# ARGON LASER TRABECULOPLASTY

– a retrospective and prospective study –

C.A.B. WEBERS

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Een wetenschappelijke proeve op het gebied van de geneeskunde en tandheelkunde

Proefschrift

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'That it takes more to see with,
than just a pair of eyes...'

Albrecht von Graefe (1828-1870)

*Aan mijn ouders*
*Voor Marianne en Casper*

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The application of laser in the treatment of open-angle glaucoma dates back from the early Seventies. Krasnov (1973) and Hager (1973) in particular attempted to create a direct link between the anterior chamber of the eye and Schlemm's canal (trabeculopuncture). The success rate of this treatment was low and its complications were serious.

When Gaasterland & Kupfer (1974) and subsequently Wickham et al. (1977) demonstrated that glaucoma could be induced in monkey eyes after laser manipulation of the trabecular meshwork, the interest in clinical application of this therapy waned.

We owe it to the perseverance of James B. Wise that today we can successfully use laser therapy of open-angle glaucoma. Wise proceeded from a pathogenetic glaucoma model in which collapse of the trabecular sheets was regarded as the cause of the outflow blockage. Shrinking and cicatrization caused by multiple laser coagulates distributed over 360° of the trabecular meshwork (Argon Laser Trabeculoplasty, ALT) will cause an increase in intertrabecular spaces and therefore diminished outflow resistance. The preliminary results of this therapy showed a high success rate (Wise and Witter 1979).

Numerous publications have confirmed these good results of ALT since its introduction, and ALT has assumed a prominent position in the treatment of glaucoma. Not all aspects have been elucidated, however, and some questions remain. What is the exact mechanism of action? Which are the optimal treatment parameters? What are the short-term and long-term complications of this therapy?

The most dangerous complication is the occurrence of postoperative increases in intraocular pressure, which may aggravate visual field defects and may even lead to loss of central vision (Thomas et al. 1982; Weinreb et al. 1983). These increases in intraocular pressure cannot always be prevented, despite modification of the ALT parameters.

Encouraged by the good results, we have performed ALT at the Department of Ophthalmology of the St. Radboud Hospital, University of Nijmegen, since 1982. A preliminary analysis of a small series of eyes thus treated showed

good results (Hendrikse 1984). Now, six years after introduction of ALT at our Department, the number of patients treated is sufficiently large for a more extensive study.

The results of this study are presented in this thesis. The success rate and the pressure-reducing effects of ALT were studied in retrospect in a group of patients treated prior to 30th June 1986. Patients treated by ALT after this date were included in a prospective study and examined for increases in intraocular pressure during the period immediately after ALT.

This thesis comprises two parts. The first part discusses some aspects of open-angle glaucoma of relevance to ALT or to the study in general, with special reference to functional anatomy, physiology and pathology of the anterior chamber, the iridocorneal angle and the trabecular meshwork. In addition, ophthalmological findings obtained in glaucoma patients are analysed.

The pathogenetic mechanisms possibly underlying the glaucomatous damage to the optic nerve are described because the optic nerve plays an essential role in the glaucoma concept. Prior to this, the first chapter outlines how current understanding of glaucoma can be explained from a historical perspective.

The second part describes the results of the retrospective and prospective study. This part starts with a review of the literature on ALT.

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# PART I

# CHAPTER 1

## THE HISTORY OF GLAUCOMA

The answer to the question of what our ancestors knew of glaucoma is not merely of importance to the ophthalmological historian but also contributes to our current view of this disorder. It seems not until recently that glaucoma as such began to be studied seriously by ophthalmologists looking into its natural history, symptoms and cure. The clinical history, however, favours the belief that glaucoma is a disease of great antiquity. Predisposing factors such as old age, racial influences, climatic conditions, inflammatory diseases of the eye and errors of refraction must always have been present. One may therefore conclude that glaucoma has always existed, although our ancestors recognized it only in its final stage as a special form of amaurosis.

Some contemplation of the history of glaucoma is required in order to gain insight into our current knowledge of this disease.

The Old Testament mentions several cases of amaurosis, some of which were undoubtedly caused by glaucoma (Isaac, Genesis 27:1; Israel, Genesis 48:10; Eli, I Samuel 4:15; Ahijah, I Kings 14:4). Old age is given as the main cause of blindness in these cases, and different terms are used to describe visual impairment and amaurosis: the Hebrew word 'wattikhena', which means extinguished, 'kabad', meaning heavy or hard, and 'kamu', which literally means that the eyes stood still. These terms refer to the chronicity of the disorder, the hardness of the eyeball, and the peculiar stare which characterizes amaurosis following glaucoma (Gordon 1938).

The ancient Greek physicians stressed the colour of the pupil as being of great diagnostic value. In the Hippocratic Aphorisms, 'glaucosis' is a disorder of the eyes becoming manifest in old age and causing blindness. "If the pupil becomes sea-coloured, sight is destroyed and amaurosis of the other eye often follows" (Gordon 1938; Sugar 1957).

The term 'green stare' may be derived from the word 'glaucos' which in Old Greek refers to 'blueish' or 'glossy' and in New Greek to 'sea-coloured' or

'greenish' (leydhecker 1960).

The Greek furthermore distinguished between a silver-grey and an greenish-blue pupil, which were referred to as cataract and glaucosis respectively.

The earliest Roman ophthalmologists regarded glaucosis and hypochyma (cataract) as identical terms. According to Ephesus Rufus (about 50 A.D.) later writers did differentiate between the two disorders, ascribing glaucosis to a watery crystalline lens and cataract to a turbid fluid which settled between the iris and the lens (Chance 1962).

In the year 395 A.D. emperor Theodosius split the Roman Empire. The East Roman Empire, unlike the western part, was well-organized, and Constantinople was its centre for trade, industry and finance. The material circumstances were optimal for a revival of the old cultures, and medical writers depended entirely on the traditional works of Hippocrates, Galen and Celsus. Paulus Aegineta (629-690) followed the Greek dictum and differentiated between amaurosis arising from glaucoma and that caused by other conditions (Graefe-Saemisch 1908).

Evidently, no new ideas were formulated in the ophthalmological field during this Byzantine period of reluctance to change. It was not until halfway the 14th century that Sams-ad-din, an Arab ophthalmologist (1348) described a characteristic picture of glaucoma as 'migraine of the eye'. In its acute stage the condition was characterized by hemicrania, deep-seated inflammation of the eye, turbidity of the humours, followed occasionally by cataract and permanent dilatation of the pupil. If chronic, it was associated with tenseness of the eyeball and loss of vision (Gordon 1938; Sugar 1957).

In 1622 Richard Banister edited 'A Worthy Treatise of the Eyes' - a triplet of ophthalmological handbooks. In the first - 'A Breviary of the Eye'- he described an incurable form of cataract - gutta serena - which in its symptoms was analogous to absolute glaucoma. However, Banister's observations like those of his Arab predecessor were lost from sight until more than 125 years after Banister's first description (Koelbing 1967).

In the first decade of the 18th century Michael Brisseau (1709) stated that glaucoma was a disease of the vitreous and not, like cataract, of the lens. His conclusions were based on his own observations and those of his colleague Marechal. The latter dissected the eyes of Bourdelet, physician to

Louis XIV, and found by coincidence the vitreous to be somewhat opaque (Draeger 1961). Although Brisseau's concept was accepted by the German ophthalmologist Lorenz Heister (1683-1756), the general opinion prevailed that glaucoma was a disease of the lens.

Johann Zacharias Platner (1745) rediscovered the signs of absolute glaucoma previously described by Sams-ad-din and Banister, but still thought the lens to be the organ affected.

Ophthalmological history provides us with numerous theories on the origin of glaucoma advanced between 1750 and 1850. Demours (1762-1836) was the first to describe "colours of the rainbow (halo vision) around a light", and ascribed the disease to gout and rheumatism. Beer (1763-1821) of Vienna and the Englishman William Lawrence (1783-1867) believed that glaucoma was caused by a chronic and malignant form of iritis, which affected the posterior coats of the eye (Leydhecker 1960).

Antonio Scarpa (1752-1832) as well as Weller (1826) gave excellent descriptions of absolute glaucoma, both referring to the 'painful tension in the eyeball'. Fabini (1831) of the university of Pest mentioned eyeballs 'as hard as stones', due to changes in the elasticity of the tunics of the eyeball.

William Mackenzie (1830) ascribed the increased tension to inflammation, leading to overproduction of fluid in the eyeball; in 1854 he advocated paracentesis of the cornea for prevention and treatment of glaucoma.

The invention of the ophthalmoscope by Hermann von Helmholtz (1850) inaugurated a new era in ophthalmological research. The ophthalmoscope enabled investigators to study pathological changes in the retina and optic disk (Von Helmholtz 1851).

In view of his great works and because he is generally regarded as the founder of modern ophthalmology, Albrecht von Graefe merits some special attention. He was born in Berlin on 28th May 1828. His father was Karl Ferdinand von Graefe (1787-1870) - a renowned teacher, general in the Prussian army and court physician who came to be regarded as the founder of modern plastic surgery. Albrecht von Graefe was a born scholar who at the age of 16 went to the university of Berlin to be taught by famous medical leaders such as Virchow, Dieffenbach, Traube, Schlemm, Romberg and Schoenlein. In 1847 he wrote his thesis on bromide and graduated from the university.

During his 'Wanderjahre' his interest in ophthalmology deepened. He performed ophthalmological research together with Arlt (Prague), Bernard (Paris), Jaeger (Vienna), Bowman (London), Mackenzie (Glasgow) and Donders (Utrecht), and finally returned to Berlin.

By the time Von Helmholtz invented the ophthalmoscope, Von Graefe had a practice at 46 Karlstrasse in Berlin. The story goes that as soon as he laid hands on an ophthalmoscope, he knew by instinct how to use it (Ullman 1954).

Several months before this happened the first description of the changes in the glaucomatous optic disk was published by Alfred Jaeger (1784-1871); he erroneously described these changes as 'globular swelling', and Von Graefe at first made the same mistake. In 1855 Weber was the first to demonstrate cupping of the disk, and Muller (1858) observed cupping of the disk in enucleated glaucomatous eyes (Sugar 1957).

Von Graefe demonstrated by close ophthalmoscopic examination that arterial pulsations, as he had described in glaucoma, could be elicited by pressure on the eyeball even in normal eyes. Further studies on the fundus preceding the final stage of glaucoma convinced Von Graefe that the increased pressure was not a complication but the cause of all the symptoms. He performed the first iridectomy ever in 1856 (Gordon 1938).

It was Franciscus Cornelis Donders (1818-1889), a close friend of Von Graefe and co-editor of "Archiv für Ophthalmologie", who proclaimed glaucoma simplex to be the basic form of glaucoma.

With the works of Von Graefe, Donders and all others mentioned in this review, we entered the modern era of glaucomology. The relation between intraocular pressure and glaucomatous damage to the optic disk was more evident then ever before. More advanced techniques were developed to measure intraocular pressure (Von Graefe 1862; Weber, Fick 1888, Schiötz 1905; Goldmann 1954). and visual field defects (Von Graefe 1855; Bjerrum 1867; Foerster 1882; Goldmann 1945). New pharmacological and surgical techniques were introduced to prevent or arrest glaucoma. It would be entirely beyond the scope of this review to mention all the other clinicians and researchers who have contributed to our current glaucoma concept. Some relevant historical aspects of the modern period, however, may be mentioned in subsequent chapters of this thesis.

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# CHAPTER 2

# FUNCTIONAL ANATOMY, PHYSIOLOGY AND PATHOLOGY

## INTRODUCTION

The interaction between clinical medicine on the one hand and its basic disciplines of anatomy, physiology and pathology on the other has led to a comprehensive scientific glaucoma concept. An understanding of anatomical relations, pathophysiological processes and pathological changes in glaucomatous eyes is not only of descriptive value to the clinician but also contributes to diagnosis and therapy.

This chapter discusses glaucoma in terms of these basic disciplines, and reduces glaucomatous changes to their morphological, physiological and pathological substrates.

The first signs of the primordium of the eye are already visible in the 22-day embryo (maximum length 2 mm). The neural tube is still open and the prosencephalon forms the optic grooves on either side (fig.2.1A). As the anterior neuropore closes on about the 25th day the optic vesicles develop from these grooves (fig.2.1B). With the growth of the central nervous system these neural ectodermal vesicles are pushed away laterally in the direction of the surface ectoderm (Langman 1976).

Induction from the neural ectoderm results in the primordium of the lens placode in the surface ectoderm (Smelser 1965). Differentiated growth causes an invagination in the optic vesicle which leads to the formation of the optic cup, while the invaginating lens placode remains in touch with the neural ectoderm (fig.2.1C). Invagination is not limited to the central part of the optic cup but also occurs on the ventral side. In this process the choroid fissure becomes manifest: a groove along which the hyaloid artery will be incorporated (fig.2.2A).

The lens placode gives rise to the lens vesicle which loses its contact with the surface ectoderm (33 days). This is the time at which the surface ectoderm closes and the space between lens vesicle and ectoderm fills with mesoderm (fig.2.2B) (Barber 1955).

From these basic embryonic structures further growth and differentiation take place until an integrated and functional organ has formed at birth. Table 2.1 presents a survey of the embryonic origins of the various intraocular structures.

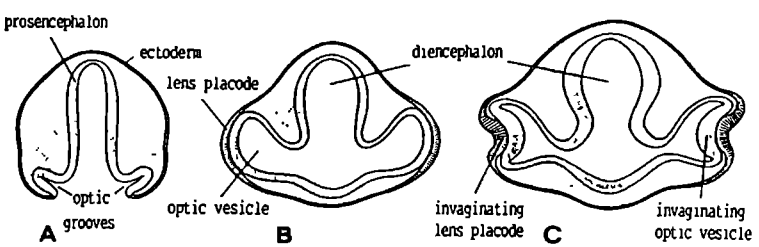


Figure 2.1. A. Cross-section through the prosencephalon of a 22-day embryo (about 14 somites) with visible optic grooves. The neural groove is wide open (after Heuser). B. Cross-section through the pros-

encephalon of an embryo in week 4. The optic vesicles are in touch with the surface ectoderm, which in this area shows some thickening (lens placode). C. Cross-section through the prosencephalon of a 5 mm embryo; the optic vesicles show indentation and the lens placode has formed (after Mann).

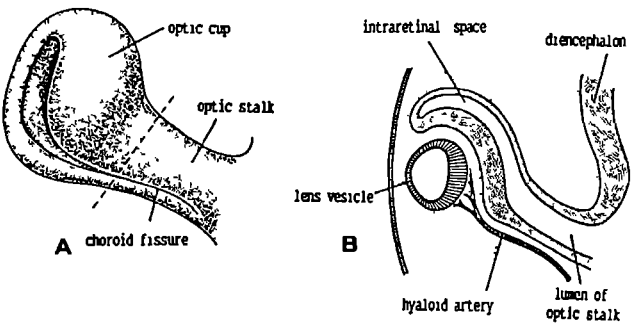


Figure 2.2. A. Ventrolateral view of the optic cup and optic stalk in a 6-week embryo. The choroid fissure is situated at the underside of the optic stalk and gradually narrows. B. Section through the lens vesicle, optic cup and optic stalk at the level of the choroid fissure (after Mann).

Table 2.1. Origin of ocular tissues

| | |
|---|---|
| **Neural ectoderm** | Retinal pigment epithelium |
| | Iris sphincter muscle |
| | Iris dilator muscle |
| | Posterior iris neuroepithelium |
| | Pigmented and non-pigmented ciliary epithelium |
| | Optic nerve fibres and glia |
| **Surface ectoderm** | Lens |
| | Corneal epithelium |
| | Lacrimal gland |
| | Surface epidermis of the lids |
| | Epithelium of the adnexal glands |
| | Epithelium of the conjunctiva |
| **Neural crest** | Corneal keratocytes |
| | Endothelium of the cornea |
| | Endothelium of the trabecular meshwork |
| | Iris and choroid stroma |
| | Ciliary smooth muscle |
| | Fibroblasts of the sclera |
| | Optic nerve meninges |
| **Mesoderm** | Striated extraocular muscles |
| | Vascular endothelia |

The pathophysiological substrate of glaucoma is nearly always to be found in a disturbed outflow of aqueous humour at the level of the anterior iridocorneal angle and/or the trabecular meshwork. Although the development of these regions is a controversial subject in the embryology of the eye (O'Rahilly 1975), a further discussion of this development is essential.

At the time when the surface ectoderm closes over the separated lens vesicle (week 5) the formation of the cornea has started. At that time it consists of two layers of ectoderm resting on a basement membrane. The area between the surface ectoderm and the neural ectoderm is filled with mesenchyma (omnipotent embryonic supportive tissue). Because the mesodermal somites are lacking in the cranial part of the embryo, much of this mesenchyma is made up of cells originating from the neural crest. This supportive tissue expands in several phases and in different directions. In the initial phase this mesenchyma grows between lens and corneal epithelium in order subsequently to form the corneal endothelium. In the second phase this growth is bidirectional: on the one hand the mesenchyma grows between corneal endothelium and corneal epithelium to form the substantia propria corneae, while on the other hand it grows between corneal endothelium and lens epithelium to form the iridopupillary layer (O'Rahilly 1975).

The future ciliary body has its embryonic origin both in the neural ectoderm and in the mesenchyma. At about week 12 the outer pigmented neural ectodermal leaf starts to show indentations which fuse with the inner non-pigmented leaf. These indentations are the precursors of the ciliary processes. The core of these processes consists of mesenchyma, with evidence of early embryonic vascularization (Ozanics & Jacobiec 1982).

The iridopupillary layer is vascularized from capillaries in the deep-seated mesenchyma. Branches of the long posterior ciliary arteries anastomose with the peripheral vessels of the iridopupillary layer and thus form the circulus arteriosus iridis major. The anterior part of this iridopupillary layer is replaced by the iridopupillary membrane, which is supplied with blood from the posterior ciliary arteries and the greater arterial circle of the iris. The pupillary part of this membrane is incorporated in the membranous part of the iris through remodelling. The posterior pigment leaf of the iris develops from the non-pigmented epithelium of the ciliary body. The process of pigmentation starts at about halfway gestation at the pupil-

lary border of the iris (Ozanics & Jacobiec 1982).

The stormy development and differentiated growth of cornea, iris and ciliary body have consequences for the primordial development of the anterior chamber, iridocorneal angle and trabecular meshwork.

The bidirectional growth of mesenchyma (towards cornea and iridopupillary layer) provides the primordium of the iridocorneal angle (Tripathi & Tripathi 1982). The anterior chamber develops through differentiated growth of originally mesenchymal structures. There is no consensus about the further development of the iridocorneal angle. The oldest theory maintains that the iridocorneal angle forms because the local mesenchyma becomes atrophic (Mann 1949; Barber 1955). Another theory postulates a cleavage process in the mesenchyma due to differences in growth rate between the component parts of the anterior segment of the eye (Allen et al. 1955; Burian et al. 1955). Neither theory is based on unequivocal evidence.

At about month 4 the trabecular meshwork consists of undifferentiated mesenchyma, linked apically to the corneal stroma and lined with corneal endothelium (Smelser & Ozanics 1971). This endothelial lining is a continuous monocellular layer (Hansson & Jerndal 1971).

Studies of foetal facility of outflow have demonstrated that this increases from month 5 on and correlates with foetal age, length and corneal diameter (Kupfer & Ross 1971; Pandolfi & Astedt 1971). Further differentiation within the trabecular meshwork seems to make this drainage possible.

Between the fourth and fifth foetal month the cells off the uveal trabeculae start to detach themselves (Wulle 1972) and the initially closed endothelial lining loses its continuity (Kupfer & Ross 1971; Smelser & Ozanics 1971; Hansson & Jerndal 1971). A persistent continuous endothelial lining could be the precursor of Barkan's membrane (Worst 1968).

The corneal trabeculae show a similar process of discontinuation, and the intercellular spaces fill with longitudinal and transverse collagenous fibres.

Between month 4 and month 8 the cribriform trabeculae show major changes at the cellular level. In early foetal stages this part of the trabecular meshwork consists of round cells with large nuclei, sparse cytoplasm and few organellae. The cells are firmly linked together by tight junctions. In later foetal stages one finds flat cells with long cytoplasmic processes and

abundant organellae. The intercellular spaces are filled with fibrous material except near Schlemm's canal. The transition from the cribriform trabeculae to Schlemm's canal is characterized by empty intercellular spaces (Wulle 1972).

The differentiation of the trabecular meshwork fulfils the primary requirement for a functional drainage system. A second requirement to be fulfilled is the development of Schlemm's canal. At about month 4 the deepest part of the mesenchyma, posterior to the iridocorneal angle, already shows a venous plexus from which Schlemm's canal is to develop (Barber 1955; Duke-Elder 1963). Between month 4 and month 9, radical changes occur in the position and structure of Schlemm's canal. Due to differentiated growth of the anterior segment the canal gradually shifts anteriorly from its initial scleral position, to attain its definitive position - the apical side of the iridocorneal angle - in month 9 (Smelser & Ozanics 1971).

The wall of the venous plexus initially consists of cells with ample cytoplasm, and parts of the wall may encompass several layers of cells. From month 6 on these cells begin to flatten, and by about month 8 one finds a monolayer of extremely flat cells. Intracytoplasmic vacuoles become larger and establish contact with the cell membrane. Fusion of the cell membrane with the vacuoles largely occurs on the basal side of the cells. In this way a connection is established between Schlemm's canal and trabeculae (Wulle 1972).

The functional drainage system in the iridocorneal angle is complete immediately before birth. The iridocorneal angle has opened through atrophy and/or cleavage, the trabecular meshwork has differentiated and Schlemm's canal is in its proper position.

The anatomy, physiology and pathology of these structures will be discussed in the course of this chapter.

## 2.2 ANTERIOR CHAMBER, IRIDOCORNEAL ANGLE AND TRABECULAR MESHWORK

### 2.2.1 Macroscopic anatomy

The anterior chamber of the eye is bounded by the corneal endothelium on

the anterior and by the iris or pupillary part of the lens on the posterior side. The anterior peripheral part of the anterior chamber is bounded by the trabecular meshwork and the posterior peripheral part by the ciliary body or the insertion of the iridal root.

The anterior chamber is shaped like an ellipse with a flattened posterior aspect. This shape is determined by the fact that the plane of the iridal root is localized about 4.2 mm behind the corneal apex, while the pupillary rim lies only about 3.6 mm behind this apex. This difference of 0.6 mm is due to the anterior displacement of the iris caused by the lens (Hogan et al. 1971). However, the absolute value of this difference is less in myopic than in hypermetrope eyes (Tripathi & Tripathi 1982).

With the aid of advanced techniques the depth of the anterior chamber can be measured objectively and accurately. Table 2.2 presents the values for the depth of the anterior chamber, corneal radius and corneal diameter respectively as measured by Weekers et al. (1961). The table shows that the depth of the anterior chamber decreases significantly with increasing age. These findings are in agreement with data reported by other authors (Rosengren 1950; Caprioli et al. 1986). This decrease in anterior chamber depth does not seem to correlate directly with the changed corneal radius or diameter, but rather with the increased size of the lens (Weekers et al. 1961).

Table 2.2. Dimension of human chamber and corneal curvature. (Weekers, R., Grieten, J., and Lavergne, G.: Ophthalmologica 142: 650, 1961).

| | Under 15 yr | 15-35 yr | 35-55 yr | Over 55 yr |
|---|---|---|---|---|
| AC depth | 3.61 ± 0.040 | 3.60 ± 0.039 | 3.27 ± 0.054 | 3.18 ± 0.054 |
| Corneal radius of diameter | 7.87 ± 0.062 | 7.96 ± 0.036 | 7.82 ± 0.046 | 7.79 ± 0.035 |
| Corneal diameter | 11.71 ± 0.079 | 11.81 ± 0.056 | 11.76 ± 0.044 | 11.75 ± 0.057 |

Not only the depth of the anterior chamber but also the width of the iridocorneal angle correlates with age. Table 2.3 presents the results of a study of correlation between age and width of iridocorneal angle by Van Herick et al. in 1969 (for grading of angle width, see Chapter 3). The angle

Table 2.3. Slitlamp grading of angles in unselected group of 2185 patients. (Van Herick, W., Shaffer, R., and Schwartz, A.: American Journal of Ophthalmology 68:626, 1969).

| Age | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Percent Grade 1 | Percent Total Grade 1 & 2 | Total Number of Patients |
|---|---|---|---|---|---|---|---|
| 0-19 | 0 | 0 | 82 | 511 | 0 | 0 | 593 |
| 20-39 | 3 | 1 | 303 | 172 | 0.63 | 0.84 | 479 |
| 40-59 | 7 | 6 | 523 | 109 | 1 | 2 | 645 |
| 60 plus | 4 | 16 | 413 | 35 | 0.85 | 4.2 | 468 |
| Total | 14 | 23 | 1321 | 827 | | | 2185 |
| Percent | 0.64 | 1 | 60 | 38.36 | | | |

Table 2.4. Slitlamp grading of angles in group of 2185 patients classified according to refractive error. (Van Herick, W., Shaffer, R., and Schwartz, A.: American Journal of Ophthalmology 68:626, 1969).

| | Hyperopia Greater than +1.0 D | | Myopia Greater than -1.0 D | | Group Between -1.0 D & +1.0 D | |
|---|---|---|---|---|---|---|
| Age | Grades 1 & 2 | Grades 3 & 4 | Grades 1 & 2 | Grades 3 & 4 | Grades 1 & 2 | Grades 3 & 4 |
| 0-19 | 0 | 199 (100%) | 0 | 445 (100%) | 0 | 524 (100%) |
| 29-39 | 0 | 82 (100%) | 1 (0.2%) | 429 (99.8%) | 3 (0.7%) | 429 (99.3%) |
| 40-59 | 4 (2%) | 213 (98%) | 1 (0.3%) | 315 (99.7%) | 8 (1%) | 743 (99%) |
| 60 plus | 14 (3.5%) | 389 (96.5%) | 0 | 159 (100%) | 6 (2%) | 350 (98%) |

width was estimated on the basis of slit-lamp findings because Van Herick et al. believed that these correlated well with gonioscopic estimates. The table shows that the incidence of narrow iridocorneal angles increases with increasing age but that the absolute value of this incidence is low. In addition, these investigators demonstrated that the distribution of narrow iridocorneal angles correlates with errors of refraction (table 2.4).

In normal physiological conditions the depth of the anterior chamber of

the eye varies with - among other things - accommodation. The maximally accommodated eye shows a less deep anterior chamber than the relaxed eye (Brown 1973). During accommodation, however, the facility of outflow increases significantly (Armaly & Burian 1958; Armaly & Jepson 1962), and the decrease in chamber depth may be compensated by an increase in angle width (Tripathi & Tripathi 1982).

The macroscopic anatomy of the iridocorneal angle is best described on the basis of the features revealed by direct or indirect gonioscopy (for details, see Chapter 3).

In principle, four structures can be identified in the iridocorneal angle (Rohen 1978):

1. The most anterior boundary is demarcated by **Schwalbe's line**. This structure is gonioscopically identifiable as a light-coloured zone between Descemet's membrane and the trabecular meshwork. At a more advanced age pigment deposits are often found around Schwalbe's line, particularly in the two lower quadrants of the iridocorneal angle (Shaffer 1962; Hoskins 1972). Differentiation from the trabecular meshwork may be difficult.
   In some cases Schwalbe's line protrudes like a ring into the anterior chamber. Burian et al. (1955) observed this in 72 out of a total of 600 eyes examined. This protrusion is probably explained by an excessive deposition of mesenchymal material during embryonic development.
2. Immediately behind Schwalbe's line the **trabecular meshwork** is found. The origin of this tissue lies on the scleral spur and ciliary body; the insertion is on Schwalbe's line. At an early age it is often difficult to identify the trabecular meshwork. It presents as a semitransparent, blueish-grey zone between the scleral spur and Schwalbe's line. Due to its microscopic structure it gives the iridocorneal angle an irregular surface. A blood-filled canal of Schlemm may occasionally serve as demarcation. Increased episcleral pressure in the eyeball due to compression of a contact glass or occlusion of the homolateral jugular vein may cause artificial reflux of blood into Schlemm's canal (Hoskins 1972).
   Even at an early age the trabecular meshwork may be readily identifiable on the basis of a pronounced degree of pigmentation. Such marked pigmentation is found in conditions like the pigment dispersion syndrome (Ro-

binson et al. 1981; Scheie & Cameron 1981; Speakman 1981; Sugar 1984; Richter et al. 1986).

An increase in pigmentation is also observed with increasing age (Hoskins 1972; Mandell 1978). The lower two quadrants are more pigmented than the upper two, and the pigment is usually deposited on that part of the trabecular meshwork that lies above Schlemm's canal (Shaffer 1962).

3. The third structure identifiable in open iridocorneal angles is the **scleral spur**, which presents as a light-coloured white band between trabecular meshwork and ciliary band.

   In various conditions it may be difficult to locate the scleral spur. When the iridocorneal angle is very narrow, the scleral spur is covered by the peripheral iris. Strongly pigmented uveal trabeculae may mask the scleral spur. Parts of the scleral spur may be concealed by peripheral anterior synechiae. Finally, there may be an abundance of iris processes: strands of tissue extending from the iris to the scleral spur. They occasionally insert on the trabecular meshwork or even on Schwalbe's line. Morphologically they have the same structure as iridal tissue, and their morphology therefore differs from eye to eye (Hogan et al. 1971). They are probably remnants of an incomplete embryonic cleavage process (Shaffer 1962). Their contribution of glaucoma is obscure. Abnormal numbers of iris processes may be found in normotensive eyes as well as in hypertensive eyes and glaucomatous eyes (Lichter & Shaffer 1970).
4. Finally, the **ciliary band** is the most posterior structure of the iridocorneal angle. This ciliary band is localized between the scleral spur and the insertion of the iridal root. The colour of this anterior surface of the ciliary body varies from greyish-white to brown, dependent on the degree of ocular pigmentation. Like the scleral spur, this ciliary band is often masked by iridal tissue, uveal trabeculae and iris processes.

### 2.2.2 Microscopic anatomy

Attempts to gain insight into the microscopic anatomy of the trabecular meshwork and Schlemm's canal date back more than a century. Despite sophisticated techniques such as transmission electron microscopy and scanning

electron microscopy, fixation techniques and immunohistochemical staining, not all questions can be answered. One of the principal problems is the question whether in-vitro phenomena may be extrapolated to in-vivo situations. Nevertheless it is worthwhile to discuss the various findings and the theories arising from them.

The outflow of aqueous humour from the anterior segment of the eye takes place along two important pathways (Fine 1964; Hogan et al. 1971; Tripathi & Tripathi 1982):

1. The conventional outflow apparatus (trabecular meshwork and Schlemm's canal).
2. Accessory outflow tracts:
   a) Posterior outflow to the vitreous body.
   b) Diffusion to iridal blood vessels and ciliary body.
   c) Transcorneal outflow.
   d) Uveoscleral and uveocortical outflow.

The accessory outflow tracts are probably responsible for a small but significant percentage of the total outflow of aqueous humour (Tripathi & Tripathi 1982).

Because most of the aqueous humour leaves the eye via the conventional outflow apparatus and because the major site of resistance to outflow is localized in this apparatus (Grant 1958), attention must focus on this apparatus.

The following structures have of old been distinguished in the conventional outflow apparatus:

1. The uveal trabeculae.
2. The corneoscleral trabeculae.
3. The trabecular wall of Schlemm's canal.
4. The corneoscleral wall of Schlemm's canal.
5. The collector channels and episcleral outflow tract.

These structures will be discussed in the following subsections.

#### 2.2.2.1 Uveal trabeculae

That part of the trabecular meshwork that constitutes the boundary between

the conventional outflow apparatus and the anterior chamber is referred to as uveal trabeculae. The classic microscopic features of this structure show a network of mostly radially arranged tissue strands extending between iris and ciliary body on the one hand, and cornea on the other (Ashton et al. 1956; Flocks 1956; Speakman 1959; Ashton 1960). Tangential sections through the trabecular meshwork reveal that these tissue strands have a four-layer structure. There is a central collagenous core (first layer), embedded in elastic fibrillae (second layer). The third layer is formed by a glass membrane - probably an equivalent of Descemet's membrane in the cornea. The fourth layer consists of endothelial cells (Ashton et al. 1956; Flocks 1956). The mean diameter of these trabeculae is 4 µm, and they are so arranged as to form large (25-75 µm) diamond-shaped orifices (Ashton et al. 1956). The dimensions of these orifices are such that they offer no resistance to the outflow of aqueous humour to Schlemm's canal (Speakman 1959).

The introduction of transmission electron microscopy cast a new light on the structure of these trabeculae. Garron et al. (1958) were the first to employ this technique in studying the trabecular meshwork. They were unable to trace the classic four-layer structure (Garron et al. 1958; Garron & Feeney 1959). The central collagenous core proved to consist of fibrillae with a periodicity of 64 nM, embedded in a homogenous matrix with an approximate thickness of 80-130 nM. This matrix comprises fibrillae with a periodicity of 100 nM and fibrillae showing no periodicity. The investigators were unable to trace a typical glass membrane. They concluded that the histologically identifiable elastic material probably consists of collagen aggregates with a periodicity of 100 nM, and that the glass membrane is identical to the ground substance. They believed this ground substance to consist mainly of mucopolysaccharides (Garron & Feeney 1959).

Application of new fixation and staining techniques by Spelsberg & Chapman in 1962 revealed that the homogenous matrix in actual fact is a thick basement membrane on which the endothelial cells rest. They also were able to trace the fibrillae with a periodicity of 64 nM and 100 nM respectively, and in addition they reported that the endothelial cells have abundant organellae and that consequently synthetic activity may be involved.

The discussion about the presence or absence of elastic material in the trabeculae continues. Some authors maintain that the presence of this mate-

rial in the trabeculae is beyond doubt (Tripathi & Tripathi 1982); others take a more moderate view and refer to an elastic-like material (Fink et al. 1978; Lütjen-Drecoll et al. 1981).

Scanning electron microscopy makes it possible to obtain three-dimensional images of the trabecular meshwork. The uveal trabeculae present themselves as an irregular low-density network of tissue strands (Spencer et al. 1968). The orifices in this network are polygonal (Anderson 1971) and exceed a diameter of 20 µm (Bill & Svedbergh 1972).

The endothelial cells lining the trabeculae are mostly elongated flat cells. Their cytoplasm comprises the usual organellae such as central nucleus, agranular endoplasmic reticulum, granular endoplasmic reticulum, Golgi complex, lysosomes, vesicles and multivesicular bodies (Tripathi & Tripathi 1982). These cells have long cytoplasmic processes that extend to contact adjacent cells (Inomata et al. 1972) via maculae occludentes and desmosomes; these processes often span an intertrabecular space (Tripathi 1977). The morphological features of these organellae suggests synthetic activity (Tripathi & Tripathi 1982). This synthetic activity receives attention in subsection 2.2.2.5.

#### 2.2.2.2 Corneoscleral trabeculae

The tissue strands of the corneoscleral trabeculae consist of parallel sheets and microscopically show the same four-layer structure as those of the uveal trabeculae (Flocks 1956; Ashton 1960). The longitudinal axis of these sheets parallels that of the scleral spur and that of Schlemm's canal (Flocks 1956; Speakman 1959). The sheets are most numerous (8-15 on average) near the scleral spur (Flocks 1956). At that site the total thickness of these sheets is 120-150 µm, each individual sheet measuring 5-12 µm (Tripathi & Tripathi 1982). The intertrabecular spaces are narrower than those of the uveal trabeculae, measuring about 5-20 µm. These spaces gradually obliterate near the transition of the trabecular meshwork to the corneal stroma (Tripathi & Tripathi 1982).

The aqueous humour can reach Schlemm's canal because the sheets are perforated. These perforations are oval-shaped and smaller than those in the

uveal trabeculae (Bill & Svedbergh 1972). Again one finds the cytoplasmic processes spanning the inter- and intratrabecular spaces (Anderson 1971). The intratrabecular spaces seem to be tunnels extending through an endothelial cell or localized at the boundary between two cells (Spencer et al. 1968). The tunnels become narrower as they are closer to Schlemm's canal. The generally seem to be randomly distributed over the trabeculae, but they are rarely if ever juxtaposed (Fine et al. 1981).

The electron microscopic anatomy of the sheets show the following structures from the inside out: a collagenous core, a layer of amorphous ground substance, a basement membrane and an endothelial lining (Tripathi & Tripathi 1982). The thickness of the collagenous core diminishes as Schlemm's canal is approached (Flocks 1956; Speakman 1959; Bill & Svedbergh 1972). According to Tripathi elastic fibrillae are present in the amorphous ground substance and in the basement membrane (Tripathi & Tripathi 1982). Ultrahistochemical studies have shown, however, that by no means all fibrillae in these areas consist of elastic material (Lütjen-Drecoll et al. 1981).

Attention should be paid to the presence of collagen with an electron microscopic periodicity of 95-125 nM in the collagenous core and basement membrane; this collagen has been described as curly collagen (Garron & Feeney 1959) or lattice collagen (Rohen 1963). Curly collagen is seen more frequently with increasing age (Rohen 1978) and is probably responsible for the thickening of the trabeculae at a more advanced age (McMenamin et al. 1986).

The lining of the sheets consists of endothelial cells whose longitudinal axes parallel those of the trabeculae. They are in touch with each other via maculae adherentes and gap junctions (Tripathi & Tripathi 1982). Their composition hardly differs from that of the cells in the uveal trabeculae.

#### 2.2.2.3 Trabecular wall of Schlemm's canal

The trabecular wall of Schlemm's canal is the area of transition between the most peripheral corneoscleral sheets and the lumen of Schlemm's canal. This area generally encompasses three components:

1. **The endothelial lining of Schlemm's canal.**
2. **A basement membrane.**

3. **A connective tissue zone.** The literature shows no consensus about the nomenclature of this zone, which on the basis of its specific microscopic features is given various names:
   - pore tissue (Flocks 1956),
   - endothelial meshwork (Speakman 1960),
   - juxtacanalicular connective tissue (Fine 1964),
   - cribriform meshwork (Rohen 1969),
   - juxtacanalicular layer (Fink et al. 1972).

   I prefer the designation 'endothelial meshwork' because this indicates the localization and emphasizes the cellular component.

The luminal side of the inner wall of Schlemm's canal proves to show irregular features with many outpouchings into the lumen and deep grooves in the wall (Flocks 1956; Speakman 1959; Unger & Rohen 1959; Rohen 1960; Kayes 1967; Tripathi 1968; Bill & Svedbergh 1972; Fink et al. 1978). The trabecular side proves to give rise to septa which link the corneoscleral and trabecular walls of Schlemm's canal (Tripathi 1969). Taking the trabecular wall of Schlemm's canal as a flat region, the surface area is about 11 $mm^2$. Taking the irregularity of its structure into account, however, Cole & Tripathi (1971) estimate the total surface area to be 40 $mm^2$.

The wall is lined by a continuous monolayer of endothelial cells (Tripathi 1969). The diameter of these cells is about 4-8 µm (Bill & Svedbergh 1972), sometimes up to 12 µm (Tripathi 1977), and their length often exceeds 100 µm (Bill & Svedbergh 1972). At their most peripheral ends these cells often have diameters of only 0.1-0.3 µm (Kayes 1967; Fink et al. 1972).

The cells are in contact via end-to-end touches, tongue-in-groove junctions, zonulae adherentes and zonulae occludentes (Kayes 1967; Tripathi 1968; Fink et al. 1972). Although Spencer et al. (1968) were unable to identify tight junctions, their presence was confirmed with the scanning electron microscope (Inomata et al. 1972).

These endothelial cells contain a nucleus, Golgi complex, mitochondriae, agranular endoplasmic reticulum, granular endoplasmic reticulum, multivesicular bodies, glycogen, free ribonucleic acid granules and lysosomes. Fibrillar elements are found in addition. The cell surface often shows invaginations on the basal side (Tripathi 1969) and is covered with micropino-

cytosis vesicles (Tripathi 1969; Fink et al. 1972). The large nucleus is responsible for the previously mentioned outpouchings into the lumen of Schlemm's canal (Kayes 1967; Tripathi 1968; Fink et al. 1972; Bill & Svedbergh 1972).

These endothelial cells differ from other endothelial cells in that they have large intracytoplasmic vacuoles (Fink et al. 1972). Speakman (1959) was the first investigator to describe these vacuoles, which he believed to be postmortem artefacts. The first transmission electron microscopic studies of the trabecular meshwork likewise revealed these vacuoles (Garron et al. 1958; Garron & Feeney 1959), and in 1960 Speakman acknowledged that they were not post-mortem artefacts.

Since these first descriptions many publications have confirmed the existence of these vacuoles (Holmberg 1959; Rohen 1960, 1969; Kayes 1967; Tripathi 1968, 1969, 1971; Inomata et al. 1972; Fink et al. 1978; McMenamin & Lee 1980; Tripathi & Tripathi 1982; McMenamin et al. 1986). Although a few authors still expressed doubt about the existence of these intracytoplasmic vacuoles (Fink et al. 1972; Shabo et al. 1973), it is now assumed that they are present in vivo as well.

The incidence of these vacuoles differs markedly from eye to eye, but also within the same eye. Although most of the vacuoles seem optically empty, some flocculent material may occasionally be encountered (Tripathi 1969).

Their diameter averages 5 µm (Speakman 1959; Tripathi 1968; Inomata et al. 1972), with a maximum of 15 µm (Tripathi 1969). Four different types can be distinguished:

1. Vacuoles opening up only on the basal side, i.e. towards the endothelial meshwork.
2. Vacuoles opening up only on the apical side, i.e. towards the lumen of Schlemm's canal.
3. Vacuoles opening up both on the basal and on the apical side.
4. Entirely intracytoplasmic vacuoles.

Excluding the entirely intracytoplasmic vacuoles, the above order of sequence also indicates the incidence of these types of vacuole. Only 1-2% of them are believed to open up on both sides (Kayes 1967; Tripathi 1968). The transcellular channel thus formed often shows a tortuous course, the apical aperture virtually never being localized above the basal one (Tripathi &

Tripathi 1982). Another finding is that the basal aperture is always larger than the apical one, and averages 1-3 µm (Inomata et al. 1972).

Studies of the behaviour of the endothelial cells and vacuoles under standardized intraocular pressure revealed that, at pressures within physiological limits (15 mm Hg), an increase in pressure causes an increase in both the incidence and size of the vacuoles. The size of the basal and apical apertures also increases in that case. Vacuoles are no longer visible when the pressure is reduced to 0 mm Hg. High intraocular pressures (>50 mm Hg) are associated with lower incidences than physiological pressures (Johnstone & Grant 1973; Grierson & Lee 1975b).

On the basis of the above data Tripathi developed a model in which these vacuoles are the regulators of intraocular pressure and responsible for transporting aqueous humour to Schlemm's canal (Tripathi 1968, 1969, 1971, 1977, Tripathi & Tripathi 1982). The sequence of events in this process is schematically represented in figure 2.3.

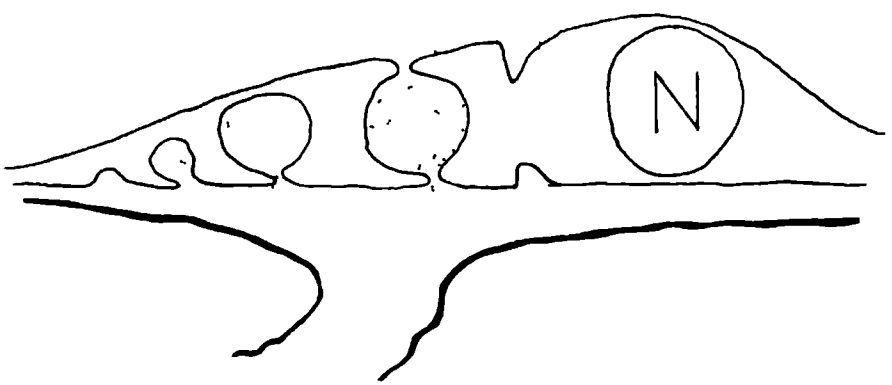


Figure 2.3. Diagrammatic representation of the cyclical sequence of events in the formation of vacuolar transcellular channels in the endothelial lining of Schlemm's canal. From left to right: basal invagination, intracytoplasmic vacuole, transcellular channel, fusion of cell membranes. N: nucleus. (after Tripathi, R.C.: The Functional Morphology of the Outflow Systems of Ocular and Cerebrospinal Fluids. Exp. Eye Res. Suppl.:65, 1977).

Hydrostatic pressure gives rise to an invagination on the basal side of the endothelial cell. This invagination becomes larger and forms a vacuole which contacts the apical side of the cell. The membrane of the vacuole fuses with the apical cell membrane and a temporary transcellular channel is formed. Finally the cytoplasm rearranges itself on the basal side and a final/initial situation is attained/restored. According to Tripathi maintenance of the steady state in intraocular pressure is achieved by this system of dynamic vacuolation (see also 2.2.2.5).

The endothelium rests on a discontinuous, irregular basement membrane. In actual fact this is not a basement membrane but a layer of homogenous, amorphous ground substance in which fibrillar elements are embedded. The thickness of these elements averages 8 nM (range 9-12 nM). The 'basement membrane' is not continuous, of irregular morphology and varying in thickness (Garron & Feeney 1959; Tripathi 1968; Hogan et al. 1971; Inomata et al. 1972; Fink et al. 1978; McMenamin & Lee 1980).

The term endothelial meshwork refers to the area between the endothelial lining of Schlemm's canal and the most peripheral trabecular sheets. This area mainly encompasses three components:

1. An amorphous-granular ground substance with fibrillar elements.
2. Electron-dense material.
3. A cellular component.

Some authors maintain that the abovementioned basement membrane should also be included in this area (McMenamin & Lee 1980).

Depending on age, the ground substance constitutes 10-40% of the surface area of the endothelial meshwork, the electron-dense material 5-25%, and the cellular component 25-45% (McMenamin & Lee 1980).

The cellular component comprises endothelial cells as well as non-endothelial cells such as plasma cells, macrophages, neutrophilic and eosinophilic granulocytes and mast cells (Tripathi & Tripathi 1982).

The structure of the endothelial cell differs from that of the cell of Schlemm's canal and is more similar to that of the trabecular cells. They contain a nucleus, Golgi complex, mitochondriae, cytoplasmic filaments, phagocytes and a granular endoplasmic reticulum which differs markedly in structure from that of the other endothelium (Inomata et al. 1972; Tripathi

& Tripathi 1982). These cells have long cytoplasmic processes in touch with each other and also with the endothelial cells of Schlemm's canal. They thus form a network of extracellular spaces in which the ground substance and fibrillar elements are embedded (Inomata et al. 1972).

The fibrillar elements in these extracellular spaces are of varying origin: collagen, basement membrane material, microfibrillae, curly collagen and elastic-like fibres. The latter are arranged in a regular, equatorial pattern and link up with the endothelial lining of Schlemm's canal on the one hand, and the anterior fibres of the ciliary muscle on the other (Rohen 1981).

A conspicuous feature of this endothelial meshwork is the presence of optically empty spaces. These were described by Garron as early as 1959, and particularly Rohen devoted considerable research to these empty spaces or cribriform pathways. They are delimited by the cells and ground substance, and according to Rohen are the principal localization of resistance to outflow (see also 2.2.2.5).

### 2.2.2.4 The outer wall of Schlemm's canal and collector channels

Like the trabecular wall, the outer wall of Schlemm's canal is lined with a continuous monolayer of endothelial cells. These cells are longer and smoother than those of the trabecular wall and their nuclei are oval-shaped, as a result of which the outpouchings into the lumen are far less prominent (Tripathi 1968).

They contain the usual organellae and their morphology resembles that of the endothelial cells of the trabeculae much more closely than that of the cells of the inner wall of Schlemm's canal (Fink et al. 1972).

They differ from the endothelial cells of the trabecular wall of Schlemm's canal in two essential features:

1. They show no vacuolation (Garron & Feeney 1959; Fine 1964; Tripathi 1968; Inomata et al. 1972; Bill & Svedbergh 1972).
2. They rest on a distinctly structured basement membrane (Tripathi 1968; Inomata et al. 1972).

The area between this basement membrane and the scleral collagen essentially resembles the endothelial meshwork (Fink et al. 1978), but the fibrillar component unmistakably dominates the cellular one (Tripathi & Tripathi 1982). This cellular component shows far more features of fibrocytes than of endothelial cells. Morphologically this area shows a much more rigid structure than the endothelial meshwork (Tripathi & Tripathi 1982).

The intraluminal septa in Schlemm's canal show a structure similar to that of the corneoscleral and trabecular wall respectively, which is to say that an endothelial layer and a basement membrane rest on a layer of fibrillar-cellular tissue. The features of these components correspond with the characteristics of the inner wall of Schlemm's canal on the trabecular side of the septa and those of the outer wall near the scleral side. There is a gradual transition from vacuolated to non-vacuolated cells as the scleral wall is approached (Tripathi 1968).

In the outer wall there are apertures which are the start of collector channels. These apertures range in diameter from 20 µm to 70 µm (Bill & Svedbergh 1972). Some 20-35 of these collector channels arise from Schlemm's canal, the number on the nasal side exceeding that on the temporal side. The endothelial lining is continuous with that of Schlemm's canal (Hogan et al. 1971).

The drainage of aqueous humour to the venous vascular system takes two principal routes (Tripathi & Tripathi 1982):

1. Drainage via collector channels to the deep scleral venous plexus. This deep plexus drains into the mid-scleral venous plexus, which is drained also from the venous ciliary plexus. From the mid-scleral plexus there is drainage to the episcleral plexus.
2. Direct drainage via 'aqueous veins' formed by collector channels which drain directly into the episcleral vascular system.

#### 2.2.2.5 Resistance to outflow of aqueous humour

Maintenance of intraocular pressure requires a resistance to the outflow of aqueous humour. On theoretical grounds, this resistance to outflow may be localized virtually throughout the conventional drainage system.

The principal barriers which the aqueous humour must overcome on its way to the episcleral vascular system are, successively:

1. The uveal trabeculae.
2. The corneoscleral trabeculae.
3. The endothelial meshwork.
4. The endothelial lining of Schlemm's canal.
5. The collector channels and aqueous veins.

Grant (1958) calculated that at least 75% of the resistance to outflow must be localized in the trabecular meshwork. Our insight into the localization of the major site of resistance to outflow has been enhanced by perfusion studies. In-vitro and in-vivo perfusions with latex particles, iron and gold particles, peroxidase, thorium dioxide and erythrocytes have contributed to the possible answers to two questions, which are still of current interest. What is the localization of the major site of resistance to outflow within the conventional drainage system? By which route(s) does the aqueous leave this drainage system? On the basis of possibilities suggested in the literature, four approaches to the latter question can be distinguished:

1. **Aqueous drainage via direct channels between the intertrabecular spaces and the lumen of Schlemm's canal.**

   The existence of direct channels of this kind has long been postulated. Dvorak-Theobald (1955) described these channels as 'Sondermann's channels', after the first investigator to describe them. Sondermann's channels were believed to be direct channels between the intertrabecular spaces and Schlemm's canal, with an average diameter of 25-30 µm. The existence of such channels has meanwhile been confirmed by such authors as Unger & Rohen (1959) and Ashton (1960), and denied by Flocks (1956), Speakman (1959) and Inomata et al. (1972). Perfusion studies have shown that these channels in the trabecular wall of Schlemm's canal do not communicate directly with the intertrabecular spaces (Inomata et al. 1972). Sondermann's channels are grooves in the wall ending blindly and provided with a continuous endothelial lining (Rohen 1969). They enlarge the surface area of the trabecular wall (Cole & Tripathi 1971). Histological findings, electron-microscopic studies and calculations indicate that

Sondermann's channels, if they did communicate directly with the intertrabecular spaces, could not offer adequate resistance to outflow (McEwen 1958; Tripathi & Tripathi 1982).

2. **Aqueous drainage via an active transport system.**

An active micropinocytosis process might play a role in transporting aqueous humour. Tracer studies have shown that this process does take place in the endothelial lining of Schlemm's canal, but that its contribution to total drainage is minimal (MacRae & Sears 1970). Moreover, the filling of the pinocytosis vesicles proves to be highly dependent on the size of the particles used in perfusion (Inomata et al. 1972).

3. **Aqueous drainage via an intercellular transport system.**

It has already been mentioned that the intercellular communications in the endothelial lining of Schlemm's canal are of the zonula occludens type. Tracer studies in fact rarely show any passage of particles along the intercellular route (MacRae & Sears 1970; Inomata et al. 1972).

Some investigators hold that the intercellular links are not zonulae occludentes but maculae occludentes with intercellular clefts of 5 nM (Shabo et al. 1973). This would imply the possibility of passage. Even if these apertures would measure 8 nM, however, it can be calculated that they drain only 1% of the total amount of aqueous humour (Bill 1975).

It has recently been demonstrated that the intercellular communications are indeed of the zonula occludens type but locally occur in a specific configuration so that limited passage is possible (Raviola & Raviola 1981); the contribution to the total drainage, however, is small.

4. **Aqueous drainage via the dynamic system of vacuolar transcellular channels.**

The results of perfusion and tracer studies seem to warrant the conclusion that most of the aqueous humour reaches the lumen of Schlemm's canal via the previously described vacuoles (Inomata et al. 1972). These vacuoles prove to fill with tracer particles, which can be found also in the lumen of Schlemm's canal (Rohen 1963; MacRae & Sears 1970; Inomata et al. 1972; Tripathi & Tripathi 1982). Owing to their malleability, erythrocytes and leucocytes can also reach Schlemm's canal via this transcellular route (Tripathi 1977).

The intertrabecular spaces show a gradual decrease in diameter from the uveal trabeculae towards Schlemm's canal.

It may be stated in summary that the apertures in uveal trabeculae measure 25-75 μm, those in the corneoscleral trabeculae 5-20 μm, and those in the endothelium 1-3 μm. This 'cribrate' aspect is also demonstrable by tracer studies. These show that small particles (<1.0 μm) can reach Schlemm's canal without difficulty. As the particle size increases, the tracer substance amount reaching the canal diminishes, because this substance is caught in the spaces of the endothelial meshwork (Karg et al. 1958; MacRae & Sears 1970; Inomata et al. 1972).

Tripathi & Tripathi (1982) postulate that ".....the endothelial lining of Schlemm's canal is an important factor in determining the outflow of aqueous humour and consequently in regulating the steady state of intraocular pressure".

Rohen (1983), however, believes that the major resistance to outflow occurs before the endothelium is reached and suggests that the empty spaces in the endothelial meshwork "....represent those parts of aqueous outflow pathways that determine the actual outflow resistance of the trabecular meshwork". The previously mentioned plexus of elastic-like material in the endothelial meshwork will dilate these empty spaces as the ciliary muscle contracts, thus reducing the resistance to outflow. Inversely, relaxation of the ciliary muscle will lead to constriction of these spaces and thus increase the resistance to outflow (Rohen 1983).

Recent morphometric studies have demonstrated that the major resistance to outflow probably lies in the endothelial meshwork (Seiler & Wollensak 1985; Ethier et al. 1986).

Apart from this physical-mechanical approach to resistance to outflow, more dynamic systems also seem to play a role. As already mentioned, the composition of the organellae of the various endothelial cells indicates synthetic activity. At least two groups of substances are formed which interfere with intraocular pressure and possibly with the outflow of aqueous humour. These are prostaglandins and proteoglycans.

**Prostaglandins**

Prostaglandins are produced by cyclization and oxidation from unsaturated

essential fatty acids. In this way linoleic acid gives rise to arachidonic acid, which is the precursor of prostaglandin $E_2$. The prostaglandins frequently studied in connection with the eye are prostaglandin $E_2$ ($PGE_2$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

Experiments on rabbits, cats and monkeys have shown that intraocular or topical application of arachidonic acid or prostaglandin leads to a significant rise in intraocular pressure (Eakins 1970; Podos et al. 1973; Conquet et al. 1975). An explanation of this phenomenon might be found in a disturbance of the blood-aqueous barrier, expressed among other things in an increased protein concentration of the aqueous humour (Eakins 1970).

Fatless parenteral nutrition leads to a reduction in prostaglandin synthesis with decreased plasma $PGE_2$ levels. Parallel to this a significant decrease in intraocular pressure is observed (Naveh-Floman & Belkin 1987).

Apart from this ocular hypertensive effect of $PGE_2$ and $PGF_{2\alpha}$, small doses of these substances have proved to produce an ocular hypotensive effect (Camras et al. 1977; Stern & Bito 1982; Bito et al. 1983). This ocular hypotensive effect is not associated with a disturbance of the blood-aqueous barrier (Stern & Bito 1982). Dependent on the dose given, this hypotensive effect is preceded by a transient increase in pressure (Bito et al. 1983). Camras et al. (1977) suggest that this hypotensive effect of the prostaglandins is caused by a reduced resistance to outflow.

In 1983 Weinreb et al. demonstrated that human trabecular cells are capable of producing $PGE_2$, $PGF_{2\alpha}$ and $6KF_1$ in vitro. Weinreb et al. assumed that these prostaglandins function as local regulators and influence the resistance to outflow.

The results of these studies (often animal experiments) of course do not warrant far-reaching conclusions; many authors, however, are convinced that prostaglandin studies will contribute to clarification of the pathogenesis of glaucoma and may also contribute to the therapeutic repertory (Camras et al. 1977; Stern & Bito 1982; Bito 1983; Weinreb et al. 1983; Yousufzai & Abdel-Latif 1983).

**Proteoglycans**

Proteoglycans are protein-polysaccharide complexes which in many tissues form the mucosubstances. Histochemically, they are divided into:

1. Acid mucosubstances, e.g. the mucopolysaccharides. These are produced from linear, acid heteropolysaccharides (glycosaminoglycans) in a complex with protein. The polysaccharide component amounts to 80%. The most common mucopolysaccharides are hyaluronic acid, chondroitin sulphate, dermatan sulphate, keratan sulphate and heparan sulphate.
2. Neutral mucosubstances, e.g. the glycoproteins. These are produced from ramified neutral heteropolysaccharides in a complex with protein. The polysaccharide component amounts to 15-40%.

Zimmerman demonstrated in 1957 that the trabecular meshwork contains mucopolysaccharides, the highest concentration of which is found in the endothelial meshwork. The localization of mucopolysaccharides was determined more accurately in the mid-Seventies. In the conventional drainage system they proved to be present at the following sites (Grierson & Lee 1975a; Armaly & Wang 1975):

1. The trabeculae (apical side endothelial cell, basal side endothelial cell, basement membrane, collagenous core, curly collagen, elastic-like material.
2. The endothelial meshwork (apical side endothelial cell, basement membrane, collagen, curly collagen, elastic-like material, empty spaces).
3. The endothelial lining of Schlemm's canal (apical side endothelial cell, basal side endothelial cell, vacuoles).
4. The corneoscleral wall of Schlemm's canal and the collector channels.

Armaly & Wang (1975) assume that these mucopolysaccharides are produced by the endothelial cells themselves and do not originate from the aqueous humour (mucopolysaccharides in the collagenous core, for example, cannot originate from the aqueous).

François (1975) suggested the correlation between mucopolysaccharides and resistance to outflow to be as follows. A decrease in intraocular pressure leads to a higher degree of polymerization of mucopolysaccharides. This implies an increase in hydration capacity and a constriction of the trabecular spaces, causing an increase in resistance to outflow. Inversely, an increase in intraocular pressure causes release of depolymerizing enzymes, leading to dehydration and reduced resistance to outflow.

The study of cell cultures from trabecular material has also contributed

to research into resistance to outflow. Cells obtained in this way closely resemble the in-vivo cells as to cell surface, cell junctions, organellae and nuclear chromatin (Alvarado et al. 1982). On the basis of these in-vitro findings the endothelial cells of the trabecular meshwork can be divided into three groups as to location and function (Rohen et al. 1982; Polansky et al. 1984):

1. **Endothelial cells.** These grow in cell cultures as a single layer and show a non-thrombogenic surface. Under thrombinogen stimulation they prove capable of producing plasminogen activator which, if necessary, keeps the outflow channels free from obstructing material via fibrinolysis.
2. **Phagocytic cells.** In-vitro cells may show phagocytic activity.
3. **Connective tissue cells.** In-vitro cells can produce various substances including glycosaminoglycans (Alvarado & Polansky 1979; Polansky et al. 1984), glycoproteins (Alvarado & Polansky 1979; Worthen & Cleveland 1982) and collagen (Polansky et al. 1984).

Glycoproteins (fibronectin and laminin) and glycosaminoglycans have also been demonstrated in the conventional drainage system by immunoassays and immunohistochemical techniques (Rodrigues et al. 1980; Radda et al. 1983; Acott et al. 1985).

On the basis of the properties of these mucosubstances and their distribution in the drainage system they are assigned a role in resistance to outflow and possibly in the pathogenesis of glaucoma (Radda et al. 1983; Floyd et al. 1985; Acott et al. 1985; Ethier et al. 1986; Gard et al. 1987).

#### 2.2.2.6 Changes in the outflow apparatus with ageing

The incidences of increased intraocular pressure and glaucoma increase with increasing age (Graham 1978). The morphological changes in the drainage system observed at an advanced age are often not readily distinguishable from those of glaucoma (Fine 1964; Nesterov & Batmanov 1974; Fine et al. 1981; Tripathi & Tripathi 1982); it is conceivable that only a quantitative difference separates ageing phenomena from glaucoma (Rohen 1969).

The changes in the trabecular sheets with increasing age are the following

(Rohen 1969; Hogan et al. 1971; Rohen 1978; McMenamin & Lee 1980; Tripathi & Tripathi 1982; McMenamin et al. 1986). The total thickness of each sheet increases, mainly through deposition of homogenous and fibrillar material ir the cortical zone of the sheet. There is an increase in collagen, elastic-like material and basement membrane material, and a striking increase in curly collagen. The collagenous core shows sign of degeneration such as fragmentation, variation in diameter and a change from regular to curly collagen. This ageing process is described as hyalinization by Rohen (1968). Hyalinized sheets are described as tending to adhere to each other (Rohen 1969; Lütjen-Drecoll 1973). Because the inter- and intratrabecular aqueous pathways are quite wide, however, this hyalinization process does not affect resistance to outflow (McMenamin et al. 1986).

The cellular component of the trabecular sheets likewise shows changes. The most conspicuous change is a decrease in the number of cells with increasing age (Tripathi & Tripathi 1982; McMenamin et al. 1986; Grierson & Howes 1987). This is an absolute decrease rather than a relative diminution as compared with the increased homogenous and fibrillar material (Alvarado et al. 1981). During the foetal period and the first years of life there is a very rapid non-linear decrease, but subsequently the relationship between cell diminution and age becomes linear (Alvarado et al. 1984).

The endothelium also shows changes in terms of intracellular organization. There is an increase in the total number of cell organellae, pigment granules and lysosomes. This could indicate increased phagocytic activity, which parallels the atrophy of the tissues in the anterior segment of the eye (McMenamin et al. 1986).

On the whole, the changes in the endothelial meshwork resemble those in the remainder of the trabecular meshwork. Again one observes a decrease in cellularity (Alvarado et al. 1981; Tripathi & Tripathi 1982; Alvarado et al. 1984) as well as in homogenous ground substance (McMenamin et al. 1986). There is a significant increase in electron-dense material (collagen, elastic-like fibres, curly collagen and intermediate fibres) (Tripathi & Tripathi 1982; McMenamin et al. 1986). This electron-dense material is not deposited at random in the endothelial meshwork but in the form of plaques. Rohen distinguishes three plaque types (Rohen 1970, 1978, 1983; Rohen et al. 1981):

"Type I : This first form has a fairly homogenous appearance, less electron-dense than the elastic fibres but easily distinguishable from deposits of precipitated protein or fibrin. The plaque size varies considerably.
Type II : ..... These are considerably more electron-dense than the Type I plaques and resemble the central core or elastic fibres. They are not usually as extensive and large as the Type I plaques.
Type III: The third form is comprised of band-like plaques with a regular periodicity of dark nodules or strips embedded in an electron-dense homogeneous material. Occasionally these striated bands resemble the sheath material of the elastic fibres within the hyalinized trabeculae."

These three types occur in primary open-angle glaucoma but may also be found in non-glaucomatous eyes in comparable age groups. There is an important quantitative difference, particularly in the incidences of Types II and III (Rohen 1983). Type III plaques are rarely observed in normotensive eyes (Rohen 1978) (see also 2.2.2.7).

Rohen (1981, 1983) postulates that local synthesis of extracellular material leads to thickening of pre-existent elastic-like fibres. McMenamin et al. (1980, 1986), however, postulate that debris from the uveal and corneoscleral trabeculae is caught in the endothelial meshwork.

With increasing age, Schlemm's canal shows an increasing incidence of local occlusion and obliteration of the lumen due to fibrosis and secondary vascularization. However, even eyes of aged persons with extensive degenerative changes still show many areas of normal morphology (Nesterov & Batmanov 1974; McMenamin et al. 1986). The endothelium of Schlemm's canal shows diminution of cellularity and a significant decrease in the number of vacuoles (McMenamin et al. 1986).

### 2.2.2.7 Morphological changes in the trabecular meshwork in primary open-angle glaucoma

The changes in the trabecular meshwork in primary open-angle glaucoma (POAG) can be summarized as follows (Rohen 1978; Tripathi & Tripathi 1982):

1. Hyalinization of the uveal and corneoscleral trabeculae (see subsection 2.2.2.6).

2. Plaque formation in the endothelial meshwork (see subsection 2.2.2.6).
3. Decreasing cellularity of the trabecular meshwork. Alvarado et al. (1984) demonstrated that the cell diminution-age curves of eyes with POAG parallel those of normotensive eyes. However, the glaucomatous eyes do show an absolutely greater decrease.
4. A decreased incidence and size of the vacuoles of the endothelial lining of Schlemm's canal.
5. Stenosis and obliteration of the lumen of Schlemm's canal.

