

8th EDITION

Becker-Shaffer's

Diagnosis
and **Therapy** of the
Glaucomas

Robert L Stamper
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Foreword

In 1961, Robert N Shaffer and Bernard Becker published the first edition of this book, which has become a classic guide for the practical management of glaucoma. At that time, glaucoma was generally believed to be a disease that could be diagnosed by the level of intraocular pressure alone. The early and progressive changes in the optic disc, although previously described, were not widely recognized or appreciated. Optic disc photography was available but was seldom used. Visual fields were examined by practitioners with varying skills, using a variety of techniques, but there was no standardization to the process. Medical treatment was limited to a few drugs, which often caused uncomfortable or even serious side effects. Surgery for open-angle glaucoma involved full-thickness procedures with a common postoperative course of hypotony, flat anterior chamber, and choroidal detachment. Most importantly, there was no systematic approach to the diagnosis, classification, and management of these diseases. Such an approach was presented in the first edition, and that may have been its greatest contribution. Practitioners received a guidebook written by knowledgeable clinicians that

could be easily understood and followed to clarify the management of these complex diseases grouped together under the heading of glaucoma.

Nearly 50 years later, there have been seven authors of new editions of this textbook. All of the authors were trained or influenced by Drs Becker and Shaffer. All of the authors pursued the goal of a book that is simple to understand and can be a guide to the busy practitioner. The eighth edition presents new material on epidemiology, genetics, pathophysiology, psychophysical testing of visual function, optic disc and nerve fiber layer imaging, clinical trials, preferred practice plans, medication, and surgery. The information is updated, but the goal of the book remains the same – a practical guide to the management of glaucoma for the practitioner. We believe Drs Stamper, Lieberman, and Drake succeeded admirably in meeting this goal.

H Dunbar Hoskins, Jr, MD
Michael A Kass, MD

Preface

This book has a proud history. It has served as a guide for treating patients with glaucoma to ophthalmologists and other eye care providers throughout the world for more than four decades. The book was originally conceived and written by Drs Bernard Becker and Robert N Shaffer. It was later revised through multiple editions by Allan Kolker and John Hetherington Jr and, more recently, by H Dunbar Hoskins Jr and Michael A Kass. This eighth edition, as well as the seventh edition, is the product of the second and third generation of glaucoma specialists who trained and/or practiced in St Louis or San Francisco, and thus were privileged to be mentored by the original authors as well as their second generation students.

We have followed the lead of our mentors to summarize our clinical experience with glaucoma and to interpret in a practical way the current, voluminous literature about glaucoma and its management. Our understanding of glaucoma and its treatment have undergone significant change in the last two decades. In the last decade alone, significant advances have been made in epidemiology, genetics, and pathophysiology. Diagnosis has been augmented by more sophisticated intraocular pressure measurement, psychophysical testing, and optic nerve analysis. Imaging of the optic nerve and the anterior segment has become widely utilized. The classification of the glaucomas has been updated to reflect the new findings in genetics, diagnostic modalities and epidemiology, compelling us all to reassess risk factors and to entertain the diverse influences on glaucoma's manifestations. Treatment has undergone a major change due to new pharmaceutical agents and innovative surgical options. Therefore, the book has undergone an extensive updating with expanded text, bibliography and illustrations. Our overarching goal in writing has been to provide the reader

guidance in conceptualizing the sciences of diagnosis and in individualizing the choices for treatment. Glimpses into the possible intervention of the future are given. We hope that the reader, like us authors, will come to humbly understand what we do and still do not know about the glaucomas.

In one major aspect, this edition differs from previous editions. Because of the exponentially expanding knowledge base related to glaucoma, we three principal authors recognized our individual limitations of expertise and called on our colleagues for assistance in specific areas. We wish to gratefully acknowledge and thank Drs Murray A Johnstone, Michael S Berlin, John Samples, Jeanette Hyer, Robert J Noecker and Larissa Camejo for their contributions, respectively, on aqueous outflow physiology, laser treatment, genetics, and optic nerve imaging. They have graciously authored or reviewed the respective chapters of their expertise. However, we have tried to maintain what has always made the Becker-Shaffer texts so appealing: the coherence of an authored, rather than an edited, text, explicating how we three glaucoma consultants apply the literature and our experience to the management of patients.

As in previous editions, our emphasis has been to provide, in one comprehensive volume, information from the clinician's viewpoint, to enable an individual engaged in the management of the glaucomas to do so effectively and with understanding. Ultimately, our goal is to reduce vision loss and improve the quality of life for our patients.

Robert L Stamper, MD
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And to all of our former, current and future ophthalmology residents at California Pacific Medical Center and the University of California San Francisco: we gratefully acknowledge the pleasure of learning together for the benefit of all our patients, now and in the future.

Dedication

We dedicate this book to our families, whose love, devotion, support, patience and sacrifice made this multi-year project, as well as most of our other accomplishments, possible.

Robert L Stamper

In memory of my parents Alfred and Netsy, with love for my brothers Victor and Elias, and with blessings for my son Michael and his cousins.

Marc F Lieberman, MD

To Brenda Drake and to Christopher and Sean Drake

Michael V Drake

And to our teachers, especially Drs. Becker and Shaffer, whose wisdom and encouragement have been a source of inspiration and strength; to our students, who help us continue learning; and to our patients, who constantly stimulate our search for better ways of managing their glaucoma.

In Memorium

ROBERT N SHAFFER, MD 1912–2007



One of the world's great physicians and glaucomatologists died on July 13, 2007. Robert N Shaffer, born in Meadville, PA in 1912, became one of the last century's leading glaucoma experts, clinicians, teachers and researchers. After receiving his medical degree and residency in ophthalmology from Stanford University School of Medicine while it was still in San Francisco, he established a practice in San Francisco which ultimately evolved into a center for excellence in patient care. He dedicated his career to the understanding and managing of the glaucomas. His keen powers of observation led to many clinical gems that are still in use today, including the Van Herrick-Shaffer slit lamp estimation of angle depth and the Shaffer classification of gonioscopic angle appearance. One of his proudest creations was the fellowship in his office that gave highly personal training to many of the next generation of glaucoma specialists from around the world: over 40 world leaders in glaucoma served as fellows in his office.

He was a prolific writer. In addition to his dozens of peer-reviewed articles in ophthalmic journals, he, together with Dr Bernard Becker, one of the other giants of glaucoma teaching and research of the last century, began what was to become one of the definitive textbooks on glaucoma – *The Diagnosis and Therapy of the Glaucomas*. This textbook, now named *Becker-Shaffer's Diagnosis and Therapy of the Glaucomas*, is currently in its eighth edition. He also served on the American Board of Ophthalmology, becoming its chairman and ultimately its executive vice-president.

Together with his partners, Drs John Hetherington and Dunbar Hoskins, he founded the Glaucoma Research Foundation which is dedicated to glaucoma research and education. Its mission is to find a cure for glaucoma and toward that end it has funded many promising pilot research projects.

Bob was a consummate teacher. In addition to his fellows, he trained residents at the University of California San Francisco where he was on the clinical faculty for over thirty years. They rotated through his office, seeing first hand his very personal brand of care as well as his clinical and surgical approaches to glaucoma. He lectured around the USA and the world, always presenting his material in an unsensational, fair, and illuminative fashion. His childhood sweetheart and wife, Virginia Shaffer, truly a life partner in so many of his activities, had a hand in making his lectures so enjoyable and educational, as she was herself an expert in public speaking and helped educate many of his fellows and residents in that skill.

One of his most memorable characteristics was his courtly, quiet and unfailingly unflappable (except on the tennis court) manner. He was truly a gentleman in all the very best meanings of the term. Those of us who were privileged to know him were enriched by his presence. He and his style of patient-centered care, bedside teaching and diplomacy will be sorely missed.

Introduction and classification of the glaucomas

DEFINITIONS

The concepts and definitions of glaucoma have evolved in the past 100 years,¹ and still they remain imprecise and subject to technical qualifications. The word *glaucoma* originally meant ‘clouded’ in Greek; as such, it may have referred either to a mature cataract or to corneal edema that might result from chronic elevated pressure. Today the term does not refer to a single disease entity, but rather to a group of diseases that differ in their clinical presentation, pathophysiology, and treatment. These diseases are grouped together because they share certain features, including cupping and atrophy of the optic nerve head, which has attendant visual field loss and is frequently related to the level of intraocular pressure (IOP).

In this text, glaucoma is defined as a disturbance of the structural or functional integrity of the optic nerve that can usually be arrested or diminished by adequate lowering of IOP. An important distinction must be noted in the criteria currently used to define primary open-angle glaucoma (POAG), in contrast to all other forms of glaucoma. Primary open-angle glaucoma is explicitly characterized as a multifactorial optic neuropathy with ‘a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons’² developing in the presence of open anterior chamber angles, and manifesting characteristic visual field abnormalities. In contrast, all other types of glaucoma – invariably the secondary glaucomas, and historically even the primary angle-closure glaucomas^{2b} – are defined first and foremost by the *presence of elevated IOP*, and not in reference to the optic neuropathy that follows sustained elevated IOPs.

Classically the primary glaucomas are not associated with known ocular or systemic disorders that account for the increased resistance to aqueous outflow; the primary diseases are usually bilateral and probably reflect genetic predispositions.³ Conversely, the secondary glaucomas are associated with ocular or systemic abnormalities responsible for elevated IOP; these diseases are often unilateral and acquired. Some have argued that the distinctions between ‘primary’ and ‘secondary’ simply reflect our imperfect understanding of pathophysiologic events that converge in the common final pathway of optic atrophy and visual field loss.⁴ Although many risk factors have been associated with the development of POAG (Table 1-1), elevated IOP remains the most prominent factor – shared among the primary and secondary glaucomas – and the only factor contemporary ophthalmic intervention can reliably affect.

Intraocular pressure is determined by the balance between the rate of aqueous humor production of the ciliary body, the resistance to aqueous outflow at the angle of the anterior chamber, and the level of episcleral venous pressure (Fig. 1-1). Elevated IOP is

usually caused by increased resistance to aqueous humor outflow. The optic nerve and visual field changes of glaucoma are determined by the resistance to damage of the optic nerve axons.

In most cases of glaucoma, progressive changes in the visual field and optic nerve are related to increased IOP; in some instances even ‘normal’ levels of IOP are too high for proper functioning of the optic nerve axons. (The concept of ‘normal’ must take into account both the range of IOPs for different ethnic groups as well as the correction factors for applanation tonometric measurements in the presence of thicker or thinner central corneal thicknesses.)^{5,20} Although there is no absolutely ‘safe’ pressure that guarantees to prevent progression of POAG,²¹ lowering IOP to the low-normal range usually arrests or slows the progress of glaucoma.^{22–26} If the glaucoma continues to progress, it is postulated that either (1) the IOP is not low enough or sufficiently free of fluctuations to stabilize the disease; or (2) the optic nerve and/or ganglion cells are so damaged that the cascade of deterioration persists, independently of IOP levels.

EPIDEMIOLOGIC AND SOCIOECONOMIC ASPECTS OF THE GLAUCOMAS

Whether manifesting as POAG, primary angle-closure, or congenital disease, glaucoma is the second leading cause of blindness worldwide, with a disproportional morbidity among women and Asians.^{27–30} Globally, POAG affects more people than angle-closure glaucoma (ACG) – with an approximate ratio of 3:1, and wide variations among populations.²⁹ Yet ACG manifests in a much more aggressive and debilitating course (especially among Asians) than was recognized a generation ago: its treatment usually requires more than iridotomy alone, frequent medical or surgical intervention³¹; and yet nevertheless ACG often leads to an appalling amount of morbidity (e.g., ACG accounts for less than half of all glaucoma cases in China, but over 90% of its glaucoma blindness).^{32–36}

In the United States, glaucoma of all types is the second leading cause of legal blindness, often despite the availability of excellent long-term management.³⁷ Among white and black populations in the US, POAG accounts for nearly two-thirds of all reported glaucoma cases.^{38–40} It is estimated that 2.25 million people in the US over the age of 40 years have POAG,^{41,42} half of whom are unaware of their disease despite demonstrable visual field loss.^{43–45} Another 10 million Americans are estimated to have IOPs greater than 21, or other risk factors for developing the disease: approximately 10% of these eyes will convert to POAG over the course of a decade.⁴⁶

Table 1-1 Risk factors for primary open-angle glaucoma		
Factor	Quality of evidence	Remarks
<i>Ocular risk factors</i>		
Intraocular pressure	Excellent	Most important
Thinner central corneal thickness	Excellent	Related to IOP and to optic nerve?
Myopia	Excellent	Related to IOP and to optic nerve?
Disc hemorrhage	Good	Prognostically important
Increased cup/disc ratio	Equivocal	May represent early POAG
Asymmetric cupping	Equivocal	May represent early POAG
<i>Non-ocular risk factors</i>		
Age	Excellent	Causal mechanisms unknown
Race (e.g. African or Hispanic descent)	Excellent	Causal mechanisms unknown
Family history	Excellent	Multifactorial genetic factors
Adult onset diabetes	Equivocal	Elevated IOPs, but 'protective' of ganglion cells?
Diastolic perfusion pressure	Excellent	Biologically plausible
Migraine and peripheral vasospasm	Equivocal	More relevant in 'low-tension' disease?
Gender	Inadequate	Contradictory reports
Alcohol consumption	Inadequate	Requires confirmation
Cigarette smoking	Inadequate	Requires confirmation
Data from References 2, 5-19.		

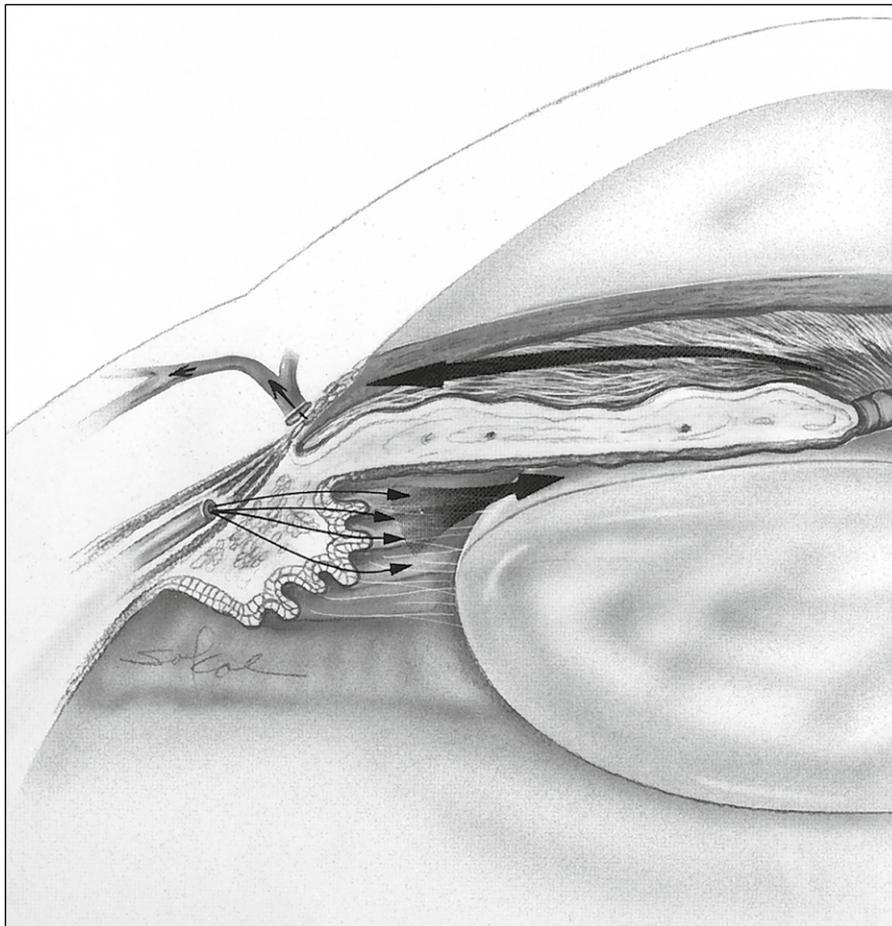


Fig. 1-1 Anterior segment of the eye. Aqueous humor is formed by the ciliary body epithelium, passes between the iris and lens to enter the anterior chamber, and leaves the eye through the trabecular meshwork and Schlemm's canal.

The relationship between IOP and glaucomatous optic neuropathy is complex. On the one hand, the higher the IOP, the higher the risk of POAG; conversely, 1 out of 6 eyes with POAG never demonstrates IOP higher than the age-appropriate normal range.^{47,48}

The complexity of the multiple parameters and variables converging in 'glaucoma' diagnosis and prognosis has led to a recent wealth of rigorously derived epidemiological data embracing the spectrum of early and advanced disease. Many of these studies are known by their acronyms and address a wide range of risk factors, with a focus on clinical applicability.^{49–53} Although these large, controlled studies were conducted in Western countries, their findings are directly applicable to addressing the management of glaucoma in the developing world as well.⁵⁴

In brief: both the Ocular Hypertension Treatment Study (OHTS) and the Early Manifest Glaucoma Trial (EMGT) addressed the value in early detection and treatment of POAG. The OHTS study refined the parameters of predictive risk factors such as central corneal thickness, age, and life expectancy for elaboration of treatment decisions.^{55–57} The EMGT study unequivocally demonstrated that early treatment delayed disease progression, in contrast to an untreated control population; and that disease progression correlated with the higher the presenting IOP.^{58,59}

The effects and parameters of various interventions in eyes with established glaucomatous damage were addressed by the Collaborative Initial Glaucoma Treatment Study (CIGTS), the Advanced Glaucoma Intervention Study (AGIS), and the Collaborative Normal Tension Glaucoma Study (CNTGS). The CIGTS demonstrated that substantial IOP reductions (40–48% with medications or surgery, respectively) preserved visual function in most patients.⁶⁰ The AGIS reports demonstrated the efficacy both of reduced IOP fluctuation and of subnormal IOPs (below 14 mmHg post-operatively, and reliably under 18 mmHg during 6 years' follow-up) in stabilizing advanced visual field loss.^{60b,60c} Similarly the CNTGS, in randomizing 'low-tension glaucoma' patients with advanced field loss to aggressive treatment or not, found that a 30% IOP reduction stabilized most visual fields, although post-surgical cataract vision loss was frequent.^{61,62}

Though the applicability of each particular study is discussed in greater detail in later chapters, it is worthwhile to discuss how our understanding of *risk* is evolving.

RISK FACTORS

A brief review of epidemiological distinctions is required to help the clinician contextualize the bewildering array of well-designed studies continuously appearing in the ophthalmic literature.^{63–67} A few basic clarifications are useful to bear in mind^{68,69}:

1. Causation is neither always linear nor applicable to individuals; 'risk factors' are not synonymous with 'causes' of disease.

2. Pathways of risk have multiple branches, sometimes converging or diverging: e.g., gender and ethnicity are *static* variables; IOP and blood pressure are *dynamic* variables (which may be either interactive or independent); different *disease stages*, whether early or advanced, may respond variably; and statistical *strength of association* may be more relevant to populations than to individuals.

3. Some risk categories are an aggregate of unspecified variables. For example, 'age' is frequently a surrogate for all time factors: aging of tissues; time of exposure to other risk factors; duration of disease; and it is variously presented as time since diagnosis, or length of

follow-up, or age of onset. Similarly 'family history' may reflect complex information about ethnicity, or multiple inherited factors which may or may not be independent: optic disc parameters; IOP levels; central corneal thickness; personal habits and attitudes towards disease risks and treatment; refractive errors; gene mutations, etc.

4. Risk factors for disease *incidence* are not necessarily the same as those for disease *progression*, nor for *response to therapeutics*. Hypertension, for example, is not associated with developing glaucoma in young patients, but it is with older hypertensives (specifically as disordered diastolic perfusion pressure)⁶; and yet in established glaucoma, systemic hypertension is not a risk for disease progression. Currently there is great interest in elaborating 'global risk assessments' for identifying ocular hypertensive patients converting into POAG.^{70,71,71b} Of enormous public health import for predicting progression is determining those factors contributing not to the conversion into glaucoma, but which lead to *blindness*; such factors include advanced field loss at the time of presentation, African ethnicity, and clinical non-compliance. Less well studied are risk factors for therapeutic responsiveness, such as thicker corneas, male gender, and lower socioeconomic status. Table 1.1 lists those factors that have demonstrated, to a greater or lesser extent, statistical correlation with either the development or the progression of POAG.

In contrast to the precision inherent in the exploding field of ophthalmic genetics,^{72,73} there is considerable controversy and confusion about the heritable parameters of 'ethnicity' and 'race,' technically being devoid of distinctive genetic substrates.^{7,74} Besides the value of these categories as markers for patterns of risk or effect in larger populations, from which hopefully more precise mechanisms will one day be elucidated, they also highlight the importance of individualizing the care of each patient, sensitively attending to the impact of heredity and of culture for the specific patient at hand.

Yet much of the epidemiological literature of the past several decades deals explicitly with the categories of race and ethnic background, characterized by comprehensive population-based studies with rigorous criteria for pressure measurements, angle evaluation, and disc and visual field assessment.^{8–10,75,76} These studies consistently report a prevalence rate for POAG in 1–2% of white adults. However, significant racial differences exist. Among blacks, the prevalence is nearly 4 times higher.⁴³ These patients are twice as likely to be blind as their white counterparts, and they have the disease nearly 27% longer.^{39,77} These facts reflect neither the supply of ophthalmologists nor the patient's personal income.⁷⁸ Even higher rates have been reported among some Caribbean populations,^{11,79,80} although there are lower and more variable prevalence rates among the genetically heterogeneous African populations from whom these New World populations descended.⁸¹

With the basic medical resources available in the developed world,⁴⁸ the 'holy grail' for clinicians is that all cases of blindness from glaucoma are preventable if the disease is detected early and proper treatment is implemented. Detection depends on education – educating the public about the importance of routine examinations, and training fellow health professionals to recognize the signs and symptoms of glaucoma. Screening strategies that rely only on IOP measures and that neglect disc and visual field assessment are inadequate⁸²; and even when full testing is performed, it may not be cost-effective.⁸³ Pending the widespread appearance of expanded and effective public health interventions, the individual clinician can be enormously successful in detecting undiagnosed glaucoma, simply by facilitating the ophthalmological examination of close relatives of existing glaucoma patients – especially siblings and older immediate family members.^{84,85}

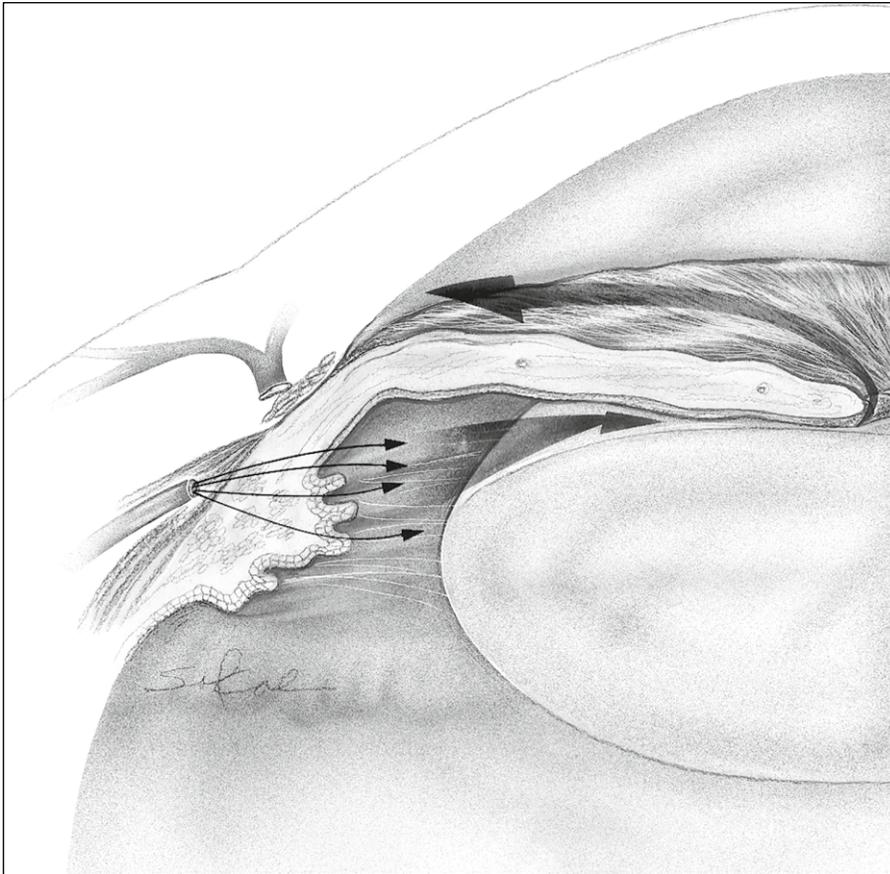


Fig. 1-2 In angle-closure glaucoma, the peripheral iris covers the trabecular meshwork, obstructing aqueous humor outflow.

CLASSIFICATION OF THE GLAUCOMAS

The most widely used classification system of the glaucomas separates angle-closure glaucoma from open-angle glaucoma. This fundamental distinction still holds, but with altered emphasis regarding the former condition. Historically, angle-closure disease has been variably defined in terms of pupillary block mechanisms (e.g., ‘miotic induced’), presenting signs and symptoms (e.g., ‘congestive’), or the presumptive time-course of the condition (e.g., ‘subacute’). The most contemporary approach continues to emphasize the final pathogenic pathway mechanism of irido-trabecular obstruction that results in functional angle closure.⁸⁶ But abetted by technologies that allow direct visualization of angle, lens, and anterior ciliary body structures, the current classification is an amalgam of both a natural history scheme that emphasizes progressive stages of disease, and a mechanistic scheme focusing on discrete sites of dysfunction in the anterior segment (Fig. 1-2).

In open-angle glaucoma, there is relative impairment of flow of aqueous humor through the trabecular meshwork–Schlemm’s canal–venous system; yet on gonioscopy the angle appears to be open (Fig. 1-3). But amidst all the details of classification, one must never lose sight of the ultimate final pathway in *all* glaucoma as manifest optic nerve damage and ganglion cell demise.

This basic classification scheme continues to be helpful because it clarifies pathogenetic mechanisms and therapeutic approaches. We propose to simplify glaucoma classification into three major divisions, which are subdivided into primary and secondary categories: (1) angle-closure glaucoma; (2) open-angle glaucoma; and

(3) developmental glaucoma, in which some anomaly of the anterior segment manifests in the first years of life. The category of ‘combined-mechanism glaucoma’ historically referred to either sequential or coincidental presentations of entities from these three basic categories, and usually involved angle-closure mechanisms; hence we relegate these idiosyncratic cases among the secondary angle-closure glaucomas.

A similar classification system divides glaucoma into conditions that affect the internal flow, and conditions that affect the outflow of aqueous humor. Internal flow block is caused by such conditions as pupillary block or malignant glaucoma. Outflow block occurs with diseases of the trabecular meshwork (e.g., neovascularization) or that compromise Schlemm’s canal, collector channels, and the venous system (e.g., elevated episcleral venous pressure).

Alternative classification systems⁴ are based on other features of the diseases, including (1) the site of the outflow obstruction, which is divided into diseases that affect the pre-trabecular passage of aqueous humor (e.g., posterior synechiae to the lens after ocular inflammation), the trabecular flow (e.g., glaucoma after administration of α -chymotrypsin), and the post-trabecular movement of aqueous humor (e.g., increased episcleral venous pressure from a carotid-cavernous sinus fistula); (2) the tissue principally involved (e.g., glaucoma caused by diseases of the lens or diseases of the retina); (3) the proximal initial events (e.g., steroid glaucoma); and (4) the age of the patient (e.g., congenital, juvenile). Specific diseases have also been subclassified, such as POAG types, based on various appearances of the damaged optic nerve,⁸⁷ or classification of disease stages by visual field damage,^{87b} or the angle-closure glaucomas, based on IOP levels and gonioscopic configurations as correlated with ultrasonic biomicroscopy.⁸⁸

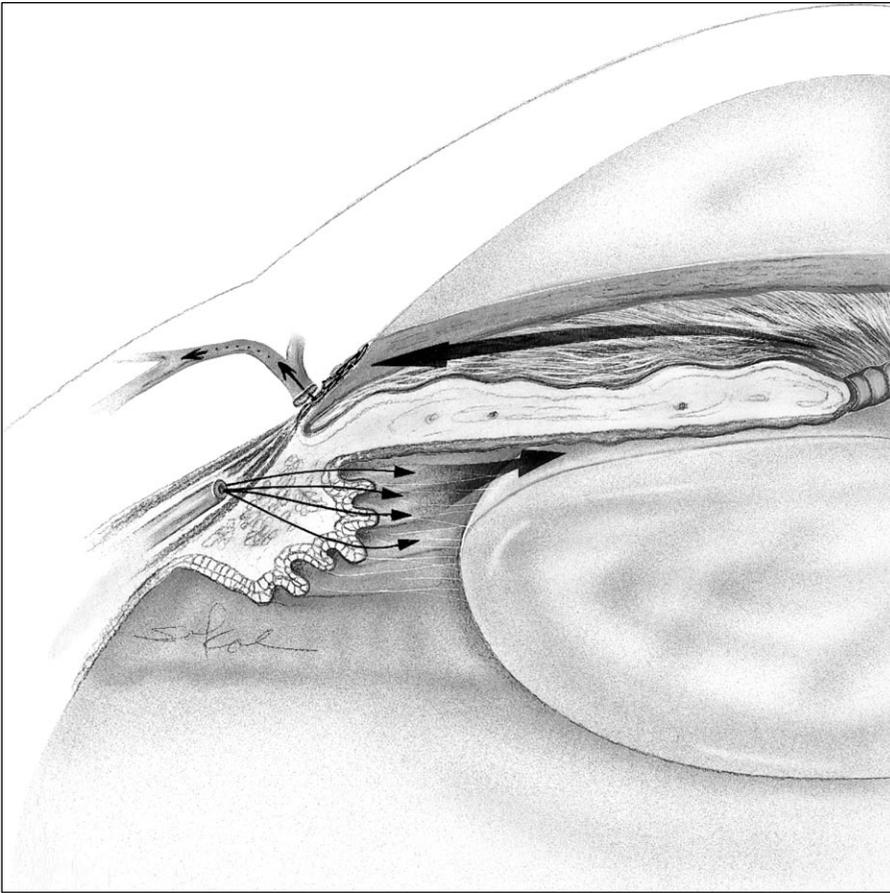


Fig. 1-3 In open-angle glaucoma, there is impaired flow of aqueous humor through the trabecular meshwork-Schlemm's canal-venous system.

The reader is cautioned that all classification schemes are arbitrary and limited. Some cases do not fit neatly into one category or another. The classification that follows is not meant to be all-inclusive, but to be an aid in thinking about pathogenesis and treatment.

I. Angle-closure glaucoma

A. Primary angle-closure disease

Irido-trabecular contact is the final common pathway of angle closure disease, obstructing aqueous outflow; it can be conceptualized in two complimentary schemes:

1. Natural history
 - a. Primary angle closure *suspect*
 - b. Primary angle *closure*
 - c. Primary angle-closure *glaucoma*
2. Anterior segment mechanisms of closure
 - a. Iris-pupil obstruction (e.g., 'pupillary block')
 - b. Ciliary body anomalies (e.g., 'plateau iris syndrome')
 - c. Lens-pupil block (e.g., 'phacomorphic block' (swollen lens or microspherophakia))

B. Secondary angle-closures

1. Anterior 'pulling mechanism'

The iris is pulled forward by some process in the angle, often by the contraction of a membrane or peripheral anterior synechiae.

- a. Neovascular glaucoma
- b. Iridocorneal endothelial syndromes (e.g., Chandler's syndrome)

- c. Posterior polymorphous dystrophy
- d. Epithelial downgrowth
- e. Fibrous ingrowth
- f. Flat anterior chamber
- g. Inflammation
- h. Penetrating keratoplasty
- i. Aniridia

2. Posterior 'pushing mechanism'

The iris is pushed forward by some condition in the posterior segment. Often the ciliary body is rotated anteriorly, allowing the lens to come forward also.

- a. Ciliary block glaucoma (malignant glaucoma)
- b. Cysts of the iris and ciliary body
- c. Intraocular tumors
- d. Nanophthalmos
- e. Suprachoroidal hemorrhage
- f. Intravitreal air injection (e.g., retinal pneumopexy)
- g. Ciliochoroidal effusions (e.g., panretinal photocoagulation)
 - (a) Inflammation (e.g., posterior scleritis)
 - (b) Central retinal vein occlusion
- h. Scleral buckling procedure
- i. Retrolental fibroplasias

II. Open-angle glaucoma

A. Primary open-angle glaucoma

1. IOPs higher than 'normal range'
2. IOPs within 'normal range' (low-tension glaucoma)

- B. Secondary open-angle glaucoma
1. Pigmentary glaucoma
 2. Pseudoexfoliation glaucoma
 3. Steroid glaucoma
 4. Lens-induced glaucoma
 - a. Phacolytic glaucoma
 - b. Lens-particle glaucoma
 - c. Phacoanaphylaxis
 5. Glaucoma after cataract surgery
 - a. α -Chymotrypsin glaucoma
 - b. Glaucoma with viscoelastics
 - c. Glaucoma with pigment dispersion and intraocular lens
 - d. UGH syndrome (uveitis + glaucoma + hyphema)
 - e. Glaucoma after neodymium:yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy
 - f. Glaucoma with vitreous in anterior chamber
 6. Glaucoma after trauma
 - a. Chemical burns
 - b. Electric shock
 - c. Radiation
 - d. Penetrating injury
 - e. Contusion injury
 7. Glaucoma associated with intraocular hemorrhage
 - a. Ghost cell glaucoma
 - b. Hemolytic glaucoma
 - c. Hemosiderosis
 8. Glaucoma associated with retinal detachment
 9. Glaucoma after vitrectomy
 - a. Intraocular gas
 - b. Intraocular silicone oil
 10. Glaucoma with uveitis
 - a. Fuchs' heterochromic iridocyclitis
 - b. Glaucomatocyclitic crisis (Posner-Schlossman)
 - c. Precipitates on trabecular meshwork (trabeculitis)
 - d. Herpes simplex
 - e. Herpes zoster
 - f. Sarcoidosis
 - g. Juvenile rheumatoid arthritis
 - h. Syphilis
 - i. Human immunodeficiency virus (HIV) infection
11. Glaucoma with intraocular tumors
- a. Malignant melanoma
 - b. Metastatic lesions
 - c. Leukemia and lymphoma
 - d. Benign lesions (e.g., juvenile xanthogranuloma, neurofibromatosis)
12. Amyloidosis
13. Increased episcleral venous pressure
- a. Obstruction of venous drainage (e.g., superior vena cava obstruction)
 - b. Arteriovenous fistula (e.g., carotid cavernous)
 - c. Ocular episcleral venous anomalies (e.g., Sturge-Weber syndrome)
- III. Developmental glaucoma
- Anomalies of the anterior segment are present at birth. Glaucoma may be present at birth or may appear in the first decades of life (see Ch. 20 for detailed classification of pediatric glaucoma diseases).*
- A. Primary congenital (infantile) glaucoma
1. Congenital glaucoma
 2. Autosomal dominant juvenile glaucoma
 3. Glaucoma associated with systemic abnormalities
 4. Glaucoma associated with ocular abnormalities
- B. Secondary glaucoma
1. Traumatic glaucoma
 2. Glaucoma with intraocular neoplasm
 3. Uveitis glaucoma
 4. Lens-induced glaucoma
 5. Glaucoma after congenital cataract surgery
 6. Steroid-induced glaucoma
 7. Neovascular glaucoma
 8. Secondary angle-closure glaucoma
 9. Glaucoma with elevated episcleral venous pressure
 10. Glaucoma secondary to intraocular infection

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Aqueous humor formation

FUNCTION OF AQUEOUS HUMOR

Aqueous humor was originally thought to be stagnant. It was not until 1921 that Seidel proved that the aqueous was, indeed, circulating. Using a needle, Seidel connected a reservoir containing a blue dye to a rabbit eye. When the reservoir was lowered, clear fluid from the anterior chamber entered the tubing; when the reservoir was raised, the dye entered the eye and eventually appeared in the blood of the episcleral venous plexus.^{1,2} Seidel concluded that aqueous humor must be continuously formed and drained. Two decades later, Ascher showed that aqueous humor enters the venous system at the limbus through the aqueous veins and first flows alongside the bloodstream in a laminar fashion before mixing completely with the blood in the veins.³ Ashton studied neoprene casts of Schlemm's canal and the aqueous veins and demonstrated a direct connection between these two structures.⁴ From the work of the last half century it is clear that aqueous humor is a relatively cell-free, protein-free fluid that is formed by the ciliary body epithelium in the posterior chamber. It then passes between the iris and the lens, enters the anterior chamber through the pupil, and exits the eye at the anterior chamber angle through the trabecular meshwork, Schlemm's canal, and the aqueous veins. In the anterior chamber, the aqueous humor is subject to thermal currents because of the temperature difference between the iris and the cornea; aqueous rises close to the warmer iris and descends close to the cooler cornea. This convection current may easily be seen clinically when there are cells or pigment in the anterior chamber, and explains the relatively inferior location of pigment deposition (Krukenberg spindle) and keratic precipitates on the inner surface of the cornea.

During its passage through the eye, the aqueous humor serves a number of important functions. It serves in lieu of a vascular system for the normally avascular structures of the eye, including the cornea, lens, and trabecular meshwork. It brings to the internal eye essential nutrients, such as oxygen, glucose, and amino acids,⁵ and removes metabolites and potentially toxic substances, such as lactic acid and carbon dioxide.^{6,7} Aqueous humor provides the proper chemical environment for the tissues of the anterior segment of the eye and provides an optically clear medium to allow good visual function. It inflates the globe and maintains intraocular pressure (IOP), both of which are important for the structural and optical integrity of the eye. In many species, including humans, aqueous humor contains a very high concentration of ascorbate, which may act to scavenge free radicals and protect the eye against the effects of ultraviolet and other radiation. Under adverse conditions (e.g., inflammation, infection), it facilitates cellular and humoral immune responses. During

inflammation, the rate of aqueous humor formation decreases, and its composition is altered to permit accumulation of immune mediators (Box 2-1).

Several risk factors probably contribute to damaging the optic nerve with its resultant visual loss in glaucoma. Intraocular pressure that is too high for the continued health of the nerve is universally accepted as one of the most important of those risk factors. Therefore the study of those elements that contribute to the creation, maintenance, and variation of IOP is material to the understanding of the pathophysiology of this disease. Aqueous formation (F), facility of outflow (C), and episcleral venous pressure (P_v) are the major intraocular determinants of IOP. These factors are related to one another by the Goldmann equation:

$$P_O = F/C + P_v$$

or if solving for F:

$$F = (P_O - P_v)C$$

in which P_O is the IOP in the undisturbed eye in mmHg, aqueous formation is in $\mu\text{l}/\text{min}$, the facility of outflow is in $\mu\text{l}/\text{min}/\text{mmHg}$, and the episcleral venous pressure is in mmHg. From the equation, it is evident that IOP will increase when the aqueous formation rate increases, the episcleral venous pressure increases, or the outflow facility decreases. More recently, with the discovery of a pressure-independent outflow mechanism(s) (the uveoscleral pathway being the main one), the equation has had to be modified and is better stated:

$$F = (P_O - P_e)C + U$$

where P_e is the sum of the external pressure such as episcleral venous pressure and other tissue pressures outside the eye, and U is the sum of the pressure-independent outflow pathways.⁸

Box 2-1 Functions of aqueous humor

- Brings oxygen and nutrients to cells of lens, cornea, iris
- Removes products of metabolism and toxic substances from those structures
- Provides optically clear medium for vision
- Inflates globe and provides mechanism for maintaining intraocular pressure
- High ascorbate levels protect against ultraviolet-induced oxidative products, e.g., free radicals
- Facilitates cellular and humoral responses of eye to inflammation and infection

ANATOMY OF THE CILIARY BODY

STRUCTURE

The ciliary body is the portion of the uveal tract that lies between the iris and the choroid (Fig. 2-1). On cross-section, the ciliary body has the shape of a right triangle. It is attached anteriorly to the scleral spur, creating a potential space (supraciliary space) between itself and the sclera. The iris inserts into the short anterior side of the ciliary body, leaving a narrow width of ciliary face visible on gonioscopy between the peripheral iris and the scleral spur. The lens is attached to the ciliary body by the zonules, which separate the vitreous compartment posteriorly from the aqueous compartment anteriorly (Fig. 2-2). The iris in turn divides the aqueous space into the posterior and anterior chambers. The junction of the iris, sclera, and cornea is called the anterior chamber angle.

The ciliary body is composed of muscle, vascular tissue, and epithelium. The ciliary muscle consists of three separate muscles – the longitudinal (meridional), the oblique (radial or intermediate), and

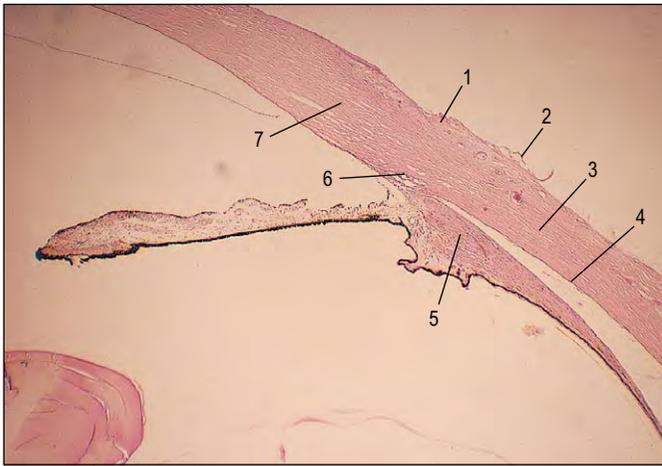


Fig. 2-1 Light micrograph of the anterior segment of the eye showing 1, Tenon's capsule; 2, episclera; 3, sclera; 4, lamina fusca; 5, ciliary body; 6, Schlemm's canal; and 7, peripheral cornea. (Courtesy of William H Spencer, MD.)

the circular (sphincteric). The longitudinal muscle attaches anteriorly to the scleral spur and trabecular meshwork and posteriorly to the suprachoroidal lamina, with some fibers connecting to the choroid and sclera as far posteriorly as the equator of the globe. When the longitudinal muscle contracts, it pulls open the trabecular meshwork and Schlemm's canal. The circular muscle fibers run parallel to the limbus. When these fibers contract they relax the zonules, allowing the lens to change shape. The radial muscle connects the longitudinal and circular muscles. The function of the radial muscle is not entirely clear, but it is postulated that contraction of the radial fibers may widen the uveal trabecular spaces. It is possible that some or all of the insertions of these ciliary muscle tendons are into an elastic fibrillar network which makes the resultant actions difficult to sort out.⁹

The ciliary body runs from the scleral spur to the ora serrata, a distance of approximately 6 mm (see Fig. 2-1). The posterior portion of the ciliary body has a relatively flat inner surface and is named the pars plana. The anterior portion of the ciliary body has approximately 70 to 80 radial ridges (the ciliary processes) on its inner surface and is named the pars plicata (Fig. 2-3). The ciliary processes are approximately 2 mm in length, 0.5 mm in width, and 0.9 mm in height.¹⁰ The surface area of the pars plicata is estimated to be 5.7 cm² in rabbits¹¹ and 6 cm² in humans.¹² Thus the pars plicata has a large surface area (approximately five times the surface area of the corneal endothelium) for both active fluid transport and ultrafiltration.

Because of the invagination of the embryonic optic vesicle, the inner surfaces of both the pars plana and the pars plicata are lined by two layers of epithelium – an outer pigmented layer that is continuous with the retinal pigment epithelium, and an inner non-pigmented layer that is continuous with the retina (Fig. 2-4). The two layers of the epithelium have their apical surfaces in apposition.

ULTRASTRUCTURE OF THE CILIARY PROCESSES

Each ciliary process is composed of a central core of stroma and capillaries covered by a double layer of epithelium (see Fig. 2-4B).¹¹ The capillary endothelium is thin and has tiny fenestrae that face toward the pigmented ciliary epithelium. The capillary endothelium is surrounded by a basement membrane that contains mural cells (pericytes).

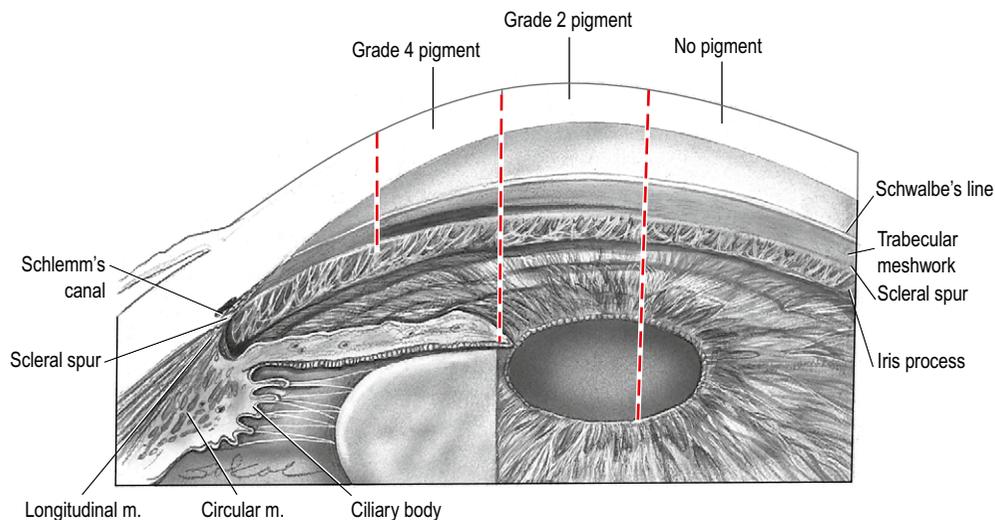


Fig. 2-2 Schematic view of the zonules separating the vitreous cavity from the posterior chamber and the iris separating the anterior and posterior chambers.

The vascular tissue is surrounded by a thin stroma composed of ground substance, collagen fibrils, and occasional wandering cells. The ground substance contains mucopolysaccharides, protein, and a solute of plasma.

The pigmented epithelium is composed of low cuboidal cells with numerous cytoplasmic melanin granules (Fig. 2-5). This layer is separated from the stroma by an atypical basement membrane, a continuation of Bruch's membrane containing collagen and elastic fibers. The function of the pigmented epithelium is not entirely clear. The basal portion of this layer has a great number of infoldings and mitochondria, suggesting a role in active metabolic processes. The cytoplasm and cell membrane of the pigmented epithelial cells stain for the presence of carbonic anhydrase.¹⁴

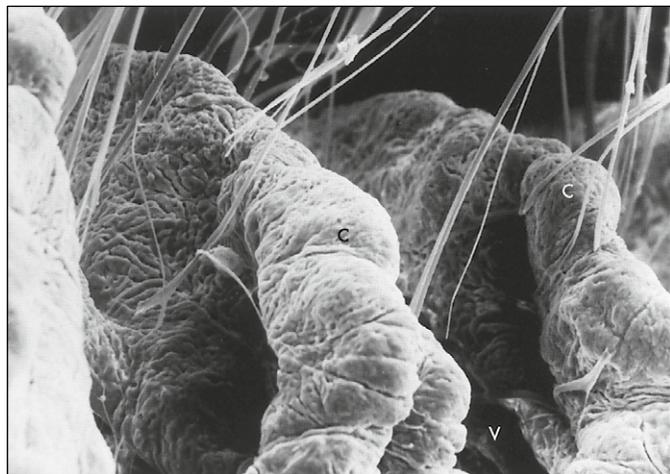
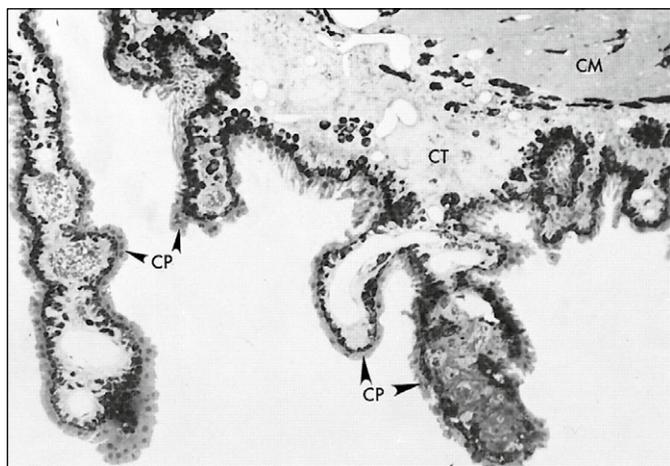
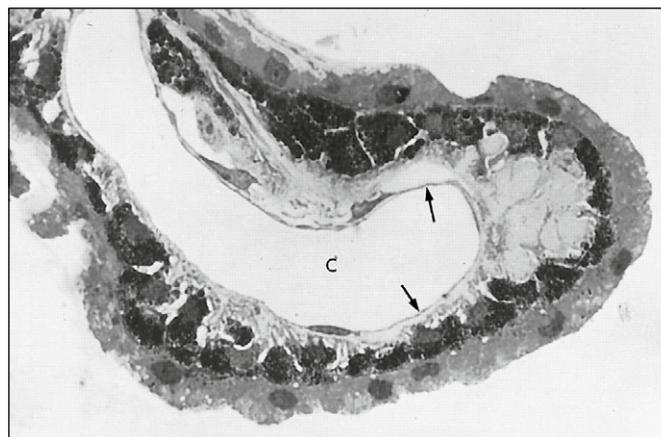


Fig. 2-3 Scanning electron micrograph of the ciliary processes (C) showing the valleys (V) and the zonular insertions ($\times 155$).

(From Tripathi RC, Tripathi BJ: *Anatomy of the human eye, orbit, and adnexa*. In: Davson H, editor: *The eye, vegetative physiology and biochemistry*, vol. 1A, 3rd edn., New York, Academic Press, 1984.)



(A)



(B)

Fig. 2-4 (A) Light micrograph of the ciliary processes (CP), with connective tissue stroma (CT) between the ciliary muscle (CM) and the two epithelial layers. The vessels extend into the processes, and the stroma also contains melanocytes and fibroblasts ($\times 197$). **(B)** Extension of the vessel layer into the ciliary process. The beaded appearance (arrows) of the thin endothelial lining of the capillary (C) is due to ultramicroscopic fenestrations increasing capillary permeability for the formation of aqueous humor (photomicrograph: $\times 800$). The pigmented and non-pigmented epithelial layers are demonstrated.

(From Tripathi RC, Tripathi BJ: *Anatomy of the human eye, orbit, and adnexa*. In: Davson H, editor: *The eye, vegetative physiology and biochemistry*, vol. 1A, 3rd edn., New York, Academic Press, 1984.)

The non-pigmented epithelial layer is composed of columnar cells, which are separated from the aqueous humor by a basement membrane. The non-pigmented ciliary epithelium has the morphologic features of a tissue involved in fluid transport, including extensive infoldings in the basal and lateral membranes, numerous mitochondria, well-developed rough endoplasmic reticulum, and tight junctions connecting adjacent apical cell membranes (see Fig. 2-5). In addition, sodium-potassium adenosine triphosphatase ($\text{Na}^+ - \text{K}^+$ ATPase) is found near the lateral infoldings of the membranes. Rows of vesicles are seen near the free surface of the epithelium and were called pinocytotic vesicles in the past. It now appears that these vesicles are a fixation artifact.¹⁵

The potential space between the two epithelial layers is called the ciliary channel. One group of investigators postulates that aqueous humor is secreted into this space, particularly after stimulation of the system with various agents, such as β -adrenergic agonists.¹⁶ This theory requires further study.

Adjacent cells within each epithelial layer and the apical surfaces of the two layers are connected by gap junctions, puncta adherentia, and desmosomes.¹⁷⁻¹⁹ Gap junctions are low-resistance pathways that provide electrical coupling of cells and facilitate transport of ions and other molecules from one cell to another.^{17,18,20,21} Some feel that these gap junctions allow the two kinds of epithelial cells to act as a functional syncytium.²² Evidence from studies in knock-out mice suggest that connexin43, a major component of the gap junction, is required for aqueous production and mice bred to exclude this component do not produce normal amounts or quality of aqueous humor.²³ Puncta adherentia and desmosomes are structural supports between cell membranes. The non-pigmented ciliary epithelial cells are also joined at their apical membranes by tight junctions (zonulae occludentae), which are thought to be an important component of the blood-aqueous barrier.²⁴⁻³¹ Tracers injected into the ciliary body pass through the stroma and the clefts between the pigmented epithelial cells until they reach the apical cell membranes of the non-pigmented ciliary epithelium, where they are restricted by the tight junctions. However, these tight junctions are permeable to low molecular weight polar solutes.

There is considerable evidence that aqueous humor is produced in the anterior portion of the ciliary processes.³² The anterior portion of the non-pigmented ciliary epithelium has morphologic features that indicate active fluid transport, including increased basal and lateral interdigitations, numerous mitochondria, and a well-developed rough endoplasmic reticulum. The epithelium is supplied by a rich capillary network with numerous fenestrations.¹⁷ With a gonioprism, systemically administered fluorescein can be observed entering the posterior chamber at the tips of the ciliary processes.³³ Finally, the non-pigmented ciliary epithelium, especially in the region of the lateral interdigitations, shows evidence of abundant Na⁺-K⁺ ATPase, considerable activity for glycolytic enzymes,³⁴ and a high rate of incorporation of labeled sulfate into macromolecules, such as glycolipids and glycoproteins.^{35,36}

Many nerve terminals are seen in the connective tissue adjacent to the pigmented epithelium,³⁷ but they do not appear to penetrate the basal lamina and reach the non-pigmented epithelium. These terminals appear to arise from sympathetic and parasympathetic fibers. In addition, the non-pigmented ciliary epithelial cells have β-adrenergic and cholinergic receptors.^{38,39} The function of these receptors and nerve terminals is not clear.

VASCULAR SUPPLY

The long posterior ciliary arteries arise as trunks from the ophthalmic artery, pierce the globe near the optic nerve, and run forward

to the ciliary body, where they anastomose to form the major arterial circle (Fig. 2-6). The anterior ciliary arteries also contribute to the major circle, but to a lesser extent than the long posterior ciliary arteries.⁴⁰ Several pre-capillary arterioles branch from the major arterial circle to supply each ciliary process. These arterioles have sphincters that may play a role in regulating blood supply and aqueous humor formation. The pre-capillary arterioles break up into plexuses of tortuous vessels within each ciliary process. The vessels collect and flow into choroidal and pars plana veins, which then flow into the vortex system. Some drainage also occurs via the intrascleral veins to the episcleral veins.

The ciliary body has a very high blood flow, estimated to be 81 μl/min in the monkey eye and, by calculation, 154 μl/min in humans.^{41,42} In cats, venous blood from the anterior uvea is only 4–5% less saturated with oxygen than is arterial blood.⁴³ This indicates that oxygen consumption is not a limiting factor in aqueous humor formation under normal conditions. The rate of plasma flow to the ciliary processes in rabbits is at least 50 μl/min.⁴⁴ If the rate of aqueous production is assumed to be 2–4 μl/min, the formation of aqueous humor removes only 4–8% of the volume of plasma available to the ciliary processes.⁴⁵ Thus a modest reduction in the rate of plasma flow to the ciliary processes might not be expected to decrease aqueous humor formation substantially. However, animal models do indicate that aqueous humor production falls if ciliary blood flow is reduced by more than 30%.⁴⁶ In fact, brimonidine, an α-adrenergic agonist commonly used for glaucoma treatment, may effect a reduction in aqueous formation by causing vasoconstriction of the ciliary body arterial supply.⁴⁷

The ciliary processes of many species, including primates, appear to have limited autoregulation of their blood supply. In general, the vascular responses of the ciliary processes are similar to those of the choroid but dissimilar to those of the iris and retina.^{45,48} Vasodilation of the ciliary blood vessels is seen following administration of carbon

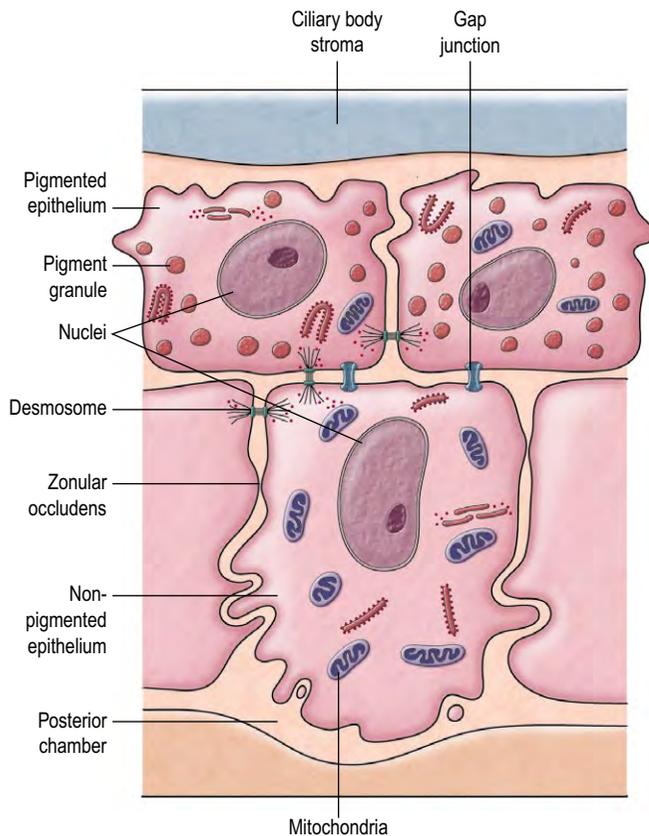


Fig. 2-5 Schematic view of non-pigmented and pigmented ciliary epithelium. (Modified from Shields MB: Textbook of glaucoma, 2nd edn., Baltimore, Williams & Wilkins, 1987.)

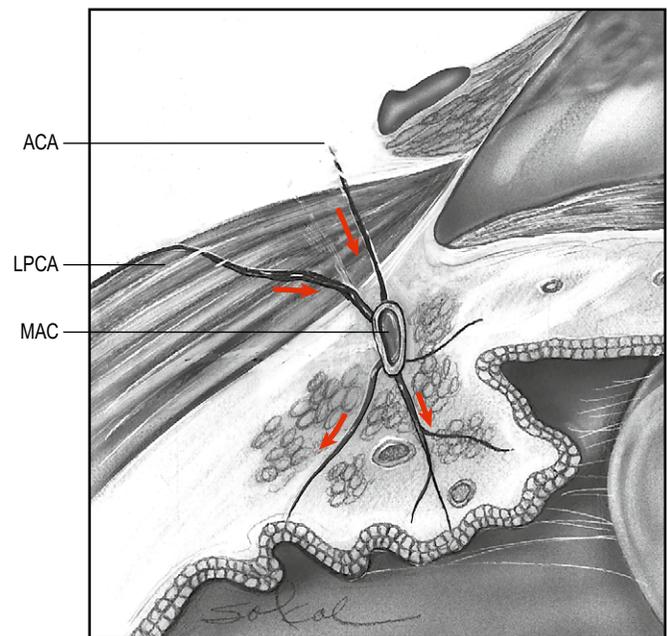


Fig. 2-6 Blood supply to the anterior segment of the eye. LPCA, long posterior ciliary artery; ACA, anterior ciliary artery; MAC, major arterial circle.

Table 2-1 Actual concentration of various solutes in aqueous humor of rabbit as compared with values of dialysate of plasma

Substance	Aqueous humour concentration (plasma concentration)	Concentration in dialysate (plasma concentration)
Na ⁺	0.96	0.945
K ⁺	0.955	0.96
Mg ⁺⁺	0.78	0.80
Ca ⁺⁺	0.58	0.65
Cl ²	1.015	1.04
HCO ₃ ²	1.26	1.04
Glucose	0.86	0.97

Modified from Davson H: Physiology of the ocular and cerebrospinal fluids, London, J & A Churchill, 1956.

dioxide,^{49,50} application of prostaglandins,⁵¹⁻⁵⁴ paracentesis,^{55,56} and parasympathetic stimulation.⁴¹ Vasoconstriction in the anterior uveal tract vessels occurs after stimulation of α -adrenergic nerves.⁵⁷⁻⁵⁹

MECHANISM OF AQUEOUS FORMATION

The formation of aqueous humor is a complex process that is difficult to study. Probes that could measure composition or cellular processes themselves may disrupt normal function so it is difficult to extrapolate from data derived this way. Work in anesthetized animals adds the further artifact that both the anesthetic agent and the reduced blood flow may alter normal physiologic processes. Finally, work in excised preparations of ciliary body or cell cultures remove the tissue under study from the influences of normal blood flow and other body homeostatic mechanisms.

What is known has been derived from studies in experimental animals, excised tissues, cell culture, where possible, human studies, and from certain assumptions. Aqueous formation has several important processes that normally happen simultaneously: these include ultrafiltration and simple diffusional exchange of water and solutes between the plasma from blood flowing through the ciliary processes and the stroma of the ciliary processes. It has been known for a long time that aqueous humor is not a simple dialysate of plasma; the concentrations of many of the elements of the aqueous humor differ from those that would be expected if ultrafiltration and passive diffusion were the only processes. The Gibbs-Donnan equilibrium describes the concentration of substances in a dialysate; Table 2-1 contrasts the actual concentration of various solutes in the aqueous humor with that found in a simple dialysate.⁶⁰ Active transport of substances from this dialysate of plasma then occurs first into the cells of the pigmented epithelium, then across the pigmented epithelium into the non-pigmented epithelium and finally from the non-pigmented epithelium into the posterior chamber. Water seems to be pulled along by osmotic forces.⁴² The fluid is further changed by diffusional exchange and active transport of substances out of the eye as it bathes other tissues, such as the lens, cornea, iris, and trabecular meshwork. Each of these processes involved in aqueous formation will now be discussed.

ULTRAFILTRATION

More than twice the weight of the ciliary processes themselves (or about 150 ml) of blood flows through the ciliary processes each minute.⁴² As blood passes through the capillaries of the ciliary processes, about 4% of the plasma filters through the fenestrations in the capillary wall into the interstitial spaces between the capillaries and the ciliary epithelium.⁴⁵ The process by which a fluid and its solutes cross a semipermeable membrane under a pressure gradient (e.g., capillary blood pressure) is called ultrafiltration. In the case of the ciliary body, fluid movement is favored by the hydrostatic pressure difference between the capillary pressure and the interstitial fluid pressure (IOP) and is resisted by the difference between the oncotic pressure of the plasma and the aqueous humor.

The rate of protein leakage through the vessel walls into the tissue space of the ciliary processes is relatively low.^{45,61} However, the ciliary epithelial layers are even less permeable to the passage of colloids into the posterior chamber. Thus the colloid concentration in the tissue space of the ciliary processes is approximately 75% of that in plasma.⁶¹⁻⁶⁴ The high concentration of colloids in the tissue space of the ciliary processes favors the movement of water from the plasma into the ciliary stroma but retards the movement of water from the stroma into the posterior chamber. Although a few investigators have postulated that ultrafiltration is responsible for the majority of aqueous humor formation,⁶⁵⁻⁶⁸ it is unlikely that the hydrostatic pressure difference between the ciliary capillaries and the posterior chamber can overcome the large oncotic pressure differential. Furthermore, a theory that proposes a predominant role for ultrafiltration does not explain why active ion transport inhibitors such as ouabain are capable of reducing aqueous humor formation by 70-80%. Thus ultrafiltration helps to move fluid out of the capillaries into the stroma but alone is insufficient to account for the volume of fluid moved into the posterior chamber. The latter step requires an active metabolic process. Ultrafiltration and active secretion occur in tandem.⁶⁹

ACTIVE TRANSPORT

Active transport (secretion) is an energy-dependent process that selectively moves a substance against its electrochemical gradient across a cell membrane. It is postulated that the majority of aqueous humor formation depends on an ion or ions being actively secreted into the intercellular clefts of the non-pigmented ciliary epithelium beyond the tight junctions (Fig. 2-7). This process is accomplished by about a million non-pigmented epithelial cells, each of which secretes aqueous humor equal to about one-third of its own intracellular volume per minute.⁴² In the small spaces between the epithelial cells, the secreted ion or ions create sufficient osmotic forces to attract water. By the time the newly secreted fluid reaches the posterior chamber, the osmotic driving force has been nearly dissipated.^{24,70,71}

First, the dialysate from the plasma has to be transported into the pigmented epithelial cells. The best current evidence suggests that the paired Na⁺/H⁺ and Cl⁻/HCO⁻ antiports actively transport Na⁺ and Cl⁻ from the stroma into the cell.⁷² Intercellular gap junctions between the two cell layers appear to be critical.²³ In addition, the natriuretic peptide precursor B (NPPB)-sensitive Cl channels at the basolateral surface in non-pigmented epithelial cells also play a crucial role in regulating the Cl movement across the functional syncytium.

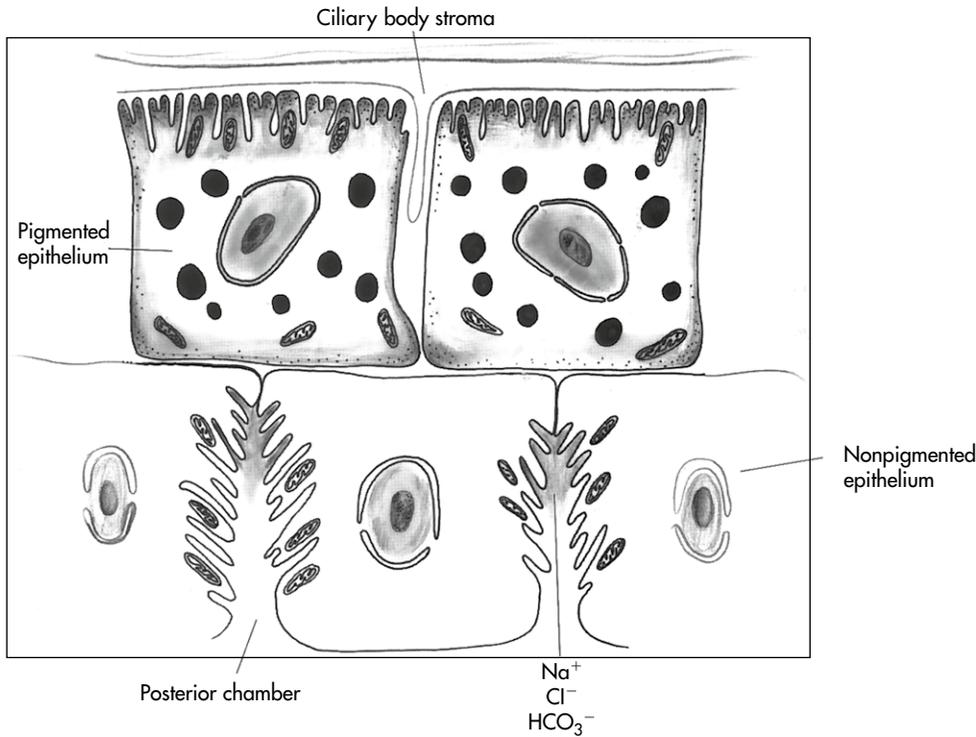


Fig. 2-7 Pigmented and non-pigmented ciliary epithelium. Ions are secreted into intercellular clefts of the non-pigmented epithelial cells. The ions create sufficient osmotic force to attract water. (Modified from Lutjen-Drecoll E: Morphologic basis for aqueous humor formation. In: Drance SM, Neufeld AH: Glaucoma: applied pharmacology in medical treatment, New York, Grune & Stratton, 1984.)

Table 2-2 Composition of anterior and posterior chamber aqueous humor in rabbit and man

Substance (nM/kg H ₂ O)	Rabbits*			Humans**	
	Anterior chamber aqueous humor	Posterior chamber aqueous humor	Plasma	Anterior chamber aqueous humor	Plasma
Na ⁺	145	144	146	163	176
Cl ⁻	105	105	112	126	117
HCO ₃ ⁻	28	34	24	22	26
pH	7.6	7.57	7.40	7.21	7.40
Ascorbate	0.96	1.30	0.02	0.92	0.06

*Modified from Kinsey VE, Reddy DVN: Chemistry and dynamics of aqueous humor. In: Prince JH, editor: The rabbit in eye research. Springfield, Ill, Charles C Thomas, 1966.

**Modified from Becker B: Chemical composition of human aqueous humor: effects of acetazolamide. Arch Ophthalmol 57:793, American Medical Association, 1957.

It is not clear which ion or ions are actively transported across the non-pigmented ciliary epithelium, though most theories include sodium, chloride, and/or bicarbonate (Table 2-2). Electrophysiologic studies of the isolated ciliary epithelium indicate that the transepithelial potential difference and the short circuit current, indicators of ion transport across membranes, are dependent on Na⁺ and HCO₃⁻.^{73,74} A number of investigators postulate that the active transport of the sodium ion is the key process in aqueous humor formation.^{7,75-77} This theory is supported by the observation that membrane-bound ouabain-sensitive Na⁺-K⁺ ATPase (the enzyme that facilitates transport of potassium into, and sodium out of, cells) is found in the non-pigmented ciliary

epithelium of many different species,^{25,30,78-81} which explains the 70-80% reduction in aqueous humor seen with ouabain.⁸²

Enough Na⁺ and K⁺ ATPase activity is present in the ciliary non-pigmented epithelium to drive aqueous humor formation mainly by the sodium gradient.⁷⁸ However, the primacy of Na⁺ as the driver for aqueous humor formation has been questioned in several species including rabbit, cat, and ox.⁸³⁻⁸⁷ Candia et al suggested that while active transport of Na⁺ is important, it cannot account for the entire rate of aqueous formation in vivo.⁸⁸ At least in the pig and some other mammals, Cl⁻ is actively transported across the non-pigmented ciliary epithelium and may be the driving force of aqueous formation.⁸⁹ Do & Civan have found

Table 2-3 Effect of acetazolamide on composition of anterior chamber aqueous humor*

Substance	Human		Rabbit	
	Before	After	Before	After
Cl ⁻	1.08	1.02	0.94	0.96
H ⁺	1.52	1.30	0.70	0.89
HCO ₃ ⁻	0.83	0.83	1.35	1.11
Ascorbate	15	18	44	52

Modified from Becker B: Chemical composition of human aqueous humor: effects of acetazolamide. Arch Ophthalmol 57:793. American Medical Association, 1957.
*Expressed as a ratio of anterior chamber concentration to plasma concentration.

that swelling-activated calcium channels in the non-pigmented ciliary epithelium modulate the formation of aqueous in both the cow and the mouse.⁹⁰ The notion that chloride transport may be important at least in some species is supported by the observation that, unlike the rabbit, the concentration of chloride ion in bovine, ovine and porcine aqueous humor is higher than in plasma.⁹¹

For many years investigators believed that the bicarbonate ion could not be actively secreted into the aqueous humor of the primate eye because the posterior chamber bicarbonate concentration is lower than the plasma concentration. However, more recent investigations indicate that bicarbonate is actually present in excess in newly formed posterior chamber aqueous humor.⁹² Bicarbonate appears to be in deficit in the aqueous humor because the fluid that is usually sampled has undergone metabolism and diffusional exchange with surrounding tissue. Carbonic anhydrase (CA) type II (isozyme C)^{93,94} is present in the cell membrane and cytoplasm of the non-pigmented and pigmented epithelium of the ciliary body. This enzyme catalyses the following reaction:



At least seven isozymes of carbonic anhydrase (CA I to CA VII) have been cloned and sequenced: each has a different location in the cell, tissue distribution, kinetic properties and reaction to inhibitors.^{95,96} Carbonic anhydrase plays an important role in many cells in pH regulation, CO₂ transport, and water and other electrolyte balance.

