients with diabetes.<sup>4</sup> This does not necessarily suggest that a low prevalence of diabetes exists in patients with acute glaucoma.

During a longitudinal study of a group of patients with acute glaucoma or ocular hypertension it became clear that there was probably an increased incidence of type 2 diabetes in that sample. This study was therefore done to determine the relation between diabetes, the primary glaucomas, and ocular hypertension.

### Patients and methods

As new and old patients attended the glaucoma clinic they were included in this study with the following criteria: all patients with acute glaucoma and one eye that had not developed the disease spontaneously and was not being treated with a miotic; all patients with chronic glaucoma who were not being, and had not been, treated with a miotic; and patients with ocular hypertension—that is, an intraocular pressure  $\geq 21$  mm Hg and no known predisposing cause and no evidence of glaucomatous damage—if they were not being, and had not been, treated with a miotic. Patients with secondary glaucoma were excluded.

A control group of 73 patients was selected with the following criteria: minimum age 40, no upper limit; new patients attending a general ophthalmic clinic for the first time; and no evidence of primary or secondary glaucoma. Patients with visually disabling cataracts were excluded.

### DIABETIC STATE

No patient was pregnant, and anyone taking a diabetogenic drug was excluded. If a patient was a known diabetic that diagnosis was accepted and a glucose tolerance test not done. Other patients had an oral glucose tolerance test done according to the recommendations of the expert committee of the World Health Organisation<sup>5</sup>—that is, after at least three days of unrestricted diet, followed by an 11-14 hour overnight fast, the patient was given oral glucose 75 g in 300 ml water to be drunk within five minutes. Intravenous blood glucose was measured at zero time and at one and two hours after ingestion of glucose. Two abnormal patterns of response were recognised: if the fasting blood glucose concentration was  $\geq 8$  mmol/l (144 mg/100 ml) or the two hour sample was  $\geq 11$  mmol/l (198 mg/100 ml), or both, then that response was classed as diabetic. No patient, however, was classed as diabetic unless that response was obtained on two separate occasions. If the fasting blood glucose concentration was  $< 8$  mmol/l and the two hour sample  $\geq 8$  mmol/l but  $< 11$  mmol/l then that response was classed as impaired glucose tolerance.

### ANTERIOR CHAMBER ANGLE

The appearance of the angle was assessed with a slit beam and the Van Herrick method,<sup>6</sup> each patient being classed as having wide or narrow angle eyes. This assessment was always made before the result of a glucose tolerance test was known, so three groups of patients were recognised: those with open angle glaucoma or ocular hypertension

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and wide angle eyes; those with open angle glaucoma or ocular hypertension and narrow angle eyes; and those with closed angle glaucoma.

#### AXIAL ANTERIOR CHAMBER DEPTH

Axial anterior chamber depth—that is, the distance between the posterior corneal surface and the anterior lens surface—was measured with a Haag Streit meter. The depth of the fellow eye was measured in patients with closed angle glaucoma; in the other groups the depth of the right eye was measured. All measurements were made before the results of a glucose tolerance test were known.

Statistical methods used were  $\chi^2$  with Yates's correction, linear regression analysis, and Pearson's correlation coefficient.

#### Results

The table shows the statistical results in the four groups of patients; each group shows similar patterns of age and a preponderance of women. Fifty five patients had diabetes, of whom one was dependent on insulin. The proportion of abnormal responses to a glucose tolerance test in the patients with wide angle eyes (20 of 109) was not significantly different from that in the control group ( $\chi^2=0.02$ ,  $p>0.5$ ). In the patients with narrow angle eyes and those with closed angle glaucoma, however, the proportions were significantly different ( $\chi^2=8.28$  and  $9.01$ , respectively,  $p<0.005$ ). Even after multiple comparisons these differences remained significant at less than the 1% level.

#### Statistical details of patients

	Wide angle eyes	Narrow angle eyes	Closed angle glaucoma	Control group
No of cases	109	101	142	73
Mean (SD) age (years)	65.1 (8.3)	67.7 (8.6)	66.1 (10.4)	66.2 (9.8)
Mean (SD) anterior chamber depth (mm)	2.61 (0.34)	2.01 (0.27)	1.87 (0.28)	2.44 (0.42)
Cases of diabetes (known diabetics)	9 (4)	17 (8)	24 (7)	5 (0)
Cases of impaired glucose tolerance	11	21	29	7
Men/women	45/64	35/66	40/102	18/55

If the clinical diagnosis is ignored and patients with ocular hypertension or primary glaucoma are classed according to their axial anterior chamber depth the probability, at any one depth, of showing an abnormal response to an oral glucose test decreases in a linear fashion as the depth increases (figure 1). There is a significant negative linear correlation between these two variables ( $r=-0.79$ ,  $p<0.001$ ); the regression equation is: probability =  $0.9 - \text{depth} \times 0.3$ . Figure 2 also shows the relation of the two hour blood glucose concentration against anterior chamber depth, excluding 19 known diabetics, 16 of whom had an anterior chamber depth  $<2.2$  mm.

#### Discussion

These results do not support the view that impaired glucose tolerance and diabetes can be associated with a particular clinical type of glaucoma. They do suggest that, given glaucoma, an association exists between diabetes and the anatomical dimensions of the anterior segment of the eye, the clinical diagnosis being of secondary importance. In fact, if the clinical diagnosis is ignored and account is taken of anterior chamber depth only the shallower the anterior chamber the greater is the probability of a patient with that attribute showing an abnormal response to an oral glucose test (fig 1).

The lens of the eye of a diabetic is larger than that of a non-diabetic,<sup>7</sup> and the association described above might simply reflect this, which suggests that one effect of diabetes is to reduce the depth of the anterior chamber, and so the eye is more likely to get closed angle glaucoma. This is probably not an adequate explanation because an eye with a shallow anterior chamber will not necessarily get glaucoma—most will not.<sup>8</sup> Also, closed angle

glaucoma is an acute event that demands an equally acute change in the anterior segment. A change in the thickness of the lens is usually gradual, so some other event or combination of events is necessary.

Acute glaucoma is often precipitated in fellow eyes, at high risk because the presenting eye has already developed the disease, by using drugs to increase the autonomic activity within the anterior segment of the eye.<sup>9,10</sup> Specifically, if pilocarpine and

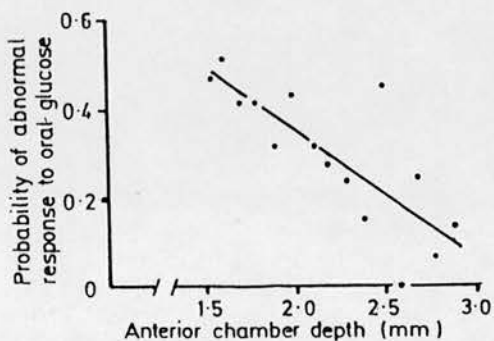


FIG 1—Probability of developing abnormal response to oral glucose test against anterior chamber depth.

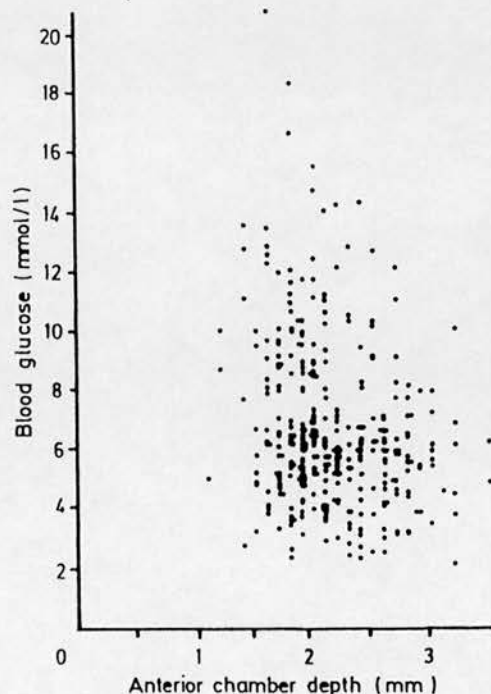


FIG 2—Plot of two hour blood glucose concentration against anterior chamber depth.

Conversion: SI to traditional units—Glucose: 1 mmol/l  $\approx$  18 mg/100 ml.

phenylephrine drops are instilled the pupil dilates in a mid-position, parasympathetic and sympathetic activity are at a maximum, and so the block force of the pupil apposing iris to lens is also at a maximum.<sup>11</sup> Consequently the diaphragm of the iris and the lens moves forwards, the iris touches the cornea, and the angle of the anterior chamber closes, producing acute glaucoma in 60% of such eyes.<sup>12</sup> This means that about one third of fellow eyes at high risk never develop acute closed angle glaucoma, mainly because the diaphragms of the iris and lens do not translate sufficiently.<sup>13</sup> The crucial factor that determines whether or not an eye develops acute glaucoma is not, therefore, the absolute value of the depth of the anterior chamber but how much it can decrease in response to autonomic stress. This in

turn is largely determined by the response of the sphincter and dilator muscles to autonomic agonist drugs.

In a group of 112 patients with spontaneous acute glaucoma 65 (58%) showed evidence of systemic autonomic dysfunction with standard autonomic function tests (Valsalva's ratio, variation of heart rate during deep breathing, immediate response of heart rate to standing and lying, and decrease in systolic blood pressure in response to standing),<sup>14</sup> compared with a prevalence of 7% in a control group matched for age and sex without glaucoma. Also, the pupils of diabetics are partially denervated and show a supersensitivity to topically applied autonomic mediators—both sympathetic and parasympathetic.<sup>15 16</sup>

Perhaps the observed association between diabetes and acute glaucoma described above is a consequence of autonomic dysfunction within the anterior segment of the eye. Because of this dysfunction some anterior segments develop a heightened response to autonomic mediators, endogenously released or exogenously applied, and the diaphragm of the iris and lens moves forwards and closes the angle. The shallower the anterior chamber at the outset the greater the probability of this occurring.

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PAPER 16

THE PREVALENCE OF DIABETES MELLITUS IN THE FAMILY HISTORY OF PATIENTS  
WITH PRIMARY GLAUCOMA

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## ABSTRACT

The prevalence of diabetes mellitus in the family history of 371 patients with primary glaucoma - closed-angle glaucoma, ocular hypertension and open-angle glaucoma - and 85 age- and sex-matched control subjects was determined. There was a significantly-increased prevalence of familial type 2 diabetes mellitus (non-insulin dependent diabetes mellitus) in patients with closed-angle glaucoma ( $p = 0.004$ ) and ocular hypertension ( $p = 0.02$ ). Primary glaucoma was not associated with familial type 1 diabetes mellitus (insulin dependent diabetes mellitus). The implications are discussed.