Various authors have pointed out that these changes are not specific of POAG but are observed also in pseudo-exfoliation glaucoma, secondary glaucoma and senescence (Nesterov & Batmanov 1974; Rohen 1978; Fine et al. 1981; Tripathi & Tripathi 1982). The morphological substrate of POAG should therefore pose not so much a qualitative as a quantitative problem (Rohen 1970; Rodrigues et al. 1976; Tripathi & Tripathi 1982; Rohen 1983).

Recent studies, however, have produced new evidence which reduces this 'quantity emphasis'. Three of these studies may be discussed here.

1. **Plaques in the endothelial meshwork.**
   Studies of the morphology of the endothelial meshwork in tangential sections have revealed a network of elastic-like fibres which links up both with the endothelial lining of Schlemm's canal and with the ciliary muscle. They also showed that some of the Type II and III plaques are not true plaques at all but merely components of the abovementioned network of elastic-like fibres (Rohen et al. 1981).
   Ultrahistochemical studies, including enzymatic digestion methods, have shown that Type I plaques occur in two varieties. The composition of one of these varieties seems specific of POAG and cannot be traced in non-glaucomatous eyes (Rohen et al. 1981; Lütjen-Drecoll et al. 1981). In addition to a quantitative difference, a qualitative difference seems to exist as well.
2. **Morphometric estimation of the concentration of electron-dense material in the endothelial meshwork.**
   Alvarado et al. (1986) demonstrated that the concentration of electron-dense material (the totality of Type I, II and III plaques) in the endothelial meshwork of glaucomatous eyes significantly exceeds that in a

non-glaucomatous control group.

Computer models imitating and calculating the permeability of the endothelial meshwork and the changes in resistance to outflow have shown that this significant difference is not sufficient to explain the difference in facility of outflow between non-glaucomatous eyes and eyes with POAG. A solely quantitative difference between glaucomatous and non-glaucomatous eyes is therefore unlikely (Alvarado et al. 1986).

3. **Glycosaminoglycans and glycoproteins.**

In-vitro studies have shown that trabecular cells are capable of producing glycosaminoglycans and glycoproteins, and immunoassays show that these can also be found in vivo (see 2.2.2.5). Computer simulation programmes show that the presence of a glycosaminoglycan gel in the empty spaces of the endothelial meshwork might very well regulate resistance to outflow (Ethier et al. 1986). Recent research has revealed that the concentration of certain glycosaminoglycans resistent to enzymes, is higher in glaucomatous eyes (Collins et al. 1987; Samuelson et al. 1987).

To summarize: beside a quantitative difference in morphological changes of the trabecular meshwork there is undoubtedly a qualitative difference too. In addition, the function and localization of products such as prostaglandins, glycosaminoglycans and glycoproteins may cast a fresh light on the pathogenesis of glaucoma.

## 2.3 AQUEOUS HUMOUR FORMATION AND DYNAMICS

Normally, no blood vessels are found in the cornea, lens, vitreous body and trabecular meshwork. For continuation of their metabolic status these avascular structures are dependent on aqueous humour, among other things. Another major function of aqueous humour is maintenance of intraocular pressure. The homoeostasis between the production on the one hand and the outflow of aqueous humour on the other, ensures a steady state in intraocular pressure.

Aqueous humour is produced in the ciliary body. A cross-section through this ciliary body shows a distinct triangular shape, of which the short an-

terior side is virtually at right angles to the sclera. The iris arises on this anterior side, which also links up with the scleral spur and the trabecular meshwork (Streeten 1982).

The ciliary body can be divided into two parts: the pars plana (ciliary orbiculus) and the pars plicata (ciliary crown). The pars plicata owes its name to the presence of some 70-80 prominent folds: the ciliary processes, which are symmetrically distributed over the ciliary body. The pars plana constitutes the posterior part of the ciliary body, bounded by the ciliary processes on the one hand, and the ora serrata on the other (Hogan et al. 1971).

The ciliary body is supplied with blood from the long posterior ciliary arteries and the anterior ciliary arteries, which form collateral anastomoses at three different sites:

1. In the episclera they form the episcleral circle.
2. In the ciliary muscle they form the intramuscular circle.
3. In the iridal root they form the greater arterial circle.

The greater arterial circle gives rise to anterior and posterior arterioles which supply blood to the ciliary processes. In these processes they form a complex anastomotic vasculature (Morrison & Van Buskirk 1986).

The innervation originates from both the parasympathetic and the sympathetic nervous system. The parasympathetic nerve fibres arise from the Edinger-Westphall nucleus and accompany the oculomotor nerve. In the ciliary ganglion they synapse, to enter the eye via the short ciliary nerves. They form an extensive plexus around the ciliary muscle.

The sympathetic neurons form an extensive plexus in the ciliary processes and arise from nerve fibres accompanying the ciliary arteries. Some of the sympathetic innervation is established via the ciliary ganglion and the long ciliary nerves (Streeten 1982).

The ciliary body comprises four layers. From the sclera these layers are known in succession as ciliary muscle, stroma, pigmented epithelium and non-pigmented epithelium. Because the ciliary muscle plays no essential role in aqueous humour formation, it will not be discussed in detail.

The stroma consists of low-density tissue composed of collagenous fibrillae with a periodicity of 50-58 nM and microfibrillae which contain some elastin. The interstitial cells are uveal fibroblasts, melanocytes and mast

cells, along with a large number of myelinated and unmyelinated nerve fibres. This area is abundantly vascularized, mainly by veins and capillaries; the latter are of the fenestrated type (Hogan et al. 1971; Streeten 1982; Morrison & Van Buskirk 1986).

The cells of the pigmented layer form a single layer extending from the ora serrata to the iris. They are cuboid cells and their basement membrane shows numerous invaginations. The lateral cell walls are straight and linked up by gap junctions, desmosomes and puncta adherentes (Raviola & Raviola 1978). Zonulae occludentes are not seen, and these cells therefore have no barrier function (Streeten 1982). Intracytoplasmic organellae such as mitochondriae, granular endoplasmic reticulum and Golgi complex are evidently less numerous than in non-pigmented epithelium. Many large, round and oval-shaped melanin pigment granules complete the cell contents (Streeten 1982).

The cells of the non-pigmented epithelium are in apex-to-apex contact with those of the pigmented epithelium. This can be explained from the invagination of the optic cup during embryonic development. The basal cell wall, which, together with the basement membrane constitutes the boundary of the posterior chamber of the eye, shows numerous invaginations. Unlike the pigmented epithelium, the lateral cell walls in the non-pigmented epithelium also show extensive invaginations. Another difference lies in the fact that the apical intercellular links are made up of zonulae occludentes, zonulae adherentes and gap junctions (Raviola & Raviola 1978). That this difference is essential is apparent from tracer studies showing that the tracer substance could not pass the zonulae occludentes (Smith 1973). Raviola & Raviola (1978) nevertheless conclude that this is not an absolute barrier but one that allows some leakage of ions and small molecules. The cytoplasm of these cells contains more organellae than that of the cells of the pigmented epithelium (Streeten 1982).

The fact that the protein concentration of the blood is many times as high as that of the aqueous humour warrants the conclusion that there must be a barrier between blood and aqueous humour (Cole 1978). Another argument in favour of this is provided by tracer studies (Smith 1973; Hirsch et al. 1980).

The blood-aqueous barrier can be divided into an anterior and a posterior part (Bill 1986). In order to reach the posterior chamber of the eye, an in-

travasal substance will have to pass in succession the endothelium of the vascular wall, the stroma, the pigmented and the non-pigmented epithelium of the ciliary body (the posterior blood-aqueous barrier). In order to pass from the iris to the posterior chamber the substance must pass the vascular wall, stroma, iridal musculature and iridal epithelium (the anterior blood-aqueous barrier). Because the anterior surface of the iris comprises no complete layers of cells, passage to the anterior chamber will occur (Hogan et al. 1971).

The vascular component of the posterior blood-aqueous barrier, i.e. the blood vessels of the ciliary processes, consist of thin-walled fenestrated capillaries which constitute no barrier to ions and small molecules. Nor does the stroma constitute an obstruction. From an anatomical point of view the barrier should be localized in the epithelium of the ciliary body (Bill 1986).

Tracer studies with relatively small molecules (horse-radish peroxidase, Smith 1973) and large molecules (autologous antiperoxidase antibodies, Hirsch et al. 1980) have shown that the major barrier consists of the intercellular junctions of the cells of the non-pigmented epithelium.

The vascular component of the anterior blood-aqueous barrier consists of relatively thick-walled capillaries (Bill 1986). The endothelial cells of these capillaries are linked via zonulae occludentes (Freddo & Raviola 1982).

It may be stated in summary that the posterior component of the blood-aqueous barrier is largely of an epithelial nature, while its anterior component is largely endothelial.

The first step in the production of aqueous humour consists of the formation of a plasma filtrate in the ciliary stroma. Because the capillaries have fenestrated walls, plasma proteins may be expected to be present in this filtrate. From this plasma filtrate water and other substances are transported to the posterior chamber of the eye, often against a concentration gradient (Sears 1975; Sears & Kondo 1986). Table 2.5 lists the concentrations of several substances in aqueous humour an plasma respectively (Cole 1978).

Aqueous humour formation exclusively by ultrafiltration seems unlikely for several reasons. Bill (1973) calculated that the transepithelial hydrostatic

Table 2.5. Concentration of the major elements of aqueous humour as compared to the normal plasma values (after Cole).

| | Aqueous Humour | Plasma | |
|---|---|---|---|
| Sodium | 153 | 143 | (µM/ml) |
| Chloride | 134 | 106 | (µM/ml) |
| Bicarbonate | 19.6 | 25.0 | (µM/ml) |
| Ascorbate | 1.06 | 0.04 | (µM/ml) |
| Glucose | 3.7-4.8 | 4.7-6.5 | (µM/ml) |
| Protein | 0.3-1.0 | 70 | (mg/ml) |

pressure in monkey eyes can never be sufficiently high to overcome the sum of the osmotic pressure in the ciliary stroma and the intraocular pressure. In addition he demonstrated that diminution of the arterial pressure hardly affects aqueous humour formation. Finally he demonstrated that aqueous humour formation is independent of the increase in blood flow through the ciliary body.

The exceptionally high ascorbate concentration in aqueous humour is based on a carrier-mediated process. The maximum is attained at a plasma concentration of 3 mg/100 ml, beyond which a further increase in plasma concentration causes no further increase in aqueous concentration (Krupin et al. 1986). The results of this and other studies indicate that aqueous humour formation is very likely based on cell-mediated processes.

That the active transport is based on the metabolic activity of the ciliary epithelium can be demonstrated with the aid of metabolic inhibitors such as dinitrophenol, styrylquinoline and fluoroacetate. Therapeutic agents acting through enzyme inhibition are likewise used in research of this type (Sears & Kondo 1986).

Current attention in the literature focuses on three enzyme systems:

1. Carbonic anhydrase.
2. Na-K-ATPase.
3. Adenylate cyclase.

The first two in particular play a role in theories on aqueous humour formation.

Cole (1978) assumes that the following intracytoplasmic processes in the

non-pigmented epithelium are of importance (figure 2.4). Sodium ions play an essential role in aqueous humour formation. Sodium influx arises from differences in concentration between intra- and extracellular milieus. Consequently sodium ions pass through the apical cell wall of the non-pigmented epithelium by diffusion. In addition, exchange against hydrogen ions probably contributes to this. As in most other epithelial structures, active outflow of sodium ions depends on the presence of Na-K-ATPase. This enzyme is

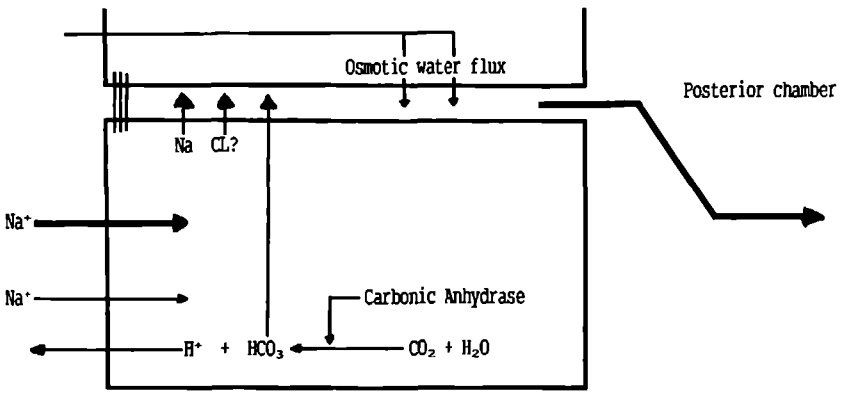


Figure 2.4. Intracytoplasmic processes in the non-pigmented epithelium involved in the production of aqueous humour (after Cole).

present in the cell membrane and can transport sodium ions to the extracellular milieu against a concentration gradient. The active transport of sodium ions along the lateral cell wall of the non-pigmented epithelium leads to the development of a hyperosmolar milieu in the intercellular spaces. In order to abolish this concentration gradient, water is attracted from the adjacent tissues (osmotic water flux). Because the lateral intercellular space is open on only one side (the apical side containing a tight junction complex), a flow in the direction of the posterior chamber of the eye results.

Carbonic anhydrase facilitates dissociation of carbon dioxide and water into hydrogen ions and bicarbonate. The hydrogen ions are probably exchanged against sodium ions on the apical cell wall. The bicarbonate probably plays a role in anion homoeostasis, the anion deficit being compensated by bicar-

bonate.

Inhibition of Na-K-ATPase, e.g. with ouabain, leads to reduced outflow of aqueous humour (Simon et al. 1962). Carbonic anhydrase inhibitors cause reduction of the inflow of sodium ions and bicarbonate, with a parallel decrease in the inflow of aqueous humour (Sears & Kondo 1986).

The following shows that the question of aqueous humour formation has certainly not yet been fully answered. Physiological and biochemical research has revealed that β-adrenergic substances play a role in regulating intraocular pressure. These substances act via adenylate cyclase. The ciliary processes prove to contain mainly $\beta_2$-adrenergic receptors (Nathanson 1981). Blockage of the β-receptors by a non-selective β-blocker proves to reduce intraocular pressure (Zimmerman & Kaufman 1977). Blockage of the β-receptors is believed to reduce aqueous humour formation (Weinreb 1987). However, Betaxolol - a $\beta_1$-selective β-blocker - also causes an adequate decrease in intraocular pressure (Stewart et al. 1986). The question thus arises wether it is the $\beta_1$- or the $\beta_2$-blocking effect that causes intraocular pressure to decrease? Does the ciliary epithelium contain $\beta_1$-receptors? Answers to these and other questions will contribute to clarification of the problem of aqueous humour formation.

## 2.4 OPTIC NERVE

### 2.4.1 Macroscopic anatomy

The optic cup is initially connected to the brain via the optic stalk. With the constant increase in the number of nerve fibres growing in the direction of the brain, the inner wall of the optic stalk increases in size and inner and outer leaf fuse. The cells of the inner layer then form a network of neuroglia cells. The optic stalk becomes the optic nerve (fasciculus opticus ), i.e. essentially an extension of the white matter of the brain.

The length of the optic nerve from the lamina cribrosa to the optic chiasm ranges from 35 to 55 mm. The site of entry into the eye is 3 mm medial to the posterior pole.

In the orbit and the optic canal the optic nerve is enveloped by the dura

mater, arachnoid and pia mater. These membranes are continuous with those of the brain and have the same structure.

The following parts of the optic nerve may be distinguished (Hayreh 1978a):

1. An intracranial part.
2. An intracanalicular part.
3. An intraorbital part, with:
   a) An anterior orbital segment (the anterior part of this segment is known as retrolaminar region of the optic nerve).
   b) A posterior orbital segment.
4. An intraocular part (optic nerve head), with:
   a) A surface nerve fibre layer.
   b) A prelaminar region.
   c) A lamina cribrosa region.

The intraorbital and the intraocular part of this optic nerve are subject to pathological changes in glaucoma.

### 2.4.2 Microscopic anatomy

The surface nerve fibre layer comprises the optic nerve fibres as they converge from the retina to the optic nerve head. This layer is separated from the vitreous body by the inner limiting membrane of Elschnig, which consists entirely of astrocytes (Anderson 1970). At the site of the physiological cup this layer may be thickened, in which case it is called the central meniscus of Kuhnt.

In the prelaminar region the nerve fibres extend in bundles enveloped by tube-like glial channels which consist of specialized astrocytes known as spider cells (Anderson 1969). This glial tissue forms trabeculae within which capillaries extend (Hayreh 1978a).

In the central part one finds a depression which corresponds with the physiological cup. The depth of this cup can vary considerably and extend as far as the lamina cribrosa (Hayreh & Vrabec 1966).

At the edges the intermediary glial tissue of Kuhnt demarcates the bound-

ary from the retina, and Jacoby's layer that from the choroid. Both tissues consists of astrocytes arranged in columns around the optic nerve (Hogan et al. 1971).

The lamina cribrosa consists of a network of compact connective tissue, of largely transverse arrangement. Thick columns link it peripherally to the retina and centrally to the vessels (Hayreh 1978a). The extracellular matrix comprises collagen types I, II and IV as well as laminin (Hernandez et al. 1986, 1987). The amount of elastic material may vary (Anderson 1969).

The lamina cribrosa constitutes a sieve with numerous perforations through which the nerve fibre bundles pass. The perforations are circular and oval-shaped and vary in size. The nerve fibre bundles are enveloped by a continuous glial membrane which separates nerve tissue from connective tissue (Hayreh 1978a).

The function of the lamina cribrosa is to reinforce the site of entry of the optic nerve and to provide support to the nerve fibre bundles (Hogan et al. 1971).

As a result of myelination the retrolaminar, intraorbital part of the optic nerve is twice as thick as its intraocular part. The membranes enveloping the optic nerve at this level are pia mater, arachnoid and dura mater. Here, too, the nerve fibre bundles extend in a network of connective tissue which is peripherally linked to the pia mater, centrally with the blood vessels and anteriorly with the lamina cribrosa. The nerve fibre bundles pass through polygonal perforations and are separated from the connective tissue by astroglia cells.

### 2.4.3 Arterial vascularization of the anterior part of the optic nerve

The vascularization of the anterior part of the optic nerve has been described in detail by Hayreh (1962, 1963, 1966, 1969, 1970, 1975a, 1975b, 1978a, 1980, 1985). Despite considerable interindividual variation the following basic pattern seems to be present in the majority of cases.

The lamina cribrosa region is supplied with blood from centripetal branches of the short posterior ciliary arteries; occasionally, blood is supplied from the arterial circle of Zinn and Haller. The central retinal

artery has no ramifications in this region.

The prelaminar region is vascularized by centripetal branches from the peripapillary choroid. The choroid is supplied from the posterior ciliary arteries, and in some cases branches from the lamina cribrosa contribute to the vascularization of this region.

As a rule there are two or three posterior ciliary arteries which arise from the ophthalmic artery. Dependent on their position in relation to the optic nerve, they are called medial and lateral posterior ciliary artery. Each supplies half the choroid and optic nerve head, the distribution usually being vertical. The vascularization in the prelaminar part, like that in the laminar part, is segmental; in this region, too, the central retinal artery does not ramify.

The surface nerve fibre layer receives blood from the retinal arterioles - usually branches from the peripapillary region. In addition, the temporal sector of the optic nerve head may be supplied from the prelaminar region.

The capillaries of the optic nerve head anastomose posteriorly with those of the prelaminar part and anteriorly with those of the peripapillary retina, but not with those of the choriocapillaris.

The anterior segment of the intraorbital part of the optic nerve is supplied from two vascular systems:

1. The axial centrifugal vascular system. In 75% of optic nerves studied the intraneural part of the central retinal artery ramifies in this region (Hayreh 1978a).
2. The peripheral centripetal vascular system. These vessels are found in 100% of cases and are made up of:
   a) Recurrent pial branches from the peripapillary choroid.
   b) Pial branches from the central retinal artery.
   c) Pial branches from the collateral branches of the ophthalmic artery.

### 2.4.4 Autoregulation of the retinal and optic nerve circulation

The presence or absence of autoregulation in the vasculature of the retina and optic nerve is of relevance in theories on the pathogenesis of glaucomatous damage.

Autoregulation may be regarded as the ability of blood vessels to maintain the blood flow at decreasing perfusion pressure. The rule of thumb is that perfusion pressure equals the difference between mean arterial pressure and intraocular pressure. Indications of the existence of autoregulation can be obtained by measuring the blood flow at diminishing perfusion pressure. This diminution is achieved by reducing arterial pressure, increasing intraocular pressure, or a combination of these.

That the retinal circulation has adequate autoregulation may be concluded from the following studies, using different parameters of blood flow:

1. **Radioactively labelled microspheres.** The distribution of the microspheres as a function of intraocular pressure shows that the retinal blood flow is independent of intraocular pressure (Alm & Bill 1973).
2. **Unlabelled microspheres.** The blood flow in the retinal circulation remains constant until the perfusion pressure has decreased to about 28 mm Hg (Geijer & Bill 1979). Dependent on the position of the body, the normal perfusion pressure value is 55-70 mm Hg (Bill 1978).
3. **The luminal diameter of retinal arteries as a function of intraocular pressure.** The luminal diameter of retinal arteries increases as intraocular pressure increases, in normal eyes as well after sympathetic denervation. This is suggestive of local autoregulation independent of innervation (Russel 1973; Wilson et al. 1981).
4. **Blue-field entoptic phenomenon.** A test subject is enabled to observe the motion of leucocytes in the macular capillaries. The speed at which the leucocytes move provides as measure for blood flow. These studies have shown that retinal blood vessels are capable of maintaining a totally undisturbed blood flow at intraocular pressures of about 6-30 mm Hg (Riva et al. 1981; Grunwald et al. 1982, 1984).

The question whether such autoregulation exists in the optic nerve cannot be unequivocally answered. One of the problems that confront investigators is the fact that the circulation in the optic nerve originates from at least two systems (2.4.3). Alm & Bill (1973) studied blood flow using labelled microspheres and found that an increase in intraocular pressure gave rise to a significant decrease in the blood flow in the choroid and prelaminar region. They concluded from this finding that this part of the optic nerve has

no autoregulation. On the other hand, Geijer & Bill (1979) demonstrated with the aid of unlabelled microspheres that the blood flow in the prelaminar part of the optic nerve does have autoregulation.

The oxygen tension in the anterior part of the optic nerve as a function of perfusion pressure in Rhesus monkeys show that a decrease in the latter pressure leads to rapid stabilization of the former, on the basis of a mechanism of autoregulation (Ernest 1974, 1975, 1976).

Recent research into the relationship between the amplitude of the visual evoked response and intraocular pressure revealed the following. Proceeding from an intraocular pressure within physiological limits, an increase in this pressure causes a decrease in the VER amplitude. From an intraocular pressure of about 30 mm Hg on, however, a plateau phase ensues during which the amplitude remains constant or even increases again. Intraocular pressures of 60 mm Hg or over consistently cause decreased VER amplitudes. These findings might suggest the presence of autoregulation in the anterior part of the optic nerve (Pillunat et al. 1985a, 1985b, 1986, 1987) (see also 'Electrodiagnostical tools' (3.7)).

### 2.4.5 Pathogenesis of optic nerve damage

Generally speaking there are two concepts of explaining the pathogenesis of glaucomatous changes in the optic nerve:

1. The vasogenic concept.
2. The mechanical concept.

#### 2.4.5.1 Vasogenic concept

This concept proceeds from the postulate that the changes in the optic nerve result from decreased arterial circulation, i.e. from ischaemia. This ischaemia is caused by a decrease in perfusion pressure, due either to an increased intraocular pressure or decreased blood pressure, or a combination of these (Hayreh 1980). Some indications in support of this concept may be listed:

**1. Fluorescein fundus angiography.** Talusan & Schwartz (1977) demonstrated

that in the heterogenous patient population they studied, only patients with chronic open-angle glaucoma and those with sectoral anterior ischaemic opticoneuropathy showed absolute filling defects in the optic disk. Loebl & Schwartz (1977) demonstrated that patients with ocular hypertension showed a higher incidence of filling defects in the optic disk than did non-glaucomatous normotensive patients. The incidence of filling defects in glaucomatous eyes was found to exceed that in eyes with ocular hypertension (Schwartz et al. 1977).

These authors conclude that the blood supply to the optic nerve is disturbed in open-angle glaucoma and ocular hypertension.

2. **Peripapillary choroidal changes.** The incidence of peripapillary atrophy is higher in open-angle glaucoma and ocular hypertension than in non-glaucomatous normotensive eyes (Airaksinen et al. 1987). Because the blood supply to the pre- and retrolaminar parts of the optic nerve partly originates from the peripapillary choroid, atrophy in this region must affect the circulation in the optic nerve.
3. **Splinter hemorrhages.** The literature contains varying reports on the prevalence of splinter hemorrhages on the optic disk. Susanna et al. (1979) reported a prevalence of 36.9% in primary open-angle glaucoma, and of 8% in ocular hypertension. Kitazawa et al. (1986) found a prevalence of 4.2% in primary open-angle glaucoma, 20.2% in low-tension glaucoma, 0.5% in ocular hypertension, 0.4% in non-glaucomatous normotensive eyes and 0% in primary angle closure glaucoma. The incidence of these splinter hemorrhages was determined by Gloster (1981) and found to be 30% in primary open-angle glaucoma. Susanna et al. (1979) as well as Hayreh (1985) believe that these splinter hemorrhages are caused by small local microinfarcts. Spaeth (1986) maintains that they may also be explained mechanically.
4. **Low-tension glaucoma.** Although low-tension glaucoma is regarded as a separate entity and shows subtle differences in optic nerve morphology from primary open-angle glaucoma (Caprioli & Spaeth 1985), a common pathogenetic basis may probably be assumed to exist (Lewis et al. 1983; Hayreh 1987). High incidences of cardiovascular diseases (Hayreh 1987), peripapillary choroidal and optic disk filling defects (Geijssen et al. 1985) and splinter hemorrhages (Gloster 1981; Kitazawa et al. 1986) in low-ten-

sion glaucoma indicate the likelihood of a vascular pathogenesis. It is virtually impossible to explain low-tension glaucoma in mechanical terms.

5. **Systemic blood pressure.** It is an established fact that an acute decrease in blood pressure may lead to (further) glaucomatous dysfunction. This seems even more evident in glaucoma patients with arterial hypertension (Kolker 1978; Hayreh 1985). The extent to which non-glaucomatous normotensive eyes are likewise susceptible to this acute decrease in blood pressure remains obscure. Drance (1966) reported that haemodynamic crises as a result of acute blood loss can lead to ischaemia of the optic nerve. This was not confirmed in a prospective study by Jampol et al. (1978).
   The importance of systemic blood pressure seems more pronounced in low-tension glaucoma. Drance et al. (1973) and Goldberg et al. (1981) found a higher incidence of low arterial pressure in patients with low-tension glaucoma than in those with primary open-angle glaucoma.
6. **Optic disk cupping in anterior ischaemic opticoneuropathy (AION).** Hayreh (1975b, 1980, 1985) reported that the majority of patients with an AION resulting from temporal arteritis develop an optic disk cupping indistinguishable from glaucomatous disk cupping. Others, however, report that they have never seen optic disk cupping after AION (Maumenee 1977).
7. **Cavernous atrophy.** Histological examination of monkey eyes with induced glaucoma reveals cavernous or lacunar atrophy in the retrolaminar part of the optic nerve (Kalvin et al. 1966). The cavernous spaces are filled with a hyaluronidase-sensitive acid mucopolysaccharide (Zimmerman et al. 1967). Hayreh (1969) postulated that this cavernous atrophy results from ischaemia caused by increased intraocular pressure. This is further emphasized by the histological findings in AION, which show changes consistent with cavernous atrophy in the retrolaminar part as well (Hayreh 1975b). He therefore maintains that, analogous to cavernous degeneration of the brain in chronic ischaemia, the circulatory disturbances in the peripapillary choroid lead to ischaemia and hence to retrolaminar cavernous atrophy (Hayreh 1980).
8. **Autoregulation of the optic nerve vasculature.** As described in subsection 2.4.4, the correlation between the amplitude of visual evoked responses and intraocular pressure warrants the conclusion that the anterior part of the optic nerve also has autoregulation. Studies by Pillunat et al.

(1985a, 1985b, 1986, 1987) have shown that the typical amplitude curve is not found in glaucoma patients. The autoregulation pathway is lacking both in primary open-angle glaucoma and in low-tension glaucoma. Perhaps glaucoma patients lack the autoregulation mechanism of the anterior part of the optic nerve.

#### 2.4.5.2 Mechanical concept

Since the intraocular pressure plays a key-role in the definition of glaucoma, a mechanical concept of the pathogenesis of optic nerve damage seems to present itself as well. Indications in support of this arise from the following studies:

1. **Histology of the lamina cribrosa.** Histological examination has revealed that damage to the optic fibres occurs at the level of the scleral lamina cribrosa. The earliest lesion consists of disappearance of neural tissue with intact astrocytes and capillaries. As the disease progresses, the lamina cribrosa shows backward and lateral bowing. An increasing cupping is not caused by degeneration of astrocytes, nor by enlargement of the scleral canal (Quigley & Green 1979; Quigley et al. 1981).
2. **Morphology of translaminar channels.** The organization of ganglion cell axons in the retina and the anterior part of the optic nerve shows that paracentral scotomata and Bjerrum's scotomata are explained by dysfunction of the superior and inferior quadrants of the optic nerve (Radius & Anderson 1979, 1981). Consistent with this are findings in the lamina cribrosa, showing that the translaminar channels are largest in these quadrants and that the laminar sheets are very thin. Consequently these two quadrants are most susceptible to mechanical pressure (Quigley & Addicks 1981; Quigley et al. 1981, 1982).
3. **Early histological findings.** The earliest histological findings in the lamina cribrosa proper is compression of the sheets, resulting in a decrease in total thickness. This occurs even before any visual field defect develops. The abovementioned backward and lateral bowing occurs in a later phase.

   Parallel with this the number of neurons diminishes, the decrease being

most marked in the superior and inferior quadrant. A loss up to 50% of the neurons is believed not necessarily to lead to clinically detectable visual field defects (Quigley et al. 1983). It is in particular the large optic nerve fibres that are lost first (Quigley et al. 1987).

4. **Loss of blood vessels.** Although the above findings strongly accentuate compression of tissues, it is not clear wether the damage to the nerve fibres occurs directly or via interference with the blood supply. Induced glaucoma in primate eyes and also findings in human eyes reveal that there is no disproportionate loss of blood vessels in the anterior part of the optic nerve with the progression of glaucomatous damage (Quigley et al. 1984).
5. **Blood flow.** Measurement of blood flow in the optic nerve with labelled tritium iodoantipyrine gives a true reflection of the flow without direct interference with it. Such flow measurements were carried out in simian eyes with induced chronic open-angle glaucoma and revealed no change in flow with the increase in intraocular pressure. Only when the pressure exceeded 75 mm Hg did a progressive decrease in flow occur (Quigley et al. 1985).
6. **Axoplasmic transport.** Because axons lack synthetic activity, they are dependent on axoplasmic transport for suppletion of proteins and other molecules as well as for maintenance of their axoplasm, axolemma and synapses. This transport takes place in two directions: orthograde axoplasmic transport from cell body to synapse, and retrograde axoplasmic transport towards the cell body. Orthograde axoplasmic transport comprises a rapid (100-500 mm/day), an intermediate (5-50 mm/day) an a slow (0.4-5 mm/day) component. The rate of retrograde axoplasmic transport is 50-260 mm/day (Bunt & Minckler 1982).

   Orthograde axoplasmic transport may be studied with the aid of labelled amino acids; retrograde axoplasmic transport with the aid of horseradish peroxidase.

   The relationship between increased intraocular pressure and axoplasmic transport has been studied in detail in simian eyes in which acute or chronic glaucoma had been induced. The following findings were obtained:

   a. Both the rapid and slow component of the orthograde axoplasmic transport show a block at the level of the lamina cribrosa. This block is

partial at moderately and complete at markedly increased pressures (Anderson & Hendrickson 1974; Levy 1974; Minckler et al. 1976; Gaasterland et al. 1978).

b. Retrograde axoplasmic transport likewise shows a block, the intensity of which also depends on the degree and duration of increased intraocular pressure (Minckler et al. 1977).

c. This axoplasmic transport block is reversible and disappears after reduction of pressure (Levy 1974; Quigley & Anderson 1976).

d. The block is not evenly distributed over the optic nerve but is more pronounced on the temporal (Minckler et al. 1977) and on the polar side (Quigley & Anderson 1977).

e. A simultaneous study of the behaviour of capillaries and axoplasmic flow reveals that the collapse of capillaries and the axoplasmic block are localized at different sites in the lamina cribrosa. This argues against a vascular cause of the axoplasmic transport block (Minckler et al. 1977).

f. In particular the retrograde axoplasmic transport block is most pronounced in the peripheral axons of an axon bundle, i.e. axons localized in the immediate vicinity of capillaries and therefore in a vascular safe zone. The fact that precisely these axons are involved, argues against a vascular cause.

g. Studies of this axoplasmic transport block under hyperbaric oxygen conditions reveal no difference from the block in eyes dissected under physiological oxygen conditions (Quigley et al. 1980).

h. An increase in intraocular pressure causes indentation of the axon by glial tissue and collagen. An axoplasmic transport block is observed at the site of this indentation - a finding arguing strongly in favour of a mechanical origin of the block (Minckler & Ogden 1987).

To summarize: axoplasmic transport studies indicate the likelihood of a mechanical pathogenesis of damage to the optic nerve.

#### 2.4.5.3 Conclusion

The pathogenesis of damage to the optic nerve may be explained in vascular

as well as in mechanical terms. There is sufficient evidence in favour of both concepts, and arguments in favour of one concept often do not exclude those in favour of the other. Analogous with other chronic diseases, primary open-angle glaucoma may also be regarded as a condition of multifactorial origin (Graham 1978), in which both mechanical and vascular factors play a role. Bill & Sperber (1987) assume that glaucoma with a relatively low intraocular pressure (<25-30 mm Hg) is probably due mainly to a vascular insufficiency, in some cases perhaps combined with a week lamina cribrosa. Intraocular pressures between 30 and 40 mm Hg will in particular cause mechanical damage, and even higher pressures will add ischaemia as complicating factor.

Further research will have to disclose the extent to which each of the concepts contributes to the pathogenesis, and whether a complete synthesis may be found.

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# CHAPTER 3

# METHODS OF EXAMINATION AND DIAGNOSTIC FEATURES IN GLAUCOMA

## INTRODUCTION

This chapter describes findings at ophthalmological examination which point in the direction of glaucoma, with special reference to open-angle glaucoma.

The various diagnostic aids are discussed in separate sections, always bearing in mind that the diagnosis 'glaucoma' cannot be made until after integration of all findings.

The discussion of patient characteristics in Chapters 5 and 6 will regularly refer back to this chapter.

This section discusses some findings obtained in routine ophthalmological examination and possibly suggestive of glaucoma. Routine diagnostic work also includes taking the history, determination of optimal visual acuity and slit-lamp examination.

It is an established fact that patients with open-angle glaucoma may be free from symptoms for considerable time. Yet it is of great importance to take the history if there is a suspicion of glaucoma, because there may be anamnestic indications of the type of glaucoma involved as well as of the presence/absence of detectable causes. If the intraocular pressure (IOP) rises rather abruptly to 40-50 mm Hg, the patient may experience this as painful. The localization of the pain is indicated in the eye or the superior part of the orbit. Unilateral headaches, too, may point in the direction of increased IOP.

Complaints about visual acuity as rule occur as a late symptom of glaucoma. In cases of this kind extensive damage to the nerve fibre layer already exists. Occasionally the presence of a Bjerrum scotoma may cause complaints about visual acuity. The most common cause of such complaints, however, is the corneal oedema resulting from a fairly acute increase in IOP.

Although a halo may be observed in association with several ophthalmological diseases - e.g. uncorrected errors of refraction and nuclear lens sclerosis - this phenomenon may also indicate glaucoma. Particularly in subacute chronic angle-closure glaucoma and in glaucomatocyclitic crises, this is frequently observed; but also in young patients with open-angle glaucoma whose IOP may initially be very high.

Black outs have been described in patients with glaucoma and homolateral carotid artery insufficiency, in whom the diminished circulation in the optic nerve may reduce visual acuity.

Apart from these more or less specific complaints, questions are always to be asked concerning other ophthalmological lesions and eye operations, traumata and inflammations. The history is completed by questions about other diseases or complaints, use of medication, and family history.

Slit-lamp examination may contribute to differentiation between various types of glaucoma. For example a shallow anterior chamber and narrow irido-

corneal angle suggest angle-closure glaucoma, and Krukenberg's spindles on the corneal endothelium indicate the possibility of pigmentary glaucoma. However, slit-lamp examination as a rule reveals no abnormalities in primary open-angle glaucoma.

## 3.2 TONOMETRY

### 3.2.1 Biophysical aspects

An increased IOP as such is not conclusive of glaucoma. The same applies to other diagnostic aids, however, and it is evident that the diagnosis 'glaucoma' cannot be made until the findings of various examinations are integrated. Nevertheless, tonometry (rightly) has a central position in the diagnosis of glaucoma. It is a simple, rapid, inexpensive test and it may be maintained in general that glaucomatous damage correlates with the degree and duration of increased IOP (Krieglstein 1980).

The only totally reliable method of measuring IOP would be open manometry - a technique which of course cannot be clinically applied. Efforts have been made to find indirect ways of estimating IOP, and the current tonometers are all based on the closed manometry principle. It should be borne in mind, however, that the contact of the tonometer with the eyeball causes volume displacement and therefore a change in pressure. The IOP measured is therefore always higher than the true IOP.

The principle on which most tonometers are based is application of a force to the eye and measurement of the resulting deformation of the eyeball. This is done in two different ways:

1. A constant force is applied to the eye and the deformation is measured **(indentation tonometry).**
2. A standard deformation of the cornea is effected and the force required for this is measured **(applanation tonometry).**

The most commonly used indentation tonometers are based on the Schiötz principle. Because the indentation depends directly on the rigidity of the eyeball (which is not clinically measurable), this type of tonometry yields

too high or too low values in the case of abnormal rigidity.

Goldmann's applanation tonometry was an important advance in the development of tonometry. Again one is confronted with the elasticity of the cornea, which counteracts applanation. In addition, however, the capillary activity of the tear film applies suction to the tonometer, which promotes applanation. These antagonistic forces cancel each other at a tonometer diameter of about 3 mm. In that case the total intraocular volume displacement amounts less than 1 µl, whereas in indentation tonometry the volume displacement may be 10-60 µl. The true IOP is about 0.98 times the IOP measured by applanation tonometry (Draeger & Jessen 1978; Chandler & Grant 1979a; Krieglstein 1980).

### 3.2.2 Clinical aspects

The course of IOP is characterized by **fluctuations in height**, the time factor of which can range from less than a second to several hours. Rapid pulsatory changes occur synchronously with the heartbeat, and the amplitude of the IOP then varies from 0.5 to 7 mm Hg (Leydhecker 1976). Perkins & Phelps (1984) found no significant difference in the mean height of this amplitude between non-glaucomatous normotensive eyes and eyes with primary open-angle glaucoma (POAG) or low-tension glaucoma. Slower oscillations (4-20 sec) are caused by respiration and vasomotor waves (Krieglstein 1980).

The diurnal rhythm is superposed on these rapid changes. This diurnal rhythm is of clinical importance for several reasons. Drance (1960) found that the peak pressure in normotensive non-glaucomatous eyes as well as in eyes with POAG occurred in 60% of cases at a time outside the regular working hours of an ophthalmologist. Measurement of a statistically normal IOP, therefore, by no means excludes the possibility of periods of increased IOP. The reverse may likewise occur. Kitazawa & Horie (1975) reported the occurrence of decreases in IOP during the night and early morning hours, 12 of 27 eyes with POAG they examined having an IOP below 20 mm Hg.

Another important clinical fact is that the difference between peak pressure and through pressure is much larger in glaucomatous eyes than in non-glaucomatous eyes (Drance 1960). Kitazawa & Horie (1975) found that in nor-

mal eyes this difference averaged 6.5 ± 0.28 mm Hg, with a maximum of 11 mm Hg. In a group of eyes with POAG, however, this difference averaged 15.6 ± 1.7 mm Hg, with a maximum of 34 mm Hg. Of course the peak pressure in eyes with POAG (37.6 ± 4.28 mm Hg) was much higher than that in normal eyes (17.0 ± 0.8 mm Hg). Precisely in cases of glaucoma, therefore, one should be prepared for peak pressures with sometimes very high values.

Finally it should be borne in mind that the difference in IOP between the two eyes of the same individual may be substantial, and that this difference is larger in glaucomatous eyes (Davanger 1965). Nevertheless the diurnal rhythm in both eyes is highly symmetrical and the effect of any therapy can be assessed only if this is applied unilaterally, the contralateral eye being used as control (Kitazawa & Horie 1975).

Apart from these more or less intrinsic fluctuations there are also **extrinsic** factors determining the variations in IOP.

Tarkkanen & Leikola (1967) demonstrated that the height of IOP depends on the **position of the body**. Proceeding from a sitting position the IOP will rise when the patient reclines. A Trendelenburg position of 30-75° causes a further increase in IOP, caused by increased venous pressure.

Using a scleral contact lens connected with a pressure transducer, Miller (1967) demonstrated that the **lid pressure** during normal periodic blinking amounts to about 10 mm Hg. Keeping the eyes closed with the eyelids firmly compressed can cause a lid pressure of 51 mm Hg.

**Repeated measurements** of IOP within a brief space of time (once per minute during 5 minutes) leads to a significant decrease in IOP. A prolonged tonometer/cornea contact time likewise causes a decrease in IOP (Wilke 1972).

**Exhausting exercise** has an ocular hypotensive effect (Lempert et al. 1967; Passo et al. 1987). This occurs during the exercise and continues for some time after its completion. The degree and the duration of the decrease in IOP are more pronounced in glaucomatous than in non-glaucomatous eyes (Lempert et al. 1967).

**Condition training** causes a significant decrease in baseline IOP but does result in a lower (exercise) decrease in pressure (Passo et al. 1987).

**Cigarette smoking** increases IOP. Proceeding from the assumption that an increase by 5 mm Hg within 5 minutes of the last puff is significant, this response is found in 11.4% of a group of non-glaucomatous eyes and in 37.1%

of glaucomatous eyes. This difference is significant (Mehra et al. 1976).

Of several **climatological parameters** (atmospheric pressure, clouding, relative humidity of the air, mean temperature, maximum temperature, minimum temperature, rain, hours of sunshine, wind velocity), only atmospheric pressure and relative humidity prove to exert a significant effect on IOP. The IOP decreases with increasing atmospheric pressure and increases with increasing relative humidity. Multiple regression analysis has shown, however, that the influence of these factors on individual IOP variations is only minimal (Jonas et al. 1986).

### 3.3 GONIOSCOPY

Gonioscopy is the principal aid in differentiating between different forms of glaucoma. Both in primary and in secondary glaucoma gonioscopy yields highly relevant information on the configuration of the iridocorneal angle and possible details of the component parts.

In principle, there are two types of gonioscopy:

1. Direct gonioscopy with the aid of, say, a Koeppe gonio-lens.
2. Indirect gonioscopy with the aid of a mirror contact glass.

Both methods give a good picture of the angle of the anterior chamber, and the choice of technique depends on the preference and experience of the investigator.

The following is a step-by-step description of a systematic examination of the angle of the anterior chamber.

**1. Evaluation of angle width.**

Since on the basis of pathophysiology, aetiology and therapeutic implications open-angle and closed-angle forms of glaucoma are distinguished, estimation of the width of the iridocorneal angle is an essential feature in gonioscopy. The distinction between open-angle and closed-angle as such is inadequate, because there are many transitional forms. A clinically adequate grading system was evolved by Shaffer (1962) and is shown in table 3.1.

Table 3.1. Shaffer grading system of angle width. (after: Shaffer, R.N.: Gonioscopic Anatomy of the Anterior Chamber of the Eye. In: Stereoscopic Manual of Gonioscopy by Shaffer, R.N. The C.V. Mosby Company, Saint Louis, 1962.).

| Angle Grade | Angle Width | Numerical Grade | Clinical Interpretation |
|---|---|---|---|
| Wide open angle | 45°-35° | Grade 4 | Angle closure is not possible |
| | 35°-20° | Grade 3 | Angle closure is not possible |
| Narrow angle | 20° | Grade 2 | Angle closure is possible |
| Narrow angle, extreme | 10° or less | Grade 1 | Angle closure is probable |
| Narrow angle, slit | The angle is critically narrowed, quite possibly against the trabecular meshwork beyond Schwalbe's line | | |
| Narrow angle, in part or totally closed. | 0° | Grade 0 | Angle is partial or complete closed |

In association with the width of the angle the shape of the iris at the site of its insertion on the ciliary band should always be described as well. A slightly convex shape is characteristic of the normal physiological situation. Pronounced convexity is usually observed in hypermetropic eyes, and in a number of these cases the iris may occlude the angle of the chamber. In myopic and aphakic eyes, however, the iridal root is flat. A concave shape of the iris can be found after posterior uveitis and after a vitrectomy via the pars plana; it is caused by contraction of cicatricial tissue behind the iris (Chandler & Grant 1979b).

2. **Structures in the angle.**

Four essential structures can be distinguished in the angle: Schwalbe's line, trabecular meshwork, scleral spur and ciliary band. The normal features of these structures have been described in subsection 2.2.1. Gonioscopy should be used to look for glaucoma-specific features of these structures.

Prominence of Schwalbe's line as such is not generally related to glaucoma. This mildest form of iridocorneal dysgenesis without concomitant lesions is observed in adults as well as in children with and without glaucoma. Only if this prominence is associated with adhesions between the peripheral iris and cornea, alone or in combination with pupillary abnor-

malities, should one be mindful of the possibility of glaucoma (Chandler & Grant 1979b).

The most conspicuous aspect of the trabecular meshwork is its degree of pigmentation. Scheie (1957) assigned to this degree of pigmentation values ranging from score 0 (total absence of pigment) to score +4 (maximum pigmentation). The latter is observed in the pigment dispersion syndrome, although in cases of pseudo-exfoliation glaucoma the trabecular meshwork may also be markedly pigmented (Hoskins 1980).

When the scleral spur is clearly visible allround in a patient with glaucoma, the diagnosis 'open-angle glaucoma' is very plausible. A very prominent scleral spur, however, may indicate a posttraumatic condition.

3. **Iridal structures in the angle.**

The distinction between iris processes and peripheral anterior synechiae is very important. As already mentioned, iris processes have the same structure as the iris and their frequency and form vary from eye to eye. They occur in normal non-glaucomatous as well as in glaucomatous eyes (Lichter & Shaffer 1970).

Peripheral anterior synechiae on the other hand show a more solid structure and often present as non-perforated structures covering the trabecular meshwork. They are always acquired and their possible causes include traumata, inflammations, rubeosis, chronic angle-closure glaucoma, essential iridal atrophy and mesodermal dysgenesis (Mandell 1978). These peripheral anterior synechiae may also be observed after operations (Chandler & Grant 1979b) and following argon laser trabeculoplasty (Traverso et al. 1984).

4. **Blood vessels in the angle.**

The presence of blood vessels in the angle does not as such indicate a pathological situation. Normal blood vessels include the circumferential arterial circle in the iridal root, and the radial vessels in the iridal stroma (Hoskins 1980). If there is neovascularization, this often takes the form of vessels arising from the ciliary body and covering iridal and angle structures. They form an irregular network (not arranged strictly radially or circumferentially) and are not covered by iridal stroma.

## 3.4 OPHTHALMOSCOPY

It is evident that assessment of the optic disk is among the most valuable methods in the clinical evaluation of glaucoma or glaucoma suspect. The predictive value of a 'glaucomatous' disk for occurrence of visual field defects, however, is neither 100% specific nor 100% sensitive (Sommer et al. 1979b). In all cases the diagnosis is clinched by a combination of more or less specific characteristics of the disk, in combination with the results of other diagnostic tests/examinations. Some of the specific glaucoma characteristics are discussed in the following subsections.

### 3.4.1 Cup/disk ratio

There are two ways of quantifying the cupping of the optic disk. One may proceed from the colour of the cup, i.e. the central pallor of the disk (colour cup), or alternatively one may proceed from the boundaries of the cup as indicated by the kinking of the blood vessels (contour cup). For several reasons the use of the contour cup is preferable to the use of the colour cup. The contour cup reflects the true size of the cupping, whereas the colour cup is only a colorimetric indication of it. Colour cup and contour cup are virtually equal in size in normal non-glaucomatous eyes, whereas in glaucomatous eyes the contour cup is larger than the colour cup (Schwartz 1973). The colour cup underestimates the true size of the cupping because even in advanced cases of glaucoma the disk often retains a proper colour, particularly on the nasal side (Schwartz 1973). Estimation of the size of the cupping on the basis of colour can be impeded if there is concomitant peripapillary atrophy. The size of the colour cup is age-dependent, showing an increase with increasing age (Schwartz et al. 1973).

The progression of the cup/disk ratio is estimated better from the contour cup than from the colour cup (Yablonski et al. 1980).

**It can be stated in general that the colour cup underestimates the true cupping, and therefore the severity of the glaucomatous damage.**

The cup disk/ratio in a glaucoma patient should be related to the distribution of cup/disk ratios in a population. Armaly (1969) demonstrated that,

in a group of 1444 non-glaucomatous persons, the cup/disk ratio distribution showed a skewing towards low values. Some 82% of his study population showed a cup/disk ratio of 0.3 or less (horizontal cup/disk ratio). The cup/disk ratio increases with increasing age, but this effect can be ascribed largely to an increase in high intraocular pressures with increasing age. In the various age groups the cup/disk ratio proves to be dependent on the height of IOP (Armaly 1969).

**It may be concluded from the above that a cup/disk ratio of 0.4 or more may be indicative of glaucoma, but does not prove its presence.** Progression in the cup/disk ratio, however, is a much more reliable characteristic of the glaucomatous optic disk.

In a group of patients with ocular hypertension Motolko & Drance (1981) found that 31% of the subpopulation that ultimately developed visual field defects showed a progressive increase in cup/disk ratio as well (versus only 8% of the subpopulation without visual field defect). Sommer et al. (1979a) found progressive increase of the cup/disk ratio in 10 of 12 eyes with ocular hypertension, and in only 11% of a control group. Yablonski et al. (1980) found no difference in absolute progression of cup/disk ratio between patients who developed visual field defects, and patients who did not. The relative progression (as percentage of the initial value), however, did show a statistically significant difference. This is compatible with the findings of Motolko & Drance (1981) and Sommer et al. (1979a), who demonstrated that patients who develop visual field defects show not only progression of the cup/disk ratio but also a higher cup/disk ratio.

Beside the absolute value and progression of the cup/disk ratio, asymmetry in a patient also seems an important indication of the presence of glaucoma. Motolko & Drance (1981) found a cup/disk ratio asymmetry of at least 0.2 in 44% of eyes with ocular hypertension and visual field defect; this was found in only 24% of the eyes without field defects. The difference was not statistically significant, but indicative.

Yablonski et al. (1980) found a statistically significant difference in the incidence of cup/disk ratio asymmetry between eyes with ocular hypertension that did, and those that did not developed visual field defects. This difference was significant both for the horizontal and for the vertical cup/disk ratio, and for colour cup and contour cup. Inversely they found that a

cup/disk ratio difference of at least 0.2 is associated in 91% of cases with a visual field defect in the eye with the higher cup/disk ratio.

Kirsch & Anderson (1973) reported that asymmetry frequently occurs in glaucomatous eyes and is rarely seen in normal, normotensive eyes. Otherwise they denied the importance of this asymmetry by concluding that "....in all our cases with definite asymmetry the glaucomatous cupping could have been recognised by examination of the affected disc without comparison to the fellow disc". This can be explained from the patient selection in their study, which involved only "definitely glaucomatous eyes".

### 3.4.2 Localized notching of the neural rim

A localized narrowing of the neural rim is called a notch. A notch is usually localized on the superotemporal or inferotemporal side of the neural rim. If there is only narrowing of the neural tissue, the notch is described as incomplete; if no neural tissue is left, the term complete notch applies.

Hitchings & Spaeth (1976) described a subpopulation of glaucomatous eyes showing only focal notching of the neural rim, without distinct cupping of the remainder of the disk. In most cases the notch was localized in the inferotemporal quadrant. In this group of 23 eyes, 19 showed a nerve fibre bundle defect. In 1977 they published a continuation of this study, reporting that at that time all 23 eyes showed a nerve fibre bundle defect. In five classified subpopulations (cupping with or without neuroretinal rim pallor, overpass cupping, beanpot cupping and focal notching of the neuroretinal rim) the presence of a notch proved correctly to predict the presence of a nerve fibre bundle defect in 100% of cases.

Motolko & Drance (1981) found notching of the neural rim in 62% of hypertensive eyes with subsequent visual field defect, versus 16% of a control group. This difference was statistically significant.

### 3.4.3 Vertical ovality of cupping

In non-glaucomatous eyes the physiological cup is usually round and some-

times shows horizontally ovality (Kirsch & Anderson 1973). In a population studied by Weisman et al. (1973), 4% of the normal and 33% of the glaucomatous eyes proved to show vertical ovality of the cup (i.e. a difference of at least 0.2 between the vertical and the horizontal cup/disk ratio); a difference of 0.1 was found in as many as 60% of the glaucomatous eyes. In the case of unilateral visual field defect 21% of the unaffected eyes were found to show vertical ovality of the cup; this percentage is significantly larger than that in non-glaucomatous eyes. The incidence of vertical ovality depends on the cup/disk ratio: it is 25% with a ratio of 0.3-0.4 and 57% with a ratio of 0.5-0.6 (Weisman et al. 1973).

Gloster (1975) calculated an ovality ratio on the basis of the cup diameters. A value below 1.0 implies horizontal ovality, and one in excess of 1.0 indicates vertical ovality. In various series he found the following values: 0.96 for normal eyes, 1.06 for eyes with ocular hypertension, 1.05 for contralateral eyes of patients with unilateral POAG and 1.20 for eyes with POAG. These values indicate that early glaucomatous damage is associated with vertical cup elongation. A striking finding in this study was that the optic disk as such, too, is more oval-shaped in glaucomatous eyes (although the vertical elongation of the cup exceeds this value). Why the optic disk also becomes more oval-shaped remains obscure.

### 3.4.4 Optic disk haemorrhages

As already mentioned in subsection 2.4.5.1, the prevalence of optic disk haemorrhages reported in the literature is rather variable, ranging from 4.2% (Kitazawa et al. 1986) to 36.9% (Susanna et al. 1979). The incidence is about 30% (Gloster 1981).

The extent and intensity of haemorrhage varies from patient to patient and depends partly on the interval between onset of haemorrhage and its ophthalmoscopic detection. The majority of these haemorrhages are linear in shape and radially orientated, although occasionally they may be circular. They are usually localized on the neural rim between the boundaries of the optic cup and the optic disk. Sometimes they extend as far as the peripapillary tissue, but they always remain in touch with the disk. They are most fre-

quently found in the inferotemporal quadrant of the disk (Gloster 1981).

The occurrence of an optic disk haemorrhage seems related to the value of the vertical cup/disk ratio, a high cup/disk ratio giving a higher incidence of haemorrhages (Gloster 1981).

Motolko & Drance (1981) found an optic disk haemorrhage in 44% of 16 hypertensive eyes which subsequently developed a visual field defect, but in only 2.6% of a control group without visual field defect.

Drance et al. (1977) reported that the incidence of progressive visual field defects in eyes with POAG is significantly higher in the presence of an optic disk hemorrhage.

Tuulonen et al. (1987) compared a group of glaucomatous eyes with optic disk haemorrhage, with a group without haemorrhage but matched for diagnosis, disk appearance and visual fields. Their principal finding was that the two groups did not differ significantly in the rate of progression of glaucomatous damage to disk and visual field. This difference from earlier studies may be explained from the fairly unique way in which the control group was formed. Despite these findings, however, occurrence of an optic disk haemorrhage should be regarded as a risk factor (Tuulonen et al. 1987).

### 3.4.5 Pallor of the optic disk

Two forms of pallor of the optic disk should be distinguished. The first is the central pallor corresponding with the colour cup (see 3.6.1). The second is a more or less localized pallor of the neural rim.

Hitchings & Spaeth (1976, 1977) established that pallor of the neural rim has a high predictive value regarding visual field defects. Visual field defects were found in 60 out of 68 eyes showing this phenomenon. Proceeding from the ophthalmoscopic features the visual field defect was correctly predicted in 58 eyes.

An explanation of this pallor of the neural rim is to be found in a reduced blood supply to the optic disk. Yet the blood supply is not the only factor determining its colour. This is apparent from the fact that the temporal edge of the disk is usually slightly paler than the nasal edge, even though this area is well vascularized both from the retinal arterioles and

from the prelaminar region. Fluorescein fundus angiography sometimes reveals a quite adequate vascularization despite clinically evident pallor of the neural rim (Spaeth 1978).

It may be concluded that localized pallor of the neuroretinal rim is frequently associated with nerve fibre bundle defects and constitutes a reliable predictor of visual field defects.

### 3.4.6 Peripapillary atrophy

Peripapillary atrophy is a common finding in glaucomatous eyes, but little is known about its role in the progression of glaucoma. Yet both in clinical and in pathogenetic terms improved insight into the relationship between peripapillary atrophy and glaucoma is very important.

Kirsch & Anderson (1973) found that most glaucomatous eyes with advanced cupping show a peripapillary halo; on the other hand, normal eyes often show peripapillary atrophy or congenital crescents and rings which are not readily distinguishable from the glaucomatous halo.

Motolko & Drance (1981) found no statistical significant difference in incidence of peripapillary atrophy between hypertensive eyes which developed visual field defects, and eyes which did not.

Airaksinen et al. (1987), however, demonstrated that the incidence of peripapillary atrophy in eyes with POAG and ocular hypertension (39% and 37% respectively) significantly exceeds that in normal eyes (18%). They also demonstrated that the development of visual field defects is not dependent on the presence of peripapillary atrophy, and that the neural rim loss is not related to concomitant peripapillary atrophy.

It may be concluded that the presence of peripapillary atrophy constitutes no 'hard' evidence of glaucoma, although high myopia with the corresponding lesions in the posterior pole of course entails an increased risk for patients with glaucoma (Krupin & Podos 1978).

### 3.4.7 Overpass cupping

Overpass cupping is the term applied to that form of glaucomatous cupping

in which retinal vessels span the cup in the manner of a suspension bridge. As a result, the cup/disk ratio may well be underestimated (Hitchings & Spaeth 1976).

Overpass cupping is not pathognomonic of early glaucoma. The phenomenon can also be observed in optic atrophy due to neurological causes. However, it is more frequently observed in contralateral eyes of patients with unilateral POAG than in non-glaucomatous eyes (Spaeth 1978).

The explanation of this phenomenon is to be sought in the blood supply to the anterior part of the optic nerve. The surface nerve fibre layer is vascularized by retinal arterioles, while the prelaminar region receives blood from the posterior ciliary arteries. Proceeding from the assumption that increased IOP exerts a greater influence on the blood supply to the prelaminar region (autoregulation not yet demonstrated) than on the retina (autoregulation demonstrated), loss of prelaminar tissue can give rise to cupping, while the tissue bridge at the level of the surface nerve fibre layer remains intact (Spaeth 1978).

### 3.4.8 Previously described criteria

Two more or less classic characteristics of glaucoma - nasal displacement of the vascular tree and undermined disk margins - are also encountered in physiological situations and therefore do not constitute 'hard' evidence of the presence of glaucoma (Kirsch & Anderson 1973).

However, this applies solely to the isolated occurrence of these features. Spaeth (1978) also regards them as so-called 'soft' signs, but observes very rightly that they are very valuable if found in combination with other glaucomatous features.

## 3.5 PERIMETRY

Perimetry is of essential importance in glaucoma, both diagnostically and therapeutically. After all, visual field defect have of old been included in the glaucoma definition; and to the patient they are often the only subjec-

tive complaint.

The purpose of this section is not to present a complete review of perimetry but rather elucidate some aspects of perimetry of relevance to this thesis.

### 3.5.1 Procedure of examination

A distinction is made between kinetic and static perimetry. In the former the stimulus moves from the periphery towards the centre. Per measurement, the size and intensity of the object are constant and the stimulus position is variable. The advantage of kinetic perimetry is its swiftness; the disadvantages are largely determined by the variability of the speed and direction of object movements, which may cause a considerable standard deviation of results. The detection capacity of kinetic perimetry is lower than that of static perimetry (Aulhorn & Harms 1967; Greve 1978).

Static perimetry entails a constant stimulus position with variable luminance. This causes less standard deviation of results and higher sensitivity in detecting early visual field defects (Greve 1978). The examination may be made as single stimulus perimetry or as multiple stimulus perimetry. The latter technique saves considerable time, which is important particularly in the detection phase. Another way of saving time is by suprathreshold perimetry, using a stimulus luminance above the threshold value. In order to avoid false-positive and false-negative results it is important to ensure that the luminance throughout the field has an equal value above the threshold (Greve & Verduin 1977).

The instruments used to perform perimetry may be divided into manual, semi-automatic and automatic perimeters. In the past decade computerized perimetry in particular has come to the fore.

### 3.5.2 Detection and assessment

With regard to the position of perimetry in glaucoma mentioned in the introduction, a distinction can be made between a detection phase and an as-

sessment phase (Greve & Verduin 1977; Greve 1978, 1980a). In both phases perimetry has to fulfil certain criteria.

In the detection phase it is important to use a rapid, reliable technique that demonstrates even small glaucomatous visual field defects. The initial defects often consist of spot-like paracentral scotomas (Aulhorn & Harms 1967) and wedge-shaped defects (Greve & Verduin 1977). Kinetic perimetry is less suitable for their detection; the value of this type of perimetry in the detection phase lies in determining the shape and size of the blind spot and the peripheral visual field. Static perimetry, on the other hand, is far more suitable to detect these small defects. Greve (1980c) demonstrated that 120-150 stimuli within the 30° visual field are sufficient to detect defects of 3-5°. An additional number of stimuli is required to examine the nasal visual field.

An instrument very suitable for this detection phase is the Peritest (Greve 1980b). Using a multiple-stimulus, threshold-related suprathreshold technique, 157 stimuli are offered within the 25° visual field. The stimuli are 0.4 log in excess of the threshold value, which reduces the risk of false-positive and false-negative results. This technique is suitable for detection of defects measuring 3° or more. The Friedmann Visual Field Analyzer is an example of a manual multiple-stimulus static perimeter. The original version with 46 stimuli has been modified in several other versions, e.g. the 100-hole front plate (Friedmann 1977) and the Amsterdam front plate with 150 positions (Greve 1978).

When a glaucomatous defect is detected in the detection phase, the general implication is that the patient must remain under supervision for the rest of his life. Perimetry has become the pivot of investigation, and a stabilized visual field indicates that therapy is adequate. This assessment phase serves a dual purpose. To begin with, an attempt is made to describe the defect accurately; secondly follow-ups will have to show wether glaucomatous defect shows any progression. Kinetic perimetry is a suitable technique to establish the shape and size of the defect, but its standard deviation renders it less suitable for follow-ups. Unlike the detection phase, the assessment phase calls for single stimulus and threshold luminance perimetry (Greve 1980a).

### 3.5.3 Glaucomatous visual field defects

#### 3.5.3.1 Early defects

It is of paramount importance to detect the earliest glaucomatous defects. As long as there are no defects, after all, one is more reluctant to start pressure-reducing therapy than in the presence of a defect. It should be borne in mind, however, that there may be non-glaucomatous visual field changes which require no therapy (3.5.4). The following will show that detection of these early changes largely depends on the definition of a visual field defect and the technique used.

Greve & Verduin (1977) demonstrated that isolated kinetic perimetry failed to reveal early glaucomatous visual field defects (defined as wedge-shaped defects) as well as more advanced defects in 68% of cases. In this phase, kinetic perimetry is in fact subordinate to static perimetry.

Aulhorn & Harms (1967) and Drance (1969), using combined static and kinetic perimetry, established that the earliest defects are spot-like absolute scotomas in the Bjerrum area. The baring of the blind spot that was previously interpreted as characteristic, turned out to be detectable in virtually all persons (Drance 1969), and enlargement of the blind spot and contraction of the visual field, too, are neither early nor specific glaucoma features (Aulhorn & Harms 1967).

The question wether the nasal step is among the earliest glaucomatous defects and wether it is pathognomonic of glaucoma, receives no unequivocal answer in the literature. Aulhorn & Harms (1967) found a nasal step as first defect in only 0.5% of cases, but its frequency rose with increasing glaucomatous defects. Zingirian et al. (1979) used a modification of kinetic perimetry to demonstrate that 13 out of 20 eyes with ocular hypertension showed a nasal step, whereas routine perimetry revealed no defects. However, they regularly found an isolated nasal step also in normotensive eyes. Drance et al. (1979) found an isolated nasal step as first defect in 20% of cases; Leblanc & Becker (1971) reported the same in 11% of cases. According to Drance (1979) the earliest glaucomatous defects consists of a combination of isolated paracentral scotomata and a nasal step.

Using multiple-stimulus static perimetry, Greve et al. (1979) found that

the earliest defect often is a reversible wedge-shaped defect. An absolute scotoma may later develop at the site of this earliest defect.

Lichter & Standardi (1979) maintain that marked asymmetry between two eyes may be indicative of an early glaucomatous defect, even though this asymmetry as such need not be immediately regarded as pathological. A unilaterally enlarged blind spot in combination with isopter contraction could be regarded as such.