Direct proof of active bicarbonate transport from ciliary non-pigmented epithelial cells into the posterior chamber has not been demonstrated. However, drugs that inhibit carbonic anhydrase, such as acetazolamide and methazolamide, decrease both the rate of entry of bicarbonate into newly formed aqueous humor⁹⁷ and the rate of entry of water into the posterior chamber. Inhibition of carbonic anhydrase also reduces sodium secretion into the aqueous. The carbonic anhydrase inhibitors, when given orally or parenterally, also produce systemic acidosis, which further decreases aqueous formation.⁹⁸ Following carbonic anhydrase inhibition, anterior chamber concentrations of Cl⁻, H⁺, and HCO₃⁻ more closely resemble plasma values (Table 2-3). On the other hand, the concentration of ascorbate rises with carbonic anhydrase inhibition because its active pump is not linked to carbonic anhydrase and because the rate of aqueous formation is diminished. Some investigators have postulated that carbonic anhydrase plays an indirect role

in aqueous humor formation by providing hydrogen or bicarbonate ions for an intracellular buffering system.⁹⁹ Although this theory has been discussed widely, it has not been substantiated directly.

Sodium is actively exchanged for potassium at the non-pigmented epithelial cell/posterior chamber interface. The classical view has held that chloride passively follows sodium ion secretion. However, there is also evidence that the chloride ion is actively transported into the posterior chamber. Chloride secretion is affected by pH and the concentration of Na⁺.^{86,100} Wiederholt and colleagues postulate that a Na⁺-K⁺-2Cl⁻ co-transporter as well as parallel Cl⁻-HCO₃⁻ and Na⁺-H⁺ exchanger/antiports are functioning in the pigmented and non-pigmented epithelial syncytium to bring sodium and chloride across into the posterior chamber in an electrically neutral way.¹⁰¹ Both the Na⁺-K⁺-2Cl⁻ co-transporter and the exchanger/antiport pair are commonly seen in secretory cells and have been located in the ciliary body in both pigmented and non-pigmented epithelial cells.^{101,102} These co-transporters and exchangers are responsible for maintaining intracellular pH and ion stability and therefore are very likely involved in secretory activity as well. The role of the co-transporters in Na⁺ and Cl⁻ transport has been amply documented with some questioning the role of the double exchangers at least as far as Cl transport is concerned.^{103,104}

Some evidence also exists for a Cl⁻ channel, ClC-3, in human non-pigmented epithelial cells that may account for some of the chloride ion transfer.^{105,106} The process, like so many cellular processes, appears to be more complex and interrelated than previously thought.

While water has traditionally been thought to passively follow the active transport of ions, recent evidence points to aquaporins as possibly playing a role in active transport of water. Aquaporins are a family of proteins located in cell membranes that may be involved in active water transport. Some have been found in the ciliary body and have been implicated as playing an active role in aqueous humor formation.¹⁰⁷

Ascorbic acid is also actively transported across the ciliary epithelium into the aqueous humor, at least in rabbit and cow, and is linked to Na⁺ transport.^{108,109} Controversy exists as to whether this active transport system can adequately explain the very high concentrations of ascorbate in aqueous humor compared to plasma in most mammalian species.

DIFFUSION

Diffusion is the movement of a substance across a membrane along its concentration gradient. As the aqueous humor passes from the posterior chamber to Schlemm's canal, it is in contact with the ciliary body, iris, lens, vitreous, cornea, and trabecular meshwork. There is sufficient diffusional exchange with the surrounding tissues, so that the anterior chamber aqueous humor resembles plasma more closely than does the posterior chamber aqueous humor (see Table 2-2).¹¹⁰ Aqueous humor provides glucose, amino acids, oxygen, and potassium to surrounding tissues and removes carbon dioxide, lactate, and pyruvate.

CHEMICAL COMPOSITION OF THE AQUEOUS HUMOR

It is difficult to obtain aqueous humor samples, particularly posterior chamber samples, from human eyes. Accordingly, most of our

knowledge about the composition of the aqueous humor is based on animal studies, particularly studies of the rabbit. It is important to emphasize that there are substantial differences among species, as indicated in Table 2-2. For example, the aqueous humor concentration of ascorbate in the rabbit eye is 18 times higher than the plasma concentration. In contrast, there is no substantial accumulation of ascorbate in the aqueous humor of the rat.

The entry of various substances into the eye depends on a number of factors, including molecular size, electrical charge, and lipid solubility. Large molecules, such as proteins, penetrate the eye poorly. The capillaries of the ciliary body are permeable to proteins, but the non-pigmented ciliary epithelium and the capillaries of the iris are not. Thus the overall entry of protein into the aqueous humor is rather low. The concentration of protein in the aqueous humor of the human eye is approximately 0.02%, whereas protein concentration in plasma is 7%. Smaller proteins, such as albumin, are present in higher concentration than the larger proteins, such as IgD, IgA, and IgM.¹¹¹ The concentration of protein leaving the eye via Schlemm's canal is quite low, suggesting that a substantial portion of the protein must exit with the uveoscleral flow.^{45,64,112-115}

Smaller, water-soluble molecules (e.g., creatinine, sucrose, urea) are not restricted by the capillaries of the ciliary body but are somewhat limited by the non-pigmented ciliary epithelium. The entry of these molecules is inversely related to their size and electrical charge.

Lipid-soluble molecules (e.g., ethanol) pass readily through the non-pigmented ciliary epithelium. It is thought that lipid-soluble molecules pass through lipid portions of membranes in proportion to the concentration gradient across the membrane. Thus lipid-soluble substances move primarily by diffusion, whereas water-soluble molecules move by ultrafiltration and secretion.

A number of substances enter the eye by facilitated transport. In the previous section it was established that Na^+ , Cl^- , and HCO_3^- are thought to be actively transported into the intercellular clefts of the non-pigmented ciliary epithelium, resulting in osmotic-driven fluid flow. In addition, a number of other water-soluble substances of larger size or greater electrical charge are thought to be actively transported into the eye, including some sugars, ascorbate, and some amino acids.

Moreover, a number of transport systems actively move substances out of the eye. One system is similar to the organic anion transport mechanism of the renal tubule. This system transports large anions – such as paraminohippurate (PAH), phenolsulfonphthalein, fluorescein, penicillin, prostaglandins, glucuronides, and sulfates – out of the posterior chamber. The system is inhibited by probenecid and bromocresol green.¹¹⁶⁻¹¹⁸ A second system transports iodide compounds out of the posterior chamber. This system is inhibited by perchlorate and thiocyanate.¹¹⁹⁻¹²¹ There is some disagreement about whether there is a third transport system for iodipamide and related compounds.¹²²⁻¹²⁴ These systems all demonstrate the common properties of facilitated transport, including saturation, Michaelis-Menten kinetics, and competitive inhibition. It is postulated that these ocular transport systems prevent the accumulation of toxic substances in the eye. For example, ocular tissues have limited ability to metabolize prostaglandins, so an active transport system in the ciliary body and retina is necessary to prevent accumulation of these potentially toxic compounds.^{125,126} The aqueous humor concentrations of many important substances are given in Table 2-2.

Sodium. Most of the sodium in the aqueous humor enters the eye by active transport either primarily or linked to bicarbonate.^{127,128}

This is an energy-dependent process that is facilitated by Na^+/K^+ ATPase.^{74,129} A lesser amount of sodium enters the eye by ultrafiltration or diffusion. The aqueous humor sodium concentration is not closely linked to the plasma sodium concentration.¹³⁰

Chloride. Chloride is actively transported into the aqueous humor. This process seems to depend on pH and the concentration of sodium.^{86,100}

Potassium. Potassium enters the eye by active secretion and diffusion.¹³¹ Some potassium is taken up by the lens.

Ascorbic acid. Ascorbic acid is actively transported into the eye against a large concentration gradient.^{110,132}

Amino acids. Some amino acids are present in the aqueous humor in low concentration and some in high concentration when compared with plasma.¹³³ It is thought that there are at least three different active transport mechanisms for neutral, basic, and acidic (dicarboxylic) amino acids.⁵

Bicarbonate. Bicarbonate is actively transported into the posterior chamber of the human eye⁹² either primarily or linked to sodium. It is thought that some bicarbonate is lost by diffusion to the vitreous and some is decomposed into carbon dioxide.

Glucose. The concentration of glucose in the aqueous humor is relatively low because most of it is lost to the vitreous or taken up by the lens and cornea.¹¹⁸

Phosphate. The concentration of phosphate in the aqueous humor is relatively low because it is incorporated into a number of active molecules.

Pyruvate and lactate. The concentrations of pyruvate and lactate are relatively high, presumably because of glycolytic activity by avascular tissues such as the lens and the cornea.¹³⁴

THE BLOOD-AQUEOUS BARRIER

The blood-aqueous barrier consists of all of the barriers to the movement of substances from the plasma to the aqueous humor. For example, in the ciliary body the barriers include the vascular endothelium, basement membrane, stroma, and pigmented and non-pigmented epithelium. Although all of the structures participate in the blood-aqueous barrier, the tight junctions (zonae occludentes) connecting the apical portions of adjacent non-pigmented epithelial cells in the ciliary processes have been most often implicated as the actual site of the barrier.^{67,135} These junctions are not as 'tight' as their name would imply – in that they do allow passage of some small ions and water.¹³⁶ The blood-aqueous barrier is responsible for maintaining the differences in chemical composition between the plasma and the aqueous humor.

Many endogenous and exogenous stimuli increase the permeability of the epithelia and vascular endothelium (i.e., break the blood-aqueous barrier), producing an increase in aqueous humor protein concentration (Box 2-2). In some cases this increase is accompanied by pupillary miosis and an accumulation of white blood cells. The breach of the barrier often is accompanied by a transient rise in IOP, which is then followed by a period of prolonged hypotonia.

In some situations (e.g., intraocular infection), a breakdown of the blood-aqueous barrier is clearly therapeutic because it brings mediators of cellular and humoral immunity to the interior of the eye. In other situations (e.g., some forms of uveitis and following trauma), the breakdown of the barrier is inappropriate and favors the development of complications, such as cataract and synechia formation.

Box 2-2 Stimuli that break down the blood–aqueous barrier

Trauma
 Mechanical injury of iris or lens
 Contusion
 Paracentesis
 Chemical irritants
 Nitrogen mustard
 Formaldehyde
 Acid
 Alkali
 Neural activity
 Stimulation of trigeminal nerve
 Immunogenic activity
 Bovine serum albumin
 Endogenous mediators
 Histamine
 Bradykinin
 Prostaglandins and other eicosanoids
 Serotonin
 Acetylcholine
 Miscellaneous
 Bacterial endotoxins
 X radiation
 Infrared radiations
 Laser energy
 Alpha melanocyte-stimulating hormone
 Parasympathomimetic agents

Modified from Eakins KE: Prostaglandin and non-prostaglandin mediated breakdown of the blood–aqueous barrier. *Exp Eye Res* 25(suppl):483, 1977.

There appear to be multiple mechanisms for compromise of the blood–aqueous barrier. One important mechanism is mediated by prostaglandins. This system is activated by a variety of stimuli, including paracentesis, and is blocked by non-steroidal anti-inflammatory agents such as aspirin and indometacin. Another important mechanism is mediated by sensory innervation and neural peptides, including substance P. This system is activated by a variety of stimuli (e.g., topical nitrogen mustard) and is blocked by retrobulbar lidocaine (lignocaine) and capsaicin.¹³⁷

When the blood–aqueous barrier is broken, protein-rich fluid collects in cysts beneath and between the epithelial cells of the ciliary body. The contents of these cysts eventually burst into the posterior chamber.^{135,138,139} Protein-rich fluid also enters the eye via reflux from Schlemm's canal in some situations.^{140,141}

RATE OF AQUEOUS HUMOR FORMATION AND MEASUREMENT TECHNIQUES

Many investigators have measured the rate of aqueous humor formation in humans with a variety of techniques. Despite the different techniques used, the majority of studies find a rate of aqueous humor formation of 2–3 $\mu\text{l}/\text{min}$ (Table 2-4). The techniques for measuring aqueous humor formation can be divided into two major categories: (1) pressure-dependent methods that use volumetric analysis of the eye; and (2) tracer methods that monitor the rate of appearance or disappearance of various substances from the eye.

Table 2-4 Rate of aqueous humor flow in human eyes

Investigator	Subject (n)	Mean \pm SD aqueous flow ($\mu\text{l}/\text{min}$)	Technique
Bloom and others ¹⁶⁸	19	2.8 \pm 0.6	Fluorescein iontophoresis
Coakes and Brubaker ¹⁷²	20	2.9 \pm 0.4	Fluorescein iontophoresis
Brubaker et al*	113	2.4 \pm 0.6	Fluorescein iontophoresis
McLaren and Brubaker**	300	2.8 \pm 0.6	Fluorescein iontophoresis

*From Brubaker RF, Nagataki S, Townsend DJ, et al.: The effect of age on aqueous humor formation in man. *Ophthalmology* 88:283, 1981.
 **From McLaren JW, Brubaker RF: A scanning ocular fluorophotometer. *Invest Ophthalmol Vis Sci* 29:1285, 1988.

PRESSURE-DEPENDENT TECHNIQUES

The theoretical background of the pressure-dependent methods is considered in more detail in the next chapter, but it can be summarized briefly as follows. When fluid is introduced into a closed system, there is an immediate rise in the pressure within the system. In the case of the eye, if fluid is injected into the globe, there is a rise in IOP, the magnitude of which depends on many factors, including the distensibility of the ocular coats. If the relationship between the volume of fluid injected and the change in IOP is known, it is possible to consider the reverse situation – that is, the relationship between the decline in IOP and the volume of fluid leaving the eye. If IOP is elevated by artificial means (e.g., placing a weight on the eye), the decline in IOP over time is a measure of the loss of fluid (e.g., egress of aqueous humor) from the eye under the condition of increased pressure. This is a measure of the facility of outflow, and after an assumption about the level of the episcleral venous pressure, the rate of aqueous humor formation can be calculated from the Goldmann equation. It should be stressed that all of the pressure-dependent methods calculate the rate of aqueous formation rather than measure it directly. On the other hand, most of them have the advantage of being able to be performed on the eye *in vivo* without significant risk.

Tonography

The most commonly used pressure-dependent method is tonography, which is based on the old observation that IOP declines when the eye is massaged. For this technique, a weight such as a Schiotz tonometer is placed on the cornea to produce a sudden rise in IOP, which then declines over time. The rate at which the IOP declines over time is related to the facility of outflow. This value and the IOP in the undisturbed eye can be used to calculate the rate of aqueous formation.^{144–146}

There are a number of problems inherent to tonography, such as difficulties in performing the technique and in calibrating the equipment. Furthermore, a number of assumptions must be made about the response of the eye to an acute elevation in IOP, including the displacement of fluid, the elastic properties of the eye, the ocular blood volume, the rate of aqueous humor formation, and

the level of episcleral venous pressure. Despite these problems, tonography has been used widely to estimate the rate of aqueous humor formation and seems to correlate reasonably well with other techniques. A full discussion of tonography and the other pressure-dependent methods is included in Chapter 3.

Suction cup

One pressure-dependent method uses a suction cup, which is applied to the sclera with a vacuum 50mmHg below atmospheric pressure.^{147–150} This occludes intrascleral and episcleral venous drainage and raises IOP. The rate of aqueous humor formation is then calculated from the rise in IOP following occlusion or from the rate of fall in IOP after the device is removed from the eye. This method suffers from many of the same problems as tonography.

Perfusion

It is possible to estimate aqueous humor production by measuring outflow facility with a perfusion apparatus.¹⁵¹ This technique has its greatest use in animal eyes and enucleated human eyes but can be done pre-operatively. After a needle is inserted into the eye, the pressure–flow relationships are determined by perfusing the anterior chamber at a known rate and measuring the resultant IOP. Alternatively, the anterior chamber can be perfused at a known pressure to determine the flow through the eye. When the rate of fluid inflow from the apparatus is plotted against the perfusion pressure (pressure in the perfusion line minus IOP), the facility of outflow can be determined, and the rate of aqueous humor formation can be calculated. Obviously, this technique is only suitable for eyes that are going to be operated on or enucleated anyway and are therefore not normal eyes.

TRACER METHODS

There are a number of techniques described for measuring aqueous humor flow that do not alter IOP. Generally these approaches measure the rate of appearance or disappearance of various tracers from the anterior chamber. Thus these techniques actually measure the rate of aqueous humor flow through the anterior chamber rather than the rate of aqueous formation. Any aqueous humor formed in the posterior chamber and passing posteriorly to the vitreous and retina would not be detected by these approaches. Despite this limitation it is thought that the tracer techniques are more accurate than the pressure-dependent techniques because the globe and IOP are not altered.

Photogrammetry

The anterior chamber aqueous humor is stained with fluorescein applied topically or using iontophoresis. Newly formed aqueous humor appears as a clear bubble emerging from the posterior chamber into the fluorescein-stained anterior chamber. The volume of the bubble can be estimated by projecting a series of light stripes onto the bubble and photographing them. By mathematically integrating the area under the stripes, a reasonably accurate measure of the volume may be obtained. The rate of change in the size of the bubble is estimated from sequential photographs and is a measure of the rate of aqueous humor formation.^{152,153} This is an accurate technique but necessitates the administration of parasympathomimetic drugs to produce a miotic pupil. It is argued that the parasympathetic agent may alter the normal aqueous dynamics and may skew the results.

Radiolabeled isotopes

There have been a number of attempts to measure the accumulation of isotopes in the anterior chamber or the decay of isotopes

after intracameral injection.¹⁵⁴ O'Rourke and co-workers^{154,155} injected radiolabeled albumin into the anterior chamber and measured the rate of disappearance of radioactivity using an external gamma counter. This technique requires the assumption that all loss of radioactivity is due to the flow of aqueous humor. Other problems with the method include leakage of fluid around the needle, breakdown of the blood–aqueous barrier, and elevation of IOP.¹⁵⁶ Infusion into the anterior chamber must be done slowly, and the tracer must be allowed to mix adequately with the aqueous humor. A push–pull apparatus is used so that fluid is injected and removed at the same time and rate to avoid disturbing IOP.¹⁵⁷ Similarly, a radiolabeled protein can be injected into the vitreous, and its disappearance can be measured using an external scintillation counter. Clearly this technique is not applicable to human eyes.¹⁵⁸ It is also possible to measure aqueous humor flow by injecting a tracer into the anterior chamber and measuring its appearance in the general circulation.¹⁵⁹ Another method is to inject intravenously a radiolabeled substance that circulates to the eye from the bloodstream and that is rapidly cleared by the kidney. Once the agent is cleared by the kidney, its rate of disappearance from the eye can be measured. This rate of disappearance is dependent on the rate of aqueous flow.^{160,161}

Fluorescein

Following oral administration of fluorescein, the dye appears in the anterior chamber. The rate of appearance can be measured with optical techniques, allowing for the calculation of aqueous humor flow.^{44,162–164} Fluorescein administered intravenously appears in the anterior chamber much like oral fluorescein as described above.^{165–168} The rate of appearance of the dye allows for the calculation of the rate of aqueous humor flow. In a related technique, the eye is exposed to infrared radiation for 2 to 3 minutes, leading to a rapid reversible breakdown of the blood–aqueous barrier and an influx of fluorescein from the plasma. When the infrared radiation is stopped, the barrier is re-established rapidly. The subsequent rate of decrease of fluorescein in the anterior chamber is related to aqueous humor flow.¹⁶⁹

Fluorescein is administered topically as multiple eye drops or by iontophoresis. After a suitable period of time, the rate of decay of the fluorescein concentration is taken as a measure of aqueous humor flow through the anterior chamber. This necessitates a mathematical analysis that considers the volume of the anterior chamber and the effect of the fluorescein depot in the cornea.^{11,42,142,170–186} This technique is now used widely to measure aqueous humor flow in clinical situations.

Fluoresceinated dextrans

Large fluorescein-labeled molecules are injected intravitreally. The loss of fluorescein over time is measured by optical techniques and is related to aqueous humor flow through the anterior chamber.¹⁸⁷ However, because the eye must be entered, disturbance of the normal physiology would seem inevitable, and the results of this kind of analysis would be suspect.

Paraminohippurate

Paraminohippurate (PAH) is injected intravenously, leading to a high plasma PAH concentration and penetration of the substance into the aqueous humor. When the intravenous infusion is stopped, there is rapid renal clearance of PAH, which leads to a low plasma concentration. Since PAH in the posterior chamber is transported out of the eye, the anterior chamber PAH concentration over time reflects aqueous humor flow. Aqueous humor is sampled in one

eye and then 1 to 2 hours later in the other eye. The difference in the PAH concentrations between the two eyes reflects the aqueous flow rate. The obvious problem with this technique is that it necessitates bilateral paracentesis for chemical analysis.¹⁸⁸

Iodide

The iodide technique is similar to the PAH technique described above. When large doses of iodide are administered, the substance diffuses into the anterior chamber from the plasma but is actively transported out of the eye behind the iris. Labeled iodide and non-labeled iodide are administered at different times, and the concentrations are measured after paracentesis. The relative concentrations in the aqueous humor reflect flow through the anterior chamber.¹⁸⁹

FACTORS AFFECTING AQUEOUS HUMOR FORMATION

As noted previously, aqueous humor formation averages about 2.6–2.8 $\mu\text{l}/\text{min}$ in normal humans during the daytime. The rate of formation at any given time is similar between the two eyes of the same individual (coefficient of variation = 15%).⁴² Like most physiologic functions, the production of aqueous humor is not static; rather, it varies. The flow does not seem to vary much from day to day in normal young individuals (coefficient of variation = 23%). Table 2-5 summarizes some of the known factors that influence the rate of aqueous formation. The important ones are discussed below.

DIURNAL VARIATION

Intraocular pressure fluctuates over the course of the day. The most common diurnal variation has the maximum pressure in the morning hours and the minimum pressure late at night or early in the morning. Some individuals reach their peak IOPs in the afternoon or evening. Other individuals follow no consistent pattern. Most authorities attribute the diurnal fluctuation of IOP to

diurnal variations in aqueous humor formation.¹⁴⁷ However, some believe there is a diurnal fluctuation in outflow facility as well (see Ch. 3). Aqueous flow is higher in the morning than in the afternoon.¹⁹³ The rate of aqueous formation during sleep is approximately one-half the rate upon first awakening.¹⁹⁴ It is postulated that the reduction in flow is the result of decreased stimulation of the ciliary epithelium by circulating catecholamines.^{181,194}

AGE AND SEX

Aqueous humor formation appears to be similar in males and females.⁶⁹ There is a reduction in aqueous formation with age,^{11,163,164,195–197} particularly after age 60.^{11,195} However, the decline with age is less than was previously thought.¹⁹⁵ Brubaker and co-workers,⁴² in a study of over 300 normal volunteers, showed a decline in aqueous production of about 3.2% per decade in adults; this represents a reduction in aqueous production of about 25% over a lifetime. Therefore age appears to have less effect on aqueous humor production than it does on IOP and anterior chamber volume.¹¹ The reason(s) for the decrease in the rate of aqueous formation with age is not clear. One study suggests that the decrease could be due to changes in the ultrastructure of aging ciliary epithelial cells.¹⁹⁸

INTRAOCULAR PRESSURE/PSEUDOFACILITY

Many investigators have postulated a feedback mechanism whereby aqueous humor formation increases or decreases to compensate for changes in IOP. One proposed example of this phenomenon is the apparent decrease in aqueous formation that occurs during tonography. This decrease could be misinterpreted as an increase in outflow facility, so this phenomenon has been termed pseudofacility. However, more recent studies suggest that pseudofacility, or the feedback control of aqueous formation, has been greatly overstated. Carlson and co-workers¹⁷¹ altered IOP by changing body position and found only slight changes in aqueous formation. In addition, prolonged alterations of IOP do not seem to affect aqueous humor formation.¹⁹⁹ For example, when topical corticosteroids are administered to sensitive patients for several weeks, IOP rises, but there is no corresponding fall in aqueous humor formation.²⁰⁰ Conversely, laser trabeculoplasty lowers IOP in glaucomatous eyes without a concomitant increase in aqueous formation.^{201–203} Another piece of evidence suggesting the lack of a negative feedback system is that fluorophotometric studies demonstrate a normal rate of aqueous formation in patients with glaucoma or ocular hypertension (Table 2-6). Furthermore, in patients with unilateral pigmentary dispersion glaucoma, the aqueous flow is equivalent in both eyes.²⁰⁴ Finally, in patients with myotonic dystrophy in which IOPs are frequently under 10 mmHg, no difference in aqueous flow rates were seen compared with normal eyes.²⁰⁵ Thus increased IOP is unlikely to affect aqueous humor production in any major way. These observations suggest one further important implication – the increased IOP in glaucoma is the result of decreased outflow facility and not increased aqueous formation.

BLOOD FLOW TO THE CILIARY BODY

A modest reduction of plasma flow to the ciliary processes does not reduce aqueous humor production substantially. In the rabbit eye though, critical levels of ciliary blood flow are close to the normal flow levels. The finding in the animal model may indicate

Table 2-5 Factors that affect aqueous humor production

Condition	Effect on aqueous humor flow
Hypothermia ^{127,190}	Decrease
Hyperthermia ¹⁹¹	Increase
Acidosis ⁹⁸	Decrease
Alkalosis ⁹⁸	Increase
Third ventricle injection of:	
Prostaglandins	Increase
Arachidonic acid	Increase
Hyperosmotic solutions	Decrease
Hypo-osmotic solutions	Increase
Calcium ¹⁹²	Increase
Diabetes mellitus	Decrease
Retinal detachment	Decrease
Ocular inflammation	Decrease
Cyclodestructive procedures	Decrease
Choroidal detachment	Decrease
Cyclodialysis	Decrease

Table 2-6 Rate of aqueous humor flow in human eyes with glaucoma or elevated intraocular pressure

Abnormality	Subjects (n)	Affected eyes mean \pm SD	Unaffected fellow eyes (normal) mean \pm SD	Comments
Open-angle glaucoma ⁶⁴	6	2.4 \pm 0.5	–	
Exfoliative syndrome with glaucoma ¹³²	9	2.3 \pm 0.8	2.9 \pm 0.9	Flow significantly lower in affected eyes; blood–aqueous barrier leaky to fluorescein
Fuchs' heterochromic iridocyclitis with increased IOP ¹³³	10	3.2 \pm 1.3	3.4 \pm 0.7	Blood–aqueous barrier leaky to fluorescein
Pigmentary glaucoma ⁶⁴	5	2.9 \pm 0.6	–	
Corticosteroid-induced glaucoma ⁶⁰	5	–	–	Ratio of flow in treated eye to untreated eye: 1.01 \pm 0.14
Elevated episcleral venous pressure ⁶⁰	1	1.7	–	
Sturge-Weber syndrome with elevated IOP ⁶⁰	1	3.4	2.9	
Progressive low-tension glaucoma ⁶⁰	1	2.2 \pm 0.4	–	
Argon laser trabeculoplasty ⁶²				No effect on flow from lowering IOP with laser treatment
Before	9	1.5 \pm 0.5	1.9 \pm 0.9	
After	9	1.4 \pm 0.6	1.9 \pm 1.0	

Modified from Brubaker RF: The physiology of aqueous humor formation. In: Drance SM, Neufeld AH, editors: Glaucoma: applied pharmacology in medical treatment, New York, Grune & Stratton, 1984.

that the glaucoma drugs that have vasoactive effects are producing small decreases in blood flow, with concomitant reductions in aqueous humor production.⁴⁶ Obviously, a profound vasoconstriction does diminish the rate of aqueous flow. Acute experimental carotid artery occlusion in rabbits and monkeys reduces aqueous humor production.^{190,206–208} However, this effect appears to be transient, and aqueous production rises to near normal levels in a few weeks.²⁰⁹ In humans with unilateral carotid artery occlusion, aqueous humor production is normal and equal in both eyes.⁶⁹

NEURAL CONTROL

There has been considerable interest in the neural control of aqueous humor formation. As mentioned, stimulation of the cervical sympathetic chain decreases aqueous humor production.^{57,58} Furthermore, stimulation of hypothalamic centers^{210–212} or injection of a number of substances – such as calcium, hyperosmotic and hypo-osmotic solutions, and prostaglandins – into the third ventricle can alter IOP.¹⁹² Studies on the transection of the optic nerve in humans and experimental animals suggest some form of central regulatory mechanism for IOP using the optic nerve as the pathway.^{213,214} In rabbits, the circadian rhythm of aqueous flow is tied to the light/dark cycle.²¹⁵ Using the technique of ventriculocisternal perfusion, Liu and Neufeld found interaction between the brain and IOP that was not easy to explain by any simple theory.²¹⁶

The sympathetic system seems to be an important pathway for signals from the brain that influence the rate of aqueous formation.

In fact, the sympathetic system may be involved in the circadian rhythms of aqueous production and IOP.²¹⁷ However, unilateral Horner's syndrome does not appear to affect the aqueous formation rate, the IOP, or the response of the eye to the commonly used adrenergic agonists and antagonists.^{186,218} Thus central nervous system mechanisms do influence aqueous secretory rates, but the mechanisms are unclear at this time.

HORMONAL EFFECTS

Although several circulating hormones (e.g., corticosteroids) may have a significant effect on IOP, few have been studied for their effect on aqueous humor formation.²¹⁹ Brubaker and co-workers studied melatonin, progesterone, and desmopressin for their possible effects on aqueous formation rates; none were found to affect aqueous formation in any significant way.^{220–222} Levene and Schwartz²²³ have suggested that systemic variations in corticosteroid levels may account for the circadian changes in IOP. A low-dose epinephrine infusion will increase nocturnal aqueous secretion in humans by about 27%.²²⁴ Using a selective β_2 -adrenergic agonist, terbutaline, Gharagozloo and co-workers²²⁵ showed that exogenously administered β -agonists exert their maximum effect of increasing aqueous secretion during sleep and had little or no effect during waking hours. Since endogenous epinephrine secretion is at its minimum during sleep, some correlation may be inferred from the reduced nocturnal aqueous formation and the status of circulating β -adrenergic agonists.

INTRACELLULAR REGULATORS

Cyclic adenosine monophosphate plays an important role in the intracellular secretory processes of rabbit ciliary body.^{226–228} Perhaps cyclic guanosine monophosphate is a secondary messenger for regulation of aqueous secretion.²²⁹ As Brubaker points out, the challenge is to determine how to link what happens on the cellular and tissue levels with the observed phenomena in the intact eye.⁴²

Cherksey and co-workers^{230,231} have found an anion-selective channel in cultured human non-pigmented ciliary epithelial cells. Although aqueous humor formation appears normal in eyes of patients with cystic fibrosis (a disease with defective adrenergically-regulated chloride channels), it is possible that some endogenous humoral or neural factor regulates the activity of this channel and thus is responsible for diurnal variation and the effect of adrenergic agents on aqueous flow.²³²

CLINICAL ASPECTS OF AQUEOUS HUMOR FORMATION

CLINICAL CONDITIONS

Many conditions affect the rate of aqueous humor production, including ocular and systemic conditions. The known conditions are summarized in Tables 2-5 and 2-6. Although Goldmann calculated from tonographic data that eyes with primary open-angle glaucoma (POAG) had decreased aqueous formation rates, subsequent data strongly suggest that aqueous formation is unaffected by POAG and by pigmentary and exfoliative glaucoma.⁴² Aqueous flow was not significantly reduced by Fuchs' heterochromic iridocyclitis.²³³ Similarly, some conditions with low IOP, such as low-tension glaucoma or myotonic dystrophy, do not affect aqueous formation.^{69,205} A long-held assumption has been that retinal detachment, cyclodialysis, and ocular inflammation are conditions that reduce the rate of aqueous formation. Many of these assumptions are based on tonographic evidence.²³⁴ However, no studies using modern techniques have been published to confirm them.

As might be expected, systemic conditions that slow metabolism also reduce aqueous formation. Hypothermia and systemic acidosis decrease aqueous production.^{98,127,190} Conversely, hyperthermia and alkalosis increase the rate of aqueous formation.^{98,191} Insulin-dependent diabetes mellitus also seems to decrease aqueous flow.²³⁵

PHARMACOLOGIC AGENTS

Many drugs have an effect on aqueous humor formation. Some stimulate secretion, others inhibit it. Only two classes of drugs have any significant role in stimulating aqueous secretion. They are β -adrenergic agents and endogenously administered corticosteroids. Contrary to early conceptions based on tonographic data that epinephrine reduces aqueous formation, acutely administered β -adrenergic agents seem to increase aqueous formation rates, especially during sleep, as noted above.⁴² This effect may diminish with chronic administration. Topical corticosteroids do not seem to have any effect on aqueous secretion. However, systemically administered hydrocortisone may significantly increase aqueous flow.²³⁶ Pilocarpine may increase aqueous formation, but only slightly and not enough to be clinically significant.⁵⁸ Intracameral atrial natriuretic factor also increases aqueous flow, but only transiently.²³⁷

Table 2-7 Agents that affect aqueous humor formation

Agent	Effect on aqueous flow
β -Adrenergic agonists	Increase
Systemically administered corticosteroids	Increase
Pilocarpine	Slight increase
Ouabain	Decrease
Cyclic guanosine monophosphate	Decrease
Atrial natriuretic peptide	Decrease
Vanadate	Decrease
Cholera toxin	Decrease
Prazosin	Decrease
Metyrapone	Decrease
Vasopressin	Decrease
Halothane	Decrease (clinically important)
Barbiturates	Decrease (clinically important)
Ketamine	Decrease (clinically important)
Forskolin	Decrease
δ -9-Tetrahydrocannabinol	Decrease
β -Adrenergic blocking agents	Decrease (clinically useful)
α -Adrenergic agonists	Decrease (clinically useful)
Carbonic anhydrase inhibitors	Decrease (clinically useful)

Although only a small number of agents increase aqueous production, over a dozen have been shown to decrease the rate of production. These are listed in Table 2-7. Because of toxicity or route of administration, most of these agents have not been found to be useful therapeutically in humans. Systemically administered carbonic anhydrase inhibitors reduce aqueous formation by approximately 40%. These agents decrease the rate of appearance of bicarbonate and water in newly formed posterior chamber aqueous humor.^{40,97} Topically applied carbonic anhydrase inhibitors lower IOP and also cause a small reduction in aqueous humor formation. Their mechanism of action seems similar to that of the systemic carbonic anhydrase inhibitors.²³⁸

The β -adrenergic antagonists are also known to reduce aqueous humor formation. Fluorophotometric studies demonstrate a 16–47% decrease in aqueous formation after the administration of topical timolol, betaxolol, bupranolol, or levobunolol.^{163,172,180,239} Other agents are also effective. Although both carbonic anhydrase inhibitors and α -adrenergic agonists decrease aqueous formation during sleep, the β -adrenergic antagonists do not.²⁴⁰ An adaptation to the ability of timolol and other β antagonists to reduce aqueous formation may occur after chronic use, but this effect seems not to be clinically significant.⁴² The effect of β -adrenergic antagonists may last for one or more weeks after cessation of administration.²⁴¹

The α -adrenergic agonist clonidine, a drug used as an antihypertensive agent, was found to reduce aqueous flow in the human eye.¹¹⁰ A derivative of clonidine, apraclonidine, was later found to be a better-tolerated clinical agent and to lower IOP by reducing aqueous formation.²⁴² Brimonidine, a relatively selective α_2 agonist, is effective at decreasing aqueous formation and also increases the uveoscleral (non-pressure-dependent) aqueous outflow.²⁴³

It was believed that topical epinephrine preparations reduced aqueous humor formation.^{244–246} Recent studies are somewhat contradictory but suggest that aqueous humor formation is either slightly increased or relatively unchanged by topical epinephrine.^{178,182,184,247} Na^+ - K^+ ATPase inhibitors, such as ouabain, decrease aqueous formation in rabbits,⁷⁵ cats,⁸² and humans.⁸² Unfortunately, these drugs

are ineffective topically and must be administered systemically or intravitreally, which is not clinically feasible. Vanadate, an inhibitor of $\text{Na}^+ - \text{K}^+$ ATPase, reduces aqueous humor formation and IOP in rabbits and monkeys, but this drug appears to act by a mechanism distinct from its effect on this enzyme.^{248–250} A variety of other drugs, including sedatives, anesthetic agents, and hormones, depress aqueous humor production.^{251,252}

SURGERY

A number of surgical procedures, including cyclocryotherapy and cyclodiathermy, reduce aqueous humor formation (see Table 2–5). It is not clear whether these procedures act on the ciliary epithelium or the ciliary body vasculature. There is considerable controversy about whether cyclodialysis decreases aqueous humor flow.^{69,165}

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Aqueous humor outflow system overview

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Aqueous humor circulation through the anterior segment of the eye represents one of the many cardiac circulatory loops that also include the various arteriovenous, lymphatic, and cerebrospinal fluid circulations. Each of these circulatory loops is driven down a continuous pressure gradient initially set up by the heart.¹ Aqueous humor is formed by the ciliary processes, passes from the posterior chamber to the anterior chamber through the pupil, and exits the eye at the anterior chamber angle. Aqueous returns to the venous system primarily by means of the conventional or canalicular pathway (83–96% of flow).^{2–5} The pathway is through the trabecular meshwork into Schlemm's canal (hence the canalicular pathway). The Schlemm's canal lumen communicates directly with the episcleral veins, completing the circulatory pathway for aqueous return to the heart.

Aqueous humor also returns to the heart by a secondary pathway known as the uveoscleral or unconventional route. The uveoscleral route accounts for from 5 to 15% of flow, an amount that decreases with age.^{3–9} Extracanalicular aqueous flow is through the anterior ciliary muscle and iris stroma to reach the supraciliary and suprachoroidal spaces. From these spaces the fluid passes through the sclera and the loose connective tissue around the penetrating nerves and vessels.

Considerable controversy at one time revolved around the issue of aqueous humor as a circulating or a stagnant fluid. However, Ascher,^{10,11} Goldmann¹² and others^{13,14} document clearly through *in-vivo* observations that aqueous humor circulates and returns directly to the venous system. Abnormalities of this flow through the aqueous circulatory system provide the basis for our present concepts of both open- and closed-angle glaucoma.

Another prominent finding of these same investigators is pulsatile aqueous flow from the episcleral to aqueous veins; pulsatile flow that originates in Schlemm's canal.^{11,15} Pulsatile flow is in synchrony with small pressure transients such as those induced by the ocular pulse, blinking, and eye movement.¹¹ Findings of pulsatile aqueous flow are not integrated into the traditional framework of passive outflow across an unyielding syncytium in the juxtacanalicular space.¹¹ However, a new conceptual model of aqueous outflow mechanisms integrates the pulsatile flow findings into the model.¹⁵

It is generally accepted that the major portion of the normal resistance to conventional outflow resides in the region between the anterior chamber and external wall of Schlemm's canal. Furthermore, it is thought that this region is the site of the abnormal resistance to outflow found in most cases of open-angle glaucoma. The nature of the resistance in this region in both the normal and glaucomatous eye is the subject of a continuing controversy.

PHYSIOLOGY ISSUES UNIQUE TO THE CONVENTIONAL AQUEOUS OUTFLOW SYSTEM

Schlemm's canal is a modified wall of a vessel. In other vessels, pressure gradients are higher in the vessel lumen. In contrast, pressures are higher external to the lumen of Schlemm's canal. Fluid moves from the higher pressure in the lumen of vessels across vessel walls to the lower pressure in adjacent tissues as a response to the hydrostatic pressure gradient. Again, in contrast, aqueous flows from the anterior chamber, across the modified vascular wall represented by the trabecular meshwork, into the lower pressure vascular lumen of Schlemm's canal. A series of adaptations is required as a result of the pressure gradient and fluid flow reversals. These adaptations are reflected in the unique tissue anatomy, geometry and responses to pressure in the wall of Schlemm's canal that differ from those of the walls of other vessels.

FUNCTIONS OF THE CONVENTIONAL AQUEOUS OUTFLOW SYSTEM

The most obvious function of the outflow pathway is a circulatory path for aqueous humor return to the vascular system. A second function permits bulk aqueous flow of aqueous out of the anterior chamber but prevents blood reflux into the anterior chamber. The trabecular meshwork is thus a crucial part of the normal blood–aqueous barrier. The barrier is important for the optical properties of the eye and limits the entrance of potentially noxious substances.

A third important function is maintenance of a relatively stable intraocular pressure (IOP). A stable IOP range is crucial for the structural integrity and optical functioning of the eye. Stable IOP must be maintained despite different rates of aqueous humor formation, different levels of IOP, and different amounts of ciliary muscle tone.

A fourth function is filtration of foreign material and debris. Trabecular endothelial cells actively phagocytize foreign material and debris. Finally, as an adaptation to pressure gradient reversal, the meshwork functions as a suspensory system for the inner wall endothelium of Schlemm's canal. The suspensory system consists of the ciliary muscle, scleral spur, trabecular lamellae, and juxtacanalicular cells all linked to Schlemm's canal endothelium through a complex network of cytoplasmic processes.

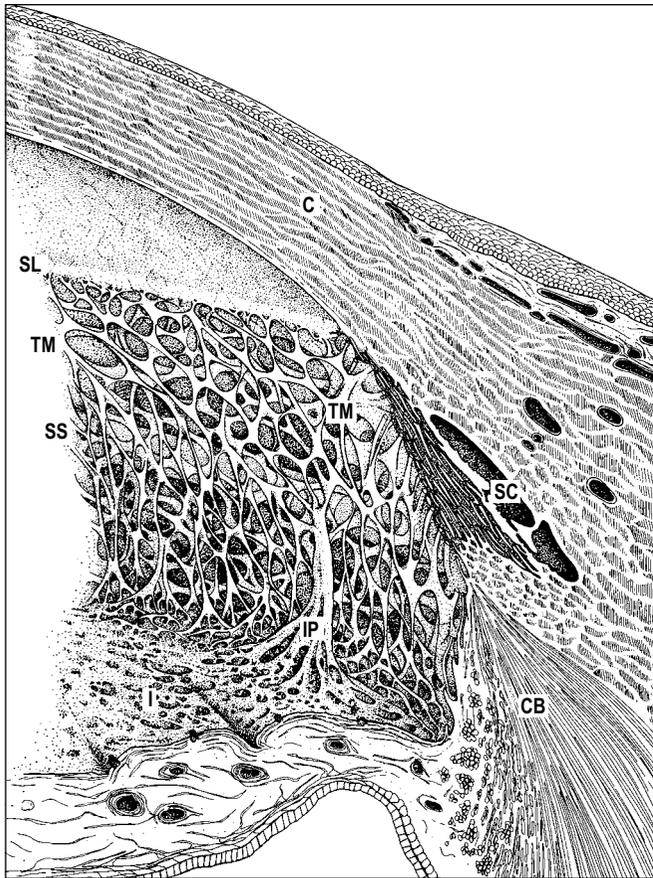


Fig. 3-1 Semi-diagrammatic representation of structures of the angle of the anterior chamber. Note the superimposed trabecular sheets with intratrabecular and intertrabecular spaces, through which aqueous humor percolates to reach Schlemm's canal. SL, Schwalbe's line; SS, scleral spur; IP, iris process; TM, trabecular meshwork; C, cornea; I, iris; SC, Schlemm's canal; CB, ciliary body. (From Tripathi RC, Tripathi BJ: Functional anatomy of the anterior chamber angle. In: Duane TD, Jaeger EA, editors: Biomedical foundations of ophthalmology, vol 1, New York, Harper & Row, 1982.)

ANATOMY OF THE CONVENTIONAL OUTFLOW SYSTEM

The limbus is the transitional region between the cornea and sclera. At the inner surface, the limbus contains a scleral indentation called the scleral sulcus. At the anterior margin of the scleral sulcus is Schwalbe's line. The scleral sulcus is defined posteriorly at its internal margin by the scleral spur, an anterior extension of sclera that partially encloses the posterior portion of the sulcus. The trabecular meshwork is interposed between the anterior chamber and Schlemm's canal by means of its attachment anteriorly to Schwalbe's line and posteriorly to the scleral spur and ciliary muscle. The trabecular meshwork thus composes the inner wall of Schlemm's canal.

SCHWALBE'S LINE

Schwalbe's line (composed of collagen and elastic tissue)¹⁶ is an irregular elevation 50–150 μm wide that runs circumferentially around the globe (Fig. 3-1). This line or zone marks the transition

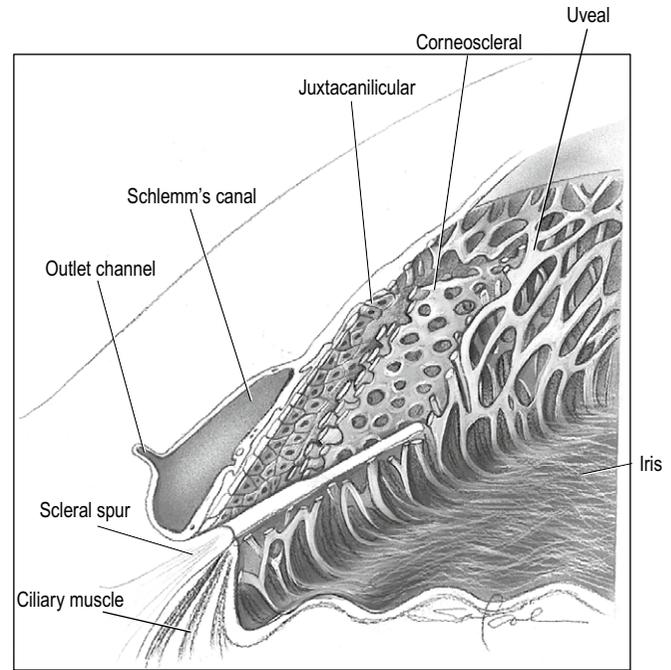


Fig. 3-2 Schematic view of different layers of the outflow system. (Modified from Shields MB: Textbook of glaucoma, Baltimore, Williams & Wilkins, 1987.)

from trabecular to corneal endothelium, the termination of Descemet's membrane, and the insertion of the trabecular meshwork into the corneal stroma. Secretory cells, called Schwalbe's line cells, are present in this area that produce a phospholipid material thought to facilitate aqueous flow.¹⁷

SCLERAL SPUR

The scleral spur is a fibrous ring that, on meridional section, appears as a wedge projecting from the inner aspect of the anterior sclera (Figs 3-1 and 3-2). The spur is attached anteriorly to the trabecular meshwork and posteriorly to the sclera and the longitudinal portion of the ciliary muscle. The spur consists of collagen types I and III and about 5% elastic tissue oriented in a circumferential arrangement.^{18–20} When the ciliary muscle contracts, it pulls the scleral spur posteriorly (Fig. 3-3). The largest trabecular lamellae near the anterior chamber are attached to the scleral spur and accordingly are rotated inward and posteriorly by ciliary muscle contraction. Rotation alters the position not only of the large lamellae, but also moves the entire attached meshwork further inward and posteriorly. Inward movement of the trabecular meshwork results in an enlargement of intertrabecular spaces and an increase in the size of Schlemm's canal, reducing the tendency of the canal lumen to narrow or collapse. Varicose axons characteristic of mechanoreceptor nerve endings are present in the spur region and may measure stresses at the scleral spur induced by IOP changes or ciliary muscle contraction.²¹

TRABECULAR MESHWORK TISSUES

In meridional section, the trabecular meshwork has a triangular shape, with its apex at Schwalbe's line and its base at the scleral spur (see Fig. 3-1). The inner layers of the trabecular meshwork border

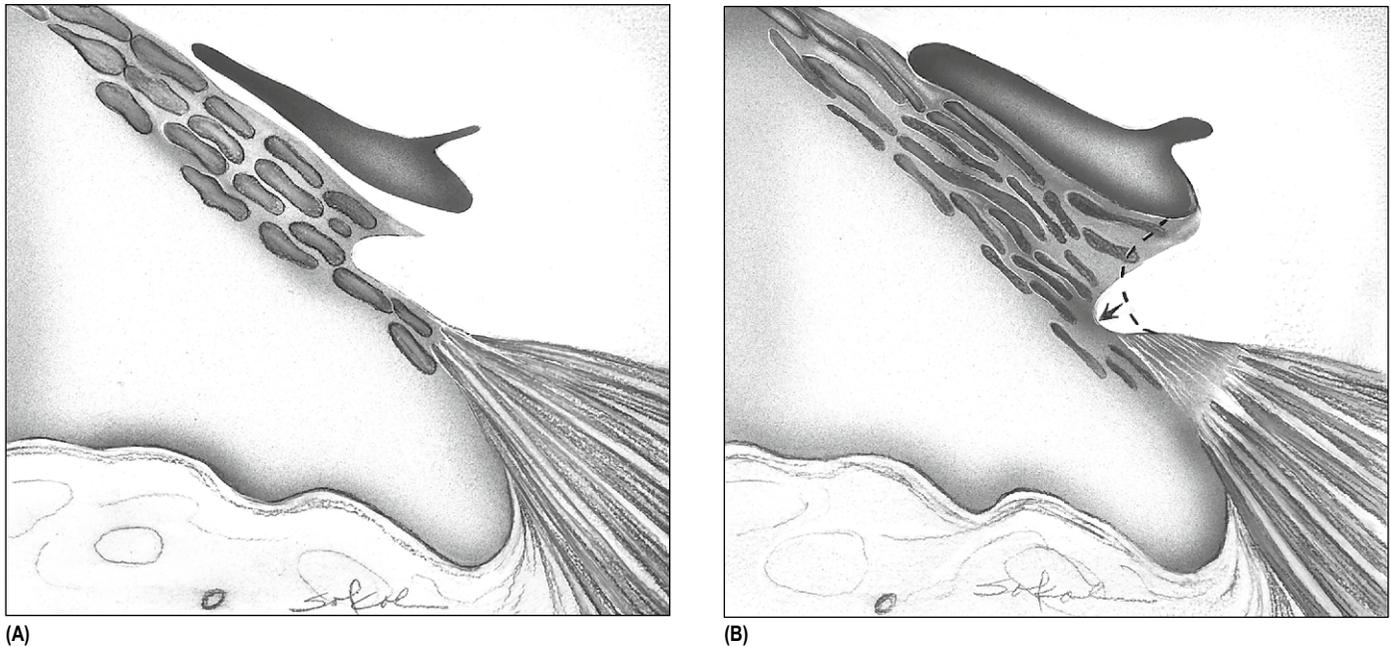


Fig. 3-3 (A) Schematic view of the system before pilocarpine treatment. **(B)** Administration of pilocarpine contracts the ciliary muscle, which pulls the scleral spur posteriorly and internally, opening the intertrabecular spaces and Schlemm's canal.

the anterior chamber and are referred to as the uveal meshwork. The next more superficial layer is the corneoscleral meshwork. The juxtacanalicular space is the next layer, which is between the corneoscleral meshwork and Schlemm's canal inner wall endothelium (see Fig. 3-2).

Uveal meshwork

The uveal meshwork is adjacent to the anterior chamber. Iris processes are fine strands of the innermost layer of the uveal meshwork present in many eyes. The processes arise from the anterior surface of the iris, bridge the angle recess, and insert into the deeper uveal trabeculae or Schwalbe's line (see Fig. 3-1). The rest of the uveal meshwork has a rope- or cord-like character, with randomly oriented interconnecting bands, and is only a few layers thick. The uveal meshwork inserts anteriorly into the region of Schwalbe's line and posteriorly into the ciliary body and iris root. The inner layers are generally oriented radially although they branch and interconnect in multiple planes.

Corneoscleral meshwork

The corneoscleral meshwork consists of a series of 8–14 flattened, perforated parallel sheets or lamellae, each 5–12 microns thick.²² The sheets closer to the anterior chamber are anchored anteriorly to Schwalbe's line. The sheets pass in a meridional fashion posteriorly to attach to the scleral spur. The anterior tendons of the longitudinal ciliary muscle fibers insert on the posterior portion of the corneoscleral meshwork as well as on the scleral spur.²³ The inner trabecular lamellae closer to the anterior chamber are considerably thicker than the outer ones closest to Schlemm's canal (Fig. 3-4).²² Trabecular lamellae are attached to one another via cytoplasmic processes (Fig. 3-4).^{24–30} The cytoplasmic processes originate from the surface of the endothelial cells covering the lamellae and meet in the intertrabecular space with a complex zone of apposition involving desmosomes and gap junctions.^{31,32} Intertrabecular collagen beams are difficult to find.²²

The trabecular sheets have a generally circumferential orientation parallel to the limbal circumference.²² The sheets are fused in such a manner that only two or three layers are seen anteriorly. The sheets separate in an anterior–posterior plane so that 12–20 layers are detectable posteriorly.

Sheets of the trabeculae are perforated by elliptical (transtrabecular) openings with an equatorial orientation, with an average dimension of 12–30 microns. Perforations become progressively smaller from the superficial layers of the uveal meshwork to the deep layers of the corneoscleral meshwork (see Fig. 3-2).^{22,33,34} The perforations are not aligned, so aqueous humor must follow a circuitous route to reach Schlemm's canal (Fig. 3-5).

Uveal and corneoscleral meshwork ultrastructure

The composition of the trabecular meshwork tissues has been compared to that of other highly compliant and resilient tissues, such as lung and other blood vessel walls.²⁰ Ultrastructurally, the uveal and corneoscleral meshworks are the same, being composed of four concentric layers.³⁵ A description of these layers follows.

First, trabecular sheets or lamellae have a central core of types I and III collagen and elastin with a typical 64 nm periodicity (Fig. 3-6).^{20,35,36} Second, elastic fibers surround the core region with a spiraling pattern and a 100 nm periodicity.³⁷ The fibers may be wound loosely or tightly thus conferring elastic properties to the meshwork.³⁸ Third, the cortical zone (also referred to as the *glassy membrane*)³⁵ is a broad zone that contains collagen types III, IV, and V; laminin; fibronectin; and heparin sulfate proteoglycan.^{20,37} Types VI and VIII collagen are also present.^{39–44} Fourth is a continuous layer of endothelial cells that covers the trabecular lamellae; cells are joined by desmosomes as well as gap junctions.^{31,45} Intercellular clefts allow aqueous to pass freely.^{38,45}

Numerous cytoplasmic processes arise from the trabecular lamellae endothelial cells.^{24–30} These cytoplasmic processes are attached to cytoplasmic processes of adjacent lamellae and to juxtacanalicular

Resisting tissue responses to IOP-induced tissue loading forces

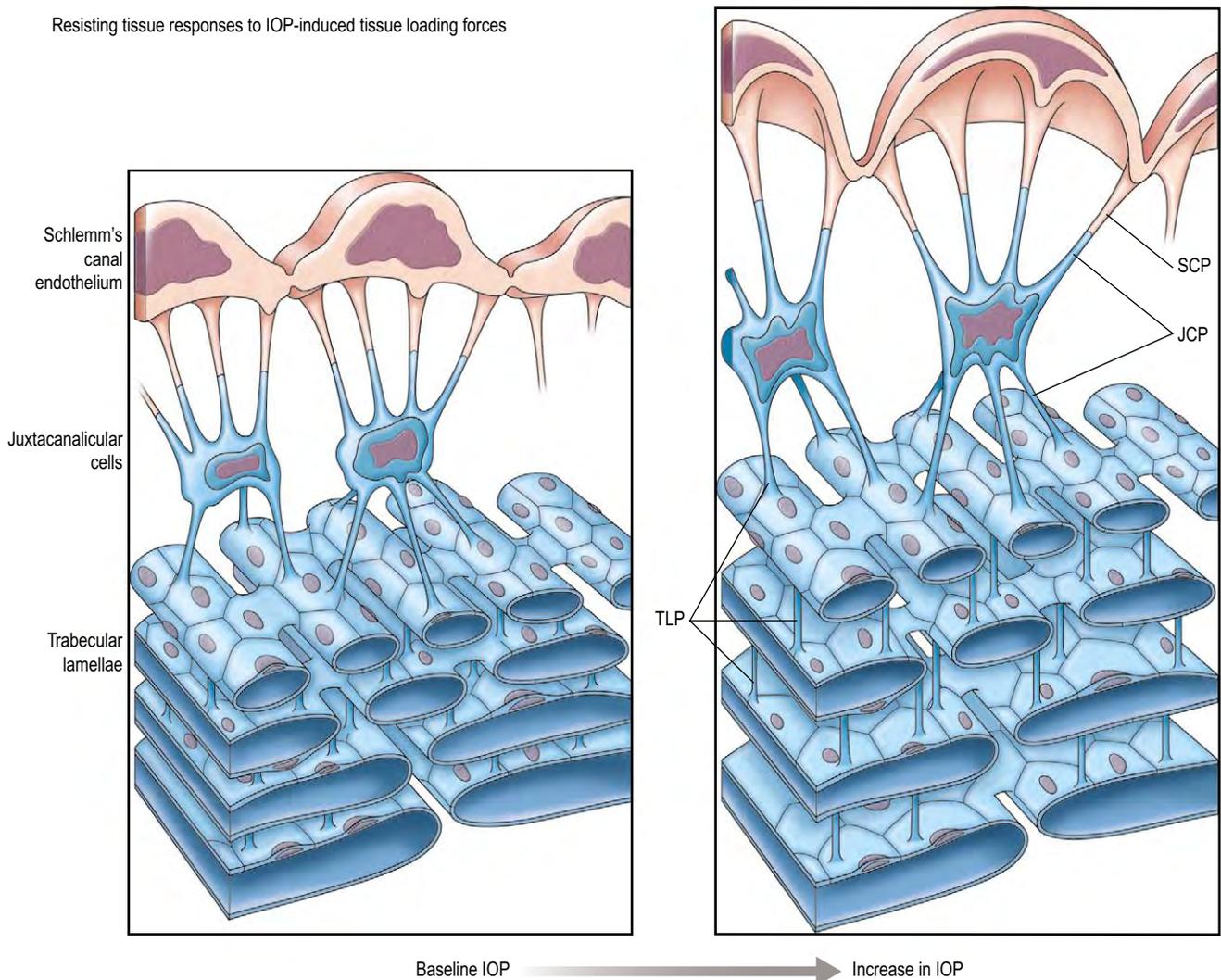


Fig. 3-4 Cell processes project from Schlemm's canal endothelial cells (SCP) and attach to juxtacanalicular cell processes (JCP). Juxtacanalicular cell processes also attach to trabecular lamellae endothelial cell processes (TLP). Trabecular lamellae endothelial cells in addition have processes that also project to adjacent trabecular lamellae cell processes. Schlemm's canal endothelial lining thus benefits from a distribution of attachments that extend to the entire system of trabecular lamellae. Tissue loading forces induced by IOP provide a means of determining resistance characteristics because outflow structures responsible for the resistance change shape. Schlemm's canal endothelium responds to IOP-induced distending forces. Cell bodies, nuclei, and cytoplasmic processes of both Schlemm's canal endothelium and juxtacanalicular cells undergo progressive deformation as a result of their role in maintaining resistance to progressive IOP-induced distention of Schlemm's canal endothelium. The system of cell processes enables the trabecular lamellae to limit distention, thus countering IOP-induced forces acting on Schlemm's canal endothelium. As a result of the countering tension, spaces between the resisting trabecular tissues progressively increase as IOP increases. At physiologic pressures (basal IOP), tensional integration is present because resistance forces are distributed throughout the trabecular tissues. Tensional integration provides an information processing network allowing finely graded responses to transient increases in IOP as well as longer term homeostasis through force-dependent mechanotransduction mechanisms.

cell cytoplasmic processes (see Fig. 3-4) by robust desmosomes.³¹ Endothelial cells lining the trabecular lamellae are anchored to a well-defined basement membrane by means of integrin attachments;⁴⁶⁻⁴⁸ this is in contrast to Schlemm's canal endothelium, where a basement membrane is sparse or absent.²⁶ Cytoskeletal elements include microfilaments (F-actin),^{23,49-51} intermediate filaments (vimentin)⁵²⁻⁵⁸ and microtubules (alpha-tubulin).⁵⁹⁻⁶¹ Endothelial cells lining the trabecular lamellae are responsible for maintaining the structural topography and extracellular

matrix composition of the lamellae in the face of constant oscillatory stresses.¹⁵ Tissue composition predicts anticipated tissue responses.⁶²⁻⁶⁴ Type I collagen provides tensile strength and type III collagen imparts resilience.⁶² Together these collagenous elements provide structural support in tension while elastin provides a recoverable response over wide excursions.⁶² The organization and distribution of collagen and elastin in the trabecular lamellae is like that of tendon,⁶⁵ which provides a mechanism for reversible deformation in response to hydrodynamic tissue loading.¹⁵

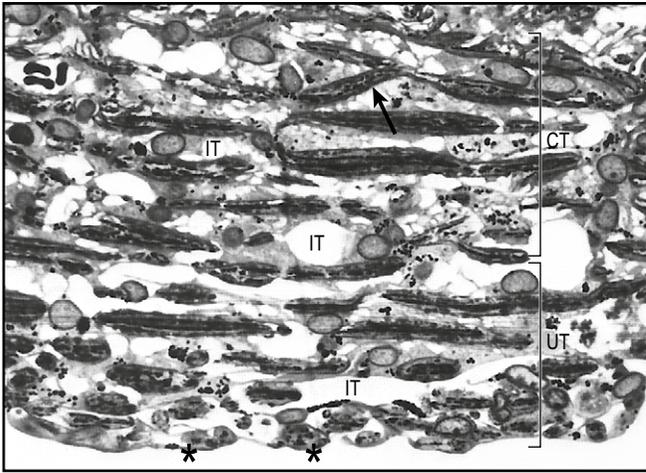


Fig. 3-5 Light micrograph of trabecular meshwork in 70-year-old human eye. Meridional section shows morphology of uveal trabeculae (UT) and corneoscleral trabeculae (CT). Note the rounded profile of inner uveal trabecular sheets (asterisks) compared with flattened profile of outer uveal and corneoscleral sheets, and a progressive narrowing of intertrabecular spaces (IT) in the latter region. The arrow denotes branching of a trabecular sheet. (Original magnification $\times 760$) (From Tripathi RC, Tripathi BJ: Functional anatomy of the anterior chamber angle. In: Duane TD, Jaeger EA, editors: Biomedical foundations of ophthalmology, vol 1. New York, Harper & Row, 1982.)

Juxtacanalicular space and cells

This space plays an important role in the debate about resistance sites. The juxtacanalicular space is 2–20 μm thick in non-pressurized eyes. The space separates the outer layers of the corneoscleral meshwork from the inner wall of Schlemm's canal and has been called by a variety of names, including cribriform space, pericanalicular space, and endothelial meshwork. Star-shaped cells in the space are referred to as juxtacanalicular, subendothelial, and cribriform cells.^{20,25,45}

Extracellular matrix material, juxtacanalicular cells and elastic-like fibers are the prominent features of the juxtacanalicular space when viewing two-dimensional histologic sections in non-pressurized eyes.²⁶ The juxtacanalicular space contains a ground substance of glycosaminoglycans, which include hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate and heparin sulfate⁶⁶ as well as complex glycoproteins, types III, IV, and V collagen; curly collagen and fibronectin.^{28,37,67} Fibronectin content is increased in elderly patients and in patients with glaucoma.⁶⁸ A network of elastic-like fibers in the juxtacanalicular space attaches both to the inner wall of Schlemm's canal and to some of the tendons of the ciliary muscle.^{26,69–71}

Juxtacanalicular cells and their cytoplasmic processes are the principal feature of the space when a three-dimensional view is achieved with scanning electron microscopy in pressurized eyes.^{15,72,73} Juxtacanalicular cell cytoplasmic processes attach to processes arising from Schlemm's canal inner wall endothelium (see Fig. 3-4). Other juxtacanalicular cell processes attach to cytoplasmic processes arising from the endothelium of the trabecular lamellae. Well-characterized robust desmosomes, capable of sustaining cellular stresses, are the mechanism of cell process attachment.^{28,29,31,32} Desmosomes attach to intracellular intermediate and actin filament

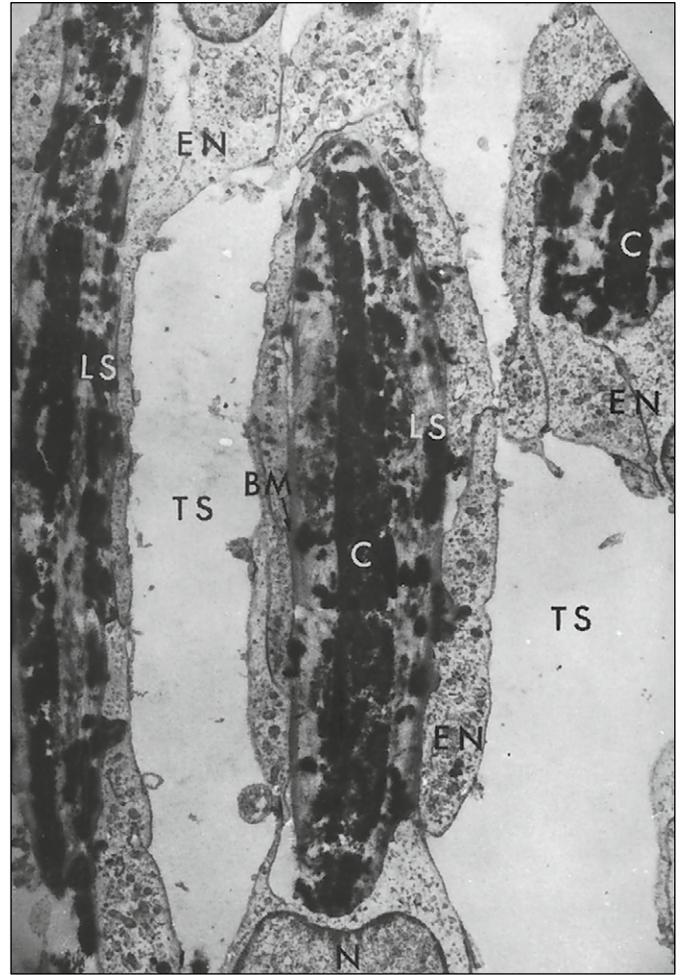


Fig. 3-6 Electron micrograph of a meridional section of human corneoscleral trabecular meshwork ($\times 11000$). TS, trabecular space; EN, endothelial cell; N, nucleus of endothelial cell; BM, basement membrane; LS, long-spacing collagen; C, collagen. (Courtesy of L Feeney, San Francisco.)

support systems⁷⁴ that enable the filaments to distribute stresses throughout the cytoplasm of involved cells to form integrated tissue relationships.^{72,75–77}

The juxtacanalicular cells thus serve the function of anchoring Schlemm's canal inner wall endothelium to the trabecular lamellae.^{15,27,28,31,72,73,78,79} By distributing IOP-induced stresses across the entire trabecular lamellae system that supports the inner wall endothelium of Schlemm's canal, the stresses are tensionally integrated, which is essential in cellular response mechanisms (see Fig. 3-4).^{76,77,80,81} Tensional integration at physiologic pressures provides constant cellular pre-stress.^{82,83} Pre-stress allows immediate graded responses^{82,83} to oscillatory pressures caused by continuously varying IOP transients⁸⁴ that force Schlemm's canal endothelium toward the canal lumen.

SCHLEMM'S CANAL

Overview

Schlemm's canal is a vascular sinus with a lumen that communicates around the entire globe. The lumen has a flattened elliptical

cross-section with a total circumference of ≈ 36 mm.⁸⁵ As the lining wall of a vessel, Schlemm's canal endothelium has properties of a vascular endothelium.⁸⁶ The lumen structure has also been likened to that of a lymphatic channel.⁸⁷ The canal is surrounded by sclera, trabecular meshwork, and the scleral spur. Generally Schlemm's canal has a lumen that is 190–370 μ m in length in the radial plane.⁸⁸ In hypotony, the shape varies, but when Schlemm's canal shape is triangular, the lumen typically measures ≈ 50 microns at its posterior base and narrows to about 5–10 microns at its apex. However, the diameter of the canal lumen is IOP dependent and the space can be absent at high pressures or very large at low pressures.^{27–29,89,90}

Schlemm's canal inner wall endothelium

The canal inner wall endothelium is of special significance because the wall represents the barrier aqueous must cross to get from the juxtacanalicular space to Schlemm's canal. This inner wall endothelium of Schlemm's canal also plays a very significant role in debate about resistance sites. The inner wall endothelium forms a continuous monolayer of long, slender endothelial cells with their long axes parallel to the canal lumen. The cells have an average diameter of 20–50 microns and a thickness of 0.2 microns.²⁴ Tight junctions (zonule occludentes) and desmosomes join the cells to one another and form a continuous belt-like region of contact encircling the apex of the cells.²⁶ Such contacts normally represent physiologic barriers to perfusion of fluid and particles.

The tight junctions are traversed by slit pores, which are meandering channels in the cell junctions. The frequency and diameter of slit pores in the tight junctions indicate that they can account for only a small fraction of aqueous humor flow.⁹¹ Gap junctions provide communication pathways. As in the cells lining trabecular lamellae, cytoskeletal elements include microfilaments (F-actin),^{23,49–51} intermediate filaments (vimentin)^{52–58} and microtubules (alpha-tubulin).^{59–61} A vascular endothelial origin of these cells is emphasized by the presence of von Willebrand factor (factor VIII-related antigen),^{86,92} and specialized cellular inclusions⁹³ including Weibel–Palade bodies.⁸⁶ The above studies, as well as others,^{43,94,95} indicate that Schlemm's canal endothelial cells have a different origin than juxtacanalicular cells or endothelial cells lining the trabecular lamellae.