KEY WORDS

Primary glaucoma; ocular hypertension; diabetes mellitus

## INTRODUCTION

Diabetes mellitus is an established aetiological factor in the pathogenesis of secondary glaucoma (Whittington & Lawrence, 1951). Recently, a significant association has been demonstrated between diabetes mellitus and the primary glaucomas (Mapstone & Clark, 1985); type 2 diabetes mellitus or impaired glucose tolerance is present in 37% of patients with closed-angle glaucoma, and 38% of narrow-angle primary glaucoma patients - either ocular hypertension or open-angle glaucoma. The aim of this study was to examine the relationship between primary glaucoma and diabetes mellitus by determining the proportion of patients with a positive family history of diabetes mellitus in each of the major categories of primary glaucoma, compared with an age- and sex-matched control group.

## SUBJECTS AND METHODS

371 patients with primary glaucoma were included in the study: 121 closed-angle glaucoma patients (mean age  $66.6 \pm 10.1$  years), 185 ocular hypertensive patients (mean age  $66.1 \pm 9.5$  years), and 65 open-angle glaucoma patients (mean age  $68.6 \pm 8.5$  years). The diagnosis of closed-angle glaucoma, ocular hypertension and open-angle glaucoma was made in accordance with the accepted criteria of Hollands and Graham (1966). 85 age- and sex-matched control subjects (mean age  $67.3 \pm 11.5$  years) were concurrently examined. The control group consisted of hospital staff, and subjects attending an ophthalmic casualty department in whom the only demonstrable ocular abnormality was minimal refractive errors consistent with normal presbyopia. Ocular examination of all control subjects included:

- i. Anterior segment assessment
  - a. slit-lamp examination of cornea, anterior chamber, iris integrity/dynamics, and lens
  - b. gonioscopy by Zeiss 4-mirror gonioscope to determine angle configuration
  - c. intraocular pressure by Goldmann applanation tonometry
- ii. Posterior segment assessment
  - a. direct ophthalmoscopy of optic disc, cup:disc ratio, retinal vessels and macula
  - b. indirect ophthalmoscopy, after pupillary dilation, to assess posterior pole and retinal periphery
  - c. visual field examination: peripheral and central

No subject in the control group had a history of glaucoma or ocular hypertension.

A comprehensive family history of first-degree relatives was taken from each of the primary glaucoma patients and control subjects; the presence of diabetes mellitus in the family history, and the type of diabetes, was recorded for each subject. Comparisons were made between the prevalence of familial diabetes mellitus in the control group and each of the primary glaucoma categories; significance was assessed by  $\chi^2$  test with Yates' correction.

## RESULTS

The prevalence of diabetes mellitus in the family history of 371 patients with primary glaucoma and 85 age- and sex-matched control subjects is shown in the table. There is a significantly-increased prevalence of type 2 diabetes mellitus in the family history of patients with closed-angle glaucoma ( $\chi^2 = 8.75$ ;  $p = 0.004$ ) and ocular hypertension ( $\chi^2 = 4.94$ ;  $p = 0.026$ ) compared with the control group; the prevalence of familial type 2 diabetes mellitus in patients with open-angle glaucoma is not significantly different from the control group ( $\chi^2 = 3.14$ ;  $p = 0.08$ ).

The prevalence of type 1 diabetes mellitus in the family history of each of the major categories of primary glaucoma is not significantly different from the control group.

## DISCUSSION

Diabetes mellitus is significantly associated with primary glaucoma; type 2 diabetes mellitus is present in 17% of patients with closed-angle glaucoma and 17% of narrow-angle primary glaucoma patients, with impaired glucose tolerance in a further 20% and 21% respectively (Mapstone & Clark, 1985). Impaired glucose tolerance is of particular significance in this population as 16% of primary glaucoma patients with impaired glucose tolerance progress to diabetes mellitus within one year of initial presentation (Clark & Mapstone, 1985). A positive family history of type 2 diabetes mellitus in first-degree relatives was present in 20% of patients with closed-angle glaucoma and 13% of patients with ocular hypertension. The observation of a significantly-increased prevalence of familial type 2 diabetes mellitus in patients with closed-angle glaucoma and ocular hypertension is consistent with the emerging association between diabetes and primary glaucoma (Mapstone, 1985).

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THE PREVALENCE OF DIABETES MELLITUS IN THE FAMILY HISTORY OF 371 PATIENTS WITH PRIMARY GLAUCOMA  
AND 85 AGE- AND SEX-MATCHED CONTROL SUBJECTS

	Negative family history of diabetes mellitus	Positive family history of diabetes mellitus		
		Type 1	Type 2	Type 1 + Type 2
Control subjects (n=85)	80	3	2	0
Closed-angle glaucoma patients (n=121)	100	1	18	2
Ocular hypertensive patients (n=185)	158	6	17	4
Open-angle glaucoma patients (n=65)	57	1	7	0

PAPER 17

PROGRESSION OF IMPAIRED GLUCOSE TOLERANCE TO DIABETES MELLITUS  
IN PATIENTS WITH PRIMARY GLAUCOMA AND OCULAR HYPERTENSION

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## SUMMARY

Diabetic status was determined in 375 patients with primary glaucoma, subdivided by irido-corneal angle configuration. 75 gram oral glucose tolerance test was repeated in 63 patients with impaired glucose tolerance one year later; 16% of patients had progressed to diabetes mellitus. The associations between diabetes mellitus and primary glaucoma are discussed, with particular reference to the effects of autonomic dysfunction on the pathogenesis of anterior chamber angle closure.

## KEY WORDS

Diabetes mellitus, impaired glucose tolerance, primary glaucoma, ocular hypertension, anterior chamber depth

## INTRODUCTION

Diabetes mellitus is significantly associated with the primary glaucomas. Recent studies have restricted this association to narrow-angle categories of primary glaucoma: closed-angle glaucoma, ocular hypertension (narrow angles), and open-angle glaucoma (narrow angles). It has also been established that the association is specifically between non insulin-dependent diabetes mellitus/impaired glucose tolerance and primary glaucoma; insulin-dependent diabetes mellitus is not significantly associated with glaucoma. (1) The aim of this study was to determine the rate of progression of impaired glucose tolerance to diabetes mellitus in patients with primary glaucoma.

## PATIENTS AND METHODS

375 patients with primary glaucoma, currently attending the Glaucoma Unit at St Paul's Eye Hospital, Liverpool, were included in the study:

- i. Closed-angle glaucoma: 123 consecutive cases of closed-angle glaucoma (mean age  $68.3 \pm 9.1$  years), presenting between 1975 and 1983.
- ii. Ocular hypertension: 186 consecutive cases of ocular hypertension (OH), referred to the Glaucoma Unit between 1979 and 1983. This group was subdivided by anterior chamber angle assessment into narrow-angle (NA) and wide-angle (WA) categories: 90 OHNA (mean age  $67.5 \pm 9.2$  years) and 96 OHWA (mean age  $64.8 \pm 9.6$  years).
- iii. Open-angle glaucoma: 66 consecutive cases of open-angle glaucoma (OAG), referred to the Glaucoma Unit between 1980 and 1982. This group was subdivided by anterior chamber angle assessment into narrow-angle (NA) and wide-angle (WA) categories: 24 OAGNA (mean age  $71.5 \pm 8.4$  years) and 42 OAGWA (mean age  $67.0 \pm 8.2$  years).

The criteria of Hollows and Graham (1966) were employed in the diagnosis of closed-angle glaucoma, ocular hypertension, and open-angle glaucoma (2); angle assessment was made by the Van Herick method using a biomicroscope (3), according to the standard Shaffer classification of angle configuration. (4)

After informed consent had been obtained, the diabetic status

of each patient was determined by a standard 75 gram oral glucose tolerance test, in accordance with the recommendations of the World Health Organisation (5) and the National Diabetes Data Group (6) ie after three days of unrestricted diet, followed by an 11-14 hour fast, a fasting venous blood sample was taken. A 75 gram oral glucose load in 300 ml water was administered over a five minute period; the commencement of drinking the glucose solution was considered zero time, and 2.5 ml venous blood samples were collected at 1 hour intervals for 2 hours. The blood samples were immediately centrifuged, and assessment of venous plasma was undertaken using a YSI Model 23AM glucose analyser (Yellow Springs Instrument Company, Ohio, USA). Diagnostic criteria for diabetes mellitus and impaired glucose tolerance in non-pregnant adults, according to the recommendations of the National Diabetes Data Group, are shown in table 1. If the fasting venous plasma glucose concentration was significantly elevated ( $\geq 7.8$  mmol/l) on more than one occasion, OGTT was not required to establish the diagnosis of diabetes mellitus. The diagnosis of impaired glucose tolerance or diabetes mellitus was made on the basis of 2 abnormal OGTT, or elevated fasting venous plasma glucose ( $\geq 7.8$  mmol/l) on 2 occasions. Known diabetics were excluded from the OGTT. Height and weight were measured on each subject, and obesity was arbitrarily defined as  $\geq 115\%$  of ideal body weight, according to the 1959 Metropolitan Life Insurance Company Tables; three patients were classified overweight. No subject had significantly elevated blood pressure, either at the initial assessment or one year later, although two subjects had a history of systemic hypertension controlled by diuretic therapy.

A comprehensive drug history was recorded; no patients were taking medication with known diabetogenic effects. (6)

Angle measurement was determined prior to assessment of diabetic status, and the patients categorised according to angle configuration: 123 patients with closed-angle glaucoma; 114 narrow-angle patients (OHNA + OAGNA), mean age  $68.3 \pm 9.1$  years; 138 wide-angle patients (OHWA + OAGWA), mean age  $65.6 \pm 9.1$  years. Categorisation on the basis of anterior chamber angle configuration was performed as the association between primary glaucoma and diabetes mellitus is specifically related to the dimensions of the anterior segment of the eye. (1)

The results of initial assessment of diabetic status have been reported, in part, in a previous paper. (1) Exactly one year after the first test, 75 gram oral glucose tolerance test was repeated in 63 of the 68 primary glaucoma patients shown to have impaired glucose tolerance: 24 closed-angle glaucoma patients (mean age  $68.5 \pm 7.8$  years), 24 narrow-angle patients (mean age  $71.0 \pm 8.6$  years), and 15 wide-angle patients (mean age  $68.9 \pm 6.4$  years).

## RESULTS

The results of diabetic assessment by 75 gram oral glucose tolerance test in 375 patients with primary glaucoma are shown in table 2. Diabetic status of primary glaucoma patients, re-categorised on the basis of anterior chamber angle configuration, are shown in table 3. The proportion of primary glaucoma patients with impaired glucose tolerance which had progressed to diabetes mellitus, following repeat 75 gram oral glucose tolerance test at one year follow-up, are shown in table 4.

No patient with impaired glucose tolerance which had progressed to diabetes mellitus was classified obese, or had a history of systemic hypertension.