**It may be concluded that the chance of early detection of visual field defects depends on the methods and definitions used; that in the detection phase static perimetry is preferable to kinetic perimetry; and that early visual field defects may include marked asymmetry, spot-like paracentral scotomata, wedge-shaped defects and nasal steps, per se or in combination with absolute scotomata.**

### 3.5.3.2 Stages of visual field defect

On the basis of many static and kinetic perimetric studies, Aulhorn (1980) divided glaucomatous visual field defects into five stages. An advantage of this system is that it gives a good impression of the sequence of events and the rate of progression. The system is of course a simplification of reality but does not violate it.

Figure 3.1 presents the five stages described by Aulhorn and shows the course of an initial relative defect which ultimately results in a collapse of the central visual field. On the basis of these stages the sequence of events will be discussed step by step.

**Stage 1.**

The initial stage is characterized by a relative visual field defect, which is usually larger than the absolute defects in more advanced cases. Its localization is often near the centre, more often in the superior than in the inferior part of the visual field. Its shape is usually arcuate, and one should be aware of the possibility of a smaller absolute defect localized within the relative one.

In some cases a relative defect disappears and an absolute scotoma subse-

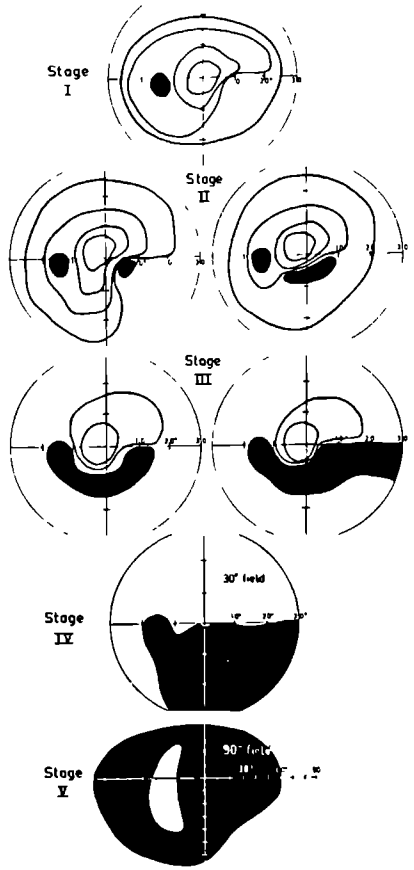


Figure 3.1. The five stages of development of glaucomatous visual field defect as described by Aulhorn (1980). As an example of the sequence of events, a beginning defect in the lower half of the visual field is shown. Stage 2 and 3 represent two possibilities for each stage (after: Aulhorn, E.: Comparative visual field study in patients with primary open angle glaucoma and anterior ischaemic optic neuropathy. In Greve, E.L. (ed.): Glaucoma Symposium. Diagnosis and Therapy. Amsterdam 1979. Doc. Ophthalmologica Proc. Series 22:3, 1980).

quently develops at this site (Greve et al. 1979). Aulhorn (1978) believes that only these small relative defects are reversible, but Iwata (1979) found that small spot-like scotomata and nasal steps may likewise disappear, if only transient.

**Stage 2.**

The first absolute defects may be small and round. Larger defects show a more arcuate shape. This stage is characterized by the fact that the scotomata are not linked to the blind spot. In some instances a larger relative defect may extend between the blind spot and absolute scotoma, but on the other hand the absolute scotoma may well be localized in an otherwise entirely normal visual field. Many patients show several small scotomata whose relative positions correspond with the course of the pericentral nerve fibre pathway.

These scotomata are characterized by the fact that they are localized relatively far from the blind spot, and move in its direction only as the defect progresses. This confirms the contention that enlargement of the blind spot cannot be regarded as conclusive of early glaucomatous visual field defect.

Aulhorn (1978) studied the positions of the scotomata in the visual field and found that the frequency distribution is virtually the same in the superior as in the inferior part of the field. He also found that the scotomata in the superior part show a more arcuate pericentral localization, that in the inferior part more scotomata are found in the nasal quadrant, and that the scotomata in the superior part are closer to the centre than those in the inferior part.

Kosaki (1979) studied the topography of scotomata in all glaucoma stages and established an overall predilection for the superior visual field, and especially the nasal quadrant. The inferotemporal quadrant often remains intact until the very last. A study involving a long-term follow-up of visual fields by computerized perimetry likewise revealed a predilection for the superonasal quadrant (Gloor et al. 1987). The even distribution reported by Aulhorn is probably due to the fact that only stage 2 patients participated in this part of his study.

**Stage 3.**

This stage is characterized by a classic Bjerrum scotoma. The small absolute scotomata of stage 2 have fused and are linked to the blind spot.

Bjerrum's scotoma is usually observed in the 10-20° visual field and has a narrow base near the blind spot, fanning out towards the centre.

Aulhorn maintains that this is the first phase in which a nasal step may be observed but, as previously noted, not all investigators agree with this. A progressive increase in disappearance of nerve fibre bundles is clinically characterized by defects in the nasal visual field - a phenomenon known as nasal breakthrough.

**Stage 4.**

There is a gradual transition from stage 3 to stage 4, and it may be maintained that stage 4 begins when a scotoma loses its arcuate shape. The superior and the inferior visual field are usually both affected, and visual complaints may develop. Central vision is not affected and visual acuity therefore remains unchanged.

**Stage 5.**

This ultimate stage is characterized by collapse of the central visual field.

The above division is base on perimetric findings obtained in over 18,000 persons, including at least 6000 glaucoma patients or glaucoma suspects. This is by no means the only conceivable classification, but it is one that, because of its relative simplicity and especially because of its sequential character, enhances our insight into glaucomatous visual field defects.

### 3.5.4 General considerations on the glaucomatous visual field

#### 3.5.4.1 Age-related changes of the normal visual field

Using kinetic perimetry, Drance et al. (1967) demonstrated that both the central and the peripheral visual field show a linear surface area diminu-

tion with increasing age. This effect is measurable from the age of 10-20 years on. The blind spot shows significant enlargement with increasing age. Since these findings were obtained in mydriasis, the effect cannot be ascribed to miosis.

More advanced techniques of examination revealed the following: using automated static perimetry, Haas et al. (1986) found a significant decrease in mean sensitivity with a linear course of about 0.58 dB loss per decade. This decrease begins at an early age. There are topographic differences, the centre and the periphery showing a greater decrease than the pericentral region. Haas et al. ascribed these findings to increasing turbidity of the media as well as changes in the sensory system.

In addition to this linear decrease in mean sensitivity Jaffe et al. (1986) also found a linear loss of surface area as well as volume of the visual field with increasing age. Unlike Haas et al., Jaffe et al. found a linear decline in topographic terms, with a mean loss of 0.0015 dB per year per degree of excentricity. A possible explanation might be that the rate of ganglion cell loss is the same throughout but is less quickly noticed at the centre due to the one-to-one linking of ganglion cells and photoreceptors.

Haas et al. as well as Jaffe et al. demonstrated that the superior visual field shows a more marked decline in sensitivity than the inferior field.

### 3.5.4.2 Visual fields, glaucoma and cataract

Niesel et al. (1978) demonstrated that cataract formation in non-glaucomatous patients can lead to visual field changes, more specifically isopter contraction and loss of central isopters.

Greve (1980c) showed that the static sensitivity curve is not only lowered but also flattened. At kinetic perimetry this flattening may lead to pseudodefects. In cases of glaucoma with concomitant cataract, therefore, static perimetry (more especially large-stimulus static perimetry) is to be preferred.

A general decline of sensitivity and loss of central isopters is to be ascribed more to the cataract than to the glaucoma in concomitant cases. A local decrease in sensitivity should be ascribed to the glaucoma. In terms of

technique of examination, it should be ensured that the pupil has a minimum diameter of 2.5 mm (Greve 1980c).

### 3.5.4.3 Rate of progression of glaucomatous field defects

It is an established fact that normalization of IOP in cases of POAG does

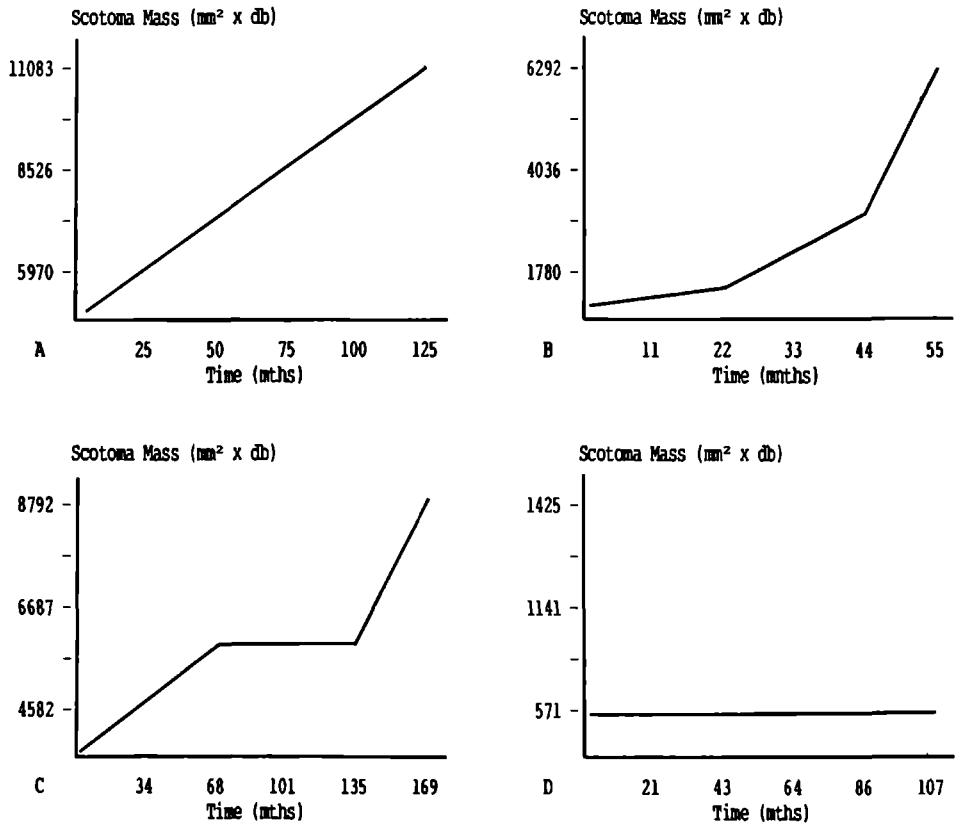


Figure 3.2. Progression in four representative patients illustrated in graphs of scotoma mass over time. A. Linear progression. B.Curvilinear progression. C. Episodic progression. D. No significant progression. (after Mikelberg, F.S., Schulzer, M., Drance, S.M., and Lau, W.: The rate of progression of scotomas in glaucoma. Am. J. Ophthalmol. 101:1, 1986).

not guarantee prevention of further visual field defects (see later). The rate of progression of visual field defects can vary considerably from patient to patient. Mikelberg et al. (1986) found four different forms in which this progression manifests itself (figure 3.2A through D). In a series of 45 eyes with POAG they observed linear progression in 49% after a mean follow-up of 91.2 months (fig. 3.2A), curvilinear progression in 20% (fig. 3.2B), episodic progression in 7% (fig. 3.2C) and no significant progression in 24% (fig.3.2D). The mean scotoma mass was significantly lower in the curvilinear than in the linear group. There was a highly significant correlation between the mean scotoma mass and the rate of progression, implying that eyes with larger scotomata show a higher rate of progression.

Granström (1985) demonstrated that progression of visual field defects is significantly more frequent as the defect at initial examination is larger.

Wilson et al. (1982) had previously shown that the rate of progression of visual field defects to a pre-determined ultimate stage indeed depends on the initial situation. In addition they found that the rate of progression is higher in males, higher if there is a positive glaucoma family history, and higher as the initial IOP is higher. There was no demonstrable correlation between the rate of progression of visual field defects on the one hand, and age and systolic blood pressure on the other.

**To summarize: the rate of progression of visual field defects is dependent on the degree already developed, and possibly related to age, family history and IOP.**

### 3.5.4.4 Glaucomatous visual field defects an intraocular pressure

The risk of development of visual field defects is small at a moderately increased IOP (Armaly & Sayegh 1969; Kitazawa et al. 1977), but increases as the IOP increases (Odberg & Riise 1987).

There is no unequivocal answer to the question of what happens with the visual field after pressure-reducing therapy in the case of manifest glaucoma. In an exhaustive review of the literature, Pohjanpelto (1985) found that progression of visual field defects occurs in an average of 50% of glaucoma patients after surgery and/or medication. His own study revealed progression

in 70-80% of eyes with POAG or pseudo-exfoliation glaucoma after a mean follow-up of 9 years. An interesting finding was that there was no significant difference in mean IOP between the group that did and the group that did not show progression.

Multiple correlation analysis applied to 81 eyes revealed no significant correlation between mean IOP and progression of visual field defects; however, this correlation became unmistakably significant when the standard deviation of IOP was included in the results (Niesel & Flammer 1980). This might warrant the conclusion that the peak pressures which occur exert more influence than the mean IOP.

The lastmentioned finding appears to be contradicted by the results reported by Radius & Maumenee (1977) in 16 eyes with angle-closure glaucoma and temporarily very high IOP, in whom they were unable to detect glaucomatous visual field defects. However, since IOP is totally normal between attacks (unlike the pressure in POAG), the results of this study must not be compared with those of the abovementioned studies.

The fact that the result of a pressure-reducing intervention in visual field terms depends on the damage already inflicted, needs no further argumentation. It is clearly illustrated by the study of Aggerwal & Hendeles (1986), who found that normalization of IOP after trabeculectomy performed on eyes with marked glaucomatous lesions does not guarantee that the central visual field is spared.

## 3.6 TONOGRAPHY AND PROVOCATIVE TESTS

### 3.6.1 Tonography

In 1950 Grant introduced tonography as a method of measuring aqueous humour dynamics. Using a continuous electronic Schiötz tonometer, Grant was able to estimate the facility of outflow and the rate of aqueous flow.

In 1951 Grant published a monumental study comprising over 1000 tonographic findings obtained in normal eyes and in various forms of glaucoma. He demonstrated the clinical applicability of his method and contributed to the clarification of the pathophysiology of various forms of glaucoma and the

mechanism of action of various surgical and pharmacological therapies. He demonstrated, for instance, that resistance to outflow rather than aqueous humour formation is increased in virtually all forms of glaucoma. The decrease in facility of outflow in POAG was so consistent a finding that Grant believed it possible to discriminate between glaucomatous and normal eyes solely on this basis. He showed that the facility of outflow decreased very markedly during an attack of angle-closure glaucoma, and returned to normal after the attack. He demonstrated that the effects of various operations and miotic medications are based on an increased facility of outflow.

It is quite evident that this study and subsequent studies have greatly contributed to our current glaucoma concept.

What is the position of tonography in the current approach to glaucoma? Apart from critical remarks on the technical aspects of tonography (Fisher et al. 1970; Fisher 1972; Dueker 1978; Armaly 1984), objections may be raised concerning the validity of its results. If a patient shows an increased IOP in combination with glaucomatous cupping and visual field defects, is it really necessary to demonstrate that this is caused by a decreased facility of outflow? And is it necessary to demonstrate that the decrease in IOP upon miotic medication results from an increased facility of outflow?

The severity of glaucoma cannot be assessed from the value of the facility of outflow. Fisher et al. (1970) demonstrated that facility of outflow correlates less with visual field defects than tonometry. Tonography does not seem to supply any additional information.

Does tonography have predictive value regarding future increases in IOP or visual field defects? Graham (1978) found no correlation between the initial facility of outflow value and the behaviour of IOP over a follow-up period of 2-3 years. Wilensky et al. (1974) performed a prospective study of the values of various methods of examination used in cases of ocular hypertension, and their correlation with visual field defects. They demonstrated that a facility of outflow lower than 0.15, although reasonably sensitive, has a low specificity; in other words: the risk that an eye with a facility of outflow below 0.15 and ocular hypertension will subsequently develop glaucoma is small.

The result of the water drinking test - increased IOP - is reasonably

sensitive but has a low specificity (Odberg & Riise 1987). Determining the facility of outflow after the water drinking test adds nothing to the test result (Kronfeld 1975).

It may be concluded that, although tonography has enhanced our understanding of glaucoma, its current clinical value for the individual patient is only relative (with a few exceptions). However, tonography can be an important aid in the evaluation of new therapeutic techniques.

### 3.6.2 Provocative tests

The purpose of using provocative tests in glaucoma research should be to discriminate between patients who do and those who do not develop visual field defects. This should apply in particular to patients with increased IOP without other evident glaucomatous damage (ocular hypertensives or glaucoma suspects).

The battery of such provocative tests so far developed encompasses the water drinking test, the pilocarpine test, the epinephrine test, the fluorescein angiography provocative test, the elevation of venous pressure test, the phenylthiocarbamide taster test and the corticosteroid provocative test The value of the corticosteroid provocative test will be discussed in some detail because this test is regarded as the one most widely used.

After topical application of corticosteroids during a certain time (generally 4-6 weeks), the following effects can be measured:

1. Non-glaucomatous normotensive eyes show an increase in IOP above the group median (Armaly 1963a; Becker & Mills 1963). There seem to be two subgroups: responders and non-responders. Responders (IOP 21 mm Hg and over) account for 30% of the entire group. The responder/non-responder ratio is age-related, the proportion of responders increasing with increasing age. Above the age of 40 the responder rate is 44% (Becker & Mills 1963).

   The increase in IOP is parallelled by a decrease in facility of outflow (Armaly 1963a; Becker & Mills 1963).

   Perimetry in this group shows that no changes are generally observed be-

fore the age of 40; above this age, however, the size of the blind spot increases and there is constriction of the I/2 isopter (Armaly 1964).

2. Patients with ocular hypertension or glaucoma suspects likewise show the abovementioned changes in IOP and facility of outflow. In this group, however, these changes are more pronounced (Becker & Mills 1963). Again there are responders and non-responders, some 25% of the patients responding with an increase in IOP by at least 5 mm Hg (Dean et al. 1975). As the IOP increases typical glaucomatous visual field defects may develop (Kolker et al. 1964).
3. Glaucomatous eyes nearly always show a marked increase in IOP and a decrease in facility of outflow after corticosteroid provocation (Armaly 1963b; Becker & Mills 1963). Perimetry often shows increased scotomata (Armaly 1964; Kolker et al. 1964), although this is not an obligatory finding (Kolker et al. 1964).
4. The hypertensive effect of corticosteroids is reversible and generally measurable after a short time (Armaly 1963a; Leblanc et al. 1970). The visual field defects are likewise reversible, but the recovery period may be as long as 4 months. The increase in IOP should at least be 8 mm Hg before a defect occurs (Hart & Becker 1977).
5. On the basis of the diversity in IOP responses Becker et al. (1964, 1965, 1970) believed that a recessively transmitted corticosteroid response could be described. This would mean that three subgroups might be distinguished: non-responders (nn), moderate responders (ng) and responders (gg). Glaucoma patients would be mainly responders,and glaucoma suspects for the most part moderate responders.

Despite the above described differences between normal eyes, eyes of glaucoma patients and eyes of glaucoma suspects, one continues to be confronted with the individual patient. In other words: what is the predictive value of the corticosteroid response? Investigations into this question are impeded by the fact that only a minority of patients with ocular hypertension ultimately develop glaucoma, and often not until after a long period of time. A prospective study by Odberg & Riise (1987) revealed that the steroid provocative test is of hardly any importance as predictor of early glaucoma (i.e. increased cup/disk ratio and/or visual field defect). A response of, say,

+10 mm Hg after steroid provocation was seen no more frequently in the group subsequently developing glaucoma. The same applies to the pilocarpine test.

It can be stated that the sensitivity of most provocative test is reasonable, but their specificity is low. Consequently their predictive value is low. Kitazawa et al. (1977) found 100% sensitivity for the corticosteroid provocative test, at a specificity of only 40%. Should all responders be treated as future glaucoma patients, therefore, then a large group would indeed be given unnecessary therapy.

## 3.7 ELECTRODIAGNOSTICAL TOOLS

Application of electrophysiological tests in clinical diagnosis and evaluation of therapy of glaucoma has so far been limited, but in terms of scientific experiments the findings are undoubtedly of importance (see 2.4.4).

### 3.7.1 Pattern reversal evoked responses (PVER)

Pillunat et al. (1985a, 1985b, 1986, 1987) studied the correlation between perfusion pressure and amplitude of PVER. The perfusion pressure was reduced by step-wise raising of IOP using a suction cup. Since there is considerable interindividual variation in the absolute value of the amplitude, this is expressed in percents, proceeding from an initial amplitude of 100%. According to Pillunat et al. the correlation between IOP and PVER amplitude can be used to differentiate between non-glaucomatous eyes (fig 3.3A), eyes with POAG (fig. 3.3B) and eyes with low-tension glaucoma (fig. 3.4).

As IOP increases, non-glaucomatous eyes initially show a rapid decrease in PVER amplitude to 50% of the initial value at an IOP of about 30 mm Hg. The amplitude then stabilizes or even shows some increase, until the IOP attains about 60 mm Hg. At the moment the noise level is attained, the IOP amounts to 80-90 mm Hg.

Eyes with POAG initially show a less rapid decrease in PVER amplitude, which is still about 90% at an IOP of 50 mm Hg. Next comes a rapid decrease which ends at a noise level when the IOP is about 80 mm Hg. There is no plateau phase.

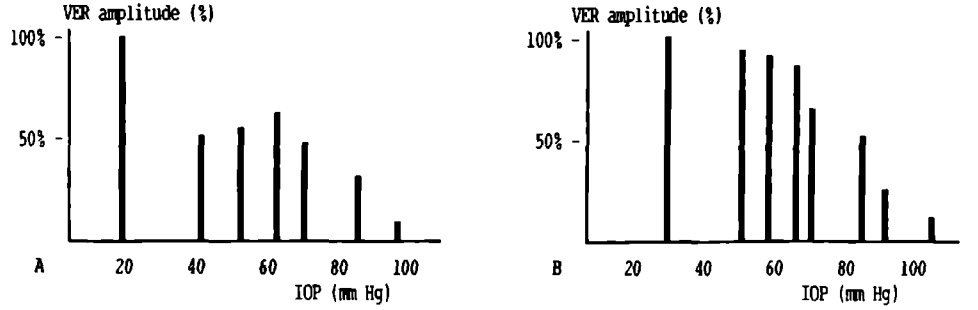


Figure 3.3. Visual evoked response amplitude plotted against intraocular pressure for A. a healthy eye and B. an eye with POAG. (after Pillunat et al. 1985a, 1985b, 1986, 1987).

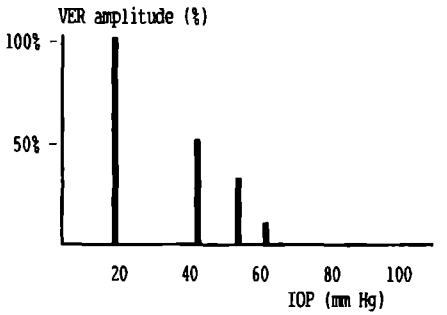


Figure 3.4. Visual evoked response amplitude plotted against intraocular pressure for an eye with low-tension glaucoma (after Pillunat et al. 1985a, 1985b, 1986, 1987).

In low-tension glaucoma the initial decrease more or less parallels that in non-glaucomatous eyes. Again there is no plateau phase, and the noise level is attained at an IOP of about 70 mm Hg.

Pillunat et al. derived two conclusions from these results. To begin with, the plateau phase which characterizes normal eyes may indicate the presence of an autoregulation mechanism in the anterior part of the optic nerve. This

mechanism is believed to be lacking in patients with POAG and low-tension glaucoma. Secondly, low-tension eyes could have a lower pressure tolerance at the level of the optic nerve than normal eyes with POAG.

### 3.7.2 Pattern reversal electroretinogram (PERG)

Van lith et al. (1984) found that the PERG of glaucomatous eyes had a significant lower amplitude and longer latency than that of normal eyes. A striking finding was that these results did not correlate with visual field defects, nor with IOP. However, a lower coefficient of correlation (0.28) was found for the correlation between PERG and cup/disk ratio. This is possibly explained by the fact that only cases of not very advanced glaucoma were included in this study.

Papst et al. (1984) believed they could describe a correlation between PERG amplitude and IOP. IOP values in excess of 30 mm Hg were always related to low amplitudes. Artificial reduction of IOP caused an increase in potential into the normal region. In the case of unilateral ocular hypertension, reduction of IOP did cause an increase in PERG amplitude but still below that in the unaffected eye. These PERG changes may indicate diminished autoregulation in the retina.

Recent reports (Wanger & Persson 1987; Korth et al. 1987) mention a decreased PERG amplitude and increased latency (Korth et al. 1987) with increasing age.

After correction of PERG results for age, glaucomatous eyes, and possibly also eyes with ocular hypertension, showed a significantly lower PERG amplitude than normal, non-glaucomatous eyes (Wanger & Persson 1987; Korth et al. 1987).

Moreover, Korth et al. (1987) found a correlation between the decrease in amplitude on the one hand, and on the other hand an increase in cup/disk ratio, increased visual field defects and a decreased temporal neuroretinal rim in glaucomatous eyes. However, the sensitivity of the PERG in detecting glaucomatous damage is low (50%).

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# PART II

# CHAPTER 4

# ARGON LASER TRABECULOPLASTY
# A REVIEW

## INTRODUCTION

In 1979 Wise & Witter published their first, preliminary results obtained by Argon Laser Trabeculoplasty (ALT) used as a pressure-reducing therapy in glaucoma. Their publication prompted application of this technique on a larger scale.

The current position of ALT in the treatment of glaucoma largely depends on the objective one seeks to achieve. ALT is being applied as an alternative to surgical intervention, as initial therapy, as an alternative to medication, and as adjuvant to medication. It is beyond argument that highly adequate medical and surgical techniques are available to reduce intraocular pressure (IOP). A review of these techniques would be beyond the scope of this thesis, but in the following chapters references will be made to prospective, randomized studies comparing ALT with medical and surgical techniques of treating glaucoma.

The advantages of ALT are simplicity of procedure - permitting its use in an out-patient setting - and the fact that it hardly interferes with the patient's general daily activities. In addition, ALT is relatively inexpensive and, if correctly indicate and performed, effective. It will be subsequently shown that ALT is not without side effects and complications, and cannot always obviate surgical intervention.

On the basis of data from the literature this chapter presents an up-to-date outline of ALT. The tables referred to are presented in an appendix to this chapter.

Table 4.1 presents a survey of the studies discussed in the following review.

In 1973 Krasnov reported some results of laser therapy in primary open-angle glaucoma (POAG). He made use of the laser property of producing not only a coagulating but also a perforating effect (micropuncture). Because coagulation causes cicatrization and (according to Krasnov) reduces outflow if applied to the trabecular meshwork, he started looking for a laser which combined a maximal perforating and a minimal coagulating effect. This he found in the Q-switched ruby laser with an ultra-short pulse time of $10^{-9}$ sec. With this laser he attempted to create a direct link between the anterior chamber and Schlemm's canal (Laser Trabeculopuncture). Nine of the ten patients this treated showed a significant fall in IOP (averaging 6.3 mm Hg). This decrease became manifest 1-4 days after treatment and persisted from 1 week to 6 months. Retreatment again produced a transient decrease in IOP. The use of the argon laser produced a less marked decrease in IOP which lasted less long, caused more inflammatory symptoms and required retrobulbar anaesthesia. Krasnov concluded from these results that it would be premature to start using the laser clinically on a larger scale.

Likewise in 1973 Hager published his results, but unlike Krasnov he did make use of the coagulating effect of laser. He performed trabeculopunctures with the aid of a continuous wave argon laser, using a power of about 1000 mW and an exposure time of 1-3 sec. In this way he attempted to create 1-3 trabeculopunctures. Of 28 eyes thus treated, 13 (46.4%) proved to show adequate regulation of IOP after a follow-up of at least 4 months. Hager concluded that it should be possible on a limited scale to ensure adequate IOP regulation by means of these trabeculopunctures, but that on the other hand damage might be inflicted on tissues due to the long exposure time involved.

Gaasterland & Kupfer (1974) demonstrated the possibility of inducing glaucoma in normal Rhesus monkey eyes by intensive coagulation of the trabecular meshwork. They used numerous burns in a procedure in which the total energy invested could be as high as 80 Joules.

Wickham et al. (1977) likewise observed diminished outflow after argon laser manipulation of the trabecular meshwork. In addition, however, they dis-

covered that the effect produced depends largely on the energy level involved (total energy = number of burns x exposure time x power). Exposing the trabecular meshwork in simian eyes to the total energy of 1.5 J resulted in an increase in outflow, while a total energy of 41 J caused a decrease in outflow.

Using a continuous wave argon laser, Ticho (1977) applied about 50 burns to 60° of the trabecular meshwork (spot size 50 µm, exposure time 0.1 sec, power 1000-3000 mW). Some of the eyes thus treated showed an initial decrease in IOP, but generally this persisted only a short while.

Stiegler (1979) used a pulsed argon laser and punctured the trabecular meshwork about 40 times in one quadrant. He reported a success rate of 81% in patients with POAG.

De Heer & Peperkamp (1979) obtained good results using a variable exposure time. They found that results in patients treated with short exposure times and high intensity (0.05 sec, 2000 mW) were better than those obtained with long exposure times at low intensity (0.1 sec., 700 mW).

The above studies would seem to indicate that results obtained by a number of techniques were promising but that optimal treatment parameters were still to be established unequivocally. **The minimum requirements to be met by laser therapy were: a short exposure time, treatment of a larger part of the trabecular meshwork, and investment of a relatively low level of total energy in the trabecular meshwork.** The question arises wether the parameters used by such investigators as De Heer & Peperkamp (1979) could in fact lead to perforation of the trabecular meshwork; in other words: was trabeculopuncture really involved?

Wise & Witter (1979) selected their parameters on the basis of a pathophysiological glaucoma model. They postulated that in the case of glaucoma the trabecular meshwork has collapsed, causing an increased resistance to outflow and therefore an increased IOP. Making superficial burns in the trabecular meshwork will cause shrinkage of the collagenous core of the laminae, and secondary retraction due to cicatrization. The intertrabecular space will be enlarged, and resistance to outflow decreases. This effect was described as tightening effect, and this form of treatment was initially known as Laser Trabeculo Tightening (Wise 1981). Later, the designation Argon Laser Trabeculoplasty (ALT) was generally accepted.

The technique applied by Wise & Witter might be described as the **Standard Wise ALT**. After local anaesthesia, 100 burns were applied to or immediately posterior to the pigmented trabecular meshwork, using a 50 μm beam diameter, 0.1 sec exposure time and a power setting of 1000-1500 mW. Pigment dispersion and gas bubble formation were chosen as criteria for a good burn. After-treatment consisted of application of eyedrops containing antibiotics.

The results of this therapy were promising. Of 41 phakic eyes with POAG, 38 (92.7%) proved to have an IOP of 20 mm Hg or lower after 3-6 months. The mean decrease in IOP was 10.29 mm Hg at an initial IOP of 26.46 mm Hg. Only one eye subsequently required pressure-reducing surgery.

After a period of 12 months, 21 of the 23 eyes followed up (91.3%) still had a regulated IOP with an unchanged decrease in IOP (mean decrease 10.64 mm Hg).

Results were decidedly less good in a smaller group of aphakic eyes, but nevertheless 8 of the 15 eyes treated were spared pressure-reducing surgery after a follow-up of at least 6 months.

Wise & Witter concluded that the results of this pilot study were promising but that further, more detailed investigations were required to establish whether this technique would be eligible for general practical use.

After this publication research into various aspects of ALT has taken a much wider scope. Several of these aspects will be discussed systematically in the following sections.

## 4.2 RESULTS OF ALT IN PHAKIC OPEN-ANGLE GLAUCOMA

### 4.2.1 Standard Wise ALT as secondary therapy

Table 4.2 presents a compilation of the studies to be discussed in this section.

The results to be discussed were obtained in studies using the Standard Wise ALT, i.e. 100 burns applied to the pigmented part of the trabecular meshwork or immediately posterior to it over a distance of 360° in one session, with a 50 μm beam diameter, 0.1 sec exposure time and a power setting of about 1000 mW.

For several reasons (some of which are mentioned in the table), comparison of the results of the various studies requires great prudence:

1. Although most of the results were obtained in prospective studies, some retrospective studies were included as well (Horns et al. 1983; Lieberman et al. 1983; Tuulonen & Airaksinen 1983a). This methodologically different basis is of course important in interpreting, in particular, the follow-up results.
2. The type of glaucoma may also vary. Some studies are limited to POAG, whereas others also describe other forms of open angle glaucoma (OAG).
3. The number of eyes treated ranges from 19 (Schultz et al. 1987) to 237 (Thomas et al. 1982) and this affects statistical analysis. Moreover, the number of patients included in a study is often smaller because ALT was applied bilaterally. This is a possible source of distortion of the results, particularly because the exact sequence of bilateral treatment is not always described. One may expect that the worst eye is treated first, and that the indication for treatment of the other eye depends on the results obtained in the first. This may imply a form of selection in that bilateral treatment is confined to cases in which the first treatment was successful. It would be better to randomize patients with bilateral glaucoma for ALT of only one eye. An alternative is to include only the eye treated first in the presentation of results, and to discuss the bilaterally treated patients separately.
4. Comparison of the absolute and relative decreases in IOP should always be correlated with the initial IOP because these are not independent variables (see later).
5. The criteria for success may differ in different studies. Because the indication for ALT was made in all cases as an alternative to surgical intervention, success may be defined as actual obviation of surgery (Wilensky & Jampol 1981; Horns et al. 1983; Demailly et al. 1985). Other criteria may be added in that success is defined as an IOP which is 21 mm Hg or lower during at least one year, without additional medication and without further damage to the optic disk and visual field (Tuulonen & Airaksinen 1983a). The consequence is that success rates on the basis of different success criteria can hardly be compared and that the success

rates reported depend largely on the success criteria accepted. This is illustrated by the study of Wilensky & Jampol (1981), who reported that ALT obviated surgery in 100% of cases. Applying the additional criterion that the ultimate IOP should be 21 mm Hg or lower, however, one would find a success rate of only 54.5%.

Bearing the above considerations in mind, we find that the IOP decrease that can be achieved by Standard Wise ALT ranges from 19.5% at an initial IOP of 21.7 mm Hg (Traverso et al. 1986) to 43.2% at an initial IOP of 28.4 mm Hg (Wise 1981). The success rate ranges from 65.4% on the basis of strict criteria (Tuulonen & Airaksinen 1983a) to 100% on the basis of milder criteria (Wilensky & Jampol 1981). These results were recorded after a specified follow-up period and therefore warrant no conclusion on a possible reduction of the IOP decrease or the success rate in the subsequent course of time.

The IOP decrease is already considerable 1 week after ALT, but seems complete after 4-8 weeks (Schwartz & Kopelman 1983; Bergeå 1984; Weinreb et al. 1983b). Nevertheless individual patients who show no initial reaction may have a decrease in IOP after a few weeks (Wise 1981; Wilensky & Jampol 1981)

### 4.2.2 Standard Wise ALT as primary therapy

Table 4.3 presents the results of ALT applied as primary therapy in newly diagnosed glaucoma. The parameters of the Standard Wise ALT were fully adopted by Thomas et al. (1984), Tuulonen (1984) and (except for a beam diameter of 100 µm) Rosenthal et al. (1984). The additional success criterion applied by these authors was that the IOP decrease after ALT should persist without further medication.

The IOP decrease achieve in these cases slightly exceeds that achieved by ALT as secondary therapy. However, if we relate this decrease to the higher initial IOP in these patients, then the IOP decreases in both groups are of the same magnitude. This is illustrated by the IOP decrease in the study of Tuulonen (1984) - 30.1% at an initial IOP of 25.6 mm Hg - which corresponds entirely with the IOP decrease following secondary ALT given comparable initial IOPs (Horns et al. 1983; Lieberman et al. 1983; Schwartz & Kopelman

1983; Bergeå 1984).

The reported success rates range from 65% (Rosenthal et al. 1984) to about 80% (Thomas et al. 1984; Tuulonen 1984). The larger spot size in the study of Rosenthal et al. may have played a role in their lower success rate.

Since the results in the different studies again may be compared only with reservations, the results reported by Tuulonen et al. (1985) can be used to compare primary ALT with secondary ALT: these results pertain to similar study populations with a similar possible bias. One of the findings in this study of factors influencing ALT results was that ALT as primary therapy - i.e. in patients not given previous local or systemic treatment for the increased IOP - yields significantly better results than ALT as secondary therapy.

The following question now arises. What is the position of ALT in the treatment of glaucoma patients or glaucoma suspects? All patients in the abovementioned studies showed evident damage to the optic disk and glaucomatous visual field defects. The position of ALT in the treatment of glaucoma seems to have changed as experience has increased in the course of the years and as ALT has proved to be a relatively safe intervention. After all, why should patients first be adjusted to maximum medication, with the known possibility of many side effects and untoward effects? This seems to apply in particular to the use of carbonic anhydrase inhibitors.

One step further might be to resort to ALT for patients with a number of glaucoma-specific features but without visual field defect. Likewise, patients with an increased IOP without other glaucoma characteristics but at an increased risk (e.g. in view of a positive family history) might be eligible for ALT. Because no pertinent data could be found in the literature, this subject will be given further consideration in the discussion of our own results. We have treated a number of patients with an increased IOP, with or without glaucomatous disk changes, but certainly without glaucomatous visual field defects.

### 4.2.3 Long-term results of Standard Wise ALT

Tables 4.4 and 4.5 respectively present the extent of the IOP decrease and

the success rate in relation to the follow-up period.

Interpretation of these tables should take into account that the patient population often diminishes as the follow-up period increases, and that the IOP decrease should always be related to the initial IOP in the subpopulation examined after a certain time.

Since for the results reported by Wise (1987) the initial IOP was not known for each subpopulation, the relative IOP decrease was determined proceeding from the initial IOP for the entire patient population (29.6 mm Hg). For the other studies, the relative IOP decrease was calculated on the basis of the initial IOP in the population involved.

Both Tuulonen et al. (1985) and Schwartz et al. (1985) reported results indicating that the IOP decrease becomes somewhat less marked as the follow-up period increases. That this phenomenon is not due to a lower initial IOP can be established by recalculation. In both studies, however, the patients with IOP decreases and the longest follow-up periods originated from subpopulations significantly smaller than the original population.

Pohjanpelto (1983) reported no diminishing tendency of the IOP decrease (either relative or absolute) with an increasing follow-up period. Wise (1987) found no diminishing tendency in the absolute decrease.

An explanation of these differences poses problems. A striking difference between the population studied by Schwartz et al. (1985) and the other study populations lies in the fact that the majority of the glaucoma patients in the former study were of the negroid race. In this study a significant difference in success rate existed between the white and the negroid patients. The extent to which this applies also to the IOP decrease remains obscure.

Another difference between the group who did and the group who did not show diminution of the IOP decrease is to be found in the initial IOP. The initial IOPs in populations with a diminishing tendency were 22.7 mm Hg (Tuulonen et al. 1985) and 24.8 mm Hg (Schwartz et al. 1985) respectively; those in the populations without a diminishing tendency were 27.6 mm Hg (Pohjanpelto 1983) and 29.6 mm Hg (Wise 1987) respectively. That a positive correlation exists between initial IOP and IOP decrease has already been noted and will be discussed in detail later. At odds with this is the fact that some authors report a lower success rate at higher initial IOPs (Schwartz & Kopelman 1983; Tuulonen et al. 1985; Moulin et al. 1987).

A third difference, finally, lies in inter-investigator differences in performing the Standard Wise ALT.

The literature shows a fair consensus about the success rate (table 4.5). The success rate diminishes as the follow-up period lengthens. Schwartz et al. (1981, 1983, 1985) reported a success rate of 46.3% after a follow-up of 5 years. It is to be noted that the white subpopulation had a success rate of 65%, while that of the negroid subpopulation was only 32% after 5 years. Using the Kaplan-Meier survival curve, Schwartz et al. calculated that the median time before an IOP exceeded 21 mm Hg was only 12 months in the negroid, and 60 months in the white subpopulation.

At odds with these findings are the results by Wise (1979, 1981, 1987), who found that the control rate (IOP less than 21 mm Hg) in negroid patients was 75% after 6 years (9 out of 12 eyes), 87% after 7 years (7 out of 8 eyes), 80% after 8 years (4 out of 5 eyes) and 100% (2 out of two eyes) after 9 and 10 years. However, Wise did confirm the diminishing tendency of the success rate. Nevertheless 7 out of 10 eyes treated are well-regulated after a follow-up of 10 years.

An alternative way of defining the success rate of ALT is to look at the annual rate of filtering surgery within a department after introduction of ALT. Martenet & Schwarzenbach (1986) found that the rate of filtering surgery during the first whole year after introduction of ALT diminished from 96 to 59. Gilbert et al. (1986) found an annual rate of filtering surgery of 16 before ALT was introduced; during the first year after introduction of ALT this rate was 1, after 2 years it was 12 and after 3 years it was 18. The authors conclude from these findings that "...ALT may be effective in delaying the need for surgery, but in many cases it probably does not prevent it...". Even though this conclusion may be quite correct in substance, two notes should be made: in this study the ALTs were performed by residents, which may have affected results (Khan et al. 1986), and the majority of patients treated were of the negroid race (75.0%).

It may be mentioned in passing that the success rate of filtering surgery (91%, Schoenleber et al. 1987) is not unfavourable influenced by ALT.

Several authors have compared ALT results with surgical results. In a randomized prospective study Watson et al. (1984) compared the results of ALT with those of trabeculectomy, using a modification of the Standard Wise ALT

by treating only one half of the trabecular meshwork, and the other half if necessary. Success was defined as a controlled IOP without further medication. After a follow-up of 6 months 10% of the ALT group required additional pressure-reducing surgery, while another 11.7% needed additional medication. In the trabeculectomy group only 6.3% required additional medication. In the ALT group the IOP decrease averaged 28.1% of an initial IOP of 28.8 mm Hg, while in the trabeculectomy group the IOP decrease averaged 51.3% of an initial IOP of 34.9 mm Hg. Watson et al. therefore concluded that, although ALT can effectively reduce the IOP, the IOP decrease is significantly less than that achieved by trabeculectomy.

Grehn & Schildwächter (1987) performed a non-randomized prospective comparative study of **ALT** and **goniotrephination**. They, too, used a modification of the Standard Wise ALT by treating only one half of the trabecular meshwork in two sessions. The study was not randomized because the functionally most affected eye was operated on. After a follow-up of 3-29 months they found an IOP decrease of 18.9% of an initial IOP of 26.5 mm Hg in the ALT group, versus 46.1% of an initial IOP of 29.7 mm Hg in the goniotrephination group. The success rate in the ALT group was 51.3%, versus 90.9% in the goniotrephination group. It should be pointed out that the ALT modification the used gives less good results - both in success rate and in IOP decrease - than the Standard Wise ALT (see 4.4). In the goniotrephination group cataracts developed in 4.5% of the patients and in 17.1% visual acuity was reduced by more than two lines; in the ALT group, no patient developed a cataract and visual acuity was reduced in only 6.9%. These authors concluded that goniotrephination is to be preferred if a marked IOP decrease is required (very high IOP or severe visual field defects) and that ALT is to be considered for eyes with still adequate vision.

In a randomized prospective study Migdal & Hitchings (1984) compared the results of **ALT**, **trabeculectomy** and **medication** in newly diagnosed glaucoma. After a 6-month follow-up they found an IOP decrease of 44.0% in the ALT group and of 53.6% in the trabeculectomy group, given the same initial IOP (33.6 mm Hg). The success rates were 73.3% for the ALT and 100% for the trabeculectomy group. They concluded that ALT as well as trabeculectomy are eligible for primary therapy in glaucoma, but that the latter should be reserved for the more advanced cases.

Wise (1987) rightly points out that ALT or trabeculectomy should be performed before serious damage to the optic disk develops. He regards the two techniques as complementary, ALT being indicated in moderate glaucoma, especially in patients over 60, and trabeculectomy in advanced glaucoma with poor patient compliance and at an age under 60.

**To summarize: the results of the Standard Wise ALT (including the long-term results) are fair, although the success rate tends to diminish somewhat with increasing time, and that the trend seems to be to carry out ALT in moderate glaucoma and resort to surgery in more advanced cases.**

## 4.3 COMPLICATIONS OF ALT

Table 4.6 presents a survey of the most common complications of ALT.
In virtually all cases mild **anterior iritis** characterized by a mild flare and cells occurs during the first week after ALT. This iritis generally disappears within a week. Most patients thus treated are given corticosteroid eyedrops to use during the first week, but even without these the iritis disappears spontaneously (Thomas et al. 1982).

**Severe iritis** develops only occasionally, the incidence generally being less than 1% (Wise 1981; Pohjanpelto 1983; Tuulonen & Airaksinen 1983a; Bergeå 1984). In two out of 22 eyes treated (9%) Wilensky & Jampol (1981) observed severe uveitis accompanied by an increased IOP and formation of peripheral anterior synechiae. In both cases the uveitis disappeared only after months of local and/or systemic therapy.

**Haemorrhages** occur in about 5% of cases; there is usually slight bleeding directly from the burn, but occasionally also from the area adjacent to the burn (Thomas et al. 1982). An additional burn at the site of the haemorrhage or slight pressure exerted with the contact glass generally stops bleeding (Wise 1981; Thomas et al. 1982; Schwartz & Kopelman 1983). The occurrence of haemorrhages is not related to the power setting nor to the presence or absence of blood in Schlemm's canal prior to treatment (Thomas et al. 1982). Reflux of blood from Schlemm's canal, as postulated by Wise (1981) and Lichter (1982), is therefore unlikely. Haemorrhages do not affect the IOP decrease or the success rate (Thomas et al. 1982; Schwartz & Kopelman 1983).

Some authors described the occurrence of **epithelial corneal burns**, which generally disappears within a few hours to days and have no apparent sequelae. Endothelial burns have not been observed.

The incidence of formation of **peripheral anterior synechiae (PAS)** ranges from 0.7% to 47.1%. These PAS usually extend between iris and ciliary band and scleral spur but in a minority of cases may reach the trabecular meshwork. These are usually small, peak-shaped synechiae generally affecting less than 30° of the iridocorneal angle (Thomas et al. 1982; Lieberman et al. 1983).

Several parameters have been tested with regard to the formation of PAS. Schwartz et al. (1981) found a correlation with a high ALT power setting, but others were unable to confirm this (Thomas et al. 1982; Traverso et al. 1984a). There is no correlation between the formation of PAS and the degree of postoperative iritis (Thomas et al. 1982), width of chamber angle, number of burns, sex (Traverso et al. 1984a), age, type of glaucoma, preoperative medication, trabecular pigmentation and visible effect of burn (Rouhiainen et al. 1988a).

Application of burns to the posterior part of the trabecular meshwork leads to a significantly higher PAS incidences (Hoskins et al. 1983; Kitazawa et al. 1984; Traverso et al. 1984a). Rouhiainen et al. (1988a) found PAS in 40.0% of cases combining posterior localization of burns with a high power setting (800 mW) and in 0% of the cases combining an anterior localization with a low power setting (500 mW).

Rouhiainen et al. (1988a) found a less marked IOP decrease in eyes with PAS formation, but other authors failed to confirm this (Thomas et al. 1982; Moulin & Haut 1983; Schwartz & Kopelman 1983; Traverso et al. 1984a).

**The principal complication of ALT is the occurrence of an IOP increase after treatment.** As table 4.6 shows, it was not until after some time that these IOP increases were identified as a complication of ALT. Wilensky & Jampol (1981) and Thomas et al. (1982) were the first to point out these IOP increases and the risks entailed. Thomas et al. (1982) described in a case report how one of their patients with an IOP increase of 12 mm Hg developed a severe visual field defect with loss of central vision afterwards.

The incidence of IOP increases depends on two essential parameters: the minimum IOP increase interpreted as significant, and the timing of the first

IOP check-up after ALT. The lower limit selected ranges from +1 mm Hg to +10 mm Hg; the timing of the first check-up ranges from the first hour after ALT to a few days later.

As experience with ALT increased and attention focused increasingly on the occurrence of IOP increases, more and more publications reported IOP increases often occurring immediately after ALT. The table demonstrates that consistent early check-ups after ALT are imperative. After rearrangement of the IOP data it is evident that the high IOP increases occur immediately after ALT and that the first check-up after 1 day or later fails to detect many of these IOP increases:

| minimum IOP increase | time of first check-up | incidence |
|---|---|---|
| +1 mm Hg | 1 hour | 70.0% (Weinreb et al. 1983a)<br>56.1% (Krupin et al. 1984)<br>42.1% (Frucht et al. 1985) |
| +1 mm Hg | 1 day or later | 25.3% (Thomas et al. 1982)<br>24.0% (Lichter 1982)<br>14.8% (Bergeå 1984)<br>9.2% (Horns et al. 1983) |
| +5 to +10 mm Hg | 1 hour | 33.0% (Lieberman et al. 1983)<br>26.2% (Zborowski et al. 1984)<br>21.1% (Frucht et al. 1985)<br>3.8% (Finnström 1985) |
| +5 to +10 mm Hg | 1 day or later | 16.0% (Smith 1984)<br>14.4% (Pohjanpelto 1983)<br>8.5% (Schwartz & Kopelman 1983)<br>6.1% (Lieberman et al. 1983) |

Further analysis revealed that most IOP increases occurred within one hour of treatment, but that they also occur as late as 4-5 hours after ALT (Weinreb et al. 1983a; Krupin et al. 1984; Frucht et al. 1985). They may even occur much later (weeks) (Thomas et al. 1982; Schwartz & Kopelman 1983).

Additional medical therapy, e.g. acetazolamide, mannitol intravenously or glycerol orally, is called for in view of an IOP increase in some 10-20% of

cases and generally produces an adequate decrease in IOP (Weinreb et al. 1983a; Krupin et al. 1984; Frucht et al. 1985).

The course of the IOP increase is generally mild, although very high IOP values have been reported. The majority of patients show a spontaneous decrease after some time (a few hours to about 3 weeks after ALT).

It is difficult to establish how often permanent IOP increases occur. It is well known that IOP increases may occur which cause immediate danger and necessitate surgical intervention (Horns et al. 1983). The question whether after a certain interval a secondary IOP increase may occur as a result of ALT cannot be readily answered. The natural cause of glaucoma is gradual and an accelerated increase in visual field defects due to ALT can be measured only if the population treated is matched with a control group for glaucoma type, height of IOP, severity of optic disk damage, visual field defect, age, sex, medication used and duration of manifest glaucoma. Of course this poses difficulties in actual practice, quite apart from the fact that it would be unethical to deprive the control group of therapy, be it medication, surgery or ALT. The literature mentions an occasional instance in which an adequate IOP decrease was initially achieved but an IOP increase occurred after a certain interval (4 weeks; Tuulonen & Airaksinen 1983a). In these specific cases the IOP had increased to far above the initial IOP, and surgical intervention was necessary. The relatively brief interval between treatment and IOP increase indicates the possibility of a causal relationship.

None of the studies in which IOP was carefully registered (Lieberman et al. 1983; Weinreb et al. 1983; Krupin et al. 1984; Zborowski et al. 1984; Finnström 1985; Frucht et al. 1985) mentions resistant IOP increases. Perhaps the early detection of these IOP increases and adequate therapy have played a role in this aspect.

Thomas et al. (1982) and Weinreb et al. (1983a) each described a patient in whom severe progression of the visual field defect was believed to have followed an IOP increase. However Thomas et al. did not record this IOP increase until after 3 days, and Weinreb et al. reported that the IOP ".....steadily increased to as high as 62 mm Hg.....", but that the onset of the IOP increase was within one hour of completion.

**Hourly check-ups on the IOP for a few hours after ALT seem to be impera-**

**tive both for preventive and for therapeutic reasons.**

Some authors maintain that an IOP increase need not reduce the IOP reduction achieved nor the success rate (Thomas et al. 1982; Moulin & Haut 1983; Bergeå 1984; Krupin et al. 1984; Smith 1984; Tuulonen et al. 1985). Others, however, report a less marked IOP decrease and a lower success rate for eyes which showed an IOP increase in the immediate post-ALT phase (Weinreb et al. 1983b; Zborowski et al. 1984).

A number of factors have been tested for correlation with the occurrence of IOP increases. The literature is not always unequivocal in its conclusions about each of these factors. Thus Krupin et al. (1984) found no significant correlation between the **power setting** used and IOP increases, whereas Rouhiainen et al. (1987b) reported an increasing incidence with higher power settings (incidences 13%, 26% and 52% at power settings of 500, 700 and 900 mW respectively). Rosenblatt & Luntz (1987) demonstrated that the power setting used had been higher for the eyes showing IOP increases.

Hoskins et al. (1983) found a lower incidence when fewer than 65 burns had been applied, but Krupin et al. (1984) found no correlation with the **number of burns.**

A number of factors have been described as not being correlated with the occurrence of IOP increases: **'good' burn criterion** (blanching, bubble, blanching and bubble; Rouhiainen et al. 1987b), **age, iris colour, initial IOP, glaucoma type** and number of agents used in **preoperative medication** (Robin et al. 1987).

Other factors do seem to correlate with IOP increases. Keightly et al. (1987) reported a correlation between **pre-ALT coefficient of facility of outflow,** and the occurrence of post-ALT IOP increases. Specifically eyes with a coefficient of 0.20 µl/min/mm Hg or less were expected to show IOP increases. Eyes with higher coefficients, however, likewise showed IOP increases. In other words, the sensitivity was reasonably high but specificity was low.

Thomas et al. (1982) found that ALT of the trabecular meshwork in **two sessions** caused evidently fewer and less high IOP increases. Application of burns to the **anterior part of the trabecular meshwork** also led to fewer IOP increases (Kitazawa et al. 1984). Because these and other treatment variables have been tested for their effects on IOP decrease, success rate and

IOP increase, they will be discussed in a separate sections (4.4).

Attempts to prevent occurrence of IOP increases with the aid of various eyedrops given as pre- and post-ALT medication, generally causes no decrease either of the incidence or of the height of IOP increases (tables 4.7 and 4.8). Because there are often slight inflammatory reactions immediately after ALT, it seems logical to look for preventive agents in particular in the group of the antiphlogistics.

Ruderman et al. (1983) found no significant difference in mean height and incidence of IOP increases between a group treated with corticosteroid eyedrops and a group not so treated.

Prostaglandins can cause a disturbance of the blood/aqueous barrier and an increase IOP (see 2.2.2.5). Laser applications in the eye disturb this barrier (Schrems et al. 1983, 1985; Schrems 1985), and in theory a release of prostaglandins could be responsible for the IOP increase following ALT. Consequently pre-ALT treatment with non-steroid anti-inflammatory drugs, e.g. the prostaglandin synthetase inhibitors flurbiprofen and indomethacin, could influence the IOP increase; the more so because in animal experiments these agents have shown a barrier-stabilizing effect after laser therapy (Schrems 1985). Unfortunately, neither flurbiprofen nor indomethacin proved to affect the incidence and height of post-ALT IOP increases in actual practice (Weinreb et al. 1984; Hotchkiss et al. 1984; Gelfand & Wolpert 1985; Pappas et al. 1985; Tuulonen 1985). These studies also show that IOP increases do not correlate with the severity of inflammatory symptoms (conjunctival redness, anterior chamber flare, anterior chamber cells) immediately after ALT. A striking finding was reported by Hotchkiss et al. (1984) and by Gelfand & Wolpert (1985): the group treated with the prostaglandin synthetase inhibitors showed a significantly less marked IOP decrease than the group not so treated (significant after 1 month (Gelfand & Wolpert 1985) and after 1 day, 1 week and 5 weeks (Hotchkiss et al. 1984)). Others were unable to confirm this difference (Pappas et al. 1985; Tuulonen 1985).

Why do these agents have no reducing effect on the incidence and height of IOP increases? Several possible explanations present themselves (Hotchkiss et al. 1984; Pappas et al. 1985; Tuulonen 1985). To begin with there might have been a release of endogenous prostaglandins after all. Alternatively, after inhibition of prostaglandin synthetase another pathway of production

may be created and other prostaglandins released. Possibly, also, prostaglandins do not play a role in the pathogenesis of IOP increases, but debris causes a mechanical block at the level of the trabecular meshwork. Makabe (1988) found that the IOP increase is parallelled by a decrease in outflow of aqueous humour. Possibly, also, other substances may play a role, e.g. histamine, 5-hydroxytryptamine, norepinephrine, slow-reacting substance of anaphylaxis, substance P or cyclic AMP. Finally, the fact that treatment with these substances sometimes causes a less marked IOP decrease might indicate that the trabecular meshwork needs a certain amount of prostaglandins (Hotchkiss et al. 1984). This is consistent with what has been pointed out in 2.2.2.5: small doses of prostaglandins have an ocular hypotensive effect. It seems obvious that this could play a role in the early post-ALT phase, but how to explain the difference in IOP decrease after 1 month, when prostaglandin synthetase inhibitors are no longer used?

Ofner et al. (1984) found an unmistakable decrease both in incidence and height of IOP increase after post-ALT administration of a 4% pilocarpine solution. Nevertheless, an IOP increase also occurred in 36.3% of the pilocarpine treated cases. Use or non-use of miotics by the patients prior to ALT is not specified in this study. The reducing effect of pilocarpine may be suggestive of a mechanical basis of the IOP increase.

Another agent with an unmistakable reducing effect is the clonidine derivative ALO 2145 [2-(4-amino-2,6-dichloro)-phenylimino-imidazolidine] - an $\alpha_2$ agonist (Robin et al. 1987; Brown et al. 1988). Clonidine reduces the blood supply to the ciliary body, thus causing hyposecretion of aqueous humour. After a one-month follow-up Robin et al. (1987) found no difference between the treated and untreated group, and results may therefore be described as encouraging. Brown et al. (1988) on the other hand found a significantly lower IOP in the placebo treated group at one week, but ascribe this difference to the fact that additional therapy was often necessary in the placebo treated group. Wether other $\alpha_2$ agonists have a function in this respect and wether ALO 2145 can assume a position among other hypotensive medications, are questions which may possibly be answered in the future.

Apart from the above described ALT modifications and substances influencing the IOP increase, and a few other factors, it seems impossible to predict which patient or eyes are at risk to develop an IOP increase. Our pros-

pective study of ocular and extraocular factors which may play a role in this respect, may provide further information on this question.

### 4.4 TREATMENT VARIABLES

Application of technical ALT parameters other than those used by Wise serves a dual purpose. To begin with, it might be possible in this way to reduce both the incidence and height of the IOP increases. Moreover, other ALT techniques (ALT modifications) might lead to better results.

On theoretical grounds, several ALT modifications are eligible. For the parameters directly related to ALT, the following alternatives may be considered:

- **burn localization**: anterior, posterior, pigmented trabecular meshwork, scleral spur and ciliary band;
- **number of sessions in which ALT is completed**: one or two;
- **part of the trabecular meshwork circumference treated**: 90°, 180°, or 360°;
- **burn diameter**: 50 μm or otherwise;
- **exposure time**: 0.1 sec or otherwise;
- **total number of burns**: 25, 50 or 100;
- **power setting**: 1000 mW or otherwise.

Various combinations of these parameters afford a total of 720 different possibilities of performing ALT. Should we also include use or non-use of pre- or post-ALT medication, type of laser (Argon blue, Argon blue-green, Krypton, YAG), iris stretching and the contact glass used (Goldmann three mirror contact lens or Ritch ALT lens) then the total would increase to 23,040.

Of course not all combinations are sensible. It makes no sense, for instance, to perform treatment of 90° of the trabecular meshwork circumference with 100 burns of 100 μm diameter at a power setting of 2000 mW and an exposure time of 0.2 sec.

Table 4.9 lists the most commonly used ALT modifications with the corresponding IOP decreases and success rates. The trend of these ALT modifications as compared with the Standard Wise ALT is to treat a smaller part of the trabecular meshwork circumference or, if the entire circumference is

treated, to do this in two sessions. The total energy invested (number of burns x exposure time x power) virtually never exceeds 15 Joules.

For the reasons presented in 4.2.1 and in view of the fact that several different ALT modifications are involved, it is difficult to compare these modifications. It is more sensible to establish how the results of the various modifications compare with those of the Standard Wise ALT.

In most cases the Standard Wise ALT gives an IOP decrease by at least 20% (see table 4.2). Also in view of the mean height of the initial IOP (about 25 mm Hg), a decrease by 20% would seem to be the minimum which an ALT modification should produce. Other authors agree with us (Lichter 1982; Hoskins et al. 1983; Traverso et al. 1986). In addition, a minimum success rate of 60% should be achieved.

Table 4.9 shows that most ALT modifications fulfil these criteria, although there are a few exceptions. One-session treatment of only 90° of the trabecular meshwork circumference leads to a small IOP decrease and a low success rate (Schwartz et al. 1983). Although Wilensky & Weinreb (1983a) found an IOP decrease by 22.7%, this could be counted as success in only 47.6% of the cases. The 22.7% IOP decrease was small if related to the initial IOP (29.9 mm Hg). Additional treatment of another 90° led to an additional IOP decrease (total IOP decrease 31.4%) and raised the success rate to 66.7% (Wilensky & Weinreb 1983a). Nevertheless, ALT over only 90° is sometimes sufficient to control glaucoma (Lehmann & Faggioni 1986). If compared with one-session ALT over 180°, this two-session treatment possibly causes a somewhat smaller IOP decrease and lower success rate (Grehn & Schildwächter 1987).

A power setting of less than 500 mW gives a smaller IOP decrease and a lower success rate (Rouhiainen & Teräsvirta 1986; Rouhiainen et al. 1987a). A factor of importance in this respect is the exposure time and therefore (indirectly) the total energy invested in ALT. Whereas Rouhiainen et al. (1987a) achieved a maximum success rate of 50.0% with a power setting of 500 mW, Blondeau et al. (1987) achieved a success rate of 100% with this setting. However, the total energy invested by Rouhiainen et al. was 3 Joules at the maximum, versus a total of 10 Joules invested by Blondeau et al. If the power setting is at least 500 mW, however, than Rouhiainen et al. (1988b) found no differences in IOP decreases at 500, 600, 700 or 800 mW.

A spot size of only 25 µm gave an IOP decrease by only 18.5% (Schwartz et al. 1983). It should be borne in mind, however, that the initial IOP was low (21.3 mm Hg). The success rate (60.0%) was likewise rather low.

Application of burns to the ciliary band generally gives good results, except with the ALT modification used by Reibaldi et al. (1985); they applied more than 100 burns with a diameter of 200 µm and achieved a successful IOP decrease in only 26.7% of cases. This may have been due to the composition of the patient population (patients with wide peripheral and total iridectomies, aniridia).

The low success rates of the ALT modifications used by Kitazawa et al. (1984) were probably based on the fact that the success criteria were stabilization of the visual field defect and an ultimate IOP below 20 mm Hg. Moreover, the total energy invested in the one-session treatment of the posterior trabecular meshwork with 100 burns was rather high (20 Joules).

**To summarize : most ALT modifications yield good results if: at least 180° of the trabecular meshwork circumference is treated, the power setting is at least 500 mW, and the total energy invested is at least 3 Joules (Rouhiainen & Teräsvirta 1986), but on the other hand should not exceed a maximum (probably 20 J).**

Two ALT parameters seem to exert a significant influence on the occurrence of post-ALT IOP increases: treatment of maximally 180° of the trabecular meshwork circumference in one session, and application of burns to the anterior part of the trabecular meshwork (table 4.10).

Distribution of ALT over two sessions does not significantly affect the total incidence of IOP increases but does influence the mean height of these increases. Thomas et al. (1982), for instance, found a total incidence of 25.2% for one-session ALT and 25.4% for two-session ALT. The distribution, however, was such that higher IOP increases (>5 or 10 mm Hg) occurred more frequently in the one-session group. Heijl (1984) reported that the height of the IOP increase exceeded 5 mm Hg in 4 out of 8 eyes in the one-session group, and in 3 out of 8 eyes even exceeded 15 mm Hg, whereas 6 eyes in the two-session group showed an IOP increase not exceeding 5 mm Hg.

The time at which the maximal IOP increases occurs was distinctly earlier in the group treated over only 180° (mean interval after ALT 1.55 hr) than in the group treated over 360° (mean interval after ALT 3.5 hrs) (Weinreb et

al. 1983a). The proportion of eyes requiring additional medication in view of an IOP increase was also higher in the 360° group than in the 180° group (Weinreb et al. 1983a).

Application of burns to the anterior part of the trabecular meshwork also reduces the height of the IOP increase, but on the other hand clearly influences the incidence of IOP increases (Schwartz et al. 1983; Kitazawa et al. 1984).

As already pointed out in 4.3, there is a correlation between the power setting used and the occurrence of IOP increases (Rouhiainen et al. 1987b). A lower power setting gives fewer IOP increases. On the other hand, however, it may also give a less marked IOP decrease and a lower success rate.

**It may be stated in summary that, in terms of incidence and height of any IOP increases, ALT modifications treating the anterior trabecular meshwork in two sessions are to be preferred to the Standard Wise ALT.**

Table 4.11 lists the various lasers which have been tested for efficacy in laser trabeculoplasty. To summarize: the Argon green and Argon blue-green lasers give statistically significant better results than the Krypton laser (Makabe 1986) and also (but not significantly) better results than the YAG laser (Martenet & Schwarzenbach 1986).

The Krypton laser initially causes an IOP decrease, but this effect is transient. After 3 months the IOP has returned to the initial value (Makabe 1986). Spurny & Lederer (1984) found no difference in IOP decrease between the Krypton red/yellow and the Argon blue-green laser, but it should be noted that these results were recorded after a follow-up of 1-10 months and that the control group treated with the Argon laser was a selected population (contralateral eyes of patients already treated unilaterally with the Krypton laser) and therefore a source of bias. According to these authors an advantage of using a Krypton laser lies in deeper penetration of the trabecular meshwork as a result of less absorption in the pigmented endothelial cells of the trabeculae. However, if the tightening effect postulated by Wise does indeed play a role in the mechanism of action of ALT, then this should be a disadvantage rather than an advantage.