The basement membrane beneath Schlemm's canal external or corneoscleral wall is continuous.⁹⁶ By contrast, Schlemm's canal inner wall endothelium is not continuous, a feature it shares with the lymphatic vessels.⁴⁵ The basement membrane of Schlemm's canal inner wall is poorly defined, inconstant, frequently interrupted and of variable thickness.^{26,45,79,89,97,98} The rudimentary basement membrane may be explained by the fact that pressure gradients force Schlemm's canal endothelium toward the vascular lumen of Schlemm's canal.^{27,31,32,72} By contrast, the higher luminal pressure gradients of other vasculature force the endothelium against the basement membrane. Schlemm's canal inner wall endothelium has a special adaptation for this gradient reversal. Instead of a basement membrane, numerous cytoplasmic processes arise from its adluminal surface and ultimately connect with processes attached to cytoplasmic processes of endothelial cells lining the trabecular lamellae (see Fig. 3–4).^{27,28,31,32,79,89,96} Tension exerted on Schlemm's canal endothelium by pressure is transmitted through the cell processes to endothelial cells lining the trabecular lamellae.^{27,28,31,32,79,89,96} The tension is further transferred to the integrin attachments of the meshwork^{47,48,99} that anchor the endothelial cells to the basement membrane of the lamellae (see Fig. 3–4). The endothelium–integrin–basement membrane complex of the cells lining the trabecular lamellae serves as a surrogate for the absent basement

membrane at Schlemm's canal inner wall endothelium.^{28,31,32,79,89,96} The arrangement provides an integrin-dependent, force-sensing architecture like that in the vasculature.^{80,100–105}

Schlemm's canal inner wall endothelial cells undergo pressure-dependent configuration changes as they progressively separate from the underlying juxtacanalicular space in response to IOP increases (see Fig. 3–4).^{27,28,31,32,79,89,96,106} The outer wall of Schlemm's canal is apposed to the scleral wall and is organized as a single layer of endothelium continuous with the endothelium of the inner wall. The outer wall does not generally undergo pressure-dependent configuration changes.

Glycocalyx

The glycocalyx is a thin layer of negatively charged (anionic) material 60–90 nm thick¹⁰⁷ that coats the luminal surface of vascular endothelia^{82,107} and the entrance to intracellular clefts.⁸² The glycocalyx modulates adhesion between cells and also surface characteristics that determine adhesion and flow properties. The layer consists of a network of fibrous proteins with sugar-based side chains. The layer acts as a size-selective molecular sieve that impedes the passage of plasma proteins.^{82,108} Vascular endothelia have an experimentally determined effective pore size of 4–5 nm.

A small pore system is present at intracellular clefts, but the openings in the clefts alone are too large (20 nm) in the open pathway around junctional strands to account for the effective pore size. Instead, the matrix of fibrous protein molecules in the clefts is organized so that spaces between these molecular chains have an effective size of 4–5 nm, small enough to restrict diffusion, create hydraulic resistance and reflect macromolecules such as albumin.⁸² Partial digestion of the glycocalyx by enzyme perfusion raises the hydraulic permeability of the wall.⁸²

In vascular endothelia, cationic ferritin binds to and reveals the presence of the glycocalyx, while neutral or anionic ferritin is not bound.^{82,109,110} Consistent with the presence of a glycocalyx found in other vascular endothelia, cationized ferritin, but not anionic ferritin, exhibits a striking binding to the luminal surface of Schlemm's canal endothelium and the associated intercellular clefts.^{111,112} As in vascular endothelia elsewhere, the glycocalyx may play an important role in maintaining hydraulic resistance characteristics as well as maintaining a barrier to passage of proteins such as albumin.

Distending cells that form invaginations or pseudovacuaes, 'giant vacuaes'

Schlemm's canal inner wall endothelium stretches to form progressively larger hemispherical outpouchings into the canal lumen as IOP increases (Figs 3–7 and 3–8).^{27,28,31,32,79,89,96} A frontal plane through such a hollow hemisphere results in a central 'vacuolated' area surrounded by the cell body, including the nucleus.^{27,72} In the enucleated eye, the number and size of the pseudovacuaes increases with progressive increases in IOP but the effect is reversible when IOP is lowered.²⁷ The structures regularly maintain a communication with the juxtacanalicular space^{27,28,32,96,113} and are generally described as balloon-shaped invaginations from the basal aspect of the cell surface.¹¹⁴ The formation of the pseudovacuaes continues in enucleated eyes and is not inhibited by hypothermia, consistent with a mechanical rather than an active metabolic rearrangement of the cell.¹¹⁵

The term *giant vacuole* was used in the 1950s and 1960s to describe these distending cells. Authorities for many years have recognized that 'giant vacuaes' represent a passive cellular response to pressure gradient changes.^{27,28,32,96,111,113} Cellular distention or invagination more accurately describes the structures. The term 'giant vacuole' captures the imagination and is still used at times.

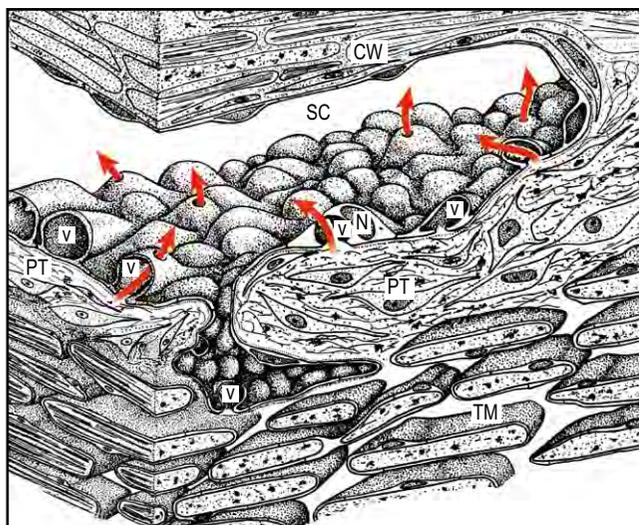


Fig. 3-7 The walls of Schlemm's canal (SC) and adjacent trabecular meshwork in a composite sectional and three-dimensional view. The endothelial lining of the trabecular wall of Schlemm's canal is very irregular, and the cells show luminal bulges corresponding to cell nuclei (N) and macrovacuolar configurations (v). The latter may represent cellular invaginations occurring from the basal aspect and eventually opening on the apical aspect of the cell to form transcellular channels (arrows), through which aqueous humor flows down a pressure gradient. The endothelial lining of the trabecular wall is supported by an interrupted, irregular basement membrane and a zone of pericanalicular connective tissue (PT) of variable thickness. The cellular element predominates in this zone, and the fibrous elements, especially elastic fibers, are irregularly arranged in a net-like fashion. Here the open spaces are narrower than those of the trabecular meshwork (TM). The corneoscleral trabecular sheets show frequent branching, and the endothelial covering may be shared between adjacent sheets. The corneoscleral wall (CW) of Schlemm's canal is more compact than the trabecular wall, with a predominance of lamellar arrangement of collagen and elastic tissue. (From Tripathi RC, Tripathi BJ: Functional anatomy of the anterior chamber angle. In: Duane TD, Jaeger EA, editors: Biomedical foundations of ophthalmology, vol 1, New York, Harper & Row, 1982.)

The term is somewhat unfortunate because it does not reflect the anatomic or physiologic characteristics of the structures. It suggests a metabolically driven mechanism of intracellular fluid transport to Schlemm's canal rather than focusing attention on the actual physiologic behavior that involves remarkable pressure-induced cellular distention and recoil.

Some authorities suggest that the pressure-induced cellular distention causes these invaginations or pseudovacuaes to form and recede in a cyclic fashion causing transient transcellular pores to form in the distending wall (see Fig. 3-7).^{33,114,116} These authorities propose the pores as a primary pathway for fluid movement.

Schlemm's canal endothelium pores

Direct aqueous passage through the non-fenestrated endothelium of the inner wall of Schlemm's canal is controversial, but such a mechanism of passage is supported by a number of studies. If aqueous passes directly through the inner wall endothelium, it must do so by a mechanism very different from that of other non-fenestrated endothelia. Hydraulic conductivity is calculated from knowing the surface area of an endothelium and the total fluid volume crossing that area. Such calculations indicate that hydraulic conductivity

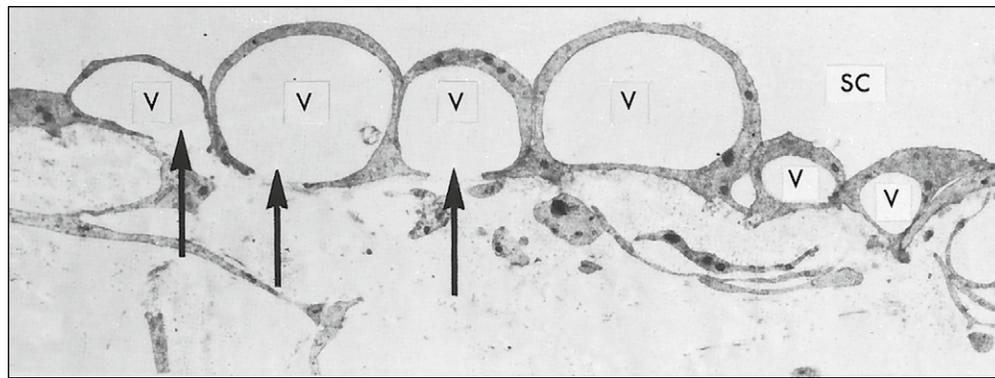
required to explain aqueous flow into Schlemm's canal is 100 times greater than any known non-fenestrated endothelium.¹¹⁷ Transient transcellular pores offer one possible mechanism to explain the required high hydraulic conductivity. The proposed pores are of two different types: the first type is transcellular pores and the second type is pores at intercellular junctions.

Transcellular or cytoplasmic channels in Schlemm's canal endothelial cells are proposed as one mechanism for aqueous passage to Schlemm's canal.¹¹⁴ Tripathi has suggested that these channels form and recede in cyclic fashion (see Fig. 3-7).^{33,114,116} The cycle begins with an invagination on the trabecular side of the endothelial cell and progresses to a transcellular channel with a small pore opening into Schlemm's canal. The model envisions only a small fraction of the invaginations open into the canal at any one time. It also proposes infrequent pore opening as a mechanism to allow the endothelium to provide the majority of the normal resistance to outflow. Transcellular pores are reported in the inner wall endothelium of Schlemm's canal in a number of studies^{24,25,33,118-120} and some studies have also shown evidence of red blood cell and tracer passage through pores.^{25,114,121}

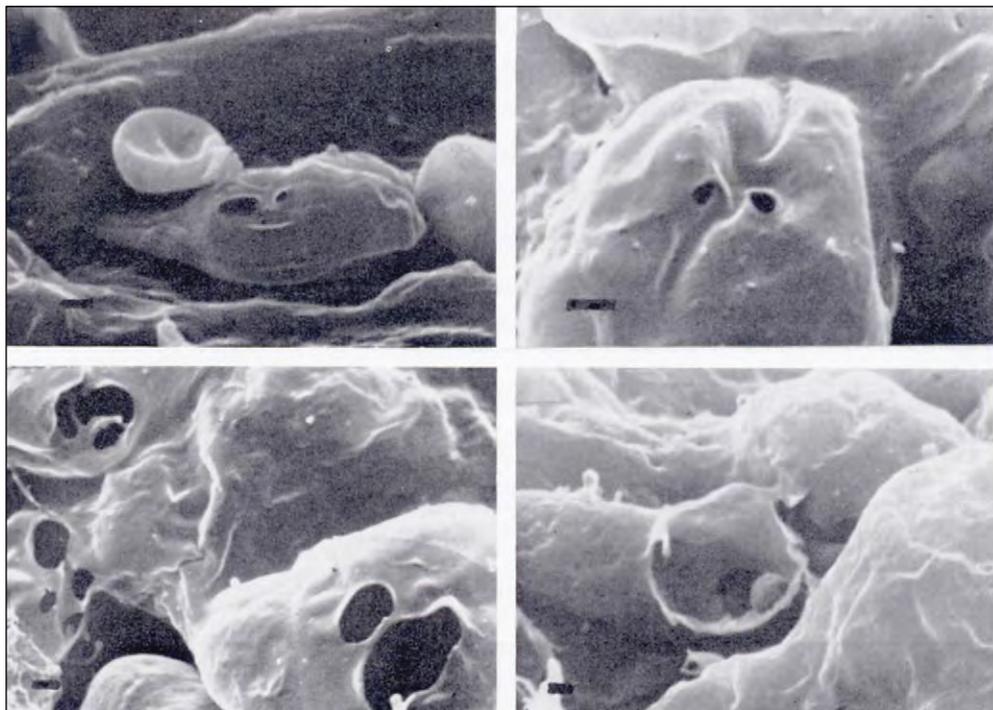
Paracellular pores or pathways are another proposed mechanism^{45,111,122-126} that may serve as an alternative or added explanation for aqueous flow to Schlemm's canal. Investigators postulate that aqueous passes between the endothelial cells, with pressure changes causing an opening and closing of cell junctions. As evidence, investigators observe that intercellular pores or interendothelial junctions respond to changes in IOP¹²⁷ and pharmacologic agents.¹²⁶ The number and size of the pores increase with increasing levels of IOP,^{28,29,96} while at low levels of IOP, the invaginations and the pores disappear.²⁹

It is important to point out that some authorities dispute this theory of aqueous egress and question whether the invaginations are really part of a fluid transport system or are merely artifacts.²⁵ Bill has estimated the total number and area of the pores and believes they are too numerous to account for the normal resistance to outflow.^{128,129} Some pores in the inner wall endothelium of Schlemm's canal as demonstrated by scanning electron microscopy are accepted as artifactual, especially those with angular shapes.^{125,128,130-133} Assessment of transcellular pore frequency and size has serious sources of error because it requires arbitrary acceptance or rejection of pores across a broad spectrum of sizes and shapes (see Fig. 3-8).¹³⁴ The pore spectrum ranges from very large round openings with complete absence of the anterior surface of the distending cellular invaginations (collapse)^{128,134} to highly angular, slightly angular or small structures with a completely round appearance.^{128,130,131,133,134} Subtle gradations in edge appearance make the grading decision difficult (see Fig. 3-8).¹³⁴ Limiting assessment to round structures does not resolve the issue because round transcellular pores are also known to be a reproducible artifact of preparation conditions for scanning electron microscopy.¹³⁵

A recent study concluded that transcellular 'pores are artifacts of tissue fixation or processing conditions'¹²² but that intercellular pores may be non-artifactual. In a subsequent study, the presence of transcellular and intracellular pores was correlated, consistent with formation by a common mechanism.¹¹⁷ The latter study concluded that 'non-linear regression of pore density versus fixative volume produced a pore density at zero fixative volume that was not statistically different from zero. If true, this implies that all (or nearly all) inner wall pores observed by scanning electron microscopy are fixation artifacts.'¹¹⁷ Schlemm's canal endothelium becomes extremely stretched and attenuated as IOP increases. Progressively thinner cells that develop with increasing IOP may be prone to the progressively increased artifact associated with scanning electron microscopy.¹¹⁷



(A)



(B)

Fig. 3-8 (A) Electron micrograph of the endothelial lining of Schlemm's canal (SC), showing the majority of the vacuolar configurations (V) at this level of section having direct communication (arrows) with the subendothelial extracellular spaces, which contain aqueous humor in life. (Original magnification $\times 23\,970$.) **(B)** Scanning electron micrographs of Schlemm's canal endothelium fixed while at 22 mmHg IOP. Micrographs illustrate 'serious sources of error' in quantitation of pore frequency and size. The upper micrographs provide detail of two bulges in which small 'natural' openings were identified. The lower micrographs demonstrate artifactual tears in the surface of the thin-walled bulges, and in the lower right micrograph, an opening in the base of the cavity can be seen. (Upper left, $\times 2500$; upper right, $\times 4500$; lower left, $\times 2500$; lower right, $\times 2000$.)

(A) (From Tripathi RC, Tripathi BJ: Functional anatomy of the anterior chamber angle. In: Duane TD, Jaeger EA, editors: Biomedical foundations of ophthalmology, vol 1, New York, Harper & Row, 1982.)

(B) (From Grierson I, Lee WR: Pressure effects on the endothelium of the trabecular meshwork and Schlemm's canal: a study by scanning electron microscopy, *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 196 : 255-265, 1975. Published with permission from Albrecht Von Graefes Arch Klin Exp Ophthalmol. Copyright by Springer-Verlag.)

Several studies have not found pores, but rather have found Schlemm's canal inner wall endothelium to be a continuous lining.⁴⁵ Studies also demonstrate that the inner wall endothelium acts as a barrier to the passage of particles such as ferritin⁶⁷ or red blood cells.^{15,136}

Sonderman's canals invaginate into the trabecular meshwork

Meandering invaginations of the inner wall endothelium in some instances appear to form circular or oval endothelial-lined

diverticulae within the meshwork. By light microscopy, these diverticulae have been reported to provide a communication between Schlemm's canal and the anterior chamber.^{137,138} Transmission electron microscopy studies, however, have since indicated there is no direct communication.^{26,96}

Septa

Along the external wall of Schlemm's canal a series of obliquely oriented septa are present at the entrance to collector channels.^{87,139}

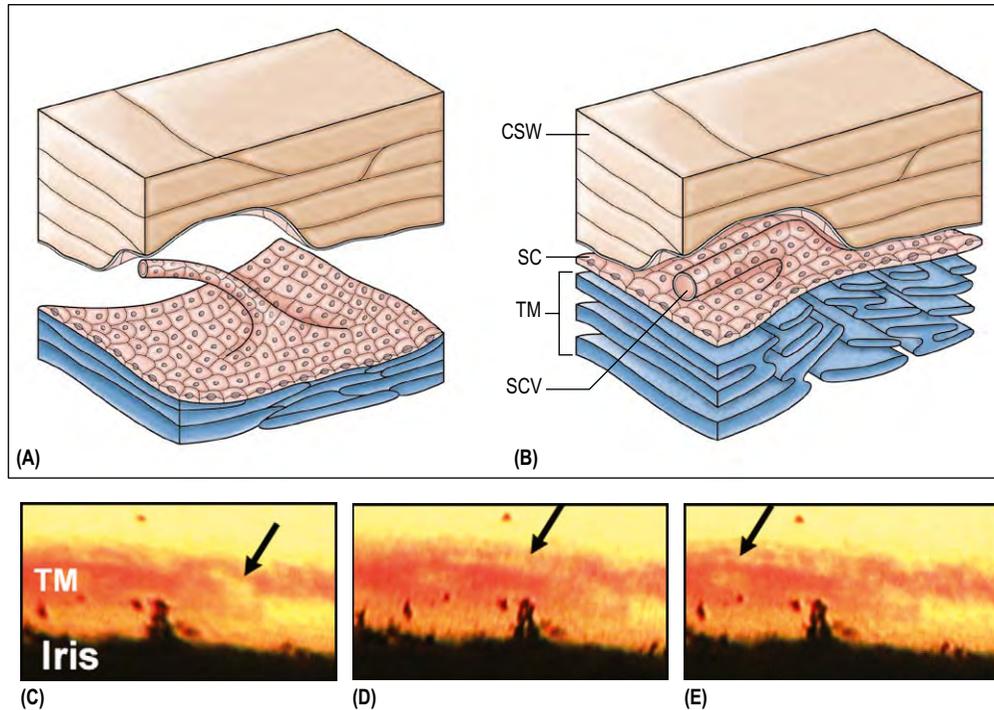


Fig. 3-9 Trabecular meshwork (TM) is collapsed and Schlemm's canal (SC) is widely dilated. Schlemm's canal valves (SCV) arise from inner wall of Schlemm's canal, then course across the canal to attach to the external or corneoscleral wall (CSW). **(A)** Intraocular pressure below episcleral venous pressure. Schlemm's canal valves are stretched across the dilated canal, the valve walls recoil and the valve lumen is small. Pressure surrounding the valves is higher than pressure in the lumen so blood cannot easily reflux through the valve lumen. **(B)** Aqueous outflow system appearance with IOP at physiologic levels. Schlemm's canal valves are oriented circumferentially in Schlemm's canal, the valve walls distend and the valve lumen is large. **(C, D, E)** Aqueous discharge to Schlemm's canal during one systolic pulse wave in the human eye. The transparent trabecular meshwork (TM) permits visualization of blood intentionally refluxed into Schlemm's canal. **(C)** Clear aqueous in funnel-shaped area at base of trabecular meshwork (arrow). **(D)** Regularly recurring sequential aqueous flow into more distal cylindrical region with site of initial swirling eddies of aqueous and blood indicating initial aqueous entry to Schlemm's canal (arrow). **(E)** Clear aqueous column ejected into Schlemm's canal as indicated by swirling eddies of mixing aqueous and blood cause circumferential flow along Schlemm's canal for a considerable distance (arrow) beyond initial mixing area identified in **D**. **(A and B)** from Johnstone MA: Pressure-dependent changes in the configuration of the endothelial tubules of Schlemm's canal, *Am J Ophthalmol* 78 : 630-8, 1974. Copyright by American Journal of Ophthalmology.) **(C-E)**, video courtesy of Robert Stegmann.)

Because of their oblique orientation, in single sections septa sometimes appear to be attached to Schlemm's canal posterior wall, but suspended unattached in Schlemm's canal anteriorly.¹⁵ Septa are composed of dense parallel collagen bundles that are continuous with and have staining characteristics identical to collagen bundles of the sclera.¹⁵ The septa typically join the collagenous walls of the canal rather than attaching to the trabecular meshwork.^{15,139} Although the canal is occasionally separated into channels, it is usually a single lumen.¹³⁹ Collector channels are at times quite large (50–70 micron) and course circumferentially adjacent to the canal for a considerable distance.^{87,139} In individual histologic sections, collagenous partitions between large collector channels and Schlemm's canal may be confused with septa within the canal and thus appear to divide the canal into more than one channel.^{87,139}

Schlemm's canal valves spanning across Schlemm's canal

Schlemm's canal valves arise from the inner wall endothelium of Schlemm's canal, develop a cylindrical configuration and course across the canal to attach to the external wall (Fig. 3-9).^{15,73,78,140-142} The valve walls are continuous with Schlemm's canal inner wall endothelium as documented by light, scanning, and transmission electron microscopy.^{15,73,78,140,141} Laboratory evidence of a lumen continuous with the juxtacanalicular space consists of studies with the dissecting,

light, scanning, and transmission electron microscope.^{15,73,140-143} Tracer studies demonstrate a communication between the anterior chamber and Schlemm's canal through the lumen of the structures using both antegrade and retrograde techniques.^{15,141} Pigment granules and amorphous extracellular matrix material are present in the lumen of the aqueous valves, a finding like that in the juxtacanalicular space.^{15,73,78,140-142} The valve walls distend and recoil in response to changes in IOP (see Fig. 3-9).^{15,140} The presence of Schlemm's canal valves is documented at the operating microscope in living human eyes during Schlemm's canal surgery.¹⁵ *In vivo*, aqueous enters Schlemm's canal in a pulsatile fashion through structures with a size and configuration like those characterized in the laboratory (see Fig. 3-9).¹⁵ Functionally, the aqueous valves have been proposed as part of a mechanical pump discharging aqueous to Schlemm's canal.^{15,140} The lumen of the valves is compressed between the walls of Schlemm's canal at a relatively low IOP of 25 mmHg.⁷⁸

Herniations or protrusions of Schlemm's canal inner wall

As the inner wall endothelium of Schlemm's canal distends outward in response to pressure, the distending endothelial wall forms projections, herniations or protrusions into Schlemm's canal.^{27,28,72,79,89,96,140} These protrusions do not attach between the walls of the canal, and the distention is completely reversible with movement

away from the external wall when pressure is low.^{27,28,72,79,89,96,140} Evidence indicates that there is no direct opening of the herniations into the canal.^{27,28,79,89,96,140} The original study of the aqueous valves illustrates, but does not emphasize, that the aqueous valves are always attached to the external wall of Schlemm's canal and have a valve-like arrangement at the level of the external wall.¹⁴⁰

One study interpreted the herniations as being the same structures as the aqueous valves and concluded that they could not carry aqueous to Schlemm's canal.¹⁴⁴ However, a salient feature of the aqueous valves is their attachment to the external wall, thus suspending them within the canal.^{15,140} The study of the protrusions or herniations completely separated the walls of Schlemm's canal, in the process disrupting the 'tissue strands'¹⁴⁴ or aqueous valves spanning the canal, and excluded the regions of disruption from observation.¹⁴⁴ Although the study was valuable in further characterizing the herniations or protrusions,¹⁴⁴ the study could not address the appearance or function of the valves spanning Schlemm's canal.^{15,78,140,141,143,145}

Collector channels, aqueous veins and episcleral veins

Schlemm's canal is drained by a series of collector channels that in turn drain into a complex system of intrascleral, episcleral, and subconjunctival venous plexus.^{146–149} The collector channels arise from the outer wall of Schlemm's canal at irregular intervals (0.3–2.8 mm) that average 1.2 per mm¹⁵⁰ creating a total of 20–30 collector channels.⁸⁷ At the origin of some collector channels, torus or lip-like openings are observed that are associated with septa.¹⁵⁰ Septa at collector channel ostia limit or prevent trabecular tissue from completely occluding the opening.^{27,150} A few (4–6) direct collector channels (≈ 70 micron diameter) proceed directly from Schlemm's canal through the sclera thus communicating directly with aqueous veins on the surface of the eye. Indirect collector channels are smaller (≈ 50 micron diameter), more numerous (15–20) and enter into the intrascleral drainage network. A few (4–6) intermediate types are present.¹⁵⁰ Aqueous veins empty into episcleral and conjunctival veins. Where aqueous and episcleral veins join, characteristic laminar flow of aqueous humor and blood is seen on slit-lamp examination at the limbus.^{10,12,13,151–154} A number of manifestations of pulsatile discharge of aqueous into the episcleral veins is also seen.^{10,12,13,151–154}

RESISTANCE SITES IN THE AQUEOUS OUTFLOW SYSTEM

Glaucoma results from an abnormality of the resistance characteristics of the outflow system, but the actual nature of that resistance remains controversial. The region of the trabecular beams is an unlikely source of significant resistance because of the large openings in the area and the lack of significant extracellular matrix material in the region. Investigators propose two very different models of the resistance location and mechanism. The first model envisions the main resistance localized to the juxtacanalicular space. The juxtacanalicular space acts as a syncytium of extracellular matrix material and elastic-like fiber network that attaches to Schlemm's canal endothelium. The syncytium must provide a sufficiently stable geometry so that the extracellular matrix material can act as a passive filter regulating resistance. After passing through the juxtacanalicular resistance, aqueous passes through low-resistance pores in Schlemm's canal endothelium.

The second model places the initial resistance to IOP-generated forces at Schlemm's canal endothelium. The model necessitates redistribution of IOP-induced resistive forces at Schlemm's canal endothelium to structural elements throughout a tensionally integrated trabecular meshwork. The force redistribution takes place via cytoplasmic process attachments to Schlemm's canal endothelium. A second component of the Schlemm's canal endothelium/trabecular meshwork resistance model is pressure-induced distention of Schlemm's canal inner wall: such a distention leads to apposition between Schlemm's canal walls. Schlemm's canal wall apposition thus becomes a resistance element integral to the model.

JUXTACANALICULAR SPACE RESISTANCE

The juxtacanalicular region is posited as a reasonable candidate for much of outflow resistance.^{71,85,155} Especially in non-pressurized eyes, the space is narrower than the region of the trabecular lamella and contains a greater concentration of extracellular and cellular elements than the rest of the meshwork.^{27–29,79,89,96,156,157} The juxtacanalicular space contains hyaluronic acid, other glycosaminoglycans (GAGs), other glycoproteins and fibronectin.⁶⁶ An elastic-like fiber network along with cellular elements, fibrils, and structural proteins is described as creating a three-dimensional cellular sponge or syncytium. One may deduce that such a stable syncytium will be able to provide a resistance unit restricting flow.⁷¹

Glycosaminoglycans have been proposed as a key physiologic component of this resistance. The GAGs are found as components of larger proteoglycans and generally function as a part of these larger molecules.^{155,158} The GAGs are heavily hydrated and able to trap a large amount of water. Therefore GAGs are able to fill a very large hydrodynamic volume.¹⁵⁸ Through hydration and fluid trapping mechanisms, the GAGs are proposed to reduce the functional diameter of flow channels through the juxtacanalicular tissues.^{155,158} A funneling mechanism dependent on the presence of GAGs and Schlemm's canal inner wall pores has been proposed to alter effective resistance to flow,¹⁵⁹ although two studies failed to find a correlation between outflow and pore density.^{66,122,125}

The previously discussed evidence is indirect, but direct evidence is cited to indicate that the region accounts for about 75% of resistance.¹⁶⁰ Because the evidence is direct, it assumes special importance and warrants careful scrutiny. The investigators carefully pointed out that the micropipette used to cannulate Schlemm's canal was 25 times the thickness of the highly compliant inner wall endothelium of Schlemm's canal and that the actual location of the tip was not known at the time of measurements.¹⁶⁰ They also referenced the previously identified compliance characteristics of the tissues as a possible cause of inaccurate interpretation of their results.²⁷ Two other studies, involving Schlemm's canal microcannulation, did not find a high proportion of the resistance within the juxtacanalicular space.^{161,162}

Alterations of extracellular matrix materials occur after laser trabeculoplasty.¹⁶³ Upregulation of metalloproteinase synthesis also accompanies improvement of aqueous outflow following laser trabeculoplasty. This relationship between metalloproteinase upregulation and outflow improvement is offered as evidence that alterations in the extracellular matrix distribution in the juxtacanalicular space contribute to outflow resistance.^{164–166} However, the response to injury is complex as is illustrated by evidence of repopulation of trabecular meshwork cells following injury.¹⁶⁷ Of interest, most of the extracellular matrix subject to remodeling responses is in the trabecular beams.

Some evidence does not favor the juxtacanalicular space resistance model. The model requires relatively unchanging juxtacanalicular space geometry so that the space may maintain its resistance characteristics. Studies of tissue biomechanics involving tissue loading described later in this chapter demonstrate that the juxtacanalicular space undergoes a two- to three-fold enlargement in response to physiologic increases in pressure. The same pressure increases induce marked increases in resistance, making the juxtacanalicular space a less likely site of significant resistance in normal eyes.

Although spaces are present in the juxtacanalicular region, in hypotonous eyes that may be construed as being filled and held open by a syncytium of extracellular matrix material, studies of biomechanics that examine boundary conditions indicate that extracellular matrix material does not act as a space-occupying syncytium. When IOP is reduced to zero in living eyes, blood refluxes into Schlemm's canal in response to the episcleral venous pressure gradient of about 8–9 mmHg. Under these conditions, the juxtacanalicular space does not act as a space-occupying syncytium. Rather, the juxtacanalicular space is almost completely obliterated.^{27,29,79,89,140} A pressure gradient reversal of as little as 5 mmHg causes obliteration of the space.¹⁶⁸ The elimination of the juxtacanalicular space in response to a modest pressure reversal is thought to indicate that the spaces within the juxtacanalicular region are dependent on hydrostatic pressure rather than on the rigidity induced by a syncytium of extracellular matrix material.⁷⁹

Histochemical studies provide additional insights.⁶⁶ For many years it was assumed that the apparently open spaces of the trabecular meshwork were filled completely with a GAG gel that was washed out in conventional histologic processing.¹⁶⁹ In recent years it has been possible to localize histochemically hyaluronan, and it is now clear that most of the open spaces are not filled with gel. Some hyaluronan is found in the juxtacanalicular region, but the amount decreases with age and no morphological study has demonstrated extracellular matrix that could generate the measured outflow resistance.^{98,169,170}

SCHLEMM'S CANAL ENDOTHELIUM RESISTANCE

Different lines of evidence support the idea of Schlemm's canal endothelium as the major site of resistance to aqueous outflow.³³ Tracer studies demonstrate accumulation of material at the inner wall of Schlemm's canal.^{25,33,118} Other evidence offered in support of Schlemm's canal endothelium as the main resistance site comes from the improvement in outflow facility that follows experimental infusion of certain substances, such as iodoacetic acid,¹⁷¹ *N*-ethylmaleimide,¹⁷² cytochalasin B or D,^{168,173–175} EDTA,^{176,177} and colchicine.¹⁷⁸ Histologic studies suggest that these agents alter the inner wall of Schlemm's canal.^{168,174,176,177} However, disruption of Schlemm's canal causes washout of extracellular material in the juxtacanalicular space.^{29,168} Because of the contemporaneous loss of extracellular matrix material with the above studies, disruption of Schlemm's canal endothelium is of unclear value in discriminating between the juxtacanalicular space and Schlemm's canal endothelium as the primary resistance site.

SCHLEMM'S CANAL ENDOTHELIUM/ TRABECULAR MESHWORK: A RESISTANCE UNIT

Studies of cellular biomechanics point to Schlemm's canal inner wall endothelium and the trabecular meshwork acting as a unified resistance unit.

PRINCIPLES OF BIOMECHANICS AS A METHODOLOGY TO IDENTIFY TISSUE RESISTANCE

The principles of biomechanics require, in turn, study of tissue geometry, tissue composition, laboratory effects of tissue loading, boundary conditions, and, finally, *in-vivo* effects of tissue loading.^{62,64} Tissue composition and geometry, issues discussed previously in this chapter, determine constraints and possible responses of the tissues to external forces.

Tissue loading studies subject tissues to normally encountered forces to determine force-induced responses. Load-bearing structural elements respond by characteristic changes in configuration. In other words, tissues causing the resistance are the ones that undergo configuration changes appropriate to the loading forces they experience.⁶² The applicable loading force in the aqueous outflow system is IOP. Boundary conditions define the maximum limits of tissue responses to induced forces. *In-vivo* tissue loading responses are discussed in a later section and are the most crucial test of the validity of conclusions from the laboratory.^{62,64}

TISSUE LOADING STUDIES

Tissue loading induced by IOP, both *in vitro* and *in vivo*, consistently demonstrates progressive distention of Schlemm's canal inner wall endothelium that correlates with IOP increases.^{15,27–29,72,73,78,79,89,96,106,140} Evidence from these same studies follows, demonstrating that the IOP-induced load on the endothelium is then distributed to the entire trabecular meshwork (see Fig. 3-4).^{15,27–29,72,73,78,79,89,96,106,140}

To induce tissue loading, the pressure gradient is systematically raised above zero (in the enucleated eye, pressure above hypotony, or in living eyes, pressure above episcleral venous pressure \approx 8–9 mm). Schlemm's inner wall begins its outward distention when the pressure gradient is as low as 5 mmHg.²⁷ Distention of Schlemm's canal inner wall continues progressively, both within the physiologic pressure range and beyond. Concomitantly, inner wall distention causes the juxtacanalicular space to enlarge,^{27–29,79,89,96,106} as much as two- to three-fold.^{27–29,90} Because of their anchoring attachments to the distending wall of Schlemm's canal endothelium, trabecular lamellae move progressively outward toward Schlemm's canal lumen, thus developing progressively increased spacing between lamellae.^{27–29,72,79,89,106,156} Cytoplasmic processes throughout the meshwork undergo progressive changes from a parallel to a perpendicular orientation.^{28,29} The processes, initially short and stubby, undergo elongation and thinning^{28,29} both in the juxtacanalicular and intertrabecular spaces. A more pronounced longitudinal orientation of the cytoskeletal filaments of the processes develops as IOP increases.²⁸

At the cellular level, Schlemm's canal endothelial cell membrane and cytoplasmic contents, as well as the nuclear envelope and its contents, change shape in a progressive fashion from a spherical configuration in hypotony to an elongated plate-like configuration.^{27–29,72,79,89,96,106,140} At cell process origins, the cytoplasm and nucleus reorganize from a neutral to an elongated cone-shaped configuration in response to tension.⁷² Juxtacanalicular cells undergo a change in configuration involving the cell membrane, the cytoplasm, the nuclear envelope, and the nuclear contents, all of which develop a progressively more cone-shaped appearance directed toward cell process origins.^{27,72} Such cellular changes are

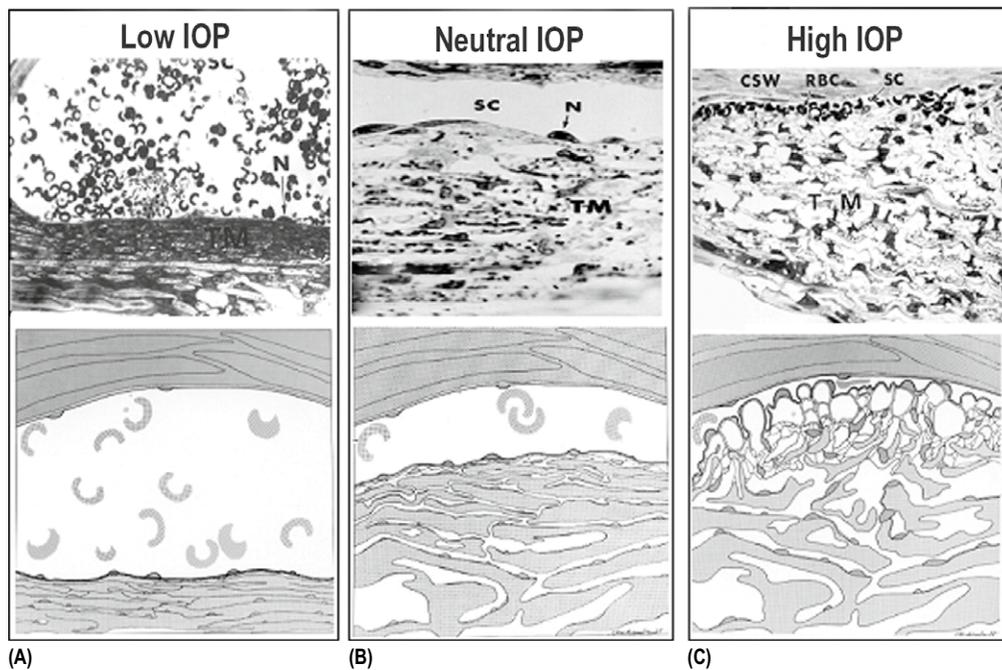


Fig. 3-10 Boundary conditions explore the limits of tissue excursions in response to physical forces. In the outflow system, boundary conditions are determined by maximal trabecular meshwork (TM) excursions induced by IOP. **Upper figures:** micrographs of boundary conditions. **Lower figures:** illustrations of boundary conditions. Upper figures **A** and **C**: micrographs of two eyes of same primate with eyes fixed simultaneously *in vivo*. **B**: human eye fixed in hypotony. **(A)** (Low IOP) IOP = 0 mmHg, episcleral venous pressure \approx 8 mmHg. Schlemm's canal (SC) is large and trabecular tissues are completely collapsed with obliteration of juxtacanalicular space. No further excursion is possible. **(B)** (Neutral IOP) Eyes fixed in hypotony, trabecular tissues in neutral position. **(C)** (High IOP) IOP = 25 mmHg during fixation. Schlemm's canal lumen is reduced to a potential space. Schlemm's canal endothelium distends to reach Schlemm's canal external or corneoscleral wall (CSW). No further excursion can take place when the external wall is reached. The juxtacanalicular space is large. Large spaces are present between the trabecular lamellae. Red blood cells (RBC) are present in SC. (N, nucleus of Schlemm's canal endothelial cell.)

(Modified from Johnstone MA, Grant WM: Pressure-dependent changes in structure of the aqueous outflow system in human and monkey eyes. *Am J Ophthalmol* 75:380, 1973. Published with permission from the American Journal of Ophthalmology.

reflective of stresses induced by progressive tension that develops between Schlemm's canal endothelium and the restraining trabecular lamellae.^{27-29,31,32,72,79,89,96}

Tissue loading by IOP thus provides evidence at both the tissue and cellular levels, placing trabecular meshwork resistance to IOP at Schlemm's canal endothelium. Attachments of Schlemm's canal endothelium to the underlying trabecular meshwork provide a dynamic tensional integration between the endothelium and the underlying load-bearing trabecular tissues.^{15,27-29,31,32,72,79,89,96} In contrast, tissue loading studies provide no evidence of hydraulic resistance in the juxtacanalicular space.^{15,27-29,31,32,72,79,89,96} Juxtacanalicular space enlargement and reduced compaction of both extracellular and cellular elements occurs.^{15,27-29,31,32,72,79,89,90,96,179} This juxtacanalicular space enlargement progressively reduces the ability of the juxtacanalicular space to act as a determinate of resistance, yet as IOP increases, measured resistance to aqueous outflow increases,¹⁸⁰⁻¹⁸² making this region an unlikely source of resistance.

BOUNDARY CONDITIONS

High IOP induces trabecular meshwork distention and Schlemm's canal lumen collapse (Fig. 3-10). As IOP progressively increases, Schlemm's canal endothelium progressively distends into the lumen

of the canal.^{27,28,31,73,79,89,90,96} At higher IOPs, Schlemm's canal endothelium becomes appositional to the external or corneoscleral wall of Schlemm's canal, effectively occluding much of the canal lumen.^{27,28,31,73,79,89,90,96} No further excursions can occur. Aqueous cannot easily pass across Schlemm's canal endothelium in these regions and circumferential flow to collector channel ostia is progressively compromised.⁹⁰ For example, in one report, one-third of sections had over 75% of the angle closed at 20 mmHg.⁹⁰ This finding in enucleated eyes may result from an absence of ciliary body tone and normal episcleral back pressure. However, in living primates, the walls of the canal also become appositional,^{27-29,73} with fairly extensive apposition present at a relatively low IOP of 20–25 mmHg.^{73,90}

Low IOP induces trabecular meshwork collapse and Schlemm's canal lumen dilation (see Fig. 3-10).^{27,29,78,79,89,96,140,168} When IOP is reduced below episcleral venous pressure (\approx 4–8 mmHg), Schlemm's canal endothelium moves inward toward the anterior chamber. The trabecular lamellae nearest Schlemm's canal are compressed together to form a uniform, solid-appearing sheet of tissue.^{27,29,78,79,89,96,140,168} No further excursions of Schlemm's canal endothelium can occur. Additionally, no blood crosses this tissue, leading in the initial report of the behavior²⁷ to the proposal that the configuration provides a means of assuring maintenance of the blood aqueous barrier.

RESISTANCE FROM APPPOSITION OF SCHLEMM'S CANAL WALLS

EVIDENCE FROM EXPERIMENTAL MICROSURGERY

Grant's microsurgical and perfusion studies stand as the foundation for characterizing the location of aqueous outflow resistance.^{183,184} Thus, it is important to understand the evidence and conclusions from his work. His earliest studies are often quoted, which indicated that 75% of aqueous outflow resistance is at the level of the trabecular meshwork.^{183,184} Grant's subsequent studies provide a very different picture, pointing to apposition between the walls of Schlemm's canal as the explanation for much of normal outflow resistance as well as abnormal resistance in glaucoma.

Grant's studies in normal enucleated eyes demonstrates that removal of the trabecular meshwork eliminates 75% of the resistance to aqueous outflow.¹⁸³ Trabecular meshwork removal also eliminates abnormal resistance found in glaucoma eyes.¹⁸⁴ The assumption was made that tissue removal with a cystitome was limited to the trabecular meshwork because gross examination during the procedure was consistent with a relatively precise removal of the meshwork tissue.¹⁸³

Later, Grant and co-workers duplicated the original studies,¹⁸⁵ duplicating the previous 75% improvement in aqueous outflow, this time including histologic evaluation. Histologic studies revealed that the cystitome damaged the external wall, collector channel ostia and structures within Schlemm's canal.¹⁸⁵ Grant and co-workers concluded that the outflow improvement seen in his earlier studies^{183,184} could not be entirely attributable to resistance generated by the trabecular meshwork and Schlemm's canal inner wall, because structures within the canal and along the external wall were also damaged.¹⁸⁵

Additional studies point to a relationship between the walls of Schlemm's canal as the probable cause of much of outflow resistance. Perfusion studies by Grant and colleagues demonstrate increasing resistance with increasing IOP,¹⁸⁰ a finding that is more prominent on glaucoma eyes.¹⁸⁰ Perfusion of the anterior chamber without peripheral iridectomy causes reverse pupillary block and chamber deepening, by pulling the scleral spur backward thus reducing Schlemm's canal wall apposition.¹⁸⁰ When the walls of Schlemm's canal are held more widely apart by this method, the increasing resistance with increasing pressure is eliminated.¹⁸⁰ These findings led Grant and co-workers to propose a new model involving apposition of Schlemm's canal inner wall and outer wall as the cause of increasing resistance.¹⁸⁰ Furthermore, the abnormally steep increase in resistance they found in glaucoma eyes led them to propose that the abnormality in glaucoma was a result of this same variable resistance mechanism associated with compression of the trabecular tissues against Schlemm's canal outer wall.¹⁸⁰

Further studies showed that removal of the external wall of Schlemm's canal causes greater than 50% reduction in outflow resistance, just as does removal of the internal wall.¹⁸⁶ The excess sum of resistances related to internalization or externalization of Schlemm's canal led them to conclude that an intact and unyielding outer wall of Schlemm's canal limits stretching of the inner wall and is required for maintenance of normal resistance.¹⁸⁶ The result is attributed to reduced ability of fluid to enter Schlemm's canal in regions of apposition and also reduced ability of aqueous to move circumferentially in Schlemm's canal to collector channel entrances.⁹⁰

Systematic tissue loading by IOP provided direct evidence that the trabecular meshwork progressively distends to come into apposition with the external wall of Schlemm's canal in enucleated,^{27,90} but more importantly in living, eyes.^{27,28,78,96} Extensive Schlemm's canal wall apposition begins to develop at relatively low pressures (20–25 mmHg)^{27,28,78,96} in the living eye with normal ciliary body tone and episcleral venous pressure. The septa around collector channel ostia tend to keep the two walls separated,^{27,29} but these regions only represent a small per cent of Schlemm's canal circumference. Van Buskirk and Grant¹⁸¹ found that aqueous humor did not flow more than 10° around the canal of enucleated human eyes. When a 30° trabeculotomy was done, facility calculations indicated that aqueous only flowed circumferentially a total of 10° to each side of the Schlemm's canal opening. When lens depression then further separated the walls of the canal, facility calculations indicated that aqueous flowed circumferentially a total of 35° on each side of the trabeculotomy site.

In support of the conclusion that facility improvement with circumferential flow is improved by reduction in Schlemm's canal apposition, the authors¹⁸¹ noted the effect of limited trabeculotomy reported by Barany et al.¹⁸⁷ Dilatation of Schlemm's canal by pilocarpine still has a large effect in improving facility,¹⁸⁷ indicating that circumferential flow is minimal after a limited trabeculotomy, and is consistent with a persistent facility improving benefit of pilocarpine related to its ability to reduce apposition of Schlemm's canal walls.¹⁸¹

Van Buskirk subsequently correlated lens depression experiments that dilate Schlemm's with perfusion and histologic data.⁹⁰ Resistance changes correlated with the degree of apposition between Schlemm's canal walls. Outflow facility was affected by lens depression 1% at 2.5 mmHg when there was no canal wall apposition, but 89% at 25 mmHg where significant apposition of Schlemm's canal was present.¹⁷⁹ As IOP increases causing increasing apposition of Schlemm's canal walls, lens depression to separate the walls is progressively more effective in improving flow with a remarkably high correlation coefficient of 0.97.

An additional study compared resistance characteristics at low pressure (7 mmHg) with those at higher pressure (25 mmHg) by doing sequential internal trabeculotomy.¹⁸⁸ At a higher pressure, where the canal walls are more extensively appositional, trabeculotomy has a greater effect on reducing resistance, further supporting the concept of Schlemm's canal apposition as the mechanism causing the variable resistance.¹⁸⁸

AQUEOUS OUTFLOW PHYSIOLOGY: PASSIVE AND DYNAMIC FLOW MODELS

THE AQUEOUS OUTFLOW SYSTEM AS A PASSIVE FILTER

The traditional model of aqueous flow is that of a passive, non-energy-dependent bulk fluid movement down a pressure gradient with aqueous leaving the eye primarily by the canalicular route.⁶⁶ The model is recognized as being somewhat oversimplified because of a component of uveoscleral flow.⁶⁶ In the model, aqueous is forced through a syncytium of extracellular matrix material in the juxtacanalicular space that acts as a passive resistance unit controlling pressure and flow.^{66,71} Evidence favoring the model is the finding of similar aqueous flow rates in living and enucleated eyes.^{183,184,189}

THE AQUEOUS OUTFLOW SYSTEM AS A DYNAMIC MECHANICAL PUMP

Aqueous flow through the outflow system has long been regarded as a passive phenomenon as noted above, but a recent model proposes that the outflow system acts as a biomechanical pump.¹⁵ The outflow system is constantly subjected to oscillatory pressure transients caused by the ocular pulse, blinking and eye movement.⁸⁴ In this model, elastic and contractile tissues of the trabecular meshwork and valves within Schlemm's canal stretch in response to transient pressure increases. The energy stored during distention is released when the pressure transients decay, causing the tissues to recoil to their prior configuration. The pressure transients thus enable energy-dependent pulsatile fluid movement through the outflow system.

Laboratory evidence of a highly compliant trabecular meshwork and valves^{27,140} predict the presence of a pumping mechanism in the outflow system coupled to IOP transients.⁸⁴ Aqueous outflow responses to pressure transients in humans represent a means of validating the predictions; in effect, a means of observing *in-vivo* tissue loading.⁶² The unique optical properties of the eye provide an opportunity to examine the effects of tissue loading at a scale usually associated with laboratory histologic examination. These observations at high magnification ($\times 80$) demonstrate pulsatile flow of aqueous from the anterior chamber into Schlemm's canal (see Fig. 3-9),¹⁵ and from Schlemm's canal into collector channels, a finding first observed by Stegmann.¹⁵ Pulsatile flow is synchronous with the ocular pulse. Pulsatile aqueous flow from Schlemm's canal into the episcleral veins is observed in response to the ocular pulse as well as in response to blinking and eye movements.^{10-12,14,15,151-153}

In the aqueous pump model, short-term pressure homeostasis occurs via alterations in the stroke volume of aqueous discharged to the episcleral veins in response to pressure transients.¹⁵ Long-term homeostasis occurs by intrinsic mechanotransduction mechanisms that optimize the pump function,¹⁵ analogous to homeostatic mechanisms elsewhere in the vasculature.^{15,62,83}

EXTRINSIC PRESSURE REGULATION MECHANISMS

A number of authorities have raised the question of whether the trabecular meshwork directly regulates IOP by extrinsic mechanisms.^{16,35,190,191} These authorities have postulated the existence of a receptor in the trabecular meshwork that responds to pressure or tissue distention and then provides feedback to modulate some process, such as aqueous humor formation,⁹⁶ ciliary muscle tone, or glycosaminoglycan synthesis.¹⁹¹⁻¹⁹³ Although this concept remains intriguing, there is no evidence to support that such a feedback system exists. In fact, in the studies done to date, elevations or depressions of IOP are not accompanied by substantial changes in the rate of aqueous humor formation,^{194,195} suggesting that pressure regulation is not aqueous secretion dependent (see Ch. 2).

UVEOSCLERAL FLOW

A lesser amount of the aqueous humor exits the eye by an alternate route through the ciliary muscle, the iris, the sclera, and other structures of the anterior segment (Fig. 3-11). This alternate pathway is known by a number of terms, including *uveoscleral*, *unconventional*, *extracanalicular*, and *uveovortex flow*. As Bill pointed out,¹²⁹ flow through the trabecular meshwork and Schlemm's canal seems

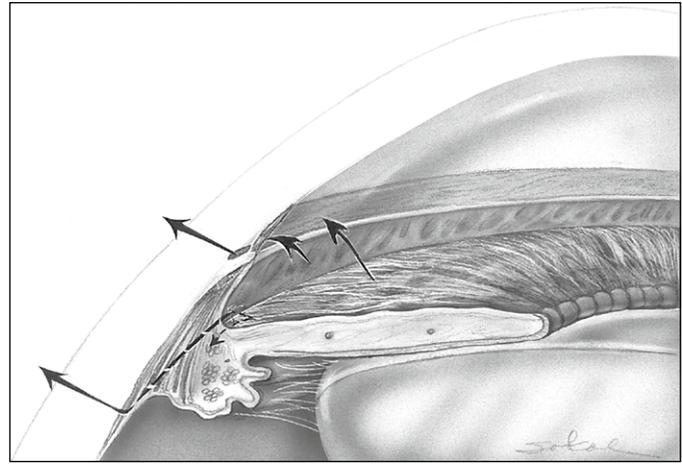


Fig. 3-11 Aqueous humor leaving the eye by trabeculocanalicular flow and uveoscleral flow.

to involve a well-designed system. In contrast, uveoscleral flow seems more primitive and resembles a leak more than a well-designed fluid transport system.¹⁹⁶

Aqueous humor enters the ciliary muscle through the uveal trabecular meshwork, the ciliary body face, and the iris root. The fluid passes posteriorly between the bundles of the ciliary muscle until it reaches the supraciliary and suprachoroidal spaces. Aqueous humor leaves the eye through the spaces around the penetrating nerves and blood vessels and through the sclera.^{3,7,9,197,198} Even large molecules such as horseradish peroxidase and albumin can pass through intact sclera.^{4,129,199}

A few investigators have questioned whether aqueous humor can exit the eye by entering the uveal vascular system. Tracer studies indicate that there is some exchange of substances between the aqueous humor and the plasma in the uveal blood vessels. However, the net fluid flow into the uveal vascular system is quite low for a number of reasons. First, the iris capillaries have thick walls that restrict movement of water and ions.¹²⁹ Furthermore, pressure in the uveal capillaries is higher than IOP. This pressure difference partially offsets the difference in oncotic pressure between the plasma and the tissue fluid of the uveal tract. Thus there is little driving force for fluid to cross the capillary walls.

Uveoscleral flow seems to be present in most species, but the portion of the aqueous humor transported by this system varies considerably. For example, unconventional flow constitutes about 3% of the total outflow in rabbit eyes but represents more than 50% of the total outflow in some species of monkeys. In human eyes, the unconventional pathway is estimated to carry 5–25% of the total aqueous outflow. It should be pointed out that direct measurements of uveoscleral flow in humans have been limited to a few eyes, many of which were scheduled for enucleation because of intraocular tumors.⁴ It is possible that such eyes are atypical and that the results are not representative of normal eyes. Calculations based on non-invasive measurements indicate that uveoscleral outflow may constitute as much as 35% of the outflow.^{196,200} Furthermore, in primate and human studies, uveoscleral outflow increases up to four-fold when the anterior segment is inflamed.^{199,201}

Uveoscleral flow has been studied with a variety of tracer substances, including fluorescein, radiolabeled molecules, and small plastic spheres.^{8,197,202} In human experiments,²⁰³ I-albumin can be traced by autoradiography from the anterior uveal tract to the posterior pole.⁴

Uveoscleral flow increases when IOP is raised from atmospheric pressure to the level of episcleral venous pressure. However, above this pressure level uveoscleral flow is largely independent of IOP. An increased IOP provides a greater driving force for uveoscleral flow, but it also compacts the anterior ciliary muscle bundles.^{198,204} These two factors must nearly offset one another, because in the uninflamed eye, the facility of uveoscleral flow is quite low at 0.02–0.052 $\mu\text{l}/\text{min}/\text{mmHg}$.^{7,199}

The main resistance to uveoscleral flow is the tone of the ciliary muscle. Factors that contract the ciliary muscle (such as pilocarpine) lower uveoscleral flow, whereas factors that relax the ciliary muscle (such as atropine) raise uveoscleral flow.^{205,206} Uveoscleral outflow is increased significantly by prostaglandins.^{207–211} Prostaglandins in low dose are among the most potent IOP-lowering agents available.^{212–217}

As mentioned above, pilocarpine decreases and atropine increases uveoscleral flow.^{205,206} This is consistent with a large body of work indicating that the therapeutic effect of pilocarpine in most glaucoma patients reflects increased trabecular outflow (caused by contraction of the ciliary muscle).^{203,218–225} Some studies have shown that pilocarpine antagonizes therapeutic prostaglandin agents,²²⁶ but clinical experience is mixed in this area.^{227,228} A few studies indicate that epinephrine may lower IOP, in large part by increasing uveoscleral flow.^{229–231} Cyclodialysis is an operation designed to lower IOP by detaching a portion of the ciliary body from the scleral spur. There is evidence that cyclodialysis acts to increase uveoscleral flow.^{195,229}

METHODS FOR MEASURING FACILITY OF OUTFLOW

FACILITY OF OUTFLOW CALCULATIONS

The Goldmann equation can be rearranged to give a simplified view of the factors that determine the ease with which aqueous humor leaves the eye by conventional outflow:

$$C = \frac{F}{P_O - P_V} \quad (3.1)$$

In this equation, C is the facility of outflow ($\mu\text{l}/\text{min}/\text{mmHg}$), F is the aqueous humor production ($\mu\text{l}/\text{min}$), P_O is the intraocular pressure (IOP) in the undisturbed eye (mmHg), and P_V is the episcleral venous pressure (mmHg). The factor referred to as C is often expressed as its reciprocal, R , which is the resistance to outflow ($\text{mmHg} \times \text{min} \times \mu\text{l}^{-1}$).

There are three common methods used to measure facility of outflow – tonography, perfusion, and suction cup. It is also possible to calculate the resistance to outflow from the Goldmann equation by measuring aqueous humor formation and IOP as discussed in Chapter 2.

Tonography

Tonography has been the most widely used clinical technique for measuring facility of outflow. Although most clinicians no longer use tonography as a routine clinical test, it is appropriate to discuss this technique in some detail because it has taught us much about the pathophysiology of glaucoma and the mechanism of action of various treatment modalities.¹⁸⁹

During tonography, a Schiötz tonometer is placed on the cornea for a few minutes. The weight of the tonometer increases IOP

and also increases the outflow of aqueous humor above its normal rate. The tonometer is usually connected to a continuous recording device that measures the subsequent decline of IOP over time. Using the Friedenwald tables, the change in the IOP readings allows the clinician to infer the volume of aqueous humor displaced from the eye.²³² If the assumption is made that the displacement of fluid from the eye, ΔV , is the only factor involved in the fall of IOP during the test, then the following equation is true:

$$\frac{\Delta V}{t} = \text{rate of fluid outflow} \quad (3.2)$$

If the weight of the tonometer raises IOP from its initial level of P_O to an average value of P_t , then the outflow facility, C , is calculated from Grant's equation¹⁸⁹ as follows:

$$C = \frac{\Delta V}{P_t - P_O} \quad (3.3)$$

Tonography was developed by Grant¹⁸⁹ and rests on a number of assumptions that can be debated, including those that follow:

1. An acute elevation of IOP alters nothing besides the rate of aqueous humor outflow. In fact, raising IOP with a Schiötz tonometer compresses the eye and affects outflow facility itself.²³³ In addition, tonography raises episcleral venous pressure by approximately 1.25 mmHg.²³⁴ Some clinicians correct for this effect by adding this number to P_O . Finally, acutely raising IOP may reduce aqueous humor formation.^{235–237} A drop in aqueous humor production would create the impression of an increased outflow facility, so this phenomenon has been termed *pseudofacility*. Recently, the concept of pseudofacility has been questioned because chronic changes in IOP are not accompanied by corresponding changes in aqueous humor formation.^{195,238,239} Even acute alterations of IOP do not appear to be accompanied by major changes in aqueous humor formation.^{236,240}

2. All eyes respond with similar distention of the ocular coats to the acute increase in IOP. In fact, the distensibility (usually expressed as its reciprocal term, ocular rigidity) varies considerably – that is, ocular rigidity is low in myopic eyes with thin sclera and high in some hyperopic eyes with thick sclera. The ophthalmologist can estimate ocular rigidity by comparing applanation and Schiötz pressure readings or by measuring IOP using a Schiötz tonometer with two or three different weights.

3. Raising IOP does not affect the ocular blood volume. In fact, when IOP is raised, blood is expelled from the eye. This means that the decline in IOP during tonography is not caused solely by aqueous humor leaving the eye.²⁴¹ Tonography is also subject to a number of errors, including operator errors, patient errors, instrument errors, and reading errors.

Perfusion

It is also possible to measure facility of outflow with a perfusion apparatus. This technique is used most often in animal eyes and enucleated human eyes, but it can also be used in living human eyes in an operative situation. With a needle in the anterior chamber, the pressure–flow relationships through the eye can be calculated by one of two methods. In the first method, known as constant-flow perfusion, IOP is measured after fluid is driven into the eye at a constant rate by a mechanical syringe. This process is repeated at two or more flow rates, and outflow facility, C , is calculated from

the formula below, in which F_2 and F_1 are the flow rates and P_2 and P_1 are the corresponding IOP readings:^{242,243}

$$C = \frac{F_2 - F_1}{P_2 - P_1} \quad (3.4)$$

In the second method, known as constant-pressure perfusion, a reservoir of fluid is placed at a known height above the eye, thereby fixing IOP. The amount of fluid entering the eye is calculated from the change in the weight of the reservoir over time. If this is done at two or more heights above the eye, outflow facility is calculated from the preceding formula.^{238,244}

Suction cup

The final method used to determine outflow facility is the suction cup. This device is applied to the sclera with a vacuum 50 mmHg below atmospheric pressure. The vacuum occludes intrascleral and episcleral venous drainage and raises IOP. The facility of outflow is calculated from the decline in IOP after the suction cup is removed. The suction cup technique usually gives lower values for outflow facility than does tonography.²⁴⁵

FACILITY OF OUTFLOW AND ITS CLINICAL IMPLICATIONS

At one time tonography was considered a crucial part of the work-up for every patient suspected of having glaucoma. Sometimes tonography was performed 30 to 60 minutes after the ingestion of a liter of water, which served as a type of stress test for the outflow system.²⁴⁶ It was also common to divide the IOP, P_O , by the outflow facility, C , to better separate glaucomatous eyes from normal eyes. The mean outflow facility in normal eyes ranged from 0.22 to 0.28 $\mu\text{l}/\text{min}/\text{mmHg}$ in various studies, and the mean P_O/C ratio ranged from 55 to 60.^{246,247}

Unfortunately, outflow facility and P_O/C are not distributed in a normal or Gaussian fashion, and there is considerable overlap between glaucomatous eyes and normal eyes (Table 3-1). When one considers this overlap and the lack of reproducibility of tonographic measurements, it is clear why clinicians no longer diagnose

Table 3-1 Tonographic results in glaucomatous eyes

	Normal eyes (n = 909)(%)	Glaucomatous eyes (n = 250)(%)
<i>C value</i>		
<0.18	2.5	65
<0.13	0.15	43
<i>P_O/C ratio</i>		
>100	2.5	73
>138	0.15	50
<i>P_O/C ratio after H₂O</i>		
>100	2.5	95
Modified from Becker B: Tonography in the diagnosis of simple (open angle) glaucoma. <i>Trans Am Acad Ophthalmol Otolaryngol</i> 65:156, 1961.		

glaucoma on the basis of outflow facility. Tonography may be unnecessary or redundant in many clinical settings, but it still has an important role in laboratory and clinical research.

FACTORS AFFECTING THE FACILITY OF OUTFLOW

Many factors influence the facility of outflow (Table 3-2), including those discussed here.

Table 3-2 Factors affecting aqueous humor outflow

Factor	Effect	Comments
Age	Decrease	
<i>Hormones</i>		
Corticosteroids	Decrease	
Progesterone	Increase	
Relaxin	Increase	
Chorionic gonadotropin	Increase	
Thyroxin	Increase	Questionable
Ciliary muscle tone	Increase	
Anterior chamber depth	Increase	Increases with increasing depth
<i>Drugs</i>		
Parasympathomimetic agents	Increase	
Parasympatholytic agents	Decrease	
Ganglionic blocking agents	Decrease	
Bradykinin	Increase	
Cyclic adenosine monophosphate	Increase	
Substance P	Decrease	
<i>Surgery</i>		
Argon laser trabeculoplasty	Increase	
Filtering surgery	Increase	
Cyclodialysis	Increase	
Cataract extraction	Decrease	Temporary effect
Penetrating keratoplasty	Decrease	Temporary effect
Water ingestion	Decrease	
<i>Neural regulation</i>		
III nerve stimulation	Increase	
III nerve ablation	Decrease	
Sympathetic stimulation	Increase	
Sympathectomy	Increase	Temporary effect
<i>Particulate matter</i>		
Red blood cells	Decrease	
White blood cells	Decrease	
Pigment	Decrease	
Heavy molecular weight protein	Decrease	
Hyaluronic acid	Decrease	
α -Chymotrypsin	Decrease	
Macrophages with foreign material	Decrease	

AGE

There is a modest decline in outflow facility with age.^{248–250} This decline appears to counterbalance a similar decrease in aqueous humor formation. Histologic studies indicate a number of age-related changes in the trabecular meshwork, including thickening and fusion of the trabecular sheets, degeneration of collagen and elastic fibrils, accumulation of wide-spacing collagen, loss of endothelial cells, hyperpigmentation of the endothelial cells, accumulation of intracellular organelles, accumulation and alteration of extracellular matrix, and decrease in the number of giant vacuoles.^{251–254}

HORMONES

A number of investigators have postulated that endogenous glucocorticoids regulate aqueous humor outflow.²⁵⁵ Corticosteroids administered topically, systemically, or periocularly are capable of reducing outflow facility. The response to corticosteroids appears to be genetic in part and is greater in certain groups, including patients with primary open-angle glaucoma (POAG) and their first-degree relatives, myopic patients, and diabetic patients. This subject is reviewed at length in Chapter 18. Other hormones, such as progesterone,^{256,257} thyroxin,²⁵⁸ relaxin, and chorionic gonadotropin,²⁵⁸ have been postulated to influence outflow facility in physiologic or pharmacologic doses. Other active substances, such as prostaglandins, substance P, and angiotensin, may affect aqueous outflow.^{259,260}

CILIARY MUSCLE TONE

Increased tone of the ciliary muscle increases total outflow facility. The increased tone can be the result of accommodation,^{261,262} electrical stimulation of the oculomotor nerve, posterior depression of the lens,^{28,29,181} or administration of parasympathomimetic drugs such as pilocarpine.²⁰⁶ The increased muscle tone pulls the scleral spur posteriorly and internally, which opens the intertrabecular spaces and Schlemm's canal (see Fig. 3-3).

DRUGS

Pilocarpine and other cholinergic agents increase outflow facility.²⁰⁶ Adrenaline (epinephrine) and dipivefrin and other β -adrenergic agonists increase both conventional and unconventional outflow.^{230,231,263,264} The parasympatholytic agents and the ganglionic blocking agents reduce outflow facility. Prostaglandins increase uveoscleral outflow.^{207–211} Alpha agonists decrease aqueous production and increase uveoscleral outflow.²⁶⁵ Bradykinin was noted to increase outflow facility in one study.²⁶⁶

SURGICAL THERAPY

Argon laser trabeculoplasty improves outflow facility. Cataract extraction and penetrating keratoplasty reduce outflow facility temporarily, perhaps by deforming the trabecular meshwork and reducing its support.²⁶⁷ Cyclodialysis, as mentioned previously, increases uveoscleral outflow.^{129,195}

DIURNAL FLUCTUATION

There has been considerable controversy about whether or not there is a diurnal fluctuation of outflow facility.^{255,268,269}

GLAUCOMA

Outflow facility is reduced in most forms of glaucoma. This can occur through a variety of mechanisms, depending on the type of glaucoma. In primary infantile glaucoma, the outflow structures develop improperly (see Ch. 19). In angle-closure glaucoma, the peripheral iris is pushed or pulled against the trabecular meshwork, preventing aqueous humor from reaching the outflow channels (see Chs 15 and 16). The trabecular meshwork can also be covered by a membrane, as in epithelial downgrowth, neovascular glaucoma, or the iridocorneal endothelial syndrome.

In the secondary open-angle glaucomas, the trabecular meshwork can be obstructed by a variety of particulate matter, including red blood cells, white blood cells, tumor cells, ghost cells, zonular fragments (after α -chymotrypsin), pigment particles, and lens particles (see Ch. 18). The meshwork can also be obstructed by non-particulate foreign matter, such as lens protein and viscoelastic substances.

There is great controversy about the fundamental defect of the outflow channels in POAG. A variety of theories have been proposed to explain the decreased outflow facility of this disease, including (1) an accumulation of foreign material in the trabecular meshwork; (2) a loss of trabecular endothelial cells; (3) a collapse of Schlemm's canal, and (4) an obstruction of the collector channels. This subject is discussed at length in Chapter 17.

EPISCLERAL VENOUS PRESSURE

Aqueous humor leaving the eye by trabeculocanalicular outflow eventually passes into the venous system. The pressure in the veins that receive the aqueous humor is referred to as *episcleral venous pressure*.

Episcleral venous pressure can be measured by a variety of techniques, including pressure chambers,^{234,270–275} torsion balance devices,^{271,276} force displacement transducers, air jets,²⁷⁰ and direct cannulation.¹⁷⁸ Most studies of normal human eyes find episcleral venous pressure to be in the range of 8–11.5 mmHg (Table 3-3). The venous pressure levels are affected by body position but do not vary in constant fashion from quadrant to quadrant of the eye. Most studies find no correlation between episcleral venous pressure and age,^{249,275} although there is one conflicting report.²⁷⁴

Table 3-3 Episcleral venous pressure in human eyes

Author	Value in normal eyes (mmHg \pm SD)	Value in glaucomatous eyes (mmHg \pm SD)
Brubaker ²⁷¹	9.1 \pm 0.14	–
Leith ²⁷⁷	10.5	11.0
Linner, Rickenbach, and Werner ²⁷⁸	11.6 \pm 1.2	12.6 \pm 1.7
Lohleim and Weigelin ²⁷⁹	9.7 \pm 2.2	8.0 \pm 1.2
Phelps and Armaly ²⁷²	9.7 \pm 2.2	–
Podos, Minas, and Macri ²⁸⁰	9.0 \pm 1.4	–
Rickenbach and Werner ²⁸¹	11.4 \pm 1.5	9.3 \pm 1.3
Talusan and Schwartz ²⁷⁴	9.1	–
Zeimer and co-workers ²⁷⁵	7.6 \pm 1.3	–

There is considerable controversy about whether episcleral venous pressure is altered in glaucoma (excluding those cases of secondary glaucoma caused by elevated episcleral venous pressure). Some investigators report similar episcleral venous pressure levels in normal and glaucomatous eyes,^{277,280} whereas others report lower episcleral venous pressure in glaucomatous and ocular hypertensive eyes (see Table 3-3).^{276,279,281} It should be emphasized that even in the studies that find lower episcleral venous pressure in glaucomatous eyes, the differences in pressure are small: the largest reported mean difference between glaucomatous patients and normal individuals is approximately 2 mmHg.²⁷⁹ From this it is clear that episcleral venous pressure is not a factor in the pathogenesis of POAG. Elevated episcleral venous pressure can be the cause of secondary glaucoma in a number of conditions that are reviewed in Chapter 18.

There are a number of experimental techniques described for raising episcleral venous pressure. The most commonly used method in humans is to place a cuff about the neck with sufficient pressure to impede venous return.^{249,282} Under these conditions, IOP rises by about 0.8 mmHg for every 1 mmHg increase in episcleral venous pressure. When episcleral venous pressure is raised by some disease process, IOP is usually increased as well. However, the relationship between the pressure increases is more complex in the chronic situation than in the acute experimental situation. Many conditions (e.g., carotid cavernous fistula) that increase episcleral venous pressure also cause ocular ischemia, which reduces aqueous humor formation and IOP.²⁸³ Furthermore, acute elevations of episcleral venous pressure increase the facility of outflow, whereas chronic elevations may produce secondary changes in the angle structures and decrease the outflow facility (see Ch. 18).²⁸²

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Intraocular pressure

INSTRUMENTS FOR MEASURING INTRAOCULAR PRESSURE

It is possible to measure intraocular pressure (IOP) directly in a living eye using a manometric technique. For this approach a needle is inserted into the anterior chamber through a self-sealing, beveled corneal puncture. The needle is connected to a fluid-filled tubing, and the height of the fluid in the tubing corresponds to IOP. The tubing can also be connected to a fluid-filled reservoir that has a pressure-sensitive membrane. The movement of the membrane, recorded optically or electronically, is a measure of IOP.¹ Although the direct method is perhaps the most accurate, its obvious clinical limitations necessitate alternative means for measuring pressure in patients.