## DISCUSSION

In a study of 204 subjects with impaired glucose tolerance ("borderline diabetes"), discovered in a screening survey of 20,000 male Civil Servants, it was shown that 13% "worsened" to diabetes over a five year period - an average of 2-3% per year. (7) In this study of 63 patients with impaired glucose tolerance, present in a survey of only 375 patients with primary glaucoma, 16% progressed to overt diabetes mellitus in one year. The prevalence of diabetes mellitus/ impaired glucose tolerance in the primary glaucoma population is estimated to be 37% in patients with closed-angle glaucoma, 38% in narrow-angle subjects, and 18% in wide-angle subjects, compared with 16% in an age- and sex-matched control group. (1) The present study reinforces this assertion, supplementing the data with prospective evidence to indicate the likely prognosis of glaucoma patients with impaired glucose tolerance, and suggesting a significantly-increased progression to overt diabetes mellitus in these patients compared with studies on "normal" subjects.

The essential anterior segment event precipitating irido-corneal contact, and therefore angle-closure, is postulated to be a change in autonomic activity - with particular emphasis on parasympathetic tone. (8) Systemic autonomic dysfunction, assessed by standard autonomic function tests (9,10), is present in 58% of patients with closed-angle glaucoma (11) and 42% of ocular hypertensives - with a significantly higher prevalence in narrow-angle patients (50%) than wide-angle patients (34%). (12) As the pathogenesis of acute angle-

closure is directly dependent upon relative parasympathetic and sympathetic activity in the anterior segment of the eye - and diabetes mellitus is the commonest cause of autonomic neuropathy in this country (13) - the proposal that the association between diabetes mellitus and primary glaucoma may be a consequence of autonomic dysfunction in the anterior segment of the eye appears reasonable; recent studies have demonstrated autonomic dysfunction in 20-40% of diabetic patients. (14,15) The prevalence of autonomic dysfunction in primary glaucoma patients with impaired glucose tolerance is the subject of current research, however the demonstration of increased progression to overt diabetes mellitus in these patients - with presumably a concomitant increased risk of developing autonomic dysfunction - supports current theories of the observed association between these previously-unrelated diagnoses.

The results of this study provide further evidence of a significant association between diabetes mellitus and primary glaucoma, emphasising the importance of diabetic assessment in patients with primary glaucoma, with repeated regular assessment to determine subsequent changes in diabetic status. It is proposed that the association may be explained on the basis of autonomic dysfunction, a frequent complication of diabetes mellitus. Progression to diabetes mellitus is a significant feature of impaired glucose tolerance in primary glaucoma patients.

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Table 1

DIAGNOSTIC CRITERIA FOR 75g ORAL GLUCOSE TOLERANCE TEST UNDER STANDARD CONDITIONS

	Venous plasma glucose concentration (mmol/L)		
	Fasting	1 hour after 75g oral glucose load	2 hours after 75g oral glucose load
Impaired glucose tolerance	< 7.8	≥ 11.1	7.8 - 11.1
Diabetes mellitus	< 7.8	≥ 11.1	≥ 11.1

Table 2

RESULTS OF DIABETIC ASSESSMENT BY 75 GRAM ORAL GLUCOSE TOLERANCE TEST IN 375 PATIENTS WITH PRIMARY GLAUCOMA

	Normal	NIDDM	IDDM	IGT
Closed-angle glaucoma patients (n=123)	75	22 (4)	1 (1)	25
Ocular hypertensives ALL (n=186)	131	24 (8)	0	31
OHNA (n=90)	56	13 (7)	0	21
OHWA (n=96)	75	11 (1)	0	10
Open-angle glaucoma patients ALL (n=66)	47	7 (2)	0	12
OAGNA (n=24)	15	3 (1)	0	6
OAGWA (n=42)	32	4 (1)	0	6

\* The number in brackets equals known diabetics

Table 3

DIABETIC STATUS OF 375 PRIMARY GLAUCOMA PATIENTS, CATEGORISED BY  
ANTERIOR CHAMBER ANGLE CONFIGURATION

	Normal	Impaired glucose tolerance	Diabetes mellitus
Closed-angle glaucoma patients (n=123)	75	25	23 (5)
Narrow-angle patients (n=114)	71	27	16 (8)
Wide-angle patients (n=138)	107	16	15 (2)

\* The number in brackets equals known diabetics

Table 4

PROGRESSION OF IMPAIRED GLUCOSE TOLERANCE TO DIABETES MELLITUS IN  
375 PATIENTS WITH PRIMARY GLAUCOMA

	No of patients with IGT at initial assessment	No of patients reassessed by 75g OGTT one year later	No of patients with IGT which had progressed to DM one year later
Primary glaucoma patients All (n=375)	68 (18%)	63	10 (16%)
Closed-angle glaucoma patients (n=123)	25 (20%)	24	3 (12%)
Narrow-angle patients (n=114)	27 (24%)	24	5 (21%)
Wide-angle patients (n=138)	16 (12%)	15	2 (13%)

PAPER 18

DIABETES MELLITUS IN THE PRIMARY GLAUCOMAS

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## SUMMARY

The association between diabetes mellitus and the primary glaucomas is evaluated. Diabetes is specifically associated with narrow-angle categories of primary glaucoma: closed-angle glaucoma and narrow-angle patients with ocular hypertension or open-angle glaucoma. The prevalence of diabetes mellitus in wide-angle glaucoma patients is not significantly different from normal age-matched control subjects. The association between diabetes and glaucoma is restricted to non-insulin dependent diabetes mellitus and impaired glucose tolerance; the prevalence of insulin-dependent diabetes mellitus in the primary glaucomas is equivalent to age-matched normal values. These conclusions are supported by 75-gram oral glucose tolerance testing, estimation of glycosylated haemoglobin, retrospective analysis of positive diabetic family history, and prospective follow-up examining progression of impaired glucose tolerance to diabetes mellitus in patients with primary glaucoma.

## KEY WORDS

Diabetes mellitus, primary glaucoma, ocular hypertension, anterior chamber depth

An association between diabetes mellitus and open-angle glaucoma was noted by Grafe in 1924 with the observation that proliferative retinopathy was less common in cases of diabetes with elevated intraocular pressure (1). The association between diabetes and open-angle glaucoma was placed in perspective by Armstrong et al in 1960; known diabetes mellitus was present in 12.6% of patients, with a further 5.7% diagnosed by oral glucose tolerance test ie a total prevalence of 18.3% (2). The prevalence of known diabetes in patients with open-angle glaucoma has been variously reported between 6-18% (2,3,4,5), and several studies have also confirmed the increased prevalence of asymptomatic diabetes in the glaucoma population (6,7). Becker (1971) examined a series of 100 consecutive patients with primary open-angle glaucoma but without known diabetes mellitus; a positive oral glucose tolerance test was obtained in 20% of the patients (8).

### *Criteria for diagnosis*

Unfortunately, comparisons between many of the previous studies have been extremely difficult to interpret, as the diagnosis of diabetes mellitus - until comparatively recently - was based upon differing diagnostic criteria applied to different forms of the oral glucose tolerance test (9), thereby precluding comparisons of diabetic prevalence within discrete populations. In North America, the 100-gram oral glucose tolerance load was widely used (10), whilst in Europe the test was performed with a 50-gram glucose loading dose (11). Recently, the National Diabetes Data Group and the World

Health Organisation Expert Committee on Diabetes Mellitus have standardised the diagnosis of diabetes mellitus within specific criteria, advocating oral glucose tolerance testing with a 75-gram glucose load (12,13). This has been well-received (14,15,16), and permits accurate comparisons of diabetic prevalence on a global basis for the first time.

The criteria proposed by the National Diabetes Data Group and the World Health Organisation subdivide the population into three categories:

- i. normal
- ii. impaired glucose tolerance
- iii. diabetes mellitus

Impaired glucose tolerance represents a region of diagnostic uncertainty, encompassing the following former diagnoses: chemical diabetes, asymptomatic diabetes, subclinical diabetes, borderline diabetes, and latent diabetes. Studies have shown that between 2-4% per year will progress to overt diabetes mellitus (17).

#### *Glycosylated haemoglobin*

Adequate categorisation of individual diabetic status requires information relating to three specific characteristics of diabetes mellitus:

- i. type: insulin dependent diabetes mellitus (IDDM) or  
non-insulin dependent diabetes mellitus (NIDDM)
- ii. duration of diabetes
- iii. control of diabetes

Several studies have indicated that glycosylated haemoglobin is a

reliable index of diabetic control (18,19,20). Improved control has been correlated with a reduction in glycosylated haemoglobin (21,22). Providing care is taken in the experimental model to eliminate recent glycaemic fluctuations (23), this technique gives an accurate estimate of prevailing glucose concentrations throughout the life of the red blood cell (24); in consequence, glycosylated haemoglobin is a clinically-useful indicator of long-term diabetic control.

#### DIABETES IN THE PRIMARY GLAUCOMAS

##### *Diabetes and anterior chamber dimensions*

Several recent studies have clarified the nature of the association between diabetes mellitus and the primary glaucomas. In 1985, Mapstone and Clark examined a series of 352 patients with primary glaucoma - closed-angle glaucoma, ocular hypertension and open-angle glaucoma - and 73 age- and sex-matched control subjects (25). Patients with ocular hypertension and open-angle glaucoma were further subdivided by the configuration of the anterior chamber angle into wide-angle and narrow-angle categories according to the Shaffer classification (26). The diabetic status of each subject was assessed by 75-gram oral glucose tolerance test (OGTT), and the results classified according to the criteria of the National Diabetes Data Group (12) (Table 1). It was noted that the prevalence of diabetes mellitus in patients with closed-angle glaucoma was significantly higher than in the control group ( $p < 0.005$ ). The proportion of abnormal responses to oral glucose tolerance test in patients with wide irido-corneal angles - either ocular hypertension or open-angle glaucoma - was not significantly different from the control group ( $p > 0.05$ ), however the prevalence of diabetes mellitus

or impaired glucose tolerance was significantly elevated in narrow-angle subjects with ocular hypertension or open-angle glaucoma ( $p < 0.005$ ). Diabetes or impaired glucose tolerance was present in 37% of patients with closed-angle glaucoma, 38% of patients with narrow irido-corneal angles, and 18% of patients with wide irido-corneal angles, compared with 16% of the age-matched control group. When the results of 75-gram oral glucose tolerance test were correlated with axial anterior chamber depth in the glaucoma patients, there was a significant negative linear correlation between the probability of an abnormal response to OGTT and anterior chamber depth ( $r = -0.79$ ;  $p < 0.001$ ). (Figure 1) A similar association is demonstrated by figure 2, which shows the relationship between 2-hour venous plasma glucose (during 75-gram OGTT) and axial anterior chamber depth. 19 known diabetics were excluded from OGTT and are therefore not included in the diagram; 16 of these subjects had an anterior chamber depth  $< 2.2$  mm. These results suggest that there is a significant association between diabetes mellitus and the anatomical dimensions of the anterior segment of the eye in patients with primary glaucoma, rather than an association with a particular clinical type of glaucoma. The study also confirmed that the association between diabetes mellitus and glaucoma is specifically with non-insulin dependent diabetes mellitus.