In the case of a narrow iridocorneal angle (or beak-shaped angle) as a result of a 'plateau iris', ALT may be preceded by iris stretching (iridoplasty or gonioplasty). For this purpose larger burns (>100 μm) are applied to

the peripheral iris. The technical details of iris stretching given in various studies vary somewhat: 6-12 spots, 50-100 µm, 0.1 sec, 750-1000 mW (Lieberman et al. 1983), 80-100 spots, 100 µm, 0.1 sec, 400-600 mW in several sessions (Reibaldi et al. 1985), or 50 spots, 200 µm, 0.2 sec, 700 mW in two sessions (Wishart et al. 1987).

The majority of authors report that iris stretching preceding ALT has no untoward effect on the result (Thomas et al. 1982; Lieberman et al. 1983; Reibaldi et al. 1985; Traverso et al. 1986). Only Wishart et al. (1987) reported very poor results in a prospective comparative study of the results obtained by various techniques to reduce IOP in narrow-angle glaucoma. Half the patients (N=8) treated by iris stretching preceding ALT developed synechial closure of the anterior chamber angle. We believe that a possible cause of these disappointing results may be found in the patient selection in this study: just patients with narrow angle glaucoma and a axial anterior chamber depth of less than 2.5 mm were submitted to iris stretching, while iris stretching is indicated in eyes with a narrow angle due to a plateau iris and normal anterior chamber depth. Furthermore, their technique differed somewhat, because per session, 180° of the trabecular meshwork circumference was treated (high maximum energy possible, because in half of the eyes treated a 0.2 sec exposure time and a spot size of 100-150 µm was used) and 180° of the iris (maximum energy 3.5 Joules). This means that the total energy invested after the first session could be high, while the second half was left untreated and thus leaving the angle narrow. Other authors needed only 6 Joules (Reibaldi et al. 1985) or 12 Joules (Lieberman et al. 1983) for treatment of 360° of the trabecular meshwork and iris.

Another treatment variable is the experience of the person performing the ALT. Using multiple step-wise logistic regression analysis, Tuulonen et al. (1985) found that one of the factors enhancing the chance of a successful ALT is its performance by a person experienced in this technique. Khan et al. (1986) found that the IOP decrease in eyes with POAG following ALT performed by residents was 22.9% of an initial IOP of 24.0 mm Hg, which is a rather small decrease. Brodell et al. (1986) found an IOP decrease by 34.2% of an initial IOP of 29.8 mm Hg following ALT performed by residents. This result does not differ from the results obtained by more experienced investigators. It seems likely, however, that any ".....surgical procedure, es-

pecially one as delicate and precise as ALT, has a learning curve. Eventual mastery of a procedure is always preceded by inexperience....." (Khan et al. 1986).

**In conclusion, an optimal ALT has the following characteristics: treatment of 360° of the anterior trabecular meshwork circumference in two sessions separated by an interval of about 4 weeks, using a total of 120 burns with a spot size of 50 µm, an exposure time of 0.1 sec and a power setting which, dependent on the degree of pigmentation among other things, causes blanching and/or bubble formation. The ALT should be performed with a Argon Continuous Wave Laser, and check-ups for IOP increases should be carried out throughout a few consecutive hours following ALT. After-treatment consists of corticosteroid eyedrops. The effect of ALT should be watched during about 4 weeks after intervention.**

The reason for adding a second session even though the first may have produced an IOP decrease is twofold. To begin with, a 360° ALT causes a more marked IOP decrease than a 180° ALT, although this difference is seldom statistically significant (Schwartz et al. 1983; Lustgarten et al. 1984). Elsås (1987) found a significant difference in success rate between 180° ALT (15%) and 360° ALT (69%) as primary therapy. Secondly, Wise (1987) examined follow-up on more than 1700 ALT patients and found the optimal number of spots to be about 120. Not everyone agrees with this. Rouhiainen & Teräsvirta (1988) belief that one should treat just 180° of the trabecular meshwork, and treat the other half if a late failure has occurred.

Apart from the previously described empirical reasons for treating the anterior part of the trabecular meshwork, this localization is theoretically also preferable to a more posterior localization. As pointed out in 2.2.2.1, this part of the trabecular meshwork comprises only the uveal strands, which form large diamond-shaped meshes. This part does not really participate in the active drainage of aqueous humour to Schlemm's canal, and destruction of trabeculae (as a result of ALT) therefore does not interfere with a system of essential importance in the outflow of aqueous humour.

Because a minimum energy level is required to achieve an adequate IOP decrease, the power setting should be sufficiently high. Good criteria for in-

dividual titration of this power are blanching and bubble formation. That high energy investments correlate with more IOP increases has to be accepted for the sake of the result.

Different values for the Standard Wise ALT parameters spot size and exposure time do not contribute essentially either to the result or to the incidence of IOP increases; these parameters therefore remain unchanged.

That Argon Continuous Wave Laser is preferable to lasers with other wavelengths has already been discussed.

It should be emphasized that a standard ALT protocol - regardless of the ALT modification used - should always include early and intensive IOP checkups. As pointed out, this is certainly of preventive and possibly also of therapeutic value. Corticosteroid eyedrops following ALT serve to prevent severe iritis and also contribute to the swift disappearance of the mild iritis observed in virtually 100% of cases. As already pointed out, there is no consensus on this subject and prescription of corticosteroids is not an obligatory feature of the standard protocol.

In view of the fact that the prostaglandin synthetase inhibitors flurbiprofen and indomethacin have unfavourably affected the IOP decrease in a number of reported cases, these should not be given after ALT.

ALO 2145 (see 4.3) seems to have a reducing effect on the incidence and height of IOP increases, but requires further clinical investigation.

## 4.5 PATIENT VARIABLES

As tables 4.2 and 4.9 indicate, the IOP decreases and success rates reported in various studies vary considerably. This may in part be explained by differences in ALT modifications used, but on the other hand there should be factors explaining differences despite similar ALT modifications. Moreover, there must be variables which affect the ALT results, because a consistent 100% success rate is never achieved. That these variables are often ocular and extraocular patient variables will be discussed in this section.

Tables 4.12 and 4.13 indicate wether the authors listed discovered a correlation between success rate and IOP decrease respectively, and some obvious patient variables. Again we must take the reservations mentioned in sub-

section 4.2.1 regarding comparison of literature data.

A superficial perusal of these tables reveals two striking aspects. To begin with, there is no consensus in the literature regarding the majority of the variables. Secondly, by no means all investigators have tested the patient population treated for these variables, although most investigators studied their material intensively.

The publications listed show that **sex** does not affect either IOP decrease or success rate and (although this is mentioned only once) that there seems no difference in success rate between **right and left** eyes.

There is also consensus about the correlation between **initial IOP** and IOP decrease. Without exception it is observed that a higher initial IOP gives a more marked decrease in IOP. For some of the studies listed table 4.14 indicates the correlation between IOP decrease and either mean initial IOP (MIIOP) or range of initial IOP values (RIIOP). The coefficients of correlation found vary rather widely: 0.335 (Traverso et al. 1987), 0.363 (Traverso et al. 1986), 0.68 (Grinichi et al. 1987), 0.73 for white and 0.75 for negroid patients (Krupin et al. 1986) and 0.848 (Bergeå 1984). The following question now arises in this context: is the IOP decrease achieved at a high initial IOP sufficient to describe an ALT as successful? Proceeding from the criterion that the ultimate IOP should be lower than, say, 22 mm Hg than an IOP decrease by 20 mm Hg from an initial IOP of 45 mm Hg would have to be described as a failure. If only the criterion of a certain IOP decrease is applied (e.g. a decrease by at least 20% of the initial value), than this should be described as exceedingly successful.

We believe that the success and failure criteria should be adapted to the indication for ALT therapy. Then the IOP decrease in the above case would be insufficient in a patient with already advanced visual field loss, but certainly adequate if the ALT had been performed prior to a cataract extraction. Some flexibility in this context is required, not in order to enhance the success rate but in order to establish whether the desired post-ALT situation is in fact achieved.

Safran et al. (1984) found that the initial IOP of the successfully treated eyes was significantly lower than that of failure eyes. Tuulonen et al. (1985) likewise found that the success rate was correlated with the initial IOP, but noted rightly that flexibility in this respect is recommenda-

ble. Moulin et al. (1987) found a lower success rate for eyes with an initial IOP in excess of 28 mm Hg.

Striking findings were reported by Schwartz & Kopelman (1983) and Schwartz et al. (1985). After a maximum follow-up of 4 years they found an unequivocal correlation between success rate and initial IOP, whereas after a 6-year follow-up this correlation was no longer significant. Because the study population diminished in size as the duration of follow-up increased, interpretation of this finding is difficult. It may be that the range of initial IOPs is smaller as the follow-up advances because eyes with a high initial IOP are more likely to be deemed failures and eliminated from the further follow-up. This would mean that the mean initial IOP remains fairly constant but that eyes with truly high initial IOP select themselves out and cloud the correlation between initial IOP and success rate.

Zborowski et al. (1984) found no correlation between initial IOP and success rate at an initial IOP limit of 30 mm Hg; Bergeå (1986a) found none at an initial IOP limit of 28 mm Hg, and Lehmann & Faggioni (1986) found none at an initial IOP limit of 25 mm Hg.

The effect of the **degree of pigmentation** of the trabecular meshwork on IOP decrease and success rate is controversial. Tuulonen et al. (1985) found no correlation between success rate and degree of pigmentation. Bergeå (1986a) found that complete absence of pigment in the chamber angle (TP 0 in the classification of Scheie (1957), see also 3.3) clearly reduced the success rate, but that the amount of pigment present (TP+1 to TP+3) did not significantly affect the success rate. The latter also applied to the IOP decrease (Bergeå 1984). Traverso et al. (1986) on the other hand found a more marked IOP decrease in the eyes showing most pigmentation. Since only a few groups were involved here, no far-reaching conclusions should be drawn from these findings (Traverso et al. 1986). Grinichi et al. (1987) found no correlation between degree of pigmentation and IOP decrease, but this must have been due in part to the gross pigmentation classification (lightly pigmented versus more heavily pigmented). Rouhiainen et al. (1988b) found a statistically significant greater IOP decrease in eyes with a heavily pigmented trabecular meshwork, but these results are probably biased because a heavily pigmented trabecular meshwork occurred more frequently in eyes with pseudo-exfoliation glaucoma, whose IOP decrease was greater then that in eyes with POAG.

No difference in IOP decrease was found between **hyperopic and myopic** eyes (Traverso et al. 1986). High myopia (-6.25 diopters or more) gave a less marked IOP decrease, but the difference was not statistically significant (Traverso et al. 1987).

Remarkably little is known about the correlation between **IOP-reducing medication** and ALT results. Tuulonen et al. (1985) found that, in general, eyes given no medication respond better to ALT. This is also apparent from the fact that ALT as primary therapy gives very good results. More specifically, Tuulonen et al. found that pilocarpine unfavourably influenced ALT results. Timolol and carbonic anhydrase inhibitors had no significant effect on success rate. Rouhiainen et al. (1988b) found on the other hand, that the pre-ALT used glaucoma medication (i.e. pilocarpine, timolol, pilocarpine and timolol, pilocarpine and timolol and acetazolamide, or other combinations) did not statistically significantly influence the amount of IOP reduction after ALT. Since these correlations are reproducible, they will be given attention in the discussion of the results in our own patient population.

**Skin colour** does not significantly affect either success rate or IOP decrease. The colour of the iris (a factor related to skin colour) likewise has no effect on these parameters. Schwartz & Kopelman (1983) and Schwartz et al. (1985) are an exception to this rule. After a maximum follow-up of 4 years they found no significant difference in success rate between white and black patients, but after a follow-up of 6 years the negroid patients had a distinctly lower success rate than whites, and patients with blue irides had better results than those with brown irides. Wise (1987), however, reported unmistakably better results for black patients, and in fact results slightly better than those for the entire population.

One might suppose that the duration of follow-up is of influence. Schwartz et al. (1985) calculated a median time until the IOP returns back to 21 mm Hg or over, and found this to be 12 months for black and 60 months for whites. Wise (1987), however, reported much better results in his black patients after a follow-up of up to 10 years after ALT. How these differences should be explained remains obscure.

In view of the data in the tables there seems to be no consensus about the correlation between **age** on the one hand, and success rate and IOP decrease on the other. There are two limitations, however, which play a role in des-

cribing this correlation. Firstly, the numbers of eyes of patients below a certain age (e.g. under 40) are generally small. Leydhecker (1979) estimates that only one out of 500 adult glaucoma patients is under 30. These small numbers have repercussions on statistical analysis. Moreover, it should be realized that the age limit used in demonstrating a correlation is of importance, and that this is not a uniform parameter in the literature: 40 years (Thomas et al. 1982), 55 (Zborowski et al. 1984), 60 (Schwartz & Kopelman 1983; Moulin & Haut 1983). Comparing mean ages of failure patients and success patients (Rouhiainen et al. 1987a), large populations are needed to demonstrate a statistically significant difference.

With the exception of the studies of Tuulonen et al. (1985) and Rouhiainen et al. (1987a), with insufficiently accurate documentation of these data, published reports indicate that the success rate increases with increasing age. The same applies to the IOP decrease. The above described limitations dictate that these correlations are not always statistically significant, but do always indicate a trend.

The why of this correlation with age is not clear. Safran et al. (1984) suppose that glaucoma is the same disease entity at an early as at a more advanced age but that the pathogenetic mechanism may differ. In my opinion another aspect also plays a role: the ageing process of the trabecular meshwork (see 2.2.2.6). Apart from the changes in the glaucomatous trabeculae there is no reason to assume that this normal ageing process should not play a role. Since changes in POAG and ageing changes in the trabecular meshwork show marked similarities and the effect of ALT is certainly at least partly produced via the tightening process postulated by Wise, this aspect must play a role.

Another factor undoubtedly involved is the **severity of glaucomatous damage** at the time of the ALT. Traverso et al. (1986) found that the progression of visual field defects was higher as more damage had already been inflicted, even though the IOP decrease in this group did not differ from that in the group with less glaucomatous damage. Wise (1987) found that the surgery rate was 51% for eyes with advanced cupping (cup/disk ratio = 0.9 or higher), versus 16% for eyes with cup/disk ratios of less than 0.9. The eyes with advanced cupping showed progressive visual field loss after ALT despite the fact that the IOP had been normalized. The implications have already been

discussed (see subsection 4.2.3).

A final factor not included in the tables is the influence of **glaucoma surgery** on the ALT results. It may be assumed in general that a single pressure-reducing operation has only a minimal effect on the ALT result (Thomas et al. 1982; Dake & Bos 1983; Elsås & Harstadt 1983; Lieberman et al. 1983; Schwartz & Kopelman 1983; Tuulonen & Airaksinen 1983b). Two or more operations have an unmistakable unfavourable effect on the success rate (Lieberman et al. 1983).

Remarkably few data are available on the type of operation in relation to the ALT result. Only Thomas et al. (1982) adequately describe the type of pressure-reducing surgery performed prior to ALT. This, too, is one of the aspects considered in the discussion of our own results.

Fellman et al. (1984) report that, after trabeculectomy failure, 67% of 30 eyes (25 patients) subsequently treated by ALT showed no further visual field loss after an average follow-up of 14 months. A striking finding was that some patients (20%) showed no progression even though the IOP was unchanged after ALT. A factor of possible influence in this respect is that ALT exerts a significant influence on various parameters of the diurnal rhythm, and reduces mean daily pressure, peak pressure, pressure range and minimal pressure (Greenidge et al. 1983). Inversely, progression has also been observed despite an IOP decrease after ALT. This is not so very unusual, because it has also been described after pressure-reducing surgery and medication (see 3.5.4.4).

## 4.6 ALT AND VISUAL FIELD

The influence of ALT on two aspects of visual field loss has been studied. An IOP decrease following ALT does not lead to an improvement of the visual field defect (Heijl & Bengtsson 1984; Holmin & Bauer 1984). Both studies used a so-called performance value, i.e. the sum of threshold values recorded on 64 test points (Competer computerized perimetry). Although an adequate IOP decrease was achieved, there was no significant change in performance value after a follow-up of one month. The occurrence of IOP increases after ALT resulted in an increases or a decrease of this performance value,

but on average no changes occurred (Heijl & Bengtsson 1984).

Studies of this type give little information on the ALT results but much about the correlation between IOP and visual field defects. An IOP decrease causes no improvement in performance value.

The long-term effect of ALT on visual field defects can be described as follows. After a 12-month follow-up Schultz et al. (1987) found that 5 out of 19 eyes (26.3%) showed exacerbation of the visual field defect (OCTOPUS computerized perimetry). Significant differences in IOP parameters were found between eyes that did and those that did not show exacerbation of visual defects: mean pretreatment IOP 30.0 versus 24.3 mm Hg ($p=0.033$), mean highest recorded posttreatment IOP 28.0 versus 21.3 mm Hg ($p=0.057$), variance of posttreatment IOP reading 25.1 mm Hg versus 5.8 mm Hg ($p=0.044$).

Traverso et al. (1986) likewise found increased visual field loss in 28.3% of cases (OCTOPUS computerized perimetry; 113 eyes; follow-up 3-22 months).

Prost et al. (1987) found stabilization of visual field defects in 30% of the eyes and improvement in 55% (OCTOPUS 2000 automatic perimetry; 20 eyes; follow-up 12 months).

**To summarize: the risk of progression of visual field defects increases as the initial IOP is higher, a higher peak pressure occurs after ALT, and considerable damage already exists.** In addition it should be borne in mind that follow-up data on perimetry still cover only a limited period as compared with those on glaucoma treated by medication or surgery.

## 4.7 RETREATMENT

Table 4.15 lists the results reported by various authors with regard to retreatment after failure of ALT.

Most authors describe the results of retreatment in patients who showed a good initial response to ALT and developed an IOP increase only after a longer time (late failures). Bergeå (1986b) also describes results of retreatment after early failure (within 2 months).

The success rate of retreatment is lower than that of initial ALT. Dependent on the success criteria applied, it ranges from 32.5% to 60.0%, but in the majority of cases it is about 35%. A more important finding than the

success rate, in my opinion, is the risk that a patient has to have pressure-reducing surgery after retreatment. This risk is about 50%, which is fairly high (Messner et al. 1987; Richter et al. 1987).

The chance that retreatment will successfully reduce IOP is smaller after early than after late failures. Retreatment proved successful in 11 out of 16 late failures (68.8%), and in only 1 out of 4 early failure eyes (Bergeå 1986b).

The median time to failure was calculated with the aid of Kaplan-Meier survival analysis and proved to be 9 months (Richter et al. 1987). Calculated with the aid of life-table analysis it was 12.3 months (Bergeå 1986b). Both values are evidently below the 60 months calculated after an initial ALT (Schwartz et al. 1985).

The IOP decrease following successful retreatment is of the same order as that after an initial ALT: 10.4 mm Hg (Brown et al. 1985b), 7.1 mm Hg (Bergeå 1986b), 8.1 mm Hg (Richter et al. 1987). Bergeå (1986b) found no statistically significant difference in IOP decrease between eyes given retreatment over 360° (7.8 mm Hg) and those given retreatment over 180° (6.6 mm Hg). After recalculation in terms of relative IOP decrease this amounts to a decrease by 28.0% of an initial IOP of 27.9 mm Hg after retreatment over 360°, and 22.4% of an initial IOP of 29.6 mm Hg after retreatment over 180°. Again the trend is evident: 360° ALT gives a more marked decrease.

Richter et al. (1987) found that results tended to be better after retreatment of the nasal than after that of the inferior trabecular meshwork, better in phakic than in aphakic eyes, and better in eyes given the initial 360° ALT in two sessions than in those initially treated by 360° ALT in one session. However, none of these differences was statistically significant.

IOP increases are again the principal complication following retreatment. The incidence depends on the criteria applied to interpret an IOP increase as significant, and ranges from 0% (Messner et al. 1987; Richter et al. 1987) to 38.5% (Brown et al. 1985b). Brown et al. (1985b) reported that 38.5% of retreatment eyes showed an IOP increase by 1 mm Hg or more, while 11.5% showed an increase by more than 10 mm Hg. Retreatment was by a two x 180° ALT modification. Eight of the 10 eyes with IOP increase involved showed increased optic nerve damage and visual field loss and required surgery within a month of retreatment. It should be noted, however, that post-re-

treatment IOP check-ups were not done until after one day, and that it could not be established whether the IOP increases occurred after the first or after the second retreatment session. Nevertheless this incidence of IOP increases, and certainly that of pressure reducing surgery, is very high.

Starita et al. (1984a) found an IOP increase by at least 10 mm Hg in 29.4% of cases, in the majority within one hour of retreatment (one-session ALT over 360° of the trabecular meshwork circumference).

Richter et al. (1987) treated only 180° of the trabecular meshwork circumference in one session and after this retreatment observed no IOP increases exceeding 6 mm Hg; they had no need for pressure-reducing surgery in view of an IOP increase.

Messner et al. (1987) performed ALT over 360° in one session but applying only 50 burns, and found no IOP increases in excess of 10 mm Hg.

Retreatment over only 180° of the trabecular meshwork circumference or with only 50 burns distributed over the entire circumference thus gives a lower incidence and height of any IOP increases.

**To summarize: the chance of success is significantly lower after retreatment than after initial ALT; in the case of success the IOP decrease is not less marked; the ocular hypotensive effect after retreatment persists less longer than that after an initial ALT; some 50% of eyes require pressure-reducing surgery after retreatment; limitation of the number of burns or of the distance over which the trabecular meshwork is treated entails only a small risk of severe IOP increases.**

## 4.8 ALT AND ITS EFFECT ON MEDICAL CONTROL OF GLAUCOMA

Table 4.16 presents data on the possibility of reducing or discontinuing ocular hypotensive medication after successful ALT.

The range of percentages reported for reduction or discontinuation of glaucoma medication is partly explained by the fact that most authors, especially in retrospective studies, use no standardized protocol in this respect. Since the success criteria vary widely, the chance of reduced medication also varies in the various studies reported.

In most of the prospective studies the investigators wants to measure the

true pressure-reducing effect of ALT, and this implies that as many variables as possible are left unchanged. Of course changed medication is a highly disturbing variable in this context.

However, some general conclusions seems justifiable. In a substantial percentage of cases it is possible to maintain proper IOP control after ALT with reduced medication. However, the chance that medication can be stopped entirely is small. A majority of the patients treated remains dependent on some form of ocular hypotensive medication after ALT.

Pollack & Robin (1982) specifically studied reduction of medication following ALT. They specified in their protocol that reduction of medication should not start until 3-6 months after an ALT, and that only one drug at a time should be discontinued until the IOP exceeded 21 mm Hg at two successive measurements. The sequence of stopping medication was: carbonic anhydrase inhibitor, miotic, adrenaline and timolol. They found that IOP control could be maintained with less medication in 38.9% of cases, and entirely without medication in 33.3%. More specifically, they reported that 6 out of 9 patients no longer required carbonic anhydrase inhibitor, and 6 out of 8 patients no longer needed a miotic. It was also established that the chance of maintaining a controlled IOP without medication diminishes with more pre-ALT medication. Fink et al. (1982) likewise found that ALT is an adequate alternative to carbonic anhydrase inhibitors.

Migdal & Hitchings (1984) performed a prospective randomized study of the results of primary therapy of glaucoma, and found that the ALT group showed an IOP decrease of 44.0%, versus 32.9% of the group treated by medication at virtually identical initial IOP values (follow-up 6 months).

Tuulonen et al. (1987) performed a retrospective study of 32 eyes treated by primary ALT, while a control group matched for diagnosis, optic disk appearance and visual field was treated by medication. After a 5-year follow-up 50.0% of the ALT group showed a controlled IOP without additional therapy, versus 21.9% of the medication group ($p<0.02$). The intervention index (higher score with more adjustments or additions to the primary therapy) was 9 for the ALT group and 25 for the medication group. The decrease in neuroretinal rim area was 0.06 for the ALT group and 0.15 for the medication group ($p<0.017$). The IOP decrease in the ALT group exceeded that in the medication group (no exact values presented). Tuulonen et al. concluded that

ALT as primary therapy yields better results than medication.

It may be stated in summary that in many cases medication can be reduced following ALT, that the percentage of eyes controlled without medication is distinctly smaller, and that the chance of discontinuing medication is smaller as pre-ALT medication was more extensive. The chance of stopping miotics and carbonic anhydrase inhibitors is great. As primary therapy, ALT would seem to be preferable to medication.

## 4.9 ALT AND CATARACT

### 4.9.1 ALT after cataract extraction

Table 4.17 presents results of ALT in aphakic eyes. Virtually all studies also presenting results in phakic eyes, show a lower success rate and less marked IOP decrease in aphakic than in phakic eyes (Wise & Witter 1981; Thomas et al. 1982; Demailly et al. 1985; Hoskins 1987; Moulin et al. 1987). Lieberman et al. (1983) found a success rate not clearly different from that in phakic eyes, but the number of aphakic eyes in their series was small. Horns et al. (1983) found similar success rates and IOP decreases in phakic and aphakic eyes after a comparable follow-up period. Van Meter et al. (1988) reported an IOP decrease by more than 5 mm Hg in 8 out of 10 aphakic or pseudophakic eyes with glaucoma after penetrating keratoplasty. The overall results seem less good in aphakic than in phakic eyes, but there is no consensus on this point.

The data in the literature warrant no unequivocal answer to the question why aphakic eyes should respond less well than phakic eyes. Descriptions of the status of the iridocorneal angle after cataract extraction are often incomplete, and important questions cannot be answered. Was there vitreous humour prolapse after the cataract extraction? Were extensive peripheral synechiae observed after the cataract extraction? Had glaucoma been present even before the cataract extraction?

Wise & Witter (1979) reported that three eyes with vitreous in the anterior chamber did not respond to ALT. Of 12 aphakic eyes without vitreous in the anterior chamber, 8 responded well to ALT.

Robin & Pollack (1983) explicitly mentioned that glaucoma was not directly related to cataract extraction; their results were good.

Moulin et al. (1987) had a success rate of 41.7% in aphakic eyes, but excluded cases of obstructive glaucoma from treatment.

Thomas et al. (1982) had a distinctly less good success rate for aphakic eyes with open-angle glaucoma than for phakic eyes with this type of glaucoma. Efforts to correlate success and IOP decrease in aphakic eyes with other ocular variables may contribute to a consensus.

Few results obtained in pseudophakic eyes are reported in the literature, but it seems that results in pseudophakic eyes are better than those in aphakic eyes (Hoskins 1987).

In our opinion it is methodologically questionable to lump aphakic with pseudophakic eyes (Schlosshardt 1986) in ALT evaluations.

The above questions concerning ALT in aphakic and pseudophakic eyes will be discussed along with our own results.

### 4.9.2 Cataract extraction after ALT

Because cataract extraction does not affect the ocular hypotensive effect of ALT, cases of glaucoma and co-existing cataract should preferably be treated first by ALT and then by cataract extraction (unless one opts in favour of pressure-reducing surgery) (Thomas et al. 1982; Brown et al. 1985b; Savage et al. 1985; Simmons 1987; Goldmann & Mellin 1988). This sequence is given extra emphasis in view of the fact that results of ALT in aphakic (and pseudophakic?) eyes are less good than those in phakic eyes.

If cataract extraction is performed after ALT, there is no difference in effect between ICCE and ECCE (Brown et al. 1985b; Goldmann & Mellin 1988).

Savage et al. (1985) found no difference in early pressure elevations after cataract extraction in glaucomatous eyes controlled by ALT or by medication. However, the incidence of these pressure elevations was higher in glaucomatous (29%) than in non-glaucomatous eyes (3%); intensive postoperative check-ups are therefore imperative.

Galin et al. (1984) found that 3 months after ALT followed by cataract extraction and implantation an IOP of less than 19 mm Hg could be maintained

with topical medication in only 25% of cases. After sclerectomy, cataract extraction and anterior chamber implantation this was achieved without topical medication in 40% of cases. They concluded that combined surgery with or without implantation effects better and more significant IOP control than ALT followed by cataract extraction and implantation. A conspicuous fact was that the original ALT group comprised 27 patients and that an IOP of less than 19 mm Hg was achieved in only 7. The ALT modification used did not differ markedly from other modifications, apart from a somewhat lower power setting (600-800 mW). An exact analysis of their results in relation to ALT is not feasible due to lack of relevant information.

## 4.10 ALT IN PSEUDO-EXFOLIATION GLAUCOMA

The results of ALT in pseudo-exfoliation glaucoma are listed in table 4.18. The studies quoted have been so chosen as to permit comparison with results in POAG.

Without exception, the IOP decrease achieved in pseudo-exfoliation glaucoma exceeds that in POAG. However, the initial IOP in pseudo-exfoliation is always higher than that in POAG, and a marked IOP decrease was therefore to be expected. Other studies not directly comparing results with those in POAG also mention marked IOP decreases: 39.7% of an initial IOP of 31.2 mm Hg (Lieberman et al. 1983); 31.0% of an initial IOP of 28.7 mm Hg (Logan et al. 1983); 51.5% of an initial IOP of 33 mm Hg (Robin & Pollack 1983); 24.9% of an initial IOP of 27.1 mm Hg (Xu et al. 1985).

Does this marked IOP decrease result in a higher success rate? At first glance the success rate for pseudo-exfoliation glaucoma indeed seems higher than that for POAG, but this impression changes when the duration of follow-up is considered. Virtually all quoted studies with a maximum follow-up of 12 months show a higher success rate for pseudo-exfoliation glaucoma than for POAG, but from 12 months on there are some shifts in that the success rate for both becomes equal. In this respect the study of Rouhiainen (1987b) is not representative because low-energy ALT modifications were used, which exert an essential influence on the success rate.

If the above suggested correlation between success rate and follow-up ap-

plies, than pseudo-exfoliation glaucoma has a higher initial response but also a higher failure rate with an increasing follow-up period. Higginbotham & Richardson (1986) used the Kaplan-Meier curve data analysis and established that pseudo-exfoliation glaucoma did show a faster rate of failure than POAG. Others, too, reported a faster diminution of the IOP decrease in pseudo-exfoliation glaucoma compared with POAG (Pohjanpelto 1983; Schwartz & Kopelman 1983; Moulin et al. 1987; Tenner & Keck 1987).

These tendencies are well illustrated in studies by Tuulonen et al. (1985, 1987) in which ALT was performed as primary therapy. The initial success rate in pseudo-exfoliation glaucoma was 94.3%, versus 72.2% in POAG. After a 5-year follow-up, however, both groups showed a success rate of 50%. This demonstrates, firstly that the success rate diminishes as the follow-up progresses, and secondly that the failure rate in pseudo-exfoliation glaucoma takes a faster course.

For the sake of completeness it is to be noted that in some studies pseudo-exfoliation glaucoma continued to show a higher success rate (Bergeå 1986a).

**To summarize: pseudo-exfoliation glaucoma shows a more marked initial decrease than POAG, which is explained by the higher initial IOP; the initial success rate is higher in pseudo-exfoliation, but the failure rate increases more rapidly.**

### 4.11 ALT IN PIGMENT DISPERSION SYNDROME AND GLAUCOMA

Table 4.19 lists the results of ALT in pigment dispersion syndrome with glaucoma. Because the number of eyes treated is usually small, direct comparison with POAG is as a rule impossible.

The pigment dispersion syndrome generally seems to respond well to ALT, but the various studies report a wide range of success rates (43.8% to 100%). This cannot be explained with the aid of the available literature data. Lunde (1983) found a correlation between age and ALT response in patients with the pigment dispersion syndrome. He found that the subgroup showing failure after a varying interval showed a higher average age than the success group (59 versus 31 year) and had a longer glaucoma history

(10.2 versus 2.5 years). Because the pigment dispersion syndrome usually becomes manifest in the fourth decade of life (Hoskins 1978), the duration of the glaucoma history must be determined largely by age. Discarding mean age in favour of proportions, we find that age was always under 40 in the success group (4 patients, 6 eyes), whereas in the failure group (6 patients, 6 eyes) only one patient was under 40, the others all being 58 years or older.

Another remarkable fact was that the eyes in the failure group had a higher IOP at the time of failure than the initial IOP. Lunde concluded that in cases of this type it is quite possible to inflict further damage on the trabecular meshwork.

Taking Lunde's data as representative, the range of success rates should in part be explicable from the age distribution. Unfortunately this age correlation cannot be studied in detail because most studies give no (specific) age definition.

Lieberman et al. (1983) found a mean age of 37.7 years in the success group and of 51 years in the failure group. Robin & Pollack found a 100% success rate at a mean age of 36 years. Traverso et al. (1986) found no difference in response between patients under and patients over 60. In view of Lunde's finding this age limit was too high. Lieberman et al. (1983), by the way, found no increase in excess of the initial IOP in failure cases.

**In summary it may be stated that ALT in the pigment dispersion syndrome gives a good response provided the patient is not older than 40-50 years and has no excessively long glaucoma history. One should be alert to the possibility of an IOP increase following ALT in the somewhat older patient.**

### 4.12 ALT IN LOW-TENSION GLAUCOMA

Because the IOP decrease largely depends on the initial IOP, one may wonder whether ALT can be successful in low-tension glaucoma.

In 8 patients with low-tension glaucoma and a maximal initial IOP of 21 mm Hg, Strasser & Stelzer (1983) found a mean IOP decrease of 4.13 mm Hg. The contralateral eyes served as control eyes and showed an IOP increase by 0.16 mm Hg. The IOP decrease in the treated eyes therefore was an ALT effect. Unfortunately these IOP changes were recorded after a very brief follow-up pe-

riod (2 weeks) and consequently are of no value in assessing the success rate of ALT in low-tension glaucoma.

Schwartz et al. (1984) reported a success rate of 72.7% after a mean follow-up of 21.6 months. They deemed an ALT successful if there was no further progression of optic disk damage and visual field loss and if the IOP decrease amounted to at least 2 mm Hg. After 12 months 16 out of 22 eyes were found to fulfil these criteria. The IOP decrease in this group was 5.8 mm Hg after 2 months, 4.9 mm Hg after 12 months, and 3.3 mm Hg after 24 months. Again we observe a diminishing IOP decrease with an increasing follow-up period. In 7 eyes of this group a diurnal IOP curve was determined before and after ALT. The mean pre-ALT IOP was 16.27 mm Hg, and the mean peak IOP was 19.43 mm Hg. After ALT, both had decreased by 6.2 mm Hg - a finding corresponding with that reported by Greenidge et al. (1983). In 18% of the eyes an IOP increase occurred after 1-21 days. Schwartz et al. concluded that ALT results in low-tension glaucoma are encouraging even though the effect diminish with increasing time.

Thomas et al. (1982) treated 65 eyes with an initial IOP of 10-19 mm Hg. After a mean follow-up of 4.7 months the IOP decrease was 4.2 mm Hg (28.0%). A subpopulation of these eyes had an initial IOP of 10-14 mm Hg and in this group the IOP decrease was 2.6 mm Hg; despite this limited IOP decrease Thomas et al. stated that eyes with an initial IOP of 13-14 mm Hg occasionally do show an IOP of 8-9 mm Hg after ALT.

Sharpe & Simmons (1985) performed ALT on 85 eyes of 67 patients with a maximum initial IOP of 19 mm Hg. Because bilateral treatment is a source of bias, only the eyes treated first were included in this study. After a mean follow-up of 30 (12-50) months a success rate of 46.3% was measured (31 eyes), the criteria applied being an IOP decrease of at least 20% and a stable visual field and optic disk. Of the 36 failure eyes, 25 showed no 20% IOP decrease but did have a stable visual field and optic disk. Only 11 eyes (16.4%) showed further glaucomatous progression or needed pressure-reducing surgery. A striking finding was that a number of eyes had an IOP between 0 and 5 mm Hg after ALT, although no eye showed this very low IOP after 30 months.

**To summarize: fairly good results can be obtained also in low-tension glaucoma; in this category, too, the IOP decrease diminishes with increasing**

time; in some cases, however, very low IOP values are achieved.

### 4.13 ALT IN SECONDARY GLAUCOMA

The following survey presents ALT results in various secondary types of glaucoma; most of the studies listed involve small number of eyes and direct comparison with POAG is therefore impossible.

| Type of glaucoma | Number | Success | Authors |
|---|---|---|---|
| Angle-recession | 4 | 3 | Thomas et al. (1982) |
| | 4 | 0 | Robin & Pollack (1983) |
| Traumatic | 4 | 1 | Tuulonen & Airaksinen (1983b) |
| | 4 | 0 | Goldmann & Mellin (1987) |
| Uveitic | 4 | 3 | Thomas et al. (1982) |
| | 6 | 2 | Horns et al. (1983) |
| | 8 | 3 | Robin & Pollack (1983) |
| | 5 | 1 | Tuulonen & Airaksinen (1983b) |
| | 11 | 3 | Goldmann & Mellin (1987) |
| Juvenile | 10 | 4 | Horns et al. (1983) |
| | 3 | 0 | Schlosshardt (1986) |
| Congenital | 4 | 2 | Robin & Pollack (1983) |
| Sturge-Weber syndrome | 2 | 2 | Robin & Pollack (1983) |

The fact that in secondary glaucoma types ALT produces an adequate IOP decrease and success rate in few if any cases is explained by the cause of the IOP increase. The possible effect of ALT is based on a collapsed trabecular meshwork which after ALT shows an increase in intertrabecular space. In most cases of secondary glaucoma the trabeculae are not collapsed and consequently ALT cannot be effective. Another reason is that many eyes with secondary glaucoma are also aphakic. which as such may explain a less good response (Tuulonen & Airaksinen 1983b).

### 4.14 MODE OF ACTION

Because ALT is applied to the trabecular meshwork, it seems obvious that

the pressure-reducing effect should result from local changes. Ocular changes following ALT will now be discussed from various points of view. That the mode of action of ALT probably involves the trabecular meshwork seems plausible on the basis of conclusions from:

**Clinical findings:**

ALT is an effective therapy for POAG (4.2) and particle block glaucomas such as pseudo-exfoliation glaucoma (4.10) and pigment dispersion syndrome (4.11). Secondary forms of glaucoma in which trabecular changes often play no major role, will generally benefit little from ALT (4.13).

**Pathogenetic findings:**

That pathological changes in the trabecular meshwork play a role has been discussed in 2.2.2.7; these changes can be summarized as follows:

1. Hyalinization of the uveal and corneoscleral trabeculae.
2. Plaque formation in the endothelial meshwork.
3. Decreased cellular density of the trabecular meshwork.
4. Decreased frequency and size of the vacuoles in the endothelial lining of Schlemm's canal.
5. Stenosis and obliteration of Schlemm's canal.
6. Increasing concentration of electron-dense material in the endothelial meshwork.
7. Increased concentration of glycosaminoglycans in the empty spaces.

That ALT causes changes in this system will be discussed below.

**Tonographic findings:**

Table 4.20 presents tonographic findings following ALT. Both after a very brief follow-up (1 day, Merté et al. 1985) and after a longer period (24 months, Schwartz & Kopelman 1985) the facility of outflow is significantly increased. Bischoff & Speiser (1985) also found an increased facility of outflow but this was evident only in eyes with low pre-ALT value. Although the above findings are consistent throughout the literature, Makabe (1988) found that the IOP decrease in the first days following ALT was attributed mainly to a reduction in aqueous humour formation, while the late IOP reduction resulted from an increase in facility of outflow.

Brubaker & Liesegang (1983) reported increased facility of outflow and diminished resistance to outflow but no changes in rate of flow of aqueous, permeability of blood-aqueous barrier, permeability of corneal endothelium, volume of anterior chamber, mean endothelial cell size and corneal thickness. Traverso et al. (1984b) found no statistically significant difference between pre-ALT and post-ALT corneal endothelial cell density. An even more impressive sign that ALT acts via this increased outflow is the fact that no increased values are found in failure eyes (Brubaker & Liesegang 1983).

**Fluorophotometric findings:**

Feller & Weinreb (1984) found a significantly increased fluorescein leakage 1 day and 1 week after ALT - a finding suggestive of a disturbance of the blood-aqueous barrier. One month after ALT there was no longer any difference from the pre-ALT value or from control eyes. The increased leakage in the immediate post-ALT phase may indicate a disturbance of the blood-aqueous barrier and may explain the IOP increase. However, the ocular hypotensive effect of ALT cannot be attributed to a lasting change in this barrier.

**Findings of Wise & Witter (1979) and Wise (1981, 1984, 1987):**

Wise suggested as hypothetical mode of action that ALT reduces the circumference of the trabecular ring by causing shrinkage of the collagen of the trabecular beams and, secondly, by retraction following cicatrization. As a result, the trabecular ring is displaced towards the centre of the anterior chamber, and the intertrabecular space increases. This is described as 'tightening effect'.

**Low-dose ALT:**

That the ocular hypotensive effect of ALT is not based solely on mechanical factors is evident from the results obtained by ALT applied to only a very limited part of the trabecular meshwork. Although the IOP decrease achieved in most of these cases is insufficient, a few successes are on record. Drance et al. (1987) achieved adequate IOP control in 2 out of 12 eyes treated by application of only 10 burns to 30° of the trabecular meshwork circumference.

**Histopathological findings:**

Post-ALT histopathological findings are only of relative value, on the one hand because no trabeculectomy material can be obtained from successfully treated patients, and on the other hand because eyes obtained postmortem after a successful ALT are hardly available. Trabeculectomy material from patients with an insufficient response to or an IOP increase after ALT does provide some information, but this findings must not be simply extrapolated to eyes successfully treated by ALT. The same applies to eyes submitted to ALT while a trabeculectomy had already been planned (Rodrigues et al. 1982).

Animal experiments, more specifically in simian eyes, provide no real solution to the problem because the anatomy of the iridocorneal angle and trabecular meshwork in simian eyes clearly differs from that in human eyes (Van der Zypen & Fankhauser 1984). Even if one accepts this, the fact remains that one must make do with non-glaucomatous eyes because induction of chronic glaucoma without interference with the trabecular meshwork is impossible.

Nevertheless, continued histopathological research is certainly to be recommended because results, in combination with other findings, may lead to plausible hypothesis concerning the ocular hypotensive effect of ALT.

**Histopathological findings as to localization of laser burns:**

By means of histopathological verification Starita et al. (1984b) demonstrated that it is possible to localize laser burns exactly on the desired part of the trabecular meshwork during ALT.

Histopathological measurements of the size of laser burns at a spot size of 50 µm produces surprising results. Melamed & Epstein (1987a) found that this spot size could lead to a burn with an average diameter of 218 µm. Several possible explanations present themselves. Wise (1984) established that only 4 of the 27 lasers he examined actually gave a spot size of 50-60 µm after setting the value at 50 µm. The others gave spot sizes with a diameter of 70 µm (twice the surface area) to 160 µm (ten times the surface area).

The size of the burn proves to depend on the power setting, higher setting giving larger burns (Starita et al. 1984b; Melamed & Epstein 1987a). The degree of pigmentation likewise correlates with burn size: larger burns are seen with increasing pigmentation (Starita et al. 1984b; Zink et al. 1984). A striking fact in this context is that both the power and the degree of

pigmentation have to meet minimum requirements if a successful IOP decrease is to be achieved.

**Histopathological findings after ALT in human eyes:**

In human eye-bank eyes submitted to ALT at an IOP of 20-40 mm Hg, Van Buskirk et al. (1984) found distention of Schlemm's canal after ALT at an IOP of 40 mm Hg; trabecular cell density in the treated eyes was 39% lower than in the treated eyes, and the distribution of incorporated $^{35}$S-sulphate in the treated eyes was evidently different. The latter finding is a reflection of the production of glycosaminoglycans and therefore of the extracellular matrix. These authors hypothesized that, apart from a mechanical effect, ALT also interferes with cellularity and with synthesis of glycosaminoglycans in the remaining cells. Bylsma et al. (1988) found that the decreased cellularity is preceded by an increase in DNA replication (1-2 days after ALT).

In trabecular material obtained shortly after ALT, Rodrigues et al. (1982) found disruption of trabecular beams, clusters of melanin pigment granules, macrophages and oedema of endothelial cells at the site of laser burn. Adjacent areas were relatively intact.

Greenidge et al. (1984) found similar changes in trabeculectomy material obtained during an IOP increase after ALT. Excessive presence of intertrabecular material after ALT may offer a mechanical explanation of the occurrence of IOP increases.

Trabeculectomy material obtained after a longer interval showed fibrosis at the site of the laser burn, this area being covered by a layer of abnormal corneal endothelial cells with migratory features. These cells obliterated the intertrabecular spaces. The chance that cells of this type migrate increases as the burn localization is more anterior; however, abnormal (trabecular endothelial?) cells have also been observed after posterior burn localization (Rodrigues et al. 1982).

These findings are compatible with the tightening effect postulated by Wise.

**Histopathological findings in simian eyes:**

Melamed et al. (1985, 1986, 1987a) also found disruption of trabecular beams, debris in the intertrabecular spaces, inflammatory cells and phago-

cytic activity of the endothelial cells in the immediate post-ALT phase. The endothelial meshwork was intact. After 4 weeks the laser burns had turned into organized scars with adherence and collapse of trabecular beams. In these studies, too, mention is made of the cellular layer continuous with the corneal endothelium.

The area without lesions showed wide open intertrabecular spaces free from debris. The undamaged parts of the inner wall of Schlemm's canal showed significantly more herniations than the damaged areas. These herniations comprised significantly more vacuoles, as confirmed by tracer studies (Melamed & Epstein 1987b). This may be explained by a shift of aqueous humour to the undamaged areas.

In the acute post-ALT phase Van der Zypen & Fankhauser (1984, 1987) likewise found the above described changes, with in addition dissolution of collagenous components in the trabecular meshwork. This collagen degradation increases, while at the same time the cells of the endothelial meshwork show a lytic degenerative process. The monolayer of endothelial cells forms simultaneously. After considerable time the laser burns no longer contain cells, and but little collagen. Besides these degenerative processes, regenerative processes are seen with cells seeming to produce collagen or to produce phagocytic action. The amount of collagen has diminished, both in the trabeculae and intertrabecularly.

## CONCLUSIONS

At least three factors would seem to play a role in the ocular hypotensive effect of ALT:

1. **A mechanical factor.** Histopathological findings are consistent with the tightening effect postulated by Wise. Another mechanical factor may be a shift of aqueous humour to undamaged areas of the trabecular meshwork.
2. **A cellular factor.** A decrease in the cellular density of the trabecular meshwork may stimulate the other cells to develop activity. Manifestations of this activity may be increased phagocytic activity, migration of cells, degeneration and regeneration of cells.
3. **A biochemical factor.** After ALT, trabecular endothelial cells show a

changed production of glycosaminoglycans, leading to a change in the composition of the extracellular matrix. The collagen turnover likewise changes with, as a result, a decrease in the amount of intertrabecular collagen.

Two theories are currently being entertained with regard to IOP increases following ALT:

1. **Disturbance of the blood-aqueous barrier** as manifested by increased fluorescein leakage in the immediate post-ALT phase. A fact compatible with this is that prostaglandins can induce IOP increases. A fact incompatible with this is that prostaglandin synthetase inhibitors exert no influence on the IOP increases.
2. A second explanation is **mechanical blockage** of intertrabecular spaces after ALT. Compatible with this are the histopathological findings, the fact that pilocarpine partly prevents IOP increases, and the limited duration of the IOP increases, which corresponds with the time required by cells to develop phagocytic activity.

# APPENDIX

# TO

# CHAPTER 4

Table 4.1. Results of laser treatment of the iridocorneal angle in the early and late Seventies.

| | Laser Type | Spot Size | Exp. Time | Number Burns | Power | Total Energy | Circum-ference | Results |
|---|---|---|---|---|---|---|---|---|
| Krasnov (1973) | Q-switched ruby | 250-500 | | 10-20 | | 2-4 | <180° | initial hypotensive |
| Hager (1973) | cont. wave argon | 50 | 1-3 | 1-3 | 1000 | 1-9 | <180° | initial hypotensive |
| Gaasterland & Kupfer (1974) | cont. wave argon | 50 | 0.2-0.5 | 200 | 400-800 | 16-80 | 360° | induced glaucoma |
| Ticho (1977) | cont. wave argon | 50 | 0.1 | 50 | 1000-3000 | 5-15 | 60° | initial hypotensive |
| Wickham et al. (1977) | cont. wave argon | 50 | 0.2<br>0.2 | 150<br>170 | 50<br>1200 | 1.5<br>41 | 360°<br>360° | outflow increase<br>outflow decrease |
| De Heer & Peperkamp (1979) | cont. wave argon | 50 | 0.02-0.1 | 30-120 | 500-2500 | 2.1-8.4 | 360° | favourable |
| Stiegler (1979) | pulsed argon | 50 | 1-1.5 | 40 | | | 90° | 81% success rate |
| Wise & Witter (1979) | cont. wave argon | 50 | 0.1 | 100 | 1000-1500 | 10-15 | 360° | 90% success rate |

Spot Size in μm.
Exposure Time in seconds.
Power in mW.
Total Energy in Joules.
Circumference : Total amount of trabecular meshwork circumference treated.
Cont. wave argon: Continuous wave argon laser.

Table 4.2. Results of Standard Wise ALT as secondary therapy in phakic, (primary) open-angle glaucoma.

| | Year | Design | Ind | Type | N | FU | IIOP ± SD | IOPD | IOPD(%) | SC | SR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wise | 1981 | pro | 1 | OAG | 150 | 6 | 28.37 | 12.3 | 43.2 | 2 | 85.3% |
| Wilensky & Jampol | 1981 | pro | 1 | OAG | 22 | 11.3 | 27.5 ± 3.2 | 7.2 | 26.2 | 6 | 100 % |
| Thomas et al. | 1982 | pro | 1 | POAG | 237 | 5 | 23.0 | 7.0 | 30.4 | 3,4,6 | 85.2% |
| Horns et al. | 1983 | retro | 1 | POAG | 174 | 10 | 25.4 ± 4.9 | 7.8 | 30.6 | 6 | 82.3% |
| Lieberman et al. | 1983 | retro | 1 | POAG | 74 | 11-26 | 25.2 | 7.8 | 30.9 | 1,4,6 | 79.7% |
| Pohjanpelto | 1983 | pro | 2 | POAG | 59 | 6 | 25.2 | 9.2 | 36.5 | 1,2,5 | 76.3% |
| Schwartz & Kopelman | 1983 | pro | 1 | OAG | 82 | 24 | 25.8 ± 6.1 | 7.3 | 29.7 | 1,3,4 | 77 % |
| Tuulonen & Airaksinen | 1983a | retro | 2 | POAG | 52 | 12 | 21.2 ± 0.7 | 4.6 | 21.7 | 2,3,4 | 65.4% |
| Bergeå | 1984 | pro | 1 | POAG | 50 | 6 | 25.9 ± 4.0 | 7.2 | 27.8 | 2 | 90.0% |
| Demailly et al. | 1985 | pro | 1 | POAG | 104 | 12 | | | | 6 | 93.3% |
| Traverso et al. | 1986 | pro | 1 | POAG | 186 | 3-22 | 21.7 ± 7.5 | 4.2 | 19.5 | 4 | 72.0% |
| Schultz et al. | 1987 | pro | 1 | OAG | 19 | >12 | 25.8 ± 5.2 | 6.7 | 26.0 | 1,2 | 68.4% |

Design : Design of study (pro: prospective; retro: retrospective).
Ind : Indication to treat patients (1: presurgical patients; 2: ALT as primary therapy included).
Type : Glaucoma type treated ((P)OAG: (primary) open-angle glaucoma).
N : Number of eyes.
FU : Follow-up (months).
IIOP ± SD : Initial IOP ± standard deviation in mm Hg.
IOPD : IOP decrease in mm Hg.
IOPD (%) : Relative IOP decrease as a function of IIOP.
SC : Success criteria (1: minimal IOPD included; 2: final maximum IOP included; 3: optic disk stable; 4: visual field defect stable; 5: stop glaucoma medication / no start of glaucoma medication; 6: avoid surgery).
SR : Success rate.

Table 4.3. Results of Standard Wise ALT as primary therapy in phakic, (primary) open-angle glaucoma.

| | Year | Design | Ind | Type | N | FU | IIOP ± SD | IOPD | IOPD(%) | SC | SR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rosenthal et al. | 1984 | pro | i | OAG | 43 | 6-18.5 | 30 | 13-14 | 43-46 | 2,5 | 65.1% |
| Thomas et al. | 1984 | pro | i | OAG | 26 | 7.5 | 30.2 | 9.9 | 32.8 | 5,6 | 83.3% |
| Tuulonen | 1984 | retro | i | POAG | 21 | 12 | 25.6 ± 0.9 | 7.7 | 30.1 | 2,3,4,5 | 81.0% |

Ind: ALT as initial therapy. Remaining abbreviations as in table 4.2.

Table 4.4. Results of Standard Wise ALT in phakic, (primary) open-angle glaucoma. IOP decrease as a function of follow-up (months).

| | Year | FU: | 6 | 12 | 18 | 24 | 30 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moulin & Haut | 1983 | mm Hg | 9.0 | 9.9 | | | | | | | | | | | |
| | | % | 37.0 | 36.9 | | | | | | | | | | | |
| Pohjanpelto | 1983 | mm Hg | 11.0 | 11.0 | 11.5 | 11.1 | 11.1 | 11.8 | | | | | | | |
| | | % | 39.8 | 39.8 | 41.7 | 40.2 | 40.2 | 42.8 | | | | | | | |
| Tuulonen et al. | 1985 | mm Hg | | 6.6 | 5.3 | 7.0 | 3.9 | | | | | | | | |
| | | % | | 29.1 | 24.5 | 31.3 | 18.0 | | | | | | | | |
| Schwartz et al. | 1985 | mm Hg | 8.9 | 7.8 | 7.7 | 7.3 | 6.9 | 7.0 | 6.8 | 4.9 | | | | | |
| | | % | 35.3 | 31.0 | 31.3 | 29.8 | 27.5 | 28.1 | 28.8 | 19.7 | | | | | |
| Wise | 1987 | mm Hg | | 11.8 | | 11.2 | | 13.0 | 11.6 | 12.3 | 12.4 | 12.5 | 12.6 | 13.4 | 12.5 |
| | | % | | 40.2 | | 37.8 | | 43.9 | 39.2 | 41.6 | 41.9 | 42.2 | 42.6 | 45.3 | 42.2 |

FU : Follow-up in months.
mm Hg: IOP decrease in mm Hg.
% : Relative IOP decrease as a function of initial IOP.

Table 4.5. Results of Standard Wise ALT in phakic, (primary) open-angle glaucoma. Success rate as a function of follow-up (months).

| | Year(s) | FU: | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|---|---|---|---|---|---|---|---|---|---|
| Moulin et al. | 1987 | | 89.0% | 71.6% | 64.4% | 59.1% | | | |
| Schwartz et al. | 1981, 1983, 1985 | | 96.3% | 76.8% | | | 46.3% | | |
| Wise | 1979, 1981, 1987 | | 91.8% | 89.1% | 84.5% | 77.3% | 71.8% | 70.0% | 63.2% |

Table 4.6. Incidence of side effects and complications after ALT.

| | Year | Iritis | Haemorr | Opacit | PAS | IOPS Incid | IOPS Min | IOPS Time |
|---|---|---|---|---|---|---|---|---|
| Schwartz et al. | 1981 | 100% | 5.7% | frequent | 28.6% | | | |
| Wilensky & Jampol | 1981 | 100% | | 25% | rare | | | |
| Wise | 1981 | common | 5.0% | frequent | 0.7% | | | |
| Lichter | 1982 | | 2.0% | | 2.0% | 24.0% | 1 | day 1 |
| Thomas et al. | 1982 | | 2.3% | | 47.1% | 25.3% | 1 | day 1 |
| Horns et al. | 1983 | common | 0.3% | | | 9.2% | 1 | day 1 |
| Lieberman et al. | 1983 | common | | | 15.0% | 33.0% | 5 | 1-6 h |
| | | | | | | 22.0% | 10 | 1-6 h |
| | | | | | | 6.1% | 10 | day 1 |
| Moulin & Haut | 1983 | | 8.0% | | 42.0% | 19.0% | 4 | |
| Pohjanpelto | 1983 | common | | | 19.4% | 14.4% | 5 | day 1 |
| Schwartz & Kopelman | 1983 | 100% | 5.0% | | 32.0% | 8.5% | 5 | day 1 |
| Tuulonen & Airaksinen | 1983a | common | 3.8% | occasionally | 3.8% | 11.1% | 5 | day 1 |
| Weinreb et al. | 1983a | | | | | 70.0% | 4 | 1-8 h |
| Bergeå | 1984 | common | | sometimes | | 14.8% | 1 | day 1 |
| Krupin et al. | 1984 | | | | | 56.1% | 1 | 1-7 h |
| Smith | 1984 | common | | | 23.0% | 16.0% | 5 | day 1 |
| Zborowski et al. | 1984 | | | | | 26.2% | 8 | 1-2 h |
| Finnström | 1985 | 59% | 1.9% | 80.0% | | 3.8% | 10 | 2-3 h |
| Frucht et al. | 1985 | 100% | | | | 42.1% | 1 | 1-4 h |
| | | | | | | 21.1% | 10 | 1-4 h |

Haemorr: Haemorrhages during ALT.
Opacit : Corneal opacities.
PAS : Peripheral anterior synechiae.
IOPS : IOP spike.
Incid : Incidence.
Min : Minimal IOP change indicating an IOPS in mm Hg.
Time : First check-up at which IOP was measured (h: hours).

Table 4.7. Incidence of IOP spikes with different pre- and post-ALT medication.

| | Year | Medication | Minimal positive change (mm Hg) | Incidence of IOPS | | p-value |
|---|---|---|---|---|---|---|
| | | | | Treated | Untreated | |
| Ruderman et al. | 1983 | prednisolone | 1 | 77.8% | 70.0% | NS |
| Ofner et al. | 1984 | pilocarpine 4% | 1 | 36.3% | 72.7% | p< 0.05 |
| Robin et al. | 1987 | ALO 2145 | 1 | 20.5% | 58.8% | p< 0.001 |
| | | | 10 | 4.0% | 17.6% | p< 0.005 |
| Brown et al. | 1988 | ALO 2145 | 5 | 9.8% | 23.8% | p= 0.095 |
| | | | 10 | 4.9% | 19.0% | p= 0.062 |
| Weinreb et al. | 1984 | flurbiprofen | 1 | 58.7% | 56.4% | NS |
| Hotchkiss et al. | 1984 | flurbiprofen | 10 | 5.6% | 20.6% | NS |
| Tuulonen | 1985 | indomethacine | 1 | 41.6% | 32.0% | NS |
| | | | 10 | 4.2% | 16.0% | NS |
| Pappas et al. | 1985 | indomethacine | 3 | 60.0% | 40.0% | NS |
| | | | 9 | 8.0% | 12.0% | NS |
| Gelfand & Wolpert | 1985 | indomethacine | 1 | 56.5% | 59.1% | NS |

NS : Not significant.
Treated : Pre- or Post-ALT treatment with the respective medication.
Untreated: Control (placebo) group.

Table 4.8. Mean maximum change in IOP with different pre- and post-ALT medication.

| | Year | Medication | Mean Maximum IOP Change (mm Hg) | | p-value |
|---|---|---|---|---|---|
| | | | Treated | Untreated | |
| Ruderman et al. | 1983 | prednisolone | + 7.72 ± 8.62 | + 7.35 ± 9.28 | NS |
| Ofner et al. | 1984 | pilocarpine 4% | no mean change | + 3.1 | p< 0.05 |
| Robin et al. | 1987 | ALO 2145 | < initial IOP | > initial IOP | p< 0.001 |
| Brown et al. | 1988 | ALO 2145 | < initial IOP | > initial IOP | p< 0.05 |
| Weinreb et al. | 1984 | flurbiprofen | + 0.9 | + 0.4 | NS |
| Hotchkiss et al. | 1984 | flurbiprofen | + 0.7 | - 1.6 | NS |
| Tuulonen | 1985 | indomethacine | + 1.7 ± 3.9 | + 2.9 ± 7.0 | NS |
| Pappas et al. | 1985 | indomethacine | + 2.2 ± 3.8 | + 2.9 ± 5.1 | NS |
| Gelfand & Wolpert | 1985 | indomethacine | + 1.39 ± 4.18 | + 1.63 ± 5.80 | NS |

Abbreviations as in table 4.7.

Table 4.9. Results of modifications on Standard Wise ALT.

| | Year | Loc | Cir | Ses | Number | Exp | Spot | C | Power | Gl | E | N | FU | IIOP | IOPD | SR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heijl | 1984 | AN | 360 | 1 | 80-115 | 0.1 | 50 | 1 | * | 1 | | 21 | 1 m | 25.7 | 30.9 | |
| Schwartz et al. | 1983 | AN | 360 | 1 | 100 | 0.1 | 50 | 1 | ** | 1 | | 16 | 6 m | 21.0 | 28.0 | 64.0% |
| Finnstrom | 1985 | AN | 360 | 1 | 80-100 | 0.1 | 50 | 1 | 700-1000 | 2 | | 52 | 12 m | 26.6 | 28.0 | 80.8% |
| Weinreb et al. | 1983b | AN | 360 | 1 | 100 | 0.1 | 50 | | 800 | 3 | Y | 20 | 2 m | 28.0 | 24.8 | |
| Lustgarten et al. | 1984 | AN | 360 | 1 | 100 | var | 50 | 2 | var | 2 | Y | 16 | 4 w | 27.2 | 35.3 | 93.8% |
| Schwartz et al. | 1983 | AN | 360 | 1 | 50 | 0.1 | 50 | 1 | ** | 1 | | 31 | 6 w | 24.6 | 21.0 | 83.9% |
| Lustgarten et al. | 1984 | AN | 360 | 1 | 50 | var | 50 | 2 | var | 2 | Y | 14 | 4 w | 26.5 | 34.3 | 100 % |
| Heijl | 1984 | AN | 360 | 2 | 78-121 | 0.1 | 50 | 1 | * | 1 | | 16 | 1 m | 25.4 | 25.9 | |
| Singh & Kaur | 1987 | AN | 360 | 2 | 100 | 0.1 | 50 | 2 | 800-1200 | 4 | | 22 | 11 m | 26.0 | 27.7 | 77.3% |
| Blondeau et al. | 1987 | AN | 360 | 2 | 100 | 0.2 | 50 | 1 | 500 | 1 | | 14 | 24 m | 22.7 | 29.1 | 100 % |
| Martenet & Schwarzenb. | 1986 | AN | 180 | 1 | 50 | 0.1 | 50 | 1 | 600-1300 | 4 | | 104 | 1-12m | 25.9 | 29.4 | 86.5% |
| Kitazawa et al. | 1984 | AN | 180 | 1 | 50 | 0.1 | 50 | 1 | *** | 2 | | 18 | | 24.5 | | 54.6% |
| Weinreb et al. | 1983b | AN | 180 | 1 | 50 | 0.1 | 50 | | 800 | 3 | Y | 20 | 2 m | 28.0 | 32.9 | |
| Jager et al. | 1987 | AN | 180 | 1 | 50 | 0.1 | 50 | 2 | | 4 | | 52 | 6 m | 29.8 | 27.7 | 88.7% |
| Lustgarten et al. | 1984 | AN | 180 | 1 | 50 | var | 50 | 2 | var | 2 | Y | 15 | 4 w | 25.8 | 27.1 | 100 % |
| Skorpik et al. | 1986 | AN | 180 | 1+ | 100 | 0.1 | 50 | 1 | 1000 | | | 47 | 3 m | 23.0 | 25.6 | 83.0% |
| Schwartz et al. | 1983 | AN | 90 | 1 | 25 | 0.1 | 50 | 1 | ** | 1 | | 11 | 5 m | 24.0 | 10.4 | 59 % |
| Kitazawa et al. | 1984 | PO | 360 | 1 | 100 | 0.2 | 50 | 1 | *** | 2 | | 35 | >6 m | 24.0 | | 37.1% |
| Thomas et al. | 1982 | PO | 360 | 2 | 100 | 0.1 | 50 | 1 | 1090 | 4 | | 102 | | | | 86.3% |
| Reibaldi et al. | 1985 | PO | 360 | 2 | 100 | 0.1 | 50 | | 1000 | 3 | | 196 | 6-30m | | | 84.5% |
| Kitazawa et al. | 1984 | PO | 180 | 1 | 50 | 0.1 | 50 | 1 | *** | 2 | | 54 | >6 m | 24.7 | | 70.1% |
| Schwartz et al. | 1983 | PO | 180 | 1 | 50 | 0.1 | 50 | 1 | ** | 1 | | 30 | 4 m | 22.7 | 22.9 | 86.7% |
| Thomas et al. | 1982 | PO | 180 | 1 | 50 | 0.1 | 50 | 1 | | 4 | | 40 | 3 m | 25.1 | 32.7 | 95.0% |
| Schwartz et al. | 1983 | PO | 360 | 1 | 100 | 0.1 | 25 | 1 | ** | 1 | | 20 | 7.8m | 21.3 | 18.5 | 60.0% |
| Sherwood et al. | 1987 | PI | 360 | 1 | 100 | 0.1 | 150-350 | 1 | 500-1000 | 1 | Y | 24 | 30-40m | 23.8 | 30 | 79.2% |
| Raitta & Letho | 1983 | PI | 360 | 1 | 107 | 0.2 | 50-100 | 1 | 1000-2000 | 2 | | 81 | | 30.8 | 28.2 | |
| Klein et al. | 1985 | PI | 360 | 2 | 60-80 | 0.1 | 50 | 1 | 800-1200 | 1 | Y | 62 | 1 m | 27.1 | 28.4 | 77.8% |
| Lehmann & Faggioni | 1986 | PI | 360 | 2 | 80-119 | 0.1 | 50 | 1 | 490-910 | 3 | | 32 | 4 m | 25.1 | 39.0 | |
| Rouhiainen et al. | 1987a | PI | 180 | 1 | 40-60 | 0.1 | 50 | | 100-500 | 2 | | 67 | 3-12m | 23.0 | 7-18 | 21-50 |
| Grehn & Schildwachter | 1987 | PI | 180 | 2 | 50 | 0.1 | 50 | 1 | 300-1500 | 3 | Y | 115 | 3-29m | 26.5 | 18.9 | 50.4% |
| Lehmann & Faggioni | 1986 | PI | 90 | 1+ | 12-35 | 0.1 | 50 | 1 | 420-560 | 3 | | 30 | 4 m | 24.0 | 26.7 | |
| Wilensky & Weinreb | 1983a | PI | 90 | 1+ | 25 | 0.1 | 50 | | 900 | 3 | | 21 | | 29.9 | 22.7 | 47.6% |
| Dake & Bos | 1983 | SP | 360 | 1 | 100 | 0.1 | 50 | | | 3 | Y | 10 | 12 m | 25.5 | 33.3 | 90.0% |
| Elsås & Harstad | 1983 | SP | 180 | 1 | 100 | 0.1 | 50 | 1 | 600-1500 | 3 | | 54 | 0.5-10m | 26.2 | 30.2 | 92.6% |
| Payer | 1985 | CB | 360 | 1 | 100 | 0.1 | 50 | 2 | 500-800 | | Y | 101 | 4 w | 25.9 | 20.7 | 94.1% |
| Bechetoille et al. | 1985 | CB | 360 | 1 | 50-100 | 0.2 | 50 | | 1000-1200 | 3 | | 44 | 18m | | | 88.1% |
| Reibaldi et al. | 1985 | CB | 360 | 1 | >100 | 0.1 | 200 | | 400-600 | 3 | | 15 | 7-24m | | | 26.7% |

Loc : Localization of laser burns (AN: anterior trabecular meshwork; PO: posterior trabecular meshwork; PI: pigmented trabecular meshwork; SP: scleral spur; CB: ciliary band).