Most techniques for measuring IOP in clinical use are indirect in that they are based on the eye's response to an applied force. A good example of this process is palpation, during which the examiner estimates IOP by the response of the eye to digital pressure – that is, he or she determines whether the globe indents easily or whether it feels firm to the touch. Palpation should be used only in the most extraordinary circumstances because it is capable of detecting only gross alterations of IOP. Even in ideal circumstances palpation is notoriously inaccurate, and the examiner may over- or underestimate the IOP by large amounts.² However, with practice, some doctors are able to get a reasonably accurate estimate of IOP which may be especially useful in patients with irregular corneas where applanation tonometry may not be possible.³

Traditionally, tonometers could be divided into two major groups, referred to as *applanation* and *indentation* instruments. With applanation instruments, the clinician measures the force necessary to flatten a small, standard area of the cornea. With indentation instruments, the clinician measures the amount of deformation or indentation of the globe in response to a standard weight applied to the cornea. More recent tonometers work on different principles such as contour matching, transpalpebral phosphene induction, indentation/rebound and intraocular implantation of pressure sensors.

APPLANATION INSTRUMENTS

Goldmann tonometer

Because the Goldmann tonometer has been the international clinical standard for measuring IOP, it is appropriate to discuss this instrument at some length (Fig. 4-1). The Goldmann tonometer determines the force necessary to flatten (or applanate) an area of the cornea 3.06 mm in diameter – a technique referred to as

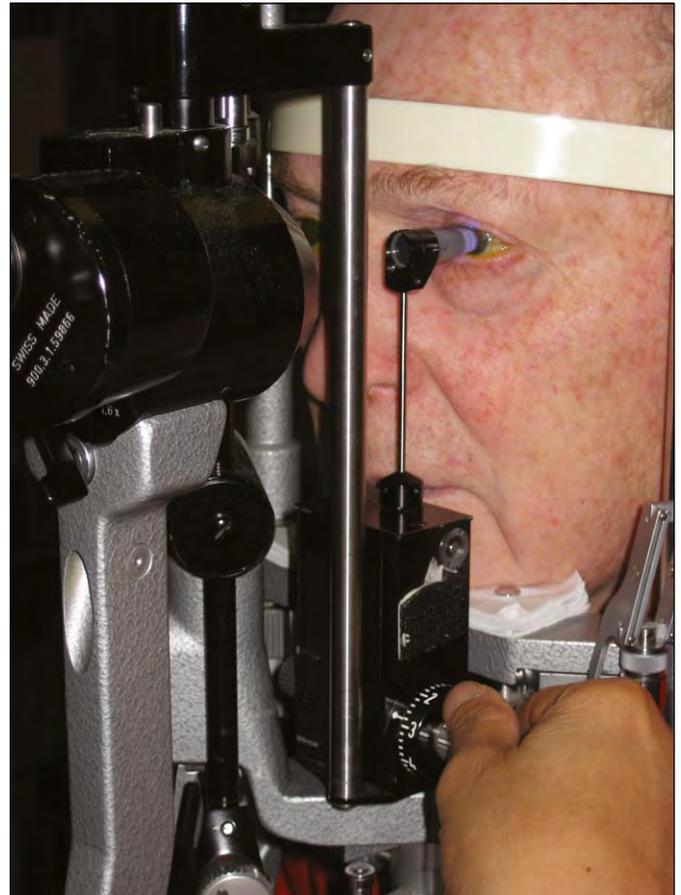


Fig. 4-1 Goldmann tonometer on the eye.

constant-area applanation. For this area of applanation and in a cornea of average thickness, the force required to bend or deform the cornea is approximately equal in magnitude and opposite in direction to the capillary attraction of the tear film for the tonometer head. Thus, under these conditions, these two forces cancel out one another. When the cornea is flattened, the force of the tonometer – supplied by a coiled spring or a weight – counterbalances and provides a measure of IOP. For this area of applanation, the IOP in millimeters of mercury is equal to the force of the tonometer in grams multiplied by 10 (Fig. 4-2).

Applanation tonometry displaces only about 0.5 μ l of aqueous humor, which raises IOP by about 3% – that is, P_t (the pressure

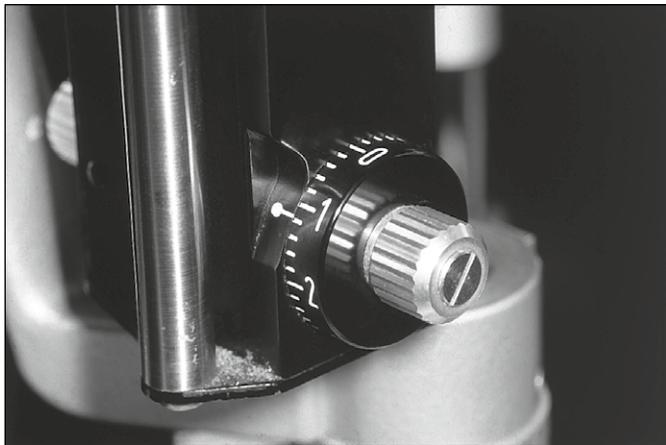


Fig. 4-2 Goldmann applanation tonometer. Dial indicates force applied to appanate cornea; this number multiplied by 10 equals intraocular pressure in millimeters of mercury.

at that moment) is 3% greater than P_O (the pressure in the undisturbed eye). Because the volume displaced is so small, ocular rigidity, or the 'stretchability' of the globe, has little effect on the pressure readings.^{4,5} In general, larger volumes are displaced with indentation tonometers, and a stretchable eye with low ocular rigidity may allow a greater degree of indentation per gram of force than the average eye, and thus indicates a falsely low pressure.

The degree of applanation is judged while viewing the cornea through a split prism device in the applanating head. To better distinguish the tear film and the cornea, which have similar refractive indexes, fluorescein is instilled in the anesthetized conjunctival cul-de-sac. When the front surface of the eye is illuminated with a cobalt blue filter, the fluorescein-stained tear film appears bright yellow-green. When the clinician looks through the split prism in contact with the eye, he or she sees a central blue circle, the flattened cornea, surrounded by two yellow-green semicircles. When the inner margins of the two semicircles are aligned in a smooth S curve at the midpoint of their pulsations, the proper degree of applanation has been achieved.

Goldmann tonometry is quite accurate and reproducible if the proper technique is used. Interobserver variability is in the range of 0–3 mmHg,^{6,7} which is less than the diurnal variation of IOP. The technique of Goldmann tonometry is as follows:

1. The patient is asked not to drink alcoholic beverages or large amounts of fluid (e.g., 500 ml or more) for 2 hours before the test, as the former will lower IOP and the latter may raise it.
2. The patient is told the purpose of the test and is reassured that the measurement is not painful. The patient is instructed to relax, maintain position, and hold the eyes open wide.
3. One drop of a topical anesthetic, such as 0.5% proparacaine, is placed in each eye, and the tip of a moistened fluorescein strip is touched to the tear layer on the inner surface of each lower lid. Alternatively, one drop of a combined anesthetic–fluorescein solution can be instilled in each eye. Contact lenses should be removed before the fluorescein is applied. Soft contact lenses can be irreversibly stained by fluorescein. Newer fluorescent solutions such as high molecular weight fluorescein or fluorexon do not stain soft contact lenses and may be used as substitutes in those patients.⁸

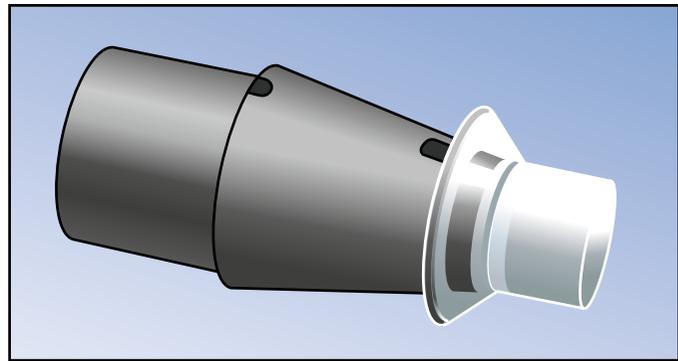


Fig. 4-3 Disposable tonometer tip designed to fit over Goldmann prism. (Tonosafe, Clement Clarke, UK)

4. The tonometer tip is cleaned with a sterilizing solution,^{2,9–12} and the tip and prism are set in correct position on the slit lamp. Care should be taken that the disinfecting solution is dry or wiped off the tip before applying the tip to the eye, as many of these solutions, especially alcohol-based ones, can be irritating to the eye or toxic to the epithelium and lead to a corneal abrasion. Sterile tonometer tip covers may be used rather than a disinfecting solution, if preferred.¹³ Disposable tonometer tips may also be used (Fig. 4-3).^{14,15} When using disposable tips, they should each be examined to be sure of a smooth applanating surface.¹⁶ The acrylic disposable tips seem to be somewhat more accurate than the silicone ones.¹⁷ While disposable shields or tips may be safer than disinfecting solutions, they are not 100% protective against prion disease.¹⁸

5. The tension knob is set at 1 g. If the knob is set at 0, the prism head may vibrate when it touches the eye and damage the corneal epithelium. The 1 g position is used before each measurement. As a rule, it is more accurate to measure IOP by increasing rather than decreasing the force of applanation.

6. The 0 graduation mark of the prism is set at the white line on the prism holder. If the patient has more than 3 D of corneal astigmatism, the area of contact between the cornea and the prism is elliptic rather than circular. In this situation the prism should be rotated to about 45° from the long axis of the ellipse – that is, the prism graduation corresponding to the least curved meridian of the cornea should be set at the red mark on the prism holder.¹⁹ An alternative approach is to average the IOP readings obtained with the axis of the prism horizontal and then vertical.^{20,21}

7. The cobalt filter is used with the slit beam opened maximally. The angle between the illumination and the microscope should be approximately 60°. The room illumination is reduced.

8. The patient is seated in a comfortable position on an adjustable stool or examining chair facing the slit lamp. The heights of the slit lamp, chair, and chin rest are adjusted until the patient is comfortable and in the correct position for the measurement. The patient's chin is supported by the chin rest, and the forehead by the forehead bar. The forehead bar should be well above the patient's eyebrows, so the frontalis muscle can be used to open the eyes wide. The patient's collar should be loosened if necessary. The patient should breathe normally during the test to avoid Valsalva's maneuver.

9. The palpebral fissure is a little wider if the patient looks up. However, the gaze should be no more than 15° above the

horizontal to prevent an elevation of IOP that is especially marked in the presence of restrictive neuromuscular disease such as dysthyroid ophthalmopathy.^{22,23} A fixation light may be placed in front of the fellow eye. The patient should blink the eyes once or twice to spread the fluorescein-stained tear film over the cornea, and then should keep the eyes open wide. In some patients, it is necessary for the examiner to hold the eyelids open with the thumb and forefinger of one hand. Care must be taken not to place any pressure on the globe because this raises IOP. Resting the thumb and forefinger against the orbital rim while retracting the lids may help the examiner avoid putting pressure on the globe.

10. The operator sits opposite the patient, in position to look through the microscope, and moves the assembly toward the subject. When the black circle near the tip of the prism moves slightly, it indicates contact between the prism and the globe. Alternatively, the assembly is advanced toward the patient with the tester observing from the side until the limbal zone has a bluish hue. Yet another approach is to use the white-appearing rings seen through the prism just before contact with the cornea is made, and these can be used to align the prism so that adjustment, once contact is made, is minimized.²⁴ The biprism should not touch the lids or lashes because this stimulates blinking and squeezing. If the tonometer tip touches the lids, the fluorescein rings will thicken, which may cause an overestimation of IOP.

11. The clinician observes the applanation through the biprism at low power. A monocular view is obtained of the central applanated zone and the surrounding fluorescein-stained tear film. Using the control stick, the observer raises, lowers, and centers the assembly until two equal semicircles are seen in the center of the field of view. If the two semicircles are not equal in size, IOP is overestimated. The clinician turns the tension knob in both directions to ensure that the instrument is in good position. If the semicircles cannot be made 'too small,' the instrument is too far forward. If the semicircles cannot be made 'too large,' the instrument is too far from the eye.

12. The fluorescein rings should be approximately 0.25–0.3 mm in thickness – or about one-tenth the diameter of the flattened area. If the rings are too narrow, the patient should blink two or three times to replenish the fluorescein; additional fluorescein may be added if necessary. If the fluorescein rings are too narrow, IOP is underestimated. If the fluorescein rings are too wide, the patient's eyelids should be blotted carefully with a tissue, and the front surface of the prism should be dried with lint-free material. An excessively wide fluorescein ring is less of a problem than a very narrow ring, but can cause IOP to be overestimated.

13. The fluorescein rings normally undergo a rhythmic movement in response to the cardiac cycle. The tension knob is rotated until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsations.

14. Intraocular pressure is measured in the right eye until three successive readings are within 1 mmHg. Intraocular pressure is then measured in the left eye.

15. The reading obtained in grams is multiplied by 10 to give the IOP in millimeters of mercury. This value is recorded along with the date, time of day, list of ocular medications, and time of last instillation of ocular medication.

16. It is possible to transfer bacteria, viruses, and other infectious agents with the tonometer head,²⁵ including such potentially serious infections as epidemic keratoconjunctivitis, hepatitis B, Jacob-Kreutzfeld and, theoretically, acquired immunodeficiency

Box 4-1 Potential errors of applanation tonometry

- Thin cornea
- Thick cornea
- Astigmatism >3 diopters
- Inadequate fluorescein
- Too much fluorescein
- Irregular cornea
- Tonometer out of calibration
- Elevating the eyes >15°
- Repeated tonometry
- Pressing on the eyelids or globe
- Squeezing of the eyelids
- Observer bias (expectations and even numbers)

syndrome. The biprism should be rinsed and dried immediately after use. Between uses, the prism head should be soaked in a solution such as diluted bleach or 3% hydrogen peroxide.²⁶ Seventy per cent ethanol and 70% isopropanol are effective as sterilizing solutions but were shown in one study to cause mild damage to the tonometer tip after one month of immersion.^{27,28} Care must be taken to be sure any sterilizing solution has been completely rinsed off the tonometer tip, as some of these solutions may be toxic to the corneal epithelium, especially after LASIK or other corneal procedures.²⁹ If the tonometer tip is not mechanically wiped after each use, epithelial cells may stick to the tip with the small but serious risk of transmitting Jacob-Kreutzfeld virus.³⁰ Disposable tonometer tips may be an acceptable alternative to soaking in, and wiping with, antiseptic solutions.³¹

17. The Goldmann tonometer should be calibrated at least once a month. If the Goldmann tonometer is not within 0.1 g (+1 mmHg) of the correct calibration, the instrument should be repaired; however, calibration errors of up to +2.5 mmHg may still be tolerated clinically. In one large clinic, approximately one-third of the tonometers were out of calibration at one month and one-half at four months.³² In addition, tonometer tips should be examined periodically under magnification as the antiseptic solutions and mechanical wiping may cause irregularities in the surface of the tip that can, in turn, injure the cornea.³³

Although the Goldmann tonometer is reliable and accurate through a wide range of IOPs, errors in measurement can arise from a number of factors, including those that follow (Box 4-1):

1. Inadequate fluorescein staining of the tear film causes an underestimation of IOP. This commonly occurs when too much time elapses between the instillation of the fluorescein and the measurement of the pressure. To avoid this problem the IOP should be measured within the first minute or so after instilling the fluorescein.

2. Elevating the eyes more than 15° above the horizontal causes an overestimation of IOP.

3. Widening the lid fissure excessively causes an overestimation of IOP.³⁴

4. Repeated tonometry reduces IOP, causing an underestimation of the true level.^{35,36} This effect is greatest between the first and second readings, but the trend continues through a number of repetitions.⁷

5. A scarred, irregular cornea distorts the fluorescein rings and makes it difficult to estimate IOP.

6. The thickness of the cornea affects IOP readings.³⁷ If the cornea is thick because of edema, IOP is underestimated.³⁷ If the cornea is thick because of additional tissue, IOP is overestimated.^{37,38} In thin corneas, the Goldmann tonometer will underestimate the IOP.^{39–41} Goldmann predicted that the tonometer would be inaccurate with thin and thick corneas, but failed to realize (since he measured corneal thickness in only a few citizens of Bern) the wide variation in corneal thickness seen in normal individuals. Some have suggested applying correction factors to the readings in corneas whose thickness is less than 545 microns or greater than 600.⁴² However, the errors are not linear and no formula has yet been derived that is accurate across the range of corneal thickness and intraocular pressures. It is probably best to use the corneal thickness as a rough guide to the direction and magnitude of the error but avoid the temptation to achieve a precision with a formula that does not match accuracy. The Goldmann tonometer is accurate after epikeratophakia.⁴³ Central corneal pressures have been shown to be lower than peripheral corneal readings following photorefractive keratectomy and LASIK.^{44–47}

7. If the examiner presses on the globe, or if the patient squeezes his eyelids, IOP is overestimated. Taking time to reassure the patient and taking care to avoid causing pressure against the globe can help guard against these problems.

8. If corneal astigmatism is greater than 3D, IOP is underestimated for with-the-rule astigmatism and overestimated for against-the-rule astigmatism.²⁰ The IOP reading is inaccurate 1 mmHg for every 3D of astigmatism.⁴⁸

9. A natural bias for even numbers may cause slight errors in readings.⁴⁹

Perkins tonometer

The Perkins tonometer is similar to the Goldmann tonometer, except that it is portable and counterbalanced, so it can be used in any position.⁵⁰ This instrument is useful in a number of situations, including in the operating room, at the bedside, and with patients who are obese or for other reasons cannot be examined at the slit lamp. The light comes from batteries, and the force comes from a spring, varied manually by the operator. Because the Perkins tonometer is portable, it is useful in circumstances in which the patients or subjects do not have access to an examination room, such as in community or remote pressure screening sessions. This tonometer does seem to underestimate the IOP, at least in Chinese eyes in supine patients, and the underestimation increases as the true IOP increases.⁵¹

Draeger tonometer

The Draeger tonometer is similar to the Goldmann and Perkins tonometers, except that it uses a different biprism. The force for applanation is supplied by an electric motor.^{52,53} Like the Perkins instrument, the Draeger tonometer is portable and counterbalanced, so it can be used in a variety of positions and locations.

MacKay-Marg and Tono-Pen™ tonometers

The MacKay-Marg tonometer consists of a movable plunger, 1.5 mm in diameter, that protrudes slightly from a surrounding footplate or sleeve. The movements of the plunger are measured by a transducer and recorded on a paper strip. When the instrument touches the cornea, the plunger and its supporting spring are

opposed by the IOP and the corneal bending pressure (Fig. 4-4A). As the instrument is advanced to the point of applanation, the corneal bending pressure is transferred to the footplate, and a notch is seen in the pressure tracing (Fig. 4.4B). The height of the notch is the measure of IOP. When the instrument is advanced farther, the cornea is indented farther, and IOP rises (Fig. 4.4C).^{54–56} The transfer of the corneal bending force occurs at an applanation area 6 mm in diameter. Applanation over this area displaces approximately 8 μ l of aqueous humor and raises IOP about 6–7 mmHg – P_i is 6 or 7 mmHg higher than P_o .

The MacKay-Marg tonometer measures IOP over a brief interval, so several readings should be averaged to reduce the effects of the cardiac and respiratory cycles. This instrument is useful for measuring IOP in eyes with scarred, irregular, or edematous corneas because the end point does not depend on the evaluation of a light reflex sensitive to optical irregularity, as does the Goldmann tonometer. The tip of the instrument is covered with a plastic film to prevent transfer of infection. The tonometer is calibrated by comparing the plunger displacement with gravity to a fixed number of units on the tonometer recording paper. The MacKay-Marg tonometer is also fairly accurate when used over therapeutic soft contact lenses.⁵⁷

A small portable applanation tonometer that works on the same principle as the MacKay-Marg tonometer is available (Fig. 4-5) (Tono-Pen® XL, Medtronic, Minneapolis, MN). It appears to be accurate in common clinical situations but not quite as accurate as the Goldmann outside the physiologic range.^{58,59} The accuracy of the Tono-Pen can be improved by taking two readings and averaging them.⁶⁰ Unfortunately, because it is an applanation device, the results of the Tono-Pen are affected by corneal thickness just like the Goldmann tonometer.⁶¹ We have found these devices particularly useful in community health fairs, on ward rounds, and in other circumstances in which rapid portable tonometry is indicated. The Tono-Pen (like the Perkins tonometer) tends to underestimate the true IOP in Chinese eyes in supine patients.⁵¹ The Tono-Pen may also be used in children as readings are obtained rapidly and the device gives an indication of the quality of the reading.⁶² However, the Tono-Pen tends to overestimate the IOP in infants so its usefulness in congenital glaucoma screening and monitoring is somewhat limited.⁶³

Because it depends on an electronic end point rather than an optical end point like the Goldmann, the Tono-Pen should theoretically be more accurate in corneas with irregular surfaces. However, in band keratopathy where the surface of the pathology is harder than normal cornea, the Tono-Pen tends to overestimate the IOP.⁶¹ The small applanating area also allows finding the smoothest part of the cornea. In a normal eye, there is little difference in IOP readings between applying the Tono-Pen to central or peripheral cornea; this allows reasonably accurate use of the Tono-Pen even if the central cornea is irregular or following photorefractive surgery.^{64–66} The Tono-Pen seems reasonably accurate even when measuring through an amniotic membrane patch graft.⁶⁷ It has been suggested that the Tono-Pen could be used to read from the sclera rather than the cornea; however, one recent study suggested that such readings are highly inaccurate.⁶⁸ A disposable latex cover which is discarded after each use provides infection control, although, in rare circumstances, the latex can cause an allergic reaction.⁶⁹

Pneumatic tonometer

The pneumatic tonometer (Fig. 4-6) has a sensing device that consists of a gas chamber covered by a polymeric silicone diaphragm. A transducer converts the gas pressure in the chamber into an

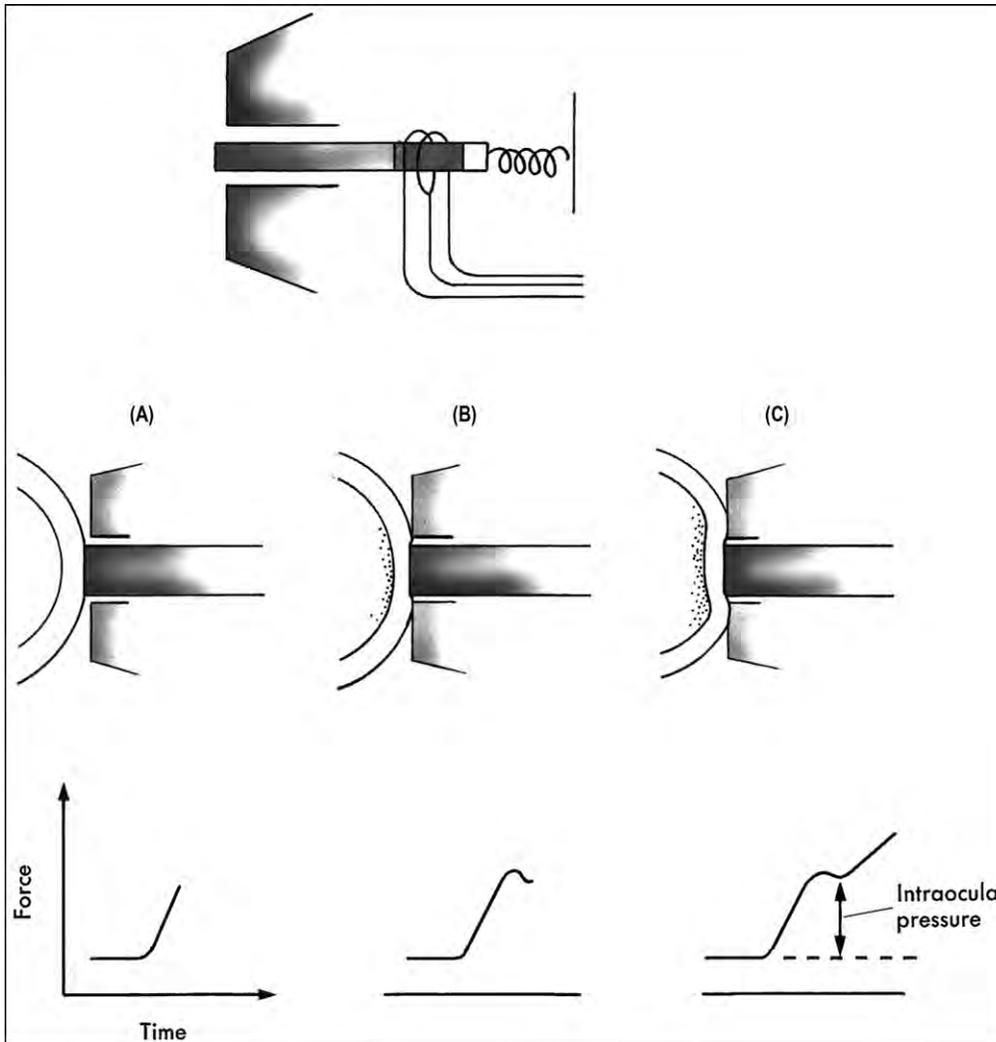


Fig. 4-4 Intraocular pressure (IOP) tracing with MacKay-Marg tonometer. **(A)** Advancing plunger is opposed by IOP and corneal bending pressure. **(B)** Notch indicates corneal bending pressure has been transferred to footplate. Height of notch corresponds to IOP. **(C)** With continued advancement of plunger, cornea is indented, and IOP rises. (Modified from Moses RA: Tonometry. In: Cairns JE, editor: Glaucoma, vol 1, London, Grune & Stratton, 1986.)

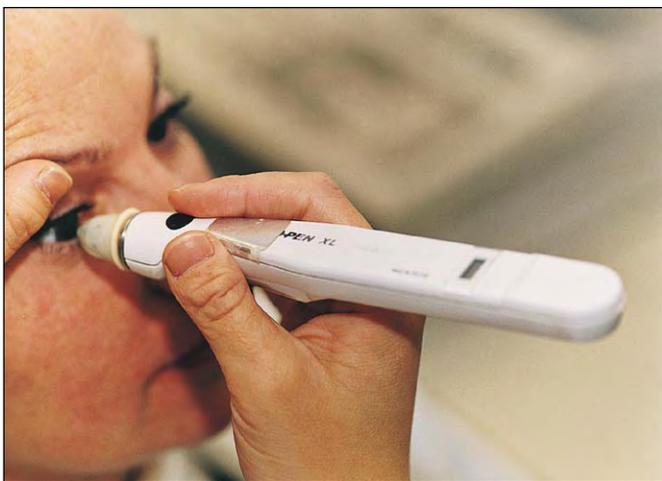
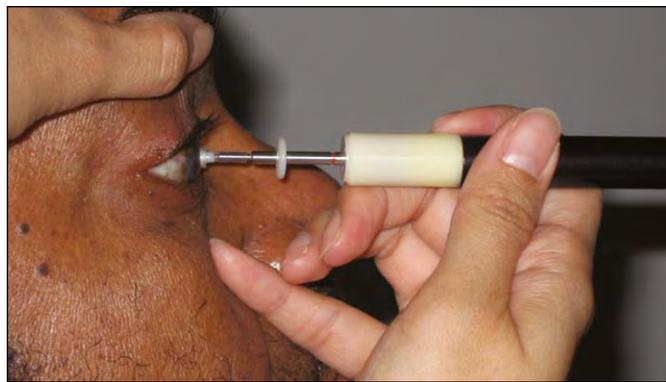


Fig. 4-5 Tono-Pen™.

electrical signal that is recorded on a paper strip. The gas in the chamber escapes through an exhaust vent between the diaphragm and the tip of the support nozzle. As the diaphragm touches the cornea, the gas vent is reduced in size, and the pressure in the chamber rises.⁷⁰⁻⁷²

Some models of this instrument use a digital display, and some a paper tracing, to record IOP. The instrument emits a whistling sound when it is placed properly on the cornea. The pneumatic tonometer was designed originally as an applanation instrument. However, as Moses and Grodzki have indicated,⁷³ the device currently marketed has some properties that are more like an indentation tonometer.

The pneumatic tonometer is useful for measuring IOP in eyes with scarred, irregular, or edematous corneas. The small applanation tip makes the instrument useful in laboratory settings in which some other tonometers can prove unwieldy.⁷⁴ The instrument provides a good measurement of IOP, although it overestimates pressure at low levels and underestimates pressure at high levels. Calibration of the instrument is empirical. The pneumatic tonometer can be used for tonography if it is fitted with weights and used in a continuous recording mode. The pneumatic tonometer is fairly accurate when used over therapeutic soft contact lenses.^{75,76} While the pneumotonometer is subject to errors related to corneal thickness, it seems less so than the Goldmann applanation tonometer.⁷⁷ Yet, in another study of large numbers of patients, pneumotometry seemed more susceptible to the effects of corneal thickness than the Goldmann applanation tonometer.⁷⁸ In addition, the repeatability of pneumotometry has been called into question.⁷⁹ Like most tonometers, repeating readings with the pneumotonometer



(A)



(B)



(C)

Fig. 4-6 (A) Pneumotonometer tip on eye. (B) Pneumotonometer base unit with high IOP reading and real time recording. (C) Pneumotonometer base unit with IOP reading and real time recording.

close together results in decreasing IOP readings; this effect seems to be lost after two minutes.⁸⁰

Non-contact tonometer

The non-contact tonometer applanates the cornea by a jet of air, so there is no direct contact between the device and the surface of the eye. This theoretically avoids the need to sterilize the instrument, but a recent study found the air puff produces a tear film aerosol that could potentially contain infectious material.⁸¹ The force of the air jet increases rapidly and linearly with time. The instrument also emits a collimated beam of light that is reflected from the central cornea and then received by a photocell. When an area of the cornea 3.6 mm in diameter is flattened, the light reflected to the photocell is at a maximum. The time required to produce the peak reflection is directly related to the force of the air jet and thus to the counterbalancing IOP.⁸²⁻⁸⁴

The non-contact tonometer is useful for screening programs because it can be operated by non-medical personnel, it does not absolutely require topical anesthesia and there is no direct contact between the instrument and the eye. The IOP readings obtained with the non-contact tonometer correlate fairly well with readings taken by Goldmann tonometry, but differences of several millimeters of mercury are not unusual, particularly with pressures higher than the low 20s.⁸⁵⁻⁸⁸ The tonometer can be used without topical anesthesia, but it is more accurate with anesthesia. The patient should be warned that the air puff can be startling, even after topical anesthetic.⁸⁹ The non-contact tonometer measures IOP over very short intervals, so it is important to average a series of readings.⁹⁰ The instrument has an internal calibration system. Several newer iterations which have increased the popularity of this type of tonometry have appeared in recent years.⁹¹⁻⁹⁴ The newer breed of units seem to be more comfortable for patients as well as improving the accuracy (at least as compared to Goldmann applanation tonometry (GAT)).⁹⁵⁻⁹⁷ One unit has software that allows indication and measurement of pulse amplitude.⁹⁸

However, not all studies have shown accuracy compared to Goldmann tonometry.⁹⁹ In general, at least three but preferably four readings should be obtained on each eye.¹⁰⁰ The accuracy of the non-contact tonometer in post-keratoplasty patients has been called into question.¹⁰¹

One interesting adaptation of the non-contact tonometer is in the new Reichert Ocular Response Analyzer™ (Reichert Ophthalmic Instruments, Depew, NY, USA). This device is basically an air puff tonometer that directs the air jet against the cornea and measures not one but two pressures at which appplanation occurs – when the air jet flattens the cornea as the cornea is bent inward and as the air jet lessens in force and the cornea recovers (Fig. 4-7). The first is the resting intraocular pressure. The difference between the first and the second appplanation pressure is called corneal hysteresis and is a measure of the viscous dampening and, hence, the biomechanical properties of the cornea. The biomechanical properties of the cornea are related to, but not the same as, corneal thickness and include elastic and viscous dampening attributes. It is thought that central corneal thickness is just one attribute that contributes to the biomechanical properties of the cornea.

Clinically, the IOPs as measured by the Ocular Response Analyzer (ORA) correlate well with Goldmann tonometry but, on average, measure a few millimeters higher since the device seems to be less dependent on central corneal thickness than the Goldmann applanation tonometer.¹⁰² Furthermore, while IOP varies over the 24-hour day, hysteresis seems to be stable.¹⁰³ Congdon et al found that a 'low' hysteresis reading with the ORA correlates with progression of glaucoma, whereas thin central corneal thickness correlates with glaucoma damage.¹⁰⁴ Not all studies have been impressed with the accuracy of this device.¹⁰³ Whether the concept of corneal hysteresis, while showing promise based on early studies, will ultimately become of practical value in the management of glaucoma remains to be demonstrated.

The Ocuton™ tonometer

The Ocuton™ (Elektronik & Präzisionsbau Saalfeld GmbH, Jena, Germany) is a hand-held tonometer that works on the appplanation principle using a probe that is so light that it is barely felt and, therefore, needs no anesthetic in most patients. It has been marketed in Europe for home tonometry (Fig. 4-8). The device is comparable to Goldmann tonometry but tends to read higher than the Goldmann tonometer when the cornea is thicker, and its accuracy may be

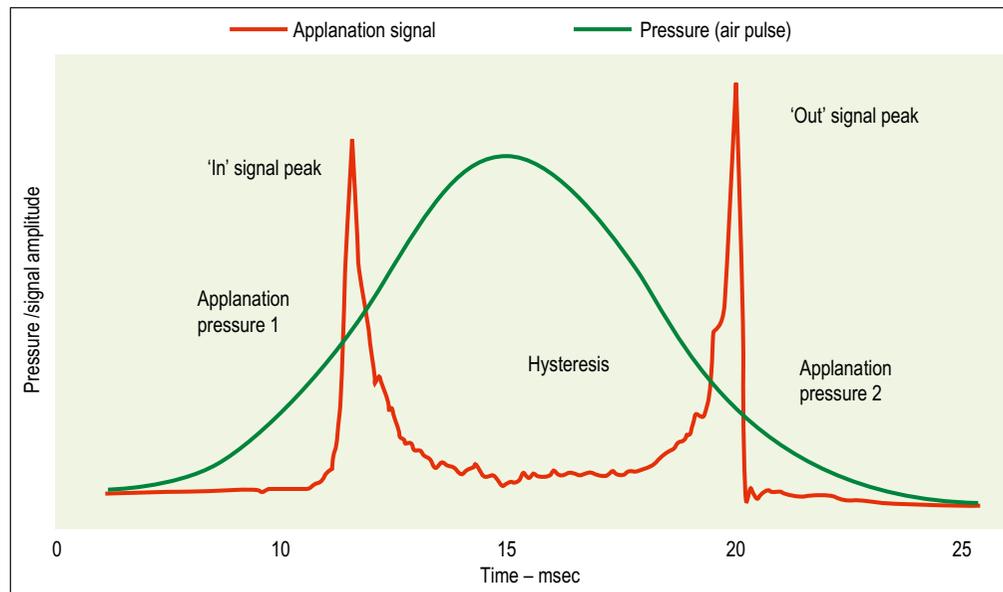


Fig. 4-7 The applanation waveform of the Ocular Response Analyzer™ (Courtesy of Reichert Ophthalmic Instruments, Depew, NY, USA.)

compromised by diurnal changes in corneal thickness.^{105–107} This device may be useful to get some idea of the relative diurnal variation in IOP if the patient or spouse (etc.) can learn to use it.

Maklakow tonometer

The Maklakow (also spelled Maklakov) tonometer differs from the other applanation instruments in that a known force is applied to the eye, and the area of applanation is measured – a technique known as constant-force rather than constant-area applanation.¹⁰⁸ The instrument consists of a wire holder into which a flat-bottom weight, ranging from 5 to 15 g, is inserted. The surface of the weight is painted with a dye, such as mild silver protein (Argyrol) mixed with glycerin, and then the weight is lowered onto the cornea. During the procedure the patient is supine, and the cornea is anesthetized. The weight is lifted from the cornea, and the area of applanation is taken to be the area of missing dye, which is measured either directly or indirectly from an imprint on test paper. Intraocular pressure is inferred from the weight (W) and the diameter of the area of applanation (d) by using the following formula:

$$P_t = \frac{W}{\pi(d/2)^2}$$

Intraocular pressure is measured in grams per square centimeter and is converted to millimeters of mercury by dividing by 1.36.

The Maklakow tonometer is used widely in Russia and China but has never achieved great popularity in western Europe or the United States. This instrument displaces a greater volume of aqueous humor than the other applanation devices (but less than a Schiötz tonometer), which means that the IOP readings are more influenced by ocular rigidity.¹⁰⁹ Attempts have been made to overcome this problem by measuring IOP with two different weights. The Maklakow tonometer does not correct for corneal bending, capillary attraction, or tear encroachment on the layer of dye.

Many instruments similar to the Maklakow device have been described, including the Applanometer, Tonomat, Halberg tonometer,¹¹⁰ and GlaucoTest.¹¹¹

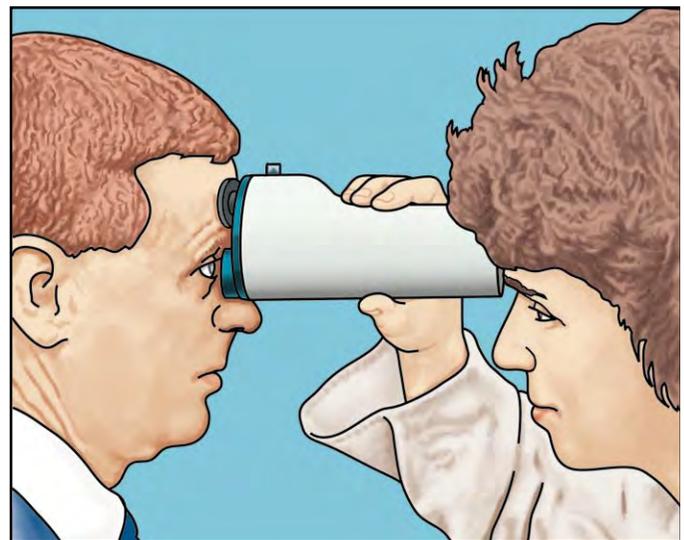


Fig. 4-8 The Ocuton™ tonometer.

INDENTATION INSTRUMENTS

In indentation tonometry, a known weight is placed on the cornea, and the IOP is estimated by measuring the deformation or indentation of the globe. The Schiötz tonometer is the prototype for this class of instruments.

Schiötz tonometer

The Schiötz tonometer consists of a metal plunger that slides through a hole in a concave metal footplate (Figs 4-9 and 4-10). The plunger supports a hammer device connected to a needle that crosses a scale. The plunger, hammer, and needle weigh 5.5 g. This can be increased to 7.5, 10, or 15 g by the addition of appropriate weights. The more the plunger indents the cornea, the higher the scale reading – that is, the lower the IOP, the higher the scale reading. Each scale unit represents a 0.05 mm protrusion of the plunger.¹¹²



Fig. 4-9 Schiøtz tonometer.



Fig. 4-10 Schiøtz tonometry technique.

The technique of Schiøtz tonometry is summarized as follows:

1. The patient lies supine and fixates on an overhead target, such as a light or a mark on the ceiling. Alternatively, the examiner may place the patient's thumb in the appropriate position to serve as a fixation target. This is useful in patients with limited vision in the fellow eye.

2. The examiner explains the nature of the test and reassures the patient that the measurement is painless. The patient is told to relax, breathe normally, fixate on the target, and open the eyes wide.

3. A drop of topical anesthetic, such as 0.5% proparacaine, is instilled in each eye.

4. The tonometer tip and footplate are wiped carefully with an alcohol swab and allowed to air dry. If the tonometer has been

stored disassembled in its case, it should be wiped with the alcohol swab before assembly. The alcohol must be allowed to evaporate before the instrument touches the eye.

5. The examiner retracts the patient's lids without placing tension on the globe. The tonometer is placed directly over the eye, and when the patient relaxes, it is lowered gently onto the cornea (Fig. 4.10). The tonometer should be perpendicular to the corneal apex. The examiner must be careful not to press the tonometer against the globe.

6. The measurement is noted to the nearest 0.25 scale units. If a wide pulse pressure is present, the center point of the fluctuation is chosen as the end point. If the scale reading is less than 3 units, additional weight is added to the plunger.

7. The IOP measurement is repeated until three consecutive readings agree within 0.5 scale units.

8. The average scale reading is converted to IOP in millimeters of mercury using a conversion chart. The examiner records the scale reading, weight, converted IOP, time of day, ocular medications, and time since last instillation of ocular medication, as well as the conversion chart used.

9. The instrument is calibrated before each use by placing it on a polished metal sphere and checking to be sure that the scale reading is zero. If the reading is not zero, the instrument must be repaired.

10. After each use, the tonometer plunger and footplate should be rinsed with water, followed by alcohol, and then wiped dry with lint-free material. It is important to prevent foreign material from drying within the footplate because this affects the movement of the plunger. The most common 'foreign material' that finds its way onto the plunger tip is fluid from the patient's tear film. The instrument can be sterilized with ultraviolet radiation, steam, ethylene oxide, or a variety of solutions that have been indicated for the Goldmann prism. As with other tonometer tips, the Schiøtz can be damaged by some disinfecting solutions such as hydrogen peroxide and bleach.¹¹³

11. If the tonometer is not going to be used for a while, it is best to disassemble the unit, clean it, and store it in its case. Disassembly allows for better cleaning of the barrel and plunger apparatus, and case storage protects the instrument from becoming bent or otherwise damaged and thrown out of calibration.

The Schiøtz tonometer is portable, sturdy, relatively inexpensive, and easy to operate. The instrument is accurate over a wide range of IOPs, although pressures may vary from those obtained with GAT, particularly when relatively untrained examiners are administering the test.^{114–116} An important concern is that placing the heavy tonometer (total weight at least 16.5 g) on the eye raises IOP. The rise in pressure reflects the dispensability of the ocular coats, a property termed ocular rigidity. All of the tables that relate the change in volume to the IOP assume a normal ocular rigidity, and this introduces a substantial error for some measurements. Eyes with high ocular rigidity (e.g., high hyperopia¹¹⁷ or longstanding glaucoma¹⁰⁹) give falsely high Schiøtz IOP readings, whereas eyes with low ocular rigidity (e.g., myopia,¹¹⁷ strong miotic therapy,¹¹⁷ retinal detachment surgery,^{118,119} or compressible gas¹²⁰) give falsely low Schiøtz IOP readings. It is possible to estimate ocular rigidity by comparing applanation and Schiøtz measurements⁵ or by repeating the Schiøtz measurements with two or more weights using the Friedenwald nomogram.¹⁰⁹ Recent data based on cadaver eye experiments suggest that the Friedenwald nomogram may have some errors and that there is a larger increment of volume change per unit pressure than was found by Friedenwald.¹²¹



Fig. 4-11 The Impact-Rebound Tonometer (ICare).
(Courtesy of Tiolat, Oy, Helsinki, Finland.)

The Schiøtz tonometer may also affect the IOP estimation by altering the outflow facility, rate of aqueous humor formation, episcleral venous pressure, and blood volume of the eye.¹²² Although none of these alterations is as important during tonometry as it is during tonography (see Ch. 3), they add to the uncertainty of the measurement. The Schiøtz pressure reading is also influenced by the size of the footplate hole and the thickness and curvature of the cornea.¹²³

Electronic Schiøtz tonometer

The electronic Schiøtz tonometer has a continuous recording of IOP that is used for tonography. The scale is also magnified, which makes it easier to detect small changes in IOP.

Impact-rebound tonometer

A new and updated version of an indentation tonometer has been developed in which a very light, disposable, sterile probe is propelled forward into the cornea by a solenoid; the time taken for the probe to return to its resting position and the characteristics of the rebound motion are indicative of the IOP (and also the biomechanical properties of the cornea).¹²⁴ The time taken for the probe to return to its resting position is longer in eyes with lower IOP and faster in eyes with higher IOP. The production model (ProTon, ICare) has been made portable (Fig. 4-11). Because the probe is extremely light and its contact with the cornea is very short (like the air puff tonometer), this type of tonometer can be used without first anesthetizing the eye.¹²⁵

The impact-rebound tonometer has been shown to be comparable to the Goldmann in both normal and post-keratoplasty human eyes.¹²⁶ While generally comparable to other clinically used tonometers, the impact-rebound tonometer does tend to read slightly higher than the Goldmann.^{127–129} Furthermore, based on its mechanism of action, it is not surprising that the accuracy falls off in scarred corneas (as does the Goldmann).¹³⁰ The rebound tonometer does correlate, like the Goldmann, with central corneal thickness.^{131,132} In general, this tonometer can be used in screening situations, when patients are unable to be seated or measured at the slit lamp, or when topical anesthetics are not feasible or usable.

The impact–rebound tonometer has been found to be particularly useful in small animal eyes such as the mouse and rat where the traditional applanation tonometer tips are too large.¹³³ The impact tonometer appears to be more accurate in rat eyes than the Tono–Pen¹³⁴ and accurate in mouse eyes.^{135,136}

Transpalpebral tonometry

Since the identification of intraocular pressure as a risk factor for glaucomatous damage, attempts have been made to measure IOP through the eyelid, obviating the need for topical anesthetic and the risk of eye-to-eye transfer of pathogenic organisms. The simplest way to accomplish this is with the fingers, but, perhaps, with very few exceptions, digital (meaning with fingers) impressions are at best qualitative and at worst not correlative with real IOP. However, a reasonable qualitative (or semi-quantitative) assessment can be made in situations where other, more accurate, devices are not practical, such as in young children, demented patients and severely developmentally-challenged patients.¹³⁷

In addition to all the problems facing indentation tonometry, such as scleral rigidity, transpalpebral tonometry adds variables such as the thickness of the eyelids, orbicularis muscle tone and potential intrapalpebral scarring. Recently, two attempts have been made to develop more quantitative transpalpebral IOP measuring devices. The TGDc-01 (Envision Ophthalmic Instruments, Livonia, Michigan, USA) was developed in Russia and bases its measurement on a weight falling within the instrument onto the closed eyelid and the amount of indentation it causes. Initial studies suggested good correlation with Goldmann tonometry, but more rigorous, controlled studies suggest that, at least in a significant minority of patients not identifiable prospectively, the accuracy is limited.^{138–141} Furthermore, interobserver and intraobserver variability was large, making the readings unreliable for most clinical purposes.

Fresco had an ingenious idea – that pressure on the eyelid in most eyes produces retinal phosphenes.¹⁴² The pressure on the eyelid required to induce these phosphenes is proportional to the intraocular pressure. He then developed this into a usable transpalpebral tonometer – the Proview (Bausch & Lomb, Rochester, NY, USA) (Fig. 4-12) – and found good correlation with GAT.¹⁴² Other studies raised the promise that patients could measure their own IOP at home, or wherever they were, and obtain information about their diurnal IOP variation that would be useful in managing their glaucoma.^{143,144}

Unfortunately, subsequent studies failed to confirm the accuracy of this device.^{145–148} The Proview could still be useful for diurnal IOP estimations by patients themselves if several validating measurements are made side-by-side with the Goldmann or other accurate transcorneal tonometer.¹⁴⁹

DYNAMIC CONTOUR TONOMETRY

Kanngiesser described a tonometer based on a totally different concept than either indentation or applanation tonometry.¹⁵⁰ This tonometer is based on the principle that by surrounding and matching the contour of a sphere (or a portion thereof), the pressure on the outside equals the pressure on the inside. In the dynamic contour tonometer (DCT) (Pascal™, Zeimer, Zurich, Switzerland) (Figs 4-13 and 4-14), the tip of the probe matches the contour of the cornea. A pressure transducer built into the center of the probe measures the outside pressure, which should equal the inside pressure, and the IOP is recorded digitally on the liquid crystal display (LCD). The concept developed from a previous

contact lens tonometer called the ‘Smart Lens.’¹⁵¹ The DCT was shown to be superior in accuracy to Goldmann tonometry and pneumotonometry in human cadaver eyes across the entire range of IOPs seen in clinical practice.¹⁵² In living human eyes, the DCT correlates well with Goldmann readings.^{153–155}

Unlike Goldmann and other tonometers, the DCT does not appear to be affected by corneal thickness in several studies.^{156–162} Also, unlike Goldmann tonometry, IOP as measured by DCT is not altered by corneal refractive surgery that thins the cornea.^{163–165}



Fig. 4-12 Proview transpalpebral phosphene tonometer in case. Spring end presses on eyelid until patient sees phosphene and then device is removed. Pressure at which phosphene was seen is recorded on scale and represents IOP.

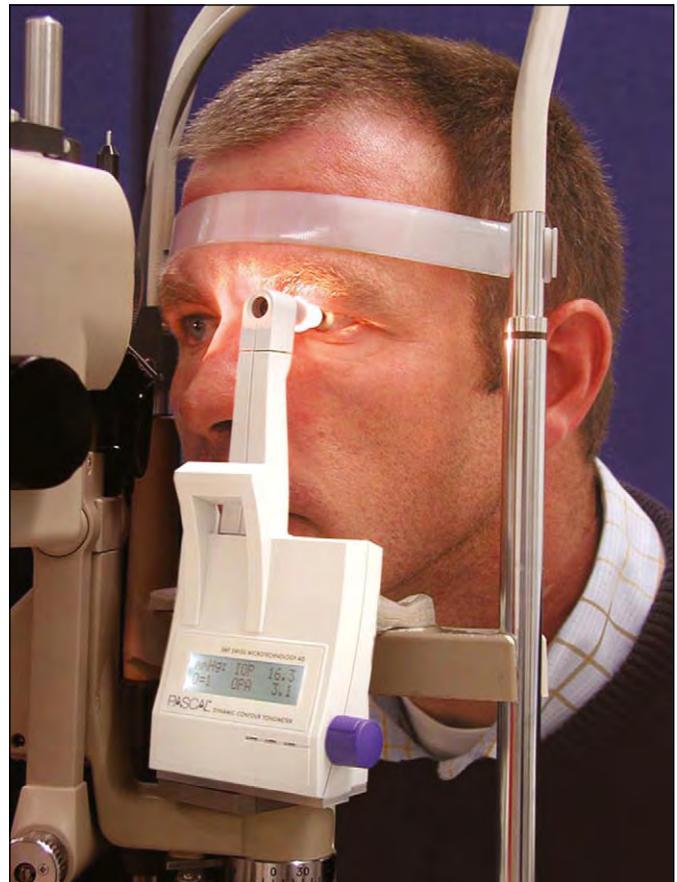


Fig. 4-13 The DCT-Pascal™ tonometer mounted on a slit lamp biomicroscope. (Courtesy of Swiss Microtechnology (Zeimer), Zurich, Switzerland.)

Because the DCT measures IOP in real time, the actual measurement, like the IOP, is pulsed. The internal electronics 'call' the IOP as the bottom of the pulsed curve and indicate it digitally on the LCD (Fig. 4-15). The reliability of the IOP measurement is also indicated on a five-point scale. Two readings are recommended. Certainly, any measurement with a poorer than average reliability reading should be repeated. One of the reasons that the IOP readings with the DCT are generally lower than GAT may be that GAT, when properly done, indicates the average difference between the maximum and minimum pressures whereas the DCT reads the minimum. The DCT also indicates the magnitude of the difference between maximum and minimum IOP as the ocular pulse amplitude.¹⁶⁶ While several studies have suggested that the ocular pulse amplitude may be indicative of the status of ocular blood flow and be differentially affected in different types of glaucoma, we have found that the ocular pulse amplitude is increased over normals in most forms of glaucoma and may be related to the level of IOP.^{167,168}

In summary, the dynamic contour tonometer (Pascal) is a promising new technology that may give the clinician better

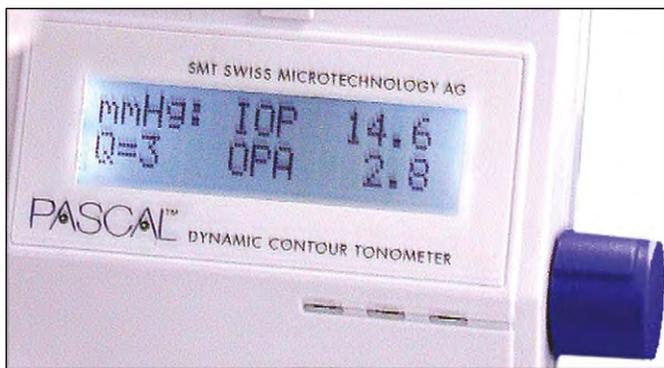


Fig. 4-14 The liquid crystal display of the DCT. (Courtesy of Swiss Microtechnology (Zeimer), Zurich, Switzerland.)

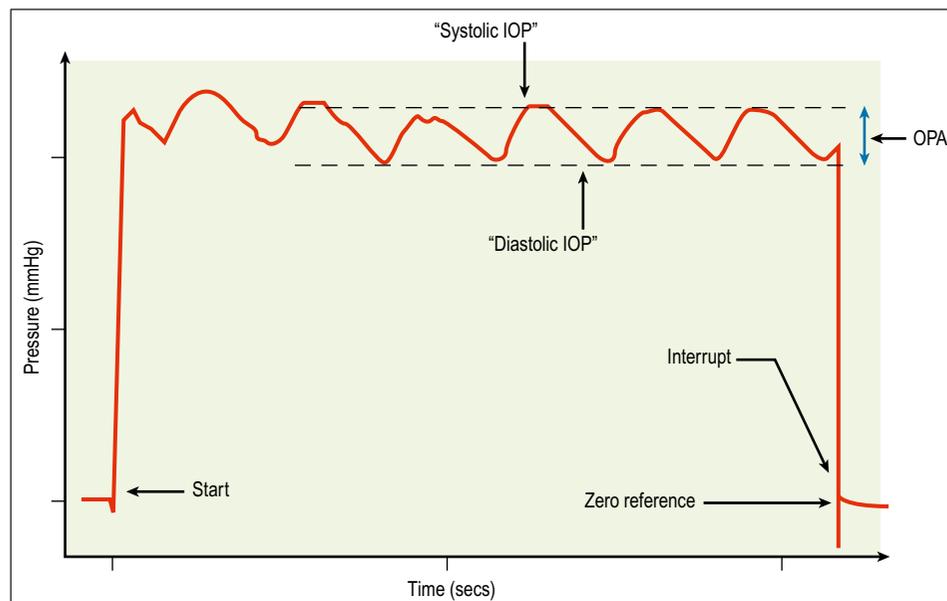


Fig. 4-15 The ocular pulse amplitude (OPA). Seen as the OPA on the LCD but available as an actual graph via download to a Bluetooth-enabled printer. (Courtesy of Swiss Microtechnology (Zeimer), Zurich, Switzerland.)

information about the actual IOP. It is independent of corneal thickness and contour and may give more accurate readings than the Goldmann tonometer in those eyes with very thin corneas. Its practical value in terms of managing clinical glaucoma remains to be demonstrated. We have found that many of our patients whose optic nerves or visual fields are progressing, despite what appear to be satisfactory Goldmann readings, have 3–5 mmHg higher readings suggesting that more aggressive pressure-lowering therapy might be helpful.

CONTINUOUS MONITORING OF INTRAOCULAR PRESSURE

There have been a few attempts to monitor IOP continuously in animal and human eyes. The devices described consist of appplanation instruments inside contact lenses or suction cups,^{169,170} or strain gauges in encircling bands that resemble scleral buckling elements.¹⁷¹ None of these instruments has achieved widespread use. One approach has used resonance appplanation tonometry measuring the sonic resonance of the eye when a continuous force over a fixed area is applied. The latest iteration is independent of corneal position making a practical home tonometer using this principle at least achievable.¹⁷² Yet another innovative approach has been to use infrared spectroscopy to measure IOP.¹⁷³ Infrared spectroscopic measurements correlate with IOP as measured by manometry in pig eyes. A newer approach has been to build a miniature pressure sensor that can reside inside the eye; one such device is part of an intraocular lens. The development of a device which can easily monitor IOP over a 24-hour period or longer would greatly aid our understanding of aqueous humor dynamics and glaucoma.

SUMMARY OF TONOMETRY

While IOP has been demoted from primacy in the diagnosis of glaucoma to just a risk factor, it still remains the single most important and only modifiable factor to assess the effectiveness of treatment.

In both traditional primary open-angle glaucoma and normal-pressure glaucoma, the IOP level is still the most important risk factor for glaucoma damage.¹⁷⁴ Furthermore, the Early Manifest Glaucoma Trial showed that for each mmHg lowering of IOP from baseline, there is a 10% decrease in the rate of progression.¹⁷⁵ From only a few instruments just a few decades ago, there seems now to be a bewildering array of devices to measure IOP. The Goldmann tonometer has stood the test of time but is beginning to show some traces of gray. By now, everyone should recognize that thin corneas will cause the Goldmann to under read the IOP and a thick cornea will likely cause the Goldmann to over read. Because the relationship is not linear, no current formula can accurately convert Goldmann readings to 'true' IOP with any given corneal thickness.

Some newer tonometers have shown independence of corneal thickness and may, therefore, be more accurate in eyes on the thick and thin extremes of corneal thickness. These include the pneumotonometer, the dynamic contour tonometer and the hysteresis non-contact tonometer. However, it is still true that most of our current understanding of the treatment of glaucoma is based on Goldmann readings. Therefore, it may take some time for the newer, perhaps more accurate, devices to work their way into the diagnostic and treatment construct that has served so well for the past 60 years or so.

Other tonometers may be particularly useful in certain situations. For example, the pneumotonometer and the Tono-Pen may be more accurate than the Goldmann when the cornea is irregular or scarred. The pneumotonometer and the non-contact tonometer

may be able to obtain reasonably accurate readings through a soft contact lens. While not very accurate for day-to-day use, the Proview tonometer, because it does not need anesthetic and is user friendly, may be helpful for home tonometry, in obtaining diurnal IOP estimations and in patients who cannot be tested with corneal contact instruments. The non-contact tonometers, pneumotonometers, and Tono-Pen may be useful for screening situations.

DISTRIBUTION OF INTRAOCULAR PRESSURE IN THE GENERAL POPULATION

There have been a number of studies on the distribution of IOP in the normal population (Table 4-1). In a classic study, Leydhecker and co-workers¹⁷⁶ performed Schiøtz tonometry on more than 10000 normal individuals. They found the mean (\pm SD) IOP to be 15.8 \pm 2.6 mmHg. At first glance the pressure readings appeared to be distributed in a normal fashion (also referred to as a Gaussian or bell-shaped distribution). However, closer inspection of the data revealed that the distribution was not Gaussian, but rather skewed to the right.^{181,184} This distinction is important because it means we cannot define an upper limit for IOP by adding 2 or 3 standard deviations to the mean. This conclusion is supported by a number of studies, all of which have found a much higher prevalence of elevated IOP (e.g., >20 or 21 mmHg) than would be predicted by Gaussian statistics (Table 4-2).

Table 4-1 Mean intraocular pressure measurements in the general population

Author	Technique	Individuals (n)	Mean	Standard deviation
Leydhecker and others ¹⁷⁶	Schiøtz	10000	15.5	2.6
Linner ¹⁷⁷	Schiøtz	78	16.7	2.4
Becker ¹⁷⁸	Schiøtz	909	16.1	2.8
Johnson ¹⁷⁹	Schiøtz	7577	15.4	2.6
Soeteren ¹⁸⁰	Applanation	70	13.7	2.5
	Schiøtz	95	15.5	2.4
Goldmann ⁴	Applanation	123	13.2	2.4
	Applanation	50	15.6	2.9
Goldmann ⁵	Applanation	400	15.4	2.5
Draeger	Applanation	178	14.5	2.8
Armaly ¹⁸¹	Applanation	2316	15.9	3.1
Loewen and others ¹⁸²	Applanation	4661	16.2	3.8
Ruprecht and others ¹⁸³	Applanation	8899	16.2	3.4

Table 4-2 Prevalence of elevated intraocular pressure in the general population

Location	Age (years)	Individuals (or eyes) (n)	Cut-off intraocular pressure (mmHg)	Prevalence of high pressure (%)
Skovde, Sweden ¹⁸⁵	>40	7275	>21	4.5
Ferndale, Wales ¹⁸⁶	40-74	4231	>20	9.4
Framingham, Mass ¹⁸⁷	52-85	5223 (eyes)	>21	7.6
Dalby, Sweden ¹⁸⁸	55-0	1511	>20.5	7.3

Modified from Leske MC: The epidemiology of open-angle glaucoma: a review. Am J Epidemiol 118:166, 1983.

Unfortunately, the skewed distribution also means that an abnormal IOP must be defined empirically – that is, an abnormal pressure is one that causes optic nerve damage in a particular eye. Because eyes differ markedly in their susceptibility to the effects of pressure, it is difficult to know *a priori* what level of IOP will be harmful to a given patient. Some individuals develop glaucomatous damage at IOPs near the population mean, whereas others maintain normal optic nerves and visual function for many years despite IOPs of 30 or even 40 mmHg.

Similar mean IOPs are found using applanation and Schiøtz tonometry (see Table 4-1). Given the theoretic and practical shortcomings of Schiøtz tonometry, this suggests some combination of compensating errors for the indentation technique.

As a general rule, IOPs are similar in the right and left eyes of normal individuals. Although differences of 4 mmHg or more between the eyes are seen in less than 4% of normal individuals,^{189,190} such differences are common in patients with glaucoma. Davanger¹⁸⁹ reported that 10% of patients with glaucoma had pressure differences greater than 6 mmHg. Lee and co-workers found in a population cross-sectional study that IOP asymmetry between the two eyes of the same older patient was often associated with undiagnosed glaucoma, whether the IOP was more than or less than 21 mmHg.¹⁹¹

Elevated IOP or the presence of glaucoma are associated with a decreased life expectancy according to the Framingham Eye Study.¹⁹² This association still persists even after the data are corrected for the usual factors associated with decreased life expectancy, such as age, gender, body mass, smoking, diabetes, and hypertension.

FACTORS THAT INFLUENCE INTRAOCULAR PRESSURE

Many different factors affect IOP (Table 4-3). A few of the more important factors are discussed here.

AGE

Most studies find a positive correlation between IOP and age.^{181,193–195} The effect of increasing age on IOP is the result, at least in part, of increased blood pressure, increased pulse rate, and obesity.^{196,197} The Barbados Eye Study showed that the highest correlations with IOP were age, systemic hypertension, and history of diabetes but female gender, larger body mass index, darker complexion, and positive family history of glaucoma.¹⁹⁸ Except for age and positive family history, these correlations did not hold for actual glaucoma. It is unclear whether the rise in IOP with age represents an increase for all individuals or a greater skewness of the data – that is, a greater minority of the people having higher pressure while the majority show no change. One careful study of aqueous dynamics in normal subjects covering two different age groups showed a reduction in aqueous production as well as a reduction in uveoscleral outflow with age.¹⁹⁹ It should be pointed out that a number of studies find little correlation between IOP and age.^{197,200} In addition, one investigative team found that IOP declined with age in a group of Japanese workers.^{201,202} This trend of decreasing IOP with age in normal Japanese eyes was confirmed

Table 4-3 Factors influencing intraocular pressure		
Factors	Association	Comments
<i>Demographic</i>		
Age	Mean IOP increases with increasing age	May be mediated partially through cardiovascular factors
Sex	Higher IOP in women	Effect more marked after age 40 years
Race	Higher IOP among blacks	
Heredity	IOP inherited	Polygenic effect
<i>Systemic</i>		
Diurnal variation	Most people have a diurnal pattern of IOP	Quite variable in some individuals
Seasonal variation	Higher IOP in winter months	
Blood pressure	IOP increases with increasing blood pressure	
Obesity	Higher IOP in obese people	
Posture	IOP increases from sitting to inverted position	Greater effect below horizontal
Exercise	Strenuous exercise lowers IOP transiently	Long-term training has a lesser effect
Neural	Cholinergic and adrenergic input alters IOP	
Hormones	Corticosteroids raise IOP; diabetes associated with increased IOP	
Drugs	Multiple drugs alter IOP	
<i>Ocular</i>		
Refractive error	Myopic individuals have higher IOP	IOP correlates with axial length
Eye movements	IOP increases if eye moves against resistance	
Eyelid closure	IOP increases with forcible closure	
Inflammation	IOP decreases unless aqueous humor outflow affected more than inflow	
Surgery	IOP generally decreases unless aqueous humor outflow affected more than inflow	

in a 10-year longitudinal study.²⁰³ In a study of Koreans, IOP also declined with age but increased with body mass index.²⁰⁴ In one important and interesting study that included both longitudinal follow-up as well as cross-sectional data in 70 000 Japanese subjects, IOP declined with age when looking at the cross-sectional data but actually increased with age in the longitudinal data.²⁰⁵ This suggests that some differences in IOP exist between different age groups that can not be explained by chronologic aging.

SEX

It has been reported that women have higher IOPs than men, especially after age 40.¹⁸¹ However, this finding was not confirmed in another study.²⁰⁶ The Barbados Eye Study showed that women were more likely to have high IOP without glaucoma damage and men were more likely to have open-angle glaucoma.²⁰⁷

RACE

In the United States, blacks have higher IOPs than whites.^{194,208,209} In part, this difference appears to be racial or genetic. There is one report that the Zuni Indians of New Mexico have relatively low IOPs.²¹⁰ It is unclear whether this phenomenon is caused by genetic or environmental factors. Because the definitions of, and differences between, various racial and ethnic groups are increasingly indistinct, it is difficult to predict the ultimate clinical utility of these observations.

HEREDITY

There appears to be a hereditary influence on IOP,^{181,211,212} which is polygenic in nature.^{210,213} A number of studies have indicated that first-degree relatives of patients with open-angle glaucoma have higher IOPs than the general population.^{181,214} In contrast, one study found that spouses have similar levels of IOP, which suggests that there are important environmental influences as well.²¹⁵

DIURNAL VARIATION

Over the course of the day, IOP varies an average of 3–6 mmHg in normal individuals.^{216–223} Patients with glaucoma have much wider swings of IOP that can reach 30 mmHg or even 50 mmHg in rare cases.^{216,218,221,224} In many people the diurnal variation of IOP follows a reproducible pattern, with the maximum pressure in the mid-morning hours and the minimum pressure late at night or early in the morning. However, some individuals peak in the afternoon or evening, and others follow no consistent pattern.^{221,224–228} In general, normal, open-angle glaucoma and normal-pressure glaucoma patients have their peak in the morning with the nadir in the afternoon.²²⁹ One study suggests that any male with a borderline IOP measured midday should have a repeat measurement early in the morning, as males, in particular, may have wider diurnal swings.²³⁰ In general, the two eyes show similar diurnal curves but there is a significant difference in how the right and left eye vary in their IOP.²³¹

Many patients have a nocturnal surge in IOP. This increase in IOP is only partly explained by postural changes.^{232,233} Furthermore, this same group showed that the pressure elevation is most likely towards the end of the dark cycle whenever in the real circadian cycle it occurs. However, short bursts of moderate light during the dark cycle had no effect on the nocturnal pressure elevation.²³⁴ Aging subjects also seem to have a relative elevation of IOP toward the

end of the dark cycle although most of it may be related to the supine recumbent position.²³⁵

Most of the diurnal pressure variation is caused by fluctuations in the rate of aqueous humor formation. There has been controversy about whether there are also diurnal variations in the facility of aqueous humor outflow, but recent studies indicate that this effect is small at most.^{224,229,236–240} The rate of aqueous formation falls to low levels during sleep and increases during the day, most likely in response to circulating catecholamines.^{241,242} The decrease in aqueous flow during sleep is as pronounced in untreated primary open-angle glaucoma patients as in normal controls, but the magnitude of the difference is so small that clinical relevance is unlikely.²⁴³ A few investigators have postulated that the diurnal IOP variation follows the diurnal glucocorticoid cycle, with IOP peaking about 3–4 hours after plasma cortisol.²⁴⁴

The diurnal variation in IOP has extremely important clinical implications for glaucoma patients. Asrani et al have shown that large diurnal variation in IOP is a risk factor for progression of glaucoma.²⁴⁵ Others have shown that the diurnal IOP curve is altered in glaucoma patients compared to normal subjects.²⁴⁶

The fact that the pressure can vary dramatically during a given day makes it unreasonable to assume that a single pressure taken at a specific time is representative of the average pressure the patient experiences over time. It is quite possible that this single pressure represents a high or low point, and that the patient's average pressures are substantially different.^{223,247} This is of particular concern in patients with normal-tension glaucoma, in whom it may be important to know whether the pressures are always in the low/normal range, or if they sail into the 20s every evening.^{248,249} A full 24-hour diurnal curve measurement is often prohibitively difficult to arrange in today's climate of cost containment. A modified diurnal curve is much more practical, while still providing useful information. It is often fairly easy to measure an 'office diurnal curve,' which generally means checking the pressure every 1 or 2 hours from about 8 a.m. to 6 p.m. Pressure swings of 6 or 8 mmHg are not uncommon.²²² Knowing the patient's daily pressure excursions allows the physician to tailor therapy toward blunting peaks in pressure, as well as controlling the average pressure during a certain time of day.²⁵⁰ Jonas and co-workers estimated that a single a.m. in-office IOP measurement has about a 75% chance of missing the diurnal IOP maximum, and they recommend that the patient's follow-up visits can be scheduled at differing times of the day to try and capture the maximum.²⁵¹ This group has also suggested that it is the level of IOP itself, not the magnitude of fluctuations, that actually is responsible for continued optic nerve damage.²⁵²

Home tonometry has been suggested as a method of following patients' pressures away from the office. It is unclear whether this method is practical in large populations, although it has been a successful adjunct in certain circumstances.²⁵³

SEASONAL VARIATION

A seasonal variation of IOP has been reported, with higher IOPs in the winter months.^{196,228,254–256} This phenomenon has been attributed to changes in the number of hours of light and to alterations of atmospheric pressure.²⁵⁵

CARDIOVASCULAR FACTORS

A number of studies have shown a correlation between IOP and systemic blood pressure.^{194,196,197,206,214,257,258} The relationship is

such that large changes in blood pressure are accompanied by small changes in IOP. For example, Bulpitt and co-workers have estimated that systemic blood pressure must rise by 100 mmHg to increase IOP by 2 mmHg.²⁰⁶ Normally, IOP fluctuates 1–3 mmHg as arterial pressure varies with each cardiac cycle.²⁵⁹ The magnitude of this IOP fluctuation is related to the height of the ocular pressure^{259,260} and to the variation of arterial pressure. Systemic hypertension and glaucoma show only a modest association, and the bulk of the effect is attributable to perfusion pressure or other vascular effects, rather than increased IOP.²⁶¹ Slower changes in IOP are seen with the Traube-Hering waves. A few researchers believe that IOP also correlates with pulse rate and hemoglobin concentration.¹⁹⁷

Elevations of episcleral venous pressure, whether from local or systemic conditions, are associated with increased IOP. The rise in IOP is usually in the same range as the rise in episcleral venous pressure.