#### *Glycosylated haemoglobin*

Glycosylated haemoglobin was estimated in a series of randomly-selected patients from the above categories of primary glaucoma, including subjects classified as diabetic or impaired glucose tolerance, and also those classified as normal by OGTT.

Assessment of glycosylated haemoglobin was concurrently performed on 31 age- and sex-matched control subjects. A micro-column chromatographic technique was used (Boehringer Mannheim, Lewes, England); by this method, the normal range of glycosylated haemoglobin is 5-8% (27,28). Factors known to produce falsely-elevated values of glycosylated haemoglobin include uraemia (29,30), lead poisoning (31), alcoholism (32), and high daily doses of aspirin (33); no subject had a history of the aforementioned factors necessitating exclusion from the study.

The results of glycosylated haemoglobin estimation in 60 patients with closed-angle glaucoma, 78 patients with ocular hypertension, 30 patients with open-angle glaucoma, and 31 age- and sex-matched control subjects are shown in table 2. The ocular hypertension and open-angle glaucoma patients were subdivided by irido-corneal angle configuration and comparisons of glycosylated haemoglobin results were made between the control group and each of the primary glaucoma categories; significance was assessed by Student's unpaired t test and corrected for multiple comparisons by Dunnett's procedure (34,35). Glycosylated haemoglobin levels were significantly higher than control values in closed-angle glaucoma patients ( $p < 0.01$ ), narrow-angle ocular hypertensive subjects ( $p < 0.01$ ), and narrow-angle open-angle glaucoma patients ( $p < 0.01$ ). Glycosylated haemoglobin levels were not significantly different from control values in ocular hypertensives with wide angles ( $p > 0.05$ ) or open-angle glaucoma patients with wide angles ( $p > 0.05$ ).

The control group and primary glaucoma categories were then subdivided on the basis of diabetic status into diabetic and

non-diabetic subjects; comparisons of glycosylated haemoglobin levels were made between the control group and each of the primary glaucoma categories for diabetic and non-diabetic subjects separately. Significantly-increased glycosylated haemoglobin levels in closed-angle glaucoma patients, narrow-angle ocular hypertensive subjects, and narrow-angle open-angle glaucoma patients were only present in diabetic subjects; glycosylated haemoglobin levels were not significantly elevated in non-diabetic subjects. These results support the initial conclusions from oral glucose tolerance testing in glaucoma patients. Glycosylated haemoglobin is less susceptible than plasma glucose to acute fluctuations, and therefore provides significant confirmation of the association between diabetes mellitus and the primary glaucomas.

The results of these papers have also been supported by subsequent retrospective and prospective studies on this subject.

#### *Retrospective study*

Retrospective analysis of 371 patients with primary glaucoma and 85 age- and sex-matched control subjects showed a significantly increased prevalence of NIDDM in the family history of patients with closed-angle glaucoma ( $p < 0.005$ ) and ocular hypertension ( $p < 0.05$ ), although not in patients with open-angle glaucoma (36). A positive family history of NIDDM in first-degree relatives was present in 20% of patients with closed-angle glaucoma, 13% of patients with ocular hypertension, and 11% of patients with open-angle glaucoma, thereby emphasising the increased association between diabetes mellitus and narrow-angle primary glaucomas.

### *Prospective study*

63 primary glaucoma subjects (from a total survey of 375 glaucoma subjects) initially classified as impaired glucose tolerance, were re-assessed by 75-gram OGTT one year later (37). 16% had progressed to overt diabetes, according to the criteria of the National Diabetes Data Group (12): 12% of closed-angle glaucoma subjects, 21% of narrow-angle patients (ocular hypertension and open-angle glaucoma), and 13% of wide-angle patients (ocular hypertension and open-angle glaucoma). By comparison, in a study of 204 subjects with impaired glucose tolerance but with no known evidence of glaucoma, discovered in a screening survey of 20,000 male Civil Servants, it was shown that 13% 'worsened' to diabetes over a five-year period - an average of 2.6% per year (17). In this study of 63 patients with impaired glucose tolerance, present in a survey of only 375 patients with primary glaucoma, 16% progressed to overt diabetes mellitus in one year, with accelerated progression in narrow-angle subjects.

### *Effects of diabetes on the anterior segment of the eye*

The role of diabetes in the pathogenesis of glaucoma is probably multifactorial. Severe systemic complications may occur secondary to diabetes mellitus, principally vasculopathy, nephropathy, retinopathy and neuropathy (somatic and autonomic), although almost every system can be affected. Adverse effects of diabetes mellitus are equally ubiquitous in the eye; anterior and posterior segments are frequently involved. Although complications in the posterior segment, with potentially-blinding retinopathy, are more comprehensively documented, anterior segment structures are also affected - with inevitable consequences in the pathogenesis of glaucoma. The lens

in diabetic eyes is characteristically large (38), thus facilitating closure of the irido-corneal angle by mechanical shallowing of the anterior chamber. Rapid changes in lens dimensions, resulting in varying refraction, are associated with fluctuating levels of plasma glucose in diabetics (39). Parasympathetic neuropathy of the anterior segment, determined by pupillary responses to 2% methacholine, is reported to be present in 81% of unselected diabetic patients (40); denervation hypersensitivity, determined by pupillary responses to 0.1% adrenaline, implying significant neuropathy of the sympathetic nervous system, have an estimated prevalence of 28.9% in diabetics with background retinopathy, although only 2.4% in diabetics without retinopathy (41). Pupillary abnormalities are well-recognised complications of diabetes mellitus, particularly impaired reflex responses to light, and excessive miosis (42,43); these have been variously attributed to somatic neuropathy (44) and autonomic neuropathy (45). The efficacy of pupillary responses has been correlated with diabetic control; pupillographic studies demonstrated a direct relationship between efficacy of pupil response and co-existent metabolic stability (46). Diabetes mellitus has been implicated in the aetiology of iritis for over 100 years, and iridopathy is a recognised complication of diabetes (47).

## CONCLUSIONS

The association between diabetes mellitus and the primary glaucomas has been accurately defined by specific determination of diabetes prevalence in each of the major categories of primary glaucoma. Concurrent examination of a comparable age-matched control group permits existing data to be viewed in perspective, whilst prevalence levels have been determined in categories where data was previously inconclusive or absent (ie ocular hypertension and closed-angle glaucoma respectively). The type of diabetes mellitus associated with primary glaucoma is specifically non-insulin dependent diabetes mellitus and impaired glucose tolerance; the prevalence of insulin-dependent diabetes mellitus in the primary glaucomas is similar to that in age-matched normal control subjects.

Significantly-increased prevalence of abnormal glucose tolerance (ie diabetes mellitus and impaired glucose tolerance) is restricted to primary glaucomas with narrow angles. Accurate comparisons with previous studies, employing different diagnostic criteria, is not possible, however several salient features are worthy of note. The prevalence of diabetes mellitus in patients with open-angle glaucoma has been reported as 18.3% (2) and 20% (8). These statistics compare favourably with the presently-defined prevalence of abnormal glucose tolerance in patients with open-angle glaucoma (18.3%) which is not significantly different from the prevalence of abnormal glucose tolerance in the comparable control group (16.4%). Similarly, the reported prevalence of diabetes mellitus in patients with open-angle glaucoma by studies not specifically determining diabetic status by OGTT was 8% (48) and 7.6% (49), compared with diabetes prevalence in

the present control group of 6.8%. Several aetiological mechanisms are implicated in the pathogenesis of glaucoma, resulting from the ubiquitous nature of diabetic anterior segment complications, however present evidence suggests autonomic nerve dysfunction to be the most significant single factor (50).

LEGENDS

Figure 1

Probability of developing an abnormal response to 75-gram oral glucose tolerance test correlated with anterior chamber depth in 352 patients with primary glaucoma

(Reproduced with permission, British Medical Journal)

Figure 2

Correlation of 2-hour venous plasma glucose concentration during 75-gram oral glucose tolerance test with anterior chamber depth in 333 patients with primary glaucoma

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Doc Ophthalmol (in press)

Table 1

DIAGNOSTIC CRITERIA FOR 75g ORAL GLUCOSE TOLERANCE TEST UNDER STANDARD CONDITIONS

	Venous plasma glucose concentration (mmol/L)		
	Fasting	1 hour after 75g oral glucose load	2 hours after 75g oral glucose load
Impaired glucose tolerance	< 7.8	≥ 11.1	7.8 - 11.1
Diabetes mellitus	< 7.8	≥ 11.1	≥ 11.1

Table 2

RESULTS OF GLYCOSYLATED HAEMOGLOBIN ESTIMATION IN 60 PATIENTS WITH CLOSED-ANGLE GLAUCOMA, 78 PATIENTS WITH OCULAR HYPERTENSION, 30 PATIENTS WITH OPEN-ANGLE GLAUCOMA AND 31 AGE- AND SEX-MATCHED CONTROL SUBJECTS  
(Group mean values  $\pm$  SEM)

	Glycosylated haemoglobin (% age)
Control subjects (n=31)	5.70 $\pm$ 0.14
Closed-angle glaucoma patients (n=60)	6.54 $\pm$ 0.12
Ocular hypertensive patients All (n=78)	6.53 $\pm$ 0.13
Narrow-angle patients (n=43)	6.81 $\pm$ 0.20
Wide-angle patients (n=35)	6.17 $\pm$ 0.12
Open-angle glaucoma patients All (n=30)	6.63 $\pm$ 0.22
Narrow-angle patients (n=13)	6.88 $\pm$ 0.32
Wide-angle patients (n=17)	6.44 $\pm$ 0.30