Cir : Total amount of trabecular meshwork circumference treated (expressed in degrees).
Ses : Number of sessions used to treat the trabecular meshwork (1+: second session performed if necessary).
Number: Total number of burns applied to the trabecular meshwork.
Exp : Exposure time in seconds (var: variable).
C : Criterion for burn (1: bubble formation and/or blanching; 2: just blanching).
Power : Power in mW (var: variable; *: 800-1650 mW, not specified for modification; **: 750-1300 mW, not specified for modification; ***: 700-1000 mW, not specified for modification).
Gl : Glaucoma type(s) treated (1: primary open-angle glaucoma; 2: primary open-angle glaucoma and pseudoexfoliation glaucoma; 3: open-angle glaucoma; 4: heterogeneous group of glaucomas).
E : Exclusion rules in selecting patients (Y: yes).
N : Number of eyes.
FU : Follow-up (m: months; w:weeks).
IIOP : Initial IOP in mm Hg.
IOPD : Relative IOP decrease in % as a function of initial IOP.
SR : Success rate.

Table 4.10. Incidence and height of IOP spikes as a function of:
a. Amount of trabecular meshwork circumference treated in one session (upper part).
b. Localization of laser burn (lower part).

| | Year | Circumference | Incidence | Height |
|---|---|---|---|---|
| Thomas et al. | 1982 | 360° vs 180° | 14.4% vs 8.8% | >5 mm Hg |
| | | 360° vs 180° | 9.4% vs 2.9% | >10 mm Hg |
| Weinreb et al. | 1983a | 360° vs 180° | 70.0% vs 55.0% | +12.1 vs +5.0 mm Hg |
| Heijl | 1984 | 360° vs 180° | 29.5% vs 17.1% | +10.9 vs +3.4 mm Hg |
| Kitazawa et al. | 1984 | 360° vs 180° | 82.1% vs 58.4% | +61.0% vs +22.6% |
| | Year | Anterior/Posterior | Incidence | Height |
| Schwartz et al. | 1983 | ant. vs post. | 6.3% vs 32.0% | -0.4 vs +3.2 mm Hg |
| Kitazawa et al. | 1984 | ant. vs post. | 22.2% vs 58.4% | +11.2% vs +22.6% |

Table 4.11. IOP decrease with different lasers of varying wavelengths.

| | Year | Laser | IOPD (mm Hg) | FU | p-value |
|---|---|---|---|---|---|
| Greenidge et al. | 1983 | Pulsed Argon vs Cont. Argon | 3.9 vs 3.6 | 8 w | not significant |
| Smith | 1984 | Argon BG vs Argon G | 7.1 vs 8.0 | 10 m | not significant |
| Spurny & Lederer | 1984 | Krypton R/Y vs Argon BG | 7.2 vs 6.9 | 5 m | |
| Makabe | 1986 | Krypton R vs Argon BG | 4.8 vs 7.0 | 24 h | $p < 0.01$ |
| | | Krypton R vs Argon G | 4.8 vs 7.6 | 24 h | $p < 0.01$ |
| | | Argon BG vs Argon G | 7.0 vs 7.6 | 24 h | $p > 0.5$ |
| | | Krypton R vs Argon BG | 2.3 vs 7.1 | 4 w | $p < 0.001$ |
| | | Krypton R vs Argon G | 2.3 vs 7.3 | 4 w | $p < 0.001$ |
| | | Argon BG vs Argon G | 7.1 vs 7.3 | 4 w | $p > 0.8$ |
| | | Krypton R vs Argon BG | 0.2 vs 7.9 | 3 m | |
| | | Krypton R vs Argon G | 0.2 vs 8.2 | 3 m | |
| | | Argon BG vs Argon G | 7.9 vs 8.2 | 3 m | |
| Martenet & Schwarzenbach | 1986 | YAG free run vs Argon BG | 3.9 vs 6.6 | 8 w | not significant |
| Schrems et al. | 1988 | YAG free run vs Argon B | 10.4 vs 9.6 | 11 m | not significant |

IOPD : IOP decrease.
FU : Follow-up (h: hours; w: weeks; m: months).
Argon : Argon laser (cont: continuous wave; BG: blue-green; G : green).
Krypton : Krypton laser (R: red; R/Y: red/yellow).
YAG free run: YAG laser, free-running mode.

Table 4.12. Correlation between success rate and patient variables.

| | Year | OD/OS | Pigm | Med | IIOP | Color | Age | Sex | Race | Glauc |
|---|---|---|---|---|---|---|---|---|---|---|
| Thomas et al. | 1982 | | | | | | YES | NO | NO | |
| Moulin & Haut | 1983 | | | | | | NO | | | |
| Schwartz & Kopelman | 1983 | NO | | | YES | NO | YES | NO | NO | |
| Safran et al. | 1984 | | | | YES | | YES | | | |
| Zborowski et al. | 1984 | | | | NO | | YES | NO | NO | |
| Demailly et al. | 1985 | | | | | | NO | | | |
| Schwartz et al. | 1985 | | | | NO | YES | NO | | YES | |
| Tuulonen et al. | 1985 | | NO | YES | YES | | NO | NO | | |
| Bergeå | 1986a | | YES | | NO | | | | | |
| Khan et al. | 1986 | | | | | | NO | | | |
| Krupin et al. | 1986 | | | | | | | | NO | |
| Lehmann & Faggioni | 1986 | | | | NO | | | | | |
| Traverso et al. | 1986 | | | | | | | | | YES |
| Rouhiainen et al. | 1987a | | | | | | NO | | | |
| Wise | 1987 | | | | | | | | NO | YES |

NO : No correlation found.
YES : Correlation found.
Pigm : Trabecular pigmentation.
Med : Pre-ALT medication.
IIOP : Initial IOP.
Glauc: Glaucomatous damage.

Table 4.13. Correlation between IOP decrease and patient variables.

| | Year | Refr | Pigm | IIOP | Age | Sex | Race | Med |
|---|---|---|---|---|---|---|---|---|
| Thomas et al. | 1982 | | | YES | YES | | | |
| Horns et al. | 1983 | | | YES | | | | |
| Lieberman et al. | 1983 | | | YES | | | | |
| Moulin & Haut | 1983 | | | | NO | | | |
| Safran et al. | 1984 | | | | YES | | | |
| Bergeå | 1984 | | YES | YES | | | | |
| Zborowski et al. | 1984 | | | YES | | | | |
| Klein et al. | 1985 | | | YES | | | | |
| Xu et al. | 1985 | | | | YES | | | |
| Brodell et al. | 1986 | | | YES | | | NO | |
| Krupin et al. | 1986 | | | YES | | | NO | |
| Lehmann & Faggioni | 1986 | | | YES | | | | |
| Traverso et al. | 1986 | NO | YES | YES | NO | | | |
| Grinichi et al. | 1987 | | NO | YES | | NO | | |
| Jäger et al. | 1987 | | | YES | | | | |
| Rouhiainen et al. | 1987a | | | YES | | NO | | |
| Traverso et al. | 1987 | NO | | YES | YES | | | |
| Rouhiainen et al. | 1988b | | YES | YES | NO | NO | | NO |

Refr.: Refractive error.
Remaining abbreviations as in table 4.12.

Table 4.14. Correlation between initial IOP and relative IOP decrease for:
a. Mean initial IOP (upper part).
b. Range of initial IOP (lower part).

| | Year | MIIOP | IOPD | MIIOP | IOPD | MIIOP | IOPD | MIIOP | IOPD | MIIOP | IOPD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Elsås & Harstad | 1983 | 17.4 | 20.1 | 22.9 | 27.5 | 26.6 | 32.7 | 32.2 | 45.6 | | |
| Klein et al. | 1985 | 19.4 | 12.9 | 24.0 | 27.9 | 29.4 | 32.0 | | | 36.9 | 36.6 |
| Brodell et al. | 1986 | | | 22.8 | 28.9 | 28.4 | 28.8 | 33.3 | 37.5 | 36.7 | 51.7 |

| | Year | RIIOP | IOPD | RIIOP | IOPD | RIIOP | IOPD | RIIOP | IOPD | RIIOP | IOPD | RIIOP | IOPD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Thomas et al. | 1982 | 10-19 | 28.0 | 20-29 | 30.4 | | | 30-39 | 39.7 | 40-49 | 47.3 | >50 | 50 |
| Schwartz & Kopelman | 1983 | | | 19-25 | 34 | 26-30 | 37 | >30 | 39 | | | | |
| Lehmann & Faggioni | 1986 | 15-19 | 19 | 20-24 | 24 | 25-29 | 42 | 30-34 | 39 | | | | |

MIIOP: Mean initial IOP (mm Hg).
RIIOP: Range of initial IOP (mm Hg).
IOPD : Relative IOP decrease in % as a function of initial IOP.

Table 4.15. Success rate and IOP spikes following retreatment.

| | | ALT | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Initial | | Retreatment | | | | | | IOPS | |
| | Year | Circ | Ses | Circ | Ses | N | Failures | SC | SR | Min | Incid |
| Starita et al. | 1984a | 360° | 1/2 | 360° | 1 | 17 | L | 1,4 | 35.0% | 10 | 29.4% |
| Brown et al. | 1985b | 360° | 1/2 | 360° | 2 | 26 | L | 1,6 | 38.5% | 10 | 11.5% |
| Bergeå | 1986b | 360° | 1 | 360° | 1/2 | 20 | E,L | 1,2 | 60.0% | | |
| Messner et al. | 1987 | 360° | 1/2 | 360° | 1 | 14 | L | 1 | 35.7% | 10 | 0 % |
| Richter et al. | 1987 | 360° | 1/2 | 180° | 1 | 40 | L | 1,3,4,6 | 32.5% | 6 | 0 % |

Circ : Total part of trabecular meshwork circumference treated.
Ses : Number of sessions (1/2: one or two sessions).
N : Number of eyes.
Failures: Failures following initial ALT (E: early failures (<2 months); L: late failures (>2 months)).
SC : Success criteria (1: minimal IOP decrease included; 2: maximum final IOP included; 3: optic disk stable; 4: visual field loss stable; 5: stop glaucoma medication/no start of glaucoma medication; 6: avoid surgery).
IOPS : IOP spike (min: minimum change in IOP indicating an IOPS (mm Hg); Incid: incidence).

Table 4.16. ALT and its effect on medical control.

| | Year | Glaucoma | FU | Medication | | |
|---|---|---|---|---|---|---|
| | | | | Less | Stopped | Total |
| Thomas et al. | 1982 | POAG | 5.2 | 26.1% | 0 % | 26.1% |
| Horns et al. | 1983 | POAG | 10 | | | 27.9% |
| Lieberman et al. | 1983 | OAG | 16 | 52.5% | 5.1% | 57.6% |
| Pohjanpelto | 1983 | POAG | 12 | 19.0% | 27.6% | 46.6% |
| Tuulonen & Airaksinen | 1983a | POAG | >12 | 17.6% | 35.3% | 52.9% |
| Zink et al. | 1984 | OAG | 1.5 | 64.9% | 17.5% | 82.4% |
| Demailly et al. | 1985 | POAG | 3 | 58.9% | 5.7% | 64.4% |
| | | | 12 | 70.4% | 10.1% | 80.5% |
| Finnström | 1985 | OAG | 12 | 55.6% | 4.0% | 59.6% |
| Xu et al. | 1985 | OAG* | 3 | 35.8% | 3.8% | 39.6% |
| | | OAG** | 3 | 35.0% | 10.0% | 45.0% |
| Sherwood et al. | 1987 | POAG | >12 | 45.8% | 12.5% | 58.3% |

Medication: Percentages of eyes with less or no medication following ALT.
Glaucoma : Glaucoma type(s) treated (POAG: primary open-angle glaucoma; OAG: open-angle glaucoma).
FU : Follow-up (months).
* : Half circumference ALT.
** : Full circumference ALT.

Table 4.17. Results of ALT in aphakic glaucoma.

| | Year | N | FU | IIOP mm Hg | IOPD % | SR |
|---|---|---|---|---|---|---|
| Wise & Witter | 1979 | 15 | 6 | 27.06 | 29.0 | 53.3% |
| Thomas et al. | 1982 | 29 | 2.7 | 21.7 | 9.7 | 58.6% |
| Bellows & Johnstone | 1983 | 15 | 8.2 | 25.3 | 32.4 | 80.0% |
| Horns et al. | 1983 | 34 | 10 | 24.7 | 27.9 | 83.3% |
| Lieberman et al. | 1983 | 7 | 11.3 | 22.7 | 26.4 | 85.7% |
| Robin & Pollack | 1983 | 6 | 7 | 34 | 50.0 | 100 % |
| Demailly et al. | 1985 | 6 | 12 | | | 50.0% |
| Hoskins | 1987 | 68 | 12 | | 6.4* | 70 % |
| Moulin et al. | 1987 | 12 | 24 | | 5.9* | 41.7% |

N : Number of eyes.
FU : Follow-up (months).
IIOP : Initial IOP (mm Hg).
IOPD : Relative IOP decrease in % as a function of initial IOP (*: mm Hg).
SR : Success rate.

Table 4.18. Initial IOP, relative IOP decrease and success rate in pseudo-exfoliation glaucoma as compared with POAG.

| | Year | FU | IIOP mm Hg | | IOPD % | | SR | |
|---|---|---|---|---|---|---|---|---|
| | | | POAG | PEG | POAG | PEG | POAG | PEG |
| Thomas et al. | 1982 | 5 m | 23.0 | 28.5 | 22.3 | 43.5 | 82.5% | 97.1% |
| Elsås & Harstad | 1983 | 0.5-10m | 23.4 | 27.4 | | 33.6 | | 94.1% |
| | | 1.0- 4.5m | | | 21.0 | | 93.7% | |
| Horns et al. | 1983 | 8 m | 25.5 | 30.2 | 30.6 | 42.4 | 82.3% | 87.5% |
| Pohjanpelto | 1983 | 6 m | 25.2 | 26.8 | 36.5 | 40.3 | 77.6% | 95.9% |
| | | | | | 35.7 | 36.9 | | |
| | | | | | 35.3 | 36.2 | | |
| Raitta & Lehto | 1983 | 6 m | 26.4 | 32.9 | 18.2 | 27.6 | | |
| | | 12 m | | | 17.4 | 30.7 | | |
| Tuulonen & Airaksinen | 1983a | 12 m | 21.2 | 24.1 | 21.7 | 36.5 | 65.4% | 68.4% |
| Bergeå | 1984 | 6 m | 25.9 | 29.9 | 27.8 | 43.8 | 90.0% | 97.6% |
| Demailly et al. | 1985 | 12 m | | | | | 93.3% | 94.1% |
| Schwartz et al. | 1985 | 2 m | | | 9.7* | 12.0* | | |
| | | 6 m | | | 8.9* | 11.8* | | |
| | | 18 m | | | 7.7* | 9.8* | | |
| | | 36 m | | | 7.8* | 7.6* | | |
| Tuulonen et al. | 1985 | 24 m | 24.4 | 28.8 | 31.3 | 32.4 | | |
| Bergeå | 1986a | 24 m | | | | | 44.9% | 75.9% |
| Higginbotham & Richardson | 1986 | 4-6w | 22.4 | 25.5 | 22.8 | 25.1 | | |
| | | 7-8w | | | 26.3 | 38.0 | | |
| Traverso et al. | 1986 | 9 m | 21.7 | 22.0 | 14.5 | 33.5 | | |
| Grinichi et al. | 1987 | 12 m | 27.1 | 29.9 | 31.3 | 37.1 | 79% | 73% |
| | | 24 m | | | | | 79% | 54% |
| | | 36 m | | | | | 59% | 54% |
| Rouhiainen et al. | 1987a | 12 m** | 23.1 | 22.5 | 9.1 | 17.8 | 35% | 50% |
| | | 12 m*** | 22.3 | 23.5 | 6.7 | 11.9 | 21% | 35% |
| Moulin et al. | 1987 | 24 m | | | | | 73.5% | 60.0% |

IIOP: Initial IOP (mm Hg).
IOPD: Relative IOP decrease in % as a function of initial IOP.
SR : Success rate.
FU : Follow-up (m: months; w: weeks).
POAG: Primary open-angle glaucoma.
PEG : Pseudo-exfoliation glaucoma.
* : mm Hg.
** : Power > 350 mW.
*** : Power < 350 mW.

Table 4.19. Success rate and relative IOP decrease following ALT in pigment dispersion syndrome.

| | Year | N | FU | IIOP mm Hg | IOPD % | SR |
|---|---|---|---|---|---|---|
| Thomas et al. | 1982 | 6 | 13.5 | 25.0 | 40.0 | 100 % |
| Horns et al. | 1983 | 6 | 7 | 23.3 | 36.5 | 100 % |
| Lieberman et al. | 1983 | 16 | | 27.8 | 11.5 | 43.8% |
| Lunde | 1983 | 13 | 18 | | | 61.5% |
| Robin & Pollack | 1983 | 11 | 7 | 32.0 | 31.5 | 72.7% |
| Strasser & Hauf | 1984 | 9 | 3.7 | | | 77.8% |
| Demailly et al. | 1985 | 17 | 12 | | | 70.5% |
| Schlosshardt | 1986 | 8 | | | | 75.0% |
| Traverso et al. | 1986 | 20 | 10.5 | 22.0 | 30.9 | 81 % |
| Moulin et al. | 1987 | 12 | 24 | | | 83.3% |

N : Number of eyes.
FU : Follow-up (months).
IIOP: Initial IOP (mm Hg).
IOPD: Relative IOP decrease in % as a function of follow-up.
SR : Success rate.

Table 4.20. Changes in facility of outflow following ALT.

| | Year | FU | | N | Facility of outflow (µl/min/mmHg) Pre-ALT | Post-ALT | Change |
|---|---|---|---|---|---|---|---|
| Wilensky & Jampol | 1981 | 1 m | | 13 | 0.105 ± 0.016 | 0.168 ± 0.31 | +0.063 |
| Thomas et al. | 1982 | 5 m | total | 173 | 0.14 | 0.23 | +0.09 |
| | | | success | 163 | 0.10 | 0.23 | +0.13 |
| Brubaker & Liesegang | 1983 | 3 m | responders | 9 | 0.09 | 0.21 | +0.12 |
| | | 3 m | non-responders | 8 | 0.14 | 0.14 | 0 |
| Schwartz & Kopelman | 1983 | 3 w | | 36 | 0.08 | 0.19 | +0.11 |
| | | 6 m | | 43 | | 0.16 | |
| | | 24 m | | 18 | | 0.15 | |
| Bischoff & Speiser | 1985 | 1-2 m | | 36 | 0.10 0.06 | 0.09 | -0.01 |
| Merté et al. | 1985 | 1 d | | 71 | | | +66%* |
| | | 1.5m | | 44 | | | +74%* |
| | | 12 m | | 35 | | | +77%* |

FU: Follow-up (d: day; w: weeks; m: months).
N : Number of eyes.
* : No absolute values available.

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# CHAPTER 5

# RETROSPECTIVE STUDY

## 5.1 AIM OF THIS STUDY

The principal aim of this retrospective study was the evaluation of changes in IOP following Argon Laser Trabeculoplasty (ALT). Success or failure were determined by changes in IOP. The second focus of this study was on the influence of ocular variables, patient variables and ALT variables on the changes in IOP.

In the event of bilateral ALT the results in the eye treated first were primarily considered (contrary to what has so far been usual in most of the literature studied). A study of results in unilaterally and bilaterally treated patients as one large group of eyes for various reasons entails a risk of distortion. To begin with, the ALT indication for the second eye of a patient already treated unilaterally may depend on the favourable response of the first eye. Secondly, it is improbable that the ALT responses in both eyes of a given individual would not correlate. Finally, patient variables can only be tested for the response in one eye in order to exclude the percentage of bilaterally treated patients to lead to systematic distortion, precluding comparisons between different studies.

However, primary evaluation of the eyes treated first also encompasses a selection (favouring functionally less good eyes) because in patients with bilateral glaucoma the eyes with the most advanced loss of function (or the highest IOP) will be treated first. Nevertheless this method merits preference, particularly if the results obtained in bilaterally treated patients are studied separately.

In studies in which patients with excessive values are selected on the basis of a given variable (e.g. IOP), repeated measurements in the course of time involves a so-called regression to the mean effect. The intensity of this effect depends on physiological variation and measuring error. Since in the study under discussion a patient was selected on the basis of repeatedly measured excessive IOP combined with 'circumstantial evidence' (optic disk

damage and visual field defect), this effect on the ALT result is bound to be very small.

A number of variables so far given insufficient attention in the literature were documented to permit evaluation of their influence on the ALT result. These variables include:

- The extent of optic disk damage and visual field loss and, inversely, the response to ALT of eyes with increased IOP, with or without glaucomatous optic disk damage but without visual field defect (suspected glaucoma).
- Already instituted medication and surgical therapy.
- Findings in aphakic eyes other than those of aphakia.
- Gonioscopic findings and their effect on ALT.
- The influence of cataract extraction in secondary glaucoma.

The influence of non-ocular features such as age and sex on ALT results will be considered as well.

The most relevant ALT features which may affect results are:
- The various ALT modifications.
- The quality of the ALT performed.
- Iris stretching and combination of ALT with iridotomy.
- The experience of the person performing the ALT.
- The ALT modification as related to the chance that repeated ALT will be successful.

Apart from these specific questions, more general aspects of ALT will receive attention.

Since the abovementioned variables can often be categorized only specifically, patient descriptions are largely devoted to this.

## 5.2 DESIGN OF THE RETROSPECTIVE STUDY

During the period 15th June 1982 through 24th June 1986, unilateral or bilateral ALT was performed on 351 patients in the Ophthalmological Department

of the Nijmegen University Hospital. Patients treated after 24th June 1986 were included in the prospective study to be presented in Chapter 6.

The only exclusion rule concerns exclusion of patients with a follow-up shorter than 6 weeks. On the basis of this reason, and for other reasons listed in table 5.1, 39 patients were excluded from this study.

Table 5.1. Reasons for non-participation of 39 patients in the retrospective study.

| | |
|---|---|
| ALT not possible (no ALT after iris stretching (4); no visualization (1); ALT not possible because of other reasons (1)). | 6 |
| Insufficient data on patient or treatment. | 7 |
| Planned trabeculectomy within 2 weeks post-ALT. | 1 |
| No follow-up because of: death of patient (colon carcinoma (1); myocardial infarction (1); CVA (1); unknown (1)); patient records no longer available (9). | 13 |
| No follow-up because of patient non-compliance. | 5 |
| Incomplete or less than 6 weeks follow-up. | 7 |
| Total | 39 |

The data of 312 patients who in the end participated were collected from the patient records and recorded on the basis of a code book (Addendum 1). For patients referred back to their own ophthalmologists, follow-up data on IOP, medication and secondary interventions (if any) were requested from these colleagues (26.6% of the total group).

On the basis of glaucoma type and/or specific ocular status at the time of ALT, the patients were included in one of the nine following subgroups:

1. Phakic primary open-angle glaucoma (phakic POAG).
2. Aphakic primary open-angle glaucoma (aphakic POAG).
3. Pseudophakic primary open-angle glaucoma (pseudophakic POAG).
4. Pigment dispersion syndrome.
5. Low-tension glaucoma.
6. Neovascular glaucoma due to diabetes mellitus.
7. Secondary glaucoma.
8. Glaucoma suspect without glaucomatous optic disk damage (disk-).
9. Glaucoma suspect with glaucomatous optic disk damage (disk+).

**Phakic POAG and glaucoma suspect:**

Eyes with increased IOP, glaucomatous optic disk features and glaucomatous visual defects, without other demonstrable glaucoma causes and without ocular data justifying inclusion in one of the other subgroups, were included in the subgroup phakic POAG.

If a patient showed only bilateral increased IOP, or unilateral increased IOP and normal contralateral IOP without glaucomatous optic disk damage and without visual field defect, then the treated eye was included in the subgroup glaucoma suspect without glaucomatous optic disk damage (disk-). If glaucomatous optic disk damage was present but no visual field defect, then the treated eye was included in the subgroup glaucoma suspect with optic disk damage (disk+).

Enlargement of the blind spot, total or central loss of sensitivity or a combination of the two at perimetry was not classified as a glaucomatous defect (see 3.5.3.1).

If on the basis of the criteria one eye would have to be included in one of the two glaucoma suspect subgroups while the contralateral eye showed evident POAG , then the first eye too was classified in one of the subgroups phakic, aphakic or pseudophakic POAG.

Of 59 glaucoma suspects, 52 had a symmetrical classification (26 bilateral glaucoma suspect without and 26 with glaucomatous optic disk damage), 5 were unilateral glaucoma suspects, 1 was a unilateral glaucoma suspect with contralateral traumatic glaucoma, and only 1 was a glaucoma suspect with optic disk damage in one eye and without damage in the other. This patient was treated by unilateral ALT (on the side with optic disk damage) and was classified in the corresponding subgroup.

Within the glaucoma suspect subgroups, no further distinction was made between phakic, aphakic and pseudophakic eyes (5 aphakic/pseudophakic eyes in 59 glaucoma suspects).

**Aphakic and pseudophakic glaucoma:**

Included in these two subgroups were eyes with evident glaucoma or increased IOP prior to cataract extraction (not resulting from cataract extraction).

**Pigment dispersion syndrome:**

Eyes with pigment dispersion syndrome and increased IOP, with or without glaucomatous optic disk changes and/or visual field defects, were included in this subgroup. Of 10 eyes treated, 1 showed only increased IOP while the remaining 9 showed glaucomatous features as well.

**Low-tension glaucoma:**

This subgroup included eyes in which glaucoma had developed while the IOP remained normal ($\leq$ 21 mm Hg).

**Neovascular glaucoma:**

This smallest subgroup included 4 eyes with rubeosis irides and increased IOP resulting from diabetes mellitus. Two eyes in addition showed glaucomatous optic disk features and/or visual field defects.

**Secondary glaucoma:**

Various types of secondary glaucoma were lumped in this group to begin with. At evaluation of results, however, each of these types will receive attention on a limited scale. Secondary glaucoma types in this subgroup included (number of eyes specified):

- Corticosteroid glaucoma (systemic corticosteroids used in the treatment of sarcoidosis (1) and uveitis (1)).
- Uveitic glaucoma (common uveitis (11) and acute exudative syphilitic uveitis (1)).
- Traumatic glaucoma (blunt trauma (6) and sharp trauma (2)).
- Glaucoma following cataract extraction (1).
- Glaucoma/IOP increase following surgery for detached retina (5).
- Miscellaneous (condition following untreated central vein occlusion (1), condition following treated central vein occlusion (1) and tapetoretinal degeneration (1)).

Seven of these eyes were submitted to ALT in view of increased IOP without glaucomatous optic disk changes or visual field defect but giving the clinical impression that IOP reduction was required for preventive reasons.

In the discussion of results, 7 eyes will be added (with congenital glau-

coma (4), juvenile glaucoma (1), congenital cataract and glaucoma (1) and hyperthyroidism (1)).

### 5.3 DEMOGRAPHIC DATA

Table 5.2 presents a survey of some demographic data, specifying in addition the rate of bilateral treatment per subgroup. The percentage of patients treated bilaterally depends on the type of glaucoma and ranges from 0% (within secondary glaucoma) to 63.2% (low-tension glaucoma). The total of eyes treated was 443 (in 312 patients) but 7 eyes of 7 patients are not included in the tables. They will be considered in the discussion of results obtained in secondary glaucoma types. The response of the contralateral eye was not evaluated in 3 patients because the diagnosis of this eye differed from that of the first eye.

Table 5.2. Demographic characteristics distributed per subgroup (Disk -/+: without/with glaucomatous optic disk damage; Bilat: percentage patients with bilateral ALT).

| Glaucoma type | Number | | | Age | | Male:Female | OD : OS |
|---|---|---|---|---|---|---|---|
| | Pat | Eyes | Bilat | Mean ± SD | Min - Max | | |
| Phakic POAG | 153 | 219 | 43.1% | 67.6 ± 11.4 | 29 - 88 | 92 : 61 | 89 : 64 |
| Aphakic POAG | 19 | 25 | 31.6% | 68.8 ± 11.3 | 37 - 84 | 6 : 13 | 12 : 7 |
| Pseudophakic POAG | 10 | 14 | 4/10 | 73.3 ± 6.6 | 63 - 83 | 5 : 5 | 6 : 4 |
| Pigment Dispersion S. | 10 | 16 | 6/10 | 41.6 ± 11.1 | 27 - 65 | 7 : 3 | 5 : 5 |
| Low-tension Glaucoma | 19 | 31 | 63.2% | 68.5 ± 8.1 | 56 - 81 | 6 : 13 | 10 : 9 |
| Neovascular Glaucoma | 4 | 5 | 1/4 | 67.3 ± 7.9 | 59 - 75 | 2 : 2 | 1 : 3 |
| Secondary Glaucoma | 31 | 35 | 12.9% | 50.2 ± 16.4 | 20 - 78 | 18 : 13 | 15 : 16 |
| Corticosteroid | 2 | 3 | 1/2 | 40.5 ± 16.3 | 29 - 52 | 2 | 1 : 1 |
| Uveitic | 12 | 14 | 16.7% | 52.8 ± 15.7 | 23 - 78 | 8 : 4 | 6 : 6 |
| Traumatic | 8 | 9 | 1/8 | 40.5 ± 16.5 | 20 - 64 | 7 : 1 | 4 : 4 |
| Post Cataract Extr. | 1 | 1 | | 72 | | 1 | 1 |
| Post Retinal Detachm. | 5 | 5 | | 57.2 ± 12.3 | 36 - 66 | 1 : 4 | 3 : 2 |
| Miscellaneous | 3 | 3 | | 52.7 ± 20.6 | 29 - 66 | 2 : 1 | 1 : 2 |
| Glaucoma Suspect, Disk- | 28 | 44 | 57.1% | 60.4 ± 15.0 | 14 - 88 | 14 : 14 | 17 : 11 |
| Glaucoma Suspect, Disk+ | 31 | 44 | 41.9% | 64.2 ± 14.9 | 17 - 81 | 16 : 15 | 17 : 14 |
| Total | 305 | 433 | 42.0% | 64.3 ± 14.1 | 14 - 88 | 166 : 139 | 172 : 133 |

The mean age was calculated on the basis of the age at the time of (the first session) of ALT. The mean age of all patients in this study was some 64 years. In the pigment dispersion syndrome and secondary glaucoma the mean age was below this.

Glaucoma suspects without disk damage averaged younger than those with disk damage. The latter averaged younger than patients with phakic POAG.

The sex distribution revealed a female predominance in the low-tension glaucoma subgroup (predominance in the aphakic POAG group is less pronounced if all eyes with cataract extraction are included), and a male predominance in the pigment dispersion syndrome and traumatic glaucoma subgroups.

## 5.4 EXTRAOCULAR FEATURES

Table 5.3 shows the frequencies of extraocular diseases as noted in the patient records.

Table 5.3. Frequencies of extraocular diseases.

| | |
|---|---|
| No Known Concomitant Diseases | 53.3% |
| Arterial Hypertension | 14.1% |
| Cardiovascular Diseases | 13.4% |
| Pulmonary Diseases | 9.5% |
| Diabetes Mellitus | 7.2% |
| Neoplasia | 2.0% |
| Neurological Diseases | 1.6% |
| Disorders of the Joints and Connective Tissue | 1.6% |
| Thyroid Diseases | 1.3% |
| Diseases of the Kidney an Urinary Tract | <1.0% |
| Diffuse Systemic Diseases | <1.0% |
| Psychiatric Diseases | <1.0% |

This table shows that virtually one out of every two glaucoma patients has one or more concomitant pathological conditions. These figures probably underestimate the true situation because it could not be established with certainty that a complete history was taken in all cases.

A number of factors have been identified as high-risk factors regarding

glaucoma (arterial hypertension, diabetes mellitus and cardiovascular conditions such as cardiac decompensation, angina pectoris, arrhythmias and myocardial infarction). At least one of these high-risk factors was evident in 34.1% of the POAG cases (phakic, aphakic and pseudophakic), 47.2% of low-tension glaucoma cases, 10.7% of the glaucoma suspects without and 29.0% of those with optic disk damage. The frequency in glaucoma suspects without disk damage was significantly lower than that in POAG ($p<0.02$) and that in low-tension glaucoma ($p<0.001$). There was an indication of a difference between the glaucoma suspect subgroups ($p<0.10$).

## 5.5 GENERAL OCULAR EXAMINATION

The mean preoperative visual acuity per subgroup is mentioned in table 5.4. As compared with phakic POAG, eyes with POAG and cataract extraction, eyes with neovascular glaucoma and eyes with secondary glaucoma had slightly lower visual acuity. Good visual acuity values were found, on the other hand in the pigment dispersion syndrome and in glaucoma suspects.

Table 5.4. Mean visual acuity before ALT, per subgroup.

| | |
|---|---|
| Phakic POAG | $0.55 \pm 0.32$ |
| Aphakic POAG | $0.34 \pm 0.29$ |
| Pseudophakic POAG | $0.35 \pm 0.31$ |
| Pigment Dispersion S. | $0.75 \pm 0.34$ |
| Low-tension Glaucoma | $0.46 \pm 0.30$ |
| Neovascular Glaucoma | $0.34 \pm 0.38$ |
| Secondary Glaucoma | $0.42 \pm 0.31$ |
| Glaucoma Suspect, Disk- | $0.79 \pm 0.27$ |
| Glaucoma Suspect, Disk+ | $0.68 \pm 0.29$ |

Apart from factors associated with glaucoma or its therapy there were in the patient population studied some concomitant ophthalmological changes which partly explained the abnormal visual acuity in some cases. Of 258 phakic eyes, 117 (45.3%) showed a more or less interfering cataract. In addition there were other findings which in some cases may have unfavourably

affected vision (table 5.5).

Table 5.5. Findings at preoperative ophthalmological examination.

| | | Eyes |
|---|---|---|
| Cornea | Cornea Edema | 3 |
| | Cornea Opacities | 3 |
| | Cornea Scar | 1 |
| | Bullous Keratopathy | 1 |
| | Cornea Neovascularization | 1 |
| | Miscellaneous | 1 |
| Iris | Iritis | 9 |
| | Rubeosis Irides | 3 |
| | Iris Transillumination | 4 |
| | Iris Atrophy | 1 |
| | Iridodonesis | 1 |
| | Iris Scar | 1 |
| Pupil | Posterior Synechiae | 5 |
| | Irregular Pupil | 1 |
| Lens | Traumatic Lensluxation | 1 |
| Retina | Central Retinal Vein Occlusion | 7 |
| | Diabetic Retinopathy | 4 |
| | Hypertensive Retinopathy | 2 |
| | Snailtrack | 1 |
| | Tapetoretinal Degeneration | 1 |
| Macula | Pigment Alterations | 20 |
| | Senile Macular Degeneration | 4 |
| | Drusen | 2 |
| | Cystoid Macular Edema | 1 |
| Strabismus | | 1 |
| Disturbed Eye Movements | | 1 |
| Congested Episcleral Veins | | 1 |
| Proptosis | | 1 |

## 5.6 SPECIFIC GLAUCOMA FEATURES

### 5.6.1 Scales for medication, optic disk and visual field function

For three glaucoma features scales were developed, or existing scales adapted.

If for example several medications are included in a scale, then the sum

of the scores determines the total score for the eye.

Table 5.6 presents a scale for topical glaucoma drugs. The number of points assigned to a particular type of eyedrop was based, on the one hand on its position in the treatment of glaucoma and on the other hand on the frequency and severity of its side effects. The scores go from 0 (no topical medication) to 3 (irreversible cholinesterase inhibitors). The use of carbonic anhydrase inhibitors was not included in this score but coded separately.

Table 5.6. Scale for topical glaucoma drugs.

| | Score |
|---|---|
| **Miotics:** | |
| Pilocarpine 1-2%, Isoptocarpine 1-2% | 1 |
| Pilocarpine 4%, Isoptocarpine 4% | 2 |
| Aciclidine (Glaucostat®), Carbachol (Isopto Carbachol®) | 2 |
| Fluostigmine (Diflupyl®), Fysostigmine, Echothiophaat (Phospholine Iodide®) | 3 |
| **Beta-Adrenerg Blocking Agents:** | |
| Timolol (Timoptol® 0.25-0.50%), Metipranolol (Beta-Ophtiole®) Betaxolol (Betoptic®) | 1 |
| **Sympathomimetic Agents:** | |
| Adrenaline (Isopto Epinal®, Eppy®) | 1 |
| Dipevrefine (Diopine®) | 1 |
| **Sympatholytic Agents:** | |
| Guanethidine (Ismelin®) | 2 |
| **Combined Agents:** | |
| Aciclidine/Epinephrine (Glaucadrine®) | 2 |
| Metipranolol/Pilocarpine (Normoglaucon®) | 2 |
| Guanethidine/Adrenaline (Suprexon®) | 2 |

Another scale was developed for the degree of glaucomatous optic disk damage (table 5.7). Proceeding on the basis of the cup/disk ratio points were assigned in numbers increasing by steps of two. Given explicitly mentioned vertical ovality, nasal displacement of blood vessels or peripapillary atro-

phy, the score was increased by one point. If there was no glaucomatous cupping or if a physiological or central cupping was described, the score was set at 0.

Table 5.7. Scale for the degree of glaucomatous damage to the optic disk.

| | Score |
|---|---|
| No glaucomatous cupping, physiological or central cupping | 0 |
| Beginning glaucomatous cupping, cup/disk ratio 0.4-0.5 | 2 |
| Moderate glaucomatous cupping, cup/disk ratio 0.6-0.7 | 4 |
| Severe glaucomatous cupping, cup/disk ratio >0.7 | 6 |
| Total cupping | 8 |
| Vertical ovality | score +1 |
| Nasal displacement of blood vessels | score +1 |
| Peripapillary atrophy | score +1 |

Finally, visual field loss was used in a classification (table 5.8) based on stages of visual field defect as described by Aulhorn (3.5.3.2).

The principal modification in relation to the existing scale was addition of categories A, B and C: enlargement and/or baring of the blind spot, a decrease in total or central sensitivity, and a combination of these respect-

Table 5.8. Classification of findings at perimetric examination.

| | Stage |
|---|---|
| No visual field defect; no visual field changes | 0 |
| Relative visual field defect | 1 |
| Absolute defects in the Bjerrum area not linked to the blind spot, unless by a relative defect; absolute nerve fiber bundle defect | 2 |
| Bjerrum scotoma; isolated nasal step | 3 |
| (Half)-ring shaped absolute paracentral defect | 4 |
| Central island, with or without temporal rest | 5a |
| Central island collapsed | 5b |
| Enlargement and/or baring of the blind spot | A |
| Decrease in total or central sensitivity | B |
| A & B | C |

ively. As already pointed out in 3.5.3.1, these are neither early nor specific glaucoma features; they were separately coded, however, because they cannot be included in the stage 'no visual field changes'.

### 5.6.2 Findings

#### 5.6.2.1 Glaucoma medication and previous glaucoma surgery

Table 5.9 shows the distribution of various types of glaucoma drugs per subgroup.

Table 5.9. Distribution of topical glaucoma drugs and carbonic anhydrase inhibitor use before ALT, per subgroup (Beta-block: Beta-adrenerg blocking agents; CAI: Carbonic anhydrase inhibitors).

| | None | Beta-block | Miotics | Sympathomimetics | Combined Agents | CAI |
|---|---|---|---|---|---|---|
| Phakic POAG | 5.9% | 83.0% | 51.0% | 13.1% | 7.8% | 19.6% |
| Aphakic POAG | 10.5% | 84.2% | 26.3% | 36.8% | 10.5% | 26.3% |
| Pseudophakic POAG | | 9/10 | 3/10 | 4/10 | | 3/10 |
| Pigment Dispersion S. | 2/10 | 7/10 | 2/10 | 1/10 | | 1/10 |
| Low-tension Glaucoma | 10.5% | 78.9% | 21.1% | 5.3% | 5.3% | 10.5% |
| Neovascular Glaucoma | | 4/4 | | | | 2/4 |
| Secondary Glaucoma | | 90.3% | 19.4% | 29.0% | 9.7% | 45.2% |
| Glaucoma Suspect, Disk- | 21.4% | 57.1% | 35.7% | 14.3% | | 14.3% |
| Glaucoma Suspect, Disk+ | 12.9% | 64.5% | 54.8% | 19.4% | 3.2% | 9.7% |
| Total | 8.2% | 79.3% | 41.0% | 17.0% | 6.2% | 21.0% |

In about 1 out of 12 eyes in this study no topical glaucoma drugs were prescribed. This concerned 15 eyes (4.9%) which had shown an allergic reaction to one or several eyedrops, and 10 eyes (3.3%) of patients who could not or would not apply eyedrops.

A majority of the patients used a β-blocker, and some 50% a miotic. Only a very small number used an irreversible cholinesterase inhibitor (2.6%). Because eyedrops were sometimes used in combination, the total percentage in a

subgroup often exceeds 100%.

Carbonic anhydrase inhibitors were used by 21.0% of the patients. As compared with phakic POAG, we find a low frequency in low-tension glaucoma, pigment dispersion syndrome and glaucoma suspects. A high frequency is observed in eyes with neovascular glaucoma and secondary glaucoma.

Table 5.10 presents the medication scores and the mean score per subgroup and in addition shows the distribution of carbonic anhydrase inhibitor in relation to the medication score.

Table 5.10. Distribution of medication scores and mean medication scores, before ALT, per subgroup (SD: standard deviation).

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | Mean ± SD |
|---|---|---|---|---|---|---|---|---|
| Phakic POAG | 5.9% | 32.7% | 39.2% | 15.0% | 2.6% | 3.9% | 0.7% | 1.9 ± 1.1 |
| Aphakic POAG | 10.5% | 26.3% | 42.1% | 15.8% | 5.3% | | | 1.8 ± 1.0 |
| Pseudophakic POAG | | 4/10 | 6/10 | | | | | 1.6 ± 0.5 |
| Pigment Dispersion S. | 2/10 | 5/10 | 3/10 | | | | | 1.1 ± 0.7 |
| Low-tension Glaucoma | 10.5% | 63.2% | 21.1% | 5.3% | | | | 1.2 ± 0.7 |
| Neovascular Glaucoma | | 4/4 | | | | | | 1.0 |
| Secondary Glaucoma | | 51.6% | 35.5% | 9.7% | 3.2% | | | 1.7 ± 0.8 |
| Glaucoma Suspect, Disk- | 21.4% | 42.9% | 25.0% | 7.1% | 3.6% | | | 1.3 ± 1.0 |
| Glaucoma Suspect, Disk+ | 12.9% | 35.5% | 32.3% | 9.7% | 3.2% | 6.5% | | 1.7 ± 1.3 |
| Total | 8.2% | 39.0% | 35.7% | 11.7% | 2.6% | 2.6% | 0.3% | 1.7 ± 1.1 |
| Carbonic Anhydrase Inhibitor | 4.0% | 15.1% | 23.9% | 37.1% | 3/8 | 3/8 | | |

The mean medication score was highest for eyes with phakic POAG. Most eyes showed a total score of 1 or 2 points, as could have been expected on the basis of the distribution of the types of drugs.

The use of carbonic anhydrase inhibitors increased with increasing medication score, which is consistent with the strategy that maximum topical medication was usually tried first. One patient used no topical medication but did receive a carbonic anhydrase inhibitor (4% of all eyes with score 0).

Apart from medication, a number of eyes had also been submitted to glaucoma surgery. Table 5.11 presents the distribution and type of glaucoma surgery performed.

Table 5.11. Frequency distribution and type of pre-ALT glaucoma surgery per subgroup (Others: iridencleisis, Scheie procedure, subscleral trepanation, Elliot procedure; Comb: combination of trabeculectomy with other filtering procedure).

| | Not Operated | Filtering Procedures: Trabeculectomy 1 | Trabeculectomy >1 | Others | Comb | Iridectomy | Cyclo-cryo | Unknown |
|---|---|---|---|---|---|---|---|---|
| Phakic POAG | 86.9% | 9.2% | 0.7% | | 0.7% | 2.6% | | |
| Aphakic POAG | 42.1% | 31.6% | | 5.3% | 5.3% | | 5.3% | 10.5% |
| Pseudophakic POAG | 3/10 | 3/10 | | 2/10 | 1/10 | | | 1/10 |
| Pigment Dispersion S. | 10/10 | | | | | | | |
| Low-tension Glaucoma | 89.5% | 10.5% | | | | | | |
| Neovascular Glaucoma | 4/4 | | | | | | | |
| Secondary Glaucoma | 54.8% | 19.4% | 19.4% | | 3.2% | | 3.2% | |
| Glaucoma Suspect, Disk- | 92.9% | | | 7.1% | | | | |
| Glaucoma Suspect, Disk+ | 90.3% | 3.2% | | | 3.2% | 3.2% | | |
| Total | 79.3% | 10.5% | 2.3% | 1.6% | 1.6% | 1.6% | 0.7% | 1.0% |

About 1 out of 5 eyes had already been submitted to one or more operations. As compared with phakic POAG, eyes with aphakic or pseudophakic POAG and those with secondary glaucoma showed a high frequency.

Most of the eyes operated on had been submitted to a single trabeculectomy; 7 eyes had been submitted to at least 2 trabeculectomies (including 2 eyes submitted to 4 trabeculectomies each).

A different filtering procedure (iridencleisis, Scheie procedure, subscleral trepanation, Elliot procedure) had been performed on 5 eyes, and 5 eyes had been submitted both to trabeculectomy and to another filtering procedure.

A peripheral iridectomy or laser iridectomy/iridotomy had been performed on 5 eyes. One aphakic eye had been treated by cyclodialysis following trabeculectomy and trabeculotomy, and one eye with traumatic glaucoma had been submitted to cyclocryocoagulation.

The exact glaucoma operation performed on 3 eyes could not be traced. One aphakic eye was believed to have been submitted to a total of 9 operations.

Four eyes (3 phakic POAG eyes and 1 glaucoma suspect with optic disk dam-

age) had already undergone ALT elsewhere.

### 5.6.2.2 Optic disk

Table 5.12 presents the distribution of optic disk scores and the mean disk score per subgroup.

Table 5.12. Distribution of disk scores and mean disk scores before ALT, per subgroup (SD: standard deviation).

| | 0 - 1 | 2 - 3 | 4 - 5 | 6 - 7 | 8 | Mean ± SD |
|---|---|---|---|---|---|---|
| Phakic POAG | 9.3% | 14.7% | 18.6% | 45.3% | 12.0% | 4.8 ± 2.3 |
| Aphakic POAG | 6.3% | 25.0% | 6.3% | 37.5% | 25.0% | 5.1 ± 2.5 |
| Pseudophakic POAG | | | 1/10 | 7/10 | 2/10 | 6.2 ± 1.1 |
| Pigment Dispersion S. | 3/10 | 3/10 | 1/10 | 3/10 | | 2.8 ± 2.5 |
| Low-tension Glaucoma | | 5.3% | 36.8% | 52.6% | 5.3% | 5.3 ± 1.5 |
| Neovascular Glaucoma | 2/4 | 1/4 | | 1/4 | | 2.0 ± 2.8 |
| Secondary Glaucoma | 25.0% | 10.7% | 7.2% | 46.4% | 10.7% | 4.1 ± 2.9 |
| Glaucoma Suspect, Disk- | 100% | | | | | |
| Glaucoma Suspect, Disk+ | 12.9% | 45.6% | 19.4% | 19.4% | 3.2% | 3.1 ± 2.6 |
| Total | 19.7% | 16.3% | 15.6% | 38.6% | 9.8% | 4.1 ± 2.6 |

For 10 eyes (3.3%) no recent disk score was traceable (3 eyes with phakic POAG, 3 with aphakic POAG, 3 with secondary glaucoma and 1 glaucoma suspect without glaucomatous optic disk damage). These eyes were classified on the basis of optic disk descriptions recorded some considerable time prior to ALT; this may have had consequences only for the glaucoma suspect without optic disk damage if during the interval between documentation and ALT optic disk damage had occurred.

Leaving aside the subgroup of glaucoma suspects without optic disk damage (these eyes have score 0 per definition), 53.4% of the eyes had a score of at least 6 points, which reflects a minimum cup/disk ratio of 0.8.

A disk score of 0-1 was found in 58 eyes, including 28 glaucoma suspects without optic disk damage. Four eyes in the subgroup glaucoma suspect with

optic disk damage had a score of 0-1 but were nevertheless classified in this subgroup on the basis of clinical impression mentioned in the patient records.

It has already been pointed out in section 5.2 that 7 eyes with secondary glaucoma and 1 eye with pigment dispersion syndrome showed no glaucoma features other than increased IOP. Two eyes with pigment dispersion syndrome showed no evidently glaucomatous cupping but did have visual field defects.

A total of 15 eyes with POAG (14 phakic and 1 aphakic) showed no glaucomatous optic disk features, but were nevertheless classified in the relevant subgroups in view of findings in the contralateral eye or because there were glaucomatous visual field defects.

A high mean disk score was found in eyes with POAG and cataract extraction and in low-tension glaucoma.

The frequency of eyes with a disk score of 6 and higher was 57.3% for phakic POAG and 22.6% for glaucoma suspects with glaucomatous optic disk damage ($p<0.001$).

#### 5.6.2.3 Visual field stages

The findings obtained at perimetry are subject to several limitations. To begin with, a visual field stage could be assigned to only 224 eyes (73.4%) because the interval between perimetry and ALT must not exceed 6 months (this in order to prevent any increase in visual field defect due to glaucoma progression from being ascribed to insufficient response to ALT). This approach implies a selection on the basis of the frequency of perimetry in an eye. In actual fact this may mean that eyes with a high perimetry frequency on the basis of glaucoma severity and/or progression of visual field defect, had a better chance of being assigned a score.

Other factors playing a role in not assigning a visual field stage were: ocular factors (conditions after detachment of the retina, with or without surgical therapy, panretinal laser coagulation for diabetic retinopathy, pronounced miosis and the presence of a marked cataract), patient-related factors (insufficient cooperation) and logistic reasons. In regard to the lastmentioned reasons it should be borne in mind that a number of patients

were referred in whom a previously diagnosed visual field defect would not always be confirmed.

When a visual field stage was assigned to an eye, this was not always done on the basis of the same perimetric technique. In our department we use Goldmann kinetic perimetry, static perimetry (Friedman Visual Field Analyser/Peritest) or a combination of these.

Table 5.13 presents the distributions of visual field stages found in the subgroups.

Table 5.13. Distribution of preoperative visual field stages per subgroup (Scored: percentage of eyes in which perimetric findings fulfilled the criteria accepted so that a value could be assigned).

| | scored | 0 | 1 | 2 | 3 | 4 | 5a | 5b | A | B | C |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phakic POAG | 71.9% | 2.7% | 12.6% | 25.2% | 20.7% | 8.1% | 8.1% | 0.9% | 0.9% | 13.5% | 7.2% |
| Aphakic POAG | 68.4% | 7.7% | | 7.7% | 23.1% | 15.4% | 15.4% | | 7.7% | 15.4% | 7.7% |
| Pseudophakic POAG | 5/10 | | | | | | 2/5 | 1/5 | | 2/5 | |
| Pigment Dispersion S. | 7/10 | 1/7 | 3/7 | 1/7 | 1/7 | | | | | | 1/7 |
| Low-tension Glaucoma | 94.7% | | | 11.1% | 33.3% | 16.7% | 22.2% | | | | 16.7% |
| Neovascular Glaucoma | 1/4 | | | | | | | | | 1/1 | |
| Secondary Glaucoma | 67.7% | 4.8% | 4.8% | 23.8% | 14.3% | | 9.5% | | 4.8% | 28.6% | 9.5% |
| Glaucoma Suspect, Disk- | 71.4% | 60.0% | | | | | | | 5.0% | 25.0% | 10.0% |
| Glaucoma Suspect, Disk+ | 90.3% | 42.9% | | | | | | | | 46.4% | 10.7% |
| Total | 73.4% | 13.4% | 8.0% | 16.5% | 16.1% | 6.3% | 8.5% | 0.9% | 1.8% | 19.6% | 8.9% |

A number of eyes with pigment dispersion syndrome, neovascular glaucoma or secondary glaucoma showed no evident visual field defects (see 5.2/5.6.2.2).

The subgroups phakic, aphakic and pseudophakic POAG included eyes without evident glaucomatous visual field defects (stages 0, A, B, and C). This was a result of the way in which the eyes were classified: partly on the basis of the findings in the contralateral eye. Another reason is that eyes were included in these groups when past perimetry had revealed glaucomatous visual field loss which, however, was absent at the time of staging.

Stages 4 and 5 are more often encountered in low-tension glaucoma and in eyes with POAG and cataract extraction than in phakic POAG.

### 5.6.2.4 Gonioscopy

The gonioscopic findings are listed in table 5.14.

Table 5.14. Pre-ALT gonioscopic findings per subgroup (PAS: peripheral anterior synechiae; TP +3/+4: trabecular pigmentation +3/+4; Miscellaneous: (local) angle obliteration, shallow anterior chamber, abnormal blood vessels in the chamber angle, trabecular meshwork not/hardly pigmented, angle recession and altered anatomy of the angle).

| | None | Narrow Angle | PAS | TP+3/+4 | Miscellaneous |
|---|---|---|---|---|---|
| Phakic POAG | 60.1% | 19.6% | 5.9% | 5.2% | 17.6% |
| Aphakic POAG | 31.6% | 10.5% | 42.1% | 5.3% | 31.6% |
| Pseudophakic POAG | 6/10 | 3/10 | 2/10 | | |
| Pigment Dispersion S. | | | | 10/10 | 1/10 |
| Low-tension Glaucoma | 78.9% | 21.1% | | | |
| Neovascular Glaucoma | 1/4 | 1/4 | 1/4 | | 2/4 |
| Secondary Glaucoma | 45.2% | 9.7% | 35.5% | 3.2% | 19.4% |
| Glaucoma Suspect, Disk- | 64.3% | 21.4% | 7.1% | 3.6% | 14.3% |
| Glaucoma Suspect, Disk+ | 61.3% | 22.6% | 16.1% | 3.2% | 9.7% |
| Total | 56.1% | 18.4% | 12.5% | 7.2% | 15.7% |

About 20% of the eyes had a narrow iridocorneal angle, caused by the presence of a plateau iris in open-angle glaucoma. In such cases the iris root inserts on the anterior part of the ciliary body and the iridal root shows a sharp angle at the level of the iridocorneal angle (beak shape). A shallow anterior chamber was found in only 9 eyes (3.0%).

The distribution of narrow angle was fairly constant within the various subgroups, except in the pigment dispersion syndrome in which no narrow angle occurred.

Peripheral anterior synechiae (PAS) were mainly seen in aphakic POAG and secondary glaucoma. The frequencies found were significantly higher than those in phakic POAG ($p<0.001$).

All eyes with a pigment dispersion syndrome showed marked pigmentation of the trabecular meshwork, while only 0 to 5.3% of the other glaucomas showed

such marked pigmentation.

The abnormalities listed under Miscellaneous included - among other things - (local) obliteration of the angle (4.3%), shallow anterior chamber (3.0%), abnormal blood vessels in the angle (2.6%), trabecular meshwork not/hardly pigmented (1.6%), angle recession (1.6%) and an altered anatomy of the angle (1.3%).

From these gonioscopic findings two variables were distilled which might influence ALT results: iridocorneal angle changes which might interfere with ALT (i.e. PAS, local obliteration of the angle and poor visualization of the trabecular meshwork) in aphakic POAG and secondary glaucoma, and a narrow iridocorneal angle due to a plateau iris in phakic POAG.

## 5.7 ARGON LASER TRABECULOPLASTY

The way in which ALT was performed in this study can be divided into three modifications: treatment of 360° of the trabecular meshwork in one session (1 * 360°), treatment of 180° of the trabecular meshwork in one session (1 * 180°) and treatment of 360° of the trabecular meshwork in two sessions (2 *

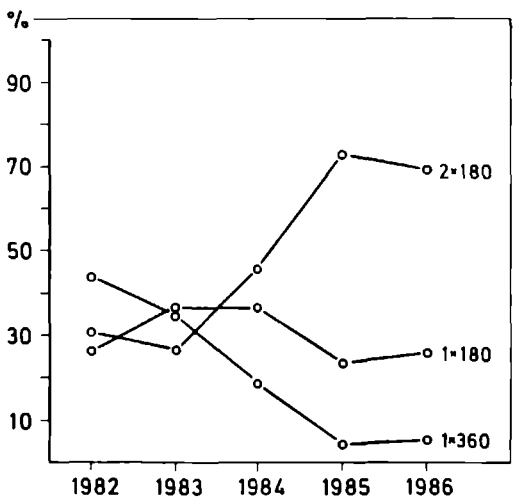



Figure 5.1. Distribution of ALT modifications by year of application.

180°). The distribution of these ALT modifications depended in part on the year in which it was performed (fig. 5.1). With increasing experience, more and more eyes were treated by 2 * 180°.

Interpretation of ALT results should take into account that eyes treated by 1 * 180° ALT have already been selected on the basis of success. If the first 180° session caused no or inadequate IOP decrease, then a second session was performed. On the other hand, a second session was often planned in advance without waiting for the result of the first. Figure 5.2 presents the cumulative frequency of the number of eyes plotted against the number of weeks between the first and second session in cases treated by 2 * 180° ALT. Up to 8 weeks (two-thirds) the eyes involved were probably eyes for which a second session had already been planned. The eyes with a longer interval between sessions than 8 weeks (one-third) were eyes showing no or no adequate response to the first session. Excluding eyes with a second session within 8 weeks, we find that in at least 39.5% of the cases a second session, although not planned, was nevertheless necessary.

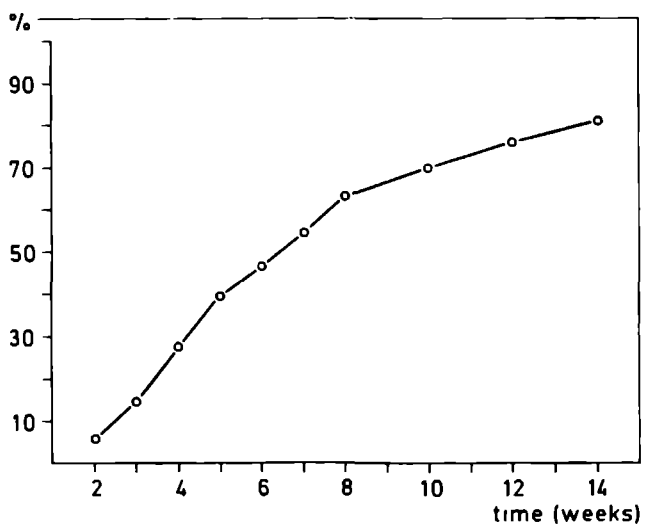



Figure 5.2. Cumulative distribution of intervals (in weeks) between two sessions in a 2 * 180° ALT modification.

Table 5.15 presents a survey of the ALT modifications used per subgroup. Most eyes treated by ALT over 360° were treated in two sessions. Including all bilateral treatments and re-treatments, 443 eyes were treated in 721 ALT sessions.

Table 5.15. Distribution of ALT modifications per subgroup.

| | 1 * 180° | 2 * 180° | 1 * 360° |
|---|---|---|---|
| Phakic POAG | 28.8% | 52.9% | 18.3% |
| Aphakic POAG | 42.1% | 42.1% | 15.8% |
| Pseudophakic POAG | 5/10 | 2/10 | 3/10 |
| Pigment Dispersion S. | 1/10 | 5/10 | 4/10 |
| Low-tension Glaucoma | 42.1% | 47.4% | 10.5% |
| Neovascular Glaucoma | 2/4 | 2/4 | |
| Secondary Glaucoma | 35.5% | 45.2% | 19.4% |
| Glaucoma Suspect, Disk- | 17.9% | 75.0% | 7.1% |
| Glaucoma Suspect, Disk+ | 25.8% | 64.5% | 9.7% |
| Total | 30.2% | 53.1% | 16.7% |

Table 5.16 presents the principal ALT parameters per ALT modification. The standard parameters of spot size (50 µm), exposure time (0.1 sec) and mean power (blanching and/or bubble formation) were used in each of the three ALT modifications. The apparatus used was a continuous wave blue-green Argon laser (Coherent Radiation Model 900).

Table 5.16. ALT parameters per type of ALT modification (Exp. time: exposure time in second; Mean N burns: mean number of burns).

| | Exp. time | Spot size | Mean power (mW) | Mean N burns | Iris stretching | Corticosteroid |
|---|---|---|---|---|---|---|
| 1 * 180° | 0.1 | 50 µm | 1000 (800-1400) | 60 (25-80) | 17.0% | 90.0% |
| 2 * 180° | 0.1 | 50 µm | 1100 (750-1500) | 120 (72-190) | 17.0% | 94.0% |
| 1 * 360° | 0.1 | 50 µm | 1000 (1000-1350) | 100 (45-144) | 20.0% | 92.0% |

The mean number of burns corresponded with the optimum, although the range was wide. Deviations toward the lower limit are explained by the fact that it was not always possible to gain a view of the trabecular meshwork over the circumference desired (PAS, obliterated angle), and occasionally treatment was stopped prematurely in view of serious complaints about pain. Deviations towards the upper limit can be explained on the basis of overlap of treated parts of the trabecular meshwork circumference in the 2 * 180° ALT.

The localization of the burns was the posterior trabecular meshwork in the first Standard Wise ALT procedures performed, and in all subsequent cases the anterior part. Iris stretching was done in 17.0-20.0% of the eyes, corresponding with the frequency of narrow and beak-shaped angles due to plateau iris. Iris stretching was effected by applying about 20 burns to the iris using 500 µm spot size, 0.5 sec exposure time, and 200-500 mW power.

ALT was occasionally combined with an iridotomy. In 13 eyes with phakic POAG this combination was regarded as an additional treatment variable.

The standard protocol called for postoperative corticosteroid medication. In 63.0% of the eyes ALT was performed by two staff members with ample experience in laser techniques and gonioscopy. In the remaining 37.0% ALT was performed by a resident.

## 5.8 CRITERIA OF SUCCESS AND FAILURE

The IOP last measured before ALT was taken as initial IOP; the finally measured IOP was taken as ultimate or final IOP. Neither before nor after ALT were several IOP values averaged because several IOP values pre-ALT were not always available and the interval between two measurements post-ALT often was too long.

The need for glaucoma surgery after ALT was considered to indicate complete failure of ALT.

Changes in the use of topical medication were calculated on the basis of the medication score. The use of carbonic anhydrase inhibitor was coded as use or non-use. The resultant from changes in this medication yielded the possibilities of increasing, decreasing or continuing the total medication. If the medication score increased by a maximum of 3 points but the use of

carbonic anhydrase inhibitor could be discontinued, this was regarded as 'no change in total medication'. If systemic medication had to be started or increased after ALT, however, then this was regarded as indicating complete failure of ALT, regardless of any changes in topical medication. An increased medication score but non-use of a carbonic anhydrase inhibitor was likewise regarded as complete failure.

When an eye was not regarded as one of the abovementioned complete failures, the IOP decrease had to be at least 20% and the final IOP had to be 21 mm Hg or lower, to regard ALT as successful.

Of the total group of 305 eyes, post-ALT visual acuity was determined in 251, a disk score in 194 and a visual field stage in 134 eyes. These data could not be completed for two reasons. Firstly, 81 patients (26.6%) were referred back to their own ophthalmologists. Moreover, the maximum acceptable interval between the last measurement of IOP and determination of visual acuity, disk score and visual field stage was held to be 6 months. This was decided in order to avoid failures to identify possible increases in glaucomatous damage, thus giving an unjustifiably favourable impression of the response to ALT. Evaluation of changes in these variables took place in cases in which pre-ALT as well as post-ALT values were available.

An increase in disk score by at least two points was interpreted as significant because it reflects an increase in cup/disk ratio.

Pre-ALT and Post-ALT visual field stages were compared, changes being defined as: - no change;

- increased visual field defect but within the pre-ALT stage;
- progression of visual field defect to a more advanced stage.