Alterations in serum osmolality produce changes in IOP. This is best exemplified by the marked changes in IOP that occur during hemodialysis.^{262–264} Hyperosmotic drugs such as glycerine, urea, and mannitol are administered systemically to reduce IOP during acute episodes of glaucoma.

EXERCISE

Strenuous exercise produces a transient reduction of IOP.^{265–270} This phenomenon is at least in part caused by acidosis and alterations in serum osmolality.^{266,270} In one study, a program of conditioning reduced baseline IOP in normal volunteers.²⁷¹ In general, those who are more physically fit are more likely to have a lower resting IOP.²⁷² However, in extremely heavy exercise involving straining, such as weight lifting, IOP can be elevated significantly, perhaps due to valsalva or even increased intracranial pressure that is transmitted to the periorbital venous system.²⁷³ In addition, holding one's breath during weight lifting further increases the IOP.²⁷⁴

WIND INSTRUMENT PLAYING

Playing a wind instrument can raise the IOP, even in ophthalmologically normal individuals.²⁷⁵ The rise in IOP is higher with high-resistance instruments.²⁷⁶ Those musicians with large numbers of playing hours on high-resistance wind instruments are more likely to have optic nerve damage or visual field loss than their low-resistance colleagues.²⁷⁶

LIFESTYLE

Increased IOP was associated with increasing body mass index, increasing alcohol consumption and increasing cigarette consumption in one Japanese study.²⁷⁷ The Blue Mountain Eye Study also showed a modest correlation between smoking and IOP.²⁷⁸ Another result of the Blue Mountain Eye Study is that there is a positive correlation between caffeine consumption and level of IOP.²⁷⁹ In the Barbados Eye Study, systemic hypertension and diabetes were associated with increasing IOP with age.²⁸⁰ The Tanjong Eye Study suggested that lower socioeconomic status is associated with increasing IOP.²⁸¹

POSTURAL CHANGES

When normal individuals go from the sitting to the supine position, IOP rises by as much as 6 mmHg.^{282–289} An even greater response

is seen in patients with open-angle glaucoma or normal-tension glaucoma.^{282,285–287,290,291} When normal volunteers are placed in an inverted position, IOP increases markedly – that is, from an average of 16.8 mmHg to 32.9 mmHg in one study.²⁹² Once again, the rise is greater in glaucomatous eyes.²⁹³ The increase in IOP occurs very rapidly and probably reflects changes in arterial and venous pressure.²⁸³ The episcleral venous pressure does increase in the supine position, at least partly accounting for the increase in IOP when lying down.²⁹⁴ However, postural changes in venous pressure cannot explain all of the IOP change since there is a difference between supine and prone IOPs.²⁹⁵ Brief elevations of IOP are unlikely to be dangerous in normal individuals, but they may be harmful in patients with advanced glaucoma.²⁸⁹

Postural changes in IOP become a problem when one depends on an examination under anesthesia to determine IOP in children or those developmentally challenged. The anesthesia reduces IOP (see below) but the act of placing the patient supine increases the IOP. Furthermore, positioning on the table, straight, Trendelenburg or reverse Trendelenburg will affect the IOP – with Trendelenburg causing an increase in IOP and the reverse Trendelenburg a decrease. All these factors have to be melded into interpreting the measurement.

NEURAL FACTORS

A number of investigators have postulated that IOP is under neural control. As of yet there is no proof for this hypothesis, although some interesting observations have been made. Sympathectomy produces a transient reduction in IOP and an increase in outflow facility from a release of catecholamines.^{296,297} In a similar fashion, adrenergic agonists and cyclic adenosine monophosphate are capable of reducing IOP.^{298–300}

Other investigators have explored neural control of IOP by the parasympathetic system. Stimulation of the third cranial nerve reduces IOP.³⁰¹ Cholinergic drugs lower IOP by increasing outflow facility. Conversely, ganglionic blocking drugs increase IOP.³⁰²

Finally, other investigators have sought central nervous system centers that might control IOP. Some researchers have found that stimulation of specific diencephalic areas in experimental animals alters IOP, whereas other researchers^{303,304} believed these effects were non-specific in nature. The third ventricle is close to the hypothalamus and other diencephalic centers. Infusion of a number of substances – including calcium, prostaglandins, arachidonic acid, cyclic nucleotides, hyperosmotic solutions, and hypo-osmotic solutions – alters IOP.^{305–307}

Changes in IOP seem to mirror changes in intracranial and cerebrospinal fluid pressure and some have suggested that IOP could be used as a marker for increased or decreased intracranial pressure in patients with known intracranial pathology.³⁰⁸

PSYCHIATRIC DISORDERS

Ocular self-mutilation is a rare finding in psychotic and other severely disturbed patients.^{309–313} The authors have seen one young man who pressed and rubbed his fists against his eyes continually unless he was heavily medicated or physically restrained. At the time of our examination his vision was 20/200 in his better eye, with no light perception in the worse eye. Both eyes showed extensive cupping typical of glaucomatous damage, although his pressures were entirely normal and he exhibited no other risk factors for glaucoma.

HORMONAL FACTORS

As mentioned previously, the diurnal intraocular fluctuation may follow the glucocorticoid cycle.²⁴⁴ Administration of corticosteroids topically, periocularly, and systemically raises IOP.

Some researchers have questioned whether sex hormones have an influence on IOP. It has been noted that IOP varies with the menstrual cycle^{314–316} and is low in the third trimester of pregnancy.^{314,316,317} However, other studies have not found good correlations between IOP and serum levels of progesterone and estrogen.^{318,319} Pharmacologic doses of progesterones and estrogens reduced IOP in experimental animals and man.³¹⁶ Hormone replacement therapy in women has no effect on IOP,³²⁰ however, esterified estrogens with methyltestosterone therapy does raise IOP.³²¹

Diabetic individuals have higher IOPs than the general population. The reason for this association is unclear. A careful population-based study found that diabetic patients did not have an increased prevalence of glaucoma when selection bias was ruled out.³²²

Other hormones, including growth hormone, thyroxine (levothyroxine), aldosterone, vasopressin, and melanocyte-stimulating hormone, may influence IOP physiologically or when administered in pharmacologic doses.³²³

REFRACTIVE ERROR

A number of studies have reported higher IOPs in myopic individuals.^{214,324,325} Intraocular pressure also correlates with axial length.³²⁶ This has been reported in several studies involving pediatric patients, with some investigators suggesting that the increased pressure leads to the increase in axial length.^{327–329} However, not all studies in children are able to confirm this association.³³⁰

FOODS AND DRUGS

A variety of foods and drugs can alter IOP transiently (Table 4-4). Topical cycloplegic agents as well as systemic agents that have cholinergic effects can raise the IOP.³³⁹ Occasionally, longer acting cycloplegics like cyclopentolate can cause prolonged and serious

Table 4-4 Food and drugs influencing intraocular pressure

Agent	Association	Comments
General anesthesia ³³¹	IOP is reduced in proportion to depth of anesthesia	Exceptions are ketamine and trichlorethylene ^{332–334}
Alcohol ^{335,336}	Reduces IOP	Acts through inhibition of antidiuretic hormone and reduction of aqueous formation ³³⁵
Marijuana	Reduces IOP	Acts through local, vascular, and central effects
Corticosteroids	Raise IOP	Effect greater on glaucomatous eyes
Topical cycloplegic agents ^{337,338}	Raise IOP	
Water	Raises IOP	Large volumes of fluid (>500 ml) can raise IOP

pressure rises in glaucoma patients; such significant pressure rises are quite rare in eyes free from glaucoma.³⁴⁰ Anesthetic and sedative agents will lower IOP.^{341,342} The effect of general anesthesia is compounded by the fact that IOP is elevated during the excitatory phase and becomes progressively lower as the anesthesia lasts longer and phases of anesthesia become deeper. Therefore, timing of measurement following induction of general anesthesia is important. If one measures too early, you may be in the excitatory phase and erroneously read a pressure that is higher than resting pressure. If one measures later, the IOP may be lower than resting IOP due to the effects of deeper anesthesia plane or longer duration of anesthesia.

MISCELLANEOUS

Significant spontaneous asymmetric fluctuations do occur among both normal subjects and glaucoma patients; such fluctuations may cause trouble in interpreting one-eyed studies as well as interpreting therapeutic interventions.³⁴³ Forced eyelid closure can cause a significant increase in IOP and attempted squeezing of the eyelids during tonometry can be a significant source of error with either the Goldmann tonometer or the Tono-Pen.^{344,345} Just the placement of an eyelid speculum, even in a child fully induced with general anesthesia, can raise the IOP by about 4 mmHg.³⁴⁶ A tight necktie can significantly raise IOP in glaucoma patients and possibly in normal subjects;^{347,348} this can have some important implications for glaucoma management, although prolonged use of a tight necktie may produce adaptive reflexes that return the eye to its pre-tight necktie level.³⁴⁹ Nevertheless, it seems reasonable to caution glaucoma patients not to wear tight neckties.

The Blue Mountain Eye Study showed a small but significant correlation between increasing iris pigmentation and IOP level.³⁵⁰ Intraocular pressure is reduced at extremely high altitudes and returns to resting levels upon descent.³⁵¹

EYE MOVEMENTS

If the eye moves against mechanical resistance, IOP can rise substantially.^{352–355}

EYELID CLOSURE

Forcible eyelid closure raises IOP by 10–90 mmHg.³⁵⁶ Repeated eyelid squeezing reduces IOP.³⁵⁷ Widening of the lid fissure increases IOP by approximately 2 mmHg.³⁵⁸ Conversely, with Bell's palsy, IOP is slightly reduced.^{359,360}

INFLAMMATION

Intraocular pressure is usually reduced when the eye is inflamed because aqueous humor formation is reduced. However, if the outflow channels are more affected than the ciliary body, IOP can be elevated.

SURGERY

In most cases, IOP is reduced after ocular surgery. However, if the outflow channels are affected by inflammation or by the surgery itself (e.g., by viscoelastic substances or by an incision that reduces support for the trabecular meshwork), IOP can be elevated.³⁶¹ Trabeculectomy seems more effective at controlling IOP over the 24-hour period than maximal medical therapy.³⁶²

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Gonioscopic anatomy

GROSS ANATOMY

ANATOMIC FEATURES OF NORMAL EYES

The anatomic structures that regulate intraocular pressure (IOP) are contained in the anterior segment of the eye.¹ Behind the rounded apex of the angle is the ciliary body, which produces aqueous humor and regulates its outflow. The position of the lens and the overlying iris determines the depth of the anterior chamber. The width of the chamber angle is defined by the point of the iris insertion on the ciliary body, the peripheral contour of the iris as it drapes around the lens, and the pupillary size. Finally, there is the corneoscleral trabecular meshwork, through which aqueous humor percolates to reach Schlemm's canal, the collector channels, and the anterior ciliary veins of the limbal area.² This region is not only the site of the prime pathologic changes responsible for the increased IOP associated with all of the glaucomas, but it is also the focus of most of the medical and surgical procedures designed to alleviate increased IOP (Fig. 5-1). This knowledge has been the bedrock of the modern understanding of glaucoma.^{3,4}

Distinguishing between the two parameters of anterior chamber *depth* and *angle width* is useful. For example, an important diagnostic distinction between pupillary-block primary angle-closure glaucoma and malignant glaucoma is that though both conditions have occluded angles, the former condition presents with a

relatively deeper central anterior chamber depth than does the latter. Conversely, a plateau iris configuration typically has a very deep central chamber but a narrow and potentially occludable angle. Distinguishing among the various components that contribute to the three-dimensional configuration of the angle has led to a detailed and novel scheme for gonioscopic grading.^{5,6}

The size and the shape of the eyeball are genetically determined. Important gonioscopic structural differences among racial groupings are beginning to be appreciated.^{7,8} These studies find a more anteriorly inserting iris root (and potentially occludable angle) in Asian patients. Such variations in angle structure may contribute to the reportedly higher incidence of primary and chronic angle-closure glaucoma among distinctive populations, such as Alaskan and Greenland Eskimos,⁹⁻¹¹ Chinese populations both in China and in Malaysia,¹²⁻¹⁴ Japanese people,^{15,16} and people of Asian ancestry in South Africa.¹⁷

The deep-chambered eye almost always has a wide angle, whereas the angle contour of the shallow-chambered eye tends to be narrow. When the angle formed between the iris and the surface of the trabecular meshwork is between 20° and 45°, the eye is said to have a wide angle. Angles smaller than 20° are termed narrow angles (Fig. 5-2). The narrower the angle, the closer the iris comes to the meshwork and the more probable angle closure becomes. The major contribution of gonioscopy is distinguishing open-angle from angle-closure glaucoma.¹⁸

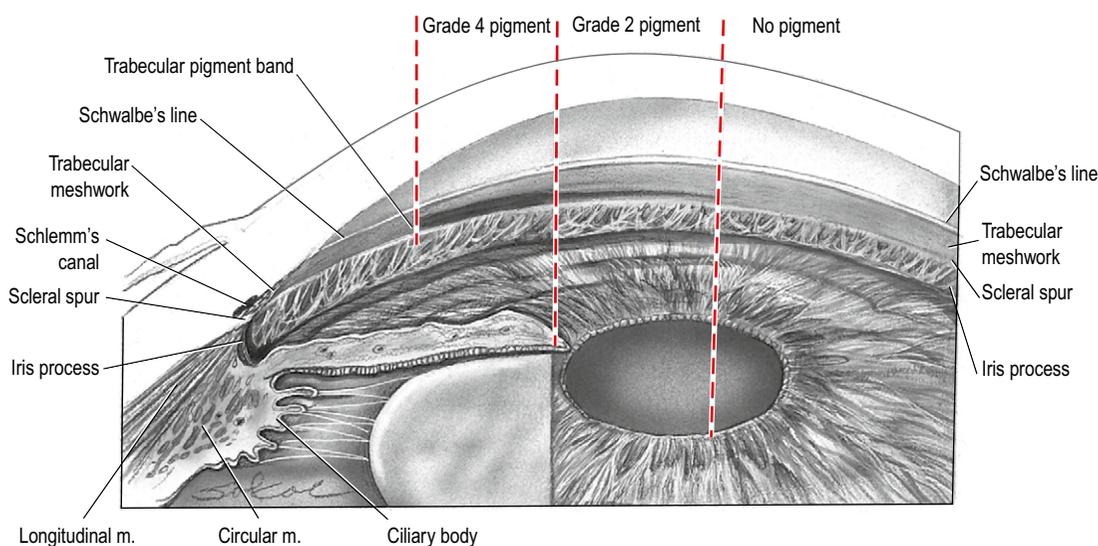


Fig. 5-1 Composite drawing of microscopic and gonioscopic anatomy.

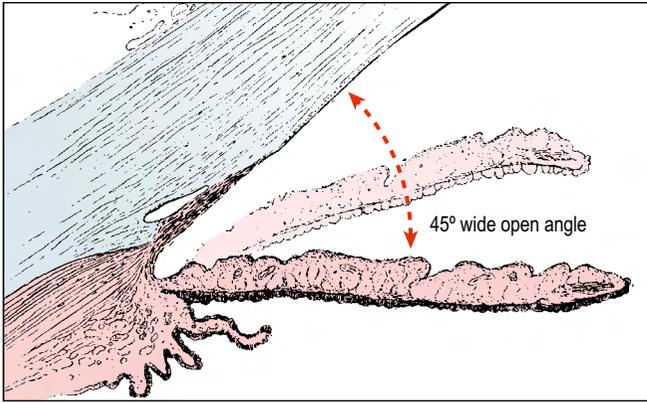


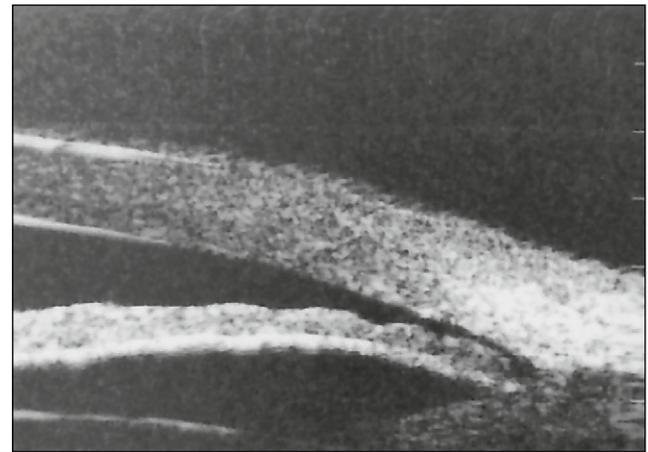
Fig. 5-2 A 'wide' angle of 45° is the benchmark against which angles of approximately half that angulation or less (0° to 20°) are defined as 'narrow'. (From Shaffer RN: Gonioscopy, ophthalmoscopy and perimetry, *Trans Am Acad Ophthalmol* 64:112, 1960.)

In the deep-chambered, wide-angled eye, the lens is held by the zonular ligaments, approximately centered in the ring made by the ciliary body. The iris originates at the inner anterior border of the ciliary body and lies with minimum contact on the anterior lens surface of the eye. An increase in IOP in such an eye must be caused by an obstruction to trabecular aqueous egress or an increase in the rate of aqueous production. The latter is rarely, if ever clinically encountered.

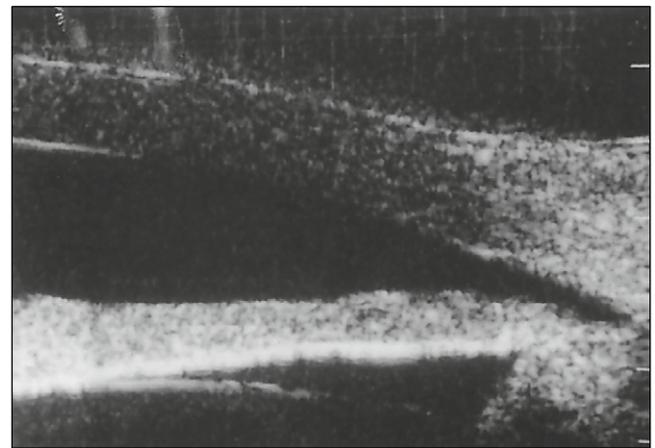
ANATOMIC FEATURES OF NARROW-ANGLED EYES

In contrast, the lens of the shallow-chambered, narrow-angled eye is well anterior to the ciliary body ring, and the iris is held more snugly against a much larger area of the posterior iris surface. Therein results a physiologic or relative pupillary block. In such an eye, a somewhat higher pressure is required in the posterior chamber to push aqueous humor through this tight iris–lens apposition than is necessary for the looser apposition of the wide-angled eye.¹⁹ An exaggeration of this pupillary block is primary cause of angle-closure glaucoma. The slight excess pressure in the posterior chamber lifts the iris root forward and may be adequate to push the iris against the trabecular meshwork in some eyes (see Fig. 7-1C and D). If the angle is sufficiently narrow, and the iris base sufficiently distensible, the iris is forced against the surface of the trabecular meshwork, blocking aqueous flow into Schlemm's canal, and an attack of angle-closure glaucoma ensues. The alternative route for aqueous egress provided by a patent iridotomy can completely reverse this propensity for angle occlusion by the iris base, as demonstrated dramatically with ultrasonic biomicroscopy (Fig. 5-3).

An important narrow-angle configuration is the anatomic abnormality associated with plateau iris. In this condition the peripheral iris is displaced anteriorly into the angle by anomalously positioned and rotated ciliary processes behind the iris root.²⁰ This has been demonstrated both by ultrasonic biomicroscopy²¹ and by histology.²² Pupillary dilation may bunch up the peripheral iris and occlude the angle, often appearing in a characteristic 'sine wave' configuration.²³ Pupillary block plays only a small role in the mechanism; laser iridotomy neither appreciably increases the central anterior chamber depth nor reverses the cramping of the angle (Fig. 5-4).²⁴ And although cataract removal deepens both the central chamber depth



(A)



(B)

Fig. 5-3 (A) Bowing of iris into angle during attack of pupillary-block angle-closure glaucoma. (B) Following laser iridotomy the contour of the iris has become flat, falling away from the angle. (From Pavlin CJ, Foster FS: *Ultrasound in biomicroscopy in glaucoma*. In Ritch R, Shields MB, Krupin T, editors: *The glaucomas*, 2nd edn, St Louis, Mosby, 1996.)

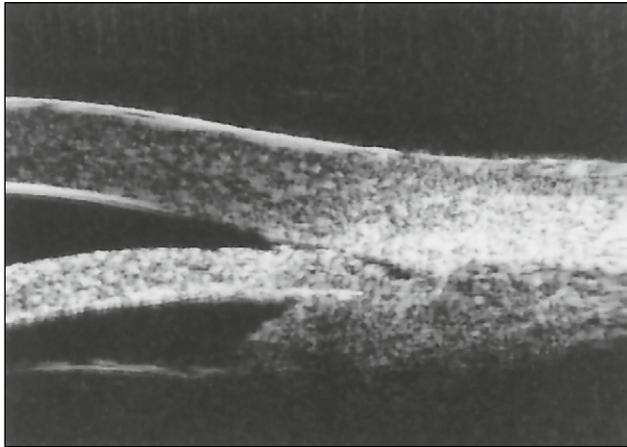
and opens the angle in normal eyes,²⁵ the angle in plateau iris remains unchanged following such surgery.²⁶

GONIOSCOPIC ANATOMY AND MICROSCOPIC INTERPRETATION

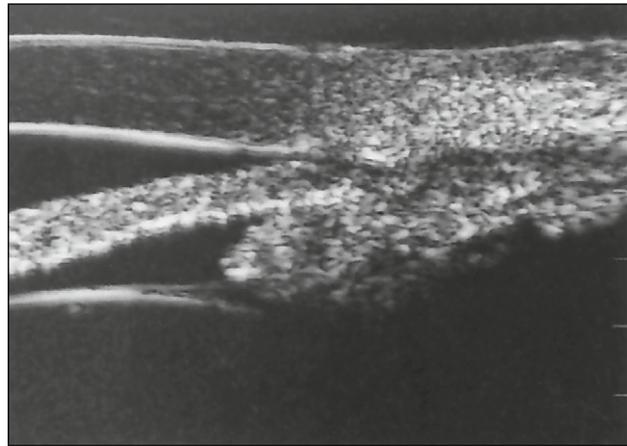
PUPIL AND IRIS

It is best to start gonioscopy by looking at the pupil for rapid orientation. The anterior lens surface can be observed for focal opacifications (*glaukomflecken*) of the anterior lens and for posterior synechiae. This position is also excellent for viewing the white dandruff-like flecks of exfoliation on the pigment at the posterior edge of the pupil, which is typical of exfoliative syndrome.^{27,28} Iridodonesis is present to a small degree in some deep-chambered normal eyes and is easily observed if of a pathologic degree.

The first of the three major iris features the examiner should carefully evaluate is the *contour* of the iris, noting its flatness when



(A)



(B)

Fig. 5-4 (A) Plateau iris syndrome with anteriorly rotated ciliary process pressing peripheral iris forward toward the angle. **(B)** Following laser iridotomy there is virtually no change in either iris or angle configuration. (From Pavlin CJ, Foster FS: *Ultrasound in biomicroscopy in glaucoma*. In Ritch R, Shields MB, Krupin T, editors: *The glaucomas*, 2nd edn, St Louis, Mosby, 1996.)

the anterior chamber is deep, its convexity (or even bowing) in eyes with a shallow anterior chamber, or its peripheral concavity in eyes with high myopia or signs of pigment dispersion.^{29,30} After assessing the configuration of the peripheral iris, attention should be paid to the *site of iris insertion* – both its apparent and actual juncture in the angle. Indentation gonioscopy is particularly helpful in distinguishing iris–trabecular touch (apposition) from genuine adhesion. The level of iris insertion can be described in reference to structures within the angle recess – at the level of the upper trabecular meshwork and Schwalbe's line; at the level of the filtering trabecular meshwork; just below the scleral spur; below the spur in the ciliary body; or deep posteriorly in the ciliary band. Anteriorly inserting irides, at the level of the spur or lower trabecular meshwork, may possibly be more common among Asians^{7,8} and in patients with hyperopia. Third, the examiner should estimate the *angulation* between the iris insertion and the slope of the inner cornea in the angle, in approximate steps of 10°. As discussed in Chapter 7, this systematic assessment of angle anatomy is the basis of the most detailed gonioscopic grading systems. Last, abnormalities such as neovascularization, hypoplasia, atrophy, and polycoria should be noted.

CILIARY BODY, IRIS PROCESSES, AND SYNECHIAE

Beyond the final iris roll is the angle recess. At birth, this recess is incompletely developed. By the age of 1 year, the recess has formed a concavity into the anterior surface of the ciliary body. The ciliary body appears as a densely pigmented band deep to the trabecular surface. Its anterior extension merges into the scleral spur, which appears as a white line between the ciliary body and the more anterior pigmented trabecular band. If there is no pigment in the trabecular meshwork, the ciliary body will be the only pigmented structure in the angle wall. In angle recession the ciliary body may be broadly exposed. Irregular, thread-like fibers of the anterior iris stroma sometimes arborize across the angle recess and are called iris processes (see Fig. 5-5A). Gonioscopically, the processes usually seem to terminate near the spur, but some may extend in front of Schlemm's canal, occasionally running as high as Schwalbe's line. Larger processes represent an incomplete embryologic separation of the iris from the angle wall, which is seen in exaggerated form in the pathologic congenital syndrome of Axenfeld. Most of the fibers lose their pigment at the scleral spur and then merge with the innermost layer of the trabecular meshwork, called the uveal meshwork.

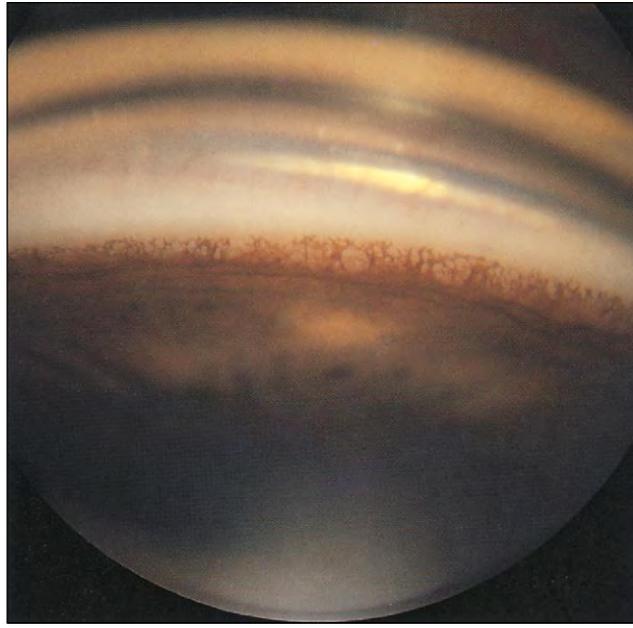
In blue eyes, the iris processes are light gray and difficult to see, but in brown eyes, the pigmented processes stand out prominently against the light background of the scleral spur. The neophyte gonioscopist may misinterpret these processes as peripheral anterior synechiae. They do not interfere in any way with outflow of aqueous humor (Fig. 5-5).

True synechiae are formed when the peripheral iris becomes attached to the trabecular wall. There are several clues for distinguishing iris processes from peripheral anterior synechiae. Iris processes are fibers or syncytial sheets that closely follow or bridge the concavity of the angle recess and that usually allow a view of the angle recess behind them unless they are extraordinarily dense. Peripheral anterior synechiae are actual adhesions of iris tissue that cover and occlude variable amounts of the angle. They can insert low at the level of the scleral spur (such as after laser trabeculoplasty) to as high as Schwalbe's line and beyond (as with the irido–corneo–endothelial syndromes). Often normal angle structures can be seen in one area but are concealed by the synechiae in other areas. Synechiae can form only when the iris is pushed against the trabecular meshwork, as in angle-closure glaucoma, or when the iris is pulled up onto the meshwork as the result of the shrinkage of inflammatory products or fibrovascular membranes attached to both iris and meshwork. In the area of a synechia, peripheral iris tissue butts flat against the trabecular surface; it does not wrap around the angle recess as does an iris process – a distinction well appreciated during indentation gonioscopy.

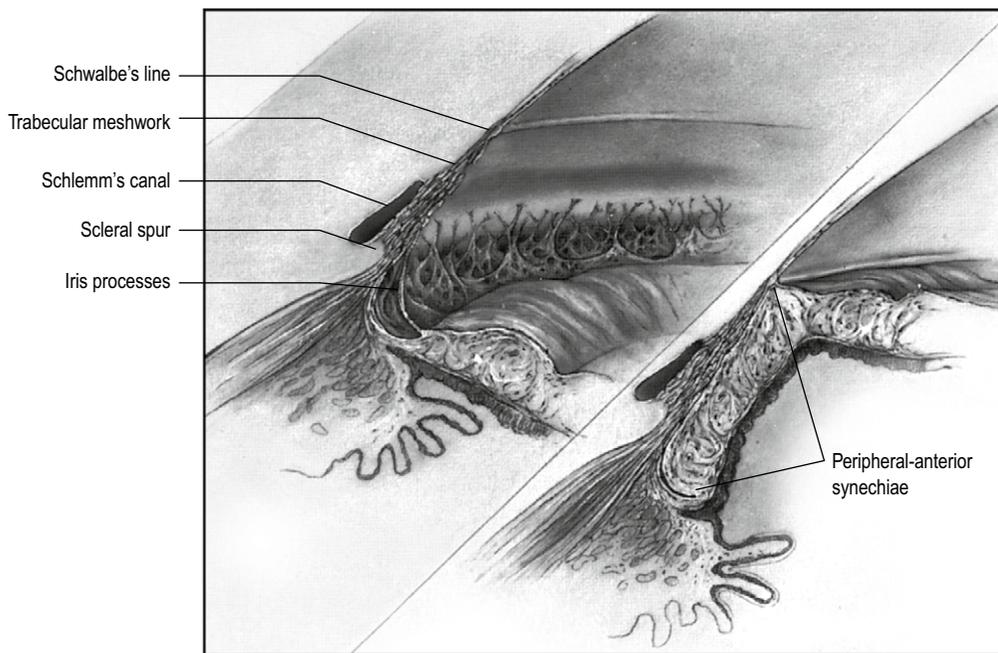
SCLERAL SPUR

The most anterior projection of the sclera internally is the scleral spur. In wide-angled eyes, it is seen gonioscopically as a gray-white line of varying width at the outer end of the angle recess, and it is the point of attachment of the ciliary body and the point of termination of most of the iris processes. If blood is in Schlemm's canal, it lies just anterior to the spur.

The spur forms the posterior concavity of the scleral sulcus. Schlemm's canal is held in the sulcus by the corneoscleral trabecular sheets that form an inner wall to the sulcus. Most of these sheets insert at the spur. The spur is also the insertion point for most of



(A)



(B)

Fig. 5-5 (A) Iris processes covering angle. This 33-year-old female had iris sweeping up over the trabecular meshwork in a dense syncytium. This is similar to the concave iris insertion in trabeculodysgenesis (see Ch. 23). Such patients often present with glaucoma before the age of 30. **(B)** Difference between iris processes and peripheral anterior synechiae.

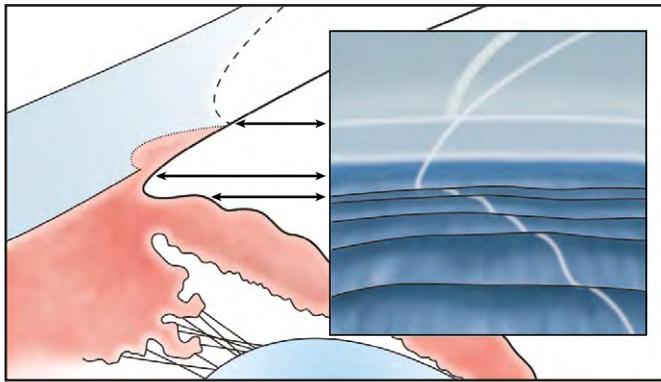
the longitudinal muscle fibers of the ciliary body, whose action alters the facility of aqueous outflow (see Fig. 5-1). The spur's crisp white appearance is the most helpful landmark in orienting the gonioscopist. It is also prominent in ultrasonic biomicroscopy because unlike other angle structures such as the posterior trabecular meshwork, it can be readily identified and thus used as an important landmark in quantifying angle measurements.^{31,31b}

SCHWALBE'S LINE

Another important gonioscopic landmark, Schwalbe's line, marks the most anterior extension of the meshwork and the termination of Descemet's membrane of the cornea. By slit-lamp examination of

normal eyes it often can be seen somewhere in the limbal circumference as a hazy zone of the inner corneal surface. With an indirect contact lens, the corneal parallelepiped of the slit-lamp beam comes together at this point (Fig. 5-6). With the use of the Koeppel contact lens (see Ch. 6 for explanation of Koeppel and Zeiss gonioscopy), Schwalbe's line is seen as a translucent or white ledge that projects slightly into the anterior chamber,³² or it may be a vague line of demarcation between the smooth surface of Descemet's membrane that covers the inner cornea and the less transparent rough texture of the uveal meshwork.

The line itself is composed of a bundle of collagenous connective tissue fibers running circumferentially around the eye at the end of Descemet's membrane. Here the corneal radius of curvature



Chamber angle of average width. In most eyes the inferior quadrant is widest, the lateral quadrants narrower, and the superior narrowest. In eyes with narrow angles, the temporal quadrant may be narrowest.

Fig. 5-6 Parallelepiped method of identifying the boundary between cornea (thick light beam) and anterior trabecular meshwork (thin strip of light). (From Palmberg P: *Gonioscopy*. In Ritch R, Shields MB, Krupin T, editors: *The glaucomas*, 2nd edn, St Louis, Mosby, 1996.)

changes to the larger radius of the sclera. This change in curvature and the beginning roughness of the trabecular surface provide a lodging place for the pigment granules that may be carried into the inferior angle by the aqueous convection currents (Sampaolesi's line). Such pigmentation is rare in healthy young eyes but becomes increasingly common in older or diseased eyes.

TRABECULAR MESHWORK AND TRABECULAR PIGMENT BAND

Between Schwalbe's line and the scleral spur lies the trabecular meshwork, through which aqueous humor flows to Schlemm's canal. The internal layer of the trabecular meshwork is a syncytium

of fibers called the uveal meshwork. The outer portion of the trabecular meshwork is composed of corneoscleral trabecular sheets that insert into the scleral sulcus and the spur. These sheets are not visible gonioscopically.

GONIOSCOPIC APPEARANCE

Gonioscopically, the trabecular meshwork has an irregularly roughened surface, which in childhood appears as a glistening, translucent-like semitransparent gelatin with a stippled surface. With increasing age its transparency decreases.³³ The roughness of its surface is caused by the large openings of the uveal meshwork. It should be stressed that the examiner's gaze should parallel the iris as nearly as possible when looking at the trabecular surface. With indirect gonioscopy, such as with the Zeiss lens, having the patient look away from the viewing mirror gives an optimal view of the meshwork in wide-angle eyes. In the narrow-angled eye, the convex plane of the iris forces a more oblique visualization (optimized with the patient looking toward the viewing mirror), which allows the angle recess to be seen, but which may give a somewhat foreshortened and distorted appearance to the meshwork.

Just anterior to the scleral spur is the effective filtering portion of the meshwork, lying in front of Schlemm's canal. In aging and disease processes, the aqueous flow carries pigment from the iris and deposits it in varying amounts and depths in the meshwork, giving rise to the trabecular pigment band, which tends to be denser in the lower angle. Such pigmentation can be homogenous in appearance (as in the pigment dispersion syndrome) or variegated (as seen after anterior segment trauma). The presence and extent of trabecular pigmentation may provide valuable clinical information, such as suggesting an occult case of pseudoexfoliative syndrome or being indicative of a favorable response to laser trabeculoplasty.

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CHAPTER
6

Methods of gonioscopy

DEFINITION

Gonioscopy is biomicroscopic examination of the anterior chamber angle of the eye, where aqueous humor gains access to Schlemm's canal. It enables the glaucomas to be classified into two main groups, angle-closure glaucoma and open-angle glaucoma. Gonioscopy is helpful diagnostically, prognostically, and therapeutically in glaucoma.¹⁻⁴

METHODS OF GONIOSCOPY

EQUIPMENT

Because of the curvature of the cornea and the difference in the index of refraction between the eye and the air, light rays coming from the far peripheral iris, the angle recess, and the trabecular meshwork undergo total internal reflection (Fig. 6-1), which prevents the clinician from examining these structures without the use of a contact lens to eliminate the air–cornea interface. Three types of gonioscopic contact lenses are available: (1) those whose surface is slightly larger than the cornea and that require a gonioscopic coupling gel (e.g., Goldmann lens); (2) those whose surface is smaller than the cornea and that use the patient's tear film as a coupling agent (e.g., Zeiss or Sussman four-mirror lens); and (3) those whose surface is quite large, that use saline or similar fluid as a coupling agent, and that necessitate that the patient lie supine (e.g., Koeppel lens) (Fig. 6-2). Devices from the first two groupings are most popular because they can be used under standard examination circumstances, with the patient sitting at the slit lamp. Advantages and disadvantages of the direct and indirect methods are listed in Table 6-1.

Goldmann and Zeiss lenses (indirect method)

The Goldmann and Zeiss types of lenses are termed *indirect gonioscopic lenses* because they have mirrors by which the angle is examined with reflected light (Figs 6-3 and 6-4). The patient can be examined with the light and magnification of the slit lamp and corneal microscope. The magnification obtained depends on the power of the microscope and should be 16× to 20×.

Koeppel lens (direct method)

The Koeppel lens allows the observer to look directly at the angle (Fig. 6-5). The curvature of this lens adds 1.5× to the magnification of the angle image. Lighting is usually obtained by a Barkan hand illuminator or fiber optic light source, and magnification is obtained by a supported, counterbalanced microscope having 1.6× objective lenses and 10× ocular lenses. With the 1.5× magnification of the Koeppel lens, a 24× magnification of the trabecular area is obtained.

A hand-held microscope may be used for less exacting gonioscopy, but without support the depth of focus is too critical at a magnification above 16×, and 6 to 10× ocular lenses should be used.

TECHNIQUE

Indirect gonioscopic lenses

The patient sits upright at the slit lamp, with the head firmly against the headrest. When the Goldmann type of lens is used, a drop of 1% methylcellulose is placed in the corneal curve of the lens. With the patient looking up, one edge of the lens is positioned in the lower fornix. The upper lid is elevated, the patient is instructed to look straight ahead, and the lens is rotated against the eye (Fig. 6-6). This is a familiar maneuver to clinicians because this model

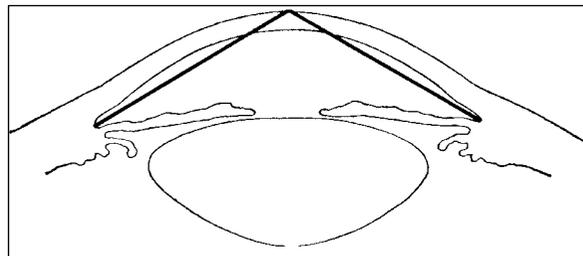


Fig. 6-1 Rays of light originating at the anterior chamber angle. These rays undergo total internal reflection by the cornea.

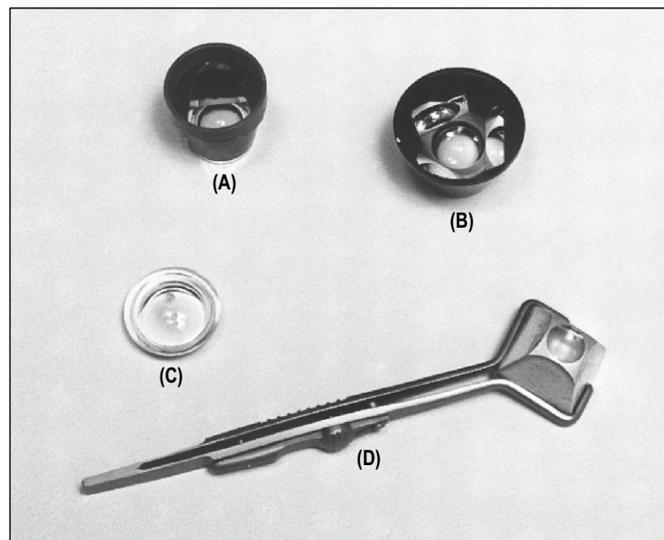


Fig. 6-2 Gonioscopic contact lenses. (A) One-mirror Goldmann; (B) three-mirror Goldmann; (C) Koeppel; (D) hand-held Zeiss.

Table 6-1 Direct versus indirect gonioscopy		
	Advantages	Disadvantages
Indirect gonioscopy	Equipment and examination posture are routine and familiar Fast Facilitates indentation gonioscopy Slit lamp gives controlled illumination and high magnification for detailed viewing	Difficult to see laterally into narrow angles Retroillumination is difficult Orientation initially confusing May require a special coupling agent
Direct gonioscopy	Greater patient comfort Binocular comparison possible Orientation simple Orientation relevant for surgical procedures (e.g., goniotomy, trabeculodialysis, goniosynechialysis) Excellent for teaching Can see over convex iris Can assess dynamic effects of pupillary light response on angle configuration Most comparable to ultrasonic biomicroscopy findings	Cumbersome and time-consuming Special equipment required Less magnification, with loss of detail

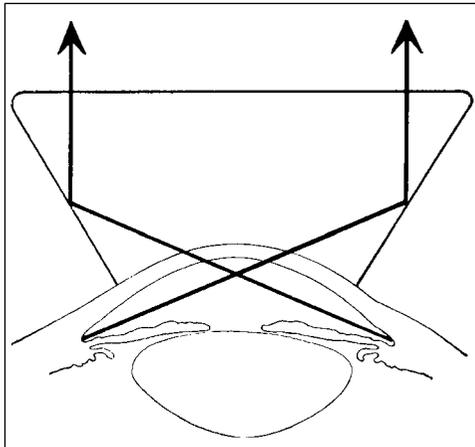


Fig. 6-3 Rays of light emerging through a Zeiss indirect gonioscopic lens.

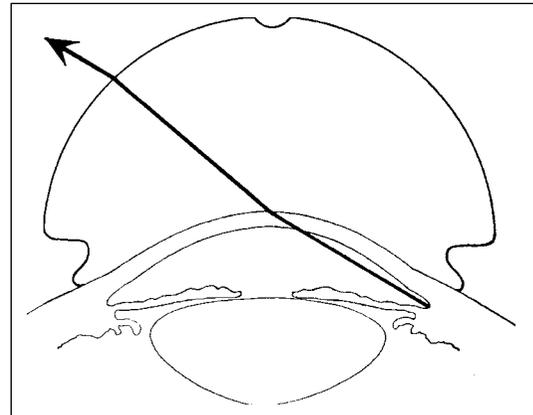


Fig. 6-5 Rays of light from the angle, emerging through a Koeppel lens.

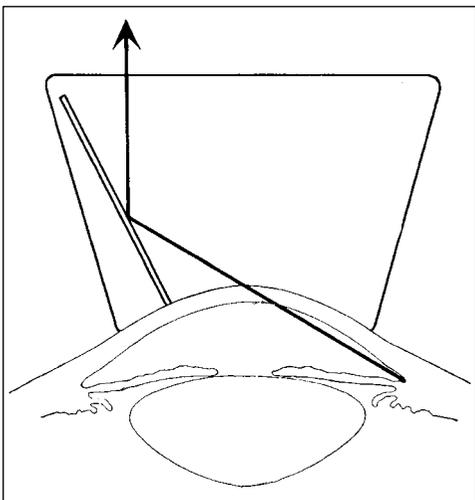


Fig. 6-4 Rays of light emerging through a Goldmann lens.

of gonioscopic lens is similar to that used for retinal evaluation and treatment. Devices such as the Zeiss lens are available with a handle and a special clamp to secure the lens, so that the physician merely advances the lens to the point of contact with the cornea of the eye to be examined, while the opposite eye follows the fixation light (Fig. 6-7). Other models include the 4-mirrored lens in a circular casing without a handle, for direct apposition to the cornea; special attention should be taken to not inadvertently indent the cornea.

The mirrored arrangement of both of these types of lenses causes the observed image of the angle to be reversed but not crossed.³ In other words, that which is seen in the mirror is 180° away, but its detail is not altered with respect to right and left (Fig. 6-8). The other important adjustment the novice gonioscopist need master is to apply the absolute minimum amount of pressure of the contact lens on the cornea, especially while maneuvering the slit-lamp beam and the lens to maximize visualization. Routine use of gonioscopy in many normal eyes will eventually eliminate such artifacts as inadvertent corneal folds, air bubbles in the coupling agent, and disorientation with respect to where the patient should gaze during the examination to most effectively reveal different aspects of the angle.⁴



(A)



(B)

Fig. 6-6 (A) The Goldmann lens is brought into contact with the inferior sclera. **(B)** The Goldmann lens tipped up into position. (From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)



Fig. 6-7 Zeiss four-mirror lens held in a diamond configuration. This position is more natural for some examiners, but the corners of the lens against the patient's eyelids can feel uncomfortable. (From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

Another crucial gonioscopic skill for the clinician to master is to minimize the artifact of light-induced miosis during the examination, which, especially in narrow-angle eyes, can alter the assessment of the angle. Always perform slit-lamp gonioscopy in a darkened room; and practice using the smallest possible slit-lamp beam, in both height and width, to view the angle structures without throwing light into the pupil.

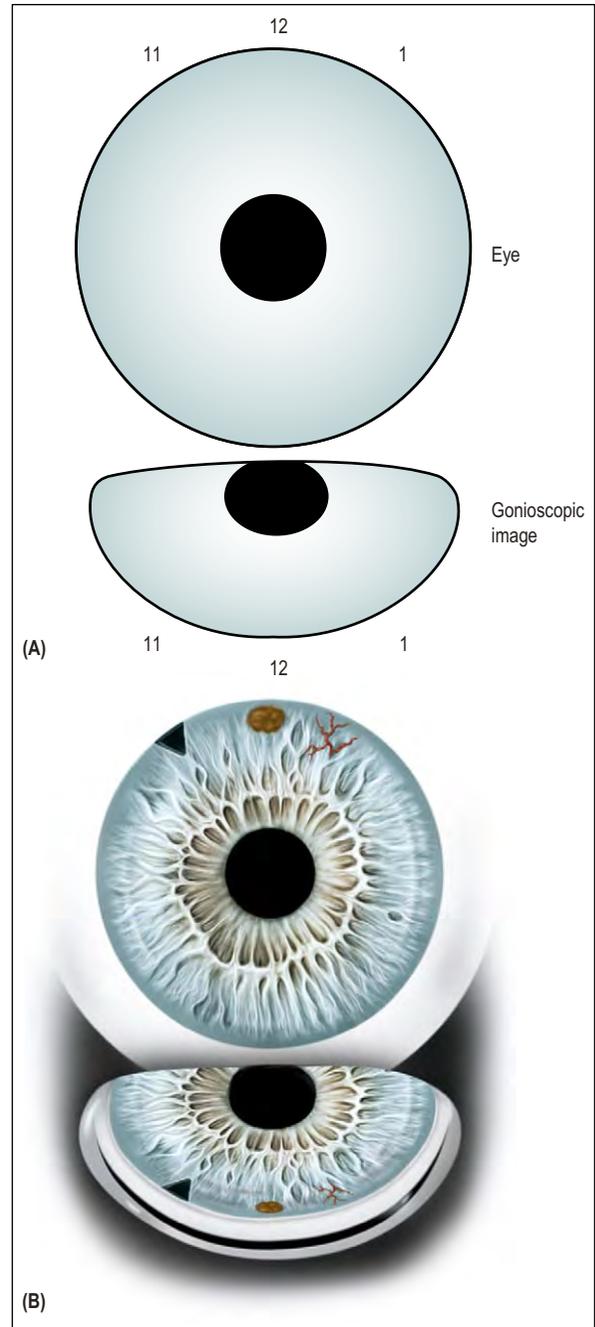


Fig. 6-8 (A) Schematic of indirect gonioscopy mirror, with images viewed 180° reversed but oriented the same right-to-left (e.g., 11 o'clock, 12 o'clock, 1 o'clock positions). **(B)** Example of indirect gonioscopy, showing location of surgical iridectomy, iris nevus, and neovascular vessels as they appear on the iris and as an image in the gonioscopic mirror.

Indentation (compression) gonioscopy⁵

By deliberately varying the amount of pressure applied to the cornea with a tear-coupled indirect (e.g., Zeiss) contact lens, the physician can observe the effects on angle width. Increased pressure indents the central cornea and displaces fluid into the angle, opening it wider (Figs 6-9 and 6-10). To the experienced examiner, this technique is valuable in evaluating the status of the angle and the presence of synechiae. The ability to visualize angle structures by indentation may be reduced in the presence of elevated intraocular pressure.

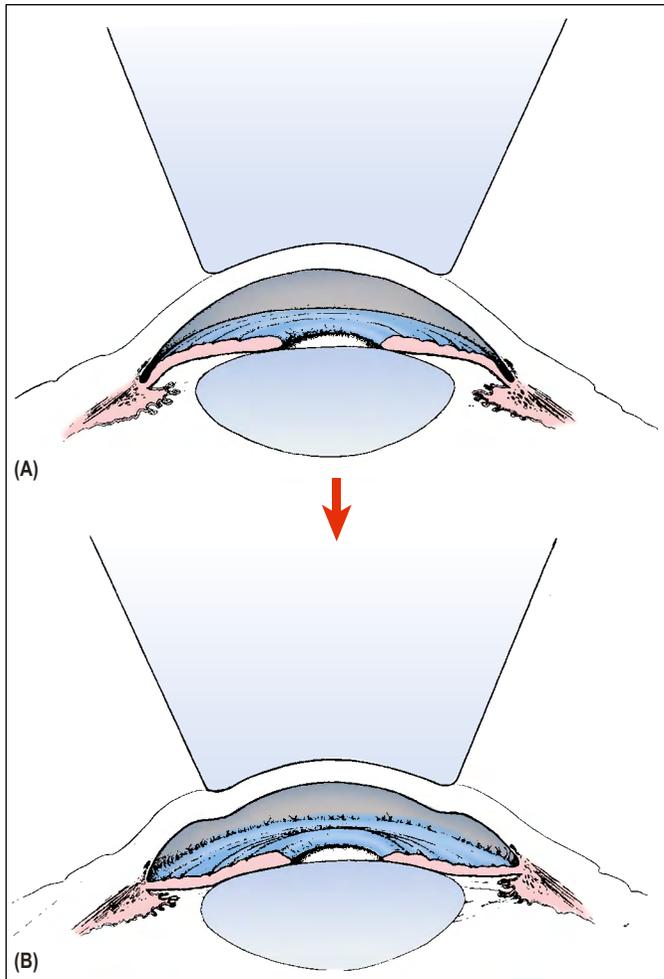
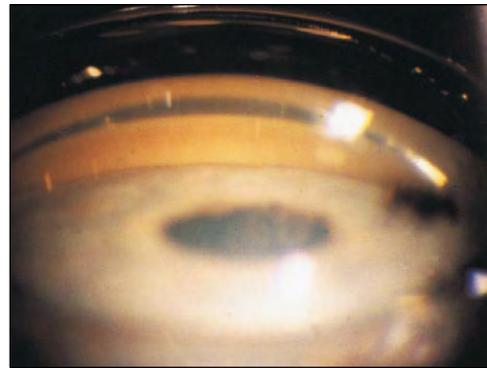
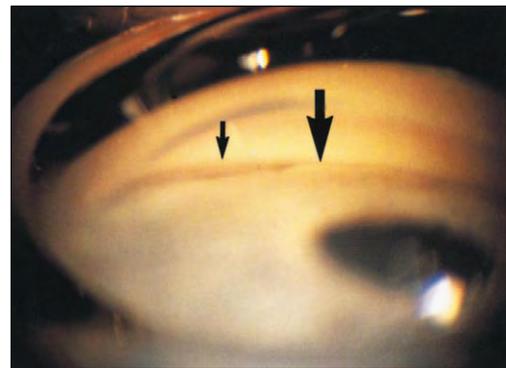


Fig. 6-9 Indentation gonioscopy. Pressure on the cornea displaces the iris to widen a narrow or closed anterior chamber angle. This maneuver exposes additional anatomic landmarks and is useful in determining the presence or absence of peripheral anterior synechiae. Synechiae, if present, can sometimes be separated. **(A)** Without pressure. **(B)** With pressure.

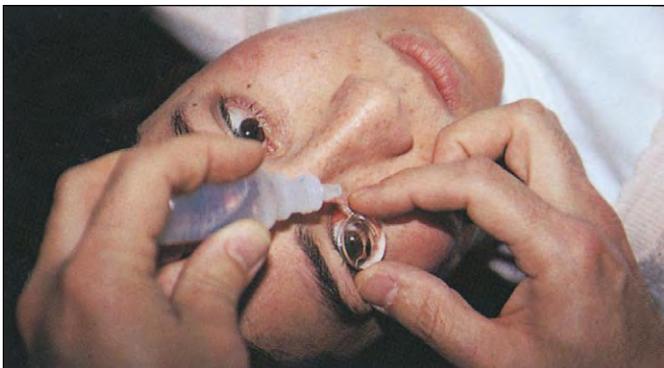


(A)

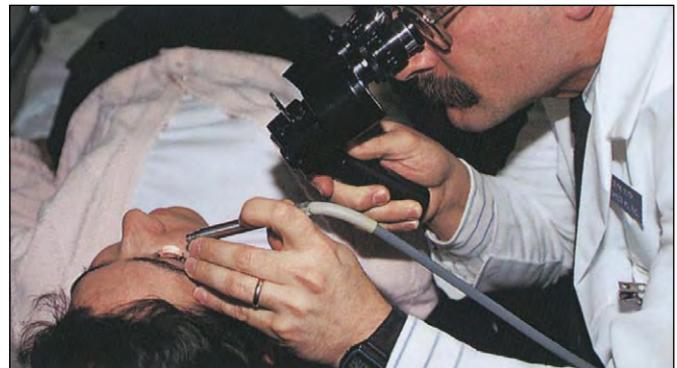


(B)

Fig. 6-10 **(A)** An eye with appositional angle closure. No trabecular meshwork is visible. **(B)** With indentation gonioscopy, parts of the trabecular meshwork are visualized (small arrow) but there is a broad peripheral anterior synechia (large arrow), which precludes visualization of the remainder of the trabecular meshwork. (From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)



(A)



(B)

Fig. 6-11 **(A)** Saline is used to bridge the gap between the Koepple lens and the cornea in a supine patient. **(B)** Examination of supine patient with Koepple lens using counterbalanced biomicroscope and Barkan illuminator. (Courtesy of Paul R Lichter, MD and A Tim Johnson, MD, PhD, University of Michigan. From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

Direct gonioscopic lens

The patient lies comfortably supine, with the head turned toward the examiner and eyes looking at the examiner's nose (Fig. 6-11). The examiner holds the Koeppel lens at the equator between the right-hand thumb and index finger for the right eye and between the left-hand thumb and index finger for the left eye and inserts

the lens between the lids. After the space beneath the lens is filled with isotonic sodium chloride solution, an assistant can steady it with a muscle hook or an applicator. If the patient is less cooperative, then more viscous 1% methylcellulose is used instead of isotonic sodium chloride solution.

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CHAPTER
7Clinical interpretation of
gonioscopic findings

GRADING OF CHAMBER ANGLE

There has been an evolution in the clinical methods used to describe the anterior chamber angle. An earlier scheme described by Scheie¹ emphasized the most posteriorly visible structures within the angle recess on gonioscopy; its scale from 0 to 4 was the reverse of what is now commonly used, with the Scheie grade 4 being the most occludable angle. For over a generation the Shaffer system has enjoyed widespread popularity, with its simplified emphasis on assessing the geometric angle width in four basic grades and its attention to the angle's potential for occlusion.² Recently a more complex classification has been elaborated by Spaeth that notates several three-dimensional aspects of the angle's configuration.^{3–5,28} These latter two schemes merit this chapter's detailed discussion.

The widest angles are characteristically seen in myopia, aphakia, and pigmentary dispersion syndrome.⁶ Such eyes have a deep chamber and a flat iris plane that makes an angle of about 45° with the trabecular surface. As the chamber depth shallows, the angle narrows. With increasing relative pupillary block there is increasing danger of angle closure, especially as the angle becomes smaller than 20°.

To compare different angles, it is convenient to have a grading system (Fig. 7-1). The most widely used scheme is the Shaffer classification, which includes numeric grades of angles that can be recorded conveniently on office charts. The widest open angle is a grade 4, and a closed angle is grade 0. There are very narrow angles in which it is impossible to decide whether an opening exists between the iris root and the trabecular surface, despite performing indentation gonioscopy. Such angles are labeled 'slit.' Table 7-1 shows the incidence difference in two ethnic populations, of grades 1 to 4 among white⁷ and Japanese patients.⁸ Table 7-2 indicates angle grades and their clinical significance.

Angle width can be estimated during a slit-lamp examination by directing the slit-lamp beam adjacent to the limbus; this is called the van Herick technique.⁷ The examiner can use the peripheral anterior chamber depth to indicate angle width (Fig. 7-2 and Table 7-3). This is a useful screening method under various circumstances – for example, when corneal clouding reduces visualization of the anterior chamber. The van Herick method has proven particularly helpful in evaluating large numbers of patients in population studies for angle-closure glaucoma; likewise, it shows its best specificity and sensitivity rate in the presence of narrow angles.^{8,9} When used in combination with other measurements, such as the tangential flashlight screening for shallow chamber (Fig. 7-3), this

estimation can be a valuable predictor of eventual angle-closure disease.^{10–12} This is not, however, recommended as a substitute for gonioscopy.^{13–15}

It is obvious that the various angle grades merge into one another, so that the usefulness of any classification system depends on the skill of the observer in judging which angles are potentially or actually occluded. Though simplified to a single grade, the experienced clinician's assessment of the angle's risk for angle closure takes into account the three-dimensional aspects of angle anatomy, such as the level of the iris insertion and peripheral iris configuration.

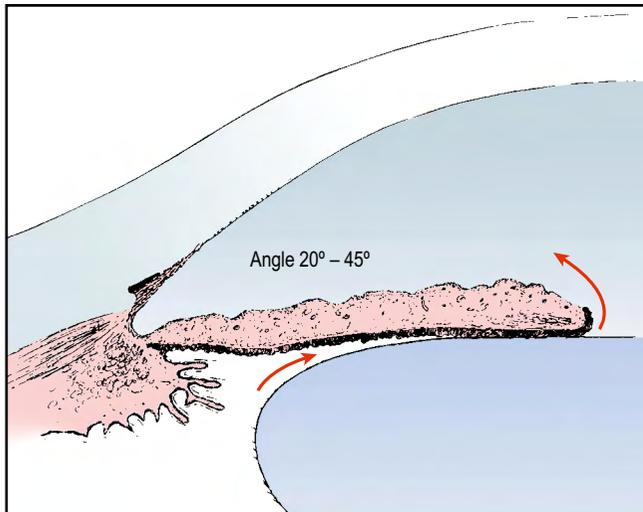
DIAGRAMMING ANGLE WIDTH,
SYNECHIAE, AND PIGMENTATION

Figure 7-4 shows a valuable method of diagramming the angles and recording the visible structures in each quadrant, as well as the position of peripheral anterior synechiae (PAS). The density of the trabecular pigment band can also be recorded. In the diagram the cornea is opened out to place Schwalbe's line outside the angle recess so that synechiae can be diagrammed as continuous with the peripheral iris stroma (Fig. 7-4A). Synechiae as high as the scleral spur do not directly block outflow. In the presence of normal outflow channels there is an inverse relationship between the extent of synechia formation and the facility of outflow.

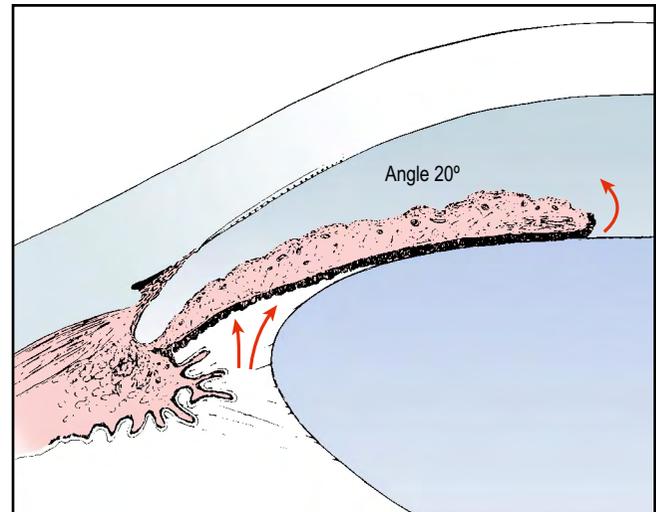
Blood may be seen in Schlemm's canal under special circumstances:^{16,17} if the patient is supine; if the eye has increased episcleral venous pressure (e.g., Sturge-Weber syndrome), hypotonia, or active uveitis or scleritis; or if the flange of the gonioscopy lens compresses the limbal vessels. Rarely blood will reflux into the anterior chamber, causing elevated intraocular pressure (IOP).

TRABECULAR PIGMENT BAND

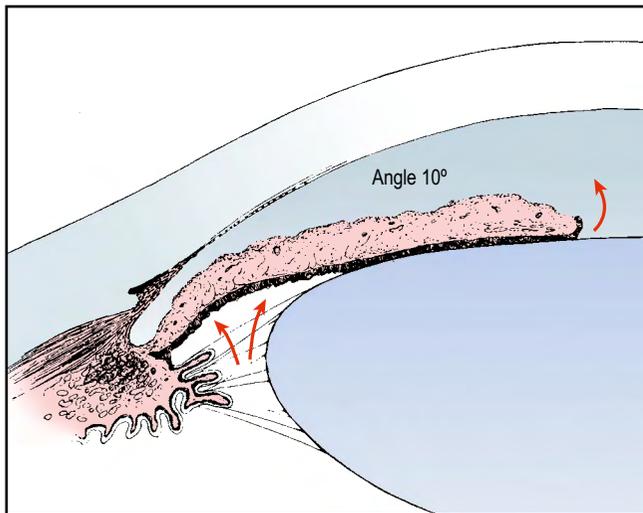
In the young normal eye, it is unusual to see any trabecular pigment band.^{17b} This is because insufficient pigment has been filtered out by the trabecular meshwork to form a visible line. The presence of such a band denotes either aging or disease.¹⁸ The pigment band is usually most prominent in the lower chamber angle. For convenience in recording, the dense dark band of pigmentary glaucoma



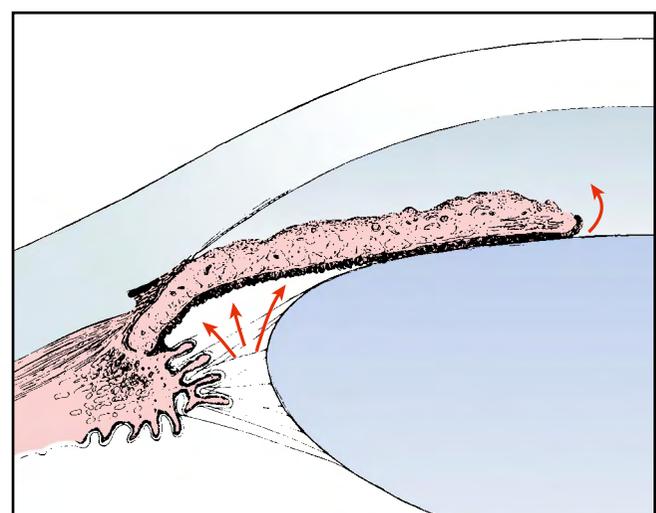
(A) Wide open angle – Grade 3–4



(B) Moderately narrow angle – Grade 2



(C) Extremely narrow angle – Grade 1



(D) Angle closure – Grade 0

Fig. 7-1 (A–D) Grading of angles by estimated angulation.

Angle depth	White (%)	Japanese (%)
Slit	–	0.3
Grade 1	0.64	2.6
Grade 2	1.0	5.1
Grade 3	60.0	92*
Grade 4	38.6*	*

* Grades 3 and 4 combined.

is recorded as grade 4, and minimal pigmentation is recorded as grade 1. When grading pigment bands, some allowance must be made for the color of the iris. Thus a brown eye generally has a denser pigment band than a blue eye.

The two most common conditions in which the pigment band is prominent are pigmentary glaucoma^{19,20} (in which the angle is usually deep) and exfoliative syndrome^{18,21–23} (in which the angle

Angle grade*	Degrees	Numeric grade	Clinical interpretation
Wide-open angle	30–40	3–4	Closure impossible
Narrow angle (moderate)	20	2	Closure possible
Narrow angle (extreme)	10	1	Eventual closure probable
Slit angle	<10	5	Portions appear closed
Closed angle	–	0	Closure present

* These grades are assigned to the various portions of the angle.

may be narrow) (see Figs. 7A–8 and 7A–9 at end of chapter). Lesser amounts of pigment are seen in many situations, including open-angle glaucoma,²⁴ trauma, iritis, and diabetes, or after laser iridotomy or anterior segment surgery.

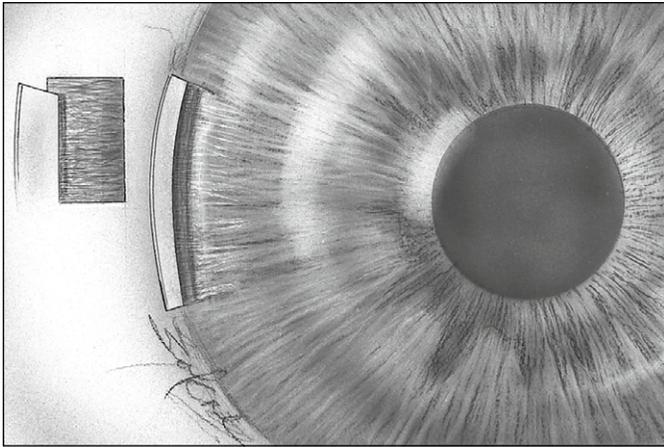


Fig. 7-2 Slit-lamp estimation of angle width: example of a grade 2 angle. Angle width can be estimated with the slit lamp by comparing the anterior chamber depth to the corneal thickness.
(From van Herick W, Shaffer RN, Schwartz A: Estimation of width of angle of anterior chamber: incidence and significance of the narrow angle, *Am J Ophthalmol* 68:626, 1969.)

SPAETH CLASSIFICATION

In an attempt to reduce a great deal of gonioscopic observational data into a concise format, Spaeth elaborated a complex grading system that captures detailed three-dimensional information in coded form.^{3,4,28} It was designed for indirect gonioscopes (e.g., Zeiss four mirror) that allow for indentation (compression) gonioscopy. Interobserver variability has been found to be minimal.²⁵ Moreover, this gonioscopic assessment shows high correlation with information obtained during ultrasonic biomicroscopy (UBM) of the angle,⁵ as well as with 'biometric gonioscopy' using a reticule to facilitate interobserver consistency in clinically grading the angle.²⁶ As such, (UBM) may be used to delineate gonioscopic findings when gonioscopy itself is difficult, as in cases of congenital glaucoma.²⁷

The Spaeth grading system uses an intricate alphanumeric scale, attempting to provide three-dimensional specificity to gonioscopic description. It addresses each of the following items in sequential order: (1) the site of insertion of the iris root in the eyewall; (2) the

Angle	Depth
Grade 4 angle	Anterior chamber depth = Corneal thickness
Grade 3 angle	Anterior chamber depth = 1/4 to 1/2 corneal thickness
Grade 2 angle	Anterior chamber depth = 1/4 corneal thickness
Grade 1 angle	Anterior chamber depth = Less than 1/4 corneal thickness
Slit angle	Anterior chamber depth = Slit-like (extremely shallow)
Closed angle	Absent peripheral anterior chamber

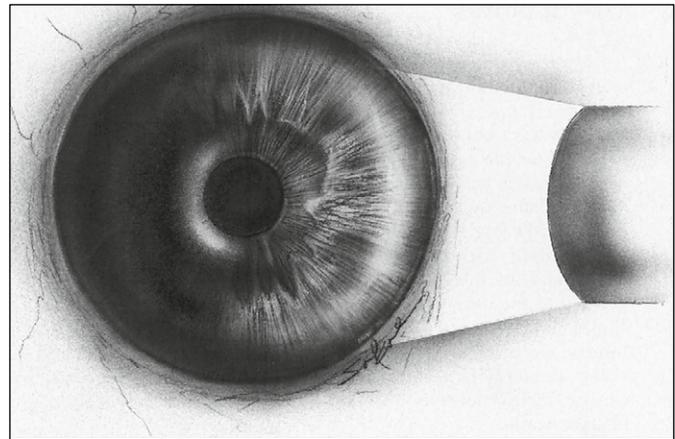


Fig. 7-3 Illumination from temporal side casts shadow on iris if there is considerable bombé.

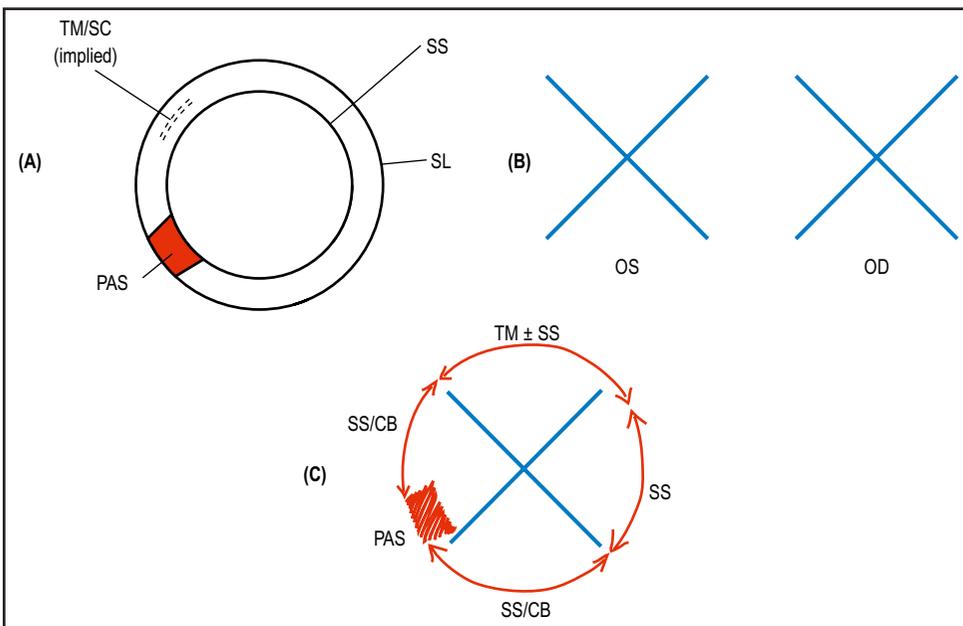


Fig. 7-4 (A) Diagramming gonioscopy with concentric circles. The inner circle represents the posterior limit of the scleral spur (SS), and the outer circle represents Schwalbe's line (SL). The trabecular meshwork (TM) occupies the same location as Schlemm's canal (SC). Here a peripheral anterior synechia (PAS) is drawn up to Schwalbe's line. **(B)** Hand-drawn Xs can suffice for charting purposes to indicate gonioscopic quadrants. **(C)** In this hand-drawn example, the superior angle shows the trabecular meshwork (TM) with equivocal viewing of the scleral spur (SS), which is elsewhere seen by itself or with the ciliary body (CB); a peripheral anterior synechia (PAS) is also seen.

width or geometric angle of the iris insertion; (3) the contour of the peripheral iris near the angle;²⁸ (4) the intensity of the trabecular pigmentation, and (5) the presence or absence of abnormalities such as mid-iris bowing, peripheral synechiae, and so on. If there is a discrepancy between the apparent and the actual site of iris insertion, as determined by indentation gonioscopy, this is so noted. Usually the grading is made for the four cardinal points of the angle, but especially in the normal angle's most narrow (superior) and open (inferior) aspects.