Figure 1

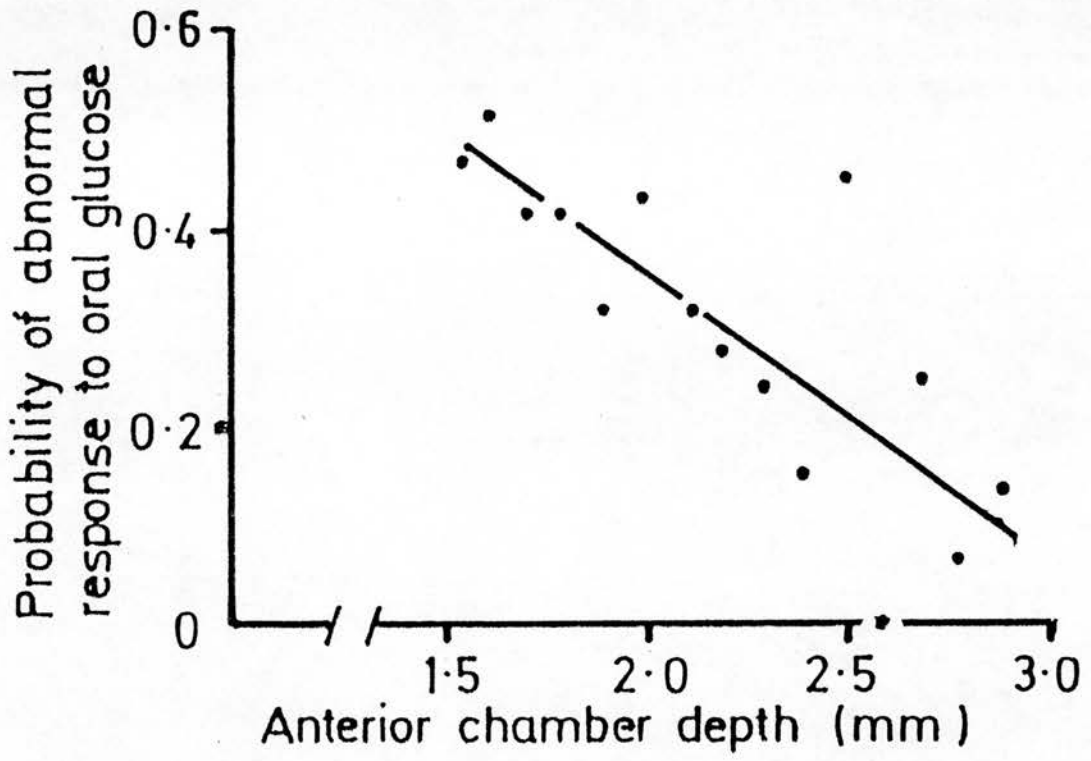
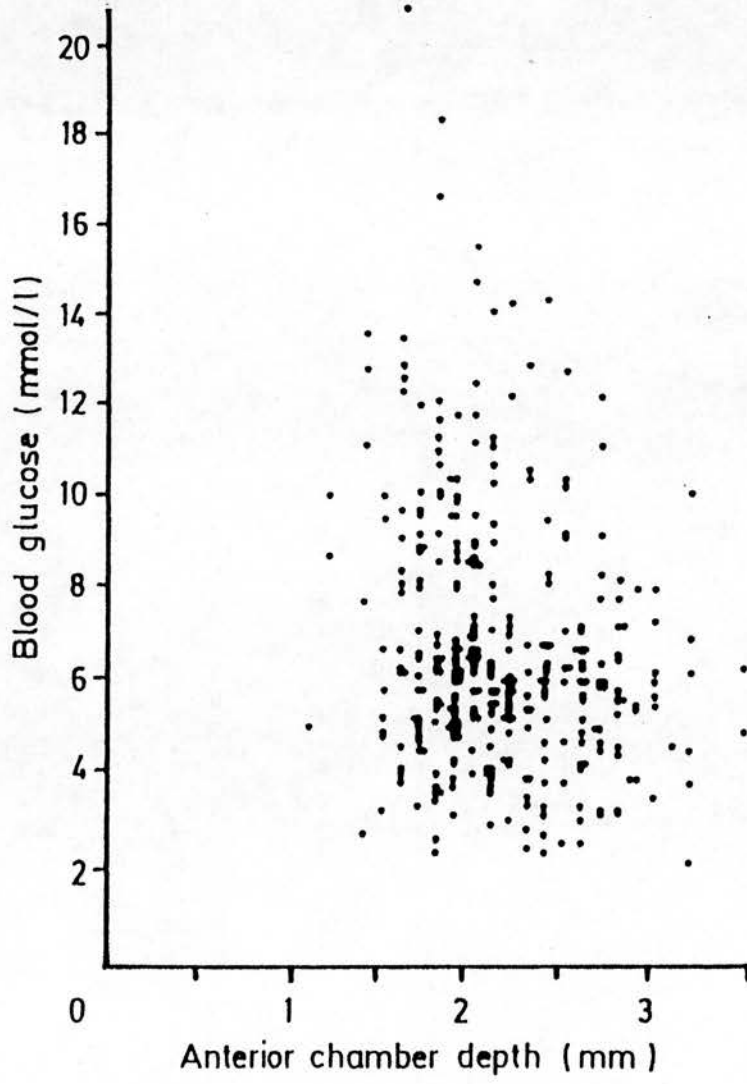


Figure 2



### 1.3 DIURNAL VARIATION

PAPER 19

DIURNAL VARIATION IN THE DIMENSIONS OF THE ANTERIOR CHAMBER

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## ABSTRACT

Anterior chamber depth and volume were measured photogrammetrically on a diurnal basis in 38 eyes from 21 normal subjects. Significant diurnal variation in anterior chamber dimensions was demonstrated. Anterior chamber depth and volume measurements in the evening were significantly lower than morning values, with particular emphasis on the periphery of the anterior chamber: axial depth decreased by 2.1%, peripheral depth by 21.1%, and anterior chamber volume by 5.7%.

## INTRODUCTION

The progressive decrease in anterior chamber depth with age, secondary to lens growth, is well established (1-4), however recent papers have demonstrated acute changes in the dimensions of the anterior chamber following topical installation of autonomic agonists (5,6), and surgical peripheral iridectomy in the treatment of closed-angle glaucoma (7,8). Peripheral iridectomy has been shown to significantly increase the depth of the anterior chamber peripherally, in the absence of significant alterations in central anterior chamber depth; this observation is of particular relevance, as it is changes in the dimensions of the peripheral anterior chamber that precipitate closure of the irido-corneal angle. The inevitable conclusion from these observations is that the depth of the anterior chamber is not static, but rather a dynamic variable which may display rapid and transient changes.

The aim of this study was to assess the anterior chamber depth and volume on a diurnal basis in a group of normal subjects, to evaluate the concept of diurnal variation in anterior chamber dimensions.

## SUBJECTS AND METHODS

After informed consent had been obtained, 21 normal subjects (mean age  $63.4 \pm 16.5$  years) were included in the study. A comprehensive past medical history was recorded, and ocular examination was performed on all subjects, as follows:

i. Anterior segment assessment

- a. slit-lamp examination of cornea, anterior chamber, iris integrity/dynamics, and lens
- b. gonioscopy by Zeiss 4-mirror gonioprism to determine angle configuration and exclude angle abnormalities
- c. intraocular pressure by Goldmann applanation tonometry

ii. Posterior segment assessment

- a. direct ophthalmoscopy of optic disc, cup:disc ratio, retinal vessels and macula
- b. indirect ophthalmoscopy, after pupillary dilation, to assess posterior pole and retinal periphery
- c. visual field examination: peripheral field by Goldmann perimetry; central field by either Goldmann perimeter or Friedmann II analyser

No subject had a past medical history/family history of eye disease, and no subject was taking any ocular or systemic medication at the time of examination. Visual acuity was  $>6/9$  ( $20/30$ ) in each eye, and no abnormalities were present on ocular examination. Angle assessment was made by biomicroscopy with a Zeiss gonioprism, using the standard Shaffer classification of angle configuration (9); angle configuration was  $> 3$  in all eyes included in the study.

Diurnal anterior chamber depth and volume was measured in 38 eyes from 21 subjects; 4 eyes were excluded from the study, as the presence of marked corneal arcus senilis precluded accurate measurement of peripheral anterior chamber depth. Anterior chamber dimensions were measured by the standard photogrammetric technique introduced by Johnson, Coakes and Brubaker in 1978 (10), using a Zeiss photographic slit-lamp with Polaroid camera attachment. Polaroid photographs of the lower half of the mid-sagittal plane of the eye were taken at an angle of 55°. A transparent anterior chamber template was aligned with the posterior corneal curve, and the depth of the anterior chamber measured to an accuracy of 0.1 mm at 0.5 mm from the optic axis; anterior chamber volume was obtained by multiplication of the individual depths by appropriate weighting factors.

Anterior chamber photographs were taken between 7.15-7.45 am, and 7.15-7.45 pm, on the same day for each subject. Diurnal variation in anterior chamber dimensions was assessed 3 weeks after the ocular examination in all subjects, to negate any residual effects of pupillary mydriasis. The following measurements were recorded from each photograph:

- i. Axial anterior chamber depth.
- ii. Peripheral anterior chamber depth: Hitchings et al (1984) proposed the anterior chamber depth 5 mm from the optic axis to be a representative and reproducible measure of peripheral anterior chamber depth (11); this definition has been observed.

iii. Anterior chamber volume

Measurements from the photographs were performed on a single-blind basis ie the observer was not aware of details relating to each photograph at the time of measurement. Significance was assessed by Student's paired t test.

## RESULTS

The results of diurnal measurement of anterior chamber depth and volume in 38 eyes from 21 normal subjects are shown in the table. Anterior chamber dimensions showed significant diurnal variation; anterior chamber depth and volume measurements were significantly lower in the evening compared with morning values. Diurnal variation was most significant in the periphery of the anterior chamber; axial depth decreased by 2.1%, however peripheral depth decreased by 21.1%. Concomitant significant diurnal changes in anterior chamber volume were noted; evening values were 8.2  $\mu$ l lower, a mean variation of 5.7%.

## COMMENT

Diurnal variation of intraocular pressure is a well-recognised phenomenon (12,13). The relative importance of diurnal changes in outflow facility (14), or changes in the rate of aqueous production, remain unknown, although daily fluctuations in outflow facility do not seem to be in phase with daily intraocular pressure variation (15). Significant diurnal changes in the dimensions of the anterior chamber are integrally related to a diurnal variation in aqueous dynamics. The observation that anterior chamber depth and volume was significantly lower in the evening - with particular emphasis on the periphery of the anterior chamber - suggests a diurnal physiological shallowing of the anterior chamber secondary to anterior translation of the iris-lens diaphragm. This may obviously facilitate the genesis of angle-closure in certain predisposed individuals; the iridocorneal distance is only approximately 0.15 mm in narrow-angle subjects (16), and peripheral anterior chamber depth may shallow by up to 0.19 mm on a diurnal basis. Individual differences in diurnal variation may explain why certain eyes with narrow angles progress to overt angle-closure, whilst other anatomically-similar eyes do not. Diurnal variation in the dimensions of the anterior chamber is thus a physiological phenomenon, which may have pathological sequelae dependent upon the pre-existing anatomical configuration of the irido-corneal angle.

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DIURNAL VALUES OF ANTERIOR CHAMBER DEPTH AND VOLUME IN 38 EYES FROM 21 NORMAL SUBJECTS

(Group mean values  $\pm$  SEM)

	AM	PM	Significance
Axial anterior chamber depth (mm)	2.86 $\pm$ 0.08	2.80 $\pm$ 0.08	p < 0.02
Peripheral anterior chamber depth (mm)	0.90 $\pm$ 0.08	0.71 $\pm$ 0.09	p < 0.001
Anterior chamber volume ( $\mu$ L)	145.3 $\pm$ 7.5	137.1 $\pm$ 7.5	p < 0.01

PAPER 20

DIURNAL VARIATION IN THE ONSET OF ACUTE CLOSED-ANGLE GLAUCOMA

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## INTRODUCTION

Acute glaucoma results from closure of the angle in the anterior chamber of the eye by apposition of peripheral iris to cornea, thereby preventing the outflow of aqueous humour from the anterior segment; with continuing aqueous production, intraocular pressure rises precipitously, producing characteristic symptoms and signs of closed-angle glaucoma: decreased visual acuity, haloes around lights, and pain - frequently severe. (1) Diurnal variation of intraocular pressure is a well-recognised phenomenon. (2) A logical progression was to determine whether the onset of acute closed-angle glaucoma varied on a similar diurnal cycle.