The general results were determined and described for each of the subgroups. Specific problems were studied per subgroup concerned. For most of the patient, ocular and ALT variables this analysis confines itself to phakic POAG because this form was regarded as most representative and constituted by far the largest subgroup. In this way disturbances by variables linked to a specific glaucoma type or the specific ocular condition were avoided.

Independence between discrete variables were tested using the Chi-square test; the Wilcoxon matched-pairs test was used to test non-systematic differences in paired observations; the Kruskal-Wallis test (one-way analysis

of variance based on ranks) was used to test differences between groups of unpaired observations.

Whenever a number is less than or equal to 10, no percentage is mentioned but the number in question. This is done to simplify interpretation of tables by ensuring that they are less influenced by incidental large or small percentages of (very) small numbers.

Evaluation of IOP changes was largely confined to success eyes for two reasons. To begin with, it is of importance to establish whether a variable of no influence on the success rate, nevertheless influences the IOP decrease. Secondly, eyes submitted to surgery after ALT can be included in the follow-up only until the operation. However, the results of post-ALT glaucoma surgery will be discussed on the basis of success criteria defined above.

## 5.9 RESULTS

### 5.9.1 Initial IOP and duration of follow-up

Table 5.17 presents the mean initial IOP and the duration of follow-up per subgroup.

Table 5.17. Mean initial IOP and mean follow-up in months per subgroup (>21 mm Hg: initial IOP exceeding 21 mm Hg).

| | Initial IOP (mm Hg) | | | Follow-up (mths) | |
|---|---|---|---|---|---|
| | Mean ± SD | Min - Max | >21 | Mean ± SD | Min - Max |
| Phakic POAG | 25.3 ± 6.7 | 11 - 60 | 71.9% | 28 ± 13 | 3 - 57 |
| Aphakic POAG | 25.2 ± 7.2 | 15 - 48 | 73.6% | 30 ± 21 | 2 - 56 |
| Pseudophakic POAG | 26.1 ± 4.3 | 19 - 32 | 8/10 | 30 ± 14 | 10 - 55 |
| Pigment Dispersion S. | 27.0 ± 6.0 | 20 - 40 | 9/10 | 31 ± 13 | 6 - 53 |
| Low-tension Glaucoma | 16.2 ± 2.1 | 12 - 20 | | 32 ± 14 | 3 - 59 |
| Neovascular Glaucoma | 39.0 ± 7.4 | 30 - 48 | 4/4 | 23 ± 11 | 13 - 36 |
| Secondary Glaucoma | 26.3 ± 7.3 | 12 - 55 | 80.6% | 23 ± 11 | 6 - 42 |
| Glaucoma Suspect, Disk- | 27.1 ± 5.4 | 16 - 40 | 85.7% | 28 ± 11 | 2 - 45 |
| Glaucoma Suspect, Disk+ | 25.2 ± 4.3 | 19 - 36 | 80.6% | 25 ± 11 | 2 - 49 |
| Total | 25.3 ± 6.7 | 11 - 60 | 72.0% | 28 ± 13 | 2 - 59 |

A mean initial IOP of 25.3 mm Hg is representative for a group of eyes likely to be submitted to ALT. Initial IOPs evidently differing from the mean were found in low-tension glaucoma and neovascular glaucoma.

Some 70% of all eyes had an initial IOP of 22 mm Hg or over; after excluding eyes with low-tension glaucoma this percentage rose to 76.6%.

Eyes with relatively low initial IOP are submitted to ALT for two reasons: firstly in order to reduce the often maximal medication, and secondly because a relatively low initial IOP value may nevertheless be too high for a given individual eye.

The mean duration of follow-up was 28 months, ranging from a minimum of 2 months to a maximum of nearly 5 years. In cases requiring post-ALT glaucoma surgery, the date of operation was chosen as follow-up date.

### 5.9.2 Complete failures

Table 5.18 lists the percentages of eyes requiring secondary surgery or increased medication after ALT (complete failures).

Table 5.18. Percentage of complete failures per subgroup (Surgery: eyes submitted to glaucoma surgery; Topical Med: eyes needing institution or increase of topical medication; Systemic Med: patients needing institution or increase of carbonic anhydrase inhibitor; Med. All: total percentage of eyes with increased medication; All Eyes: total percentage of complete failure eyes).

| | Surgery | Topical Med | Systemic Med | Med All | All Eyes |
|---|---|---|---|---|---|
| Phakic POAG | 13.1% | 7.8% | 1.3% | 6.5% | 19.6% |
| Aphakic POAG | 15.8% | 15.8% | 5.2% | 10.5% | 26.3% |
| Pseudophakic POAG | 3/10 | 2/10 | | 2/10 | 5/10 |
| Pigment Dispersion S. | 1/10 | | | | 1/10 |
| Low-tension Glaucoma | 10.5% | 10.5% | | 10.5% | 21.1% |
| Neovascular Glaucoma | 1/4 | | 1/4 | 1/4 | 2/4 |
| Secondary Glaucoma | 45.2% | 6.5% | 6.5% | 9.7% | 54.8% |
| Glaucoma Suspect, Disk- | 10.7% | 3.5% | | 3.5% | 14.3% |
| Glaucoma Suspect, Disk+ | 9.7% | 3.2% | | 3.2% | 12.9% |
| Total | 16.4% | 7.5% | 2.0% | 7.2% | 23.6% |

In the entire group, 72 eyes (23.6%) were ultimately classified as complete failures. Some 70% of these eyes required secondary surgery, while the remainder required increased medication after ALT, i.e. more topical medication in 23 eyes (7.5%) and institution of systemic medication in 6 (2.0%). In the majority of cases (87.0%) increased medication entailed a 1-point increase in medication score.

The incidence of surgery was low in pigment dispersion syndrome, low-tension glaucoma and glaucoma suspects. Eyes with secondary glaucoma showed a significantly higher incidence of surgery than eyes with phakic POAG ($p < 0.001$).

The total number of complete failures in pseudophakic POAG and in secondary glaucoma significantly exceeded that in phakic POAG ($p<0.02$ and $p<0.001$ respectively). The incidences in the other subgroups did not differ significantly from that in phakic POAG.

Table 5.19 supplies additional information on indication for surgery, interval between ALT and surgery, and type of operation performed.

In 70.0% of the cases the indication for surgery was no or an inadequate response to ALT; progression of the visual field defect despite an adequate

Table 5.19. Characteristics of pressure-reducing interventions after ALT (PVFD: progressive visual field defect; IOPS: IOP spike: ALT-surgery interval in weeks (w) or months (m); TE: trabeculectomy; CCC: cyclocryocoagulation; Molteno: Molteno implant; IE: iridectomy).

| | Indication | | | | Surgical Procedures | | | |
|---|---|---|---|---|---|---|---|---|
| | No Response | PVDF | IOPS | ALT-Surgery Interval | TE | CCC | Molteno | IE |
| Phakic POAG | 85.0% | 5.0% | 10.0% | 12 ± 13m (3w - 51m) | 90.0% | 5.0% | | 5.0% |
| Aphakic POAG | 3/3 | | | 3m, 7m, 43m | 1/3 | 2/3 | | |
| Pseudophakic POAG | 1/3 | | 2/3 | 3w, 2m, 7m | 2/3 | | | 1/3 |
| Pigment Dispersion S. | 1/1 | | | 25m | 1/1 | | | |
| Low-tension Glaucoma | | 2/2 | | 4w, 44m | 2/2 | | | |
| Neovascular Glaucoma | 1/1 | | | 1w | 1/1 | | | |
| Secondary Glaucoma | 64.3% | | 35.7% | 5 ± 6m (1w - 22m) | 85.7% | 7.1% | 7.1% | |
| Glaucoma Suspect, Disk- | 2/3 | | 1/3 | 3w, 19m, 23m | 2/3 | 1/3 | | |
| Glaucoma Suspect, Disk+ | 1/3 | | 2/3 | 3m, 4m, 31m | 3/3 | | | |
| Total | 70.0% | 6.0% | 24.0% | 10 ± 13m (1w - 51m) | 84.0% | 10.0% | 2.0% | 4.0% |

response to ALT was involved in 6.0%, and in 24.0% surgery was resorted to in view of an early or late IOP increase. The lastmentioned category comprised 12 eyes (3.9%) (5 with secondary glaucoma (4 uveitic and 1 traumatic) 2 with pseudophakic POAG, 2 with phakic POAG and 3 glaucoma suspects).

The incidence in view of a post-ALT IOP spike was significantly higher in secondary glaucoma than in phakic POAG ($p<0.001$), and in the secondary glaucoma subgroup it was higher in uveitic glaucoma (33.3%) than in the other forms (5.3%) ($p<0.05$).

Most of the eyes requiring surgery were submitted to a trabeculectomy (74.0%), while 10.0% required at least two trabeculectomies. The success rate of surgery was 74.0% as measured by the same criteria as those applied to ALT. In eyes requiring increased medication it was 36.4%. The success rate of surgery in view of an IOP spike (66.7%) did not differ significantly from that of surgery for other indications (76.3%) ($p<0.50$).

### 5.9.3 Success rates

Table 5.20 presents the success rates, mean initial IOP, mean final IOP and mean absolute and proportional IOP decrease per subgroup. The IOP parameters pertain to success eyes.

After a mean follow-up of 28 months the overall success rate was 54.1% with a mean proportional IOP decrease of 38.8%.

Taking phakic POAG as frame of reference, a significantly lower success rate was found in low-tension glaucoma ($p<0.05$) and in secondary glaucoma ($p<0.02$). The differences between the other subgroups and phakic POAG were not statistically significant.

As compared with the final IOP in phakic POAG, that in aphakic POAG was significantly higher ($p=0.014$), that in glaucoma suspect without optic disk damage was significantly higher ($p=0.002$), and that in low-tension glaucoma was significantly lower ($p=0.009$). Only in low-tension glaucoma were the mean absolute and proportional IOP decreases significantly less marked ($p=0.003$ and $p=0.005$ respectively).

Apart from the eyes which fulfilled the success criteria, 32 other eyes (10.5%) also derived some benefit from ALT. These 32 eyes included 15 with

Table 5.20. Success rate and IOP parameters per subgroup (IIOP: mean initial IOP; FIOP: mean final IOP; IOPD mm Hg: mean absolute IOP decrease; PIOPD %: mean proportional IOP decrease; SD: standard deviation).

| | Success Rate | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
|---|---|---|---|---|---|
| Phakic POAG | 58.8% | 25.7 ± 5.4 | 15.1 ± 2.8 | 10.6 ± 5.0 | 39.7 ± 12.0 |
| Aphakic POAG | 42.1% | 26.0 ± 9.5 | 16.6 ± 3.3 | 9.4 ± 9.3 | 32.2 ± 16.2 |
| Pseudophakic POAG | 4/10 | 27.0 ± 2.6 | 17.5 ± 2.6 | 9.5 ± 4.7 | 34.4 ± 13.9 |
| Pigment Dispersion S. | 9/10 | 26.3 ± 5.9 | 15.4 ± 3.1 | 10.9 ± 6.5 | 39.3 ± 16.4 |
| Low-tension Glaucoma | 31.6% | 17.0 ± 2.5 | 11.8 ± 1.5 | 5.2 ± 1.7 | 29.9 ± 7.5 |
| Neovascular Glaucoma | 2/4 | 44.0 ± 5.7 | 17.5 ± 2.1 | 26.5 ± 7.8 | 59.6 ± 10.0 |
| Secondary Glaucoma | 35.5% | 27.5 ± 4.5 | 14.8 ± 3.1 | 12.7 ± 4.7 | 45.2 ± 13.1 |
| Glaucoma Suspect, Disk- | 50.0% | 27.9 ± 3.7 | 16.9 ± 2.3 | 11.1 ± 4.3 | 38.6 ± 11.9 |
| Glaucoma Suspect, Disk+ | 67.7% | 25.0 ± 4.4 | 15.8 ± 2.5 | 9.2 ± 4.2 | 35.8 ± 10.8 |
| Total | 54.1% | 25.9 ± 5.8 | 15.4 ± 2.9 | 10.5 ± 5.5 | 38.8 ± 12.6 |

an initial IOP of 22 mm Hg or higher which fulfilled one of the two criteria; in 5 of these eyes medication could be discontinued (carbonic anhydrase inhibitor stopped in 4, and topical medication stopped in 1). In addition there were 17 eyes with an initial IOP of 21 mm Hg or lower in which some IOP decrease was achieved (mean proportional IOP decrease: 5.0 to 19.0%) and in 4 of which medication could be stopped.

Having considered complete failure eyes, success eyes and eyes which derive some benefit from ALT, 36 eyes (11.8%) remain that cannot be unequivocally classified under any of these headings. Data on these are presented in table 5.21. These eyes in actual fact represent failure eyes, because they did not show any, or insufficient, response to ALT. However, because they were not operated on and medication was not increased they were not classified as complete failures.

Twenty-two eyes (7.2%) had a final IOP which exceeded the initial IOP. In 8 of these eyes the increase was less than 10%, and may be ascribed to other than ALT effects.

In 5 of the remaining eyes with an increase by at least 10% this was due to postoperative reduction or discontinuation of medication.

In the end 9 eyes (3.0%) had a final IOP at least 10% higher than the ini-

Table 5.21. Eyes not classified as complete failures.

| | |
|---|---|
| Initial IOP >21 mm Hg | |
| IOP decrease <20%, continued or less medication | 9 eyes (3.0%) |
| IOP decrease 0% | 2 eyes (0.7%) |
| Final IOP > Initial IOP | 7 eyes (2.3%) |
| Initial IOP ≤21 mm Hg | |
| IOP decrease 0%, continued or less medication | 3 eyes (1.0%) |
| Final IOP > Initial IOP | 15 eyes (4.9%) |

tial IOP for no discernible reason. The increase ranged from +14.3% to +100%. Related to initial values, this means that 7.0% of the eyes with an initial IOP of 21 mm Hg or lower and 1.4% of those with an initial IOP of 22 mm Hg or higher showed an IOP increase at longer time after ALT. The difference in the incidences found was statistically significant ($p<0.01$). Seven of these 9 eyes initially showed a satisfactory IOP decrease after ALT.

### 5.9.4 Success rate, initial IOP and ALT modification

Tables 5.22 and 5.23 respectively show the distribution of success rates per subgroup by initial IOP (table 5.22) and by ALT modification (table 5.23).

In each of the subgroups except low-tension glaucoma the success rate in eyes with an initial IOP of at least 22 mm Hg exceeded that in eyes with an initial IOP of 21 mm Hg or lower. Overall, this was statistically significant ($p<0.02$).

The highest success rate was achieved with the 1 * 360° ALT, although the difference from 1 * 180° or 2 * 180° was not statistically significant.

In phakic POAG, however, the difference between 1 * 360° ALT and 2 * 180° ALT was statistically significant ($p<0.02$), and that between 1 * 360° ALT and 1 * 180° was very nearly statistically significant ($p<0.10$). There was no significant difference between 1 * 180° and 2 * 180° ALT, leaving aside the bias in favour of success eyes in the 1 * 180° group (see section 5.7).

Table 5.22. Distribution of success rate per subgroup by initial IOP, taking 21 mm Hg as central value.

| | IIOP >21 mm Hg | IIOP ≤21 mm Hg |
|---|---|---|
| Phakic POAG | 62.7% | 48.8% |
| Aphakic POAG | 42.9% | 2/5 |
| Pseudophakic POAG | 4/8 | 0/2 |
| Pigment Dispersion S. | 8/9 | 1/1 |
| Low-tension Glaucoma | | 31.6% |
| Neovascular Glaucoma | 2/4 | |
| Secondary Glaucoma | 36.0% | 2/6 |
| Glaucoma Suspect, Disk- | 54.2% | 1/4 |
| Glaucoma Suspect, Disk+ | 68.0% | 4/6 |
| Total | 58.4% | 43.0% |

Table 5.23. Distribution of success rate per subgroup by ALT modification.

| | 1 * 180° | 2 * 180° | 1 * 360° |
|---|---|---|---|
| Phakic POAG | 56.8% | 53.1% | 78.6% |
| Aphakic POAG | 5/8 | 3/8 | 0/3 |
| Pseudophakic POAG | 2/5 | 1/2 | 1/3 |
| Pigment Dispersion S. | 1/1 | 4/5 | 4/4 |
| Low-tension Glaucoma | 1/8 | 5/9 | 0/2 |
| Neovascular Glaucoma | 0/2 | 2/2 | |
| Secondary Glaucoma | 45.5% | 21.4% | 3/6 |
| Glaucoma Suspect, Disk- | 2/5 | 57.1% | 0/2 |
| Glaucoma Suspect, Disk+ | 7/8 | 60.0% | 2/3 |
| Total | 52.2% | 52.5% | 62.7% |

### 5.9.5 Changes in IOP in success eyes

Tables 5.24, 5.25 and 5.26 show the changes in IOP in success eyes as a

function of the ALT modification used (table 5.24) and of both the initial IOP and the ALT modification (tables 5.25 and 5.26).

Table 5.24. IOP parameters per subgroup by ALT modification (N: number of eyes; IIOP: mean initial IOP; FIOP: mean final IOP; IOPD mm Hg: mean absolute IOP decrease; PIOPD % : mean proportional IOP decrease; SD: standard deviation).

| 1 * 180° | N | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
|---|---|---|---|---|---|
| Phakic POAG | 25 | 25.6 ± 5.0 | 15.2 ± 3.4 | 10.4 ± 5.1 | 39.3 ± 13.9 |
| Aphakic POAG | 5 | 25.2 ± 3.1 | 17.4 ± 2.2 | 5.8 ± 1.9 | 24.7 ± 5.8 |
| Pseudophakic POAG | 2 | 29.0 ± 1.4 | 17.0 ± 4.2 | 12.0 ± 5.7 | 40.9 ± 17.5 |
| Pigment Dispersion S. | 1 | 40 | 16 | 24 | 60 |
| Low-tension Glaucoma | 1 | 14 | 11 | 3 | 21.4 |
| Secondary Glaucoma | 5 | 25.2 ± 4.8 | 15.2 ± 4.1 | 10.0 ± 5.1 | 38.7 ± 16.2 |
| Glaucoma Suspect, Disk- | 2 | 27.5 ± 0.7 | 17.5 ± 2.1 | 10.0 ± 1.4 | 36.4 ± 6.1 |
| Glaucoma Suspect, Disk+ | 7 | 24.3 ± 3.2 | 16.7 ± 1.3 | 7.6 ± 2.6 | 30.5 ± 7.3 |
| Total | 48 | 25.4 ± 5.1 | 15.7 ± 3.1 | 9.6 ± 5.1 | 36.4 ± 13.4 |
| 2 * 180° | N | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
| Phakic POAG | 43 | 26.9 ± 5.2 | 15.7 ± 2.7 | 11.2 ± 5.2 | 40.1 ± 11.9 |
| Aphakic POAG | 3 | 30.7 ± 15.2 | 15.3 ± 5.0 | 15.3 ± 14.3 | 44.7 ± 21.8 |
| Pseudophakic POAG | 1 | 24 | 19 | 5 | 20.8 |
| Pigment Dispersion S. | 4 | 23.5 ± 1.3 | 16.3 ± 1.3 | 7.3 ± 1.3 | 30.8 ± 4.7 |
| Low-tension Glaucoma | 5 | 17.6 ± 2.3 | 12.0 ± 1.6 | 5.6 ± 1.5 | 31.6 ± 7.0 |
| Neovascular Glaucoma | 2 | 44.0 ± 5.7 | 17.5 ± 2.1 | 26.5 ± 7.8 | 59.6 ± 10.0 |
| Secondary Glaucoma | 3 | 32.3 ± 1.3 | 15.7 ± 2.1 | 16.7 ± 3.5 | 51.3 ± 8.6 |
| Glaucoma Suspect, Disk- | 12 | 28.0 ± 4.0 | 16.8 ± 2.5 | 11.3 ± 4.6 | 39.0 ± 12.7 |
| Glaucoma Suspect, Disk+ | 12 | 25.7 ± 4.9 | 15.5 ± 2.9 | 10.2 ± 4.9 | 38.3 ± 12.4 |
| Total | 85 | 26.8 ± 6.3 | 15.7 ± 2.7 | 11.2 ± 6.0 | 39.6 ± 12.5 |
| 1 * 360° | N | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
| Phakic POAG | 22 | 23.5 ± 5.6 | 13.9 ± 2.2 | 9.6 ± 4.7 | 39.3 ± 10.3 |
| Pseudophakic POAG | 1 | 26 | 17 | 9 | 34.6 |
| Pigment Dispersion S. | 4 | 25.8 ± 4.3 | 14.5 ± 4.7 | 11.3 ± 5.9 | 42.5 ± 21.0 |
| Secondary Glaucoma | 3 | 26.7 ± 1.2 | 13.3 ± 2.1 | 13.3 ± 2.1 | 50.0 ± 7.7 |
| Glaucoma Suspect, Disk+ | 2 | 24.0 ± 7.1 | 14.5 ± 3.5 | 9.5 ± 3.5 | 39.1 ± 3.3 |
| Total | 32 | 24.2 ± 5.1 | 14.1 ± 2.5 | 10.1 ± 4.5 | 40.6 ± 11.4 |

Table 5.25. The same as 5.24, for eyes with an initial IOP ≤21 mm Hg.

| 1 * 180° | N | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
|---|---|---|---|---|---|
| Phakic POAG | 6 | 18.8 ± 1.3 | 12.5 ± 2.4 | 6.3 ± 3.1 | 33.1 ± 14.7 |
| Aphakic POAG | 1 | 18 | 14 | 4 | 22.2 |
| Low-tension Glaucoma | 1 | 14 | 11 | 3 | 21.4 |
| Secondary Glaucoma | 2 | 20.0 | 14.0 ± 2.8 | 6.0 ± 2.8 | 30.0 ± 14.1 |
| Glaucoma Suspect, Disk+ | 2 | 20.5 ± 0.7 | 16.0 | 4.5 ± 0.7 | 21.9 ± 2.7 |
| Total | 12 | 18.8 ± 1.9 | 13.3 ± 2.4 | 5.5 ± 2.6 | 28.8 ± 12.0 |
| **2 * 180°** | **N** | **IIOP ± SD mm Hg** | **FIOP ± SD mm Hg** | **IOPD ± SD mm Hg** | **PIOPD ± SD %** |
| Phakic POAG | 5 | 19.8 ± 1.1 | 13.8 ± 0.8 | 6.0 ± 1.4 | 30.1 ± 6.1 |
| Aphakic POAG | 1 | 18 | 10 | 8 | 44.4 |
| Low-tension Glaucoma | 5 | 17.6 ± 2.3 | 12.0 ± 1.6 | 5.6 ± 1.5 | 31.6 ± 7.0 |
| Glaucoma Suspect, Disk- | 1 | 20 | 16 | 4 | 20 |
| Glaucoma Suspect, Disk+ | 1 | 19 | 14 | 5 | 26.3 |
| Total | 13 | 18.8 ± 1.8 | 13.0 ± 1.8 | 5.8 ± 1.5 | 30.7 ± 7.5 |
| **1 * 360°** | **N** | **IIOP ± SD mm Hg** | **FIOP ± SD mm Hg** | **IOPD ± SD mm Hg** | **PIOPD ± SD %** |
| Phakic POAG | 10 | 19.7 ± 1.5 | 13.2 ± 1.5 | 6.5 ± 1.6 | 32.8 ± 7.2 |
| Pigment dispersion S. | 1 | 20 | 16 | 4 | 20 |
| Glaucoma Suspect, Disk+ | 1 | 19 | 12 | 7 | 36.8 |
| Total | 12 | 19.7 ± 1.4 | 13.3 ± 1.6 | 6.3 ± 1.7 | 32.1 ± 7.7 |

Two IOP parameters are of interest in evaluating the response to ALT: the final IOP achieved, and the mean proportional IOP decrease. The latter is a function of the initial IOP and therefore more significant than the absolute IOP decrease.

Consideration on these two parameters as a function of the ALT modification revealed that eyes treated by 1 * 360° ALT reached a significantly lower final IOP than those treated by 1 * 180° ($p=0.008$) and those treated by 2 * 180° ALT ($p=0.006$), while the mean proportional IOP decrease was significantly more marked than after 1 * 180° ($p=0.05$).

When only eyes with an initial IOP of 21 mm Hg or lower were considered (table 5.25), the various modifications failed to show differences, either

Table 5.26. The same as 5.24, for eyes with an initial IOP >21 mm Hg.

| 1 * 180° | N | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
|---|---|---|---|---|---|
| Phakic POAG | 19 | 27.7 ± 3.6 | 16.0 ± 3.2 | 11.7 ± 5.0 | 41.2 ± 13.4 |
| Aphakic POAG | 4 | 24.5 ± 1.3 | 18.3 ± 1.3 | 6.3 ± 1.9 | 25.3 ± 6.5 |
| Pseudophakic POAG | 2 | 29.0 ± 1.4 | 17.0 ± 4.2 | 12.0 ± 5.7 | 40.9 ± 17.5 |
| Pigment Dispersion S. | 1 | 40 | 16 | 24 | 60 |
| Secondary Glaucoma | 3 | 28.7 ± 1.2 | 16.0 ± 5.3 | 12.7 ± 4.6 | 44.4 ± 17.2 |
| Glaucoma Suspect, Disk- | 2 | 27.5 ± 0.7 | 17.5 ± 2.1 | 10.0 ± 1.4 | 36.4 ± 6.1 |
| Glaucoma Suspect, Disk+ | 5 | 25.8 ± 2.3 | 17.0 ± 1.4 | 8.8 ± 1.8 | 33.9 ± 5.2 |
| Total | 36 | 27.6 ± 3.7 | 16.5 ± 2.9 | 11.0 ± 5.0 | 39.0 ± 13.0 |
| **2 * 180°** | **N** | **IIOP ± SD mm Hg** | **FIOP ± SD mm Hg** | **IOPD ± SD mm Hg** | **PIOPD ± SD %** |
| Phakic POAG | 38 | 27.8 ± 4.8 | 15.9 ± 2.7 | 11.8 ± 5.1 | 41.4 ± 11.8 |
| Aphakic POAG | 2 | 37.0 ± 15.6 | 18.0 ± 2.8 | 19.0 ± 18.4 | 44.9 ± 30.8 |
| Pseudophakic POAG | 1 | 24 | 19 | 5 | 20.8 |
| Pigment Dispersion S. | 4 | 23.5 ± 1.3 | 16.3 ± 1.3 | 7.3 ± 1.3 | 30.8 ± 4.7 |
| Neovascular Glaucoma | 2 | 44.0 ± 5.7 | 17.5 ± 2.1 | 26.5 ± 7.8 | 59.6 ± 10.0 |
| Secondary Glaucoma | 3 | 32.3 ± 1.5 | 15.7 ± 2.1 | 16.7 ± 3.5 | 51.3 ± 8.6 |
| Glaucoma Suspect, Disk- | 11 | 28.7 ± 3.3 | 16.8 ± 2.6 | 11.9 ± 4.2 | 40.8 ± 11.8 |
| Glaucoma Suspect, Disk+ | 11 | 26.3 ± 4.6 | 15.6 ± 3.0 | 10.6 ± 4.9 | 39.4 ± 12.4 |
| Total | 72 | 28.3 ± 5.7 | 16.2 ± 2.6 | 12.1 ± 6.0 | 41.2 ± 12.6 |
| **1 * 360°** | **N** | **IIOP ± SD mm Hg** | **FIOP ± SD mm Hg** | **IOPD ± SD mm Hg** | **PIOPD ± SD %** |
| Phakic POAG | 12 | 26.7 ± 5.7 | 14.5 ± 2.6 | 12.2 ± 4.9 | 44.8 ± 9.4 |
| Pseudophakic POAG | 1 | 26 | 17 | 9 | 34.6 |
| Pigment Dispersion S. | 3 | 27.7 ± 2.5 | 14.0 ± 5.6 | 13.7 ± 4.2 | 50.0 ± 18.0 |
| Secondary Glaucoma | 3 | 26.7 ± 1.2 | 13.3 ± 2.1 | 13.3 ± 2.1 | 50.0 ± 7.7 |
| Glaucoma Suspect, Disk+ | 1 | 29 | 17 | 12 | 41.4 |
| Total | 20 | 26.9 ± 4.5 | 14.5 ± 2.9 | 12.4 ± 4.1 | 45.7 ± 10.3 |

in terms of final IOP or in terms of mean proportional IOP decrease.

In eyes with an initial IOP of at least 22 mm Hg (table 5.26), however, the final IOP reached the lowest value after 1 * 360° ALT ($p=0.015$ in comparison with 1 * 180° ALT and $p=0.024$ in comparison with 2 * 180° ALT) and a more marked proportional IOP decrease ($p=0.017$ if compared with 1 * 180° ALT).

### 5.9.6 Changes in medication

Table 2.27 shows the changes in use of topical medication as a function of the pre-ALT medication score. Eyes submitted to secondary surgery after ALT were not included.

Table 5.27. Changes in use of topical medication as a function of the pre-ALT medication score (Lower: post-ALT score lower but not 0).

| Pre-ALT Medication Score | Post-ALT Higher | Same | Lower | Score 0 |
|---|---|---|---|---|
| 0 | 16.7% | 83.3% | | |
| 1 | 10.8% | 60.8% | | 28.4% |
| 2 | 8.1% | 48.8% | 32.6% | 10.5% |
| 3 | 3.2% | 54.8% | 41.9% | |
| 4 | | 3/6 | 3/6 | |
| 5 | | 1/5 | 4/5 | |
| 6 | | | 1/1 | |
| Total | 9.0% | 56.9% | 19.2% | 14.9% |

In 9.0% of the eyes a higher medication score was found after ALT, and these eyes were regarded as complete failures. In 56.9% of the eyes there was no post-ALT change in medication, and in 34.1% (37.7% of the eyes medicated), topical medication was reduced or discontinued. The chance of reduced medication increased, but the chance of discontinued medication decreased, with an increasing medication score. The largest group able to stop topical medication was that of eyes with a pre-ALT score of 1, which is to say only one type of eyedrop. From medication score 3 on, no discontinuation of topical medication was possible.

In the majority of the pertinent cases the increase in medication scores after ALT amounted to only 1 point (87.0%). This means addition of another type of eyedrop or an increase in the concentration of miotics.

Table 5.28 lists the changes in medication after ALT for success eyes per subgroup.

The mean medication score diminished in each of the subgroups (the neovas-

Table 5.28. Post-ALT changes in medication in success eyes (Pre/Post: pre- or post-ALT; Cont: continued; Systemic: carbonic anhydrase inhibitor; No Medication: percentage of eyes using no medication).

| | Mean Medication Score | | Topical | | | Systemic | No Medication | |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Cont | Lower | Stopped | Stopped | Pre | Post |
| Phakic POAG | 2.0 ± 1.1 | 1.4 ± 1.0 | 59.3% | 26.7% | 14.0% | 84.6% | 4.4% | 17.8% |
| Aphakic POAG | 1.9 ± 1.0 | 1.5 ± 1.1 | 4/7 | 3/7 | | 0/2 | 1/8 | 1/8 |
| Pseudophakic POAG | 2.0 | 2.0 | 4/4 | | | | 0/4 | 0/4 |
| Pigment Dispersion S. | 1.0 ± 0.7 | 0.4 ± 0.5 | 3/7 | 1/7 | 3/7 | | 2/9 | 5/9 |
| Low-tension Glaucoma | 1.2 ± 0.8 | 0.7 ± 0.5 | 3/5 | 1/5 | 1/5 | 0/1 | 1/6 | 2/6 |
| Neovascular Glaucoma | 1.0 | 1.0 | 2/2 | | | 1/1 | 0/2 | 0/2 |
| Secondary Glaucoma | 1.2 ± 0.4 | 0.6 ± 0.5 | 45.5% | 9.1% | 45.5% | 54.5% | 0 % | 45.5% |
| Glaucoma Suspect, Disk- | 1.1 ± 0.7 | 0.9 ± 0.8 | 72.7% | 9.1% | 18.2% | 1/1 | 21.4% | 35.7% |
| Glaucoma Suspect, Disk+ | 1.8 ± 1.4 | 1.3 ± 1.3 | 63.2% | 15.8% | 21.1% | 2/2 | 9.5% | 33.3% |
| Total | 1.7 ± 1.1 | 1.2 ± 1.0 | 59.9% | 21.7% | 18.4% | 67.7% | 7.9% | 24.8% |

cular glaucoma and pseudophakic POAG subgroups comprising respectively only two and four eyes).

Topical medication could be reduced or discontinued in 40.1% of the eyes. The chance of stopping carbonic anhydrase inhibitors after successful ALT was 67.7%. Some of the patients using systemic medication, however, underwent surgery. Of the 64 patients using carbonic anhydrase inhibitors prior to ALT, 31 eyes (48.4%) were classified as success eyes. In 21 of these the inhibitors could be discontinued; the chance of successful ALT and discontinued systemic medication was therefore 32.8%.

The rate of eyes requiring no post-ALT medication as related to the pre-ALT situation was significantly higher in phakic POAG ($p<0.01$) and in secondary glaucoma ($p<0.001$).

### 5.9.7 Optic disk, visual acuity and visual field function

Table 5.29 lists the mean disk scores in success eyes before as well as after ALT, per subgroup.

Table 5.29. Mean pre-ALT and post-ALT disk scores per subgroup for success eyes (N: number of eyes in which a score could be determined).

| | N | Pre-ALT | Post-ALT |
|---|---|---|---|
| Phakic POAG | 52 | 4.7 ± 2.4 | 4.7 ± 2.5 |
| Aphakic POAG | 7 | 6.3 ± 1.4 | 6.3 ± 1.4 |
| Pseudophakic POAG | 4 | 6.0 | 5.0 ± 2.0 |
| Pigment Dispersion S. | 5 | 2.0 ± 2.5 | 2.0 ± 2.5 |
| Low-tension Glaucoma | 5 | 5.6 ± 1.7 | 5.2 ± 2.3 |
| Neovascular Glaucoma | 1 | 0 | 0 |
| Secondary Glaucoma | 5 | 4.4 ± 2.2 | 4.0 ± 2.8 |
| Glaucoma Suspect, Disk- | 10 | 0.0 | 0.0 |
| Glaucoma Suspect, Disk+ | 16 | 3.3 ± 2.5 | 3.6 ± 2.5 |
| Total | 105 | 4.0 ± 2.7 | 4.0 ± 2.8 |

Per subgroup the mean disk score remained virtually unchanged. Of these 105 success eyes, 7 (6.7%) showed an increase in disk score by at least 2 points despite a good response to ALT. These included 5 with phakic POAG and 2 with suspected glaucoma and optic disk damage. In 10 success eyes with suspected glaucoma without disk damage, no increase in score was observed.

Mean visual acuity in success eyes did not change post-ALT (table 5.30).

Table 5.30. Mean pre-ALT and post-ALT visual acuity per subgroup for success eyes (N: number of eyes in which visual acuity was determined).

| | N | Pre-ALT | Post-ALT |
|---|---|---|---|
| Phakic POAG | 74 | 0.53 ± 0.31 | 0.54 ± 0.29 |
| Aphakic POAG | 7 | 0.32 ± 0.24 | 0.45 ± 0.32 |
| Pseudophakic POAG | 3 | 0.45 ± 0.30 | 0.25 ± 0.31 |
| Pigment Dispersion S. | 8 | 0.71 ± 0.37 | 0.74 ± 0.40 |
| Low-tension Glaucoma | 5 | 0.40 ± 0.19 | 0.70 ± 0.20 |
| Neovascular Glaucoma | 1 | 0.50 | 0.40 |
| Secondary Glaucoma | 9 | 0.49 ± 0.39 | 0.52 ± 0.47 |
| Glaucoma Suspect, Disk- | 13 | 0.86 ± 0.24 | 0.73 ± 0.32 |
| Glaucoma Suspect, Disk+ | 18 | 0.68 ± 0.28 | 0.68 ± 0.29 |
| Total | 138 | 0.57 ± 0.32 | 0.58 ± 0.31 |

Table 5.31 shows the changes in visual field stages as a function of the pre-ALT stage and as a function of the response to ALT. For eyes submitted to secondary surgery, the post-ALT stage immediately preceding this surgery was chosen in order to enable measurement of an ALT effect.

Table 5.31. Post-ALT visual field stages as a function of the pre-ALT visual field stage and as a function of success and failure.

| Visual Field Stage | No Change | Worsened | |
|---|---|---|---|
| | | Same Stage | ≥1 Stage |
| 0 | 94.1% | 5.9% | |
| 1 | 83.3% | 16.7% | |
| 2 | 52.6% | 26.3% | 21.1% |
| 3 | 56.0% | 32.0% | 12.0% |
| 4 | 7/10 | 3/10 | |
| 5a | 33.3% | 41.7% | 25.0% |
| A/B/C | 61.5% | 20.5% | 17.9% |
| Success Eyes | 69.0% | 21.1% | 9.9% |
| Failure Eyes | 57.6% | 27.0% | 15.9% |
| Total | 63.4% | 23.9% | 12.7% |

In 63.4% of the eyes there was no deterioration in visual field stage after ALT. About 25% of the eyes did show progression of the visual field defect, but within the same stage as before ALT. Progression to a more advanced stage occurred in 12.7% of cases. More specifically, this progression was seen in the following stages:

Stage 2 Fusion of multiple absolute defects to form a Bjerrum Scotoma.

Stage 3 Progression to (semi)circular paracentral defects.

Stage 5a Loss of central remnant. In 3 of 12 eyes showing this pre-ALT stage loss of central vision occurred despite a good response to ALT. These 3 eyes had all shown a transient IOP increase after ALT, but in only 1 eye was it possible to confirm that this was responsible for the progression. This could possibly have been prevented if the patient had presented at the appointed times for

IOP check-ups. At worst, this meant that 3 out of 305 eyes (1.0%) suffered a serious visual field defect as a result of ALT.

Stages A-C In 17.9% of the eyes showing one of these changes before ALT, a glaucomatous visual field defect developed. None of these eyes had suspected glaucoma with or without optic disk damage. Progression occurred only if an eye had been interpreted as glaucomatous on the basis of earlier perimetric findings or findings in the contralateral eye.

Thus progression to a more advanced stage occurred if an absolute defect was already present or if the eye was at risk.

The differences between success eyes and failure eyes were minimal. We intend to revert to this point in the Discussion (5.15).

### 5.9.8 Re-treatment

Of the total group of 305 eyes, 24 (7.9%) were submitted to re-ALT. In 16 eyes re-ALT was performed after an initial 2 * 180°, and in 8 eyes after a 1 * 360° ALT. The re-ALT involved treatment of 180° of the trabecular meshwork circumference or a 1 * 360° ALT, but in that case applying only 60 burns. Five eyes were submitted to a 2 * 180° re-ALT. The mean time between the initial ALT and re-ALT was 19.4 ± 13.9 months (range 1-50 months).

In 13 of 24 eyes (54.2%) glaucoma surgery was after all required, and 2 eyes (8.3%) needed increased medication. The complete failure rate was therefore 62.5%. The failure rate for the initial 2 * 180° ALT (10/16 eyes) was the same as that for the initial 1 * 360° (5/8 eyes).

Of the remaining eyes without complete failure 7 showed adequate IOP control and the success rate after re-ALT was therefore 29.2% at a mean follow-up period of 9.7 ± 5.1 months (range 2-12 months).

### 5.9.9 Bilateral ALT

Table 5.32 lists the results of ALT in patients whose first eye had al-

Table 5.32. Success rate and IOP parameters in second eyes of patients treated bilaterally (IIOP: mean initial IOP; FIOP: mean final IOP; IOPD mm Hg: mean absolute IOP decrease; PIOPD %: mean proportional IOP decrease; SD: standard deviation).

| | N | SR | Success Eyes IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD % |
|---|---|---|---|---|---|---|
| Phakic POAG | 66 | 54.5% | 25.2 ± 5.2 | 15.3 ± 2.8 | 9.9 ± 5.1 | 37.7 ± 12.3 |
| Aphakic POAG | 6 | 1/6 | 20 | 14 | 6 | 30 |
| Pseudophakic POAG | 4 | 1/4 | 23 | 16 | 7 | 30.4 |
| Pigment Dispersion S. | 6 | 3/6 | 21.0 ± 4.4 | 12.3 ± 3.8 | 8.7 ± 3.2 | 41.4 ± 14.7 |
| Low-tension Glaucoma | 12 | 50.0% | 18.0 ± 2.2 | 12.7 ± 1.8 | 5.3 ± 1.2 | 29.6 ± 5.5 |
| Neovascular Glaucoma | 1 | 1/1 | 28 | 16 | 12 | 42.9 |
| Secondary Glaucoma | 4 | 0/4 | | | | |
| Glaucoma Suspect, Disk- | 16 | 56.3% | 25.4 ± 3.7 | 16.3 ± 2.5 | 9.1 ± 3.4 | 35.3 ± 9.6 |
| Glaucoma Suspect, Disk+ | 13 | 46.2% | 23.0 ± 3.5 | 16.0 ± 2.5 | 7.0 ± 2.0 | 30.3 ± 6.7 |
| Total | 128 | 49.2% | 24.1 ± 5.0 | 15.1 ± 2.8 | 9.0 ± 4.4 | 35.9 ± 11.1 |

ready been treated.

Except in low-tension glaucoma and suspected glaucoma without optic disk damage, the success rate was always slightly lower than in the first eye. The success rate in the total group, however, did not differ statistically from that in the eyes treated first. The final IOP of success eyes differed hardly from that of the eyes first treated by ALT.

Table 5.33 presents the results expressed as success or failure in the two eyes of a patient. The majority of patients proved to show a symmetrical response.

Table 5.34 indicates the chance of a similar response in the second as in the first eye. The chance of success in the second eye after a good response of the first is 71.8%, which is significantly higher than the expected result (54.1%) if the responses of the two eyes would be independent. There is a statistically significant correlation between the ALT responses of both eyes in a given individual (McNemar test, $p<0.01$).

Although the percentages indicate that the responses of the two eyes in a given individual are not independent, they are of little predictive value because late failures are also included in these figures, and success may

Table 5.33. Distribution of symmetrical (bilateral success/failure) and asymmetrical (success-failure/failure-success) responses per subgroup.

| | Bilateral Success | Bilateral Failure | Success-Failure | Failure-Success |
|---|---|---|---|---|
| Phakic POAG | 50.0% | 28.0% | 16.7% | 4.6% |
| Aphakic POAG | | 2/6 | 3/6 | 1/6 |
| Pseudophakic POAG | 1/4 | 2/4 | 1/4 | |
| Pigment Dispersion S. | 3/6 | | 3/6 | |
| Low-tension Glaucoma | 33.3% | 50.0% | | 16.7% |
| Neovascular Glaucoma | 1/1 | | | |
| Secondary Glaucoma | | 2/4 | 2/4 | |
| Glaucoma Suspect, Disk- | 50.0% | 43.8% | | 6.3% |
| Glaucoma Suspect, Disk+ | 46.2% | 38.5% | 15.4% | 5.5% |
| Total | 43.8% | 33.6% | 17.2% | 5.5% |

Table 5.34. Chance of success/failure of the second eye after success/failure of the eye treated first.

| | Success | Failure |
|---|---|---|
| Phakic POAG | 75.0% | 86.4% |
| Aphakic POAG | 0/3 | 2/3 |
| Pseudophakic POAG | 1/2 | 2/2 |
| Pigment Dispersion S. | 3/6 | |
| Low-tension Glaucoma | 4/4 | 6/8 |
| Neovascular Glaucoma | 1/1 | |
| Secondary Glaucoma | 2/2 | 2/2 |
| Glaucoma Suspect, Disk- | 8/8 | 7/8 |
| Glaucoma Suspect, Disk+ | 6/8 | 5/5 |
| Total | 71.8% | 86.0% |

have prevailed during a certain period of time.

In this respect the need for glaucoma surgery is more revealing because this was often performed shortly after ALT. In the total group of bilaterally treated patients, 14 first ALT eyes required secondary surgery; in 8 of

these 14 cases the contralateral eye was submitted to surgery (57.1%). In the group of first ALT eyes not operated on, only 3 second ALT eyes needed subsequent surgery (2.6%).

In the phakic POAG subgroup, 9 first ALT eyes needed surgery and in 5 of these the contralateral eye was operated on as well, while in 57 first ALT eyes not requiring surgery not a single contralateral eye needed an operation.

## 5.10 VARIABLES IN PHAKIC POAG

Table 5.35 and figure 5.3 present the success rate as a function of the follow-up, estimated on the basis of the Kaplan-Meier technique.

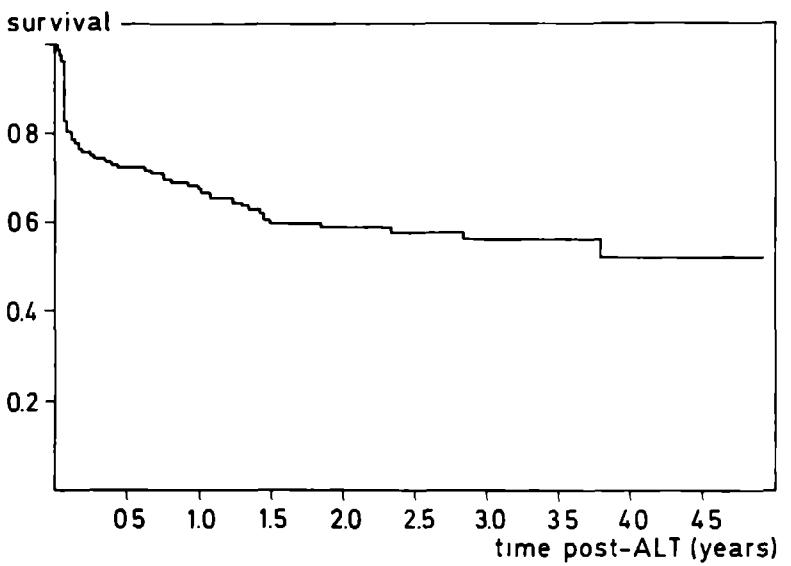



Figure 5.3. Success rate as a function of follow-up in phakic POAG.

The success rate readily diminished during the first few months following ALT. This was determined on the one hand by the secondary surgery required

Table 5.35. Success rate as a function of follow-up in phakic POAG.

| Follow-up | Success rate |
|---|---|
| 1 month | 83.0% |
| 3 months | 75.2% |
| 6 months | 72.5% |
| 12 months | 67.6% |
| 24 months | 59.0% |
| 36 months | 56.3% |
| 48 months | 52.3% |

shortly after ALT, and on the other by the criterion that the failure date was determined from a one-month follow-up on.

Table 5.36 presents success rates and IOP parameters as a function of some patient variables.

Table 5.36. Success rate and IOP parameters as a function of patient variables in phakic POAG (SR: success rate; $IIOP_{total}$: mean initial IOP of the total group; FIOP: mean final IOP; IOPD mm Hg: mean absolute IOP decrease; PIOPD %: mean proportional IOP decrease; SD: standard deviation).

| | | | | | Success Eyes | | | |
|---|---|---|---|---|---|---|---|---|
| | | SR | p-value | $IIOP_{total}$ | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD% |
| ODS | OD | 62.9% | 0.23 | 26.4 ± 7.5 | 26.2 ± 5.7 | 15.0 ± 3.1 | 11.2 ± 5.3 | 41.2 ± 12.3 |
| | OS | 53.1% | | 24.0 ± 4.9 | 24.8 ± 4.6 | 15.3 ± 2.4 | 9.6 ± 4.5 | 37.2 ± 11.1 |
| Sex | Male | 65.2% | 0.05 | 26.8 ± 7.1 | 26.2 ± 5.4 | 14.8 ± 2.8 | 11.4 ± 5.4 | 42.0 ± 12.0 |
| | Female | 49.2% | | 23.3 ± 5.2 | 24.6 ± 5.2 | 15.7 ± 2.9 | 8.9 ± 3.9 | 35.0 ± 10.7 |
| Age | 20 - 29 yr | 1/1 | | 20 | 20 | 12 | 8 | 40 |
| | 30 - 39 yr | 3/3 | | 27.7 ± 5.7 | 27.7 ± 5.7 | 18.0 ± 3.5 | 9.7 ± 4.0 | 34.5 ± 9.9 |
| | 40 - 49 yr | 4/7 | | 26.7 ± 15.1 | 21.8 ± 3.3 | 14.3 ± 2.6 | 7.5 ± 3.3 | 33.8 ± 12.0 |
| | 50 - 59 yr | 45.0% | | 24.5 ± 5.4 | 24.3 ± 5.7 | 14.0 ± 2.1 | 10.3 ± 4.4 | 40.9 ± 9.8 |
| | 60 - 69 yr | 59.2% | | 24.7 ± 4.7 | 25.2 ± 4.5 | 15.6 ± 2.9 | 9.6 ± 3.4 | 37.6 ± 9.8 |
| | 70 - 79 yr | 54.2% | | 26.3 ± 7.6 | 26.9 ± 6.1 | 14.7 ± 3.0 | 12.2 ± 6.6 | 43.0 ± 14.5 |
| | 80 - 89 yr | 72.0% | | 25.2 ± 5.7 | 26.1 ± 5.6 | 15.3 ± 2.6 | 10.8 ± 5.3 | 39.8 ± 12.7 |

Neither in success rate nor in IOP parameters was a statistically significant difference found between OD and OS.

Men had a higher success rate than women ($p<0.05$); it is to be noted that women had a lower initial IOP. The final IOP in success eyes was lower in men, who showed a more marked absolute and proportional IOP decrease.

The age distribution reveals a small proportion of eyes of patients under 40. There was no statistically significant difference in success rate between patients over and those under 60. There were no significant differences in IOP parameters between the various age categories.

Table 5.37 shows the effect of glaucoma variables in the response to ALT. The initial IOP was one of the determinants of the chance of success. Not one of 5 eyes with an initial IOP of 11-15 mm Hg achieved a lasting IOP decrease of at least 20%, whereas 2 eyes with an initial IOP of 46 mm Hg or higher failed to fulfil the criteria accepted.

The success rate was 45.9% for eyes with a low initial IOP (11-20 mm Hg), 65.0% for those with a moderately increased IOP, and 46.2% for eyes with a high initial IOP (>35 mm Hg). There was no statistically significant difference in success rate between eyes with a high and those with a low initial IOP; but eyes with a moderately increased IOP attained a significantly higher success rate than those with a low initial IOP ($p<0.05$).

Mean absolute and proportional IOP decreases became more marked with increasing initial IOP values and the differences between them were statistically significant.

Pearson's coefficient of correlation for initial IOP-IOP decrease was 0.85. The final IOP in eyes with a low initial IOP was significantly lower than that in eyes with a moderately increased initial IOP.

Differences in success rates between eyes without or with moderate glaucomatous optic disk damage (score 0-3), with moderate-to-severe damage (score 4-7) and with very severe damage (score 8) were not statistically significant; the same applies to the IOP parameters.

The same also applies to the visual field stages. Differences in success rates between the different stages were not statistically significant and, although eyes with visual field stage 5a and 5b had a higher initial IOP, there was no difference in IOP decrease and final IOP.

In terms of pre-ALT medication there were no demonstrable differences be-

Table 5.37. The same as 5.36, for glaucoma variables (Disk Score: pre-ALT optic disk score; VFS: pre-ALT visual field stage; Med Score: pre-ALT medication score; Syst Med: pre-ALT systemic medication used; Miotics: pre-ALT miotics used; Not Operated: eyes not being submitted to previous glaucoma surgery; Trabeculectomies: eyes being submitted to one or more trabeculectomies; All Operated: all eyes being submitted to glaucoma surgery).

| | | | | Success Eyes | | | |
|---|---|---|---|---|---|---|---|
| | | SR | $IIOP_{total}$ | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD% |
| IIOP mm Hg | 11-15 | 0/5 | 14.2 ± 1.3 | | | | |
| | 16-20 | 53.1% | 19.0 ± 1.4 | 19.1 ± 1.3 | 12.9 ± 1.7 | 6.2 ± 2.1 | 32.0 ± 9.8 |
| | 21-25 | 63.0% | 23.4 ± 1.4 | 23.4 ± 1.3 | 14.6 ± 2.6 | 8.8 ± 2.5 | 37.6 ± 10.4 |
| | 26-30 | 62.5% | 28.0 ± 1.5 | 28.0 ± 1.6 | 17.0 ± 2.7 | 11.0 ± 3.0 | 39.3 ± 9.7 |
| | 31-35 | 8/9 | 32.9 ± 1.2 | 32.8 ± 1.2 | 16.0 ± 2.6 | 16.8 ± 2.6 | 51.2 ± 7.8 |
| | 36-40 | 5/9 | 37.1 ± 1.8 | 37.6 ± 2.2 | 15.2 ± 3.0 | 22.4 ± 4.3 | 59.3 ± 9.3 |
| | 41-45 | 1/2 | 42.0 ± 1.4 | 41 | 16 | 25 | 61 |
| | 46-50 | 0/1 | 48 | | | | |
| | >50 | 0/1 | 60 | | | | |
| Disk Score | 0-3 | 69.4% | 25.3 ± 5.5 | 26.1 ± 5.8 | 15.6 ± 2.7 | 10.5 ± 6.0 | 38.2 ± 13.1 |
| | 4-7 | 57.3% | 24.8 ± 6.0 | 25.5 ± 5.0 | 15.0 ± 2.9 | 10.4 ± 4.5 | 39.9 ± 11.5 |
| | 8 | 50.0% | 29.2 ± 10.3 | 26.3 ± 7.6 | 15.1 ± 2.6 | 11.2 ± 5.8 | 40.8 ± 11.4 |
| VFS | 0/A/B/C | 55.6% | 25.4 ± 5.2 | 26.7 ± 5.5 | 15.3 ± 2.7 | 11.3 ± 5.1 | 41.0 ± 11.7 |
| | 1-2 | 61.9% | 24.3 ± 5.6 | 25.3 ± 5.3 | 14.5 ± 2.8 | 10.8 ± 5.2 | 41.3 ± 12.1 |
| | 3-4 | 65.6% | 24.4 ± 6.2 | 24.7 ± 5.2 | 15.0 ± 3.1 | 9.7 ± 4.7 | 38.2 ± 12.2 |
| | 5 | 4/10 | 27.2 ± 5.9 | 30.8 ± 7.1 | 17.0 ± 3.2 | 13.8 ± 8.2 | 42.5 ± 16.9 |
| Med Score | 0 | 4/9 | 24.4 ± 4.4 | 25.3 ± 2.2 | 15.8 ± 4.0 | 9.5 ± 2.9 | 38.0 ± 13.5 |
| | 1-2 | 57.3% | 24.7 ± 6.6 | 25.0 ± 5.5 | 14.9 ± 2.5 | 10.1 ± 5.1 | 38.8 ± 11.4 |
| | 3-6 | 67.7% | 27.8 ± 6.8 | 27.7 ± 4.9 | 15.7 ± 3.4 | 12.1 ± 5.1 | 42.6 ± 13.3 |
| Systemic Med | Yes | 43.3% | 27.2 ± 7.6 | 25.5 ± 5.1 | 15.0 ± 3.4 | 10.5 ± 5.4 | 39.7 ± 14.4 |
| | No | 62.6% | 25.0 ± 6.4 | 25.7 ± 5.4 | 15.1 ± 2.8 | 10.6 ± 5.0 | 39.7 ± 11.6 |
| Miotics | Yes | 64.1% | 25.5 ± 6.0 | 26.3 ± 4.8 | 15.3 ± 3.0 | 10.9 ± 4.9 | 40.5 ± 11.8 |
| | No | 54.6% | 25.4 ± 7.6 | 24.9 ± 6.3 | 14.7 ± 2.5 | 10.2 ± 5.5 | 38.7 ± 12.3 |
| Not operated eyes | | 60.8% | 25.6 ± 6.9 | 25.7 ± 5.5 | 15.0 ± 2.9 | 10.7 ± 5.2 | 40.0 ± 12.3 |
| Trabeculectomies | | 60.0% | 24.1 ± 4.7 | 24.8 ± 4.7 | 14.9 ± 2.4 | 9.9 ± 3.9 | 38.9 ± 9.7 |
| All operated Eyes | | 50.0% | 23.8 ± 4.6 | 25.3 ± 4.8 | 15.4 ± 2.8 | 9.9 ± 3.7 | 38.3 ± 9.3 |

tween eyes with score 0, those with score 1-2 and those with score 3 or higher. Nor was there a significant difference in success rate between eyes

treated with miotics and those not so treated. There was an indication of a lower success rate in patients using a carbonic anhydrase inhibitor ($p=0.07$). There were no statistically significant differences in final IOP between success eyes with different medication scores, with or without miotics and with or without carbonic anhydrase inhibitors.

Eyes already submitted to trabeculectomy before ALT had a similar success rate as those not previously operated on. These categories did not differ in final IOP or IOP decrease. A similar result was obtained when all surgical treated eyes were lumped together.

Of 153 eyes with phakic POAG, 24 were submitted to extracapsular cataract extraction after ALT. The success rate in this group was 70.8%, versus 55.8% in eyes without cataract extraction. This difference was not statistically significant ($p=0.17$). The final IOP and the IOP decrease were the same in these groups.

Table 5.38 presents results in relation to ALT variables. The respective success rates after iris stretching, ALT performed by a staff member and ALT of good quality were higher than those in the counterparts of these variables, but in none of these instances was the difference statistically significant; nor were significant differences in final IOP or IOP decrease observed. ALT combined with iridotomy gave a higher success rate than ALT without iridotomy, the difference not being statistically significant.

Table 5.38. The same as 5.36, for ALT variables.

| | | | Success Eyes | | | |
|---|---|---|---|---|---|---|
| | SR | $IIOP_{total}$ | IIOP ± SD mm Hg | FIOP ± SD mm Hg | IOPD ± SD mm Hg | PIOPD ± SD% |
| Iris Stretching Yes | 68.6% | 26.3 ± 6.9 | 26.8 ± 6.3 | 15.7 ± 2.4 | 11.1 ± 6.1 | 39.2 ± 12.6 |
| No | 55.9% | 25.1 ± 6.6 | 25.3 ± 5.0 | 14.9 ± 3.0 | 10.4 ± 4.6 | 39.9 ± 11.8 |
| Staff Member | 63.6% | | | | | |
| Resident | 50.9% | | | | | |
| ALT easy | 58.6% | 24.7 ± 5.6 | 25.4 ± 5.5 | 14.9 ± 2.9 | 10.6 ± 5.3 | 39.9 ± 12.7 |
| laborious | 41.7% | 29.6 ± 12.0 | 26.0 ± 2.6 | 16.2 ± 2.0 | 9.8 ± 1.9 | 37.6 ± 5.9 |
| ALT + Iridotomy | 76.9% | 28.2 ± 7.9 | 27.4 ± 5.5 | 16.4 ± 2.3 | 11.0 ± 4.2 | 39.1 ± 8.6 |

## 5.11 VARIABLES IN APHAKIC POAG

Of the eyes with aphakic POAG, 11 had undergone glaucoma surgery prior to ALT; 5 of these eyes responded well to ALT. Of the 8 eyes not previously submitted to surgery, 3 showed a good response.

Twelve eyes showed pre-ALT gonioscopic abnormalities which might interfere with ALT (e.g. PAS, local obliteration of the iridocorneal angle, poor visualization of the trabecular meshwork). Four of these eyes were treated successfully. Of the remaining 7 eyes without the abovementioned abnormalities, 4 showed a good response.

## 5.12 AGE AND PIGMENT DISPERSION SYNDROME

The mean age of the 10 patients with a pigment dispersion syndrome was 41.6 $\pm$ 11.1 years. Seven patients were under 50. In the group of eyes treated first, 1 eye was a complete failure. This patient was 53 years old.

## 5.13 SECONDARY GLAUCOMA

Table 5.39 presents the results in various forms of secondary glaucoma as so far discussed together, adding to these 4 eyes with congenital glaucoma, 1 eye with juvenile glaucoma, 1 eye with congenital cataract and glaucoma, and 1 eye of a patient with hyperthyroidism.

The overall success rate in this group was low. Decidedly moderate results were obtained in uveitic glaucoma and traumatic glaucoma. Less poor results were obtained in glaucoma with detached retina, in glaucoma with central vein occlusion and in congenital glaucoma.

Within the secondary glaucoma group 11 eyes showed extensive PAS in the chamber angle, while 14 eyes showed no abnormalities in the angle. Eyes with PAS had a success rate of 18.2%, versus 42.9% for eyes without angle abnormalities.

The success rate in phakic eyes with secondary glaucoma was 40.0%, versus 27.3% in eyes after cataract extraction.

Table 5.39. Success rate distribution in various forms of secondary glaucoma with, in addition, 4 eyes with congenital glaucoma, 1 with juvenile glaucoma, 1 with congenital cataract and glaucoma, and 1 eye with hyperthyroidism.

| | Number | Complete Failure | Success |
|---|---|---|---|
| Uveitic Glaucoma | 12 | 10/12 | 2/12 |
| Traumatic Glaucoma | 8 | 4/8 | 2/8 |
| Post Retinal Detachment | 5 | 1/5 | 3/5 |
| Corticosteroid Glaucoma | 2 | 1/2 | 1/2 |
| Central Vein Occlusion | 2 | | 2/2 |
| Tapetoretinal Degeneration | 1 | 1/1 | |
| Post Cataract Extraction | 1 | | 1/1 |
| Congenital Glaucoma | 4 | 2/4 | 2/4 |
| Juvenile Glaucoma | 1 | | 0/1 |
| Congenital Cataract | 1 | 1/1 | |
| Hyperthyroidism | 1 | | 0/1 |
| Total | 38 | 20/38 (52.6%) | 13/38 (34.2%) |

## 5.14 SUSPECTED GLAUCOMA

Table 5.40 once again summarizes the results of ALT in phakic POAG, suspected glaucoma without glaucomatous optic disk damage, and suspected glaucoma with optic disk damage.

Suspected glaucoma without optic disk damage showed a higher initial IOP than suspected glaucoma with optic disk damage or phakic POAG. This is because the firstmentioned subgroup comprises more eyes receiving no medication (21.4%) than the two lastmentioned subgroups (12.9% and 5.9% respectively).

In terms of two important results - success rate and final IOP - suspected glaucoma without optic disk damage seemed to be inferior to those in the other two forms. However, only the differences in final IOP were statistically significant ($p=0.002$ when compared with phakic POAG and $p=0.04$ when compared with suspected glaucoma with optic disk damage). The highest success rate, lowest complete failure rate and most favourable changes in medication score were found in suspected glaucoma with optic disk damage, but

Table 5.40. ALT response of eyes with phakic POAG, suspected glaucoma without optic disk damage and suspected glaucoma with optic disk damage, in terms of various parameters.

| | Phakic POAG | Suspected Glaucoma | |
|---|---|---|---|
| | | Disk- | Disk+ |
| Mean Initial IOP (mm Hg) | 25.4 ± 6.7 | 27.1 ± 5.4 | 25.2 ± 4.3 |
| Mean Final IOP (mm Hg) | 15.1 ± 2.8 | 16.9 ± 2.3 | 15.8 ± 2.5 |
| Mean absolute IOP decrease (mm Hg) | 10.6 ± 5.0 | 11.1 ± 4.3 | 9.2 ± 4.2 |
| Mean proportional IOP decrease (%) | 39.7 ± 12.0 | 38.6 ± 11.9 | 35.8 ± 10.8 |
| Complete Failures | 19.6% | 14.3% | 12.9% |
| Success Rate All Eyes | 58.8% | 50.0% | 67.7% |
| Success Rate initial IOP >21 mm Hg | 62.7% | 54.2% | 68.0% |
| Topical Medication Less or Stopped | 40.7% | 21.4% | 36.8% |
| Stop All Medication | 13.4% | 14.3% | 23.8% |

the differences from the other two subgroups were not statistically significant.

## 5.15 DISCUSSION AND CONCLUSIONS

**Phakic POAG:**

In 153 first treated eyes with phakic POAG the success rate was 58.8% after a mean follow-up of 28 months. The mean proportional IOP decrease in the success group was 39.7%; the mean final IOP was 15.1 mm Hg.

The success rate diminished with an increasing follow-up period. The failure rate during the first few months after ALT was 20%, but from 6 months post-ALT on (success rate at that time 72.5%) an annual maximum failure rate of 10% occurred, resulting in a success rate of 52.3% after a follow-up of 48 months. The initial failures were caused on the one hand by surgery on non-responding eyes soon after ALT, and on the other hand because a minimum follow-up of 1 month was completed before an eye was interpreted as failure. Particularly during the period immediately after introduction of ALT, a few eyes were submitted to surgery shortly after ALT which today would have been given more time to show whether a late response to ALT might occur.

In 70.0% of cases needing secondary surgery, the operation was performed within 6 months of ALT. In 30%, however, it was a late failure of ALT that necessitated surgery: within a year in 3 eyes, within 2 years in 1 eye, within 4 years in 1 eye and after 4 years in 1 eye.

Our success and failure criteria were confined to changes in IOP with unchanged or reduced medication. Criteria relating to glaucomatous optic disk cupping and visual field defects were not applied. It is true of course, that it was not intraocular pressures that were treated, but glaucoma types; in that sense the non-application of the lastmentioned criteria may be regarded as a shortcoming. It should be borne in mind, however, that in any case a decrease in IOP should be regarded as one of the primary objectives of glaucoma therapy, hoping that the optic disk and visual field show no progressive increase of damage. Another reason was that in this retrospective study both the degree of optic disk cupping and the perimetry were not recorded in a standardized protocol in glaucoma patients treated by ALT, and that an analysis can consequently be performed only with great prudence. If only because of a time limit between perimetry and ALT, a visual field stage could not be assigned in a number of cases. It has already been discussed that this method would entail a selection based on the frequency of perimetric examinations. Inclusion of a criterion relating to the perimetric findings would have meant that a proportion of the population would be studied in a limited way, on the basis of a selection. We opted in favour of studying essential changes in IOP, with glaucomatous optic disk changes and visual field defects as a result of ALT playing a subordinate role.