STEP 1: SITE OF IRIS INSERTION (FIG. 7-5A)

The first grading decision assesses the site of the iris insertion, both as it appears functionally (without pressure on the cornea) and as it actually inserts anatomically (after indentation). The capital letters A through E have simple alphabetic correspondences for the site of iris insertion:

- A = Anterior to trabecular meshwork (i.e., Schwalbe's line)
- B = Behind Schwalbe's line (i.e., at level of trabecular meshwork)
- C = Centered at the level of the scleral spur
- D = Deep to the scleral spur (i.e., anterior ciliary body)
- E = Extremely deep in the ciliary body.

When the iris appears to be cramping the angle, with or without appositional touch (grade A or B), indentation gonioscopy may reveal an actual posterior site of insertion – the apparent level is placed in parentheses preceding the actual site. For example, a '(B)D' notation means the iris appeared to insert at the level of the upper trabecular meshwork, but on indentation the actual insertion was revealed to be posterior to the scleral spur.

STEP 2: ANGLE WIDTH (FIG. 7-5B)

Exactly as with the Shaffer system, the geometric angle is estimated at the perceived intersection of the imaginary tangents formed by the peripheral third of the iris and the inner wall of the corneo-scleral junction. Though some examiners prefer increments of 10°, as with the Shaffer system, and others use increments of 15°, these

clinical assessments tend to overestimate by 5° the actual angle, as measured by the ultrasonic biomicroscope.⁵

STEP 3: CONFIGURATION OF PERIPHERAL IRIS (FIG. 7-5C)

Originally Spaeth discriminated three contour configurations of the peripheral iris,^{3,4} designated in reverse alphabetical order:

- s = 'steep' or convexly configured (e.g., plateau iris)
- r = 'regular' or flat (the most common contour seen)
- q = 'quixotic' or 'queer' for deeply concave (e.g., pigment dispersion syndrome).

The newer system describes four iris configurations, indicated by the first letter of their description:²⁸

- b = 'bows 1 to 4 plus' (usually indicative of optically-appearing closure, altering with indentation)
- p = 'plateau' (comparable to older 's' designation)
- f = 'flat approach': the commonest iris appearance (comparable to the older 'r' designation)
- c = 'concave' as in posteriorly bowed iris (comparable to the older 'q' designation).

STEP 4: TRABECULAR MESHWORK PIGMENTATION

As with the Shaffer scheme, the degree of trabecular meshwork pigmentation (TMP) is labeled from 1 to 4: minimal or no pigment is graded 1, and dense pigment deposition is indicated as grade 4, with lesser degrees between.

EXAMPLES

- E40c, 4+ TMP = An extremely deeply inserting iris root, in a 40° angle recess, with posterior bowing of the peripheral iris and extensive TMP (as might be seen in a myopic eye with pigment dispersion syndrome).

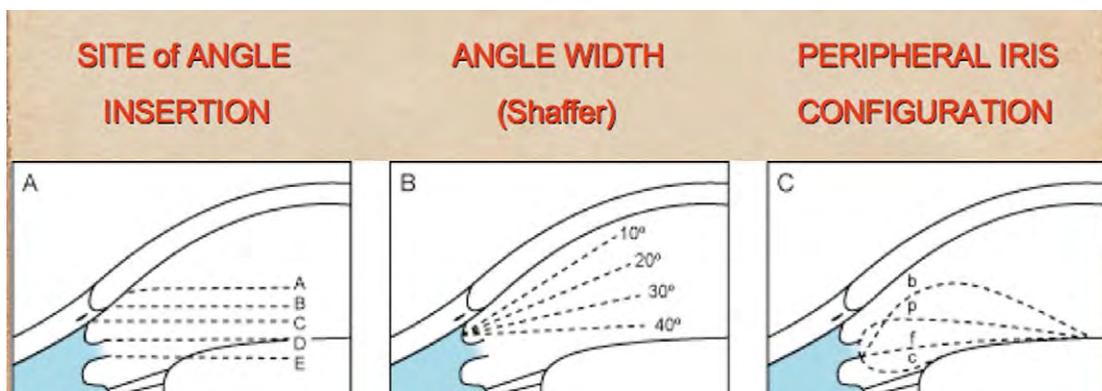


Fig. 7-5 Spaeth's gonioscopic classification of anterior chamber angle. **(A)** Site of iris insertion. This iris appears to insert at one of five levels. A = Anterior to trabecular meshwork, at Schwalbe's line; B = behind Schwalbe's line; C = centered at the scleral spur; D = deep to the scleral spur, at the anterior ciliary body; E = extremely deep, revealing most of the ciliary body. **(B)** Angle width. Four approximate geometries of the peripheral iris with respect to the angle. **(C)** Configuration of the peripheral iris. Four configurations are characterized: b = bowing anteriorly (1 to 4 +); p = plateau; f = flat; c = concave.

- (B)C10f, tr TMP = An iris initially appearing (indicated in parentheses as 'B') to be anteriorly in apposition to the trabecular meshwork, but which on indentation reveals a true insertion at the scleral spur (C), creating a 10° angle recess with a flat contour, and with minimal TMP (as might be seen in a hyperopic eye at risk of pupillary block).
- (A)B20b3+ < 2+ TMP = An apparent obscuration (indicated in parentheses as 'A') of all angle detail by a convex-appearing peripheral iris, until indentation shows the bowed iris inserting above the scleral spur (B), with mild TMP (as might be seen in a plateau iris following iridotomy).

Mastering the Spaeth classification has several merits. The observational precision required by discriminating the various parameters for notation will, with practice, become easier, and hence more useful during the long-term care of a patient. By the same token, mastery of this tool in training programs and multi-partner clinical settings allows for inter-observer consistency in describing angle changes over time. And lastly, this scheme precisely correlates with findings of contemporary imaging devices, such as UBM and anterior segment optical coherent tomography (AS-OCT), which are becoming ever more clinically available. (See Chapter 15 'Primary Angle-Closure Glaucoma' for illustrative examples.)

DIFFICULTIES AND ARTIFACTS IN GONIOSCOPY

Errors in gonioscopy most often result from misinterpretation of poorly visualized structures. In performing gonioscopy with any gonioscopic lens, the examiner should realize that certain artifacts^{29,30} may be induced by the method and lens used. Angles tend to look somewhat wider with the Koepple lens.³⁰ The Koepple lens sometimes has a scleral lip. This lip can press on the outer sclera and indent it toward the iris, thereby narrowing the angle (Fig. 7-6), perhaps because the

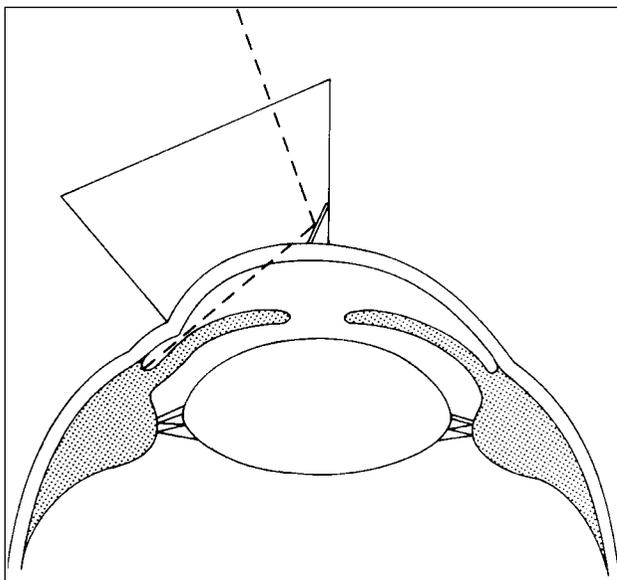


Fig. 7-6 Left edge of goniolens had indented cornea, creating an artificially narrow angle. (From Hoskins HD Jr: Interpretive gonioscopy in glaucoma, Invest Ophthalmol 11:97, 1972.)

supine position allows the lens and iris diaphragm to press posteriorly. Rotating the lens away from the portion of angle under observation and avoiding any pressure on the lens reduce this error. Similarly, excessive pressure by the Zeiss lens on the central cornea can artifactually widen the angle by displacing the lens and iris diaphragm posteriorly. Such pressure frequently produces folds in Descemet's membrane that obscure the view of the angle. For proper gonioscopy, the pressure on the lens should be just sufficient to retain a capillary fluid level between the lens and the cornea without inducing folds in Descemet's membrane. When the lens is properly adjusted, a slight reduction in pressure causes intrusion of an air bubble under the lens.

A slightly different view of the angle topography is achieved when the same eye is examined with different gonioscopic lenses. In most cases, this is of little clinical importance. In a few instances, however, inexperience with a particular lens can lead to false interpretation of the gonioscopic findings. Awareness of such differences and acquisition of sufficient clinical experience with one technique of gonioscopy will largely eliminate these problems.

The mirror on the Goldmann lens is closer to the center of the cornea than are the mirrors of the Zeiss lens – hence the Goldmann lens permits easier visualization into the angle recess in eyes with markedly narrowed angles. Moving the lens toward the part of the angle to be examined helps the examiner see the angle depths (Fig. 7-7).³⁰ A similar effect occurs if the patient looks toward the mirror used for observation. In confusing circumstances, the continuity of the slit-lamp beam of light often helps the gonioscopist know that she is seeing the point at which the iris meets the angle wall (Fig. 7-8 and Fig. 7-A3).

Tiny air bubbles sometimes adhere to the inner surface of a gonioscopic lens if oil secretions have formed a film on the surface. This film should be removed with soap and water. Similar residues of methylcellulose or secretions may collect on the Goldmann and Zeiss lenses and cloud the appearance of the angle. All lenses should be cleaned with diluted bleach or hydrogen peroxide and sterilized immediately after use.

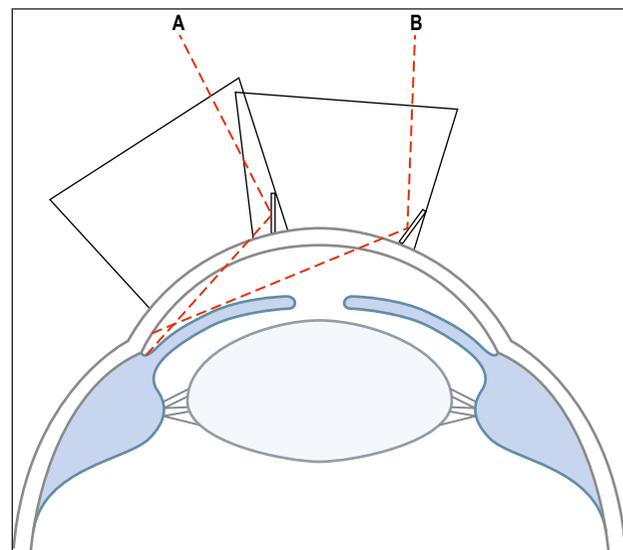


Fig. 7-7 With goniolens centered on cornea, line of sight (B) does not reach depths of angle. Lens must be rotated toward angle (A). (From Hoskins HD Jr: Interpretive gonioscopy in glaucoma, Invest Ophthalmol 11:97, 1972.)

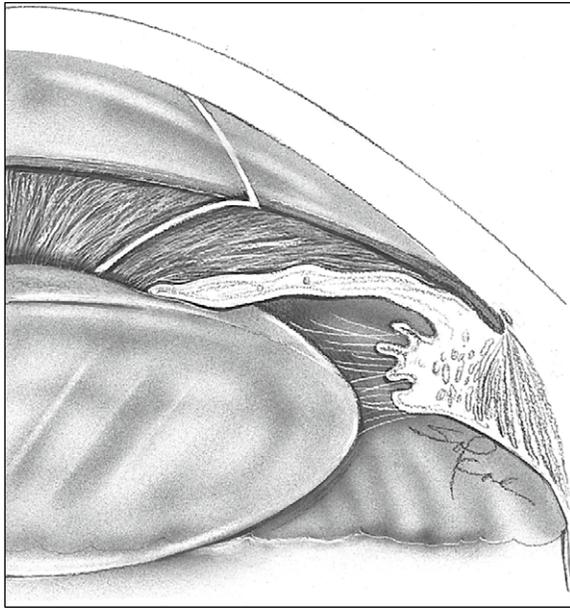


Fig. 7-8 Gonioscopic evaluation of the angle necessitates careful evaluation of the confluence of the slit-lamp beams as they course down the cornea and across the iris to meet in the angle. If the true depth of the angle is being visualized, then the beam will meet in the angle as illustrated here. If one is not seeing fully into the angle where the iris and cornea come together, these beams will be slightly misaligned from one other.

With a Koeppel lens, the patient's nose sometimes prevents adequate visualization of the upper temporal angle. Gonioscopy is accomplished by having the patient look up and temporally. To avoid intrusion of bubbles, the lens should be held by an assistant. With any of the indirect gonioscopic lenses it is difficult for the examiner to retain binocularity when examining the horizontal areas of the angle. Accurate centering of the mirror or prism is helpful. When high IOP produces corneal epithelium edema, the use of multiple topical glaucoma drugs, or even an oral hyperosmotic agent, can improve visualization by lowering pressure. Anhydrous glycerol drops administered topically also will dehydrate the corneal epithelium. Rarely, as for goniotomy, it is necessary to remove the hazy edematous corneal epithelium by curettage.

Endothelial dystrophy, or even mild cornea guttata, decreases the clarity of the angle image. Focusing on the cornea during gonioscopy provides an oblique view of the defective endothelium, which has a pebbled, shagreen appearance against the white background of the scleral tissue. The diagnosis of cornea guttata is often easier with this method than with direct slit-lamp microscopy.

CLINICAL USEFULNESS OF GONIOSCOPY

AID IN DIAGNOSIS OF TYPE OF GLAUCOMA

Using gonioscopy alone, the examiner can determine which eyes are in critical danger of angle closure and which are completely safe from closure. This finding forms the basis for classifying eyes into angle-closure glaucoma and open-angle glaucoma types. It is also important to remember that an eye's gonioscopic status is not static and determined in perpetuity by a single baseline

examination. Long-term dynamic factors such as lens changes, medication effects, aging, and disease processes make *periodic gonioscopy an important feature of appropriate glaucoma management.*

In open-angle glaucoma, gonioscopy may reveal inflammatory precipitates³¹ or a fibrovascular membrane, or it may reveal a tumor that is covering or invading the trabecular meshwork. An early sign of impending neovascular glaucoma may be a network of blood vessels growing anteriorly on the trabecular wall. Usually, a similar network appears around the pupil at a slightly earlier stage of the disease, but even the lightest pressure of an indirect gonioscopes, such as the Zeiss, may blanch small neovascular tufts and render them invisible.³² Blood vessels seen crossing the scleral spur are considered a definitive sign of pathology.³³ These new vessels can extend as high as Schwalbe's line. When the accompanying fibrous tissue shrinks, peripheral anterior synechiae and ectropion uveae are produced. New vessels branch and wander irregularly over the surface of the iris; this is in contradistinction to normal radial vessels, which are straight, uniform, and usually covered by iris stroma. Portions of the major circle of the iris normally are seen in the angle posterior to the spur as thickened vessel loops rising up from the stroma in a 'sea serpent' appearance. Normal vertical vessels are seen intermittently within the depths of the posterior angle wall. All of these differ from the superficial, arborizing small vessels that are typical of neovascularization.

With the patient lying supine for Koeppel gonioscopy, mild iridodonesis can be seen in some normal eyes, particularly if they are myopic (as with pigment dispersion syndrome). Iridodonesis is particularly prominent in eyes with aphakia, a dislocated lens, pseudo-phakia, or pseudoexfoliation. A marked trabecular pigment band is characteristic of both pigment dispersion and the pseudoexfoliative syndrome. The exfoliated material often is well visualized as poised on the edge of the pupil, against the contrasting dark pigment of the iris pigment layer.

Easily overlooked causes of secondary glaucoma can be revealed by careful inspection at the time of gonioscopy: finding a foreign body in an angle; seeing holes in the peripheral iris caused by the passage of an intraocular foreign body; observing a traumatic angle recession; appreciating precipitates on the trabecular surface; or recognizing blood in Schlemm's canal, suggestive of increased venous pressure or inflammation. If no obstruction at the trabecular meshwork can be seen, the block to outflow must be beyond the trabecular surface – and by default the diagnosis is open-angle disease.

EVALUATION OF SYMPTOMS

When a patient complains of halos around lights, this symptom should suggest episodes of angle-closure glaucoma if the angles are found to be critically narrowed. If the angles are wide open, however, the risk of sudden, catastrophic tension elevation by angle closure is virtually non-existent, and the history of halos warrants another explanation. Appreciation of the signs of pigment dispersion syndrome, such as Krukenberg's spindle, iris transillumination defects, and heavily pigmented trabecular meshwork, can explain sudden episodes of visual disturbance from 'pigment storms' following intense activity.^{34,35}

USE OF DRUGS

If an angle is found to be wide open, it is safe to use strong miotics, mydriatics, or sympathomimetics freely. Such use might

cause the angle to close completely in eyes with narrow angles, precipitating an acute rise of IOP. If miotics become necessary for the management of glaucoma in an eye with a narrow angle, the angle should be re-evaluated after therapy has begun. Occasionally, miotics narrow the angle further as a result of forward lens shift and enhanced pupillary block. Therefore, in narrow-angled eyes, any change in therapy should be monitored by periodic and frequent gonioscopy.

Particularly in eyes with narrow angles, the decision to operate may rest largely on the gonioscopic findings. If IOP is elevated at a time when the angle is definitely open but narrow, iridotomy will not cure the glaucoma.

When planning intraocular surgery, the surgeon should be sure to note the position of peripheral anterior synechiae and large blood vessels. Avoiding such areas may prevent serious complications.

POSTOPERATIVE EXAMINATIONS

The success of iridotomy in opening an angle and of cyclodialysis in producing a suprachoroidal cleft (Fig. 7A-14) can be evaluated promptly. After filtering procedures, the surgical stoma can be seen gonioscopically. If filtration is impaired, the appreciation of a patent ostium will direct attempts to restore the bleb by addressing the episcleral surface – suture lysis, bleb needling, or resections of scar tissue beneath the conjunctiva. If the ostium is occluded by the iris or adhesions, it may be re-opened using laser.

CONDITIONS OTHER THAN GLAUCOMA

The diagnosis of peripheral tumors or cysts often can be made by gonioscopy. Operability can be determined by an accurate view of the extent to which the iris and ciliary body are involved, supplemented by anterior segment imaging with UBM. Foreign bodies in the angle and holes in the peripheral iris from penetrating foreign bodies may be discovered. Inflammatory and traumatic conditions, such as keratic precipitates covering the meshwork and iridodialysis, can be visually evaluated.

When a portion of the cornea is hazy, it may be possible by gonioscopy to look through a clear portion of cornea to see the reason for the haze. Tears in Descemet's membrane, epithelial downgrowth, and areas of vitreous adhesions can be diagnosed in this way.

Gonioscopic examples are given in the 'Color illustrations' at the end of this chapter (Figs 7-A3 through 7-A16).

SUMMARY OF IMPORTANT GONIOSCOPIC TECHNIQUES

In clinical practice, unusual situations can arise. The following special techniques can be used to arrive at a correct diagnosis:

1. *Flashlight test* (see Fig. 7-3). In the absence of slit-lamp or gonioscopic equipment, the shallow chamber of the narrow-angled eye can be identified by holding a small-beam light source parallel to the plane of the iris at the limbus, shining across the eye. With a potentially occludable angle, the lens diaphragm can be seen to bow forward and produce a shadow on the side opposite the light.

2. *Slit lamp* (see Fig. 7-2). A slit-lamp estimation of the angle without a goniolens (van Herick method) is helpful in screening

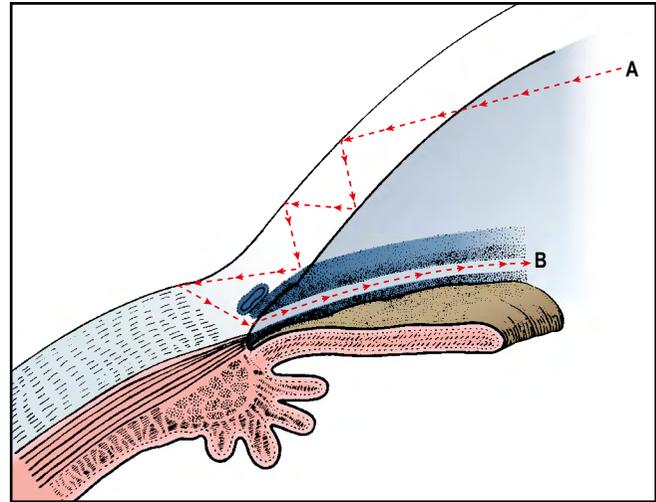


Fig. 7-9 Retroillumination of angle structures. Light directed from point A strikes the cornea anterior to the angle and is internally reflected within the cornea and sclera. The pigment in the trabecular meshwork and ciliary body prevent the light from entering the angle. The scleral spur (B) lights up brightly. (From Hoskins HD Jr: Interpretive gonioscopy in glaucoma, Invest Ophthalmol 11:97, 1972.)

patients. It is particularly useful when contact lens visualization of the angle is poor through a cloudy cornea. Training in the use of a commercially available reticule for the viewing lens of the slit lamp can allow for consistent, quantitative assessment of angle depth – of great value in population surveys.²⁶

3. *Simultaneous bilateral gonioscopy*. Comparison of corresponding areas of the angles of the two eyes is facilitated by placing a Koeppel contact lens on each eye simultaneously. Thus the examiner can go back and forth comparing corresponding sectors of each angle. Subtle differences, such as unusual iris processes, angle anomalies, peripheral anterior synechiae, and especially areas of angle recession, often are identified best by this comparison.

4. *Gonioscopy of the fellow eye*. When conditions prevent accurate gonioscopy of the affected eye, examination of the fellow eye may aid in the diagnosis.

5. *Indentation (compression) gonioscopy* (see Fig. 6-9). Indentation of the central cornea with a Zeiss lens widens the peripheral angle. This is useful in a narrow-angled eye to distinguish between areas of iris apposition and permanent peripheral anterior synechiae. Also, it helps the examiner estimate the width of a narrow angle because additional angle structures are exposed to viewing.

6. *Management of corneal edema*. Epithelial edema can be reduced by lowering the IOP, particularly by using hyperosmotic agents intravenously or orally, in conjunction with a variety of topical medications. Mechanical removal of the edematous epithelium is effective and is of particular value in infantile glaucoma.

7. *Retroillumination of the angle structures*. By using scleral scatter (Fig. 7-9), angle structures sometimes can be seen during gonioscopy and identified more accurately than with direct illumination.

8. *Endothelial mosaic*. Gonioscopic visualization of the endothelium may show subtle degenerative changes.

9. *Pseudoexfoliative syndrome*. Exfoliated material is diagnosed best in the undilated eye by seeing the dandruff-like deposits on the pigment epithelium beneath the edge of the pupil.

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APPENDIX



Fig. 7-A1 Deep pigment in the trabecular meshwork near Schlemm's canal forming a smooth, brown band. A solitary iris process is present. (From Alward WLM: *Color atlas of gonioscopy*, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

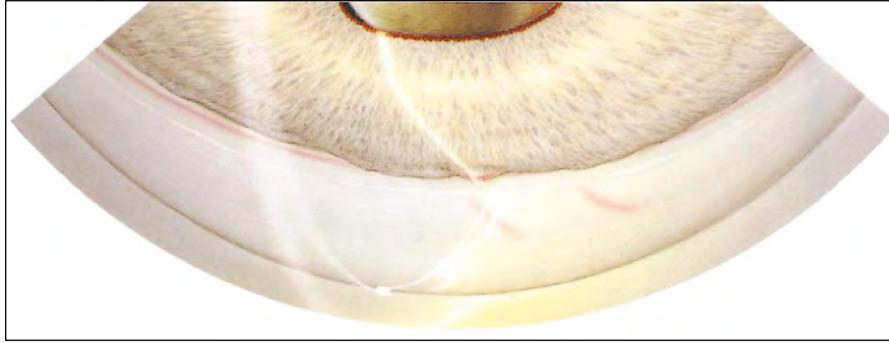


Fig. 7-A2 Narrowing of segmental angle caused by ciliary body melanoma. Note that the iris is pushed forward in the center of the figure and obscures the trabecular meshwork, which is visible both to the right and to the left of this area. This patient has a rather prominent Schwalbe's line and has blood in Schlemm's canal.

(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)



Fig. 7-A3 Iris bombé. No trabecular structures are visible. Note that the inner and outer lines of the corneal wedge do not meet in the anterior chamber, meaning that Schwalbe's line and the trabecular meshwork are hidden by the iris.

(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)



Fig. 7-A4 Gonioscopic view of an eye with angle closure following surgical iridectomy. This is the same eye as in Figure 7A-3. There are extensive synechiae, and only the most anterior portion of the trabecular meshwork is seen in some areas with the slit-lamp beam.

(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)



Fig. 7-A5 Gonioscopic view of eye with peripheral anterior synechiae caused by inflammation of unknown etiology. Peripheral anterior synechiae have developed over 360°. Pigment has been deposited anterior to the peripheral anterior synechiae at the 6 o'clock position.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

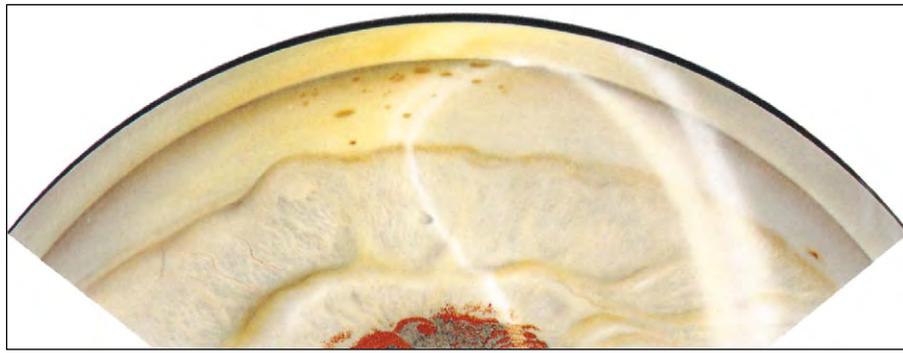


Fig. 7-A6 Extensive angle closure in chronic granulomatous uveitis. Trabecular meshwork can be seen only in the left-hand portion of this illustration, the remainder of the angle having been closed by synechiae. There are also central posterior synechiae at the pupil. Keratic precipitates are visible on the corneal endothelium.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

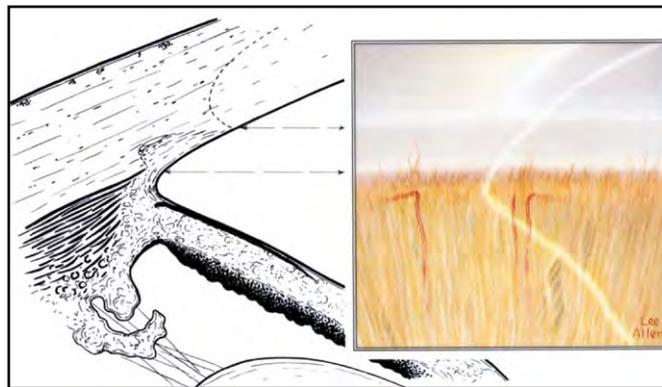


Fig. 7-A7 Gonioscopic view showing flat, featureless iris with neovascularization in Fuchs' heterochromic iridocyclitis.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

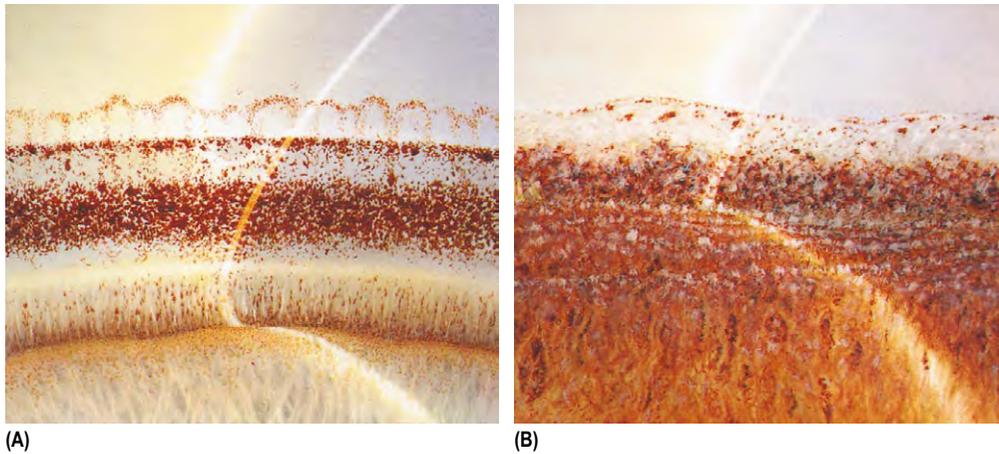


Fig. 7-A8 (A) The angle in pseudoexfoliation. Note the clumped brown pigment over the pigmented trabecular meshwork. There is also a line of pigment along Schwalbe's line and another, wavy line of pigment anterior to this line. **(B)** Pseudoexfoliation with a dense pigmentation of the angle that obscures most angle structures. The corneal wedge identifies Schwalbe's line.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

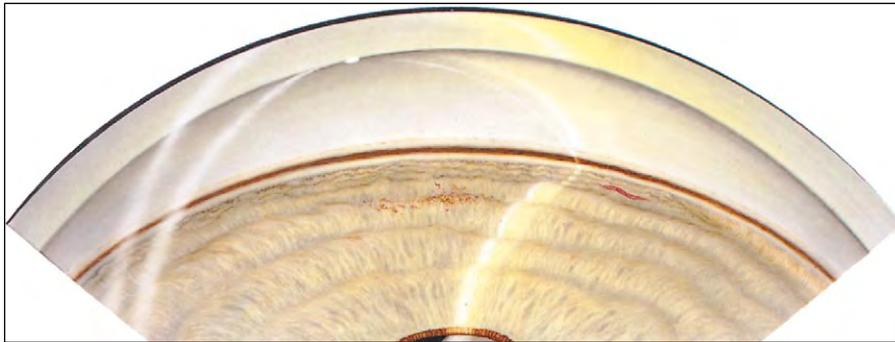


Fig. 7-A9 Patient with the pigment dispersion syndrome. The angle demonstrates a dense band of black pigment in the posterior trabecular meshwork.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

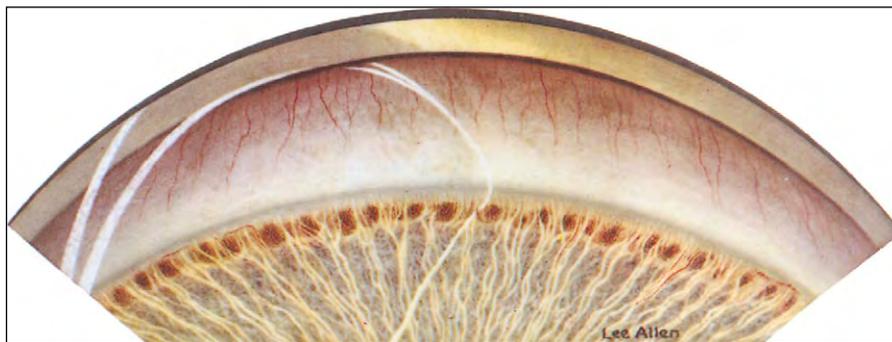


Fig. 7-A10 Fifteen-year-old girl with primary infantile glaucoma. She was first seen at 6 years of age with severe buphthalmos. There is generalized atrophy of the iris with islands of visible pigment epithelium. The iris inserts anterior to the scleral spur. The cornea anterior to the trabecular meshwork is opaque and thin.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

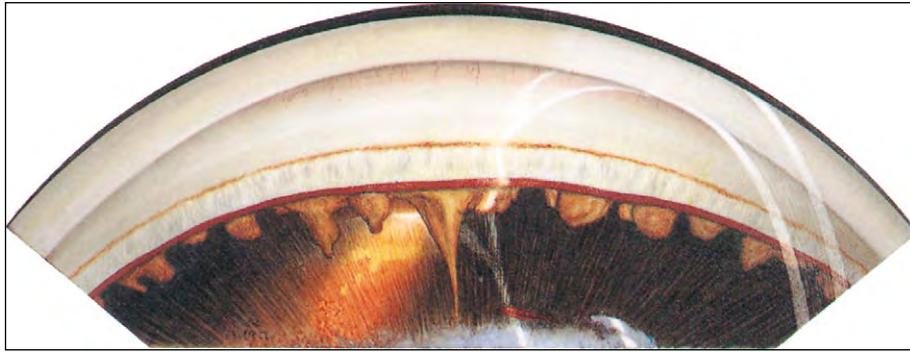


Fig. 7-A11 Inferior angle in aniridia demonstrating a small iris stump and a pale trabecular meshwork. The eye had undergone a previous cataract extraction. Some opaque lens material remains at the bottom of the illustration. The peripheral fundus is visible. (Copyright by Abbott Laboratories, North Chicago, Ill.)

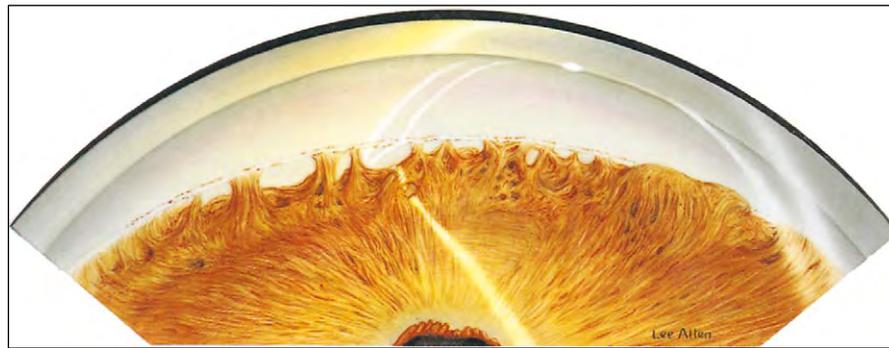


Fig. 7-A12 Axenfeld's anomaly with dense iris adhesions that almost completely cover the trabecular meshwork. Particles of pigment are deposited along a very prominent Schwalbe's ring. (From Burian HM, Braley AE, Allen L: Visibility of the ring of Schwalbe and the trabecular zone, Arch Ophthalmol 53:767, 1955. Copyright by the American Medical Association.)



Fig. 7-A13 Glass in the inferior angle after trauma. The patient had broken his glasses while working in a sawmill. A fragment of glass was removed earlier. The patient presented with discomfort and injection. The chip of glass is wedged between the trabecular meshwork and the iris, distorting both structures. There is a small tear in the iris and clotted blood under the fragment. Some blood is present in Schlemm's canal. (Copyright by Abbott Laboratories, North Chicago, Ill.)

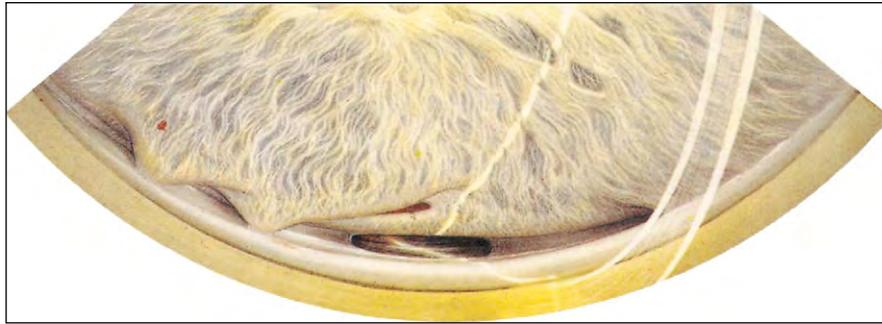


Fig. 7-A14 Aphakic glaucoma status after surgical cyclodialysis showing an open cleft with surrounding synechiae.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

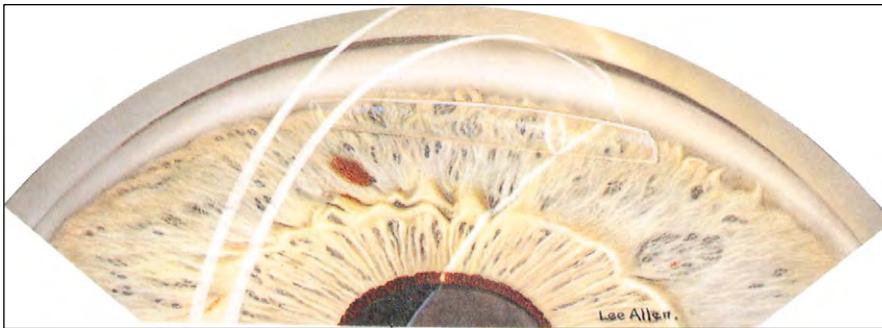


Fig. 7-A15 Inferior scroll of Descemet's membrane after surgery.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

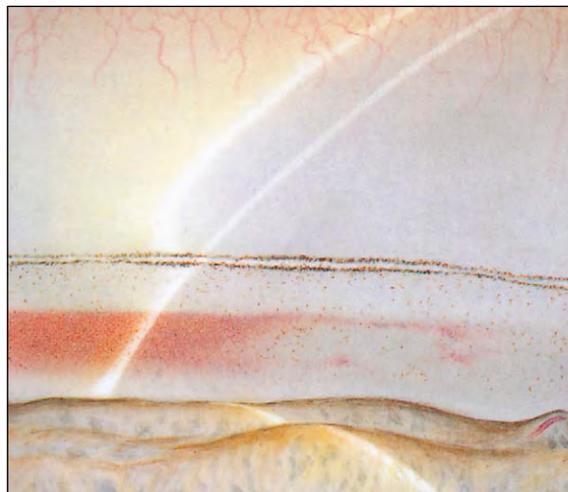


Fig. 7-A16 Gonioscopic view of an angle showing blood in Schlemm's canal. There is, incidentally, a prominent Schwalbe's line.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

Visual field theory and methods

THE NORMAL VISUAL FIELD

The normal visual field has been described as an island of vision in a sea of darkness.¹ This island has a sharp central peak, corresponding to the fovea, with sloping sides. The sides are slightly steeper superiorly and nasally.² The island of vision extends roughly 60° superiorly and nasally, 75° inferiorly, and 100° temporally (Fig. 8-1). The actual topography (sensitivity of various parts) of the island depends on the level of light adaptation of the retina.³ The peak is most sensitive when the retina is light adapted. The edges of the island have poor light sensitivity, so stimuli must be up to 3500 times (3.5 log) more intense to be perceived.^{4,5} If the retina is fully dark adapted, the cones of the fovea (center of the island) are less sensitive than the rods of the periphery.

Visual field testing is usually done in the photopic (light-adapted) or mesopic (partially light-adapted) state. Thus in the normal visual field examination, the fovea is the most sensitive point tested and represents the peak.

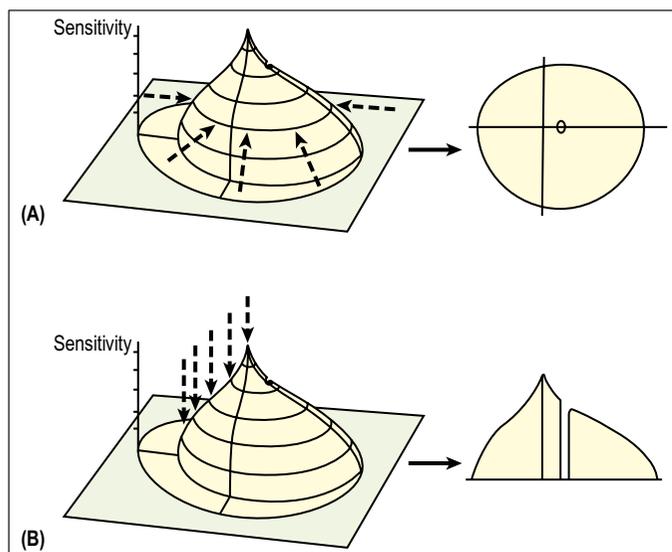


Fig. 8-1 (A) Isopter (kinetic) perimetry. Test object of fixed intensity is moved along several meridians toward fixation. Points where the object is first perceived are plotted in a circle. **(B)** Static perimetry. Stationary test object is increased in intensity from below threshold until perceived by the patient. Threshold values yield a graphic profile section. (Modified from Aulhorn E, Harms H. In: Leydecker W, editor: Glaucoma, Tutzing symposium, Basel, S Karger, 1967.)

VISUAL ACUITY VERSUS VISUAL FIELD

Visual acuity measurement tests the resolving power of the retina for objects of distinct form. Static visual field measurement tests a more primitive retinal function – *differential light sensitivity*. Differential light sensitivity is the measure of the ability of the retina to distinguish a stimulus that is some degree brighter than the background illumination.

TERMINOLOGY AND DEFINITIONS

Fixation. That part of the visual field corresponding to the fovea centralis. Also, the ability of patients to keep their eyes directed at the center of the visual field apparatus. Patients with poor fixation move their eyes repeatedly and produce an unreliable visual field test result.

Central field. That portion of the visual field within 30° of fixation.

Bjerrum's area (arcuate area). That portion of the central field extending from the blind spot and arcing above or below fixation in a broadening path to end at the horizontal raphe nasal to fixation. Bjerrum's area usually is considered to be within the central 25° of the visual field. This part of the visual field is quite susceptible to glaucomatous damage (see Fig. 10-9). Bjerrum's area does not include non-specific peripheral depression that is commonly seen along the uppermost border of automated visual field charts. These defects may appear to arc because of the placement of test points, but they do not constitute a classic arcuate scotoma (Fig. 8-2; see also Fig. 10-2).

Peripheral field. That portion of the visual field from 30° to the far periphery. The shape of the normal peripheral field is governed by the shape and structures of the face.

Kinetic perimetry. Visual field test wherein the intensity and size of the stimulus are held constant while the stimulus location is moved.

Static perimetry. Visual field test wherein the position of the stimulus is held constant while the stimulus intensity is varied.

Isopter. The outline of a contiguous area of the visual field capable of perceiving a given stimulus. The isopter is most often used to define an area outlined by a given stimulus in kinetic perimetry.

Threshold. At a given retinal point, the intensity of a stimulus that is perceived 50% of the times it is presented.

Fluctuation. The variability in visual field measurement when tests are repeated over time.

Short-term fluctuation. The variability within a field during the time of its measurement. The test–retest interval is short: typically a few seconds or minutes.

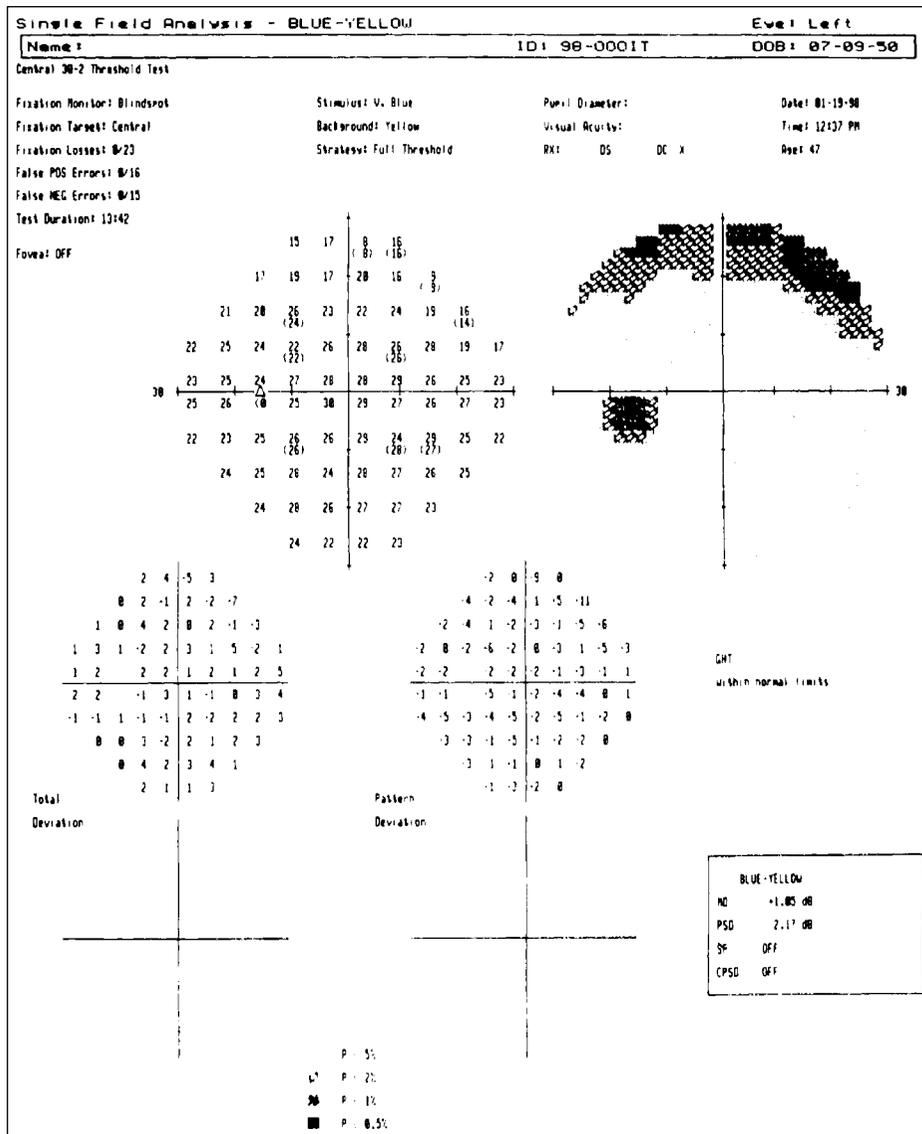


Fig. 8-2 The dark areas at the top of this printout are artifacts. The patient has a normal field.

Long-term fluctuation. The variability between two visual fields performed sequentially on the same eye that cannot be attributed to pathologic change. The test-retest interval is typically days to months or longer.

Short wavelength, automated perimetry (SWAP). Visual field test in which short wavelength-sensitive (blue) cones are isolated by using blue light stimuli projected on a yellow background. Also called *blue-on-yellow* perimetry.

Frequency doubled perimetry. Visual field test in which stimuli are alternating high-frequency contrast bands.

Depression. A reduction in expected (normal) sensitivity.

Scotoma. A localized defect or depression within the visual field.

Absolute defect. A field defect that persists when the maximum stimulus of the testing apparatus is used. The normal blind spot is an absolute scotoma.

Relative defect. A field defect that is present to weaker stimuli but disappears when tested with brighter stimuli. A defect that is not absolute (see Fig. 10-4).

Candela per square meter (cd/m^2). The international unit of luminance.

Apostilb. $0.1 \text{ millilambert} = 3.183 \text{ cd}/\text{m}^2$.

Log unit. Logarithm base 10 of the luminance in apostilbs.

Decibel. One-tenth of the log unit.

THEORY OF VISUAL FIELD TESTING

The purpose of visual field testing is to define the topography of the island of vision to recognize any variation from normal. It is used to detect abnormalities and to follow abnormalities while the patient is under observation or treatment. The visual field is tested by adapting the eye to the background luminance and then presenting a stimulus that is some degree brighter than the background at a given position in the field. The ability of the patient to perceive the stimulus may be tested kinetically, statically, or with some combination of the two techniques.

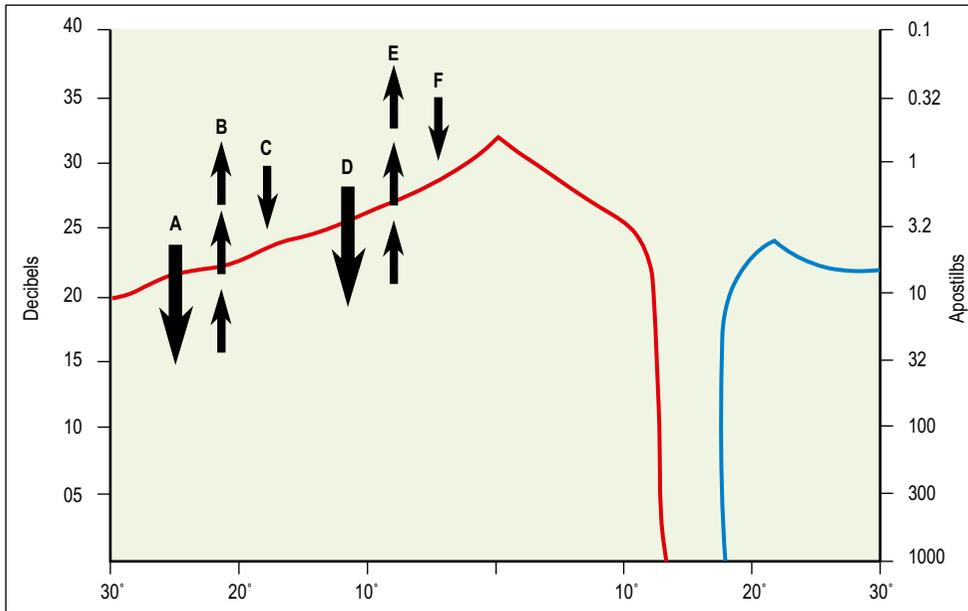


Fig. 8-3 Static testing for threshold sensitivity. **(A)** A bright stimulus is presented that the patient can see. **(B)** The stimulus intensity is decreased until the patient can no longer see it. **(C)** The stimulus intensity is then increased again until the patient just sees it. This establishes the threshold sensitivity for that spot in the retina. **(D-F)** A similar maneuver then is carried out in an adjacent part of the retina. The increment of change in stimulus intensity governs the sensitivity of the test.

KINETIC PERIMETRY

Kinetic perimetry is typically performed manually by confrontation, on a tangent screen, or with a Goldmann perimeter. In kinetic perimetry, the stimulus usually is presented in the non-seeing periphery and moved at approximately 2° per second toward fixation until the patient first perceives it. The stimulus is subsequently moved to another meridian in the periphery out of view and advanced toward fixation again until the patient sees it. By repeating these maneuvers at approximately 15° intervals around 360° of the visual field, the examiner defines a series of points that can be connected to describe an isopter corresponding to the stimulus used (see Fig. 8-1). By decreasing or increasing the size or brightness of the stimulus, a smaller or larger isopter will be outlined. If the stimulus is presented into randomly selected areas of the visual field, the isopters will be slightly constricted and irregular compared with sequentially presented stimuli. Reproducibility may be greater with sequentially presented stimuli.⁶

After initial detection, a scotoma can be defined more precisely with kinetic perimetry by placing the stimulus in the scotoma and moving the stimulus outward until it is perceived. This process is repeated in various directions until all edges of the scotoma have been defined. If the edges of the scotoma are sloping (the change from normal to abnormal regions within the field is gradual), a brighter stimulus will define a smaller scotoma, and a dimmer stimulus will define a larger scotoma. If the margins of the defect are steep, changing the stimulus size or intensity will affect the size of the scotoma only slightly.

STATIC PERIMETRY

In static perimetry, the test stimulus size usually remains constant throughout the test. For computerized full-threshold testing, each point in the visual field is evaluated by positioning the stimulus at a test point and varying the intensity until the threshold for that particular retinal location is defined (Fig. 8-3). This process is repeated



Fig. 8-4 Humphrey 700 series perimeter.

until all of the positions of the retina to be measured have been tested.

The more retinal positions tested, the more defects will be found and quantified. There is, however, a point of diminishing returns, at approximately 80 locations, wherein patient fatigue seriously reduces the accuracy and consistency of responses.^{7,8} Most computerized perimeters (Figs 8-4 and 8-5) use static visual field testing techniques for their standard tests.

Alternatives and modifications to standard full-threshold testing of each retinal position have been devised to reduce the number of patient responses required without reducing the amount of information obtained at each testing session.⁹⁻¹² Such alternatives include threshold-related testing and zone testing, as well as



Fig. 8-5 Octopus 123 perimeter.

algorithms that use less precise bracketing to estimate the threshold. These methods generally produce results that are similar to, but can be somewhat more variable than, standard threshold determining strategies.^{13–16} The most widely used modification of standard repeat-bracketing threshold testing is the Swedish Interactive Testing Algorithm (SITA) program used on the Humphrey Field Analyzer, which adjusts the starting and ending points of the bracketing procedure during the examination based on the patient's responses.^{17,18} This is done in a fashion that reduces redundancy, decreases testing time, and increases accuracy and patient acceptance without compromising the sensitivity and specificity of the test (see also p. 95).^{19,20}

THRESHOLD-RELATED TESTING

The 'normal' state of the visual field is a statistically determined figure obtained from the testing of many normal individuals of different ages, genders, etc.^{21,22} Each retinal location has a statistically determined 'normal' sensitivity range that can be expressed in decibels of stimulus intensity related to stimulus size, background intensity, and patient age.²³ This sensitivity is not constant from patient to patient, or even within the same patient from test to test. Therefore, for a particular retinal location to have a strong possibility of being abnormal, its sensitivity should be reduced from normal by roughly two standard deviations of the mean of normal, or approximately 4 or 5 dB on average. This is conveniently expressed as twice the average short-term fluctuation (SF). It is similar to the traditional rule of thumb that suggests that significant measurement deflections are at least twice the baseline noise level. The average short-term fluctuation is lower at or near fixation than it is in the periphery, so a deviation of 4 or 5 dB centrally has a greater chance of representing a reproducible change in sensitivity than does a defect of similar depth in the periphery. A 4 dB depression in an area of the field that has a SF of 1.2 dB is more likely to represent pathology than a 10 dB depression in an area that has a SF of 8 dB, which can be the case at 24° or more from fixation.

In threshold-related testing (Fig. 8-6), if the patient is presented with a stimulus that is roughly 4 dB brighter than the expected normal level for that retinal position and the patient sees it, the location is considered normal, and the stimulus is moved to the next position without measuring the threshold of the location precisely.

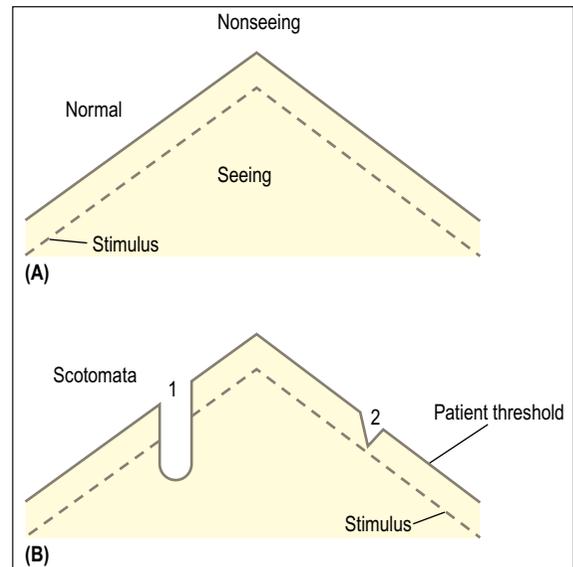


Fig. 8-6 Threshold-related testing. (A) A single stimulus, usually 4 or 5 dB brighter than the anticipated threshold, is exposed across the visual field. If the patient sees it, that part of the field is considered normal. (B) Defect 1 will be detected by the technique, but defect 2 will be missed.

The disadvantage of this technique is that it only finds defects equal to or greater in depth than the suprathreshold stimulus used. This technique also provides no information regarding subtle variation in the contour of the field, which is important in recognizing early changes from normal.²⁴ The rapidity of testing normal areas using the technique, however, allows a larger area of the retina to be examined. If defects are detected, they can be quantified with the full-thresholding strategy.

ZONE TESTING

Zone testing uses three levels, or zones, of stimulus intensity to locate and then quantify defects. The first zone is a suprathreshold stimulus 4 or 5 dB brighter than the anticipated normal threshold, as described in the section on threshold-related testing, above. If the patient sees this stimulus, the response is recorded as normal. If the patient fails to see the initial stimulus, a maximally bright stimulus is shown. If the patient sees this stimulus (but failed to see the initial, relatively dim, stimulus), the machine indicates a relative defect. If the patient fails to see either stimulus, the machine records an absolute defect. Responses can thus be grouped in three zones – normal, relative defect, or absolute defect. There are multiple variations on this theme that allow a greater number of zones to be defined, or for zones to be defined at different levels. The obvious disadvantage of this technique is that subsequent testing can only recognize major change because the difference between the test stimuli is great. The advantage is that it is fast.

SCREENING TESTS

Screening tests for visual field defects are available by manual perimetry and with most computerized perimeters. Unfortunately, they only detect rather large changes in the visual field.^{25–27} Most screening programs use a technique that recognizes defects that are greater than 4 or 5 dB below an expected level. As such, they may not detect early glaucomatous defects. Also, if a defect is found, the

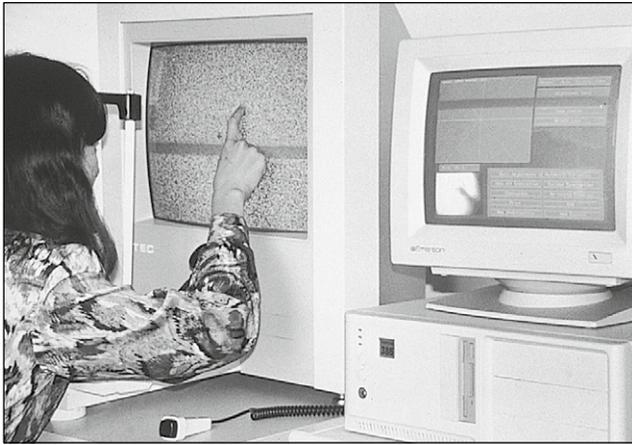


Fig. 8-7 Patient viewing 'snowfield' on computer monitor. Defects are noticed by the patient as smudges or fuzzy areas on screen.

patient must undergo a full visual field examination to establish a baseline against which future change can be measured. Therefore, in persons suspected of having visual field defects, screening programs and other fast strategies that reduce examination time at the expense of evaluating the critical sensitivity area within 5 dB of threshold are of questionable value.²³ Screening tests are used most appropriately to diagnose pathology rather than to follow or quantitate the degree of damage in a patient known or suspected of having disease.

OTHER STATIC TESTING TECHNIQUES

Single-stimulus level static testing was used commonly in some of the early computerized perimeters. Because the visual threshold slopes from the center to the periphery of vision, a single-stimulus intensity cannot be effective in testing a large area of the retina. This technique is useful only as a relatively crude screening method. A variety of innovative screening techniques has been developed to aid clinicians in obtaining the maximum amount of useful information in the minimum amount of time. A few of these bear mention for illustrative purposes.

Noisefield perimetry, also known as white-noise perimetry or campimetry, is performed by having the patient observe a computer screen (Fig. 8-7) or home television set.²⁸⁻³⁰ The screen projects a 'noise' pattern of small (roughly 1–4 mm), irregularly shaped dark and bright spots oscillating at 50 Hz. Patients with localized defects notice the defective region as a smudge or blank area on the screen. In simple terms, they detect the noise pattern in normal regions of the field, and its absence in the abnormal areas is perceivable. Detection takes only seconds in alert patients, but not all patients can cooperate fully with the test requirements. The information gained is useful mainly for screening.³¹⁻³³ Optokinetic perimetry is a novel approach to visual field screening in which the patient is presented a series of cards with static stimuli arranged in a set pattern. While maintaining steady fixation, the patient is asked how many spots she sees.³⁴⁻³⁶ Stimuli in defective areas of the field are not detected, and by evaluating the points missed during the test, the examiner can gain a fairly clear idea of the nature and extent of the field loss.³⁷⁻⁴⁰ This method is very fast, taking perhaps only 30–50% of the total time needed for screening fields conventionally. These methods are used rarely, if at all, in clinical practice.

The Swedish Interactive Test Algorithm (SITA) was developed to address the issue of patient fatigue and discomfort during tedious full-threshold static automated perimetry examinations, which can require 30 minutes or more per eye. Long, boring examinations are stressful for patients; fatigue and a resultant lack of concentration can decrease test reliability. The SITA was developed to reduce testing time without reducing reliability or sensitivity. The basic approach is fairly straightforward, although the programming required to achieve these aims was very sophisticated. The SITA relies on a continually updated model of the patient's predicted field, based on all of the information available on the patient, including, importantly, answers to test questions as the test itself progresses.¹⁷ The program is termed 'interactive' because it changes the questions it asks based on the patient's responses, in real time. In addition to predicting the model of the patient's field, the program assesses the certainty of its prediction at each test point. Testing is interrupted as soon as a predetermined level of certainty is reached. This is in contrast to standard testing algorithms in which testing follows a more rigid pattern, whether or not additional information will further refine the model.

The initial model of the patient's field is based on a large databank of normal and glaucomatous fields, adjusted for age. As test points within the field undergo threshold evaluation, the model is updated. If, for example, the first few test points are characteristic of a generally depressed field, subsequent stimuli will be brighter than if the initial test points had suggested a normal field. An important feature of SITA is that it uses all of the available information as it refines its model. As more information is accumulated, the program develops a more accurate prediction of the final field, and can confirm its prediction with fewer additional test questions. During an initial evaluation, SITA used fewer test points in normal and glaucomatous fields. Because the interval between stimulus presentations is also adjusted, the actual testing time can be reduced by an even greater amount. In clinical tests, SITA standard examinations require less than half the time required to perform a full-threshold exam.⁴¹ Because of its combination of speed, accuracy, and patient acceptance, most centers and offices with SITA equipped perimeters use this as their basic testing strategy.

THE FUTURE OF VISUAL FIELD TESTING

The current generation of computerized perimeters allows placement of stimuli of varying sizes, intensities, and colors into backgrounds of varying intensities, and they accurately chart the patient's responses.⁴² This flexibility facilitates design of an almost infinite number of testing protocols. Recent improvements have involved both hardware and software. A wide variety of test and interpretation protocols are in use, and more are being developed continually. Most commercially available protocols have been standardized against groups of normal patients. A few disease-specific protocols have been standardized against groups of patients with the target condition.^{4,43-47} Although these programs do not fully replace careful interpretation by a trained observer, they certainly help to guide us toward more consistent evaluation of visual field information.

Differential light sensitivity is a rather primitive retinal function. Quigley and Green found that up to 50% of retinal nerve fibers may be lost before a diagnostic glaucomatous visual field defect is detected by manual kinetic measurement.⁴⁸ Computerized static perimetry with statistical analysis of the results is more sensitive,⁴⁹

but some amount of nerve fiber loss precedes even computerized field loss in most cases.⁵⁰ These lost nerve fibers assist in other visual functions that may be more sophisticated than simple differential light sensitivity. One of the more intriguing ways that this has been investigated is with *blue-on-yellow*, or *short wavelength, automated perimetry* (SWAP). A series of studies has indicated that the short wavelength-sensitive (blue) system may be more sensitive to early glaucoma.^{51–53} The test is similar to conventional perimetry except blue stimuli are projected on a yellow background to isolate the short wavelength-sensitive system. The results of these studies have been quite interesting. In one study, Johnson and co-workers⁵⁴ tested 38 ocular hypertensive patients and 62 normal controls with conventional white-on-white (w/w) perimetry and subsequently with SWAP. All 38 ocular hypertensive patients had normal w/w perimetry at the time the study began. Nine of these eyes had a defect detected by SWAP at the beginning of the study. Five years later, 5 of the 9 eyes that initially showed a SWAP defect but were normal by w/w perimetry had developed w/w visual field loss. The w/w defects were in the same locations of the visual field as the SWAP defects, but the SWAP defects were larger. No eye that was initially normal on SWAP testing developed w/w field loss during the period of study. Thus SWAP perimetry was very sensitive (100%) for early glaucoma; its specificity (using w/w defects as the standard) was 55% (5/9) at 5 years, but this may rise with longer follow-up.

Other studies have generated similar findings. The general pattern is that SWAP defects, although similar in location and shape, appear earlier and are larger than subsequent w/w defects.^{55–58} This method is not entirely without cost, however. Short wavelength, automated perimetry takes longer than equivalent w/w perimetry, and increased patient fatigue and decreased dynamic range may contribute to significantly higher fluctuation values. Newer combinations of SWAP and more interactive programs that shorten test time will make SWAP testing more acceptable to patients.^{59,60} The increased testing time and fluctuation have limited the use of SWAP in routine clinical settings. It is employed most frequently to help confirm the diagnosis, or detect subtle progression in a patient with early disease.

In addition to perimetric techniques, there are a host of other psychophysical methods of detecting and following glaucomatous damage. Some of these are discussed in Chapter 11.

COMBINED STATIC AND KINETIC PERIMETRY

Combined static and kinetic perimetry uses the speed of kinetic perimetry and the sensitivity of static testing. It is used routinely in manual perimetry, and rarely with automated perimeters. Generally, the peripheral field and scotomata are defined by kinetic methods, and the central field is examined by static perimetry. With manual perimetry, a threshold stimulus is chosen for testing the central field. This stimulus is chosen by a variety of methods, but commonly it is the weakest stimulus visible at the point either 15° above or 15° below the horizontal meridian 25° temporal to fixation.

Aulhorn and Harms,³ Armaly,^{61–63} Drance and Anderson,²⁴ and Rock and co-workers⁶⁴ suggested methods using this approach to rapidly detect and define scotomata. The threshold stimulus is used to kinetically define the central field and any scotomata demonstrated by the static presentations. Static stimuli are presented at various locations for no more than 1 second. Hesitant or absent patient response indicates a potential defect, which then can be more completely analyzed by kinetic perimetry using varying stimulus sizes and intensities (Fig. 8-8).

With automated perimetry, the central field is examined in the standard static fashion, and one or two peripheral isopters are examined to avoid missing defects that do not involve the central field.^{65–67} The peripheral field can be examined by static-threshold perimetry, but this is a time-consuming and tedious process. Full-threshold testing of the periphery costs a great deal in terms of patient fatigue and satisfaction for relatively little gain, and is therefore performed rarely. Static two- or three-zone screening tests are a reasonable compromise that allow the examiner to de-emphasize, but not ignore, the periphery.

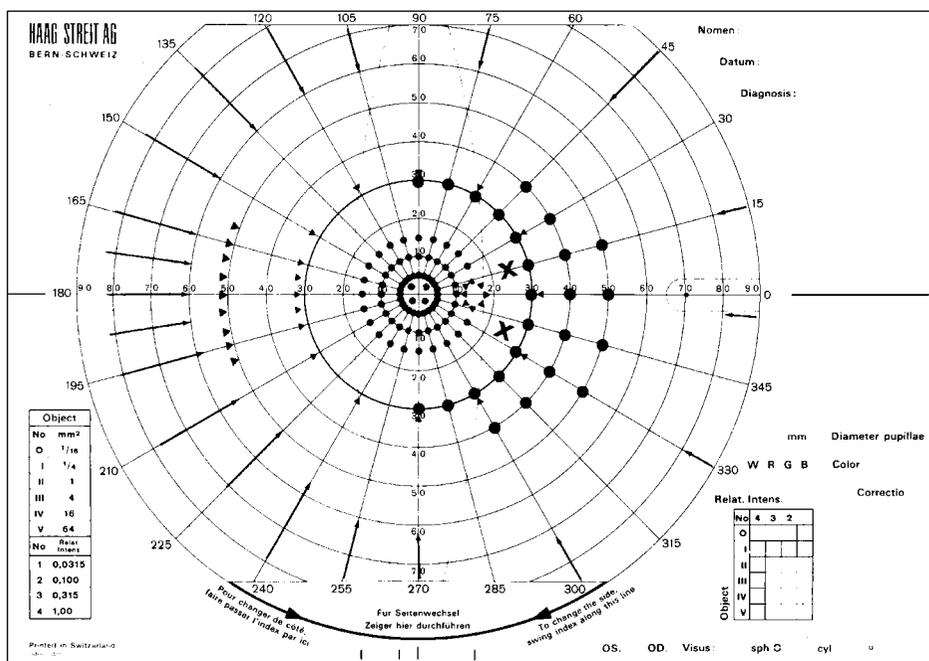


Fig. 8-8 Goldmann visual field chart illustrating both static (dots) and kinetic (arrows) points of examination. Note that 72 points are tested statically with a threshold target in the central field. This is considered a reliable search for early glaucomatous field defects. The I4e target is used to check for nasal step in the peripheral field. Testing of the peripheral temporal field for a step will identify the occasional patient in whom this is the earliest evidence of glaucomatous damage. Tangent screen can be tested in a similar manner within the central 30° by exposing and hiding the stimulus to stimulate static perimetry.

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CHAPTER

9

Techniques and variables in visual field testing

A number of factors can affect a visual field test^{1–16} other than the disease being studied. It is important to minimize the influence of these variables as completely as possible in order to assess accurately and document precisely the abnormalities present so that deviations from normal and future changes can be recognized easily. Fluctuation, the combination of normal physiologic variability and measurement error, complicates the recognition of pathologic change. If all other possible variables are eliminated, then change in the disease must be responsible for any alteration in the visual field. Unfortunately it is impossible to eliminate all other variables. Awareness of factors influencing the visual field, however, can help minimize these variables and improve interpretation (Box 9–1).