## PATIENTS, METHODS AND RESULTS

Retrospective analysis was made of 100 consecutive patients (mean age  $66.3 \pm 10.1$  years) presenting with acute closed-angle glaucoma referred to the Glaucoma Unit of St Paul's Eye Hospital, Liverpool, during the 8 years to 20th December 1983. Each patient was questioned individually - by a single observer - to determine the time of day (to the nearest hour) when symptoms of acute glaucoma became apparent; as angle-closure produces rapidly-progressive, severe effects, onset of symptoms represents a reasonable approximation to the commencement of the acute attack. Details were verified from patients' case records. Acute closed-angle glaucoma was significantly more prevalent in females than males (71 women v 29 men;  $\chi^2 = 17.64$ ,  $df = 1$ ,  $p < 0.001$ ).

The table shows the diurnal variation in the time of onset of acute closed-angle glaucoma, with a peak incidence during the evening and a trough in the morning. Comparison of the 12-hour periods 0400-1500 with 1600-0300 yielded a significant difference ( $\chi^2 = 31.36$ ,  $df = 1$ ,  $p < 0.001$ ). The hypothesis of a constant incidence throughout the day was not reasonable ( $\chi^2 = 86.24$ ,  $df = 23$ ,  $p < 0.001$ ), but when the logarithms of the observed counts were submitted to regression on a sine (hour) and cosine (hour) scale jointly on a 24-hour cycle assuming Poisson type errors, the regression

was highly significant ( $\chi^2 = 35.83$ ,  $df = 2$ ,  $p < 0.001$ ).

## COMMENT

The depth of the anterior chamber of the eye is a dynamic variable which may show rapid and transient changes. (3) Diurnal shallowing of anterior segment dimensions has been demonstrated; anterior chamber depth and volume measurements in the evening are significantly lower than morning values, with particular emphasis on the anterior chamber angle which decreases by 21%. (4) This may obviously facilitate the onset of angle-closure; individual differences in diurnal shallowing of the anterior chamber may explain why certain eyes progress to overt angle-closure, whilst other apparently-similar eyes do not.

Closed-angle glaucoma is a medical emergency; during a typical episode, intraocular pressure is frequently  $> 50$  mmHg (normal range 10-20 mmHg) producing irreversible ischaemic ocular damage within a few hours. Although previous clinical impressions have suggested that acute glaucoma occurs mainly during the evening hours, this is the first statistically significant evidence to confirm this hypothesis, with the following implications. Delay in management overnight may result in significant impairment of sight; effectively, closed-angle glaucoma represents a form of preventable blindness - but only if management is instituted at an early stage. The onset of closed-angle glaucoma is not easily recognised,

however suspicious features would include pain or decreased visual acuity with a relatively-acute onset during the evening hours. A history of similar self-limited episodes occurring at the same time of day, suggestive of intermittent partial angle-closure, would reinforce the diagnosis. Immediate ophthalmic treatment only serves to arrest the rapidly-progressing ocular damage; of infinitely-greater importance is early recognition by the general practitioner and immediate referral.

In summary, significant diurnal variation in the onset of acute closed-angle glaucoma has been demonstrated, with most cases occurring in the evening and least in the morning. Diurnal variation in ocular dimensions follows a similar temporal distribution, and may be a significant factor in the pathogenesis of acute angle-closure. Acute glaucoma is an ophthalmological emergency requiring specialist care, however optimal management is determined by the clinical acumen of the general practitioner. The aim of this paper was to describe the major presenting features of the condition, and the time of day at which it frequently presents, thereby increasing medical awareness and presumably improving management - by prevention.

#### ACKNOWLEDGEMENTS

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HOURLY DISTRIBUTION OF ONSET OF ACUTE CLOSED-ANGLE GLAUCOMA OVER 8 YEARS

Time	No of patients presenting with acute closed-angle glaucoma
0100	2
0200	6
0300	1
0400	2
0500	0
0600	2
0700	8
0800	4
0900	0
1000	2
1100	1
1200	1
1300	0
1400	0
1500	2
1600	6
1700	6
1800	11
1900	13
2000	13
2100	6
2200	6
2300	3
2400	5
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	<u>100</u>

1.4 MISCELLANEOUS

PAPER 21

Posterior synechiae after glaucoma operations:  
aggravation by shallow anterior chamber and  
pilocarpine

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TAVISTOCK SQUARE, WC1H 9JR

## Posterior synechiae after glaucoma operations: aggravation by shallow anterior chamber and pilocarpine

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**SUMMARY** Posterior pupillary synechiae affect a proportion of eyes subjected to iridectomy with or without drainage operation because (1) aqueous humour bypasses the pupil; (2) traumatic iridocyclitis occurs; (3) there is immobility of the iris in the iridectomy sector; (4) in eyes with angle closure glaucoma closer apposition of the iris to the anterior lens capsule increases the tendency; (5) pilocarpine aggravates (4) both in angle closure glaucoma and open angle glaucoma and produces a small immobile pupil facilitating pupillary membrane formation (occlusio pupillae). Pilocarpine should be avoided if possible as medical treatment at any time after a drainage operation. A beta blocker is the drug of choice. To eliminate posterior synechiae over a fair number of degrees of pupil (say 30°) sector iridectomy can be done.

Iridectomy is a well established procedure in the treatment of glaucoma,<sup>1</sup> specifically angle-closure glaucoma (ACG).<sup>2</sup> In patients with closed-angle glaucoma (CAG) 45-70% of untreated fellow eyes will develop closed angles within 10 years of initial presentation.<sup>3,4</sup> Prophylactic peripheral iridectomy—or laser iridotomy—is therefore advocated for prevention.<sup>5</sup> There are some complications of surgical iridectomy.<sup>5-8</sup> However, these are usually considered to be infrequent or innocuous enough, so that the operation is done in preference to the risk of acute closed-angle glaucoma.

This paper examines the prevalence and distribution of posterior synechiae, a common side effect of surgical procedures in the treatment of glaucoma—particularly of surgical iridectomy—and the role of postoperative pilocarpine as an aggravating factor, especially in eyes with shallow anterior chambers.

This series preceded our adoption of laser iridectomy for ACG, but, as far as posterior synechiae are concerned, laser iridectomised eyes behave very much like eyes which have had surgical iridectomy.<sup>9,10</sup> Indeed, posterior synechiae are easier to miss after laser iridectomy, so that the surgeon must remain vigilant with this newer treatment.

### Patients and methods

Retrospective analysis of 63 consecutive patients attending a glaucoma clinic who were operated on for glaucoma determined the prevalence of postoperative posterior synechiae and their association with the postoperative administration of pilocarpine. Sixty-three eyes from 63 patients (mean age 69.8, SD 10.4 years) were included in the study. There were 39 eyes from 39 patients with closed-angle glaucoma (mean age 69.0, SD 9.9 years) and 24 eyes from 24 patients with open-angle glaucoma (mean age 71.0, SD 11.1 years). There was no significant sex predilection (30 males : 33 females). Patients with 'secondary' glaucoma were excluded. All patients had had glaucoma operations during the preceding 15 years. The classification of surgical procedures is shown in Table 1. A detailed history was recorded from each patient, with particular reference to postoperative medical treatment, which information was available from the case records. The presence of posterior synechiae was assessed by (attempted) dilatation of pupils by guttae 1% tropicamide and guttae 10% phenylephrine. A diagram of the ensuing pupil size and shape was drawn, and the presence or absence of posterior synechiae noted on a clock diagram divided into 12 sectors.

Only one eye was chosen from each patient, since both eyes in one patient can be expected to behave similarly; thus each individual observation would not then be completely independent of all others. The choice was random: right eyes were chosen from patients whose years of birth ended in even numbers and left eyes from odd numbers.

**Results**

Comparisons were made between the prevalence of posterior synechiae in patients who had required operation for ACG/CAG (excluding acute cases) and for open-angle glaucoma (OAG). Each group was subdivided into those who had or had not required pilocarpine afterwards. Assessments were 'single masked,' and significance was assessed by the  $\chi^2$  test with Yates's correction. The results are shown in Tables 2 and 3.

Even without pilocarpine some posterior synechiae were present: 6/19 for CAG (Table 2) and 2/10 for OAG (Table 3). Although the proportion is

Table 1 Glaucoma surgery in 63 eyes from 63 glaucoma patients

	Closed-angle glaucoma	Open-angle glaucoma
Peripheral iridectomy	22	3
Trabeculectomy	5	11
Sector iridectomy	5	0
Sector iris inclusion	2	2
Scheie's operation	3	2
Trephine	2	6
Total	39	24

Table 2 Prevalence of postoperative posterior synechiae in 39 eyes from 39 patients with closed-angle glaucoma

	Posterior synechiae absent	Posterior synechiae present
No pilocarpine postoperatively	13	6
Pilocarpine postoperatively	1	19

$\chi^2=14.4$ , DF=1,  $p<0.001$ .

Table 3 Prevalence of postoperative posterior synechiae in 24 eyes from 24 patients with open-angle glaucoma

	Posterior synechiae absent	Posterior synechiae present
No pilocarpine postoperatively	8	2
Pilocarpine postoperatively	1	13

$\chi^2=10.3$ , DF=1,  $p<0.001$ .

higher for CAG, the difference is not significant ( $\chi^2=0.05$ , DF=1,  $p>0.05$ ).

The presence of posterior synechiae was highly significantly associated with postoperative pilocarpine as judged by a comparison between eyes which had received no pilocarpine at any time after operation and those which had received the miotic, in each category separately: see Table 2 for closed-angle glaucoma ( $\chi^2=14.4$ , DF=1,  $p<0.001$ ), and Table 3 for open-angle glaucoma ( $\chi^2=10.3$ , DF=1,  $p<0.001$ ), and both together CAG+OAG ( $\chi^2=27.1$ , DF=1,  $p<0.001$ ). The type of iridectomy performed was not a significant factor in the predisposition to posterior synechiae in closed-angle glaucoma patients, there being no significant difference between the prevalence of posterior synechiae in patients who had sector iridectomy and those who had peripheral iridectomy ( $p>0.05$ ).

Fig. 1 shows a typical eye with ring posterior synechiae, only revealed by powerful mydriatics.