The complete failure rate was 19.6%. In the majority of cases this concerned eyes showing no or an inadequate response to ALT. Of the 20 eyes submitted to surgery, 17 were successful (85.0%), which is consistent with glaucoma surgery success rates reported in the literature. Two eyes had an initial IOP of 21 mm Hg or lower and even after trabeculectomy did not meet the criterion of a 20% IOP decrease; another eye did attain a final IOP of 21 mm Hg or less but showed no 20% IOP decrease. These results in eyes submitted to secondary surgery showed that ALT had no untoward effect on the result of this surgery.

The success rate was higher in men than in women. The mean absolute and proportional IOP decreases were likewise significantly higher in men than in

women. These differences can partly be attributed to the lower initial IOP in women, although the final IOP in men showed a tendency to be lower than that in women (p=0.09).

Age did not affect the ALT results but the number of young patients with phakic POAG was too small to investigate this with sufficient power.

The success rate correlated with the height of the initial IOP. No success was achieved in eyes with a decidedly low ($\leq$ 15 mm Hg) or decidedly high (>45 mm Hg) initial IOP.

There was no unequivocal correlation between success rate and preoperative optic disk score or visual field stage. There were slight differences in final IOP, but these were not statistically significant for any of these variables. Taking into account the frequency of secondary glaucoma surgery, however, the correlation between severity of glaucoma and ALT result emerged. The frequency of surgery was 0% for eyes with a disk score of 0-1, 0% for score 2-3, 10.7% for score 4-5, 17.6% for score 6-7 and 27.8% for score 8. It was 0% for a visual field stage 0-1, 17.6% for stage 2-3, 21.1% for stage 4-5, and 12.5% for stage A, B or C.

The high initial IOP values of eyes with disk score 8 (29.2 $\pm$ 10.3 mm Hg) and/ or visual field stage 5 (27.2 $\pm$ 5.9 mm Hg) partly explain the necessity of an operation, but the initial IOP values of eyes with lower disk scores or less marked visual field defects were not different in comparison. In other words: the chance of success in terms of an IOP decrease was not dependent on the severity of glaucoma, but the need for secondary surgery increased with an increasing glaucoma severity. An eye with severe optic disk damage or a marked glaucomatous visual field defect was more likely to need secondary surgery after ALT.

Perimetry revealed that, even in success eyes, progression of the glaucomatous visual field defect is dependent on the loss during performance of the ALT. Progression to more advanced stages was observed in particular in eyes with absolute defects in the Bjerrum area, with Bjerrum scotomata and in patients with a central remnant. Another group at risk was that of eyes with an enlarged blind spot/baring of the blind spot, central or general decrease in sensitivity or combination of these, if the contralateral eye already showed unmistakable glaucomatous visual field loss. This is by no means to say that the lastmentioned perimetric findings should therefore be

regarded as early or specific signs of glaucoma, because it cannot be excluded that they are caused by concomitant lesions (cataract), or that the presence of glaucoma in the contralateral eye per se implies an intrinsic predisposition to developing a visual field defect.

There were only minor differences in progression of visual field defects between success eyes and failure eyes. On the one hand because the visual field in eyes given secondary surgery was assessed before the operation, i.e. shortly after ALT, and on the other hand because the failure group also comprises eyes which did not fulfil the success criteria even though some IOP decrease occurred. Despite an insufficient IOP decrease, ALT might have had a favourable effect on the visual field.

None of the glaucoma therapies given - be it topical medication, systemic medication or surgery - had a statistically significant effect on the success rate, although eyes treated with carbonic anhydrase inhibitors showed an unmistakably lower success rate. Systemic medication was used in 64 patients (21.0%). The fact that not all used a carbonic anhydrase inhibitor is explained, not only by intolerance to this medication in some cases, but also by the position of ALT in glaucoma therapy. It seems hardly sensible first to give this medication for a certain time (knowing that this cannot be long) and then try discontinuation of this medication after ALT. The lower success rate in these patients confirms this. Systemic medication does possibly serve a purpose in protecting patients before and after ALT, as an aid in preventing or arresting an increase in IOP.

What was regarded as one of the principal variables was the ALT modification used, i.e. 1 * 180°, 2 * 180° or 1 * 360° ALT. The results of a 1 * 360° ALT were better than those of the other modifications in terms of success rate as well as in terms of final IOP and mean proportional IOP decrease. The differences between 1 * 180° ALT and 2 * 180° ALT were not statistically significant. An estimate showed that at least 39.5% of the eyes treated by 1 * 180° ALT required a second session; the actual success rate of 1 * 180° ALT in the follow-up in question was 31.6%. An additional question is whether failure eyes after a 1 * 180° ALT, submitted to a second session and thereby transferred to the 2 * 180° ALT group, do not constitute a higher-than-expected proportion of the ultimate failure eyes in this group. A 1 * 360° ALT in one or two sessions gives a better result than a 1

* 180° ALT.

Pre-ALT iris stretching in the case of a beak-shaped iridocorneal angle gives the same result as ALT alone in the absence of such an angle shape.

A qualitatively good, easily performed ALT had a higher chance of success than an ALT performed with difficulty, although the difference (possibly due to the limited number of eyes with a cumbersome ALT: N=12) was not statistically significant. If in this context only eyes treated by one-session ALT are considered, then 2 of 8 eyes can ultimately be classified as success eyes.

ALT combined with iridotomy if indicated (13 eyes) had a higher success rate, but this difference was likewise not significant.

**Aphakic and pseudophakic POAG:**

The success rate in aphakic and pseudophakic POAG was lower than that in phakic POAG, but the differences were not statistically significant. The subgroups were too small to permit conclusions on (possible) differences. Another factor which plays role in aphakic eyes is that vitreous prolapse into the anterior chamber as a cause of IOP increase was not represented in this subgroup. Only eyes with pre-existent POAG and cataract extraction were included.

As in phakic eyes, pre-ALT surgery did not affect the success rate in aphakic POAG. An iridocorneal angle configuration unfavourable for ALT caused a lower success rate.

In the event of success, the final IOP in aphakic POAG was higher than that in phakic POAG.

Because post-ALT cataract extraction in phakic POAG has no significant effect on the result, and because ALT results are less good in aphakic and pseudophakic POAG, the preference in cases of glaucoma and concomitant cataract is for ALT followed by extracapsular cataract extraction.

**Pigment dispersion syndrome:**

The results obtained in the pigment dispersion syndrome were very good, both as to success rate and as to IOP decrease. Some investigators have found that younger patients with a pigment dispersion syndrome show better results than older ones, but this could not be confirmed due to the limited

number of eyes studied. However, the only complete failure eye in this group was that of a 53-year-old patient, whereas 7 eyes of patients under 50 were all treated successfully. After lumping unilaterally and bilaterally treated patients, there were still no complete failures in the group under 50. However, two second ALT eyes of patients under 50 showed a response to ALT which was insufficient to fulfil the success criteria.

**Low-tension glaucoma:**

Success rate, mean absolute and proportional IOP decreases in this group were significantly lower than the corresponding values in phakic POAG ($p<0.05$, $p=0.003$ and $p=0.005$ respectively). In the success eyes a low final IOP was achieved. Many eyes (21.1%) did show some IOP decrease, but less than 20%.

The question arises whether the 20% IOP decrease criterion was not too high, particularly for eyes with an initial IOP of 21 mm Hg or lower. We believe that this was not the case. Particularly in patients with low-tension glaucoma the IOP is such that glaucomatous damage becomes manifest at relatively low pressures, and a further reduction of pressure is required. However, in eyes with other glaucoma types and normal IOP values associated with maximum medication ALT should likewise lead to an IOP decrease if success is to be achieved. The possibility of reducing medication can certainly be regarded as a benefit derived from ALT, but in the cases of maximum pre-ALT medication in this study the chance of post-ALT IOP control without medication proved to be nil.

Another reason is that, in the end, ALT is not free from complications. In 9 out of 305 eyes (3.0%) the final IOP exceeded the initial IOP. In 7 of these cases the initial response to ALT had been good, and the question arises whether the increase in IOP should not been ascribed to progression of the glaucoma in these cases. Three other eyes showed loss of central vision after ALT, and in one of them it was confirmed that this was due to a transient IOP increase after ALT. Proceeding from the assumption that both the increase in IOP and the loss of central vision in these cases resulted from glaucoma, the conclusion must be that in at least 1% and at most 3.9% of the eyes ALT led to exacerbation of glaucoma.

**Secondary glaucoma:**

This group showed a low success rate and a high complete failure rate. Nearly 50% of the eyes in this group required secondary glaucoma surgery.

One should be alert after ALT in uveitic glaucoma: 4 of the 12 eyes treated required secondary surgery in view of a post-ALT increase in IOP.

Pre-ALT cataract extraction and the presence of PAS affect the success rate unfavourably.

Looking at age regardless of the type of secondary glaucoma, we found a success rate of 40.9% in patients over 40, 47.1% in those over 50, and 63.3% in those over 60. The difference between patients over and under 60 was statistically significant ($p<0.02$).

A reason for the higher success rate in older patients may lie in the normal ageing process of the trabecular meshwork, which shows similarities to the changes observed in POAG (see 2.2.2.6 and 2.2.2.7). In the senescent trabecular meshwork ALT may cause changes which it cannot produce in a young trabecular meshwork.

**Suspected glaucoma:**

Results in eyes with phakic POAG and those with suspected glaucoma with or without optic disk damage showed no significant differences other than a higher final IOP in suspected glaucoma without optic disk damage. A combination of success parameters (final IOP, success rate in eyes with an initial IOP of at least 22 mm Hg and changes in medication) revealed the least favourable effects in suspected glaucoma without optic disk damage and more favourable features (also in comparison with phakic POAG) in suspected glaucoma with optic disk damage.

Bearing in mind that the lastmentioned group had the highest success rate and lowest complete failure rate and that the complete failure rate increases with the severity of phakic POAG, it would be justifiable to conclude that ALT should not be regarded as ultimate alternative to surgery in cases already showing considerable damage, but merits the consideration at a much earlier stage in the therapeutic approach to glaucoma. An increased IOP per se (suspected glaucoma without optic disk damage), however, is not the indication of ALT in view of the less favourable results. This is more evident in view of the fact that patients with suspected glaucoma without optic

disk damage had the lowest mean age and - as indicated by the success rate in the ALT follow-up - a grave risk of failure in the subsequent course of life. A re-ALT performed at that time has a low chance of success (29.2%).

An explanation of the fact that the best results are obtained in suspected glaucoma with optic disk damage may be sought in the degree of degeneration already shown by the trabecular meshwork. Perhaps degeneration is not very pronounced in eyes with (still) only increased IOP, while on the other hand degeneration in eyes with evident glaucoma is often too advanced to warrant the expectation of an optimal ALT effect.

This is not to say that ALT is of no value for eyes already showing glaucomatous damage; it does mean, however, that the chance of stopping progression diminishes, as it also does for pressure reducing surgery.

**Bilateral ALT:**

The results in patients treated bilaterally revealed a high degree of dependence between the two eyes, both in success and in failure. This was even more evident in cases requiring secondary surgery. The chance that after failure in the first eye the second eye could be successfully treated, was 14.0%. The inevitable conclusion, therefore, is that the decision to apply ALT to the second eye of a patients whose first eye failed to respond, must be made with considerable reservations.

# CHAPTER 6

# PROSPECTIVE STUDY

## 6.1 AIM OF THIS STUDY

The principal aim of this study was to describe the changes in IOP (the IOP course) during the period immediately after ALT, because early recognition of eyes with IOP spikes after ALT is important to ensure adequate treatment.

Several variables were documented in an effort to trace possible high-risk factors predisposing to IOP spikes following ALT. In this respect emphasis was placed on gonioscopic findings and on ALT parameters, but other ocular and patient variables were considered as well.

The primary choice was to study the eyes treated first in patients submitted to bilateral ALT, in order to exclude the bias of selection (see 5.1).

ALT was consistently performed in two sessions, and the ocular status at the second session could therefore differ from that at the first. In order to eliminate a possible bias in this respect also, the abovementioned variables were studied with regard to their influence on IOP changes following the first session. The IOP course in untreated contralateral eyes was used as control.

The following problem definitions were formulated:

1. What does the IOP course after standardized ALT look like, and how do eyes with IOP spikes compare with those not showing these IOP spikes after ALT?
2. Are there patient-, eye-, or ALT-related variables which correlate statistically with post-ALT spikes?
3. Does the occurrence or non-occurrence of an IOP spike after the first ALT session have any predictive value for the IOP changes to be expected after the second session?
4. Does the occurrence or non-occurrence of an IOP spike in the eye treated first have any predictive value for the post-ALT IOP changes to be expected in the second eye in cases of bilateral ALT?

Independence between discrete variables was tested using the Chi-square test, and interdependence between discrete variables was tested using the McNemar test.

## 6.2 DESIGN OF THE PROSPECTIVE STUDY AND DEMOGRAPHIC DATA ON PATIENTS

Between 30th June 1986 and 12th October 1987, 93 eyes of 62 patients were treated and followed up.

Five patients were excluded from this study for the following reasons:

- In two patients ALT was not feasible, once because the patient collapsed after application of 4 burns, and once because the trabecular meshwork could not be visualized even after iris stretching.
- Three patients were excluded because ALT could not be performed in a standardized way. In one case only 180° of the trabecular meshwork circumference was treated because before the second session this patient had to be hospitalized with serious pulmonary complaints related to pre-existent COLD (Chronic Obstructive Lung Disease). In one patient the trabecular meshwork was not accessible over the full 360°; 70 burns were applied allround in both eyes. Finally, one patient with a diabetic retinopathy was treated by panretinal laser coagulation after the first ALT session, and a second session was postponed for the time being.

The eyes were divided into subgroups on the basis of glaucoma type and specific ocular status:

**Phakic POAG** (N=42):

This subgroup included eyes with an increased IOP, glaucomatous optic disk features and visual field defect, without other demonstrable glaucoma causes and without ocular details which would justify inclusion in one of the other subgroups.

Eyes with an increased IOP with or without other glaucomatous features but with evident glaucoma of the contralateral eye, were likewise included in this group.

Two eyes in this subgroup were from patients showing an IOP increase and

glaucomatous optic disk featured in both eyes, but without visual field defect. The clinical impression and the findings at other examinations justified their inclusion in this subgroup (see also 6.6).

**Pseudophakic POAG** (N=1):

This was an eye in which glaucoma was already manifest prior to cataract extraction.

**Pigment dispersion syndrome** (N=4):

These four eyes showed the characteristic features of the pigment dispersion syndrome and glaucomatous optic disk damage, but without visual field defect.

**Low-tension glaucoma** (N=4):

This subgroup included eyes in which glaucoma had developed while the IOP remained normal (<22 mm Hg).

**Secondary glaucoma** (N=2):

One of these eyes showed features of scleritis (systemic corticosteroid medication), while the other showed an increased IOP following surgery for retinal detachment.

**Suspected glaucoma** (N=2):

Two eyes with increased IOP but without any other glaucomatous features were included in this subgroup.

**Thyroid disease** (N=2):

These two eyes showed an increased IOP in association with hyperthyroidism.

Table 6.1 presents demographic data on these patients and also that the total number of eyes treated was 87.

With the exception of two patients whose first eye showed phakic POAG while the second showed pseudophakic POAG, all patients treated bilaterally showed symmetrical glaucoma types. The two patients just mentioned are not

Table 6.1. Demographic data by subgroup (Bilat: percentage of patients treated by bilateral ALT).

| | Number | | | Age | | | Male : Female | OD : OS |
|---|---|---|---|---|---|---|---|---|
| | Pat | Eyes | Bilat | Mean | SD | Min - Max | | |
| Phakic POAG | 42 | 64 | 52.4% | 65.0 | ± 14.3 | 22 - 84 | 20 : 22 | 21 : 21 |
| Pseudophakic POAG | 1 | 1 | | 74 | | | 1 | 1 |
| Pigment Dispersion S. | 4 | 7 | 3/4 | 38.3 | ± 9.6 | 25 - 47 | 4 | 1 : 3 |
| Low-tension Glaucoma | 4 | 6 | 2/4 | 63.0 | ± 9.2 | 54 - 75 | 4 | 2 : 2 |
| Secondary Glaucoma | 2 | 2 | | 74.5 | ± 3.5 | | 2 | 2 |
| Glaucoma Suspect | 2 | 4 | 2/2 | 64.5 | ± 6.4 | | 1 : 1 | 2 |
| Thyroid Disease | 2 | 3 | 1/2 | 49.0 | ± 33.9 | | 1 : 1 | 2 |
| Total | 57 | 87 | 52.6% | 62.9 | ± 15.7 | 22 - 84 | 28 : 29 | 29 : 28 |

included in the discussion of IOP changes in second ALT eyes.

Despite the small numbers, this prospective study likewise revealed the early age at onset and the male preference of the pigment dispersion syndrome, as well as the female preference of low-tension glaucoma.

## 6.3 DATA SAMPLING, FOLLOW-UP AND INTERVENTION PROTOCOL

The data on the 57 patients who at the end participated were recorded on the basis of a code book (Addendum 2).

ALT was performed between 09.00 and 10.30 hrs. The initial IOP was measured about 1 hour prior to ALT. Postoperative check-ups comprised IOP measurements at 6 consecutive one-hour intervals after ALT. Check-ups were likewise made 24 hours and 1 week after ALT. These check-ups preceded and followed both the first and second session.

Because 8 patients developed adenoviral keratoconjunctivitis after ALT, the decision was taken to perform IOP measurements with disposable Parafilm "M" as a barrier between the prism of the tonometer and the cornea. This method is practical and prevents contamination of the prism and consequently dissemination of bacteria and viruses.

The effect of this Parafilm "M" on the IOP is at most 3 mm Hg, but in some

85% of cases the difference from the regularly measured IOP is only 1 mm Hg (Assia et al. 1986).[1]

Postoperative IOP increases were not treated unless they fulfilled one or more of the following criteria:

1. An IOP increase by at least 10 mm Hg from the initial IOP.
2. An IOP increase to 30 mm Hg or higher if the preoperative IOP was less than 30 mm Hg.
3. An IOP increase which endangered the eye in view of the severity of the glaucoma (e.g low-tension glaucoma and eyes with an end-phase visual field defect).

Whenever an IOP increase fulfilled one or more of these criteria, a carbonic anhydrase inhibitor (250 mg Diamox) was given orally; another dose of 250 mg Diamox was given if the IOP showed no or an inadequate response to the first dose, In only one instance was Diamox given intramuscularly. This was a functionally monocular patient with a central visual field remnant and a post-ALT IOP increase from 17 to 22 mm Hg (+5 mm Hg). Because this patient developed an attack of COLD 3 hours after ALT, he was hospitalized. Six hours after ALT the IOP had decreased to 15 mm Hg. One day after ALT the IOP was 15 mm Hg and the patient was discharged. Unfortunately, another severe attack of COLD occurred 2 weeks later; the patient was again hospitalized and no further follow-up was possible.

### 6.4 EXTRAOCULAR FEATURES

Six patients (10.5%) had diabetes mellitus (insulin-dependent in three). Fifteen patients (26.3%) had arterial hypertension (10 were using antihypertensive medication). The mean systolic blood pressure was 132.8 $\pm$ 20.8 mm Hg and diastolic 83.1 $\pm$ 11.8 mm Hg. The lowest blood pressures were measured in patients with low-tension glaucoma (116.3 $\pm$ 12.5 mm Hg systolic and 77.5 $\pm$ 9.6 mm Hg diastolic).

The incidences of diabetes mellitus and arterial hypertension exceeded

1 Assia, E., Bartov, E., and Blumenthal, M.D.: Am. J. Ophthalmol. 102:397, 1986.

those in the retrospective study, due to the fact that in this study a general history was part of the standard protocol.

A non-ophthalmological operation had been performed under general anaesthesia in the past in 44 cases (77.2%). Eight patients (14.0%) had undergone at least five operations.

Some 25% of patients were smokers and regularly drank alcoholic beverages (at least two glasses per day).

## 6.5 OCULAR ANAMNESIS AND HISTORY

Table 6.2 lists the complaints and findings from the ocular anamneses of the patients.

Table 6.2. Frequencies of preoperative ocular complaints.

| | |
|---|---|
| Loss of vision | 59.6% |
| Mouches volantes | 19.3% |
| Diplopia | 15.8% |
| Haloes | 12.3% |
| Scotomas | 7.0% |
| Ocular allergy | 7.0% |
| Strabismus | 5.3% |
| Trauma | 3.5% |
| Epiphora | 3.5% |
| Metamorphopsia | 1.8% |
| Flashing light | 1.8% |
| Shadows | 1.8% |
| Transient ischaemic attacks | 1.8% |
| Colour vision disorder | 1.8% |
| Pain | 1.8% |

Poor vision was the most common complaint. The mean preoperative visual acuity was $0.67 \pm 0.24$. In most cases the less-than-optimal vision was explained by the presence of a more or less disturbing cataract in phakic patients (78.5%).

Seven patients (12.3%) had had haloes; 3 of them had a pigment dispersion syndrome, 2 had phakic POAG, 1 had pseudophakic POAG and 1 had low-tension

glaucoma.

One patient with phakic POAG and one with a pigment dispersion syndrome had a history of a trauma of the ALT eye. In both instances conservative therapy had led to a complete cure.

## 6.6 GLAUCOMA VARIABLES

### 6.6.1 Previous therapy

The mean medication score as determined on the basis of the medication scale (table 5.6) was 1.5 ± 0.9. With the exception of one eye with phakic POAG and two with a pigment dispersion syndrome, all eyes were receiving topical glaucoma medication. The maximum medication score was 6. In most eyes the medication score was 1 or 2 (87.7%).

Eight patients (14.0%) also used a carbonic anhydrase inhibitor. Nine eyes (15.8%) had already been submitted to one or several pressure-reducing interventions. The distribution was as follows:

- Phakic POAG : trabeculectomy (1), iridencleisis (1), ALT (4).
- Pseudophakic POAG : trabeculectomy and cyclodialysis (1)
- Pigment Dispersion S. : ALT, Scheie procedure and Elliot procedure (1).
- Low-tension glaucoma : trabeculectomy (1).

Four eyes with phakic POAG had previously undergone ALT in our department. In all cases the initial ALT was a 2 * 180° modification.

The eye with the pigment dispersion syndrome had been submitted to ALT elsewhere, and the exact ALT parameters could not been traced.

### 6.6.2 Anterior eye segment

The standard protocol included a detailed examination of the anterior eye segment. The following abnormalities and particulars were discovered:

- One female patient with phakic POAG showed mild rotatory nystagmus, but this did not impede the ALT procedure.

- Six eyes (10.5%) showed a Marcus Gunn pupillary reaction, indicating an afferent conduction defect. Two of these eyes had glaucomatous visual field defects, two eyes showed an enlarged blind spot and diminished sensitivity, and two eyes had no perimetric abnormalities.
- One female patient with hyperthyroidism showed minor residual infiltrates of the cornea after keratitis as a result of a chicken-pox infection.
- Krukenberg spindles were observed in 4 eyes with a pigment dispersion syndrome. One of these eyes showed a diaphanous iris as well.
- One eye with secondary glaucoma after retinal detachment treated by surgery showed irregular pupil contours.
- Eleven eyes (19.3%) showed pigment sprinkling of the anterior iridal surface; six of these had phakic POAG. The degree of pigmentation in these six eyes was TP+1 (1 eye), TP+2 (2 eyes) and TP+3 (3 eyes). None of these showed features of the pigment dispersion syndrome.
- One eye with phakic POAG showed segmental iridal atrophy. Gonioscopy revealed a wide iridocorneal angle (grade 3) and trabecular pigmentation degree of TP+2. There were no peripheral anterior synechiae and there was no anamnestic evidence of angle closure glaucoma in the past.
- None of these eyes showed iridal nodules, iris bombé or iridal colobomas.

The protocol did not provide in a pre-ALT examination of the lens in mydriasis. After completion of the investments, however, we felt that this had to be done in order to look for any signs indicating a pseudo-exfoliation syndrome in the patients to which this applied (i.e. phakic POAG and suspected glaucoma). Of the 44 patients with phakic POAG or suspected glaucoma, 36 were examined in mydriasis after ALT (in 8 patients this was not possible because of: death of patient (1), cataract extraction (1), patient not traceable (1) and in 5 patients this examination was not undertaken because of the presence of a (very) severe visual field defect). Of these 36 patients, one with phakic POAG (2.8%) had evident signs of the pseudo-exfoliation syndrome. This patient was included in the phakic POAG group.

**Gonioscopy:**

Gonioscopy was performed immediately before ALT, and the various items

were classified in cooperation by the same ophthalmologist with experience in this field. Whenever structures could not be visualized due to a beak-shaped angle as a result of plateau-iris, iris stretching took place first (7 eyes, 12.3%).

The angle width was determined on the basis of the angle width grading system (Shaffer 1962; see also 3.3). An abbreviated version of this grading system is presented in table 6.3.

Table 6.3. Abbreviated version of angle width grading system (see also 3.3).

| Angle Grade | Angle Width | Numerical Grade |
|---|---|---|
| Wide Open Angle | 45°- 35° | 4 |
| | 35°- 20° | 3 |
| Narrow Angle | 20° | 2 |
| Narrow Angle, extreme | 10° or less | 1 |
| Narrow Angle, partial or complete closure | 0° | 0 |

Table 6.4 lists the gonioscopic findings per subgroup. The distribution of angle widths shows that 35.1% of all eyes had a wide angle. Most eyes with a pigment dispersion syndrome had a wide angle, and only one eye in this subgroup had a grade 2 angle. This eye had previously been submitted to two operations (Scheie procedure and Elliot procedure), with postoperative cataract formation. This eye had a trabecular pigmentation degree of TP+2. The ophthalmological history showed that a pigment dispersion syndrome was nevertheless involved. The contralateral eye of this patient likewise showed features of the pigment dispersion syndrome (Krukenberg spindle, trabecular pigmentation TP+4, and a grade 4 angle).

A beak-shaped angle was observed in 17 eyes (29.8%). That this had implications for the angle width was apparent from the numerical angle grades of these eyes: 6 eyes with grade 1 and 11 eyes with grade 2 angles. Iris stretching was performed on all eyes with a grade 1 angle and one eye with a beak-shaped grade 2 angle.

Angle recession was observed in one eye (without any anamnestic evidence

Table 6.4. Pre-ALT gonioscopic findings (PDS: pigment dispersion syndrome; LTG: low-tension glaucoma).

| | Phakic POAG | Ps.Phakic POAG | PDS | LTG | Secondary Glauc | Glauc Suspect | Thyroid Disease | Total |
|---|---|---|---|---|---|---|---|---|
| Angle Grade 0 | | | | | | | | 0 % |
| 1 | 16.7% | 1/1 | | | 1/2 | | 1/2 | 15.8% |
| 2 | 47.6% | | 1/4 | 3/4 | 1/2 | 2/2 | | 49.1% |
| 3 | 31.0% | | 2/4 | 1/4 | | | | 28.1% |
| 4 | 4.7% | | 1/4 | | | | 1/2 | 7.0% |
| Beak-shaped Angle | 35.7% | | | 1/4 | | 1/2 | | 29.8% |
| Recession | | | | | | | 1/2 | 1.8% |
| Scleral Spur Visible | 95.2% | 1/1 | 3/4 | 4/4 | 2/2 | 2/2 | 2/2 | 94.7% |
| Scleral Spur Normal | 95.2% | 1/1 | 3/4 | 4/4 | 2/2 | 2/2 | 1/2 | 93.0% |
| White | | | | | | | 1/2 | 1.8% |
| Iris Processes Present | 33.3% | 1/1 | 3/4 | 3/4 | 1/2 | 1/2 | 1/2 | 42.1% |
| Trab. Identification Easy | 52.4% | | 3/4 | 3/4 | 1/2 | 2/2 | 1/2 | 56.1% |
| Moderate | 33.3% | 1/1 | 1/4 | 1/4 | | | 1/2 | 31.6% |
| Laborious | 14.3% | | | | 1/2 | | | 12.3% |
| Trabecular Pigmentation 0 | 2.4% | | | | | | | 1.8% |
| +1 | 21.4% | 1/1 | | 1/4 | | 1/2 | 1/2 | 22.8% |
| +2 | 50.0% | | 1/4 | 2/4 | 2/2 | 1/2 | | 47.7% |
| +3 | 26.2% | | | 1/4 | | | 1/2 | 22.8% |
| +4 | | | 3/4 | | | | | 5.3% |
| Blood in Schlemm's Canal | 2.4% | | | | | | | 1.8% |
| Prominence of Schwalbe's Line | 47.6% | 1/1 | 3/4 | 2/4 | | 1/2 | 1/2 | 49.1% |
| Blood Vessels Circumferential | 11.9% | | 1/4 | | | | 1/2 | 12.3% |
| Trabecular | 2.4% | | | 1/4 | | | | 3.5% |
| Peripheral Anterior Synechiae | 4.8% | | | | 1/2 | | | 7.0% |
| Particles in the Angle | | | | | | | | 0 % |

of a trauma).

In most eyes the scleral spur could be visualized, with or without iris

stretching. In 3 eyes (5.3%) the scleral spur was not seen: due to a grade 1 angle in 2 eyes and due to excessive pigmentation in 1. The scleral spur showed a normal appearance in all eyes except one, which showed a decidedly white spur (but again without any demonstrable trauma in the anamnesis).

Iris processes were observed in 24 eyes (42.1%). The extent ranged from a few small process to numerous processes distributed over the entire circumference of the chamber angle.

Trabecular pigmentation was scored according to Scheie (1957; see 3.3) and ranged from complete absence of pigment (TP 0) to maximum trabecular pigmentation (TP+4). All eyes with TP+4 in this study had a pigment dispersion syndrome. Because the degree of pigmentation varied within the individual eye (the lower two quadrants often showing more pigmentation), the entire angle was examined first, and then an overall score was assigned.

Trabecular pigmentation did not correlate with the colour of the iris. Absence of pigment (TP 0) or only slight pigmentation (TP+1) occurred in 25.0% of blue and 27.3% of brown eyes; moderate pigmentation (TP+2) occurred in 50.0% of blue and 48.5% of brown eyes; 25.0% of blue and 24.2% of brown eyes showed marked trabecular pigmentation. Not included were eyes with a pigment dispersion syndrome, which all had blue irides.

Identification of the trabecular meshwork became more laborious as less pigmentation was present. In eyes with TP+3 and TP+4 the trabecular meshwork was always identified without difficulty. In 11.1% of the eyes with TP+2 and 23.1% of those with TP+1 identification of the meshwork was difficult. In one eye with TP 0 it was virtually impossible to identify the trabecular meshwork. None of the eyes with laborious identification of the trabecular meshwork was scored a "good ALT" (see 6.7).

In one eye with phakic POAG blood was seen in Schlemm's canal; no haemorrhage occurred during ALT in this eye.

Schwalbe's line was described as 'normal' or 'prominent'. To establish this, a look through the central lens was required to see whether Schwalbe's line presented as a thickening in the anterior chamber. This prominence was observed in 49.1% of the eyes. In most cases the thickening was very slight, and a posterior embryotoxon as seen in some forms of iridocorneal dysgenesis was never observed.

Two eyes (one with phakic POAG and one with low-tension glaucoma) showed

blood vessels in the chamber angle which bridged the trabecular meshwork. Neither eye showed signs of rubeosis iridis.

Peripheral anterior synechiae were seen in 4 eyes (7.0%): 1 eye with pseudophakic POAG in which band- and spike-shaped synechiae extended over 5 clock hours between iris and the anterior part of the trabecular meshwork; 1 eye with secondary glaucoma after retinal detachment treated by surgery, in which synechiae extended over 2 clock hours between the iris and the scleral spur; 1 eye with phakic POAG and previous iridencleisis in which synechiae extended over 1 clock hour between iris and Schwalbe's line; 1 eye with phakic POAG and previous trabeculectomy in which synechiae extended over 2 clock hours between the iris and the filter.

In 30 patients the abovementioned structures were scored bilaterally in the same way. The gonioscopic findings in the primarily examined eye were not recapitulated at examination of the second eye (at least 2 months later).

Table 6.5 indicates the degree of symmetry of angle grade trabecular pigmentation, iris processes and prominence of Schwalbe's line in these bilat-

Table 6.5. Frequencies of symmetrical findings as to angle grade, iris processes, trabecular pigmentation and prominence of Schwalbe's line.

| | | |
|---|---|---|
| Angle Grade | Bilateral Grade 1 | 3.3% |
| | Bilateral Grade 2 | 33.3% |
| | Bilateral Grade 3 | 23.3% |
| | Bilateral Grade 4 | 3.3% |
| | Total | 63.3% |
| Iris Processes | Bilateral Present | 30.0% |
| | Bilateral Absent | 43.3% |
| | Total | 73.3% |
| Trabecular Pigmentation | Bilateral TP+1 | 10.0% |
| | Bilateral TP+2 | 30.0% |
| | Bilateral TP+3 | 10.0% |
| | Bilateral TP+4 | 6.7% |
| | Total | 56.7% |
| Prominence of Schwalbe's Line | Bilateral Present | 43.3% |
| | Bilateral Absent | 30.0% |
| | Total | 73.3% |

erally examined patients. All these items showed a fair degree of symmetry. A difference of at least 2 points in the scores for angle grade or trabecular pigmentation was observed in only 2 eyes (6.7%).

### 6.6.3 Optic disk

The optic disk was likewise described on the basis of a standard protocol. In 8 eyes no details were discernible: in 4 this was due to a corticonuclear cataract, and in 4 it was caused by a combination of cataract and use of miotics. In 4 of these eyes a cup/disk ratio could be estimated.

The cup disk ratio was estimated on the basis of the contour cup (see 3.4.1). Table 6.6 presents the mean horizontal and vertical cup/disk ratios per subgroup.

Table 6.6. Mean pre-ALT horizontal and vertical cup/disk ratio.

| | Horizontal Cup/Disk Ratio (Mean ± SD) | Vertical Cup/Disk Ratio (Mean ± SD) |
|---|---|---|
| Phakic POAG | 0.57 ± 0.20 | 0.63 ± 0.22 |
| Pseudophakic POAG | 0.4 | 0.4 |
| Pigment Dispersion S. | 0.60 ± 0.08 | 0.70 ± 0.14 |
| Low-tension Glaucoma | 0.83 ± 0.06 | 0.83 ± 0.06 |
| Secondary Glaucoma | 0.45 ± 0.07 | 0.60 ± 0.14 |
| Glaucoma Suspect | 0.25 ± 0.07 | 0.3 |
| Thyroid Disease | 0.55 ± 0.35 | 0.60 ± 0.42 |
| Total | 0.57 ± 0.21 | 0.63 ± 0.22 |

Most of the eyes (54.7%) showed vertically oval optic disk cupping. The relationship between horizontal and vertical cup/disk ratios is outlined in figure 6.1. The vertical cup/disk ratio exceeded the horizontal one by 0.1 in 22 and by 0.2 in 7 eyes. Two eyes showed horizontally oval optic disk cupping.

The frequencies of specific optic disk features are listed in table 6.7.

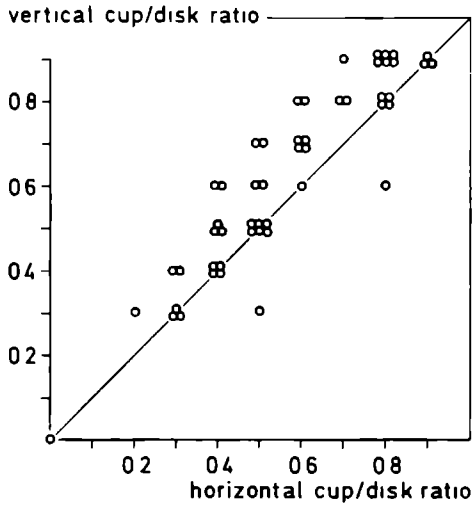



Figure 6.1. Scatter diagram of pre-ALT horizontal and vertical cup/disk ratios.

Table 6.7. Frequencies of preoperative glaucomatous optic disk features (PDS: pigment dispersion syndrome; LTG: low-tension glaucoma).

| | Phakic POAG | Ps.Phakic POAG | PDS | LTG | Secondary Glauc | Glauc Suspect | Thyroid Disease | Total |
|---|---|---|---|---|---|---|---|---|
| Localized Polar Notch Absent | 52.1% | 1/1 | 3/4 | 1/3 | 1/2 | 2/2 | 1/2 | 59.2% |
| Incomplete | 34.3% | | 1/4 | 2/3 | 1/2 | | 1/2 | 34.7% |
| Complete | 8.6% | | | | | | | 6.1% |
| Peripapillary Atrophy | 22.9% | | | | | | | 16.3% |
| Localized Pallor of the Neural Rim | 22.9% | | 2/4 | 1/3 | | | 1/2 | 24.5% |
| Overpass Cupping | 2.9% | | | | | | | 2.0% |
| Displaced Blood Vessels | 42.9% | | 3/4 | 1/3 | 2/2 | | 1/2 | 44.9% |
| Optic Disk Haemorrhage | 2.9% | | | | | | | 2.0% |

Twenty eyes (40.8%) showed localized notching of the neural rim; three of these eyes showed a complete notch. The notch was localized in the supero-

temporal quadrant in 55.0% and in the inferotemporal quadrant in 45.0%. The 3 eyes with a complete notch showed glaucomatous visual field defects. For 1 eye with an incomplete notch no recent perimetric findings were available. Of the remaining 16 eyes, 12 (75.0%) showed glaucomatous visual field defects. The mean cup/disk ratio in these eyes was 0.71 ± 0.14 horizontally and 0.80 ± 0.13 vertically.

Peripapillary atrophy was observed in 8 eyes (16.3%). all with phakic POAG. The atrophy occurred in eyes with a low as well as in those with high cup/disk ratios.

Localized pallor of the neural rim was seen in 12 eyes (24.5%). The mean cup/disk ratio in these eyes was 0.71 ± 0.12 horizontally and 0.81 ± 0.10 vertically. Nine (75.0%) of this 12 eyes with localized pallor also showed a localized notch.; of eyes without localized pallor (N=37), only 29.7% showed a notch.

Overpass cupping and optic disk haemorrhage were each observed on only one instance.

Unmistakable nasal displacement of blood vessels was seen in 22 eyes (44.9%).

### 6.6.4 Perimetry

The perimetric findings were classified in accordance with the same scale as in the retrospective study (table 5.8). On 3 patients (1 eye with phakic POAG and 2 with secondary glaucoma), no recent perimetric findings were available. The perimetric findings are presented in table 6.8.

Six eyes with phakic POAG showed no visual field defect or changes (stage 0). They were nevertheless included in this subgroup for the following reasons: 2 eyes were of patients whose contralateral eye did show a glaucomatous visual field defect; 2 eyes showed no abnormalities at examination for classification, but on a previous occasion had shown a visual field defect; 2 patients showed no visual field defect in either eye but the other features justified inclusion in this subgroup (female patient 053, age 41, had a positive family history of glaucoma, Marcus Gunn pupillary reaction and progressive increase in cup/disk ratio; female patient 057, age 54, had dia-

Table 6.8. Distribution of pre-ALT visual field stage (see also 5.8).

| | 0 | 1 | 2 | 3 | 4 | 5a | A | B | C |
|---|---|---|---|---|---|---|---|---|---|
| Phakic POAG | 14.6% | 26.8% | 26.8% | 9.8% | 4.9% | 9.8% | 2.4% | 2.4% | 2.4% |
| Pseudophakic POAG | | | 1/1 | | | | | | |
| Pigment Dispersion S. | 1/4 | | | | | | 1/4 | 1/4 | 1/4 |
| Low-tension Glaucoma | | 1/4 | 2/4 | 1/4 | | | | | |
| Glaucoma Suspect | | | | | | | 2/2 | | |
| Thyroid Disease | 1/2 | 1/2 | | | | | | | |
| Total | 14.8% | 24.1% | 25.9% | 9.3% | 3.7% | 7.4% | 7.4% | 3.7% | 3.7% |

betes mellitus, arterial hypertension, Marcus Gunn pupillary reaction and progressive increase in cup/disk ratio with vertical ovality, nasal displacement of blood vessels, and peripapillary atrophy).

Three eyes with phakic POAG respectively showed an enlarged blind spot, general diminution of sensitivity and a combination of these two. Two of these eyes had shown glaucomatous visual field defects at an earlier examination, and 1 eye was the contralateral eye of a patient with evident glaucomatous visual field defect.

None of the 4 eyes with a pigment dispersion syndrome showed glaucomatous visual field defects. Particularly on the basis of the optic disk features, these patients were nevertheless submitted to ALT (patient 001: horizontal cup/disk ratio 0.5, vertical ratio 0.5, nasal displacement of blood vessels; patient 035: cup/disk ratio 0.6 horizontally and 0.7 vertically, localized superotemporal incomplete polar notch, localized pallor of neural rim and nasal displacement of blood vessels; patient 042: cup/disk ratio 0.6 horizontally and 0.8 vertically, localized pallor of neural rim and nasal displacement of blood vessels; patient 050: progressive increase in cup/disk ratio, 0.7 horizontally and 0.8 vertically).

Two eyes of patients with suspected glaucoma showed no optic disk damage and no visual field defect.

## 6.7 ARGON LASER TRABECULOPLASTY

ALT was performed always by the same staff member, over 360° of the trabecular meshwork circumference in two sessions, separated by a period of 4 weeks. Per session, an attempt was made to apply 60 burns with a diameter of 50 μm and an exposure time of 0.1 sec. The burns were applied to the anterior part of the trabecular meshwork, and occurrence of pigment dispersion and bubble formation was accepted as criterion for a 'good burn'. The apparatus used was a continuous wave blue-green Argon laser (Coherent Radiation Model 900).

All eyes were treated with corticosteroids during one week following ALT. Mean power and number of burns per session are indicated in table 6.9. The lowest power setting was used for eyes with the pigment dispersion syndrome (700-1100 mW). The mean power for the two sessions was virtually the same.

Table 6.9. Mean power setting (mW) and mean number of burns per ALT session.

| | Mean ± SD Power (mW) | | Mean ± SD Number of Burns | |
|---|---|---|---|---|
| | First Session | Second Session | First Session | Second Session |
| Phakic POAG | 1128 ± 143 | 1167 ± 146 | 61 ± 3 | 60 ± 2 |
| Pseudophakic POAG | 1200 | 1200 | 55 | 60 |
| Pigment Dispersion S. | 925 ± 171 | 975 ± 189 | 60 | 62 ± 4 |
| Low-tension Glaucoma | 1250 ± 108 | 1263 ± 125 | 61 ± 1 | 60 |
| Secondary Glaucoma | 1075 ± 106 | 1200 ± 71 | 60 | 60 |
| Glaucoma Suspect | 1200 | 1200 | 61 ± 1 | 61 ± 1 |
| Thyroid Disease | 1200 ± 283 | 1200 ± 283 | 60 | 60 |
| Total | 1127 ± 153 | 1164 ± 153 | 61 ± 3 | 60 ± 2 |

Table 6.10 shows that in the vast majority of sessions the burns could be applied to the anterior trabecular meshwork. In 5 sessions (4.4%) this could not be established with certainty.

In 75.4% of the sessions pigment dispersion as well as bubble formation were seen; in 24.6% only one of these criteria was fulfilled (pigment dispersion being seen more often than bubble formation).

Table 6.10. Number of sessions during which the anterior trabecular meshwork was treated with certainty, and distribution of visible effects (both: pigment dispersion and bubble formation).

| | Localization | | Visible Effect | | |
|---|---|---|---|---|---|
| | Anterior | Not Sure | Bubble | Dispersion | Both |
| Phakic POAG | 95.2% | 4.8% | 4.8% | 23.8% | 71.4% |
| Pseudophakic POAG | 2/2 | | | | 2/2 |
| Pigment Dispersion S. | 8/8 | | 1/8 | | 7/8 |
| Low-tension Glaucoma | 7/8 | 1/8 | | | 8/8 |
| Secondary Glaucoma | 4/4 | | 1/4 | 1/4 | 2/4 |
| Glaucoma Suspect | 4/4 | | | | 4/4 |
| Thyroid Disease | 4/4 | | | 1/4 | 3/4 |
| Total | 95.6% | 4.4% | 5.3% | 19.3% | 75.4% |

Seven eyes were submitted to iris stretching before ALT. The number of iris burns was 19 ± 2 (16-22) and the power setting averaged 325 ± 56 mW (250-400 mW), at a spot size of 500 µm and an exposure time of 0.5 sec.

During two sessions haemorrhage from the burnt parts of the trabecular meshwork occurred; in both cases this was arrested simply and effectively by compression with the contact glass.

The ALT quality was good in virtually 50% of the sessions, as measured by

Table 6.11. ALT quality and patients complaints.

| | ALT Quality | | | Complaints | |
|---|---|---|---|---|---|
| | Good | Fairly Good | Moderate | Minor | Severe |
| Phakic POAG | 48.8% | 31.0% | 20.2% | 77.4% | 22.6% |
| Pseudophakic POAG | | 1/2 | 1/2 | 1/2 | 1/2 |
| Pigment Dispersion S. | 7/8 | 1/8 | | 8/8 | |
| Low-tension Glaucoma | 2/8 | 5/8 | 1/8 | 4/8 | 4/8 |
| Secondary Glaucoma | 2/4 | 1/4 | 1/4 | 4/4 | |
| Glaucoma Suspect | 2/4 | 2/4 | | 3/4 | 1/4 |
| Thyroid Disease | 2/4 | | 2/4 | 4/4 | |
| Total | 49.1% | 31.6% | 19.3% | 78.1% | 21.9% |

the good burn criteria, the localization of the burns and the patients fixation (table 6.11). A moderate ALT was usually caused by difficulty in identifying the trabecular meshwork or inadequate fixation of the patient. The majority of patients were not greatly inconvenienced by the ALT.

## 6.8 RESULTS

### 6.8.1 IOP course on the day of ALT

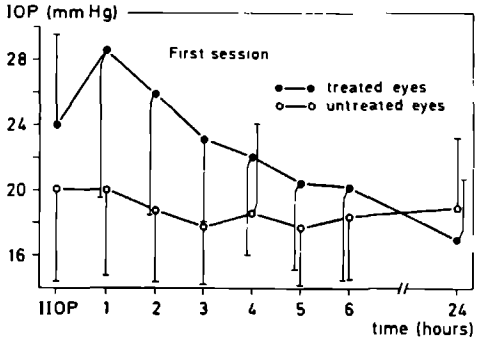
Table 6.12 and figure 6.2 indicate the course of the IOP in 57 first treated eyes after the first and the second ALT session. They also outline the IOP course in untreated contralateral eyes.

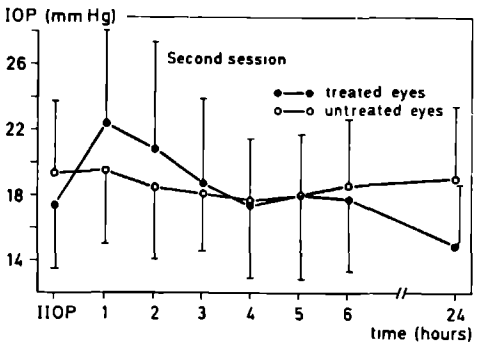
The initial IOP measured 1 hour before the first ALT session was higher in the eyes to be treated (24.0 ± 5.7 mm Hg) than in the not-to-be-treated contralateral eyes (20.0 ± 5.7 mm Hg). This is explained by the fact that the ALT was primarily performed in the eye with the highest IOP. Moreover, in a number of cases the contralateral eye had a well-controlled IOP.

The treated eyes showed an increase in mean IOP which reached a maximum 1 hour after ALT (σ: +4.4 ± 7.2 mm Hg). From 1 hour after ALT on the IOP decreased , and 3 hours after ALT it was lower than the initial IOP (σ: -1.0 ± 5.2 mm Hg). This decrease continued and after 6 hours the mean IOP decrease was 3.9 ± 4.4 mm Hg; after 24 hours it was 7.1 ± 4.6 mm Hg. That this decrease was consistent was evident from the fact that the initial IOP in the treated eyes before the second session was lower than that in the untreated contralateral eyes.

A similar IOP course was observed after the second session: an increase in mean IOP after 1 hour (σ: +4.9 ± 5.5 mm Hg), followed by a decrease. However the mean IOP attained a value lower than the initial IOP after the second session after more than 6 hours (σ: -2.4 ± 3.7 mm Hg at 24 hours).

The increase in mean IOP following both sessions was virtually the same (σ: +4.4 ± 7.2 mm Hg and σ: +4.9 ± 5.5 mm Hg), but due to the lower initial IOP the maximum IOP after the second session was significantly lower than that after the first session (22.3 ± 6.0 mm Hg and 28.4 ± 8.9 mm Hg respectively).




| | First Session | | Second Session | |
|---|---|---|---|---|
| | Treated Eyes | Untreated Eyes | Treated Eyes | Untreated Eyes |
| IIOP | 24.0 ± 5.7 | 20.0 ± 5.7 | 17.4 ± 3.8 | 19.3 ± 4.5 |
| 1 h | 28.4 ± 8.9 | 20.0 ± 5.2 | 22.3 ± 6.0 | 19.5 ± 4.5 |
| 2 h | 25.9 ± 7.5 | 18.8 ± 4.5 | 20.8 ± 6.7 | 18.5 ± 4.5 |
| 3 h | 23.0 ± 5.2 | 17.7 ± 3.7 | 18.8 ± 5.2 | 18.2 ± 3.7 |
| 4 h | 22.0 ± 6.0 | 18.5 ± 5.7 | 17.5 ± 4.5 | 17.8 ± 3.8 |
| 5 h | 20.4 ± 5.7 | 17.7 ± 3.8 | 18.0 ± 5.3 | 18.0 ± 3.8 |
| 6 h | 20.2 ± 5.7 | 18.4 ± 3.8 | 17.8 ± 4.4 | 18.6 ± 4.4 |
| 24 h | 17.0 ± 3.8 | 18.9 ± 4.5 | 15.0 ± 3.8 | 19.0 ± 4.5 |
| 1 w | 20.4 ± 6.9 | 19.7 ± 4.5 | 16.7 ± 4.5 | 19.2 ± 3.8 |

Table 6.12 and Figure 6.2. IOP course (Mean ± SD; mm Hg) until 24 hours after ALT in treated and untreated eyes after the first and second session (IIOP: initial IOP; h:hour(s); w:week).

The IOP in untreated contralateral eyes showed no change within the first hour after ALT, either after the first or after the second session. From the first hour post-ALT on, these eyes likewise showed an IOP decrease; this was more pronounced after the first than after the second session. Subsequently the IOP rose again until its initial value was attained. This transient decrease in IOP in the untreated contralateral eyes resulted from the fact that a number of patients were given Diamox in view of an IOP increase which had to be treated according to the criteria set (25 patients (43.9%) after the first and 13 (22.8%) after the second session).

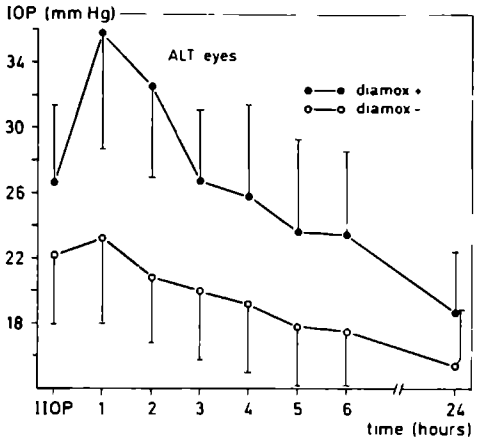
Table 6.13 and figure 6.3 illustrate this for the first ALT session. The IOP course in treated and in untreated contralateral eyes is shown separately for patients who did and those who did not receive Diamox after ALT. A fairly constant IOP was observed in contralateral eyes not treated with Diamox, whereas Diamox-treated eyes showed a distinct post-ALT IOP decrease. The mean IOP of these subgroups taken jointly revealed a decreasing tendency for untreated contralateral eyes. The fact that this IOP decrease was less pronounced after the second than after the first session (maximum decrease 1.5 mm Hg and 2.3 mm Hg respectively) must be ascribed to the smaller number of patients given Diamox after the second session.

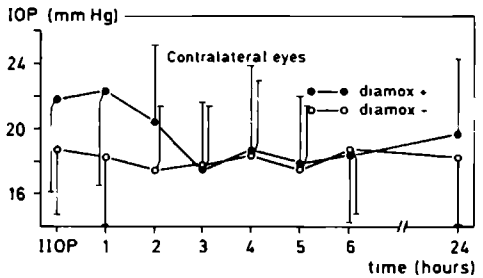
Table 6.13 an figure 6.3 in addition show that the maximum IOP in ALT eyes treated with Diamox was so high (35.5 $\pm$ 7.0 mm Hg one hour after ALT) that this temporary additional therapy was indeed indicated.

That the decrease in mean IOP from the first postoperative hour on was an ALT effect rather than a Diamox effect, is evident from the IOP course in ALT eyes not treated with Diamox (figure 6.3). These eyes, too, showed a consistent IOP decrease following a mild increase.

Table 6.14 and figure 6.4 show the IOP course in ALT eyes with phakic POAG, pigment dispersion syndrome and low-tension glaucoma after the first and the second session (the other subgroups were too small for presentation of the mean IOP values in this form, but the results will be discussed in a later section). The increase in mean IOP within 1 hour of ALT and the subsequent IOP decrease proved to occur in each of three subgroups described here.

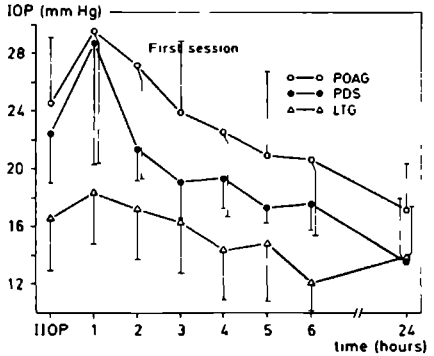
A bilateral ALT was performed in 30 patients. The IOP course after ALT of the second eyes showed the expected pattern (table 6.15 and figure 6.5):

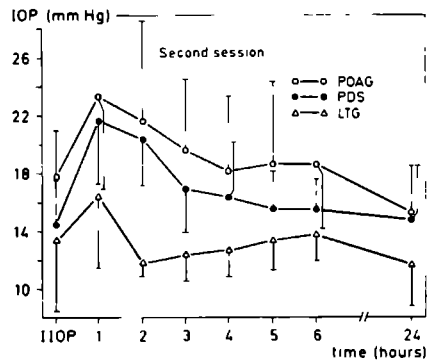



| | Diamox Post-ALT | | No Diamox Post-ALT | |
|---|---|---|---|---|
| | Treated Eyes | Contralateral Eyes | Treated Eyes | Contralateral Eyes |
| IIOP | 26.5 ± 4.7 | 21.8 ± 5.9 | 22.1 ± 4.2 | 18.6 ± 4.1 |
| 1 h | 35.5 ± 7.0 | 22.3 ± 5.8 | 23.1 ± 5.3 | 18.3 ± 4.2 |
| 2 h | 32.3 ± 5.4 | 20.4 ± 4.7 | 20.8 ± 4.0 | 17.5 ± 4.0 |
| 3 h | 26.7 ± 4.4 | 17.6 ± 4.0 | 20.0 ± 4.2 | 17.7 ± 3.8 |
| 4 h | 25.7 ± 5.6 | 18.6 ± 5.4 | 19.2 ± 4.2 | 18.5 ± 4.8 |
| 5 h | 23.8 ± 5.8 | 17.8 ± 4.0 | 17.8 ± 4.0 | 17.6 ± 4.1 |
| 6 h | 23.6 ± 5.3 | 18.3 ± 4.1 | 17.5 ± 3.4 | 18.4 ± 4.0 |
| 24 h | 18.8 ± 3.8 | 19.6 ± 4.7 | 15.5 ± 3.4 | 18.3 ± 4.4 |
| 1 w | 23.4 ± 5.8 | 20.6 ± 4.8 | 17.9 ± 6.9 | 19.0 ± 4.5 |

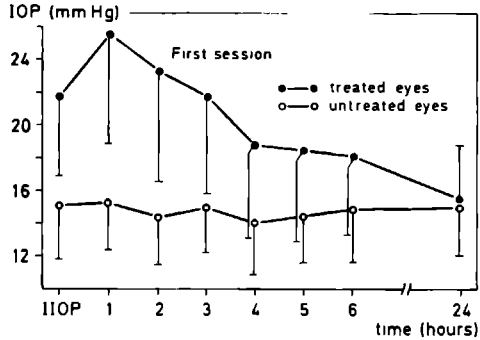
Table 6.13 and Figure 6.3. IOP course (Mean ± SD; mm Hg) until 24 hours after ALT in treated and untreated eyes after the first session, separately for post-ALT Diamox treatment.

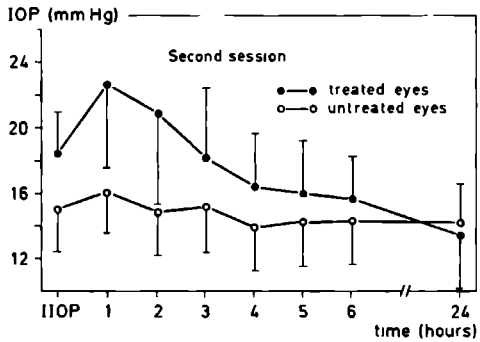



| | Phakic POAG | | Pigment Dispersion S. | | Low-tension Glaucoma | |
|---|---|---|---|---|---|---|
| | 1st Session | 2nd Session | 1st Session | 2nd Session | 1st Session | 2nd Session |
| IIOP | 24.3 ± 4.5 | 17.6 ± 3.2 | 22.3 ± 3.4 | 14.3 ± 3.4 | 16.5 ± 3.6 | 13.3 ± 4.8 |
| 1 h | 29.2 ± 9.0 | 23.1 ± 6.5 | 28.5 ± 8.4 | 21.5 ± 4.2 | 18.5 ± 3.4 | 16.5 ± 4.8 |
| 2 h | 27.0 ± 7.8 | 21.5 ± 7.0 | 21.3 ± 2.2 | 20.3 ± 3.0 | 17.3 ± 3.4 | 12.0 ± 0.8 |
| 3 h | 23.8 ± 5.1 | 19.5 ± 5.1 | 19.0 ± 2.6 | 16.8 ± 3.0 | 16.3 ± 3.4 | 12.5 ± 1.8 |
| 4 h | 22.5 ± 5.8 | 18.0 ± 5.2 | 19.3 ± 2.0 | 16.3 ± 4.0 | 14.5 ± 3.4 | 12.8 ± 2.0 |
| 5 h | 20.9 ± 5.8 | 18.5 ± 5.8 | 17.3 ± 1.0 | 15.5 ± 2.6 | 15.0 ± 4.0 | 13.3 ± 2.0 |
| 6 h | 20.6 ± 5.2 | 18.4 ± 4.4 | 17.5 ± 1.8 | 15.3 ± 2.2 | 12.3 ± 1.8 | 13.8 ± 1.8 |
| 24 h | 17.1 ± 3.2 | 15.1 ± 3.2 | 13.8 ± 4.4 | 14.8 ± 3.8 | 14.0 ± 3.6 | 11.8 ± 2.8 |
| 1 w | 20.0 ± 6.4 | 16.9 ± 3.0 | 16.3 ± 4.4 | 13.5 ± 1.8 | 14.3 ± 2.2 | 12.8 ± 3.0 |

Table 6.14 and Figure 6.4. IOP course (Mean ± SD; mm Hg) until 24 hours after ALT for treated eyes with phakic POAG (POAG), pigment dispersion syndrome (PDS) and low-tension glaucoma (LTG) after the first and second session.




| | First Session | | Second Session | |
|---|---|---|---|---|
| | Treated Eyes | Untreated Eyes | Treated Eyes | Untreated Eyes |
| IIOP | 21.7 ± 4.9 | 15.1 ± 3.3 | 18.4 ± 2.7 | 15.0 ± 2.7 |
| 1 h | 25.5 ± 6.6 | 15.3 ± 2.7 | 22.6 ± 4.9 | 16.1 ± 2.2 |
| 2 h | 23.2 ± 6.5 | 14.5 ± 2.7 | 20.8 ± 5.5 | 14.9 ± 2.7 |
| 3 h | 21.7 ± 5.8 | 15.0 ± 2.6 | 18.1 ± 4.3 | 15.2 ± 2.7 |
| 4 h | 18.8 ± 5.5 | 14.1 ± 3.3 | 16.4 ± 3.3 | 14.0 ± 2.7 |
| 5 h | 18.5 ± 5.5 | 14.5 ± 2.7 | 16.1 ± 3.3 | 14.3 ± 2.7 |
| 6 h | 18.1 ± 4.8 | 14.9 ± 3.2 | 15.8 ± 2.7 | 14.4 ± 2.7 |
| 24 h | 15.6 ± 3.3 | 15.0 ± 2.7 | 13.6 ± 3.3 | 14.3 ± 2.7 |
| 1 w | 18.3 ± 4.4 | 15.0 ± 2.7 | 16.4 ± 4.4 | 14.6 ± 3.3 |

Table 6.15 and Figure 6.5. IOP course (Mean ± SD; mm Hg) until 24 hours after ALT in second eyes and control eyes after the first and the second session.

a brief transient IOP increase followed by a consistent decrease. In this context it is to be noted that the contralateral eyes described in this table and figure, which at the time served as control eyes, had been previously submitted to ALT. Consequently the IOP in these eyes was low.

The mean IOP in ALT eyes showed an increase at a check-up after 1 week, both after the first and the second session. There are two reasons for ascribing this IOP increase to post-ALT treatment with corticosteroid eyedrops, which in corticosteroid responders must have caused an IOP increase. These reasons are as following:

- To begin with, although the mean IOP of these eyes had increased after 1 week, it subsequently fell to the value measured 24 hours after ALT, as evident from the initial IOP before the second session (IOP after 24 hours 17.0 mm Hg, after 1 week 20.4 mm Hg and before the second session 17.4 mm Hg respectively; table 6.12).
- Secondly, this IOP increase was not observed in the untreated contralateral eyes (which had not received no post-ALT corticosteroid application).

The second eyes likewise showed an increase, but on the average there was no IOP decrease until the second session. However, the subgroup with phakic POAG did show a decreasing tendency, be it less marked than that in eyes treated first (IOP after 24 hours 15.9 mm Hg, after 1 week 19.6 mm Hg and before the second session 18.8 mm Hg respectively). Three second eyes with a pigment dispersion syndrome in particular showed no increase at the 1-week check-up, but the IOP thereafter increased, perhaps because no adequate response to ALT had yet occurred.

A second reason to assume that the group of second eyes also included corticosteroid responders derives from the differences in the standard deviation from the mean IOP values after 1 week and before the second session. The smaller standard deviation from the mean IOP before the second session may be explained from an IOP increase in a proportion of the eyes (pigment dispersion syndrome) and a decrease in the eyes responding to corticosteroids.

### 6.8.2 Eyes with IOP spikes and variables in these eyes

#### 6.8.2.1 Eyes with IOP spikes

An IOP spike is defined as a minimal IOP increase by at least a given number of (whole) mm Hg within 24 hours of ALT.

This may be illustrated by the following description of a single aspect of the IOP pattern after ALT, separately for patients in whom the IOP increase did (Y) or did not (N) exceed the spike value.

Proceeding from any increase in IOP observed - i.e. a spike value of 1 mm Hg or higher - one may conclude that 75.4% of the eyes showed such an increase after the first session, and 86.0% after the second session. In view of the standard deviation of measurement error, however, it is not justifiable to regard such a 'spike' as indeed a significant increase. A second reason to opt in favour of a higher minimum spike value, in this study 10 mm Hg is its clinical relevance (it constituted an indication for Diamox treatment). By way of illustration the analyses are performed also with a lower spike value (5 mm Hg) to indicate possible consequences of taking this value as a Diamox criterion. By way of example figure 6.6 presents the cumulative frequency distribution of all IOP spikes measured after the first and second session. After the first session these spikes ranges from 1 to 20 mm Hg (median 8 mm Hg), and after the second session they ranged from 1 to 22 mm Hg (median 7 mm Hg).

Table 6.16 lists a number of IOP parameters for the 57 eyes treated first, divided into eyes with an IOP spike of at least 5 and those with a spike of at least 10 mm Hg.

Some 50% of the eyes showed an IOP spike by at least 5 mm Hg after the first session. The maximum IOP of these eyes was 35.2 $\pm$ 7.0 mm Hg, and the mean proportional IOP decrease 6 hours after ALT was less than that in eyes without an IOP spike of 5 mm Hg or more. The two groups showed a mean proportional IOP decrease of the same order of magnitude 24 hours after ALT.

An IOP spike of at least 10 mm Hg occurred in 29.8% of the eyes. These eyes, too, attained a high maximum IOP (37.9 $\pm$ 5.0 mm Hg), while the mean proportional IOP decrease 6 hours after ALT was not marked. A check-up on IOP one day later, however, revealed an adequate decrease in IOP.