PATIENT VARIABLES

AGE

With age, the visual field has a linear decrease in sensitivity and the slope steepens.^{13,17,18} The increase in fluctuation that occurs as

the test moves toward the periphery is also greater with age. The combined effect of these variables is a field with an increasingly steep slope as one moves away from fixation. The effect of age on the central field is gradual and can usually be ignored in the evaluation of individual patients. Mean sensitivity of the visual field decreases approximately 0.58–1.0 dB per decade.⁹ Increased age may be associated with increased variability in repeated test results over time. The standard deviation of the mean sensitivity of points tested ranges from about 1.0 to 2.0 dB in the normal central field of a young patient. Patients older than 60 years of age may have standard deviations up to twice that amount centrally and up to 10 dB per point at 30° eccentricity.^{2,4,5,13,14,16,18,19}

FIXATION

Most patients maintain acceptable fixation on the central target of the perimeter.^{20–22} Patients with poor fixation can be encouraged to stabilize their fixation, but this does not always prevent them from looking around.²³ Technicians and computerized systems usually monitor or grade patient fixation in some way. Machines that monitor fixation continuously, generally by some form of eye movement or pupillary reflex assessment, often have algorithms that disregard responses generated during fixation losses. These machines return to the same test location later during the examination and present the stimulus again. This programming feature helps ensure that the responses recorded by the machine occur during periods of steady fixation. Other machines use a monitoring system with blind spot fixation in which stimuli are projected on the physiologic blind spot at intervals throughout the test. If fixation is steady these stimuli will continue to land on the blind spot and will not be detected. If fixation has shifted the stimuli will land on photoreceptors and be detected. The machine records and/or alerts the operator that a fixation loss has occurred. If the patient generates fixation losses more than 20–30% of the time, the test can be considered only an approximation of the true visual field.^{24,25}

RELIABILITY

In addition to monitoring fixation, patient reliability should be graded as good or poor by the technician. Computerized machines can provide some index of reliability based on false-positive or false-negative responses and fixation losses.²⁶ Fatigue, drugs, age, and illness can all affect patient reliability and must be considered when assessing the accuracy of a given test. Even in well-rested patients, the test itself can be fatiguing, so that reliability tends to decrease with prolonged or extensive examination sessions.

Box 9-1 Some artifacts that affect visual field results

Examination artifacts

Technician: results vary with different technicians
 Equipment: results vary with different equipment
 Test: results vary with different types of tests
 Software: results vary with different testing or interpretation algorithms

Eye artifacts

Refraction: should have distance prescription with proper addition for near vision
 Pupil size: should be 3 mm or more; must be consistent
 Fixation: results vary with quality of fixation control
 Media opacity: visual acuity should be recorded

Patient artifacts

Misunderstanding the test
 Fatigue
 Inattentiveness
 Physiologic/pathologic/psychologic/mental status
 Systemic illness, hangover, anxiety, and so on

Analysis artifacts

Is the visual field normal? Requires standards for normal
 Has the visual field changed? Requires knowledge of fluctuation
 Misinterpretation

Although long test sessions can fatigue a patient, experience with the machine usually decreases variability over repeated testing sessions (learning curve).^{27,28} Thus the first visual field may be the least accurate. Patients with experience on manual perimeters may have less of a learning curve effect.²⁹ We tend to repeat the initial test if the results are abnormal in any way. Although computerized machines are automated, they are not automatic. Patient/technician interaction can have a substantial impact on the reliability of the examination and may also aid in patient satisfaction.

OCULAR VARIABLES

PUPIL SIZE

A pupillary diameter of less than 3 mm can cause generalized depression of the visual field.³⁰ It is usually best to test the field with a pupil that is at least 3 mm in diameter. If it is not possible to dilate the pupil to 3 mm, the test should be performed with a pupil that is no smaller than that which existed during previous tests.^{31,32}

MEDIA CLARITY

Any opacity of the ocular media can cause a localized or generalized depression in the visual field. This is particularly problematic when following a glaucoma patient who is developing cataracts. As the lens opacity become denser, field defects may appear to enlarge or become denser because of the reduced amount of light reaching the retina or because of image distortion or light scattering.^{33,34} Patterns of localized loss tend to remain consistent before and after cataract extraction, however.^{35,36} Visual acuity, refraction, and the appearance of the lens can help in determining the influence of cataract on the field. If acuity has dropped by more than one line on the Snellen chart, the examiner should suspect that the cataract is accentuating the appearance of visual field defects. Some analysis programs compensate for this reduction by factoring out generalized depression from the visual field so that scotomata are exposed (Fig. 9-1).³⁷ However, the pattern deviation is not perfect in identifying purely localized defects if the cataract is significant. The most reliable criteria for identifying glaucomatous loss appear to be a glaucoma hemifield test 'outside normal limits', two hemifield clusters that fall below the 5% population limit, and four abnormal points (<5%) in a hemifield on the pattern standard deviation plot.^{38,39}

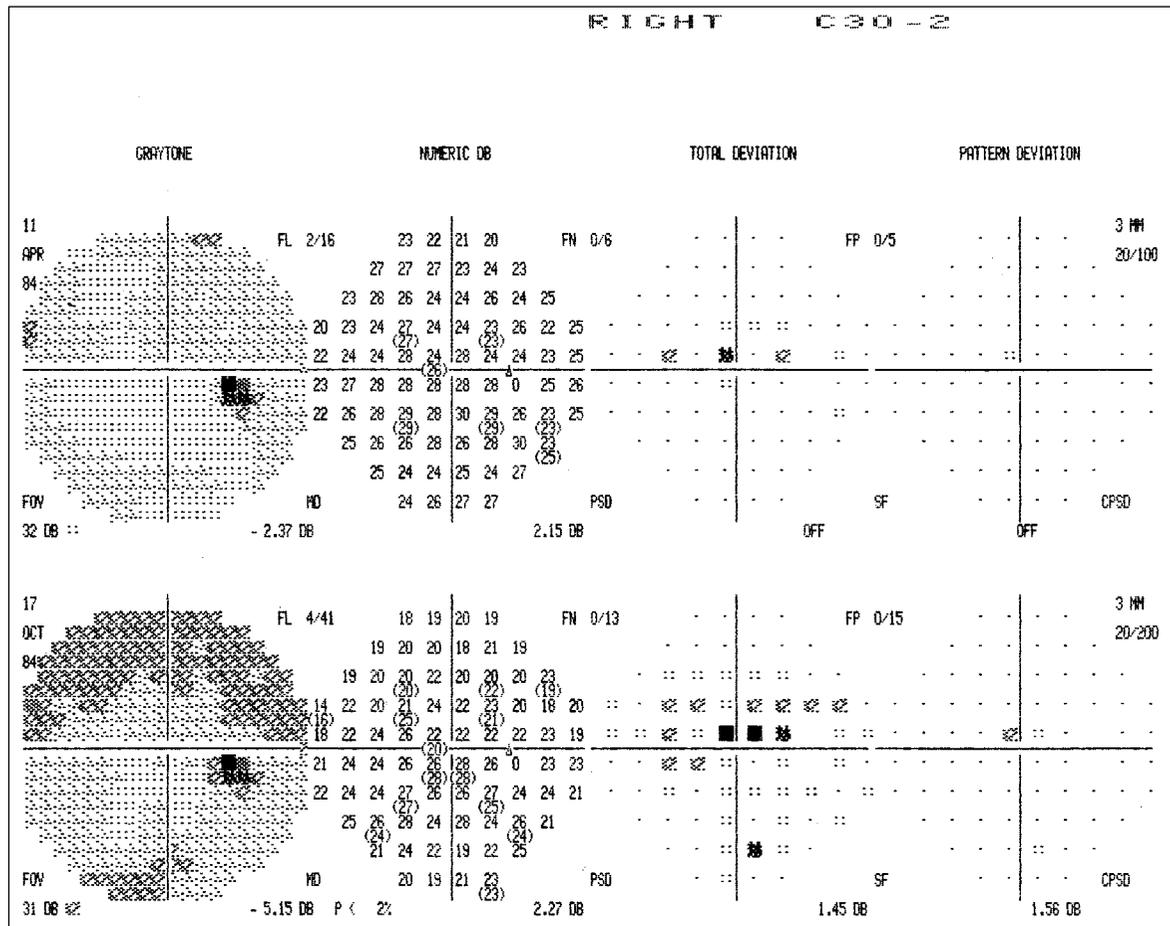


Fig. 9-1 Developing cataract in a glaucoma patient. Note the increasing depression of the visual field in the left grey-scale printout and in the total deviation graphic presentation (third from the left). The pattern deviation that is presented in the far right column shows little change over time. Cataract extraction with intraocular lens implantation was performed prior to the last field test. Note that the generalized depression and the total deviation have reversed while the pattern deviation remains similar. This methodology allows improved ability to follow glaucoma patients in the presence of developing cataracts.

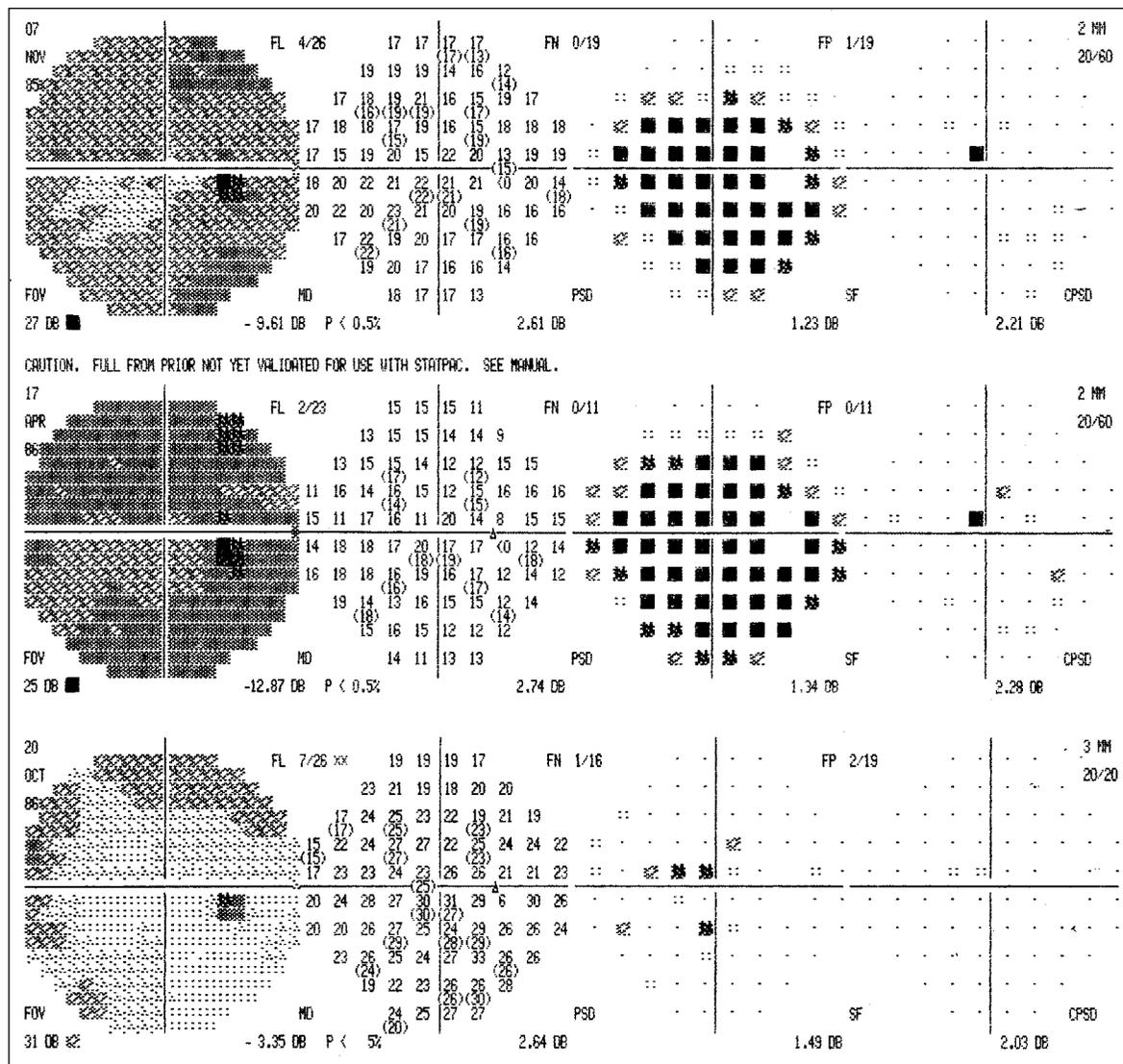


Fig. 9-1 continued

REFRACTIVE CORRECTION

Proper refraction with appropriate correction for presbyopia and patient age are required for accurate testing. In one series of experiments, overcorrection of +1.00D in the sphere reduced mean sensitivity 3.6 ± 0.8 dB, and overcorrection of +2.00D caused a reduction of 5.3 ± 0.9 dB.^{40,41} Another study found a decrease in threshold sensitivity as high as 7.6 dB with +6.00D overcorrection.⁴²

TESTING VARIABLES

TECHNICIAN

It is virtually impossible for two technicians to administer a manual visual field examination in precisely the same manner. Even the same technician inadvertently varies technique at least slightly from one examination to another. Thus to accurately interpret visual fields, the interpreter must be familiar with the skills and

variations of the technician performing the tests. The technician can improve patient performance by monitoring the patient consistently during the examination, but this has few advantages over intermittent monitoring following a brief introductory orientation.⁴³ Computerized perimetry has a great advantage over manual perimetry because it allows repeated performance of a standardized test. However, technical supervision is mandatory during the entire test to ensure the best possible results.

BACKGROUND ILLUMINATION

The level of background illumination affects the contour of the hill of vision and thus the appearance of the visual field. Brighter background illumination increases the slope of the central field and may influence the appearance of field defects. Different perimeters have different backgrounds: the Humphrey, Goldmann, and more recent Octopus perimeters use 31.5 apostilbs of background illumination. By contrast, older Octopus machines used 4 apostilbs of background illumination.

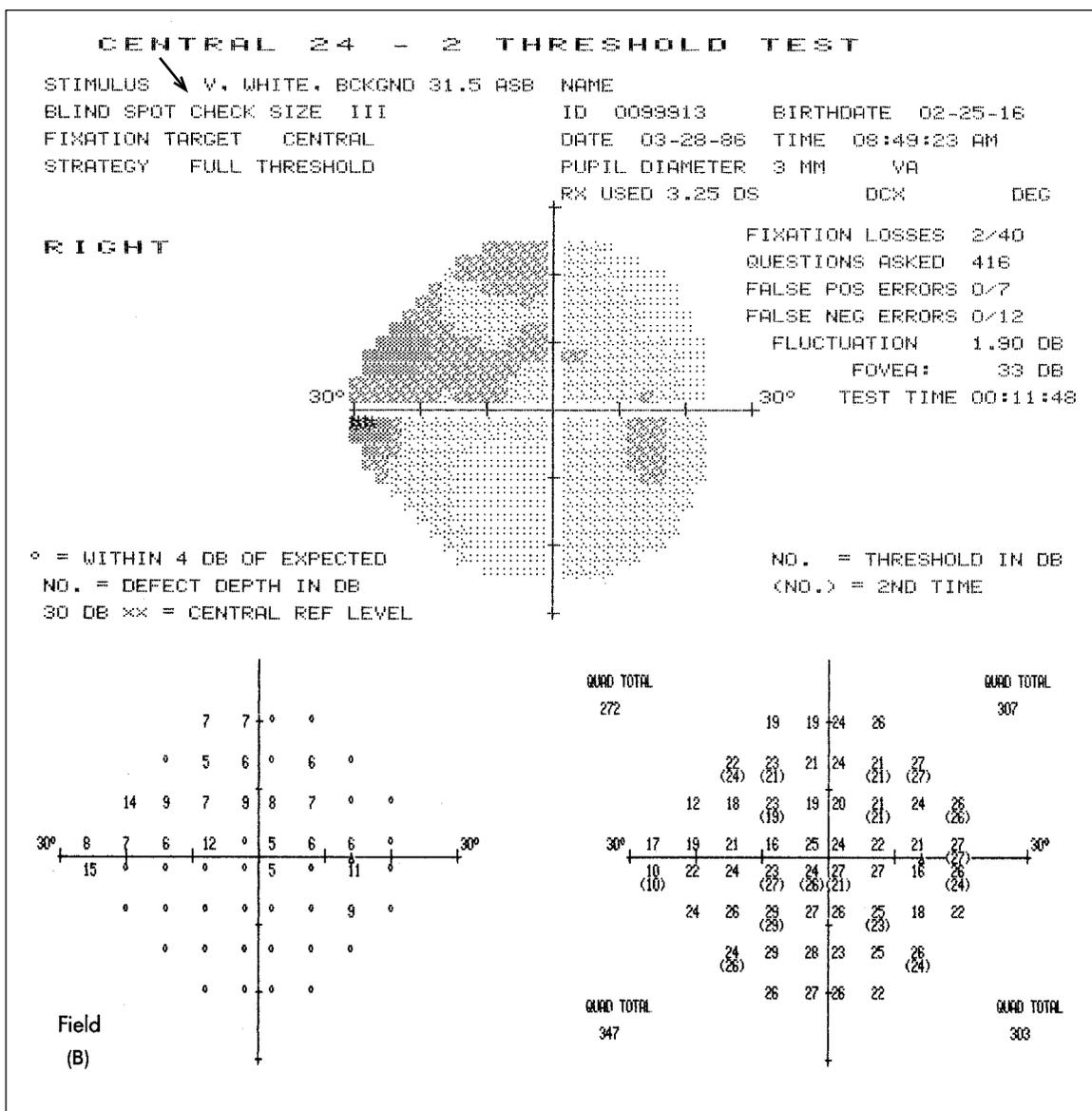


Fig. 9-2 Field (B) stimulus size V shows a subtle field defect superonasally in the grey scale. Care must be taken not to be misled by the change in stimulus size when interpreting a field change.

AREA TESTED

To compare visual field charts, the same region of the visual field must be tested during serial examinations (Fig. 9-4). For most purposes, tests that examine alongside vertical and horizontal meridians are more useful than are tests that examine on the meridian (the latter are rarely used today).

EQUIPMENT AND TECHNIQUES

GENERAL PRINCIPLES

Regardless of the equipment used, there are certain fundamental requirements for accurate visual field testing. Accurate distance refraction, with the appropriate addition for the distance from

patient to stimulus, should be used. Because accommodative capacity varies with age, the amount of addition should be adjusted for the patient's age and the instrument used (Table 9-1).

In kinetic perimetry, the rate of motion of the test object should be constant within a given test and for subsequent field examinations. Two degrees per second is conventional. The test object should be moved from the non-seeing area of the visual field to the seeing area. Most important, however, is that the same technique be used each time.

Constant fixation is necessary to obtain reliable visual fields. The visual field is mapped accurately only if the patient looks steadily at the central fixation target. Some assessment of the patient's fixation should be recorded on the field chart, and the patient should be gently encouraged throughout the test to look at the fixation target.

For valid comparison of visual fields, follow-up field examinations should use the same stimulus sizes and intensities for

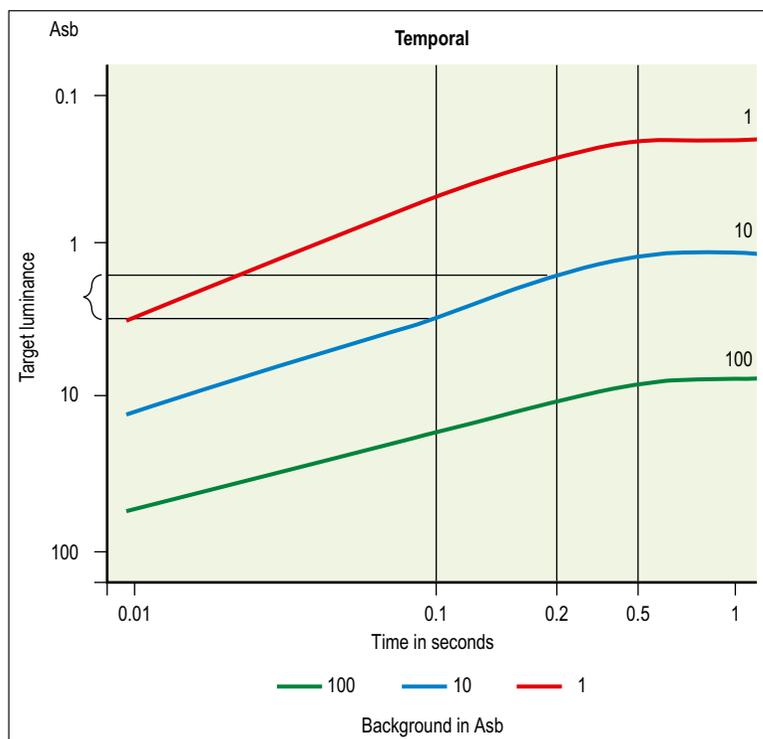


Fig. 9-3 Temporal summation related to background luminance. Using the 10 dB background curve, approximately a 3 dB increase (I) can be anticipated by increasing stimulus exposure time from 0.1 to 0.2 seconds.

(Modified from Aulhorn E, Harms H. In: Jameson D, Hurvich LM: editors: Handbook of sensory physiology, vol 7, New York, Springer-Verlag, 1972. With kind permission of Springer Science and Business Media.)

kinetic perimetry; the stimulus size and testing strategy should be duplicated for sequential static examinations. Other variables such as pupil size, technician, visual acuity, and testing equipment should be standardized as much as possible to reduce artifactual field fluctuations and to facilitate recognition of true pathologic change.

TANGENT SCREEN

The tangent screen may be used at 1 or 2 meters.⁴⁵ It should be large enough to allow testing of the full 30° of the central field at whichever distance is chosen and should have a uniform illumination of 7 foot candles. Examiners can use the tangent screen for either kinetic or static testing. For static testing, the test object is placed on the side of the test wand so that it can be obscured by being rotated out of view. The wand should be covered by black felt material similar in composition to the tangent screen so that the wand itself is largely unseen during the test.⁴⁶ While the patient maintains steady fixation, the wand is moved to the area of interest and the target is quickly rotated in and out of view. The patient responds to the on/off presentation.

The smallest test object the patient can see consistently just temporal to the blind spot is used for testing the central field. For a 1-meter test distance, this is usually a white test object that is 1 mm in diameter.

Fixation can be tested repeatedly by concealing and exposing the test object in the blind spot area. If the patient sees it, fixation has shifted. The test strategy is the same as that used for the central 30° of the visual field during Goldmann perimetry. The tangent screen is generally not sensitive enough to diagnose early field loss in glaucoma patients. It finds its greatest usefulness in patients with established field defect who are being followed in centers that do not have access to Goldmann or automated perimeters. Tangent

screen fields are also useful for patients who cannot use a bowl perimeter for physical or other reasons.

BOWL PERIMETRY

In the mid-twentieth century, Goldmann developed the first bowl perimeter that provided standardized background and stimulus intensity. He improved fixation monitoring by allowing the technician to see the patient's eye through a telescope. He also provided a system for simplified test recording and facilitated reproducible test object positioning and movement. The perimeter that bears his name is the standard for manual bowl perimetry (Fig. 9-5). Many of its features have been incorporated into computerized visual field machines.

Using the light meter provided, the machine should be calibrated each day before the initial examination. The maximum stimulus, V4e, should be 1000 apostilbs; the background, or bowl, illumination should match the V1e stimulus, equivalent to 31.5 apostilbs.

Preparing the patient

Patient preparation for the examination is similar whether the bowl perimeter is to be used for manual or computerized testing. Refractive correction with the appropriate addition should be inserted into the lens holder for examination of the central portion of the visual field.

The patient should be comfortably seated so that the chin and forehead are firmly against the supports and the eye is centered in the observer's telescope or display screen. After the patient is positioned, the lens holder should be placed as close as possible to the patient's eye without touching the lashes. The eye should be centered in the lens holder. Corrective lenses should be 'full-field' type with thin rims so that they do not interfere with peripheral vision.

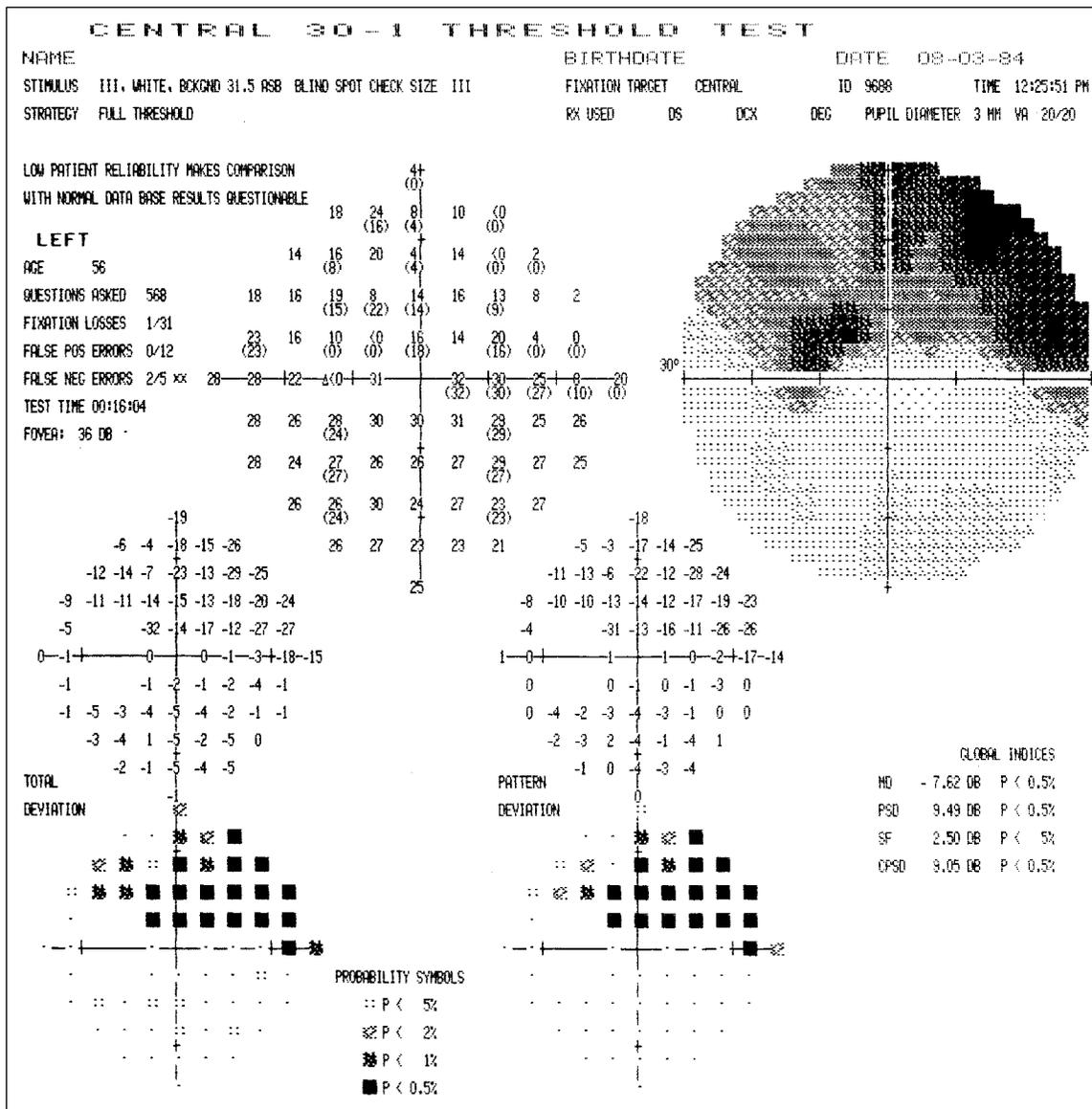
For manual machines, the patient should be instructed to push the button on the patient response indicator if one is available. If not, the patient should tap the table with a coin to indicate when he or she sees the test object. Verbal responses are discouraged because they move the head and adversely affect fixation and concentration. For automated machines, the patient uses the patient response button.

It is important to encourage the patient throughout the test, even if the computer is doing the testing. Many patients are more comfortable interacting with another person rather than with a machine; reliability is increased when a technician is present during computerized perimetry.⁹

Technique of manual bowl (Goldmann) perimetry (see Fig. 8.8)

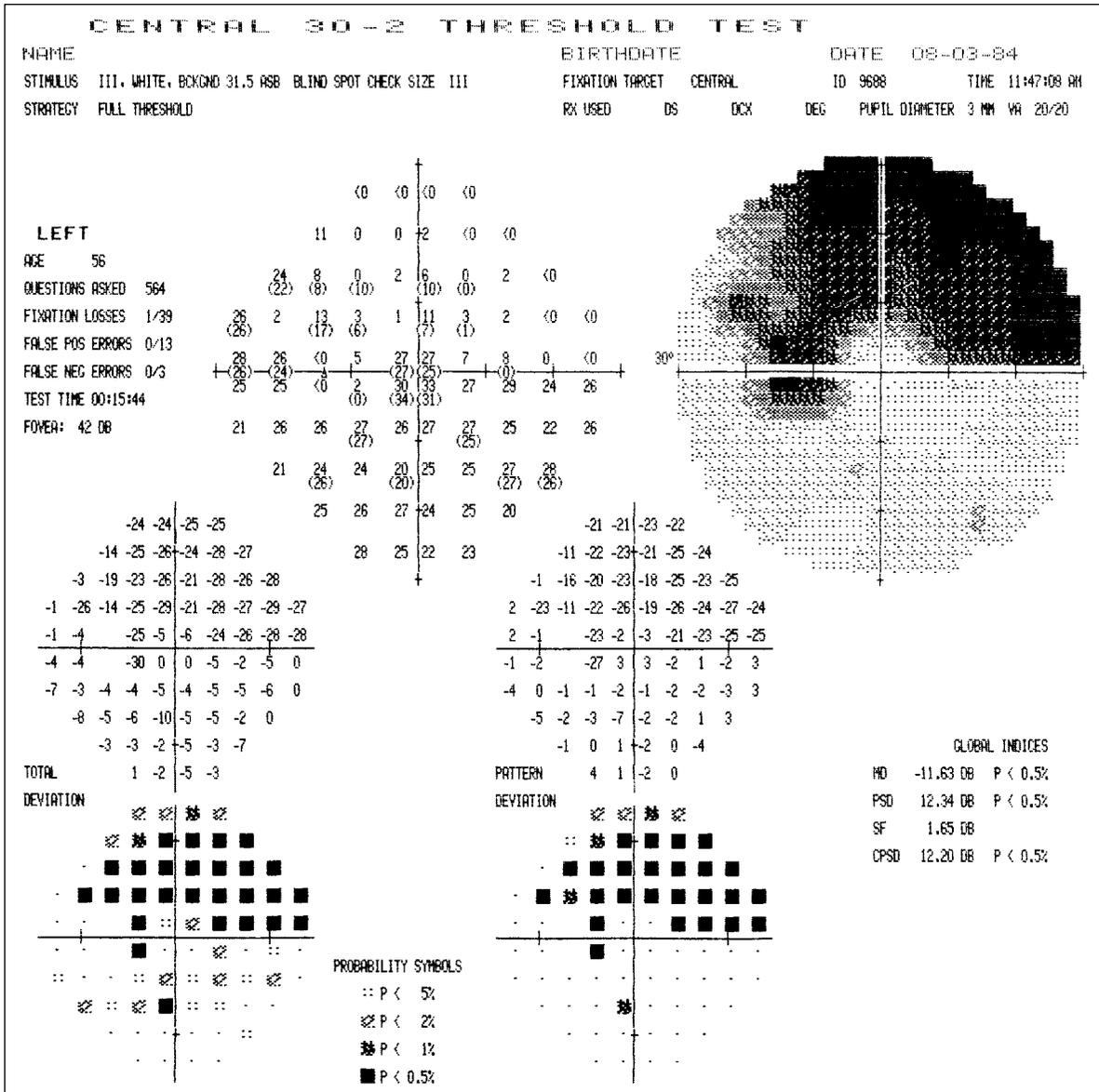
Aulhorn and Harms,⁴⁴ Armary,^{47,48} Drance and co-workers,⁴⁹ and others⁵⁰ contributed concepts that provide the basis for techniques in

glaucomatous visual field testing and analysis. For the central field, a test object that is just detectable at the temporal horizontal meridian at 25° eccentricity, 15° above and 15° below this point, is appropriate. This threshold target is used to define the limits of the central isopter and blind spot by kinetic perimetry. Particular attention is given to the nasal and temporal meridians in looking for a step. Careful investigation of the 5°, 10°, and 15° isopters is necessary to reveal the isolated scotomata that are characteristic of early glaucoma. These three central isopters are examined by static and, if necessary, by kinetic perimetry (from non-seeing to seeing). Any paracentral field defects found with the threshold target should be checked at least twice, because artifacts are possible in any subjective test. Hesitant responses (especially in the Bjerrum area) should be noted. The I2e is the established standard test stimulus for the central visual field and provides a comparison for other patients and eyes. Selected higher intensity objects will determine the density of a defect. An I4e test



(A)

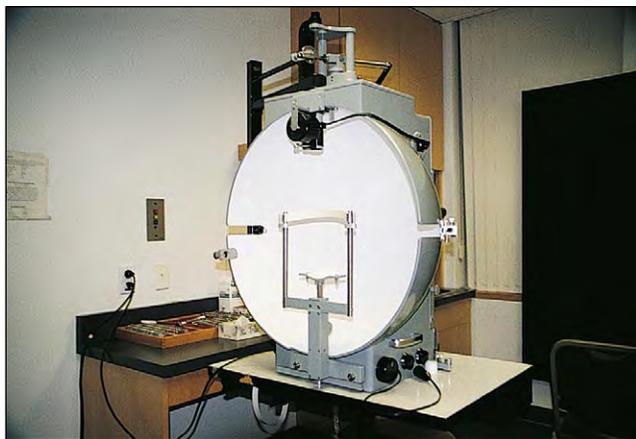
Fig. 9-4 Although these two visual fields appear to reveal tremendous change (see Fig. 9.4B), the tests were performed on the same day. (A) The 30-1 visual field positions the spot on the horizontal and vertical midlines and then positions subsequent spots 6° off these midlines.



(B)

Fig. 9-4 (B) The 30-2 program positions the spots 3° to either side of the midlines. The 30-2 program is better for recognizing change along horizontal and vertical meridians such as those that occur in patients with glaucoma and neurologic deficits.

Table 9-1 Addition for near, bowl perimetry				
Age	Octopus, Model 500	Octopus, Model 201	Humphrey analyzers	Goldmann perimeter
30-39	Plano	Plano	+1.00	+0.50
40-44	+1.00	+0.50	+1.50	+1.00
45-49	+1.25	+1.00	+2.00	+1.50
50-54	+1.75	+2.00	+2.50	+2.25
55-59	+2.00	+2.00	+3.00	+3.00
>59	+2.00	+2.00	+3.00	+3.50



(A)



(B)

Fig. 9-5 Goldmann perimeter for visual field examination as viewed from the patient's side (A) and the examiner's side (B).

object is used to test the far periphery, and a V4e stimulus will outline the maximum area of the visual field.

Technique of computerized bowl perimetry

The Octopus was the first computerized visual field machine that provided enough flexibility to allow accurate detection and quantification of visual field defects. This machine used only static testing strategies. The Humphrey and some other computerized perimeters offer a kinetic option,^{51,52} but the overwhelming majority of clinical tests are performed using static techniques only.

Each of these machines provides a variety of testing programs for different situations. The physician should designate the program to be used for each patient. In practice, it is appropriate to have a standard program that is used by default. If a particular patient has special needs or circumstances, the physician can order a test that addresses that patient's needs. If a wide variety of tests are used routinely, it is difficult to gain sufficient experience with any one test to interpret the results optimally. We have found it much better to be comfortable with a few tests we know well than to try to master the entire menu offered by the manufacturer.

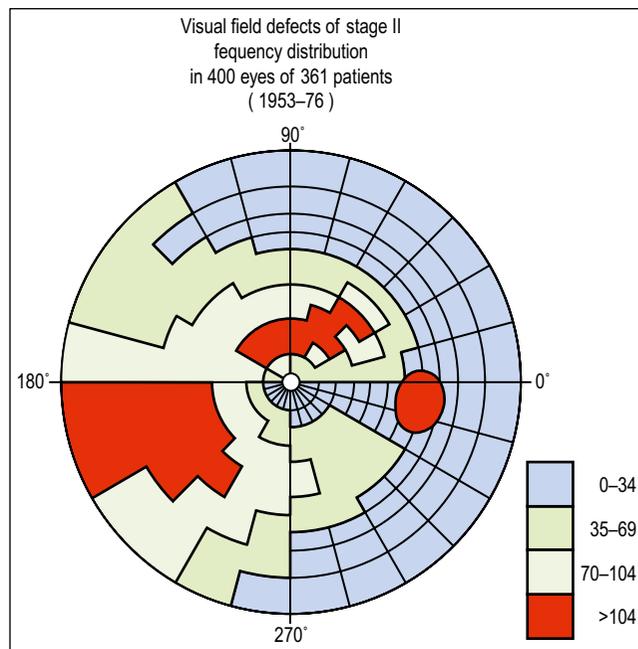


Fig. 9-6 Frequency distribution of the location of early glaucomatous visual field defects found in 400 eyes of 361 patients.

(From Aulhorn E. In: Krieglstein GK, Leydecker W, editors: *Glaucoma update*. Berlin, Springer-Verlag, 1979. With kind permission of Springer Science and Business Media.)

In addition to perhaps dozens of standard options, computerized machines offer custom programs that allow the examiner to tailor the area tested as well as the testing algorithm. This sounds like a good feature, but using custom programs is a risky practice. Remember that the hallmark of successful serial perimetry is consistency. For a custom test to be useful in the future, it must be duplicated exactly on subsequent examinations. It is not practical in most busy clinics and practices to take the time to reprogram the machine before each test. It is also difficult to remember to do this for the occasional patient.

For glaucoma testing, most visual field defects are located in the central 30° of the visual field (Fig. 9-6). Programs that test the central 24° produce adequate results for most patients, and save substantial testing time. Testing out to 30° may allow better definition of peripheral nasal step defects in the occasional patient. We tend to use the 30° program for new patients and when patient acceptance is good and testing time is not critical. The number of points tested varies but is roughly 60 to 70 depending on the program. In each case, the test grid is chosen to gather sufficient information without tiring the patient excessively. For the most part there is a direct relationship between the amount of time spent testing and the amount of information obtained. But overly long tests produce inconsistent results. Patient fatigue leads to errors that may be clinically significant. There is a point of diminishing returns with automated perimetric tests.⁵³⁻⁵⁵ Several programs allow the machine or the examiner to shorten the test if certain parameters are met (indicating that further testing is unlikely to improve the quality of the result or change the ultimate interpretation). For example, the patient may be a young adult with no obvious pathology and a previously normal baseline examination. Rechecking a representative sample of the previous test points may be enough to reassure the examiner that no change has occurred. The most sophisticated

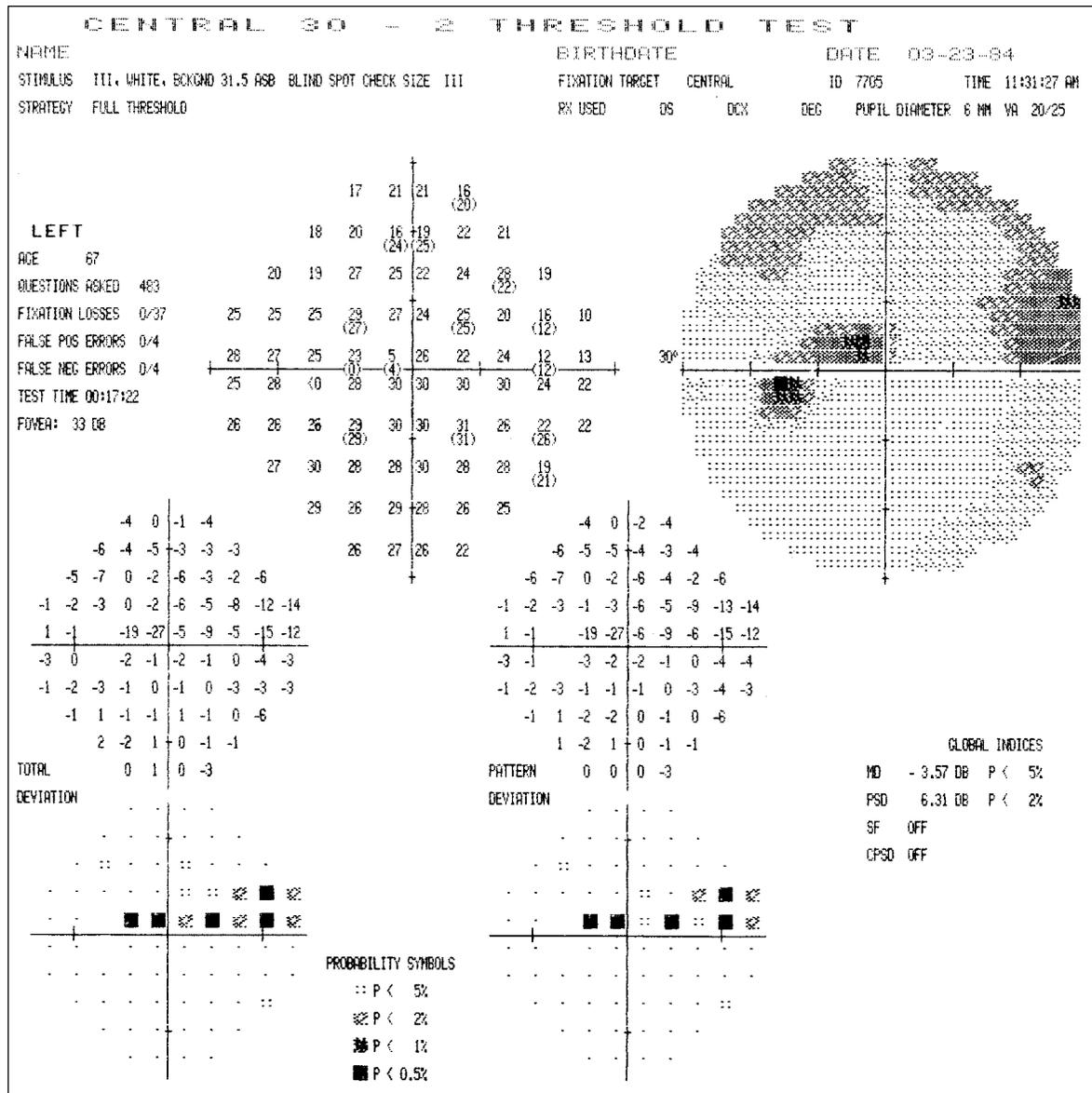


Fig. 9-7 The grey scale (upper right) indicates depression superiorly, just above the macula, and in the upper nasal aspect of the field. The total deviation plot (lower left) shows the significance of this deviation compared with a normal population of this patient's age. The pattern deviation (lower right) subtracts generalized depression, of which there is very little in this patient, leaving the scotomatous defect obvious.

programs, like the Humphrey Swedish Interactive Thresholding Algorithm program, spend more time testing suspicious areas of the field and less time on normal or clearly defective areas.

Defects that approach fixation are especially worrisome and can be plotted within 1.0° or 1.5° spatial frequency using macular programs. Central fields can also be plotted using the Goldmann or tangent screen perimeter in glaucoma patients who have only a central island remaining. Full-field automated tests are very time-consuming and discouraging for these patients, and they do not provide enough useful information to warrant the time and aggravation they cause.

Glaucomatous defects may occur solely in the peripheral visual field. This is rare, however, and probably occurs in 0–8% of cases depending on the examination technique.^{56–63} Many of the computerized perimeters supply a separate program that carefully examines the nasal area to detect most isolated peripheral defects.

Other machines have screening programs that test the periphery. If the periphery is tested, the lens holder and lens should be removed from in front of the eye.

The constant dilemma facing physicians with computerized perimeters is matching a patient's ability with the program(s) to be used.⁶⁴ Younger, more vigorous patients can tolerate longer tests. Most people are bored or fatigued after 20 minutes of consecutive testing and need a rest. The machine never gets tired and is capable of testing the visual field in minute detail. Patient reliability decreases, however, with increasing fatigue. The physician must select the appropriate tests to obtain the most accurate information for each patient. Healthy patients can generally tolerate a full-threshold visual field that measures the central 30° visual field (Fig. 9-7). Patients with visual field loss may have a difficult time with such a test. This is partly because of the length of time it takes to map the defective field, and partly because sitting in front of

the bowl and missing stimulus after stimulus can be quite depressing. Depending on the results of the initial test, follow-up visual field tests may be performed with a program that tests only the central 24°. This allows speedier testing, although the ability to recognize early change may be reduced in rare cases.⁶⁵ In addition to

employing time-saving steps, such as faster pacing when appropriate, software programs that allow the machine to interact with the patient and modify the test based on a real-time evaluation of the patient's responses allow faster testing without sacrificing sensitivity or accuracy.⁶⁶⁻⁶⁸

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CHAPTER
10

Visual field interpretation

GLAUCOMATOUS CHANGES IN THE VISUAL FIELD

Damage in glaucoma can be conveniently divided into two types: structural and functional. Structural damage to the eye is seen as a characteristic abnormality in the nerve fiber layer or optic nerve, representing deterioration following ganglion cell loss. Functional loss is determined by a variety of tests that assess visual function, including visual field examinations.

ANATOMY OF VISUAL FIELD DEFECTS

Visual field defects reflect visual pathway abnormalities; their appearance should correlate well with the anatomic arrangement of neurons in that pathway (Fig. 10-1). Glaucomatous field damage results from damage to the intraocular portion of the optic nerve extending from the retinal ganglion cells to just posterior to the lamina cribrosa.

TYPES OF VISUAL FIELD LOSS**Generalized loss**

Generalized, or diffuse, visual field loss is thought to be caused by a diffuse loss of axons, whereas localized defects result from loss or damage to a contiguous group of axons. The early visual field investigators recognized that generalized constriction, enlargement of the blind spot, and diminished night vision were all seen in early glaucoma. Unfortunately, these same findings occur with age and with other non-specific forms of visual field loss. Previously it was

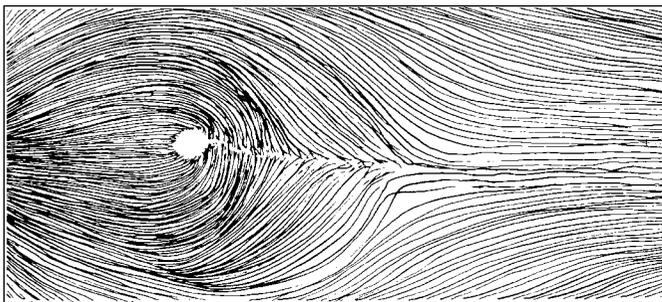


Fig. 10-1 Pattern of the nerve fiber layer shown in a drawing of the region of the temporal raphe that has been reconstructed from low-power photographs. (From Vrabcic F: The temporal raphe of the human retina. *Am J Ophthalmol* 62:926, 1966.)

impossible to quantify these changes precisely enough to define normal limits and recognize variations from those limits. This was because isopter plotting with manual Goldmann kinetic perimetry has inherent variability that makes it difficult to distinguish or quantitate mild generalized loss. The quantitative measurements made by static automated perimetry, however, are ideally suited to comparisons between a patient and his or her age-matched normal. Thus we are better able to recognize and quantify diffuse visual field loss (Fig. 10-2).

Localized defects (scotomata)

Scotomata, or localized depressions of the visual field, are more easily recognized than are generalized depressions because the normal neighboring field makes the defect stand out. The margins or walls of the defect may be steep or sloping. Scotomata are also described as *absolute* or *relative*.¹ In an absolute scotoma, the brightest stimulus of the machine is not perceived. In a relative scotoma, the brightest stimulus is visible, but dimmer stimuli are not.

GLAUCOMATOUS VISUAL FIELD DEFECTS

Functional loss as determined by visual field testing has long been a diagnostic criterion for glaucoma. A variety of field defects are seen in early- and mid-stage glaucoma, all progressing to the dense defects of late-stage glaucoma. In a retrospective study of 102 glaucoma patients followed for at least 15 years, Eid and colleagues found that 29% of their patients had paracentral scotomas, 20% had nasal steps, and 18% had simple arcuate defects as the predominant diagnostic field abnormality.²

Generalized depression

Generalized depression can be an early sign of glaucoma, but it can also occur with aging, miosis, or hazy media. In kinetic perimetry, generalized depression is seen as a generalized constriction of the peripheral and central isopters. Unfortunately, this too is a rather non-specific finding. Kinetic perimetry, at least by manual methods, lacks the precision necessary to differentiate generalized depression from normal aging unless there is an obvious difference between the patient's two eyes or the depression is substantial.

Generalized depression can increase the physician's suspicion that glaucomatous damage has occurred, especially if it is unilateral or more pronounced in the eye with the higher pressure or larger cup:disc ratio. Interestingly, both the Humphrey and Octopus field machines use *MD* to represent the amount of generalized loss found in the field. On the Octopus machine, this stands for 'mean defect' (Figs 10-3 and 10-4). If the patient has loss (i.e., a defect), then the MD has a positive sign indicating the presence of a defect. If the patient sees better than expected, the MD has a negative

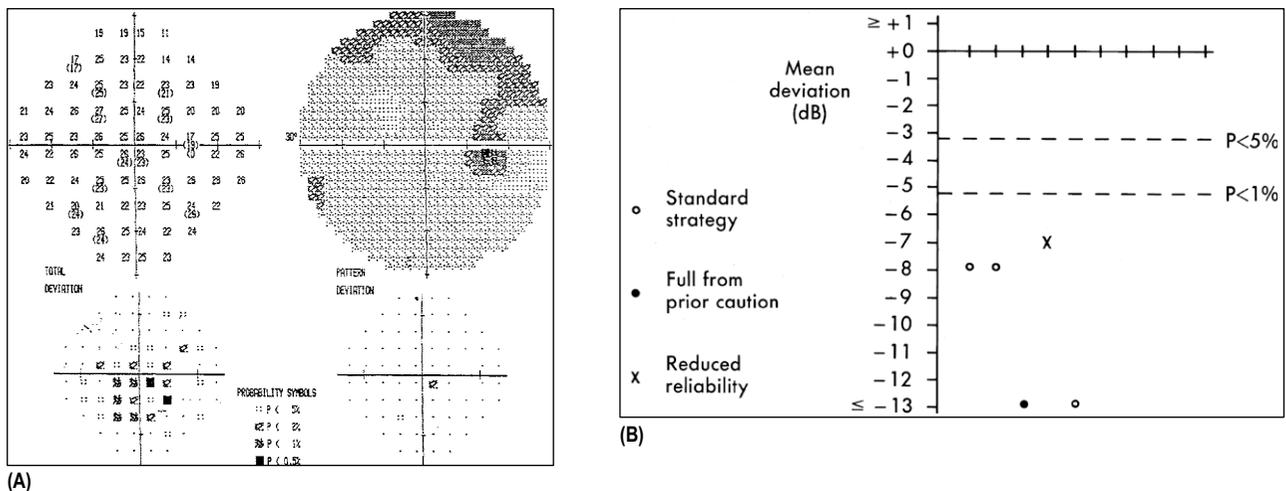


Fig. 10-2 (A) Computerized perimeters have their greatest value in having a normal database against which individual patients' results can be compared. In this figure, the grey scale indicates a superior visual field loss. The total deviation plot (lower left), however, indicates central visual field depression as compared with normal eyes. The pattern deviation (lower right) indicates only a single spot adjacent to fixation that is reduced below normal. The pattern deviation has subtracted the general depression that is present to expose any scotomatous defect that may be deeper than the general depression. This patient actually does not have glaucoma but rather a cataract is causing this central depression. The superior field slopes more precipitously than does the inferior field, causing the grey scale to appear more depressed in that area. This does not necessarily represent pathology. The deviation plots indicate decreasing probability that a spot may be normal by increasing the density of the symbol. A totally black square has a probability of being normal of less than 0.5%. **(B)** This graph, taken from a Humphrey STATPAC printout, indicates how a patient's visual fields compare with normal data. The horizontal line at the zero point represents a normal mean sensitivity level. Negative numbers extending down from that point indicate a mean decibel shift below normal. As can be seen, a mean deficit of slightly more than 3 dB occurs in less than 5% of normal eyes, whereas a mean deficit of slightly more than 5 dB occurs in less than 1% of normal eyes. This patient has had five visual fields. The first two were done with standard strategy. The third was full from prior strategy, which is not calibrated for STATPAC. The fourth had reduced reliability. The fifth was done with standard strategy. It appears that the patient started with a mean deviation of 28 dB, which is distinctly pathologic, and the field has worsened over time. (From the Humphrey STATPAC program.)

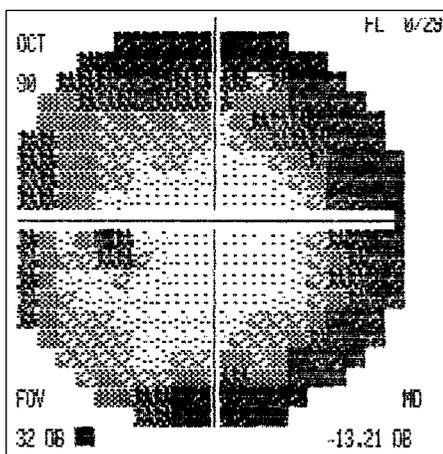


Fig. 10-3 Humphrey field showing moderate to severe generalized depression. The mean deviation (MD; lower right) is -13.21 .

sign; a negative defect indicates above-normal sensitivity. On the Humphrey machine, MD stands for 'mean deviation' and measures the difference between the patient's response and normal. If the patient has field loss, the MD has a negative sign; if the patient sees better than expected, the MD is positive – just the reverse of the Octopus nomenclature. Luckily it is easy to tell which system

is being used clinically, and in common parlance an abnormal MD means that the patient has some component of generalized loss.

Irregularity of the visual field

There may be a lack of uniformity in the visual field. With computerized perimetry, this 'roughness' appears as a variation of decibel level among contiguous points that is greater than that anticipated in normal patients of the same age. These areas of loss appear non-uniformly throughout the field. This variation is expressed statistically as the standard deviation of the deviations found in the field (Humphrey) or the variance (square of standard deviation) of the mean of all points tested (Octopus). Humphrey uses the term *pattern standard deviation*, whereas Octopus uses the term *loss variance*. These functions are sensitive to localized loss but are relatively unaffected by generalized loss (see Figs. 10-3 and 10-4).

Nasal step or depression

The nasal portion of the visual field is often affected early in glaucoma, and defects may persist until the last stages of the disease.³ The nasal area is the most important region of the midperipheral and peripheral field to test.⁴ Depression may be evidenced by hesitancy in patient response when testing this area, as an inward turning of the isopter in manual perimetry, or by reduced sensitivity on static testing. If a true step that respects the horizontal raphe develops, a defect is present. Such defects may occur centrally (Fig. 10-5), peripherally, or both (Fig. 10-6) and may be isolated or associated with other Bjerrum area defects.

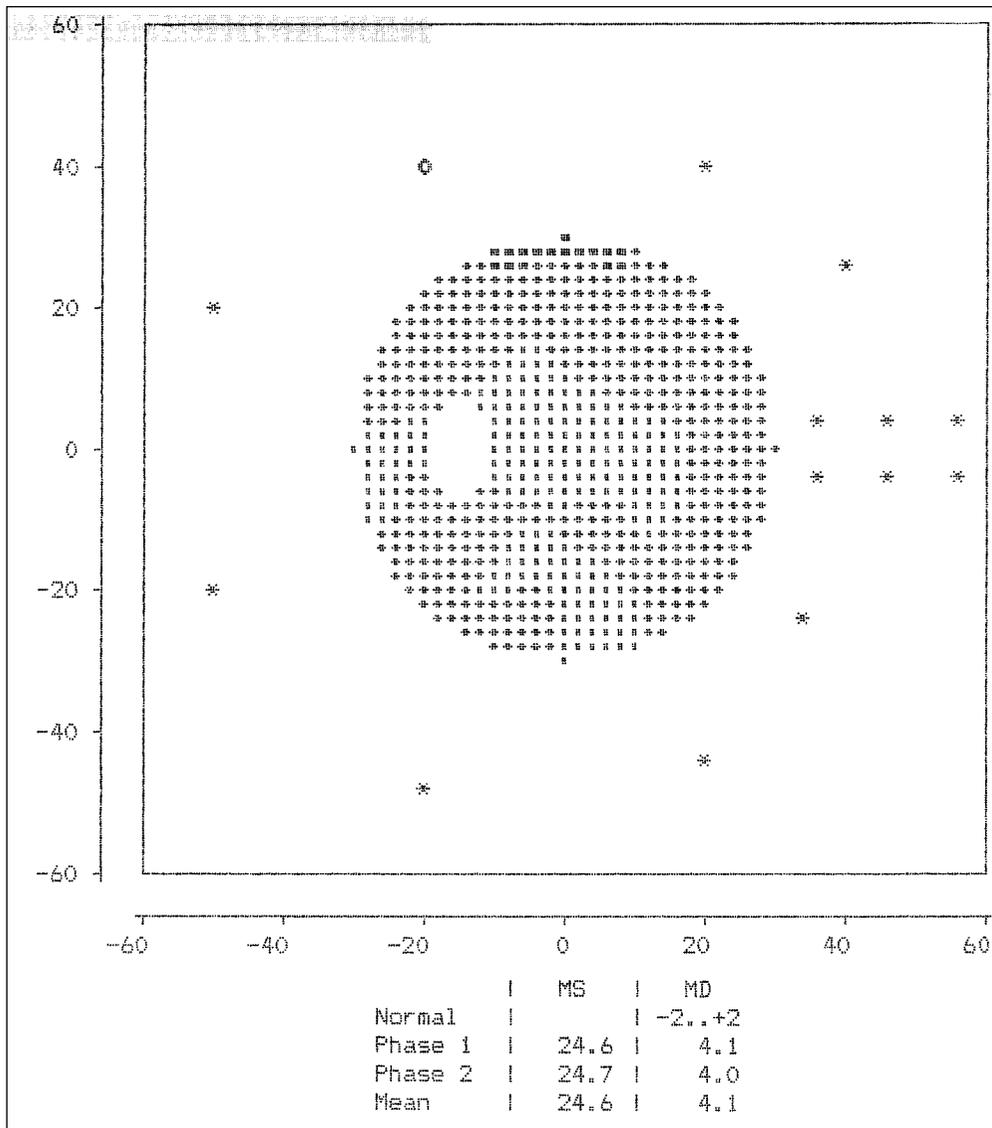


Fig. 10-4 Octopus field showing slight generalized depression. The mean defect (MD) is +4.1. MS, mean sensitivity; MS + MD, normal sensitivity for the patient's age.

Temporal step or depression

A temporal depression or step may develop as an isolated finding or in conjunction with other glaucomatous defects. They may be detected at any stage of glaucoma but are more commonly found as a component of late-stage disease.⁵ Drance and co-workers⁶ suggest careful testing of the temporal area to recognize the occasional patients who may develop this condition as their only defect (Fig. 10-7).

Enlargement of the blind spot

Enlargement and baring of the blind spot are considered non-specific changes that can occur in normal patients (Fig. 10-8). If the blind spot enlarges in an arcuate manner, it is called a *Seidel's scotoma* and may be seen in early glaucoma (Fig. 10-9).

Isolated paracentral scotomata

Careful manual perimetry using combined static and kinetic techniques may demonstrate small paracentral scotomata. In a classic study, Aulhorn and Harms⁷ found similar small defects that

did not connect to the blind spot in 20% of glaucomatous visual fields. Early glaucomatous defects may have a small, dense center. If the glaucoma is progressive, these defects enlarge, deepen, and coalesce over time to form arcuate scotomata. Inconsistency of responses in the paracentral area may be an early sign of glaucomatous change.^{6,8,9}

Static testing through these scotomata may confirm that they are true defects. The most commonly used computerized perimeters use the equivalent of the 30-2 spacing of test spots which are 6° apart; scotomata smaller than 6° may be missed. This is particularly critical in the paracentral region where even very small scotomata can be visually symptomatic. Spacing the test spots closer than 6° (for example 3° apart) increases the chances of identifying such scotomata but also increases the test time to an impractical level. If one is concerned about identifying or monitoring a paracentral scotoma, both the Octopus and the Humphrey have programs that increase the density of tested spots within the central 10° of the visual field – the G-1 or the 10-2 respectively (Fig. 10-10).

Arcuate defects (nerve fiber bundle defects)

The arcuate scotoma represents a complete nerve fiber bundle defect. It begins at the blind spot, arcs around fixation, and ends at the horizontal nasal raphe. The defect may break through into the

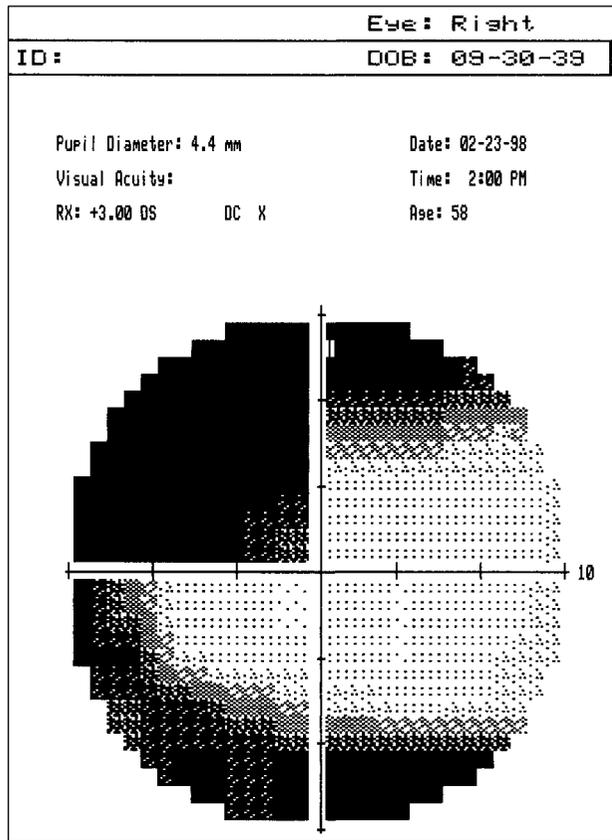


Fig. 10-5 Central 10° field from the right eye of a patient with advanced glaucoma. The nasal horizontal step (left side in this figure) runs all the way to fixation.

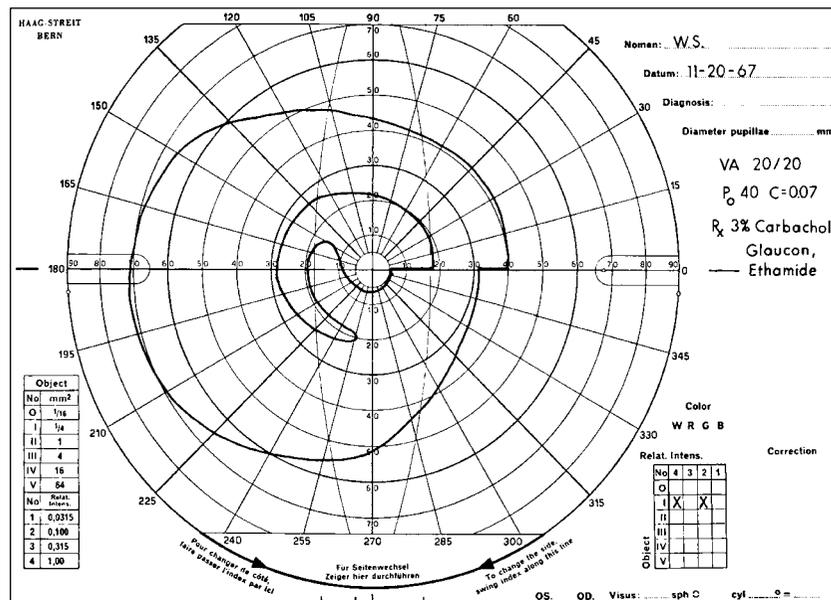


Fig. 10-6 Note the inferior nasal step present on the peripheral and central isopters in this patient. There is an inferior arcuate scotoma present also.

periphery nasally and then expand further to ultimately become an altitudinal defect (Fig. 10-11). The arcuate defect as described by Bjerrum is a classic finding in middle- to late-stage glaucoma.

End-stage defects

Central and temporal islands

In the later stages of glaucoma, most of the axons at the superior and inferior poles of the disc are destroyed, leaving only the papillomacular bundle and some nasal fibers. This destruction produces the characteristic end-stage field, with a small central island and a larger temporal crescent remaining. The central island may split fixation so that only fibers from half of the papillomacular bundle remain (Fig. 10-12). Kolker¹⁰ found that patients with split fixation are more susceptible to central vision loss at surgery, although this is still a very rare outcome.¹¹ These patients may need to have their pressures controlled in the mid teens or below to slow further progression.

Reversal of visual field defects

Fluctuation and increasing familiarity with the test or random chance may cause subsequent visual field examinations to appear improved.^{12,13} Nevertheless, at least slight reversibility of visual field defects seems to be a real phenomenon in occasional patients following therapy for glaucoma.¹⁴⁻¹⁷ The rule, unfortunately, is that glaucoma patients do not regain visual function under treatment, but rather they continue to lose field even when controlled. The rate of loss varies, and about 1 in 5 patients are stable over 20 years, but in general some degree of loss is usual. The rate and degree of loss in treated eyes are less than that reported in rare studies of untreated glaucoma.¹⁸

ANALYSIS OF VISUAL FIELD LOSS

CHRONIC OPEN-ANGLE GLAUCOMA

Any of the preceding types of visual field loss may be seen in chronic open-angle glaucoma.¹⁹ In the early stages there may be

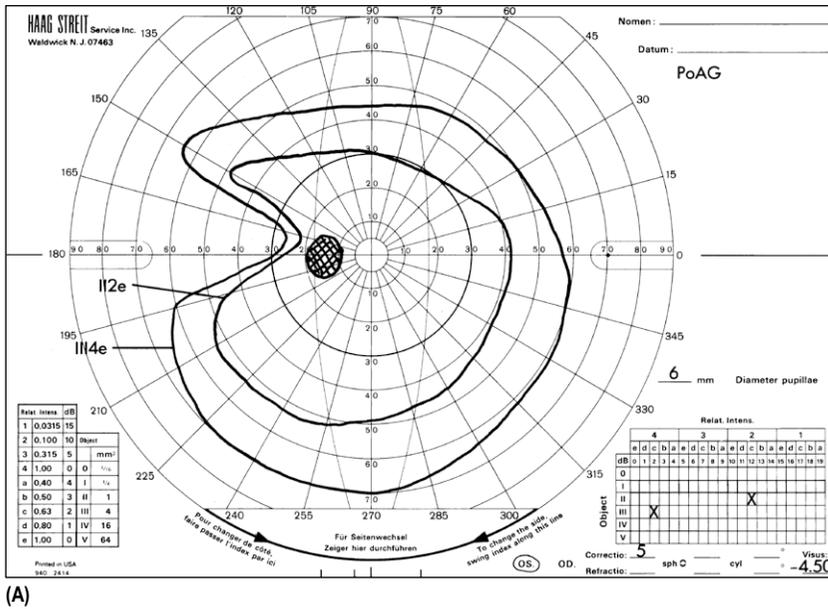


Fig. 10-7 Visual field temporal defect. **(A, B)** Note the temporal wedge that occurred in this patient with erosion of the nasal aspect of the optic nerve.

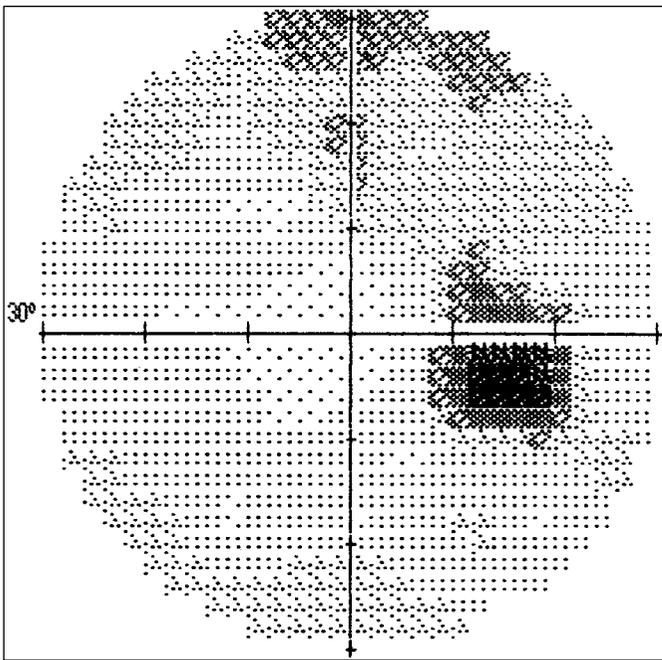


Fig. 10-8 Visual field chart from the right eye of a 56-year-old woman with early glaucoma. Generalized blind spot enlargement is not necessarily a glaucomatous defect. This blind spot is roughly 14° × 14°, with sloping margins. The normal blind spot is about 7° vertically and 5.5° horizontally, with sharp borders.

a generalized depression that progresses gradually or sometimes in steps from paracentral scotomata to arcuate to altitudinal to end-stage defects. Defects usually become denser and then increase in area in one hemifield before progressing to the next hemifield (Fig. 10-13). Scotomata may show episodic (stepwise), linear, or curvilinear progression.²⁰⁻²²

Many recent investigations have suggested that the two forms of glaucomatous visual field loss, diffuse and localized, may have different pathogenic origins.²³ It has been speculated that increased intraocular pressure (IOP) may cause diffuse loss²⁴ but have less influence on the development of localized defects.²⁵ Observer bias may have some influence on these findings, however, because patients with mild diffuse loss and normal pressure are often not identified as abnormal. Conversely, patients with elevated IOPs are examined closely because of the pressure, and, because suspicion is high, mild diffuse defects are recognized. Patients with dense localized defects tend to have localized optic nerve changes and may have visual field studies based on the appearance of the optic nerve. If the IOP is normal, a diagnosis of glaucoma is more likely when the field defect is local and dense rather than diffuse or non-specific. Drance,²⁶ however, found that patients with increased IOP with localized defects in one hemifield had nearly double the amount of generalized reduction in sensitivity in the other hemifield compared with a similar group of patients with normal-tension glaucoma. Many others have investigated this issue, and there is general agreement that early glaucomatous field loss may appear in different forms.