The sectors of pupillary circumference occupied by posterior synechiae are shown in Table 4 (and diagrammatically in Fig. 2). 83% of all patients had either no posterior synechiae (40%) or total posterior synechiae (43%); only 17% had an intermediate degree of posterior synechiae (95% confidence interval: 9%–25%). Of those eyes developing posterior synechiae there was involvement of the whole pupil circumference in 76% of CAG patients, which is more than the 62% found in open-angle glaucoma patients (71% of all glaucoma subjects), but this difference was not significant ( $\chi^2=0.31$ ,

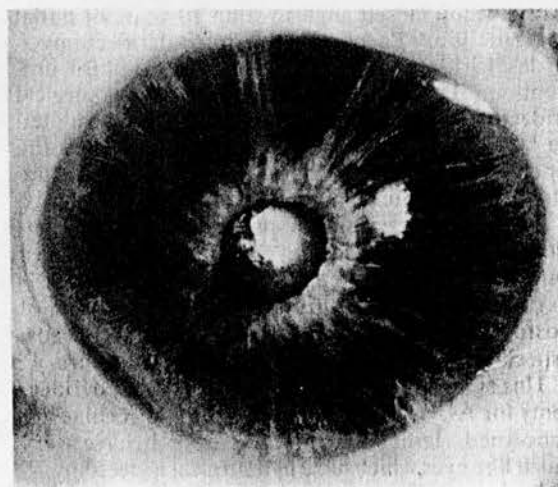


Fig. 1 Total posterior synechiae in an eye operated on for chronic CAG—owing to the bypassing of the pupil by aqueous, plus traumatic iridocyclitis, aggravated by pilocarpine and a shallow anterior chamber—become obvious only when strong mydriatics are used.

Table 4 Proportion of pupil circumference occupied by posterior synechiae in 63 eyes from 63 glaucoma patients

	0°	30°	60°	90°	120°	150°	180°	210°	240°	270°	300°	330°	360°
Closed-angle glaucoma (n=39)	14	2	2	1	0	0	1	0	0	0	0	0	19
Open-angle glaucoma (n=24)	11	1	2	0	0	0	2	0	0	0	0	0	8
Total (n=63)	25	3	4	1	0	0	3	0	0	0	0	0	27

DF=1,  $p > 0.05$ ). Of eyes with subtotal posterior synechiae the peripheral iridectomy quadrant was always involved (other sectors might be free from posterior synechiae), but the numbers were too small for analysis.

### Discussion

The prevalence of posterior synechiae in closed-angle glaucoma following peripheral iridectomy, without postoperative pilocarpine, has previously been reported to be 33% with a predilection for the iridectomy quadrant.<sup>11</sup> In the present study the prevalence of posterior synechiae in closed-angle glaucoma following a number of different surgical procedures in patients not treated with postoperative pilocarpine was remarkably similar at 32%. In ACG patients after peripheral iridectomy alone the prevalence was 3/12 or 25%. A similar tendency exists in cases of laser iridectomy, with a prevalence reported as 14%.<sup>10</sup> Almost all the points discussed here can be applied to this newer technique. Three of 22 patients developed posterior synechiae after argon laser iridectomy, prevented in 19/22 by topical steroids and mydriasis.<sup>9</sup> In patients with open-angle glaucoma the prevalence of posterior synechiae in patients not treated with postoperative pilocarpine was 2/10 or 20% (Table 3).

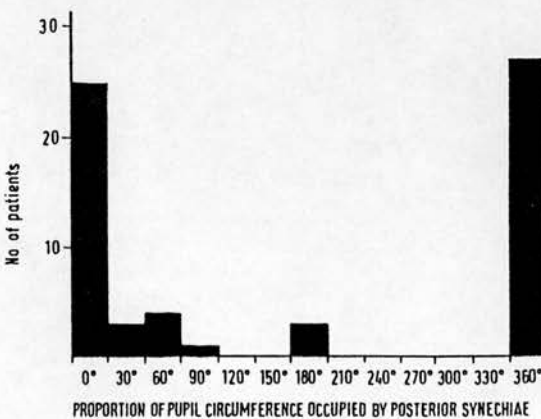


Fig. 2 Proportion of pupil circumference occupied by posterior synechiae.

A clinician may remain complacent about the prevalence of posterior synechiae in his surgical cases unless and until he has reason to attempt to dilate the pupils with a mydriatic.

Given the validity of the proposition that posterior synechiae do not develop spontaneously in a normal eye (we present no evidence here, other than clinical impression, for that null hypothesis), it is noteworthy, though not surprising, that 8/29 eyes (Tables 1 and 2) not receiving postoperative pilocarpine developed posterior synechiae, in spite of mydriatic treatment, with or without steroids, in the immediate postoperative period. We would attribute that finding to several factors in order of importance:

(1) All aqueous humour will take the line of least resistance through the iridectomy (peripheral or sector), so that no aqueous flow will lift the pupil as it enters the anterior chamber.

(2) In the immediate postoperative period some generalised traumatic iridocyclitis must be present to make the whole iris sticky and synechiae-prone.

(3) In eyes with peripheral iridectomy the remaining bridge of iris between pupil and iridectomy probably suffers ischaemic inflammation as well as a greater traumatic iridocyclitis than other areas of iris (that property would be minimal in laser iridectomy).

(4) In eyes with peripheral iridectomy, especially large ones, the involved sector of iris will be relatively immobile, hence tending to allow posterior synechiae to form more readily because of factors 1 to 3 above (a minimal effect in laser iridectomy).

As the prevalence of posterior synechiae in ACG and OAG patients treated with postoperative pilocarpine was 95% and 93% respectively, one may reasonably conclude there was a significant association with miotics.

From first principles, and because of the slightly higher prevalence of posterior synechiae in ACG patients (32%) than in OAG patients (20%), we would add to the above list:

(5) In ACG patients greater pressure contact between iris and lens because of the more anterior plane of the pupil in ACG eyes than in OAG eyes.

Since pilocarpine almost eliminated that 32% versus 20% discrepancy, two further aggravating factors are added:

6 (a) Immobility of the pupil miosed by pilocar-

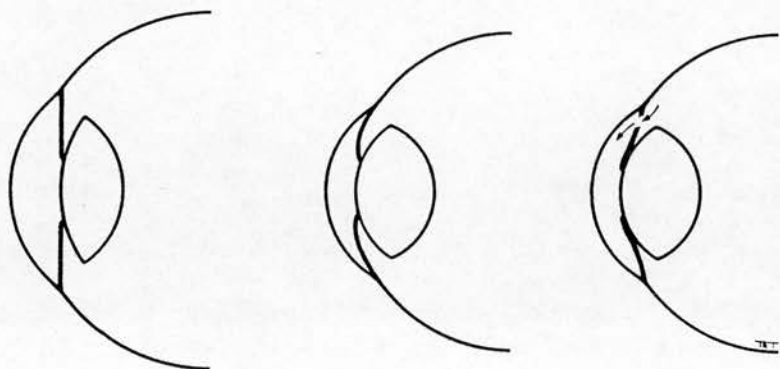


Fig. 3 The emmetropic or myopic eye on the left has less risk of posterior synechiae because the pupil probably exerts little pressure on the lens. The iris on the right is very likely to develop wide posterior synechiae, especially if inflamed by operative traumatic iridocyclitis and/or miotic treatment, because aqueous humour will take the line of least resistance through the peripheral iridectomy, leaving a wide area of iris constantly pressing on the anterior lens surface. The central diagram shows an eye predisposed to angle-closure glaucoma, with iris bombé.

pine; (b) even greater pressure contact between iris and lens in both ACG and OAG eyes because of pilocarpine than implied in (5) above.

Anatomical predisposing factors in the pathogenesis of posterior synechiae are illustrated in Fig. 3.

A further disastrous consequence of the small miosed pupil is the ease with which a membrane may fill it (occlusio pupillae), resulting in loss of vision. We have not tried optical iridectomy alone in such cases, because they are impossible to differentiate clinically from cataract.

We also suspect that the posterior synechiae in iridectomised ACG eyes will be more extensive radially than in OAG eyes, but evidence for that would be difficult to obtain.

It is our clinical impression that, once posterior synechiae have started, it is difficult to prevent their spreading to involve the whole pupil, since immobility of the pupil immediately adjacent to an established synechia must facilitate the advance. Even frequent movement of the free areas of pupil by maximal atropine or other anticholinergic plus sympathomimetic will mitigate that fixity only to a limited extent. Table 4 and Fig. 2 (as well as Fig. 1) we would interpret as strongly supporting that 'all-or-none' phenomenon. 40% of eyes show no posterior synechiae, and 43% show total posterior synechiae, whereas only 17% show an intermediate involvement (with a 95% confidence interval of 9%–25%).

Seclusio pupillae (100% posterior pupillary synechiae) can readily occur in eyes which have had iridectomy, because no aqueous will pass under and lift the pupil, preferring the line of least resistance through the iridectomy. The presence of the iridectomy allows the eye to avoid iris bombé of course.

#### DELETERIOUS EFFECT OF POSTERIOR SYNECHIAE

Do posterior synechiae matter? We have already mentioned above the tendency for a membrane to form across the miosed pupil. We would also expect

posterior synechiae to become predisposed in the course of time to cataract formation because of damage to the lens capsule. By analogy there is some support for that from the generally accepted view that a penetrating injury or iridocyclitis tends to be complicated by cataract, at least in the long term. We will not present some statistics which did show a lower visual acuity in eyes with total posterior synechiae (i.e., peripheral iridectomy) than in others (most with sector iridectomy), because the surgeons were different in the two groups.

In all five eyes which suffered flat chamber for several days immediately after drainage operations (these eyes have not been included in the series reported here), the visual acuity was eventually reduced to counting fingers or hand movements. It would not be justifiable to blame the total posterior synechiae entirely for the very poor vision due to eventual cataract.

Apart from the risk of occlusio pupillae and cataract, fixity of the pupil in response to light and the near reflex will probably be little handicap.

#### PREVENTION

Even if the possible deleterious effects mentioned in the preceding paragraph are denied, it would nevertheless be reasonable to claim that, if posterior synechiae can be prevented by safe treatment, that should be done. Steroids or non-steroidal anti-inflammatory drugs for several weeks before and after operation probably have a place, in spite of the added risk of infection when the former are used. In the immediate postoperative period we aim to keep the pupil semidilated and moving, with careful monitoring especially to avoid over-dilatation in ACG. For a blue iris or easily dilated pupil (for example, in a younger person) tropicamide 1% each evening supplemented by adrenaline 1:1000 or phenylephrine 5% each morning (lest systemic absorption of the adrenergic at night produce

insomnia) for 7–10 days will usually suffice. In dark brown or very immobile irises homatropine or even atropine each evening or twice daily, plus phenylephrine 10% each morning, may be necessary.

A closely similar situation arises with posterior synechiae in iridocyclitis, although aqueous is passing through the pupil in these eyes. In cases of iridocyclitis we apply maximum effort to avoid any posterior synechiae, or to eliminate them entirely if at all possible, by means of subconjunctival glucocorticoid and mydrinicaine plus maximum mydriatics (atropine and phenylephrine) at the patient's first visit. Repeat maximal mydriasis often succeeds in breaking down residual synechiae on the 2nd or 3rd day following subconjunctival steroids, unless of course the iridocyclitis is long-standing. If some residual posterior synechiae remain, we prescribe atropine and phenylephrine 10% (the latter several times daily), at least while there is active iridocyclitis and for some weeks afterwards to impose maximum movement on sectors of free pupil, which minimises the spread from foci of fixed posterior synechiae.