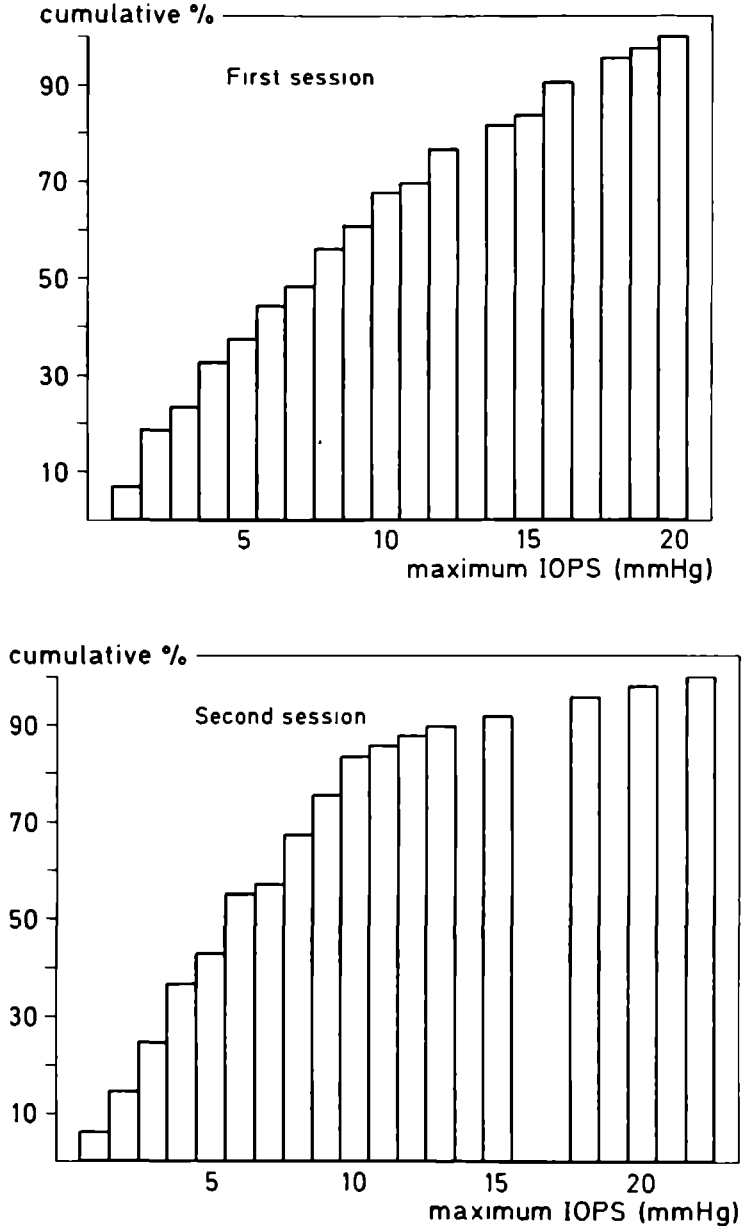



Figure 6.6. Cumulative frequency distribution of maximum IOP values after the first and second session.

Table 6.16. Frequencies of eyes with an IOP spike (IOPS) of at least 5 or 10 mm Hg after the first and the second session, with corresponding initial IOP (IIOP), maximum IOP (MAXIOP), proportional IOP decrease after 6 hours and 24 hours (PIOPD 6h, 24h) (All as Mean ± SD). Also separately for eyes with and without post-ALT Diamox treatment.

| First Session | | N | IIOP mm Hg | MAXIOP mm Hg | PIOPD 6h % | PIOPD 24h % |
|---|---|---|---|---|---|---|
| IOPS ≥5 mm Hg | Yes | 50.9% | 23.9 ± 5.6 | 35.2 ± 7.0 | 7.3 ± 20.8 | 24.1 ± 16.7 |
| | No | 49.1% | 24.1 ± 4.2 | 24.9 ± 4.8 | 23.4 ± 11.7 | 31.7 ± 14.9 |
| IOPS ≥10 mm Hg | Yes | 29.8% | 23.6 ± 4.0 | 37.9 ± 5.0 | 4.6 ± 22.1 | 25.3 ± 16.4 |
| | No | 70.1% | 24.2 ± 5.3 | 26.8 ± 6.5 | 19.7 ± 15.2 | 28.9 ± 16.2 |
| Diamox | Yes | 43.9% | 26.5 ± 4.7 | 37.6 ± 4.4 | 9.9 ± 21.0 | 28.0 ± 14.2 |
| | No | 56.1% | 22.1 ± 4.2 | 24.3 ± 4.4 | 19.3 ± 15.7 | 27.7 ± 17.8 |
| **Second Session** | | **N** | **IIOP mm Hg** | **MAXIOP mm Hg** | **PIOPD 6h %** | **PIOPD 24h %** |
| IOPS ≥5 mm Hg | Yes | 54.4% | 17.3 ± 4.0 | 27.0 ± 6.5 | - 7.4 ± 20.1 | 9.3 ± 23.0 |
| | No | 45.6% | 17.6 ± 3.6 | 19.1 ± 3.2 | 0.1 ± 19.6 | 14.9 ± 15.9 |
| IOPS ≥10 mm Hg | Yes | 21.1% | 18.4 ± 4.3 | 32.5 ± 6.1 | -16.5 ± 20.7 | 11.5 ± 25.2 |
| | No | 78.9% | 17.2 ± 3.7 | 21.0 ± 4.1 | - 0.9 ± 18.8 | 11.9 ± 18.9 |
| Diamox | Yes | 22.8% | 19.5 ± 4.5 | 32.9 ± 5.5 | -14.3 ± 18.5 | 10.5 ± 22.8 |
| | No | 77.2% | 16.8 ± 3.4 | 20.6 ± 3.6 | - 1.1 ± 19.7 | 12.2 ± 19.5 |

In 43.9% of the eyes, Diamox was required after the first ALT session in view of an IOP spike which fulfilled the criteria for additional treatment.

The frequency of occurrence of IOP spikes after the second ALT session did not differ markedly from that after the first session. Because the initial IOP before the second session was unmistakably lower, however, lower maximum IOP values were attained. This was also evident from the smaller proportion of eyes requiring Diamox after the second session (22.8%, versus 43.9% after the first session; $p<0.01$).

Contrary to the IOP course following the first session, a mean proportional IOP increase was observed 6 hours after the second session; 24 hours after ALT, however, these eyes also showed a mean proportional IOP decrease.

The mean interval after which a maximum IOP spike occurred was 1.4 ± 0.8

hours (≥5 mm Hg) and 1.4 ± 0.6 (≥10 mm Hg) after the first session, and 1.4 ± 0.5 (≥5 mm Hg) and 1.9 ± 1.7 hours (≥10 mm Hg) after the second.

The time at which Diamox was indicated is of greater clinical importance. This was 1.5 ± 0.8 hours after the first, and 1.5 ± 0.5 hours after the second session. In most cases requiring Diamox this was given within 2 hours of ALT (68.0% 1 and 28.0% 2 hours after the first session; 69.2% 1 and 23.1% 2 hours after the second session).

In only one eye was an IOP decrease observed first, followed by a spike which necessitated Diamox treatment 4 hours after ALT.

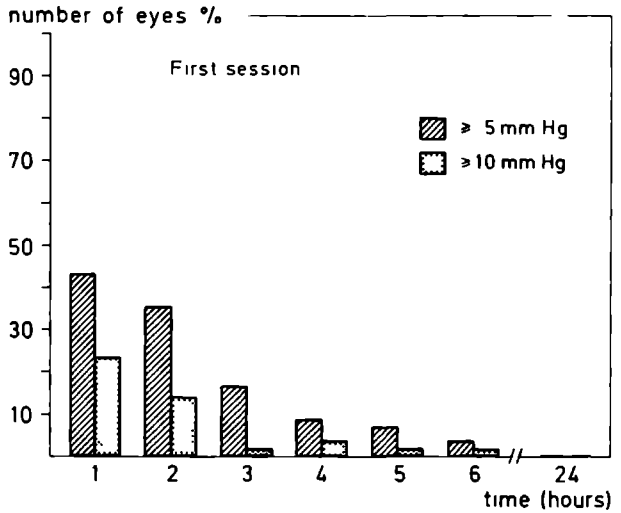
Of 25 eyes requiring Diamox after the first session, 15 (60.0%) received 250 mg, 9 (36.0%) 500 mg and 1 (4.0%) 750 mg before the IOP tended to decrease. After the second session 9 eyes (69.2%) received 250 mg, and 4 (30.8%) 500 mg.

Table 6.17 lists the frequencies of IOP spikes after the first and second session per subgroup. The subgroups were often too small to reveal inter-subgroup differences. The pigment dispersion syndrome tended to show high IOP spikes. Alertness is imperative also in low-tension glaucoma.

Table 6.17. Frequencies of IOP spikes of at least 5 or 10 mm Hg after the first and the second session, per subgroup.

| | First Session | | Second Session | |
|---|---|---|---|---|
| | ≥5 mm Hg | ≥10 mm Hg | ≥5 mm Hg | ≥10 mm Hg |
| Phakic POAG | 57.1% | 33.3% | 57.1% | 23.8% |
| Pseudophakic POAG | - | - | - | - |
| Pigment Dispersion S. | 2/4 | 2/4 | 4/4 | 1/4 |
| Low-tension Glaucoma | 1/4 | - | 1/4 | - |
| Secondary Glaucoma | - | - | 1/2 | 1/2 |
| Glaucoma Suspect | - | - | 1/2 | - |
| Thyroid Disease | 2/2 | 1/2 | - | - |
| Total | 50.9% | 29.8% | 54.4% | 21.1% |

Figure 6.7 shows the distribution of eyes with an IOP spike of at least 5 or 10 mm Hg as a function of the post-ALT check-up time after the first and second session.



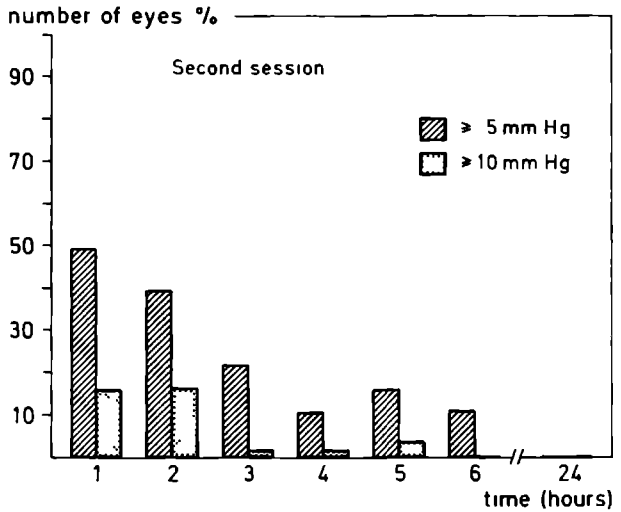




Figure 6.7. Frequencies of eyes with an IOP spike of at least 5 or 10 mm Hg after the first and the second session as a function of the time of post-ALT check-up.

After the first session the highest frequency of these two IOP spikes was measured 1 hour after ALT; subsequently the number of eyes with an IOP spike diminished consistently. Similar findings were obtained after the second session: highest frequency of IOP spikes after 1 hour, with a subsequent decrease in frequency. After neither session did eyes show a spike of at least 5 mm Hg 24 hours after ALT.

### 6.8.2.2 Variables in eyes with IOP spikes

In order to reach a conclusion about high-risk factors correlating with post-ALT IOP spikes, the occurrence of these spikes was submitted to an exploratory analysis in correlation with the values of several variables. This analysis was:

1. confined to IOP spikes of at least 5 or 10 mm Hg;
2. confined to IOP spikes observed after the first session;
3. applied both to the entire population (N=57) and separately to the eyes with phakic POAG.

The variables and the corresponding frequencies of IOP spikes are presented in table 6.18.

Table 6.18. Frequencies of IOP spikes of at least 5 or 10 mm Hg after the first session in all eyes and in eyes with phakic POAG as a function of patient, ocular, gonioscopic and ALT variables.

| Patient Variables | IOPS All Eyes | | IOPS Phakic POAG | |
|---|---|---|---|---|
| | ≥5 mm Hg | ≥10 mm Hg | ≥5 mm Hg | ≥10 mm Hg |
| Age <60 yr | 41.2% | 17.6% | 4/10 | 1/10 |
| ≥60 yr | 55.8% | 35.0% | 62.5% | 40.6% |
| Male | 60.7% | 39.3% | 70.0% | 40.0% |
| Female | 41.4% | 20.7% | 45.5% | 27.3% |

(continued)

Table 6.18 continued

| Ocular/Glaucoma Variables | IOPS All Eyes ≥5 mm Hg | IOPS All Eyes ≥10 mm Hg | IOPS Phakic POAG ≥5 mm Hg | IOPS Phakic POAG ≥10 mm Hg |
|---|---|---|---|---|
| OD | 44.8% | 27.6% | 57.1% | 33.3% |
| OS | 57.1% | 32.1% | 57.1% | 33.3% |
| Brown Eyes | 70.0% | 35.0% | 72.2% | 38.9% |
| Blue Eyes | 40.5% | 27.0% | 45.8% | 29.2% |
| Hypermetropia | 41.7% | 20.8% | 52.9% | 29.4% |
| Myopia | 56.0% | 32.0% | 55.6% | 27.8% |
| IIOP <20 mm Hg | 64.3% | 35.7% | 6/8 | 3/8 |
| ≥20 mm Hg | 66.7% | 27.4% | 52.9% | 32.4% |
| <25 mm Hg | 51.4% | 35.1% | 57.1% | 39.3% |
| ≥25 mm Hg | 50.0% | 20.0% | 57.1% | 21.4% |
| Miotics | 50.0% | 35.7% | 58.3% | 41.7% |
| Other topical medication | 50.0% | 25.0% | 58.6% | 31.0% |
| Diamox pre-ALT Yes | 5/8 | 3/8 | 3/4 | 2/4 |
| No | 49.0% | 28.6% | 55.3% | 31.6% |
| Previous Surgery | 1/5 | 1/5 | 1/2 | 1/2 |
| Previous ALT | 2/4 | 1/4 | 2/4 | 1/4 |
| No Previous Surgery | 54.2% | 31.2% | 58.3% | 33.3% |
| **Gonioscopic Variables** | | | | |
| Angle Grade 1-2 | 51.4% | 27.0% | 63.0% | 37.0% |
| Grade 3-4 | 50.0% | 35.0% | 46.7% | 26.7% |
| Beak-shaped Angle Absent | 52.5% | 37.5% | 59.3% | 44.4% |
| Present | 47.1% | 11.8% | 53.3% | 13.3% |
| Iris Processes Absent | 39.4% | 24.2% | 42.9% | 25.0% |
| Present | 66.7% | 37.5% | 85.7% | 50.0% |
| Trabecular Pigmentation TP 0 - TP+2 | 41.5% | 22.0% | 48.4% | 29.0% |
| TP+3 - TP+4 | 75.0% | 50.0% | 81.8% | 45.5% |
| Prominence of Schwalbe's line Absent | 48.3% | 27.6% | 54.5% | 31.8% |
| Present | 53.6% | 32.1% | 60.0% | 35.0% |
| Peripheral Anterior Synechiae Absent | 52.8% | 30.2% | 57.5% | 32.5% |
| Present | 1/4 | 1/4 | 1/2 | 1/2 |

(continued)

Table 6.18 continued

| ALT Variables | IOPS All Eyes ≥5 mm Hg | IOPS All Eyes ≥10 mm Hg | IOPS Phakic POAG ≥5 mm Hg | IOPS Phakic POAG ≥10 mm Hg |
|---|---|---|---|---|
| Bubble or Dispersion | 50.0% | 18.8% | 53.8% | 23.1% |
| Bubble and Dispersion | 51.2% | 34.1% | 58.6% | 37.9% |
| Power <1000 mW | 4/6 | 4/6 | 2/4 | 2/4 |
| ≥1000 mW | 49.0% | 25.9% | 57.9% | 31.6% |
| Iris Stretching Performed | 3/7 | 0/7 | 3/7 | 0/7 |
| Not Performed | 52.0% | 34.0% | 60.0% | 40.0% |
| ALT Quality (fairly) Good | 54.5% | 34.1% | 60.6% | 36.4% |
| Moderate | 38.5% | 15.4% | 4/9 | 2/9 |
| Patient Complaints Moderate | 50.0% | 27.1% | 55.9% | 29.4% |
| Severe | 5/9 | 4/9 | 5/8 | 4/8 |

The number of eyes with the following variables was too small for a sufficiently powerful analysis:

- pre-ALT Diamox treatment,
- pre-ALT glaucoma surgery,
- presence of peripheral anterior synechiae,
- ALT with a power setting <1000 mW,
- severe post-ALT complaints.

A significantly high frequency of IOP spikes of at least 5 mm Hg was found in eyes with brown irides, eyes with iris processes and eyes with trabecular pigmentation degree TP+3 and TP+4 ($p<0.05$ respectively).

A significantly lower frequency of IOP spikes of at least 10 mm Hg was found in eyes with a beak-shaped iridocorneal angle and those submitted to iris stretching prior to ALT ($p<0.05$ respectively).

The low frequencies of IOP spikes in eyes with a beak-shaped angle and eyes submitted to iris stretching were not independent findings because iris stretching was performed only in eyes with a beak-shaped angle. This type of angle existed in 15 eyes with phakic POAG, and 7 of these were submitted to

iris stretching. None of the latter eyes showed an IOP spike of at least 10 mm Hg, which was found in 2 of the 8 eyes not submitted to iris stretching.

A high trabecular pigmentation degree (TP+3 and TP+4) was associated with more IOP spikes. This also explained why 4 of the 6 eyes with a first ALT session at less than 1000 mW power setting showed an IOP spike of at least 10 mm Hg: two of these had TP+3, and two had TP+4.

An analysis confined to eyes with phakic POAG revealed no correlation between ALT power setting and the occurrence of IOP spikes (frequency of spikes of at least 5 mm Hg: 58.8% at power setting <1100 mW, 56.0% at power setting ≥1100 mW, 52.2% at power setting <1200 mW and 63.2% at power setting ≥1200 mW).

Brown irides were associated with more IOP spikes than blue ones. Because the two iris colours did not differ in degree of trabecular pigmentation, this could not be a consequence of differences in degree of pigmentation.

ALTs described as (fairly) good were associated with more IOP spikes than moderate ALTs. This is explained by the fact that most good ALTs caused pigment dispersion as well as bubble formation, and this combination produced more IOP spikes than either criterion alone.

### 6.8.3 First and second session IOP spikes

Table 6.19 lists first and/or second session IOP spikes of at least 5 or 10 mm Hg, both for the entire group and for phakic POAG eyes.

Table 6.19. Frequencies of eyes with an IOP spike of at least 5 or 10 mm Hg after no, one or both session(s) for all eyes and for eyes with phakic POAG.

| | All Eyes | | Phakic POAG | |
|---|---|---|---|---|
| | ≥5 mm Hg | ≥10 mm Hg | ≥5 mm Hg | ≥10 mm Hg |
| Both Sessions | 29.8% | 10.5% | 35.7% | 14.3% |
| First Session Only | 21.1% | 19.3% | 21.4% | 19.0% |
| Second Session Only | 24.6% | 10.5% | 21.4% | 11.9% |
| None of Both Session | 24.6% | 59.6% | 21.4% | 54.8% |

On the basis of the data in table 6.19 the distribution of eyes with a second session IOP spike can be outlined as a function of the occurrence or non-occurrence of a first session IOP spike. This is done in table 6.20.

Table 6.20. Frequencies of IOP spikes (IOPS) of at least 5 or 10 mm Hg after the second session as a function of the response to the first session, for all eyes and for eyes with phakic POAG.

| | | Second Session IOPS | No second Session IOPS |
|---|---|---|---|
| First Session IOPS ≥5 mm Hg | All Eyes | 58.6% | 41.4% |
| | Phakic POAG | 62.5% | 37.5% |
| First Session No IOPS ≥5 mm Hg | All Eyes | 50.0% | 50.0% |
| | Phakic POAG | 50.0% | 50.0% |
| First Session IOPS ≥10 mm Hg | All Eyes | 35.5% | 64.7% |
| | Phakic POAG | 42.9% | 57.1% |
| First Session No IOPS ≥10 mm Hg | All Eyes | 15.0% | 85.0% |
| | Phakic POAG | 17.9% | 82.1% |

For each of the two sessions the chance of an IOP spike at least 5 mm Hg was about 50%, the events occurring independently. The chance of an IOP spike of at least 10 mm Hg was virtually 30% after the first and 20% after the second session. These IOP spikes, too, occurred independently.

### 6.8.4 First and second eye IOP spikes

All other things being equal, the analysis applied to first and second session spikes may also be carried out for patients treated bilaterally. Table 6.21 shows the distribution of IOP spikes after the first session in bilaterally treated patients.

Table 6.22 presents the distribution of eyes with an IOP spike after the first session of the second eye, as a function of the reaction after the first session of the first eye.

A small number of patients showed an IOP spike after the first session of the second eye although it had not occurred after the first session of the

Table 6.21. Frequencies of IOP spikes (IOPS) of at least 5 or 10 mm Hg after the first session in no, one or both eye(s).

| | All Eyes | | Phakic POAG | |
|---|---|---|---|---|
| | ≥5 mm Hg | ≥10 mm Hg | ≥5 mm Hg | ≥10 mm Hg |
| Both eyes | 36.6% | 20.0% | 45.0% | 30.0% |
| First Eye Only | 26.7% | 23.3% | 25.0% | 15.0% |
| Second Eye Only | 6.7% | 3.3% | 5.0% | 5.0% |
| None of Both Eyes | 30.0% | 53.3% | 25.0% | 50.0% |

Table 6.22. Frequencies of IOP spikes of at least 5 or 10 mm Hg after the first session in the second eye as a function of the response of the first eye to the first session.

| | | Second Eye IOPS | Second Eye No IOPS |
|---|---|---|---|
| First Eye IOPS ≥5 mm Hg | All Eyes | 57.9% | 42.1% |
| | Phakic POAG | 64.3% | 35.7% |
| First Eye No IOPS ≥5 mm Hg | All Eyes | 18.2% | 81.8% |
| | Phakic POAG | 1/6 | 5/6 |
| First Eye IOPS ≥10 mm Hg | All Eyes | 42.2% | 53.8% |
| | Phakic POAG | 66.7% | 33.3% |
| First Eye No IOPS ≥10 mm Hg | All Eyes | 5.9% | 94.1% |
| | Phakic POAG | 9.1% | 90.9% |

the first eye. As expected, therefore, there is a statistical indication ($p<0.10$) of a correlation between occurrence of spikes after first sessions of ALT in both eyes of the same individual.

A related, and clinically more important, finding is that whenever the first eye shows no IOP spike of at least 10 mm Hg after either session, no IOP spike of at least 10 mm Hg is seen in the second eye in 93.3% of all and 88.9% of the phakic POAG eyes. If on the other hand an IOP spike of at least 10 mm Hg occurs in the first eye after one of the two sessions, then a similar spike is observed after at least one session in 53.3% of all and in 72.7% of the phakic POAG second eyes.

There is a statistically significant ($p<0.05$) interdependence in occurrence of IOP spikes of at least 10 mm Hg in the two eyes of an individual.

### 6.8.5 Success rate and visual field function

Table 6.23 shows the results of ALT in the various subgroups. One patient with phakic POAG dropped out and was not considered in the compilation of these results. Success was defined as a proportional IOP decrease of a least 20% and a final IOP of 21 mm Hg or lower.

Table 6.23. ALT results per subgroup (CFR: complete failure rate; SR: success rate; IIOP: initial IOP; FIOP: final IOP; IOPD: absolute IOP decrease; PIOPD: proportional IOP decrease (All as Mean± SD) FU: follow-up ).

| | CFR | SR | Success Eyes IIOP mm Hg | FIOP mm Hg | IOPD mm Hg | PIOPD % | FU (mths) |
|---|---|---|---|---|---|---|---|
| Phakic POAG | 7.3% | 75.6% | 25.7 ± 5.4 | 14.7 ± 3.1 | 11.0 ± 6.3 | 40.9 ± 15.2 | 7.0 ± 3.9 |
| Pseudophakic POAG | | 1/1 | 19 | 15 | 4 | 21.1 | 5.8 |
| Pigment Dispersion S. | | 3/4 | 25.0 ± 4.4 | 13.3 ± 0.6 | 11.7 ± 4.2 | 45.6 ± 9.6 | 7.0 ± 3.1 |
| Low-tension Glaucoma | 1/4 | 1/4 | 14 | 10 | 4 | 28.6 | 10.5 ± 3.1 |
| Secondary Glaucoma | | 1/2 | 32 | 16 | 16 | 50.0 | 8.9 ± 1.9 |
| Glaucoma Suspect | | 2/2 | 29.0 ± 5.7 | 19.5 ± 4.0 | 9.5 ± 4.9 | 36.1 ± 17.0 | 4.3 ± 0.5 |
| Thyroid Disease | | 0/2 | | | | | |
| Total | 8.9% | 69.6% | 25.5 ± 5.6 | 14.7 ± 3.1 | 10.8 ± 6.0 | 40.2 ± 14.6 | 7.3 ± 3.7 |

After a mean follow-up of 7 months the success rate in phakic POAG was 75.6%, which is in accordance with expectations based on the estimated Kaplan-Meier survival curve in the retrospectively studied patient population (table 5.35, figure 5.3).

These eyes again showed differences in success rate as a function of the initial IOP: eyes with an initial IOP of at least 22 mm Hg had a success rate of 88.9%, versus one of only 50.0% in eyes with an initial IOP below 22 mm Hg ($p<0.01$).

Three eyes with phakic POAG were evaluated as complete failures (7.3%);

two required increased medication and the third was treated by trabeculectomy after ALT. This eye had previously been submitted to ALT in our department, and after the re-ALT it showed IOP spikes of +2 mm Hg after the first and +8 mm Hg after the second session. The last IOP spike was arrested with Diamox. Because no adequate IOP decrease occurred in spite of additional Diamox (initial IOP 30 mm Hg, IOP 3 weeks after the second session 28 mm Hg), a trabeculectomy was performed.

The relationship between IOP spikes and success rate in eyes with phakic POAG was as follows. Occurrence of an IOP spike of at least 5 or 10 mm Hg after at least one session correlated with a success rate of 78.1% or 89.5% respectively. On the other hand, an IOP spike of at least 10 mm Hg was observed in 54.8% of the success eyes, versus only 20.0% of the failure eyes ($p<0.10$). If no IOP spike of at least 5 or 10 mm Hg occurred after either session, then the respective success rates were 66.7% and 63.6%. Even the occurrence of an IOP spike of at least 5 or 10 mm Hg after both sessions did not result in a lower success rate (IOP spike $\geq$5 mm Hg: success rate 88.2%; IOP spike $\geq$10 mm Hg: success in 5 out of 6 eyes).

In view of the small numbers in the other subgroups it would make little sense to present a detailed discussion of the results in these subgroups. However, the trends were similar to those seen in the retrospective study: good responses in eyes with a pigment dispersion syndrome and moderate results in low-tension glaucoma).

An eye with the features of scleritis and requiring systemic corticosteroids showed a good response to ALT. Two eyes of patients with hyperthyroidism showed no response to ALT.

In none of the eyes visual acuity was reduced by more than 2 lines.

Post-ALT perimetric findings were available on 46 eyes, the mean interval between ALT and perimetry being 4.2 $\pm$ 2.5 months. Three of these 46 eyes (6.5%) showed progression of visual field defects to the next higher stage; 6 eyes (13.0%) showed deterioration, but within the same stage, and 37 eyes (80.4%) showed no change.

Six of the eyes with visual field deterioration had shown a good IOP decrease and all had shown an IOP spike of at least 5 mm Hg (3 one of at least 10 mm Hg) after at least one session. Two of these eyes showed progression to the next higher visual field stage.

To summarize: the visual field defect had progressed to the next higher stage in 2 out of 32 eyes (6.3%) with an IOP spike of at least 5 mm Hg after at least one session and a good response to ALT. Eleven eyes without an IOP spike of at least 5 mm Hg and with an adequate response to ALT showed no progression of visual field defects to the next higher stage. This difference was not statistically significant ($p<0.50$).

## 6.9 DISCUSSION AND CONCLUSIONS

**IOP course on the day of ALT:**

The mean IOP of eyes treated by ALT showed an increase during the immediate post-ALT phase. This increase was transient, because from the third hour after the first session on the IOP was lower than the initial IOP. After the second session it took more than 6 hours before the IOP was lower than the initial IOP; this may be explained by the fact that the post-ALT IOP decrease correlates with the initial IOP level. Because the increase in mean IOP was the same after the first and after the second session but a higher maximum IOP was attained after the first, an IOP decrease after the first session was more likely to result in an IOP lower than the initial IOP.

That the IOP increases and decreases measured were predominantly an effect of ALT may be concluded from the course of the IOP in untreated contralateral eyes: excluding eyes temporarily showing a Diamox effect, this course showed no significant changes in IOP.

An increase in mean IOP was observed after first as well after second sessions, in first and in second eyes, and in the three major subgroups phakic POAG, pigment dispersion syndrome and low-tension glaucoma.

The mean IOP measured 4 weeks after the first session (17.4 $\pm$ 3.8 mm Hg) equalled the IOP recorded 24 hours after the first session (17.0 $\pm$ 3.8 mm Hg). Apart from a transient IOP increase during the first week after ALT which should be ascribed to post-ALT corticosteroid medication, there was no essential change in IOP after the first 24 postoperative hours. The maximum IOP decrease was attained within 24 hours of the first session (mean proportional IOP decrease 27.8 $\pm$ 16.2%). The mean proportional IOP decrease recorded 24 hours after the second session was 11.9 $\pm$ 20.0%.

This ready IOP decrease after the first session can be considered in the discussion about the mechanism of action of ALT. The fact that the IOP decrease became manifest within a few hours of ALT is indicative of a mechanical action. This is consistent with the tightening effect described by Wise: shrinking of the collagenous core of the trabeculae is an immediate laser effect. The contraction of the iris in iris stretching could be regarded as an analogous process.

Biochemical changes in the trabecular meshwork also occur fairly soon after ALT (see 4.14), but they attain a maximum only a few days later. Yet cellular and biochemical changes must also play a role, but possibly in maintaining the IOP decrease after ALT. Organization of the laser burns and reorganization of the trabecular meshwork are processes not observed until a few weeks after ALT.

A plausible mechanism might thus comprise a mechanical factor (responsible for the ready IOP decrease after ALT), and secondary biochemical and cellular factors which maintain the decrease in IOP. The occurrence of so-called late failures is not at odds with this concept because in these eyes the ready IOP decrease has occurred (as evident from the initially good response), but the secondary changes are insufficient.

**Eyes with IOP spikes and variables in these eyes:**

In some 50% of all eyes an IOP spike of at least 5 mm Hg occurred, and IOP spikes of at least 10 mm Hg were seen in virtually 1 out of 4 eyes. The maximum IOP increase was on average found 1.5 hours after an ALT session. On the basis of our criteria Diamox was indicated for 43.9% of the eyes after the first and 22.8% after the second session. At least 500 mg Diamox was required after the first session in 40.0% and after the second session in 30.8%.

A check-up on the IOP 1 and 2 hours after ALT would have adequately identified 96.0% of the eyes requiring Diamox after the first, and 92.3% of those requiring it after the second session.

These results emphasize a point already discussed in chapter 4: IOP check-ups 1 and 2 hours after ALT should be part of the standard ALT protocol. Whenever an IOP spike is found to fulfill certain criteria (e.g. 10 mm Hg) and additional medication is indicated, these eyes should be followed up and

treated until an adequate IOP decrease is achieved.

Given this strategy, only one eye out of 114 sessions (0.9%) in this study would not have been selected as requiring Diamox. In one other eye an IOP spike was visible after 1 and after 2 hours, but the decision to give Diamox was not made until 3 hours after ALT.

On the basis of the variables studied, eyes with the following features seemed to run a graver risk of developing an IOP spike after ALT: eyes with brown irides, those with iris processes and those with a high degree of trabecular pigmentation (TP+3 or TP+4).

In particular the high frequency of IOP spikes in eyes with iris processes and those with a high degree of pigmentation provides an indication of the pathogenetic mechanism underlying these IOP spikes. ALT applied to such eyes will lead to release of pigment and debris which is trapped between the trabeculae, reducing the facility of outflow and thus causing an increase in IOP. The fact that most IOP spikes are of short duration also argues in favour of a mechanical obstruction. The tightening effect of ALT will soon cause an increase in intertrabecular space and thus a clearing of the obstructing material.

A disruption of the blood-aqueous barrier may also play a role in this respect, although this cannot be a decisive role. Virtually all eyes submitted to ALT subsequently showed increased congestion of conjunctival vessels. Unmistakable signs of iritis (aqueous flare and cells in the anterior chamber) were observed in 41.2% of the eyes with an IOP spike of at least 5 mm Hg; in 58.8% of these eyes, however, there was only a mild flare or no visible signs at all. Distinct evidence of iritis was found in 15.9% of the eyes without IOP spikes. The higher incidence of signs of iritis in eyes with an IOP spike was statistically significant but their occurrence was not sufficiently consistent to warrant the conclusion that iritis was the sole cause of these IOP spikes.

Another finding in this study which indicates a mechanical pathogenesis was the fact that no eye submitted to iris stretching subsequently showed an IOP spike of 10 mm Hg or higher. If disruption of the blood-aqueous barrier really played an essential role, then it would be precisely after iris stretching that a high frequency of IOP spikes might be expected. After all, the iris is a prostaglandin depository par excellence, and a release of

these prostaglandins would have lead to disruption of the blood-aqueous barrier. However, the opposite seemed more likely: eyes with a beak-shaped chamber angle showed an IOP spike of at least 10 mm Hg in 2 out of 8 cases without preceding iris stretching. The effect of iris stretching might be based on traction upon the trabecular meshwork, producing an additional tightening effect. From a clinical point of view, iris stretching is indicated for eyes with a beak-shaped chamber angle.

ALTs of good quality by our criteria produced slightly more IOP spikes than ALTs of moderate quality. This difference cannot be ascribed to a difference in power setting, because no correlation was found between power setting and occurrence of IOP spikes in phakic POAG. On the contrary: a power setting of less than 1000 mW caused an IOP spike of at least 10 mm Hg in 4 out of 6 eyes. In a highly pigmented trabecular meshwork pigment dispersion and bubble formation will become visible at a lower power setting, and the high frequency of IOP spikes at a power setting of less than 1000 mW and after ALTs of good quality can be traced to a high degree of pigmentation.

**Predictive value of first session or first eye IOP spikes:**

The risk of occurrence of an IOP spike of at least 5 mm Hg after the second session was not higher when such an IOP spike had been observed after the first session. An IOP spike of at least 10 mm Hg after the second session was more frequently seen when a similar spike had occurred after the first; even then, however, the spikes occurred independently. About 1 eye out of 6 showed an IOP spike of at least 10 mm Hg after the second session although no such spike had occurred after the first.

The conclusion should therefore be that the occurrence of a first session IOP spike has little predictive value for the reaction after the second session.

The occurrence of IOP spikes in bilaterally treated patients, however, showed a different pattern.

Assuming that an IOP spike of at least 10 mm Hg should be regarded as clinically most relevant (68.0% of the eyes requiring Diamox after the first, and 84.8% of those requiring Diamox after the second session), the risk that second eyes would show such an IOP spike after at least one session after occurrence of the spike after at least one session in the first

eye, proved to be 53.3% for all eyes and 72.7% for eyes with phakic POAG.

If the first eye showed no IOP spike of at least 10 mm Hg after either session, then the chance that the same would apply to the second eye was 93.3% for all eyes and 88.9% for eyes with phakic POAG.

This symmetry in occurrence of IOP spikes is not surprising in view of the fact that there was a fair symmetry of gonioscopic findings and the ALT was always performed in a standardized way. The findings would seem to warrant the conclusion that an IOP spike of at least 10 mm Hg after one of the two sessions implies a high risk that the contralateral eye will show a similar spike after ALT.

**IOP spikes, success rate and visual field function:**

The success rate was not negatively affected by the occurrence of IOP spikes in phakic POAG. On the contrary: there was a statistical indication of a difference in frequency of IOP spikes of at least 10 mm Hg between success eyes (54.8%) and failure eyes (20.0%).

If there was a positive correlation between occurrence of IOP spikes and success rate, then this should be traceable to factors which on the one hand predispose to developing an IOP spike and on the other hand exert a favourable influence on ALT results. One of these factors is probably the degree of pigmentation. This study revealed that a high degree of trabecular pigmentation was associated with more IOP spikes. Confining analysis to eyes with phakic POAG (in order to eliminate a disturbing effect of other variables), we found the success rate of eyes with trabecular pigmentation TP 0 or TP+1 was 60.0%, versus 81.3% for eyes with TP+2 or TP+3. Although this difference was not statistically significant, it provided an indication to why eyes with an IOP spike showed a higher success rate than those without an IOP spike.

Two out of 32 phakic POAG eyes with an IOP spike of at least 5 mm Hg and a good ALT result showed progression of visual field defects to the next higher stage. In one of these eyes, however, an exudative diabetic retinopathy had become manifest.

The extent to which the IOP spikes were responsible for this visual field deterioration cannot be established with certainty. On the one hand, a causal relationship is conceivable - which would imply that 6.3% of the suc-

cessfully treated eyes showed progression of visual field defect as a result of an IOP spike. On the other hand, at least one of these eyes with progression was also subject to another complicating factor, and the interval between ALT and perimetry (4.2 months on the average) was too long to permit definite demonstration of a causal relationship.

This thesis describes an investigation into the effects of Argon Laser Trabeculoplasty (ALT). Its aim was to evaluate the results of ALT (retrospective study) and to study the course of the intraocular pressure (IOP) during the period immediately after ALT (prospective study).

The thesis is divided into two parts. The first part (chapters 1, 2 and 3) discusses a number of aspects of glaucoma considered to be of relevance to this study. The second part (chapters 4, 5 and 6) presents a review of the literature on ALT and describes the results of the retrospective and prospective study.

**Chapter 1** describes how the glaucoma concept developed through the ages. Until well into the Middle Ages glaucoma was regarded as a disease of the lens, but numerous new theories were introduced between 1750 and 1850. Albrecht von Graefe was the first to describe increased IOP not as a complication but as a cause of glaucoma.

**Chapter 2** describes the functional anatomy, physiology and pathology of the angle of the anterior chamber and the trabecular meshwork. Embryological development and macroscopic anatomy are discussed.

The microscopic structure of the uveal trabeculae (and to a lesser degree that of the corneoscleral trabeculae) shows that these contribute little to the resistance to aqueous outflow required to produce IOP. The major resistance is provided by the trabecular wall of Schlemm's canal.

Perfusion studies and other research have shown that the transport of aqueous humour to the lumen of Schlemm's canal takes place via a system of dynamic vacuolation. Prostaglandins and proteoglycans possibly contribute to maintenance of the resistance to outflow.

The ageing process of the trabecular meshwork results in hyalinization, plaque formation, a decrease in cellularity, a decrease in number and size of vacuoles in the endothelium and constriction of the lumen of Schlemm's canal. Similar changes are observed in glaucoma. Besides quantitative differences from the normal ageing process, however, qualitative differences play a role. Morphological findings indicate that some plaques occur in glaucoma but are not observed in ageing; and enzyme-resistant glycosamino-

glycans are found only in glaucomatous eyes.

This chapter closes with a section on the optic nerve. Today there are indications that the vascularity of the anterior part of the optic nerve has a mechanism of autoregulation. Disturbed autoregulation possibly plays a role in the pathogenesis of glaucomatous optic disk damage. There are two theories on the pathogenesis of glaucomatous lesions of the optic nerve: a vasogenic and a mechanical concept. Indications in favour of both concepts are discussed.

**Chapter 3** describes the ocular findings which suggest the possibility of glaucoma. Biophysical and clinical aspects of tonometry and findings at gonioscopy are discussed. Various aspects of glaucomatous optic disk cupping are described with special reference to their correlation with visual field defects.

Early glaucomatous visual field defects may manifest themselves as paracentral scotoma, a wedge-shaped defect or a nasal step (isolated or otherwise). Classification of visual field defects may be based on the visual field stages defined by Aulhorn. The fact that adequate therapy cannot always prevent progression of the visual field defect is discussed.

Tonography as well as most provocation tests can be described as having fair-to-good sensitivity but low specificity, so that they have a low predictive value as to possible visual field defects in patients with suspected glaucoma.

**Chapter 4** outlines the results of ALT as reported in the literature. Both the original Wise ALT and the various modifications of this technique give good results in primary open-angle glaucoma, pseudo-exfoliation glaucoma and the pigment dispersion syndrome. Results are less good in low-tension glaucoma, and only moderate results are obtained in various forms of secondary glaucoma as well as after cataract extraction.

ALT applied as primary therapy gives better results than secondary ALT. The success rate diminishes as the follow-up increases, and 6 years after ALT it is still about 50%.

The degree of the decrease in IOP correlates with the level of the initial IOP. The degree of pigmentation of the trabecular meshwork may also play a role in this respect. The success rate is unfavourably influenced by an early age and moderate trabecular pigmentation, and may be lower in patients

of the negroid race.

Most modifications of the original Wise technique give good results, except one session ALT treating only 90° of the trabecular meshwork circumference, or a power setting below 500 mW.

A transient increase in IOP (IOP spike) is the principal complication observed after ALT. Its incidence largely depends on the time of measurement and on the lower limit set, and ranges from 0% to 70%. These IOP spikes may lead to visual field defects. Treatment of only 180° of the trabecular meshwork per session and application of burns to the anterior part of the meshwork reduces the incidence and height of IOP spikes. Corticosteroids and prostaglandin synthetase inhibitors exert no significant influence.

Re-ALT has a lower success rate and, dependent on the modification used, produces more IOP spikes. ALT does not unfavourably affect the results of ocular hypotensive surgery.

The mechanism of action of ALT seems to involve mechanical, cellular and biochemical changes.

**Chapter 5** describes a retrospective study of the results of ALT performed on 433 eyes of 305 patients between 15th June 1982 and 24th June 1986. For methodological reasons, however, only the eyes treated first were considered in the evaluation.

In 16.4% of cases ALT was followed by glaucoma surgery, indicated in 25% of these cases by an increase in IOP. More medication was required in 7.5% of cases. Eyes with secondary glaucoma required post-ALT surgery in 45.2% of cases.

A decrease in IOP by at least 20% and a final IOP of 21 mm Hg or lower was observed in 54.1% of the eyes treated. The mean decrease in IOP in these eyes was 10.5 mm Hg (38.8%).

Once the IOP was controlled, topical medication could be reduced or discontinued in 40.1% of cases, while systemic medication could be stopped in 67.7%.

In eyes with an adequate response to ALT there was no further glaucomatous damage to the optic disk in 93.3%, and 69.0% showed stabilization of the visual field defect.

Moderate results were obtained in eyes with low-tension glaucoma and those with secondary glaucoma. Good results were obtained in the pigment disper-

sion syndrome and in suspected glaucoma with damage to the optic disk. Aphakic and pseudophakic eyes showed less good results than phakic eyes.

Progression of glaucoma as a result of ALT was observed in 1% of the eyes. The results in bilaterally treated patients showed a high degree of similarity between the two eyes of an individual.

The success rate for phakic eyes with primary open-angle glaucoma was higher in males than in females (due to the lower initial IOP in females), related to the initial IOP level and lower in the case of pre-ALT Diamox medication. The coefficient of correlation between initial IOP and decrease in IOP was 0.85. Due to the limited number of young patients in this study, no correlation between age and success rate was established.

Treatment of 360° of the trabecular meshwork circumference in one session gives a significantly lower final IOP. One session ALT treating 180° has a lower success rate.

A chamber angle configuration unfavourably for ALT caused a lower success rate in aphakic eyes or eyes with secondary glaucoma; the results in the latter group were age dependent.

In view of these findings the preferable sequence in the treatment of glaucoma with concomitant cataract is: ALT followed by extracapsular cataract extraction.

The position of ALT in the treatment of glaucoma is discussed on the basis of the results obtained in primary open-angle glaucoma and in suspected glaucoma.

**Chapter 6** describes a prospective study of the changes in IOP in the period immediately after ALT in 57 patients.

Alt was performed in a standardized way, treating 360° of the trabecular meshwork circumference in two sessions separated by an interval of 4 weeks, applying a total of 120 burns of 50 µm diameter at an exposure time of 0.1 second. The burns were applied to the anterior part of the trabecular meshwork and the power was titrated on the basis of visible pigment dispersion and bubble formation. Corticosteroid eyedrops were given after ALT. This technique is now the standard procedure used in our department.

The IOP was measured 1 hour before ALT, every hour for 6 hours after ALT, and 24 hours after ALT.

One hour after ALT a transient increase in mean IOP was observed, both af-

ter the first and after the second session, in the first as well as in the second eyes treated and in the three major subgroups. Within 3 hours of the first ALT session an IOP value was found which averaged lower than the initial IOP. After the second session this took at least 6 hours.

In 50.9% of the eyes an increase in IOP of at least 5 mm Hg was seen after the first session, and in 29.8% of the eyes the increase was at least 10 mm Hg. The incidences after the second session were not strikingly different from those after the first. The height of the increases in IOP ranged from 1 to 22 mm Hg.

Additional medication in view of an IOP spike which met the criteria accepted was required after the first session in 43.9% of cases and after the second in 22.8%.

A significantly higher incidence of IOP spikes of at least 5 mm Hg was found in eyes with brown irides, eyes with iris processes, and eyes with a high degree of trabecular pigmentation. A significantly lower incidence of IOP spikes of at least 10 mm Hg was found in eyes with a beak-shaped angle of the anterior chamber and eyes submitted to iris stretching (these two variables of course correlate).

IOP spikes after the first and after the second session occurred independently.

There was a statistically significant dependence of occurrence of an IOP spike of at least 10 mm Hg in both eyes of the same individual.

The success rate after a mean follow-up of 7 months was 75.6% in phakic eyes with primary open-angle glaucoma. There is a statistical indication that IOP spikes of at least 10 mm Hg occur more frequently in these eyes than in eyes in which no adequate control of IOP is achieved.

Two eyes with an IOP spike of at least 5 mm Hg and adequate IOP control showed progression of the visual field defect. The discussion considers the (un)likelihood of a causal relationship.

On the basis of the changes in IOP after ALT and in view of the correlation between certain gonioscopic findings and the occurrence of IOP spikes, the discussion considers a mechanical explanation of the decrease in IOP as well as the transient increase in IOP after ALT.

Dit proefschrift beschrijft een onderzoek naar de effecten van Argon Laser Trabeculoplasty (ALT). Het doel van dit onderzoek is het evalueren van het resultaat van ALT (retrospectief onderzoek) en het verloop van de intraoculaire druk (IOD) in de onmiddellijke periode na ALT (prospectief onderzoek).

Het proefschrift bestaat uit twee delen. In het eerste deel (hoofdstukken 1, 2 en 3) wordt ingegaan op een aantal aspecten van glaucoom, voor zover deze relevant zijn voor het onderzoek. Het tweede deel (hoofdstukken 4, 5 en 6) bestaat uit een literatuuroverzicht van ALT en uit een beschrijving van de resultaten van het onderzoek.

**Hoofdstuk 1** beschrijft hoe het ziektebeeld glaucoom door de eeuwen heen vorm kreeg. Tot ver in de middeleeuwen wordt het glaucoom gezien als een ziekte van de lens, maar tussen 1750 en 1850 treden tal van nieuwe theorieën naar voren. Albrecht von Graefe beschreef als eerste dat de verhoogde IOD geen complicatie, maar de oorzaak van glaucoom is.

**Hoofdstuk 2** beschrijft de functionele anatomie, fysiologie en pathologie van de voorste oogkamerhoek en het trabeculum. De embryologische ontwikkeling en de macroscopische anatomie worden besproken.

De microscopische bouw van het trabeculum uveale en, in mindere mate van het trabeculum corneosclerale, laat zien dat deze slechts weinig bijdraagt aan de weerstand die het oogkamervocht dient te ondervinden om IOD op te bouwen. De grootste weerstand wordt gevormd door de trabeculaire wand van het kanaal van Schlemm.

Uit onder andere perfusieonderzoek blijkt dat het transport van oogkamervocht naar het lumen van het kanaal van Schlemm via een systeem van dynamische vacuolisatie verloopt. Mogelijk dragen prostaglandinen en proteoglycanen bij aan het handhaven van de weerstand.

Het verouderingsproces van het trabeculum resulteert in hyalinisatie, plaquesvorming, afname in cellulariteit, afname van het aantal en de grootte van de vacuolen in het endotheel en vernauwing van het lumen van het kanaal van Schlemm. Deze veranderingen worden ook gezien bij glaucoom. Naast kwantitatieve verschillen met het normale verouderingsproces echter, spelen ook kwalitatieve verschillen een rol. Morfologisch lijken sommige plaques wel

bij glaucoom, maar niet bij veroudering gezien te worden. Ook enzymresistente glycosaminoglycanen komen slechts voor in glaucomateuze ogen.

Dit hoofdstuk wordt afgesloten met een paragraaf over de nervus opticus. Er zijn thans aanwijzingen dat de vascullariteit van het anteriore deel van de nervus opticus een autoregulatiemechanisme heeft. Een gestoorde autoregulatie speelt mogelijk een rol in het ontstaan van glaucomateuze papilbeschadiging. Omtrent het ontstaan van glaucomateuze beschadiging van de nervus opticus bestaan 2 theorieën: een vasogeen versus een mechanisch concept. Aanwijzingen voor beide concepten worden besproken.

**Hoofdstuk 3** beschrijft de bevindingen bij het oogheelkundig onderzoek die in de richting van glaucoom wijzen. Biofysische en klinische aspecten van tonometrie komen aan de orde evenals de bevindingen bij gonioscopie.

Diverse aspecten van de glaucomateuze papilexcavatie worden beschreven, met name in hun relatie tot gezichtsvelduitval.

Vroege glaucomateuze gezichtsvelduitval kan zich manifesteren als een paracentraal scotoom, een wigvormig defect en een al dan niet geisoleerde 'nasal step'. Het classificeren van de mate van uitval kan gebeuren aan de hand van de stadia die door Aulhorn werden beschreven. Dat adequate therapie de progressie van gezichtsvelduitval niet steeds kan voorkomen wordt besproken.

Zowel ten aanzien van de tonografie als van de meeste provocatietesten geldt dat ze een redelijke tot goede sensitiviteit, maar een lage specificiteit en dus een lage predictieve waarde hebben ten aanzien van het voorspellen van gezichtsvelduitval in glaucoom suspecte patiënten.

**Hoofdstuk 4** schetst de resultaten van ALT zoals deze in de literatuur beschreven worden.

Zowel de oorspronkelijke Wise ALT, als ook diverse modificaties van deze techniek geven goede resultaten in het primair open kamerhoek glaucoom, het pseudo-exfoliatieve glaucoom en het pigment dispersie syndroom. Minder goede resultaten worden behaald in het low-tension glaucoom en matige resultaten in diverse vormen van secundair glaucoom en na cataractextractie.

ALT toegepast als primaire therapie geeft betere resultaten dan wanneer deze als secundaire therapie wordt toegepast. Met het vorderen van de follow-up daalt de succes rate en 6 jaar na ALT bedraagt deze nog ongeveer 50%.

De mate van IOD daling is sterk gecorreleerd aan de hoogte van de initiële IOD. Ook de pigmentatiegraad speelt hierbij mogelijk een rol. De succes rate

wordt nadelig beïnvloed door een jonge leeftijd, een matig gepigmenteerd trabeculum en is mogelijk lager in patiënten van het negroïde ras.

Het merendeel van de modificaties van de originele Wise techniek geeft goede resultaten, behoudens het eenmalig behandelen van slechts 90° van het trabeculum en een vermogen van minder dan 500 mW.

De belangrijkste complicatie na ALT bestaat uit een tijdelijke stijging van de IOD. De incidentie is sterk afhankelijk van het tijdstip van meten en van de ondergrens die men aan een stijging toekent, en varieert van 0% tot 70%. Deze IOD stijgingen kunnen tot gezichtsvelduitval leiden.

Het behandelen van slechts 180° van het trabeculum per sessie, als ook het plaatsen van de coagulaten op het anteriore deel van het trabeculum geeft een lagere incidentie en hoogte van drukstijgingen. Corticosteroiden en prostaglandinesynthetase-remmers hebben geen significante invloed.

Hernieuwde ALT geeft een geringere kans op succes en, afhankelijk van de modificatie, meer IOD stijgingen. ALT heeft geen nadelige invloed op het resultaat van een drukverlagende operatie.

Ten aanzien van het werkingsmechanisme van ALT lijken mechanische, cellulaire en biochemische veranderingen een rol te spelen.

**Hoofdstuk 5** beschrijft een retrospectief onderzoek naar de resultaten van ALT, die verricht werd bij 433 ogen van 305 patiënten in de periode van 15 juni 1982 tot en met 24 juni 1986. Om methodologische redenen echter werden slechts de eerst behandelde ogen in de evaluatie betrokken.

In 16.4% van de ogen werd na ALT een drukverlagende operatie verricht, waarvan in een kwart vanwege een IOD stijging. Meer medicatie was in 7.5% van de ogen nodig. Ogen met secundair glaucoom werden in 45.2% van de gevallen geopereerd.

In 54.1% van de ogen trad een IOD daling van tenminste 20% op en werd een uiteindelijke IOD van 21 mm Hg of lager bereikt. De gemiddelde daling in deze ogen bedroeg 10.5 mm Hg (38.8%).

Na drukregulering was het in 40.1% mogelijk lokale medicatie te verminderen of stoppen en in 67.7% mogelijk systemische medicatie te stoppen.

In ogen met een goede IOD regulering werd in 93.3% van de gevallen geen verdere glaucomateuze papilbeschadiging en in 69.0% een stabilisering van de gezichtsvelduitval gezien.

Matige resultaten werden bereikt in ogen met low-tension glaucoom en in

ogen met secundair glaucoom; goede resultaten in ogen met het pigment dispersie syndroom en in glaucoom suspecte ogen met papilbeschadiging. Aphake en pseudophake ogen lieten minder goede resultaten zien dan phake ogen. Een progressie van het glaucoom door ALT werd in 1% gevonden.

De uitkomsten in bilateraal behandelde patiënten lieten een hoge mate van samenhang zien tussen de resultaten in beide ogen van een individu.

Voor phake ogen met primair open kamerhoek glaucoom was de succes rate hoger voor mannen dan voor vrouwen (hetgeen te wijten is aan de lagere initiële IOD die voor vrouwen bestond), gerelateerd aan de hoogte van de initiële IOD en lager wanneer voor ALT Diamox werd gebruikt. De correlatiecoëfficient tussen initiële IOD en drukdaling bedroeg 0.85.

In dit onderzoek werd, tengevolge van het gering aantal jonge patiënten, geen correlatie tussen leeftijd en succes rate gevonden.

Een eenmalige behandeling van 360° van het trabeculum gaf een significant lagere uiteindelijke IOD. Een eenmalige behandeling van 180° geeft een lagere succes rate.

Een voor ALT ongunstige configuratie van de kamerhoek in aphake ogen of in ogen met secundair glaucoom gaf een lagere succes rate. De uitkomst in deze laatste groep was leeftijdsafhankelijk.

In geval van glaucoom en concomiterend cataract dient op basis van deze bevindingen de voorkeur gegeven te worden aan eerst ALT en dan extracapsulaire cataractextractie.

Aan de hand van de resultaten in ogen met primair open kamerhoek glaucoom en in glaucoom suspecte ogen wordt over de plaats van ALT binnen het behandelingsschema van glaucoom gediscussieerd.

**Hoofdstuk 6** beschrijft een prospectief onderzoek naar het IOD verloop in de periode onmiddellijk na ALT bij 57 patiënten.

ALT werd op een gestandaardiseerde wijze verricht: behandeling van 360° van het trabeculum in 2 sessies, gescheiden door een periode van 4 weken, met in totaal 120 coagulaten van 50 µm diameter en een exposure tijd van 0.1 seconde. De coagulaten werden geplaatst op het anteriore deel van het trabeculum en het vermogen werd getitreerd op een zichtbare pigmentdispersie en luchtbelvorming. Nabehandeling vond plaats met corticosteroiden druppels. Deze techniek is thans de standaardwijze om een ALT te verrichten in onze kliniek. De IOD werd onder andere 1 uur voor, op 6 achtereenvolgende en 24

uur na ALT gemeten.

Één uur na ALT werd een tijdelijke stijging van de gemiddelde IOD gezien. Dit werd zowel na de eerste als tweede sessie, in het eerste als tweede oog en in de 3 grootste subgroepen gevonden. Na de eerste sessie werd reeds 3 uur na ALT een druk gevonden die gemiddeld lager was dan de initiële IOD. Na de tweede sessie duurde dit langer dan 6 uur.

In 50.9% van de ogen trad een IOD stijging van tenminste 5 mm Hg en in 29.8% van tenminste 10 mm Hg op na de eerste sessie. De frequenties na de tweede sessie waren niet opvallend verschillend van die na de eerste sessie. De spreiding van de hoogte van de drukstijgingen was 1 tot 22 mm Hg.

Additionele medicamenteuze therapie in verband met een IOD stijging die aan vastgestelde criteria voldeed was in 43.9% na de eerste en in 22.8% na de tweede sessie noodzakelijk.

Een significant hogere frequentie van drukstijgingen van tenminste 5 mm Hg werd gevonden in ogen met bruine irides, in ogen met iris processi en in ogen met een hoge trabeculaire pigmentatiegraad. Een significant lagere frequentie van IOD stijgingen van tenminste 10 mm Hg in ogen met een snavelbekvormige kamerhoek en in ogen waarin iris stretching werd verricht. Deze beide laatste variabelen zijn uiteraard gecorreleerd.

IOD stijgingen na de eerste en tweede sessie traden onafhankelijk van elkaar op, maar er was een statistisch significante afhankelijkheid tussen het optreden van IOD stijgingen van tenminste 10 mm Hg in beide ogen van een individu.

Voor phake ogen met primair open kamerhoek glaucoom werd een succes rate van 75.6% gevonden, bij een gemiddelde follow-up van 7 maanden. Er bestaat een statistische aanwijzing dat IOD stijgingen van tenminste 10 mm Hg in deze ogen frequenter optreden dan in ogen waarin geen goede drukregulering wordt bereikt.

In twee ogen met een IOD stijging van tenminste 5 mm Hg en een goede drukregulering werd een progressie van de gezichtsvelduitval gevonden. In de discussie wordt ingegaan op een al dan niet causaal verband.

Aan de hand van het IOD verloop na ALT en op basis van de correlatie tussen zekere gonioscopische bevindingen en het optreden van IOD stijgingen, wordt in de discussie ingegaan op een mechanische verklaring van zowel drukdaling als tijdelijke drukstijging na ALT.

## ADDENDUM 1

| | |
|---|---|
| **Demographic data:** | Patient number<br>Date of birth<br>Sex<br>Treated by |
| **Glaucoma:** | Glaucoma type<br>Date of previous cataract extraction<br>Complaints<br>Duration of glaucoma |
| **Previous therapy:** | Previous topical therapy: score<br>Carbonic anhydrase inhibitor use: yes/no<br>Previous glaucoma surgery: number and type(s) |
| **Medical history:** | General medical history<br>Ocular history |
| **Ocular examination:** | Visual acuity & refraction<br>General ocular examination<br>Gonioscopy<br>Optic disk: score<br>Visual field: stage<br>ALT indication |
| **Argon Laser Trabeculoplasty:** | Right/left eye<br>Nasal/temporal<br>180°/360°<br>Power (mW)<br>Number of coagulates<br>Iris stretching: yes/no<br>Corticosteroids: yes/no<br>Specifications |
| **Post-ALT surgery or re-ALT:** | Secondary glaucoma surgery: number and type(s)<br>Re-treatment: parameters as in initial ALT<br>Cataract extraction<br>Miscellaneous |
| **Post-ALT IOP records:** | Date<br>IOP<br>Specifications |
| **Final ocular examination:** | Date<br>IOP<br>Topical medication: score<br>Carbonic anhydrase use: yes/no<br>Visual acuity<br>Optic Disk: score<br>Visual field: stage |

## ADDENDUM 2

| | |
|---|---|
| **Demographic data:** | Patient number<br>Date of birth<br>Sex<br>Race |
| **Glaucoma:** | Glaucoma type<br>Date of cataract extraction<br>Complaints<br>Year of diagnosis<br>Time (months) not treated<br>Compliance |
| **Previous therapy:** | Previous topical therapy: score<br>Carbonic anhydrase inhibitor use: yes/no<br>Previous glaucoma surgery: number and type<br>Allergic reactions to medical therapy<br>Postoperative complications |
| **General examination and history:** | Blood pressure<br>Special child diseases<br>Diabetes mellitus<br>Arterial hypertension<br>Ischaemic heart disease<br>Transient ischaemic attacks<br>Thyroid disease<br>Migraine<br>Number of operations (general anaesthesia)<br>Medication<br>Intoxication<br>Allergies |
| **Ocular history:** | Loss of vision<br>Diplopia<br>Mouches volantes<br>Haloes<br>Scotomas<br>Metamorphopsia<br>Shadows<br>Flashing light<br>Micropsia/macropsia<br>Transient ischaemic attacks<br>Colour vision disorder<br>Nyctalopia<br>Congenital disorders<br>Pain<br>Uveitis<br>Ocular traumata<br>Ocular surgery |

**Ocular examination**

**Gonioscopy iris:**

- Colour
- Pupillary contours
- Pigment dispersion
- Atrophy
- Nodules
- Iridodonesis
- Colobomas

**Gonioscopy iridocorneal angle:**

- Angle grade
- Plateau iris
- Recession
- Scleral spur visibility
- Scleral spur aspect
- Iris processi
- Trabecular identification
- Trabecular pigmentation
- Blood in Schlemm's canal
- Prominence of Schwalbe's line
- Blood vessels
- Peripheral anterior synechiae

**Optic disk:**

- Horizontal cup/disk ratio
- Vertical cup/disk ratio
- Localized polar notching
- Localized pallor of the neural rim
- Overpass cupping
- Peripapillary atrophy
- Displaced blood vessels
- Optic disk haemorrhage
- Papilloedema

**Preoperative visual field stage**

**Argon Laser Trabeculoplasty:**

- Date
- Right/left eye
- Nasal/temporal
- Visible effect
- Power
- Number of coagulates
- Anterior localization
- Iris stretching
  - Power
  - Number of coagulates
- Haemorrhage
- Postoperative corticosteroids
- Quality
- Patient complaints
- IOP 1 hour preoperative
- IOP 1-6 hours postoperative
- Diamox postoperative

| | |
|---|---|
| | Conjunctival injection<br>Anterior chamber reaction |
| **Post-ALT IOP records:** | IOP (day 1 and day 7)<br>Conjunctival injection (day 1 and day 7)<br>Anterior chamber reaction (day 1 and day 7) |
| **Regular out-patient check-ups** | |
| **Final ocular examination:** | Date<br>IOP<br>Topical medication score<br>Carbonic anhydrase inhibitor use: yes/no<br>Visual acuity<br>Visual field stage |

# DANKWOORD

Vanaf deze plaats wil ik mijn waardering uitspreken voor allen die bijgedragen hebben aan de totstandkoming van dit proefschrift.

Helaas verbieden reglementen mij de personen te bedanken, die hun vertrouwen in mij gesteld hebben en zonder wiens hulp dit proefschrift niet geschreven zou zijn. Anderen mogen wel genoemd worden:

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## CURRICULUM VITAE

Carroll Webers werd geboren op 5 maart 1960 te Conrad (U.S.A.). Na het behalen van het diploma Atheneum-B aan de Albert Schweitzer Scholengemeenschap te Geleen, werd in 1978 begonnen met de studie geneeskunde aan de Katholieke Universiteit te Nijmegen. Het artsexamen werd behaald in mei 1985.

De basis van het in dit proefschrift beschreven onderzoek werd gelegd tijdens een keuzestage oogheelkunde als onderdeel van de postdoctorale studie geneeskunde in de kliniek voor Oogheelkunde van het St. Radboud Ziekenhuis te Nijmegen (Hoofd: Prof. Dr. A.F. Deutman). Het onderzoek werd begeleid door Dr. F. Hendrikse.

Naast de researchactiviteiten werd in de periode van 9 juli 1985 tot 1 maart 1987 de militaire dienstplicht vervuld als reserve-officier-arts bij het 473 Regionaal Geneeskundig Detachement (GCKL).

Sinds 1983 is hij getrouwd met Marianne Zaicsek en sinds oktober 1987 hebben ze een zoon, Casper.

# STELLINGEN

behorende bij het proefschrift

## ARGON LASER TRABECULOPLASTY

**-a retrospective and prospective study-**

**C.A.B. WEBERS**

I

De kans op secundaire glaucoomchirurgie na ALT is evenredig met de reeds bestaande glaucomateuze schade.

Dit proefschrift.

II

Zowel ten aanzien van het resultaat als ten aanzien van intraoculaire drukstijgingen na ALT bestaat een grote mate van afhankelijkheid tussen beide ogen van een individu.

Dit proefschrift.

III

Bij patienten met een verhoogde intraoculaire druk, zonder andere glaucoomkenmerken, dient niet zonder meer ALT uitgevoerd te worden.

Dit proefschrift.

IV

De relatie tussen intraoculaire drukstijgingen na ALT en het aspect van de voorste oogkamerhoek maakt een mechanische verklaring waarschijnlijk.

Dit proefschrift.

V

De conclusie van Rouhiainen et al. dat de trabeculaire pigmentatiegraad geen rol speelt bij het optreden van intraoculaire drukstijgingen na ALT is niet juist.

Rouhiainen, H.J. et al., Arch. Ophthalmol. 105:1352, 1987.

VI

De slechte resultaten van Wishart et al. met betrekking tot de combinatie van ALT en iris stretching berusten op een onjuiste indicatiestelling en onjuiste techniek van zowel ALT als iris stretching.

Wishart, P.K. et al., Eye 1:567, 1987.

VII

Het plaatsen van een achterste oogkamerkunstlens is niet gecontraindiceerd bij glaucoom.

VIII

Als algemene regel kan gesteld worden dat voor elke significantietoets geldt dat deze niet valide is wanneer de 'sample size' groter is dan het aantal individuen in een onderzoek.

Newcombe, R.G., and Duff, G.R., Br. J. Ophthalmol. 71:645, 1987.

IX

In sommige gevallen kan een spontane linkszijdige pneumothorax zonder medische hulpmiddelen gediagnostiseerd worden.

Eigen waarneming.

X

Toenemende bezuinigingen leiden ook in figuurlijke zin tot een verarming van de gezondheidszorg.

XI

Door laakbaar gedrag van fokkers en houders is de pit-bull terrier thans de gebeten hond.

Nijmegen, 30 september 1988