*We avoid pilocarpine if at all possible when medical treatment is required to control pressure at any time postoperatively, even long after the operation, because of the very high risk of total posterior synechiae.*

In this situation we regard a topical beta blocker as the first line of defence, and it is usually adequate, because it has no effect on the pupil. Timolol's effectiveness after operation on CAG is already established.<sup>12</sup> (We also regard a beta blocker as a valuable adjuvant to weak pilocarpine for a fellow ACG eye awaiting iridectomy, because the reduced production and flow of aqueous humour will reduce the height of the iris bombé. The same consideration will apply to those occasional patients who unfortunately refuse both surgical and laser iridectomy.) Occasionally pilocarpine does have to be added to a beta blocker, but we are always very reluctant to do that.

#### A PLACE FOR SECTOR IRIDECTOMY

If we suspect that an eye will need medical treatment, especially pilocarpine, after operation for glaucoma, we perform a sector iridectomy. Indeed, the need for medical supplementation to a drainage operation is frequent enough, especially in the long term, for us to favour sector iridectomy in most drainage procedures. Rather similarly, in ACG eyes which we judge may not respond completely to peripheral iridectomy, surgical or laser, but which probably do not need a drainage procedure, we do a sector

iridectomy. In the latter case our rationale is twofold: in the operation of sector iridectomy the iris has to be pulled well out of the eye to allow the pupil to present, so that the breaking down of the freshest goniosynechiae inferiorly is facilitated, unlike the situation in the less disturbing peripheral iridectomy.<sup>12–16</sup> A more important rationale applies to both groups, whether or not pilocarpine is used after operation: even if a membrane does spread inwards into the pupil area from the edge of a pupil immobilised by total posterior synechiae, in the sector where the pupil margin is missing that complication cannot occur. The British climate makes the glare through a sector iridectomy more tolerable than in sunnier situations.

We thank Dr R Vogel, Merck Sharp and Dohme Ltd, for computer facilities.

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PAPER 22

## Topical Dexamethasone Lowers Rabbit Ocular Tension, as Does Topical Mifepristone (RU 486), a Peripheral Blocker of Dexamethasone and Progesterone

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**Abstract.** The variability of the response of the rabbit eye to topical 1% dexamethasone has been shown in two groups of 20 young albino rabbits each (total 40) tested in succession. The pressure anomalously fell significantly (but by only 1 mm Hg) in both groups in the first 4 weeks of administration, but not in subsequent weeks. Mifepristone (RU 486), a peripheral antagonist of dexamethasone and progesterone, reduced the pressure significantly, again by only 1 mm Hg, in the first group of 20 rabbits, not the second. Accordingly, no conclusion was possible on the originating question: does pre-treatment with mifepristone prevent the dexamethasone-induced rise in rabbit intra-ocular pressure?

### Introduction

Mifepristone (RU 486) has been shown consistently to produce a fall in rabbit ocular tension [1-4]. Either its peripheral dexamethasone-blocking or its progesterone-blocking property is probably responsible, although an indirect mechanism via prostaglandins is possible [5]. To elucidate the first, an experiment was planned to establish whether pre-treatment with mifepristone 1% suspension would inhibit the dexamethasone-induced rise of ocular tension to which

small young albino animals are particularly susceptible [5, 6]. The results failed to answer the question but the variable response of the rabbit ocular tension to topical treatment with dexamethasone, previously recorded [7], is confirmed.

### Materials and Methods

Each of two groups of 20 young albino rabbits (total 40) was treated identically, effectively double-masked, but in successive periods of 15 weeks for each. All rabbits were aged 3-6 months at the start; their mean weights  $\pm$  SD rose from  $2.61 \pm 0.37$  kg

(Nos 1-20) and  $2.20 \pm 0.15$  kg (Nos 21-40) at the start to  $3.52 \pm 0.33$  and  $3.74 \pm 0.46$  kg, respectively, at 14 weeks. Week 1 was 'settling in' for the rabbits in new surroundings, and weeks 2 and 3 were 'running in' for rabbits and tonometrist (a different one for

each group); drops of 'vehicle of mifepristone' were instilled twice daily just after tonometry twice daily. In weeks 4-7, 10 randomised rabbits received two drops twice daily of 1% mifepristone suspension into both eyes; the other 10 received mifepristone vehicle.

Table 1. Effect of topical dexamethasone 1% eye drops

Rabbit No.	Weeks	Dexamethasone in one eye minus vehicle (of dexamethasone) in fellow <sup>1</sup>									
		RU 486 in both eyes					vehicle (of RU 486) in both eyes				
		n	difference		t	p	n	difference		t	p
			mean	SE				mean	SE		
		(sum)				(sum)					
1-20	8 <sup>3</sup>	9 <sup>4</sup>	-9.1	3.0	-3.0	<0.02	10	-6.8	2.3	2.9	<0.02
	11 <sup>3</sup>	9 <sup>4</sup>	-2.2	3.4	-0.7	<0.50	10	-0.9	3.0	-0.3	<0.80
21-40	8 <sup>3</sup>	9 <sup>4</sup>	-6.5	4.3	-1.5	<0.20	10	-10.6	4.7	-2.3	<0.05
	11 <sup>3</sup>	9 <sup>4</sup>	-2.3	5.3	-0.4	<0.70	10	-0.4	4.0	-0.1	0.9

<sup>1</sup> See Materials and Methods for scheme of randomisation.

<sup>2</sup> Background = weeks 4-7 when only RU 486 or vehicle of RU 486 was administered.

<sup>3</sup> Weeks 9 and 10 have been excluded in both series because in rabbits Nos. 1-20 tonometry could not be done on account of the tonometrist's illness.

Table 2. Effect of RU 486 1% eye drops

Rabbit No.	Weeks	Change in intra-ocular pressure from run-in, i.e. week 3 <sup>1</sup>					
		(A) RU 486 in both eyes			(B) vehicle of RU 486 in both eyes		
		n	mean	SE	n	mean	SE
1-20	6 + 7	9 <sup>2</sup>	21.5	6.2	10	-9.9	7.0
	14 + 15	8 <sup>2</sup>	49.9	8.6	10	37.3	5.4
21-40	6 + 7	10	-6.8	8.2	10	-9.45	5.3
	14 + 15	7 <sup>3</sup>	0.0	16.5	10	20.6	12.3

<sup>1</sup> Sum of 20 readings ( $2 \times 5$  days  $\times 2$ , right/left).

<sup>2</sup> In series 1-20, 1 rabbit died in week 7 (see footnote 4 in table 1) but another died in week 13.

<sup>3</sup> In series 21-40, 2 more RU 486 rabbits died in weeks 12 and 15, 1 with pneumococcal eyelid infection and the other found dead without identifiable cause (1 had already died in week 7: see footnote 4 in table 1).

In weeks 8-11, that treatment was continued but 1% dexamethasone drops were given four times daily into one eye chosen at random, the other eye receiving dexamethasone vehicle; 50% of dexamethasone-treated eyes were right and 50% left, since tonometry

was always done on right then left eyes. In weeks 12-15, treatment was as in weeks 4-7, to check the expected reversal of the expected dexamethasone effect.

An Alcon pneumatonograph machine was used. The graphs obtained by open-stopcock calibration were linear in the range observed in our rabbits so that the raw pneumatographic pressures were used for statistical purposes.

The mifepristone powder was suspended, 1 g/100 ml, in hypromellose 0.3% solution BPC while 'vehicle' drops had only hypromellose 0.3% BPC (British Pharmaceutica Codex). Dexamethasone 1% was in a buffered vehicle with two 'preservatives' while 'vehicle' drops omitted the dexamethasone.

Typical single reading change (SE) in pressure due to dexamethasone

uncorrected for background <sup>2</sup> paired difference	p	corrected for background <sup>2</sup> paired difference	p
-0.79 (0.19)	highly significant	-0.85 (0.16)	highly significant
-0.16 (0.22)	< 0.50	-0.22 (0.23)	0.30
-0.85 (0.32)	highly significant	-0.91 (0.19)	highly significant
-0.09 (0.33)	0.8	-0.20 (0.24)	0.40

<sup>4</sup> In series 1-20, 1 of the 10 RU 486 rabbits died of intercurrent disease in week 7; in series 21-40, 1 of those 10 rabbits died of gastro-enteritis in week 7.

Difference A-B: mean changes (i.e. effect of RU 486, allowing for effect of vehicle for RU 486)				Typical single reading change (SE) in pressure due to RU 486
n	SE	t	p	
31.4	9.4	3.4	< 0.005	1.57 (0.47)
12.6	10.1	1.2	< 0.30	0.63 (0.50)
2.65	10.0	0.26	< 0.80	0.13 (0.50)
-20.6	18.9	-1.1	< 0.30	-1.03 (0.94)

## Results

For details see tables 1 and 2.

Dexamethasone 1% eye drops surprisingly caused a small but significant mean fall of 1 mm Hg pressure in week 8 and 11, compared with the fellow vehicle-treated eyes in both the first group of 20 rabbits ( $t = -2.9$ ,  $p < 0.02$ ) and the second ( $t = -2.3$ ,  $p < 0.05$ ). Weeks 9 and 10 have been excluded in both groups because the tonometrist in group 1 was absent through illness.

Consistent with previous observations [1-3], topical mifepristone caused a small but significant fall in ocular tension of about 1 mm Hg, but only in the second 2 weeks of the period 4-7 weeks and only in the first group of 20 rabbits ( $t = 3.4$ ,  $p < 0.005$ ), not in the second group ( $t = 0.26$ ,  $p = 0.80$ ).

## Discussion

The ultimate objective is a clinical trial of mifepristone eye drops in glaucomatous human eyes which has not yet been possible. The rationale is that since glucocorticoids

raise human intra-ocular pressure, especially in patients with open-angle glaucoma, a peripheral glucocorticoid blocker should lower it, especially if such patients have raised free plasma cortisol [8].

The present rabbit experiments were aimed at finding out whether a *selective* peripheral dexamethasone blocker would be worth evolving, to obviate the possible disadvantages of mifepristone which also has a peripheral progesterone-blocking property. (A similar separate experiment has been designed to find out whether mifepristone's progesterone-blocking property has an ocular hypotensive effect).

We have no satisfactory explanation for the *fall* in pressure we observed with dexamethasone topically, which confirms a previous observation of an anomalous response [7]. Possibilities are our use of a dexamethasone alcohol (not a salt) or inadequacy of instillations of drops restricted to a 6-hour period daily or our choice of young albino animals when the New Zealand Red strain might have been more suitable.

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