A study by Gazzard and colleagues found that the pressure level at diagnosis correlated with the amount of visual field loss measured by Advanced Glaucoma Intervention Study (AGIS) score and by mean deviation (MD), but not by pattern standard deviation (PSD) or corrected pattern standard deviation (CPSD).²⁷ In other words, higher presenting pressures were associated with the degree of diffuse damage but not with the degree of localized damage. The association was stronger for patients with primary angle-closure glaucoma (PACG) than those with primary open-angle glaucoma (POAG). This supports the concept that increased IOP is the proximal cause of damage in PACG, but that other factors may predominate in at least some patients with POAG. In both circumstances, the amount of field loss correlated well with the amount of optic nerve damage.²⁷

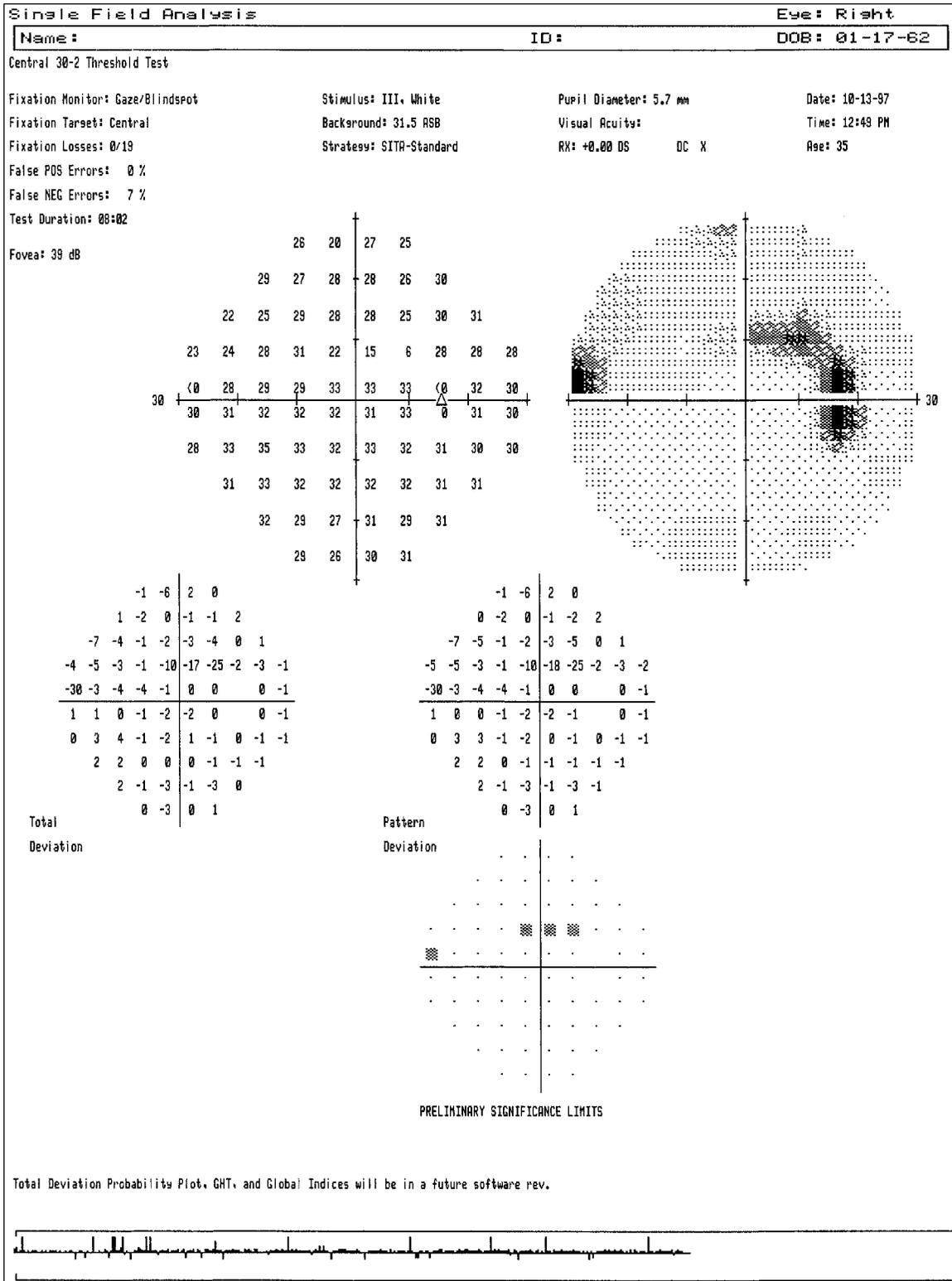


Fig. 10-9 Chart from the right eye of a patient with normal-tension glaucoma showing a Seidel's scotoma extending from the blind spot. There is also a small peripheral superior nasal step defect.

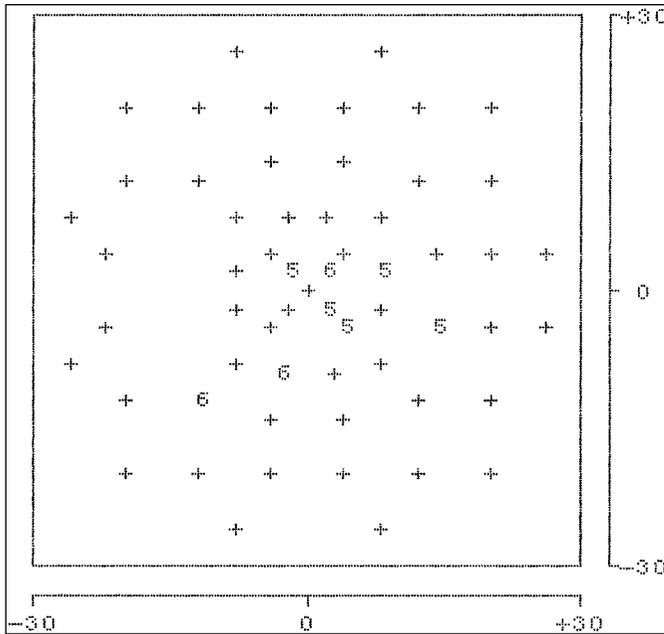


Fig. 10-10 Test grid pattern from the Octopus G-1 program. Twenty-one test points are placed in the central 12° rather than the 16 test points in the more standard Octopus 31 or 32 program. Humphrey has a similar program, the 10-2, which is very useful for identifying and monitoring paracentral scotomata.

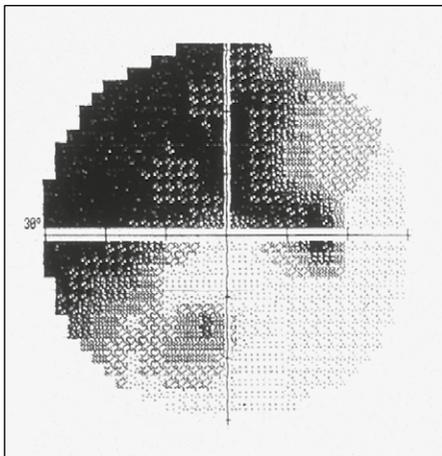


Fig. 10-11 Field from the right eye of patient with advanced glaucoma. The superior arcuate defect has expanded to include the entire superonasal quadrant and includes half of the superotemporal quadrant as well. The inferior half of the field is much less severely affected.

ANGLE-CLOSURE GLAUCOMA

During the acute phase of angle-closure glaucoma in patients with high IOP, corneal edema and retinal ischemia can produce bizarre field defects that have little clinical value for following disease progression. After the pressure has been normalized, field defects may remain and may sometimes be extensive if ischemic atrophy of the nerve has occurred. In such cases, pallor of the nerve may be more severe than cupping. This is one situation in which glaucomatous field defects may not correspond well to the amount of cupping of the nerve head.

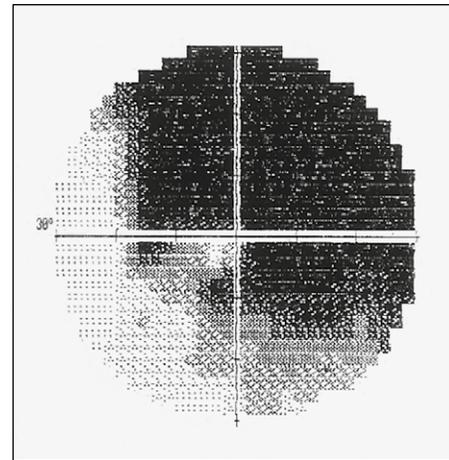


Fig. 10-12 Central island of a patient's left eye with field defects encroaching on fixation. The temporal field is partially spared.

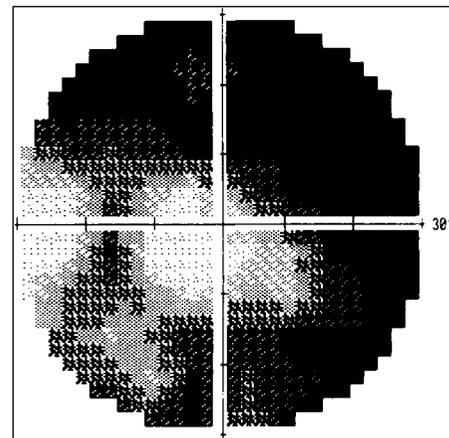


Fig. 10-13 The superior field (left eye) exhibits similar, but more advanced, loss compared with the inferior field. If the disease is unchecked, both fields will continue to progress.

OTHER CAUSES

Other diseases may cause arcuate nerve fiber bundle visual field defects (**Box 10-1**) that may be confused with glaucomatous damage. Generally, if excavation of the optic nerve does not correspond with the appearance of the field, other causes must be sought to explain the defect. If visual field defects occur or progress with normal pressures, normal-tension glaucoma may be the cause (see Ch. 17), but the examiner must be sure that other retinal or visual pathway lesions are not present, *especially if the process is occurring unilaterally*. Glaucoma is a jigsaw puzzle in which all the 'pieces' of the disease should fit. If a piece does not fit properly, the physician should be suspicious that it may belong to some other puzzle (disease). Generally, the configuration of the optic nerve and the appearance of the visual field correspond. Superior visual field defects are accompanied by erosion of the inferior portion of the optic disc and vice versa. The nerve in a patient with a temporal visual field defect should have a thinned nasal rim. Although normal-tension glaucoma may account for 10% or more of glaucoma patients, depending on definitions and the patient

Box 10-1 Some causes of nerve fiber bundle-associated visual field defects

Chorioretinitis
 Myopic retinal degeneration
 Refractive scotomata
 Trauma
 Retinal laser damage glaucoma
 Optic nerve ischemia
 Optic nerve compressive lesions
 Optic neuritis
 Drusen of optic nerve head

population being studied, IOP is elevated at some time in most glaucoma patients. If these factors do not occur in appropriate patterns, the possibility of glaucoma is not excluded, but the physician's suspicions should be heightened and a thorough evaluation should be undertaken to exclude other possible diseases.

ESTERMAN DISABILITY RATING

Assessment of disability resulting from visual field loss is often needed, although it can be difficult to quantitate. The American Medical Association (AMA) adopted the Esterman disability rating.^{1,28,29} This binocular assessment used by government and industry is described more fully in the *AMA Guides to the Evaluation of Impairment* and the *Physicians' Desk Reference for Ophthalmology*.

ANALYSIS OF COMPUTERIZED STATIC PERIMETRY

Computerized static perimetry provides numbers that represent the patient's responses to stimuli in various areas of the retina. These numbers can be manipulated mathematically and statistically to provide information about the reliability of patient responses and test results. Although not identical, Goldmann visual field plots and computer-generated grey-scale visual field patterns usually are similar (Fig. 10-14).

RELIABILITY INDEXES**False-positive and false-negative responses**

Reliability indexes usually include false-positive and false-negative responses and some analysis of fixation. *False-positive responses* occur when the patient indicates that he or she has seen a stimulus when one was not presented. This is usually a reaction to random noise generated by the perimeter. *False-negative responses* occur when the patient fails to respond to a stimulus that is at least as bright or brighter than one that he or she had previously recognized in that position. This indicates that the response was erroneous at least one of the two times that the position was tested. The lower the percentage of false-positive or false-negative responses, the more reliable is the test. False-positive or false-negative scores in excess of 20–30% indicate a test of questionable reliability.

Fixation reliability

Fixation reliability can be monitored in a number of ways. The technician can offer a subjective assessment of the patient's fixation reliability; the computer may stop the test if a video or infrared fixation monitor indicates that the eye has shifted; or the blind spot may be stimulated periodically (Heijl-Krakau technique) with a bright stimulus, anticipating that the properly fixing patient will not see it.

All of these techniques have flaws. It is difficult for technicians to see tiny fixation shifts, and only with considerable experience are they able to judge the shifts' effects on the test. In addition, it is practically impossible for a technician in a darkened room to maintain concentration on patients' eye movements all day long. Automatic fixation monitors that interrupt the test can be quite precise; however, most patients cannot fixate 'perfectly.'³⁰ Even the most attentive patient will have minor head and eye movements associated with breathing, heartbeat, etc. If the monitor is set to be very sensitive, the test will be prolonged by frequent interruptions. If the monitor is too insensitive, it has little value. Although constant monitoring is desirable, it is probably not necessary in most patients.³¹

The blind spot is not constant. Only one of eight to ten presentations is directed at the blind spot, so the computer has no way of knowing about the patient's fixation between those checks. If the computer incorrectly located the blind spot at the beginning of the test, subsequent checks might fall outside the real blind spot and give a false impression of bad fixation. If there is a large scotoma adjacent to the blind spot or a hemianopic field defect, fixation may be poor but the blind spot check will fall into the scotoma and falsely indicate good fixation.

Most patients either fixate well or poorly. Fixation behavior can be improved by encouragement from the technician, but the improvement may be small and inconsistent from test to test. Generally, the clinician needs to know the quality of fixation to help judge the accuracy of the field, and this can be provided by any of the preceding methods. Fixation losses exceeding 20% are considered poor in most circumstances, although the exact effect of such losses on the usefulness of the test is unclear and may vary substantially from patient to patient. Some studies have suggested that fixation losses up to 33% may still produce repeatable and reliable visual fields especially in an urban poor population.³²

FLUCTUATION**Short-term fluctuation**

Short-term fluctuation (SF) is measured by most computerized perimeters. This statistical analysis is the result of checking several loci in the visual field twice. The Octopus G-1 program tests each point in the central field twice. The variability that is noted between each of the double tests is reported as its root mean square and defined as SF. For most normal young subjects, overall SF is between 1.5 and 2.5 dB.^{33,34} Short-term fluctuation is affected by age and eccentricity from fixation. Although the overall SF printed on the field chart may be as high as 2.5 dB in normals, a fluctuation of 2.5 dB a few degrees from fixation in a young patient with clear media is unusual whereas fluctuation at 30° eccentricity in a normal 70-year-old individual may be 8 or 10 dB.^{35–37}

Short-term fluctuation is increased in glaucoma suspects,^{38–41} patients who cannot cooperate well for the test, and patients

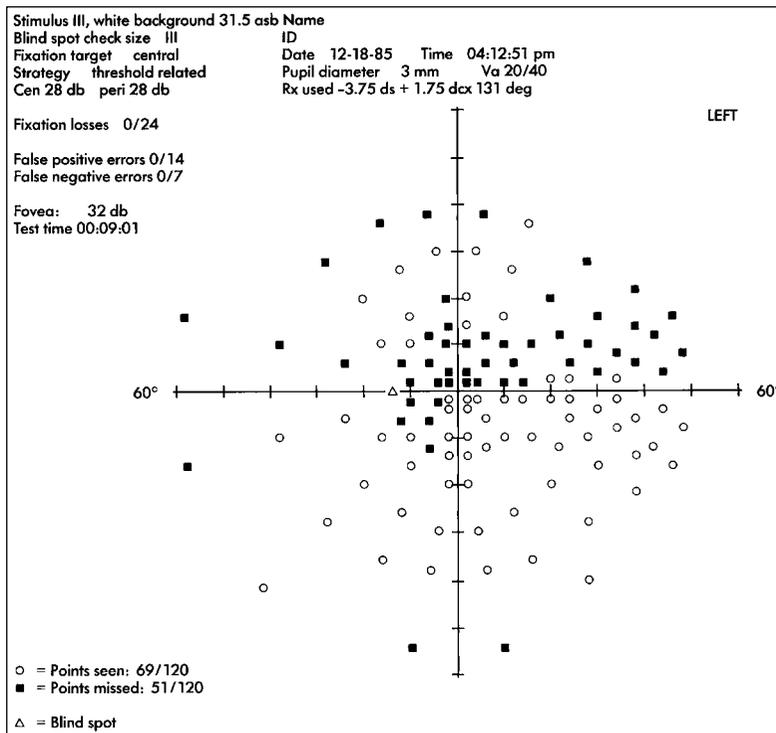
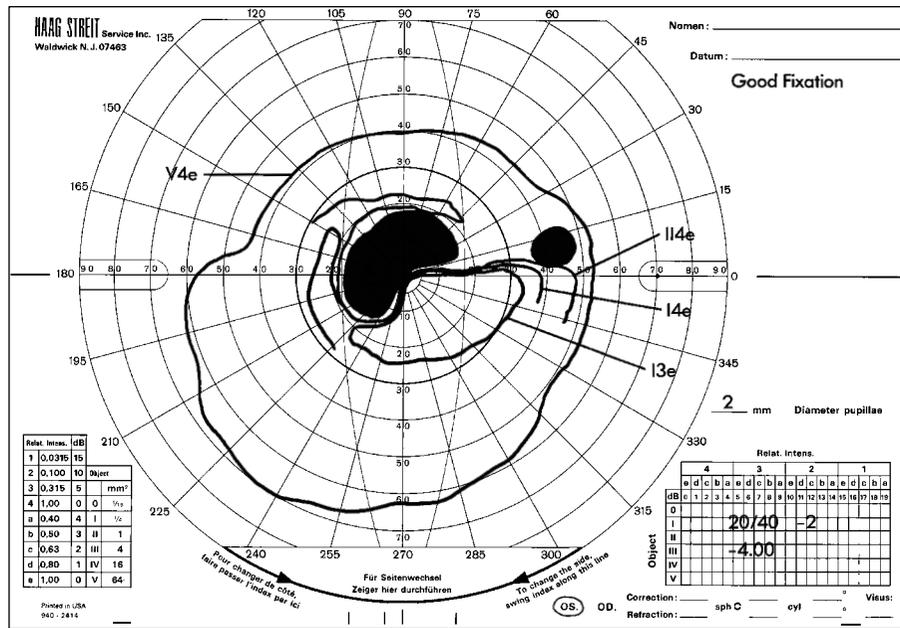


Fig. 10-14 (B) Goldmann perimetry (top) demonstrates an altitudinal type of defect with a large arcuate scotoma. A similar pattern is seen on the full-field suprathreshold screening test performed by the Humphrey perimeter (bottom). The black squares indicate areas of deficit.

who have decreased sensitivity in areas of the visual field.^{42,43} It is increased dramatically in patients with significant field loss. Heijl and colleagues found SF in glaucoma patients to range between 8 and 18 dB.⁴⁴ This indicates that points within the central field can lose and regain as much as half of their sensitivity between examinations due to SF alone.

Short-term fluctuation also provides a guideline for the amount of deviation required to indicate that the amount of depression exceeds the variability inherent in the test. At the 95% confidence

level, this approximates two times the SF (roughly equivalent to two times the baseline noise). Thus, as a general rule, a deviation should exceed about 5 dB to be considered abnormal.⁴⁵ This rule has several important exceptions, however. Because normal variation in the parafoveal region is much less than that in the mid-periphery, deviations smaller than 5 dB can represent significant reproducible pathology when they occur near fixation. Conversely, as mentioned above, a deviation of 10 dB or more may occur at 30° in a normal middle-aged patient. In addition to the age of the

patient and the location of the test point, the status of surrounding points can help determine whether a small deviation is significant. A mildly depressed point has a greater likelihood of being pathologic if its neighboring points are also depressed.^{36,37}

Fluctuation also increases locally in areas of reduced sensitivity.¹³ There are several possible explanations for this. It is well known that an area of inconsistency often precedes a permanent depression with Goldmann perimetry. Inconsistent responses on Goldmann perimetry appear as increased fluctuation on computerized automated perimetry. Another explanation is that the nature of the test for fluctuation – repeating the test twice during the examination – means that different areas of the field may be tested because of a small fixation shift. In an area of pathology, the second test can examine a slightly different area that legitimately has different sensitivity. The machine compares the first and second tests and indicates the difference between them as SF.

Long-term fluctuation

Long-term fluctuation is that which occurs between two separate visual field tests. This is discussed further in the section on recognition of change, p. 122–125.

GLOBAL INDEXES

Global indexes, which reflect the results of the visual field examination, are mathematic summaries of the actual sensitivity data produced by the examination (Figs. 10-15 and 10-16).

Mean sensitivity

Mean sensitivity is the average of the patient's responses for all of the points tested.

Mean deviation or defect

Mean deviation or defect (MD) is the measurement of how the mean of the patient's responses varies from the mean of the responses of a series of normal patients of similar age under similar testing conditions. It is a statement of the generalized depression of the visual field and is useful in recognizing early diffuse visual field loss in glaucoma. Although the MD can be decreased with local defects as well as general ones, there is no way to distinguish large local defects from generalized ones just from the MD (Fig. 10-16A.)

Standard deviation or variance

The standard deviation of the mean of the patient's responses is the same as the square root of the variance. The Humphrey perimeter analysis program reports standard deviation (pattern standard deviation, **PSD**), whereas Octopus reports variance (loss variance, **LV**). Each is a measurement of the variation in responses across the visual field. Normal patients have a small standard deviation, indicating a 'smooth' surface to the hill of vision. A high standard deviation or variance indicates an irregular surface to the hill of vision and may be indicative of localized visual field damage.^{33,40,42} These indexes can be corrected by SF and then are labeled as *corrected* (i.e., *corrected* pattern standard deviation, **CPSD** or *corrected* loss variance, **CLV**). When the indexes are corrected, they become more sensitive to recognizing true localized defects in the visual field because the variability caused by SF is removed.

GRAPHIC PLOTS

One of the greatest values of computerized perimetry lies in the ability of the computer to analyze the numeric data and present

MD:	-23.20 dB	P < 0.5 %
PSD:	11.08 dB	P < 0.5 %
SF:	5.90 dB	P < 0.5 %
CPSD:	8.85 dB	P < 0.5 %

Fig. 10-15 Detail of visual field indexes from Humphrey field analyses. MD, mean deviation; PSD, pattern standard deviation; SF, short-term fluctuation; CPSD, corrected pattern standard deviation. *P* values indicate the likelihood that values are normal. These values are severely disturbed.

them graphically for easier comprehension. The grey-scale printout of the Octopus was the first of these. Printouts that show variation from normal are widely available today (Fig. 10-17). The Humphrey STATPAC analysis printout includes probability maps that allow quick assessment of the likelihood that a response is disturbed. Patterns of disturbed points are easily detected. These printouts can also be adjusted for generalized depression so that scotomata are more obvious. This latter function is especially useful for follow-up of patients with glaucoma and other causes of generalized depression such as constricted pupils or cataracts (Figs 10-18 and 10-19).

AREA OF THE VISUAL FIELD TO BE TESTED

Most computerized perimeters measure the threshold sensitivity of 56–72 locations in the central 24–30°. Flammer and co-workers⁴⁶ and Jenni and co-workers⁴⁵ developed the G-1 program to focus more attention on the areas of particular interest in glaucoma (see Fig. 10-10).

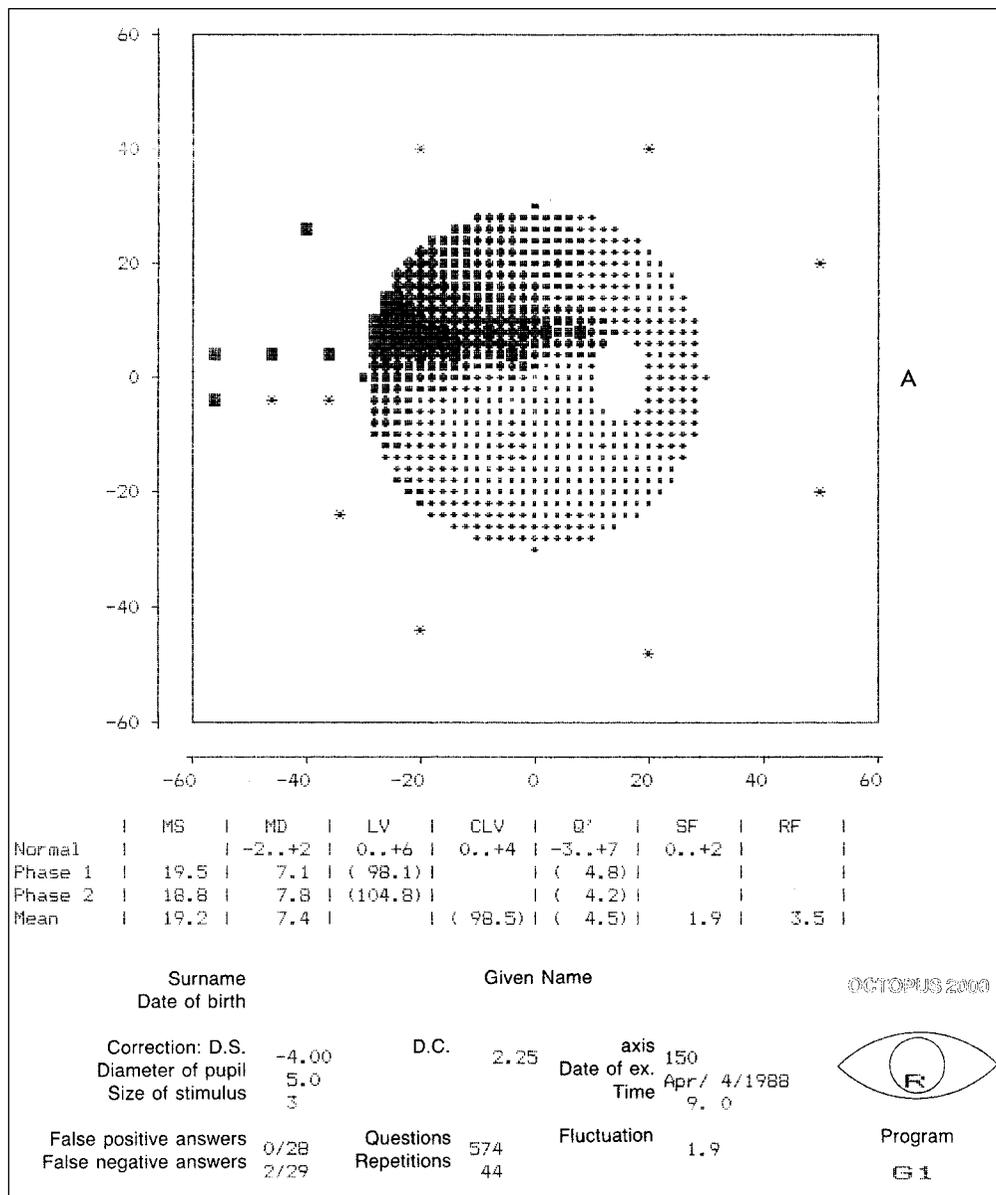
LONG-TERM ANALYSIS

By selecting a series of similar tests, computerized perimeters can analyze the results over time to evaluate whether the visual field is changing. This may be accomplished by linear regression or *t*-test techniques.⁴⁷ Even with these methods, however, several visual fields of good reliability from the same eye are needed to analyze change well. Trying to recognize change from fewer fields is fraught with hazard and requires a large amount of change.^{48,49} This is discussed further in the section on recognition of change, pp. 122–125.

DETERMINATION OF NORMAL VISUAL FIELD

Evaluation of the visual field in glaucoma patients or glaucoma suspects attempts to answer two important questions: is the visual field abnormal (detection), and has it worsened (progression)?

There are three basic ways by which the physician can determine whether the field is abnormal: (1) by recognizing deviation from normal values; (2) by recognizing variation between two eyes of the same patient, and (3) by establishing significant variation within the given field. Several of the computerized machines have analysis programs that will indicate abnormalities by graphic plots or by a written phase.^{36,37,50,51}



(A)

Fig. 10-16 (A) Grey-scale printout of the Octopus G-1 program indicating an upper arcuate defect in the right eye. Global indexes are printed below the grey-scale plot.

DEVIATION FROM NORMAL VALUES

There are no published normal values for Goldmann perimetry. This is probably because results vary widely from technician to technician and from technique to technique. Certain guidelines, however, are helpful. Generally, the I2e isopter falls between 25° and 30°. The I4e isopter usually falls between 40° and 50° nasally. In the absence of lens opacity in patients older than 75 years of age, these isopters may contract 5° or so. Contraction may be greater in the presence of cataracts.

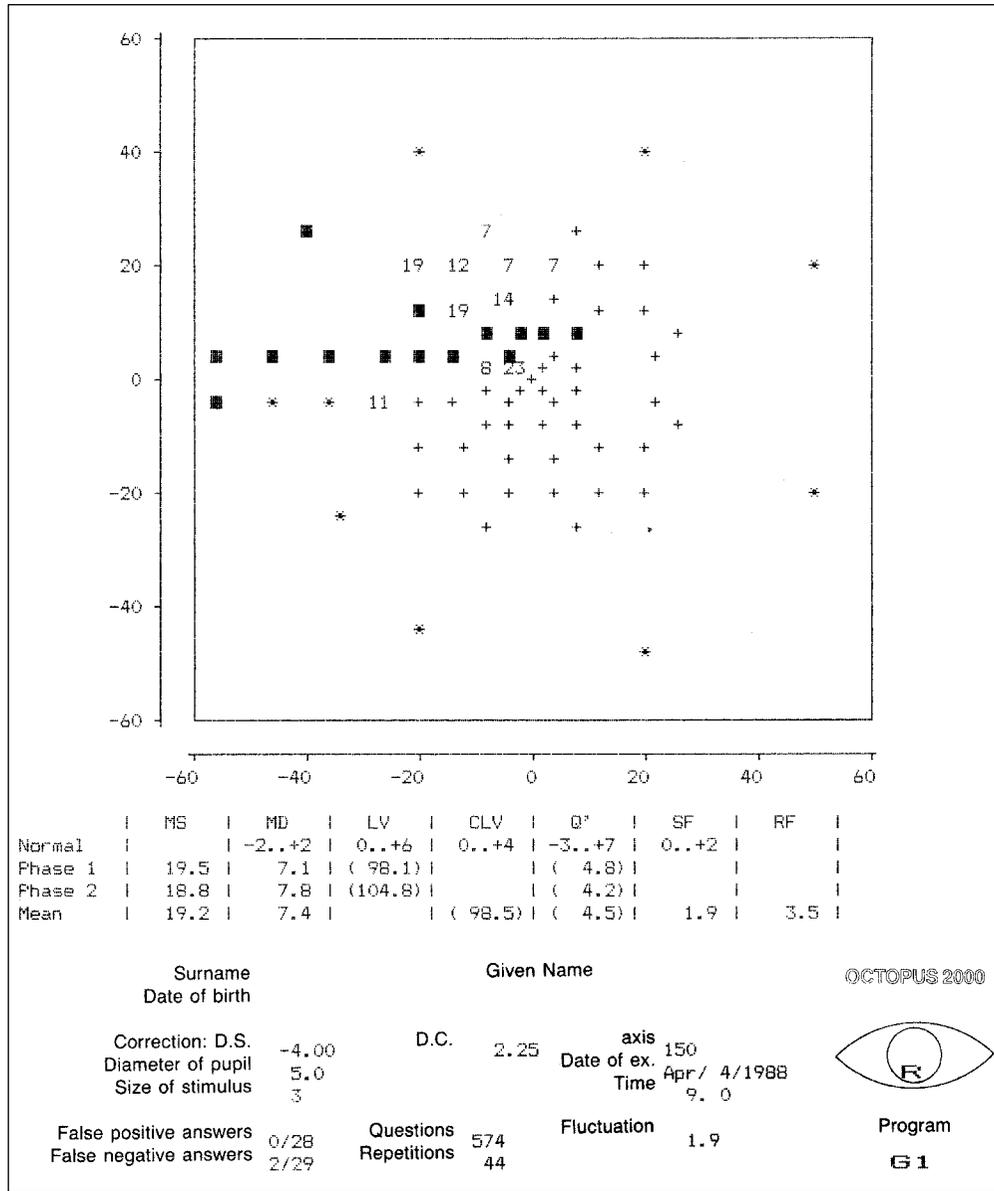
Graphic plot of points varying from normal

The Humphrey and Octopus perimeters have age-matched normal values stored in their computer memories for each point

tested. The Humphrey perimeter provides the deviation from normal in a graphic printout through its STATPAC program.⁵² For each point tested, STATPAC provides the statistical probability that the patient's threshold would be found in the normal population (Fig. 10-20). The Octopus program provides a printout of how many decibels a point deviates from the norm for that age (see Fig. 10-17). Regardless of the technique used, it is unwise to depend on one or two deviant points within a field to indicate abnormality unless they are severely depressed or contiguous.

Global indexes

Measurements of single points are more likely to contain error than are averages of measurements of all points within the visual field. Therefore global indexes are helpful in recognizing deviation from



(B)

Fig. 10-16 (B) Raw data provided by the G-1 program. The crosses indicate normal spots, the black squares indicate absolute defects, and the numbers represent depth of defect in decibels. MS, mean sensitivity; MD, mean defect; LV, loss variance; CLV, corrected loss variance; SF, short-term fluctuation; RF, reliability factor (the ratio of false-positives and false-negatives expressed as a percentage).

normal. The Octopus MD may be statistically abnormal with less deviation from normal than that required for a single point. For the Octopus, 95% of the population will fall within 2 dB of the normal mean sensitivity provided on the Octopus printout.³⁸ By contrast, an individual point may need to be depressed two to three times this amount to be even mildly suspicious. The Humphrey printout provides a table indicating the lower 5% probability of normal for each of the global indexes. Deviations greater than these may be abnormal. The greater the deviation, the greater the likelihood that it is abnormal.

Comparison with the other eye

Published data⁵³ indicate that the mean sensitivities of the two eyes fall within 1 dB 95% of the time and within 1.4 dB 99% of

the time. Therefore unexplained variation of mean sensitivity between the two eyes greater than 1 dB would be suspicious, and greater than 2 dB may be abnormal. If the lower sensitivity occurs in the eye with higher IOP or greater excavation of the optic nerve head, it would be highly suspicious of glaucomatous visual field loss.⁵⁴

Localized variation within the visual field

Localized depression within the field may not be enough to cause a statistically significant reduction of mean sensitivity or be deep enough to be recognized by the computers as an increased MD. However, one of the most important types of early change in glaucoma is mild inconsistent depression in the paracentral area.^{9,55}

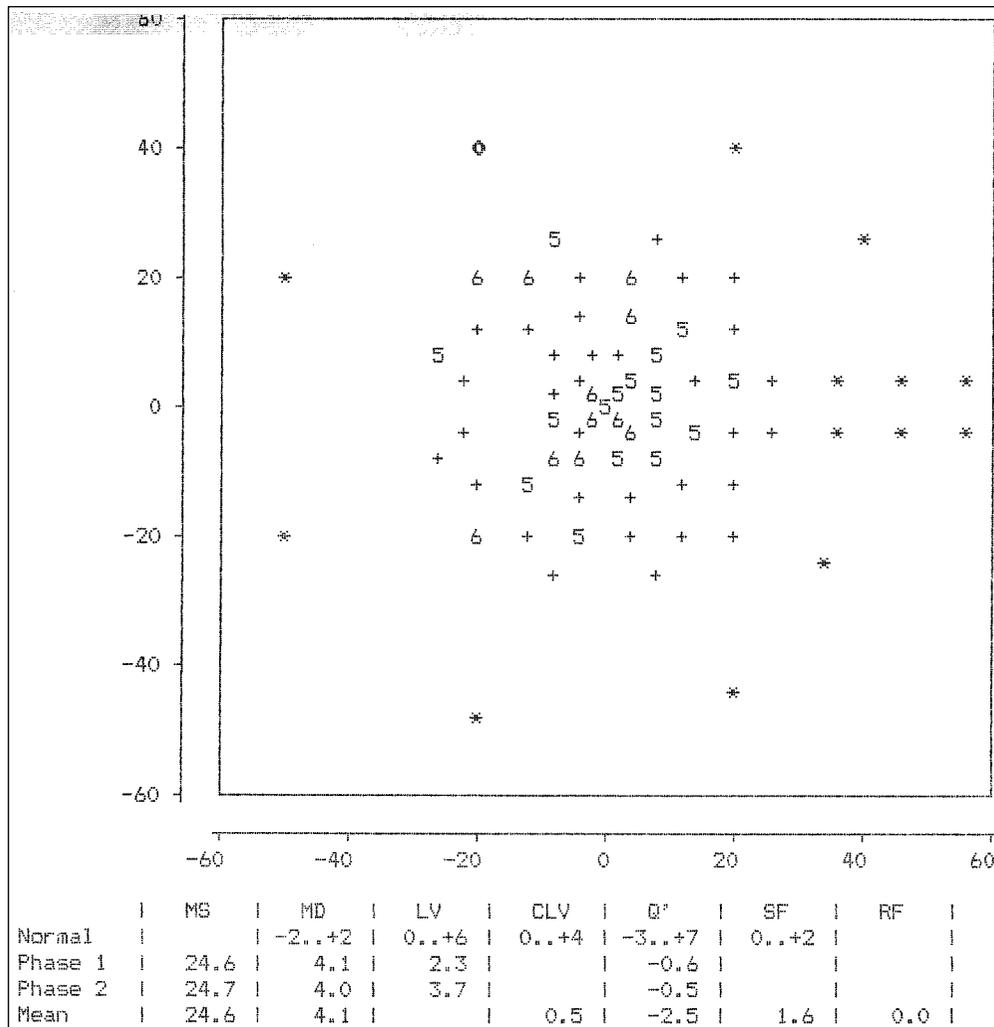


Fig. 10-17 Printout from the Octopus G-1 program showing a subtraction scale plot. Numbers represent depth of the defect at the corresponding point.

Careful examination of the raw data may show a small cluster of points that vary from their neighbors by no more than 2 or 3 dB. These may be early visual field defects. The Humphrey corrected pattern standard deviation and the Octopus corrected loss variance are designed to highlight these defects statistically (Fig. 10-21). Occasionally such deviations may be so subtle as to fail to reach statistical significance. Katz and Sommer⁵⁶ suggest comparing the upper and lower hemifields for earlier recognition of glaucomatous change based on evidence that change in one hemifield precedes change in the other.

It is often difficult to be certain that minor changes in the visual field represent true deviations from normal. Minor change in an eye with other suspicious findings, such as increased IOP or optic nerve cupping, lends them credibility. Persistence on repeated examinations often confirms them.

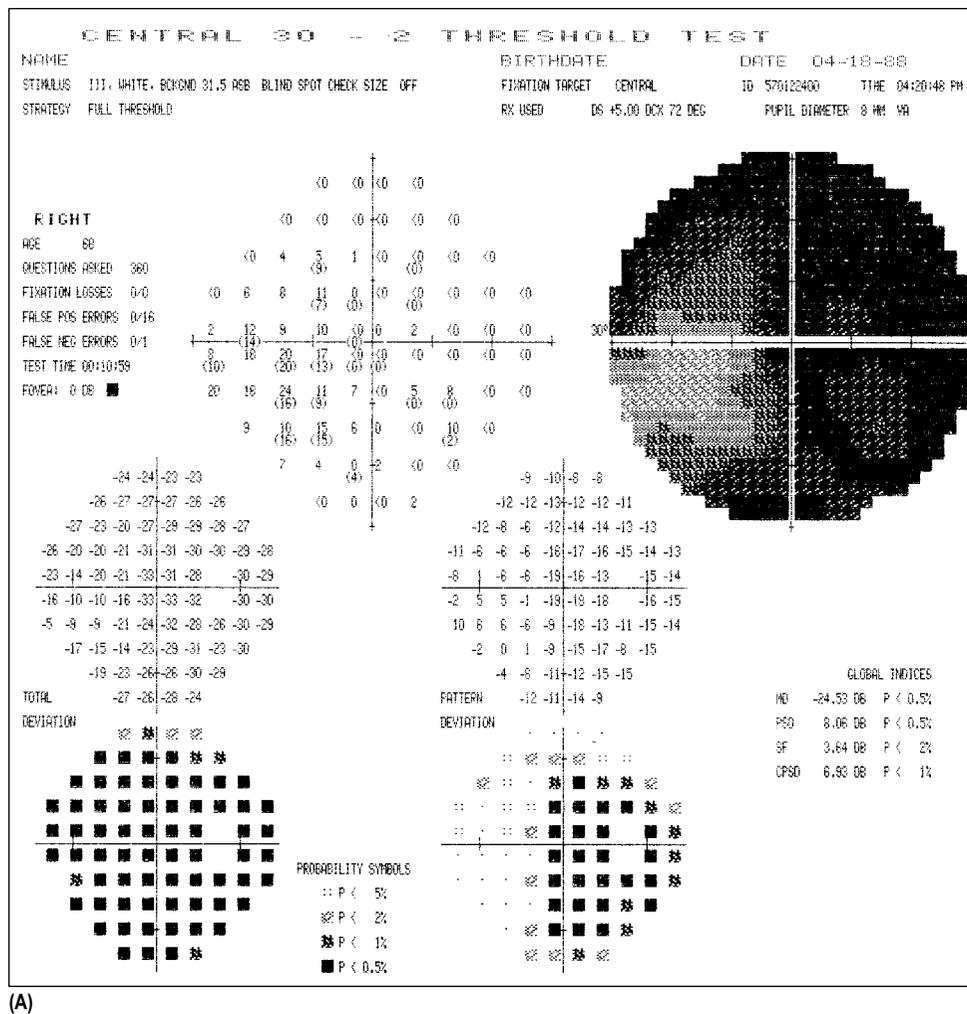
RECOGNITION OF CHANGE

Change from one field to another is difficult to determine because of the fluctuation that occurs within and between tests. This is particularly important in patient with defective fields, because of

the increased fluctuation seen in these circumstances. Several studies have indicated that fields must be repeated half a dozen times or more to confirm an abnormality.⁵⁷ The Ocular Hypertension Treatment Study found that a newly recognized glaucomatous visual field defect in an ocular hypertensive patient was MOST likely NOT to be repeatable or confirmable.⁵⁸ In fact, in that study, over 80% of the the visual fields showing a first abnormality after multiple normal visual fields could not be confirmed on subsequent testing. Furthermore, of those whose visual field tests were abnormal on at least two successive occasions, the third visual field was normal over 60% of the time. Only after three successive visual field tests were abnormal was it likely that the abnormality was real and would persist in further testing.⁵⁹

With Goldmann perimetry, areas of isopters within the central 30° were found to fluctuate by as much as 30% between tests in patients whose glaucoma was apparently controlled.⁶⁰ As described previously, computerized perimetry suffers from the same problem (Fig. 10-22), but the amount of inter-test variation is reduced by the administration of a more standardized test. Also, the amount of fluctuation can be measured easily and analyzed both for populations and for individual patients.

To address this problem, investigators have assembled large databases of normal and glaucomatous patients to aid the examiner, by



(A)

Fig. 10-19 Bitemporal hemiopia. **(A)** Right eye. **(B)** Left eye. The grey-scale image (upper right) could be misinterpreted as advanced glaucomatous visual field loss. The total deviation pattern (lower left) indicates marked generalized depression. The pattern deviation (lower right), however, demonstrates a hemiopic defect. The right eye has such poor vision that the patient's fixation shifted slightly to the left, which explains the overlapping of the vertical meridian.

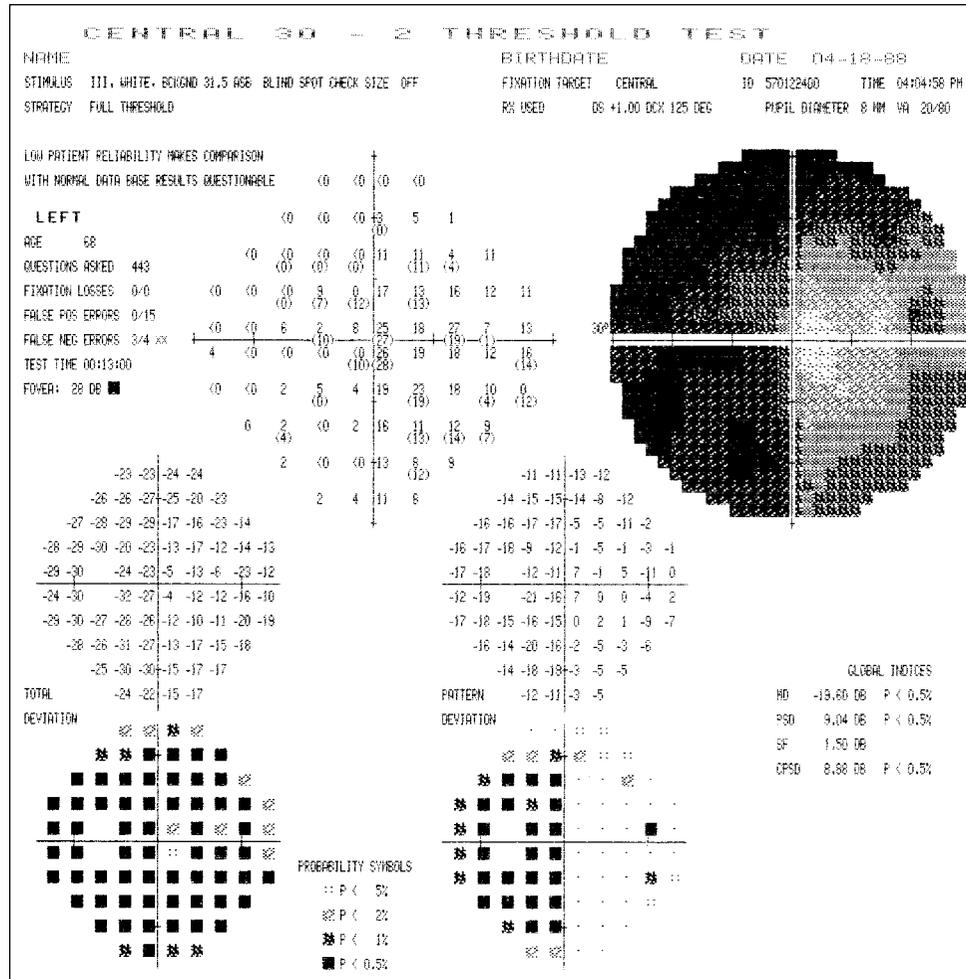
that the disease exists may be higher or lower than the prior probability. With an accurate and appropriate test, the disease may be ruled in or out by the results. A patient with a very large cup:disc ratio and high pressures who shows a Bjerrum scotoma on visual field testing is easy to diagnose. This occurs when the prior probability of the disease is high and the test results are pathognomonic.

As the prior probability becomes lower and the test results less definitive, small irregularities in the test results become more worrisome. It is under circumstances like these that visual field examinations may have to be repeated several times to improve accuracy and reduce fluctuation. One of the potential techniques is to establish a baseline from the averaged results of three visual field tests performed approximately a few weeks apart. If subsequent fields, as compared by *t*-test, vary from this baseline, two additional fields are performed and averaged with the follow-up field. The average of the baseline visual fields is then compared with the average of the follow-up fields by *t*-test, and smaller deviations can be recognized as statistically significant because there are more observations (see Fig. 10-3).⁵⁴ This works well in experimental situations or for long-term patients for whom there is already a wealth of data, but it is impractical in a busy or managed care clinic where the luxury

of testing a patient half a dozen times or more within several weeks may not exist.

A second technique is to perform linear regression analysis of the visual fields over time.⁶² This technique incorporates fluctuation into the analysis and recognizes a series of visual fields whose means produce a slope that is significantly different from zero. If the slope is negative, the field may be deteriorating. At least five observations (visual field examinations) are needed for such analysis, and more observations are better. Nouri-Mahdavi and colleagues showed that pointwise linear regression was at least as good as other techniques such as the AGIS in detecting change.⁶³ However, pointwise linear regression may not be quite as sensitive as the change probability function in very early glaucoma.⁶⁴

There are a host of other techniques to manipulate and display the data from the patient's test to help the examiner reach a conclusion. One of the more popular of these is the probability map and pattern deviation printout on the Humphrey machine (see Fig. 10-20). The probability maps compare the patient's response at each point to a large age-matched control group. If the patient's response falls within a range that encompasses 95% of normals, a small dot is printed on the field chart at the test point. If less than



(B)

Fig. 10-19 Continued.

5% but more than 2% of normals generated a response as low as the patient, a different, more dense, symbol is printed. The darkest symbol is used if less than 1 in 200 normals had a value as low as the patient's. Because the points are tested in pseudorandom order, contiguous points with similar levels of depression are highly significant. Sometimes it is important to separate generalized loss, such as that caused by cataract, from localized loss, which is more often seen with moderate glaucomatous damage. The pattern deviation (not to be confused with the pattern *standard* deviation) of the Humphrey is a method to assist with this interpretation. The pattern deviation essentially subtracts generalized depression from the field to compensate for developing media opacities (see Fig. 10-1). The physician must judge whether this depression is due to glaucoma or has some other cause. The precise manipulation performed by the computer to produce the pattern deviation plot is quite complicated, but the resultant printout is very easy to read. Zeiss-Humphrey has released 'Glaucoma Progression Analysis' software which is based on visual field data from the Early Manifest Glaucoma Trial; the software uses the range of variation of individual points in stable visual fields of subjects in the trial as the basis for determining if the change in any given point exceeds the variation of stable visual fields and calculates a probability of that point having truly

progressed. This software has, to date, not had any published studies validating its premise. However, it does promise some help in determining if any given point is likely to be progressing.

An additional widely used method of comparing serial visual data is to compare visual field indexes over time. A patient who has a steadily increasing corrected loss variance (CLV) on the Octopus (or CPSD on the Humphrey) may have a subtle deepening of his or her scotoma. The field should be repeated, perhaps several times, depending on the level of pathology and the degree of glaucoma control indicated by the remainder of the history and physical examination.

QUANTIFYING VISUAL FIELD CHANGE

Several large multi-center collaborative studies have examined various approaches to glaucoma management over recent years. All of these studies include visual field testing as at least outcome measurement or end point in the follow-up of glaucoma patients. The Advanced Glaucoma Intervention Study (AGIS), Collaborative Initial Glaucoma Treatment Study (CIGTS), Ocular Hypertension

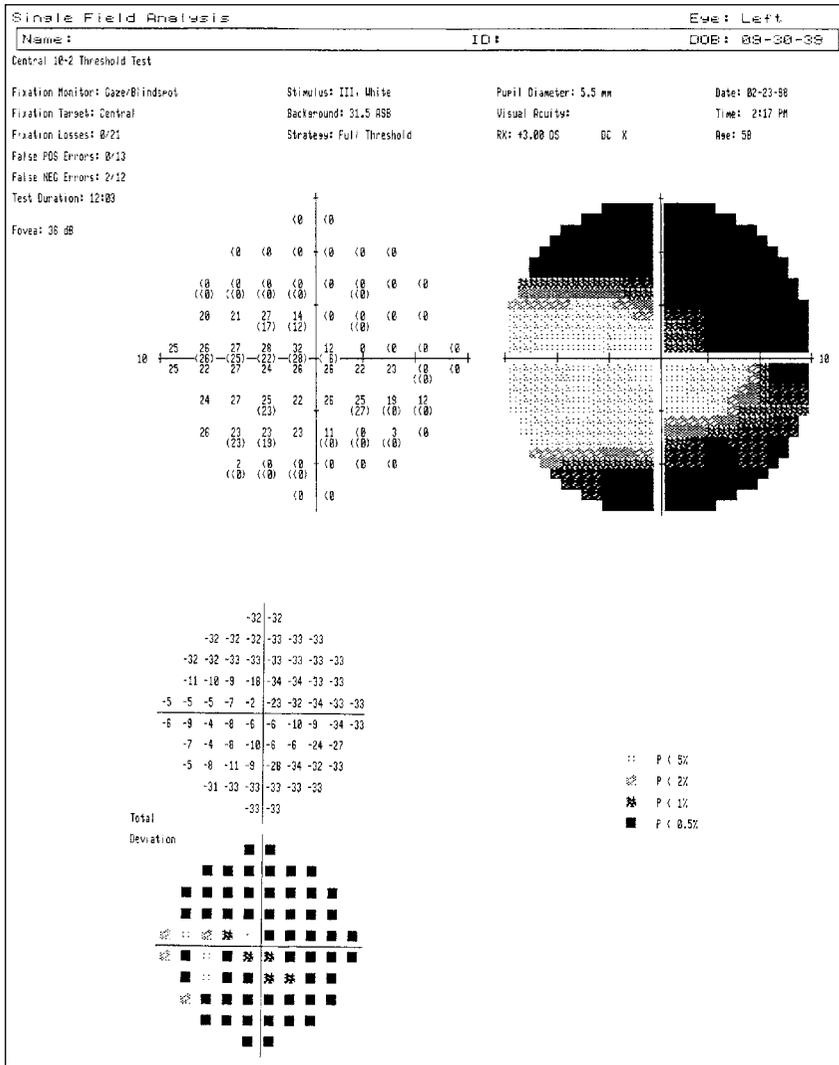


Fig. 10-20 Humphrey STATPAC with probability map. The upper numerical printout represents sensitivity measured during the test. The lower numerical printout represents deviation from normal. Symbols represent the likelihood that measured points are within normal limits, according to the key at the lower right.

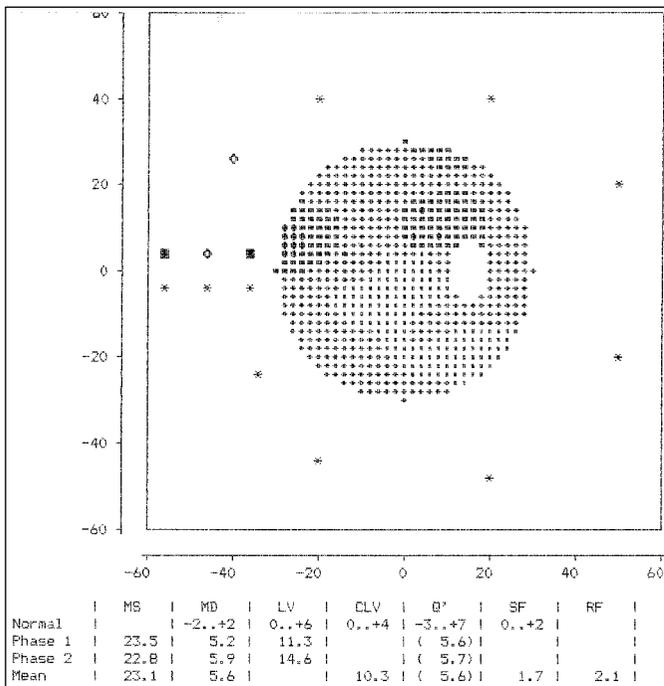


Fig. 10-21 Subtle superior peripheral nasal step and a subtle superior Seidel's scotoma in the right eye of a patient with normal-tension glaucoma. Note the slightly elevated mean defect (MD) and moderately elevated corrected loss variance (CLV), which help alert the physician to the presence of an abnormality.

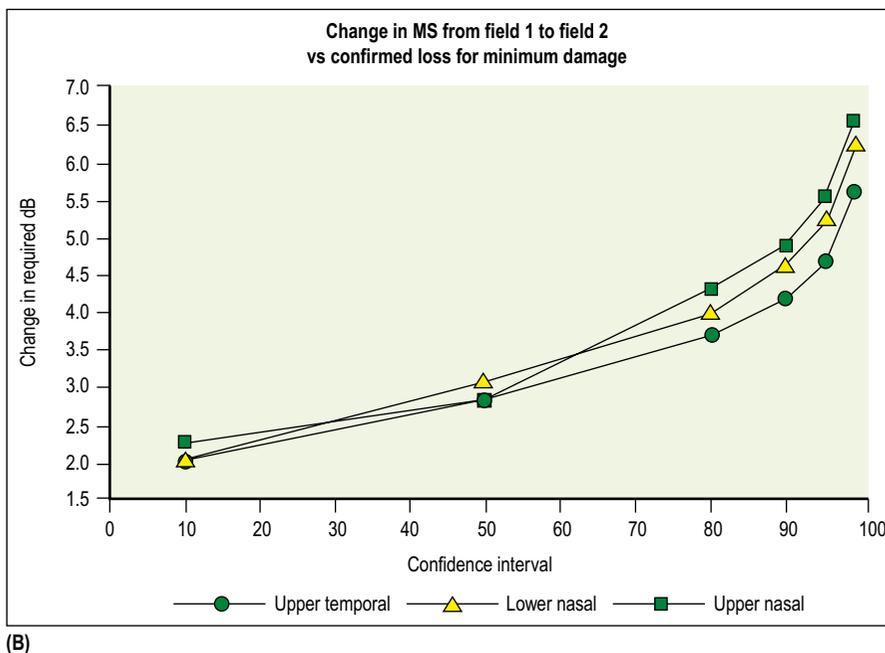
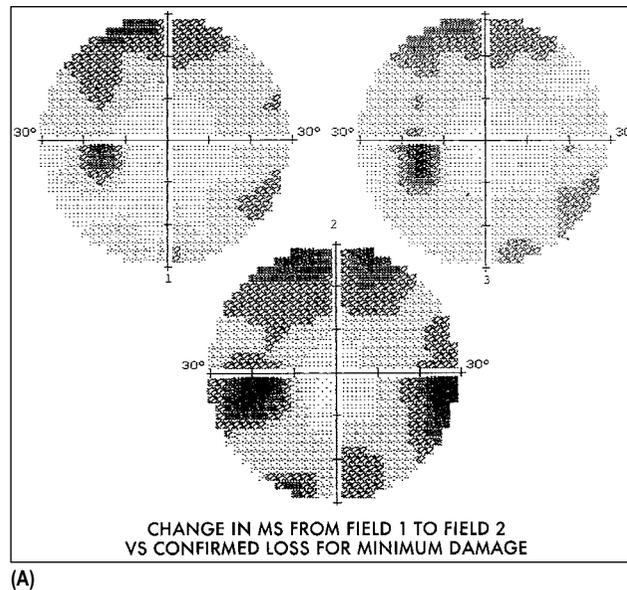


Fig. 10-22 (A) These three visual fields were performed approximately 4 months apart. The second field (bottom) shows apparent worsening compared with the first and third fields, which appear quite similar. This amount of fluctuation is not uncommon in glaucoma patients. **(B)** Confidence level of change between the two fields. To obtain 95% confidence levels, the change in the portion of the field under study must be at least 5–7 dB when comparing two fields. UT, upper temporal; LN, lower nasal; UN, upper nasal; IB, interior Bjerrum. (From Hoskins HD Jr, Magee SD: A system for the analysis of automated visual fields. Paper presented at the Seventh International Visual Field Symposium of the International Perimetric Society, Amsterdam, September 7–10, 1986.)

Treatment Study (OHTS) and other studies have developed visual field scoring plans that assist clinicians as they follow patients with newly diagnosed or progressive glaucoma.

The AGIS was designed to determine the better of two surgical management strategies for glaucoma that continued to progress despite medical therapy. The investigators developed a scoring system based on the number and depth of clusters of adjacent depressed test sites in the upper and lower hemifields and the nasal field, measured with the Humphrey Field Analyzer 24–2 program.⁶³ The STAPAC Total Deviation plot is used to determine defective points. Depending on its location in the field, a test point must deviate from -5 dB to -9 dB to be considered depressed. Central and inferior test points are considered depressed at lower values than superior and peripheral test points. For the nasal field, the scoring system assigns one point if there is an isolated nasal step defect with one or two contiguous depressed points above or below the horizontal without a reciprocal depression, or if there are

three or more contiguous depressed points but less than half of the nasal test points are depressed by 12 dB. It assigns two points if there are three contiguous depressed points and more than half of the nasal test points are depressed by 12 dB. The nasal area can generate a score of zero: no qualifying abnormality; 1: moderate abnormality, or 2: severe abnormality. In the remaining superior and inferior hemifields, clusters of three or more contiguous depressed points are identified and counted. Three to five such clusters generate a score of 1, six to twelve a score of 2, thirteen to twenty a score of 3, and more than twenty a score of 4. If half or more of the depressed points are depressed between 12 dB and 15 dB, an additional point is added, 2 points if depressed 16–19 dB, 3 points if 20–23 dB, 4 points if 24–27 dB, and 5 points if more than half of the depressed points are depressed by >28 dB. Each hemifield can generate a maximum score of 9 points. The AGIS scoring system has a range from 0 (no qualifying defects) to 20 (all points depressed severely). A reliability score is also generated, ranging from 0, very reliable, to 7, not at all

level and 4 points for the 0.5% level. If more than two adjacent sites are depressed, points are assigned based on the two most depressed neighbors. As with the AGIS scoring system, the two points above and below the blind spot are excluded, resulting in a total of 52 scored test sites per exam. The raw score ranges from zero in a normal field to 208 in a totally, severely depressed field. The raw score is divided by 10.4 to generate a scale score of zero to 20, which is comparable to the score used in the AGIS system.

The OHTS uses a visual field abnormality detection strategy that was modified from one used in the Optic Neuritis Treatment Trial (ONTT).⁶⁵ Because the OHTS was initiated to determine whether lowering the IOP of ocular hypertensive glaucoma suspects would prevent or delay the onset of structural or functional glaucomatous abnormalities, all patients entering the study were required to demonstrate normal visual fields before randomization. The visual field assessment strategy used in follow-up was designed to detect initial visual field loss. This contrasts with the visual field strategy used for AGIS or CIGTS which were developed to monitor change in already defective fields. For OHTS, the entry criteria specified normal results for the standard visual field indexes measured by the Humphrey Field Analyzer STATPAC-2 using a 30-2 program. These indexes are the MD, PSD, CPSD, and GHT. Fixation losses, false positive, and false negative responses were limited to 33%. This is a slightly more relaxed allowance for fixation losses than the 20% which is standard for STATPAC-2, but this more relaxed level did not compromise the reproducibility of the field tests and reduced the number of qualifying examinations required to enroll subjects. Study end points for OHTS patients were either a GHT outside normal limits, a CPSD $P < 0.05$, or both. Confirmation of an end-point defect required at least two repeat field examinations which revealed the same abnormality at the same test site.⁶⁶

As of this printing, no single technique of determining progression works all the time or for all patients. The AGIS criteria have stood the test of time and have been validated in other countries as well as the USA.⁶⁷

THE FUTURE OF COMPUTERIZED PERIMETRY

Although in its present form computerized perimetry may not always offer a diagnostic advantage over meticulously performed combined kinetic and static manual perimetry,⁶¹ the consistency of computerized perimetry provides less variation in technique over time than does manual perimetry. In addition, only the very best technicians can hope to equal or surpass the current generation of computerized machines. The average human is really no match for the computer in this realm. Computers also offer rapid statistical data analysis, graphic presentation of results, and simplified storage and retrieval of data. All of these factors make computerized perimetry the standard method for assessing the visual field.

As more and more patients are followed up over a longer time, ophthalmologists are gaining a better understanding of what represents true glaucomatous change in the visual field.^{35,49} By increasing the frequency of field examinations, more data points will be available and the time needed to recognize incremental change will be reduced. This will help physicians initiate and change therapy sooner and should reduce the number of patients who progress to blindness from glaucoma.^{47,68} In patients whose glaucoma is poorly controlled or who have central fixation threatened, three or four well-standardized visual field examinations per year will demonstrate progression of the disease earlier than any other currently available technique.

Perimetric software such as the Swedish Interactive Thresholding Algorithm program offered by Humphrey promises to make perimetry faster and more acceptable to patients. Artificial intelligence or pseudoartificial intelligence will allow the machines to refine the information they gather from the patient and to make more accurate diagnostic suggestions.^{69,70} The hope is that we can improve the predictive or confirmatory value of visual field testing and thus improve our ability to diagnose and follow glaucoma.

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Other psychophysical tests

INTRODUCTION

Glaucoma diagnosis and monitoring require assessments of both structure and function of the optic nerve and ganglion cell layer. The traditional tests of these parameters for the past half century or more have been structurally through ophthalmoscopy or photography and functionally by white light perimetry – either kinetic and, more recently, threshold static. Over the last few decades, these tests have been improved via computerized automation and/or laser-assisted quantitative structural analysis. Yet, the testing of both structure and function leave something to be desired. The assessment of structure by ophthalmoscopy and by stereo photography is subjective and varies greatly even among experts.¹ Newer modalities of evaluating the optic nerve and ganglion cell layer using lasers and computerized analysis have greatly improved the subjectivity of this type of testing (see Ch. 14).

The ‘gold standard’ of modern functional assessment is automated threshold white-on-white perimetry (see Chs 9 and 10). While this type of testing is a big improvement in sensitivity, specificity, and repeatability compared to kinetic perimetry, significant problems are still present. Problems with this modality include tediousness for the patient, a significant learning curve, great variability even in experienced subjects from test to test, difficulty with interpretation, and difficulty detecting both early damage and early progression (Box 11-1).^{2,3}

One of the biggest problems with standard automated white-on-white threshold perimetry (SAP) is that it often does not show an abnormality until between 25% and 50% of the ganglion cells have

been lost.⁴ In trained glaucomatous monkeys, about 50% ganglion cell loss must occur before significant white-on-white perimetric loss is seen.⁵ Thus, sensitivity of SAP to early glaucomatous damage is fair to poor. For some time now, researchers have been attempting to identify visual functions that may be more sensitive to early damage, either because the tests would be inherently more sensitive or because they target a subset of ganglion cells that by being fewer in number may have their specific function disturbed earlier than the more general functions of the total mass of ganglion cells.

There are several types of ganglion cells. Initially, it was thought that certain ganglion cells are damaged earlier in the glaucomatous process than other types.⁴ However, more recent studies suggest that all ganglion cells are damaged or killed by glaucoma but that some types of ganglion cells have less redundancy (fewer partner cells to cover for them if they become injured).^{6,7} Therefore, if a test can be targeted at ganglion cell functions that have little redundancy, the hope is that these functions will be affected early in the process. Short-wavelength automated perimetry (SWAP) and frequency-doubling technology (FDT) are two such tests (Fig. 11-1).

Another strategy is to find tests that have less noise (more reliable first tests with less variability between tests) than white-on-white (monochromatic) automated threshold perimetry. High-pass resolution perimetry and FDT are examples of this approach. Finally, attempts are being made using modern computer algorithms to either reduce the noise and variability or to better interpret from the standard test what is real and what is noise. The Swedish Interactive Test Algorithm (SITA) is one example of the former; neural network interpretation and the Glaucoma Progression Analysis (GPA) (Zeiss-Meditec, Dublin, CA) are examples of the latter. This chapter will discuss the most developed of these technologies, including SWAP, FDT, high-pass resolution perimetry, multifocal visual-evoked potential and multifocal electroretinogram. For a discussion of SITA and GPA, see the preceding chapters.

Box 11-1 Problems with automated threshold perimetry

- Tedious
- Not all patients can perform reliably
- Difficult for very young and for elderly
- Instructions may be difficult for those not speaking the same language
- Time-consuming
- Device not portable
- Requires darkened and secluded environment
- Needs supervision
- Not suitable for mass screening
- Variability from test to test
- Significant learning curve
- Not sensitive to early glaucoma
- Difficult to detect progression
- Cataract or other media opacity may confound results

COLOR VISION AND SHORT-WAVELENGTH AUTOMATED PERIMETRY

As understanding of the differential functions of the several types of ganglion cells became known, tests began to be developed that were targeted at specific ganglion cell functions that might have less redundancy than white-on-white perimetry. That color vision is affected in the glaucomatous process has been known for many decades.⁸ Acquired optic nerve disease affects the blue-yellow end of the spectrum as well as the red-green, whereas inherited defects tend to be limited to the red-green. So tests that include the

blue-yellow end of the spectrum will be more specific for glaucomatous damage.

While cones are scattered throughout the retina, most are concentrated in the macula and surrounding area. Clinical color vision tests, either by design or accident, usually involve only the central cone-concentrated portion of the retina. The most commonly used color vision test is the Ishihara which does not effectively test the blue-yellow spectrum. Color vision tests that have been associated with early glaucomatous damage do evaluate, at least to some degree, that end of the spectrum and include the anomaloscope, Hardy-Ritter-Rand color plates, Farnsworth D-100, and Farnsworth D-15.⁸ Several studies have shown that color vision defects as demonstrated by these tests appear early in glaucoma, and may even precede defects seen on white-on-white perimetry which has been considered the gold standard for glaucoma diagnosis.^{9,10} Unfortunately for the clinical usefulness of color vision tests, these instruments are insensitive, non-specific, too time-consuming or too difficult to interpret.^{8,11}

It has been known for more than 80 years that the defects associated with acquired optic nerve disease such as glaucoma could be amplified on the tangent screen by using colored test objects as compared to the standard white test objects. However, tangent screen color testing was even more variable and dependent on ambient illumination, technical skill, and cleanliness of the test objects than white-on-black tangent screen testing. So, even though color vision is largely a central retinal function, enough color perception remains in the periphery to allow color perimetry. The Goldmann perimeter allowed for testing using colored test objects, but because of the technical skills required was rarely utilized.

The advent of computerized visual field testing gave us the possibility of eliminating or markedly reducing many of the variables that plagued manual perimetry. Early studies with SWAP determined that abnormalities detected by SWAP were predictive of ultimate white-on-white perimetry defects and that SWAP actually detected glaucomatous progression earlier than SAP.¹² Abnormal SWAP results were found in ocular hypertensive eyes without white-on-white perimetry abnormalities that were at high risk for developing glaucoma, suggesting that the sensitivity of SWAP to early glaucoma

defects was higher than white-on-white perimetry. Abnormalities found on SWAP in early glaucoma mapped well to abnormalities found in the structure of the optic nerve or nerve fiber layer.¹³⁻¹⁵ Eyes with normal SAP but with SWAP abnormalities were likely to have thin corneas and glaucomatous optic nerve appearance.¹⁶ Clearly, a characteristic glaucomatous abnormality on a SWAP test is likely to be correlated with glaucomatous optic neuropathy, abnormalities on laser scanning of the optic nerve and nerve fiber layer, and with thin corneas and, therefore, indicative of early glaucoma.

Early concerns that yellowing of the crystalline lens nucleus with age would reduce the function and require an age or lens color correction factor did not materialize.¹⁷ Fortunately, these observations made it possible to eliminate lens density testing and shorten the test to a clinically acceptable duration.

Short-wavelength automated perimetry tests the blue-cone mechanisms and the small bistratified ganglion (konio) cells that carry this information (SWS system). Several theories have been proposed for why SWAP should work. One is that the blue cones themselves, or their partner ganglion cells, are preferentially damaged in glaucoma; however, this is very unlikely since the patterns of ganglion cell loss are in the arcuate areas which do not correspond to the distribution of the blue cones or their ganglion cell partners. More likely is the fact that the K (konio-) ganglion cells that carry the information from the blue-cone system only represent a small proportion of the total ganglion cells ($\approx 20\%$) and loss of even a few of these cells would interfere with the total function since there is little functional overlap or cross-coverage.^{18,19}

In the actual test performed on an optionally equipped Humphrey or similar automated perimeter, a blue-violet (440 nm), Goldmann-size V stimulus is projected onto a bright yellow (500 nm) background (Fig. 11-2). Note that the stimulus size is significantly larger than that usually used in white-on-white threshold perimetry (Goldmann size III). The brightness is gradually increased in randomly spaced trials until the stimulus is seen approximately 50% of the time. The determination of threshold in the standard SWAP test is the same as used in the full-threshold SAP. As of the writing of this chapter, the SITA, used so effectively in SAP, has been adapted to the SWAP test, allowing much shorter test times with less fatigue

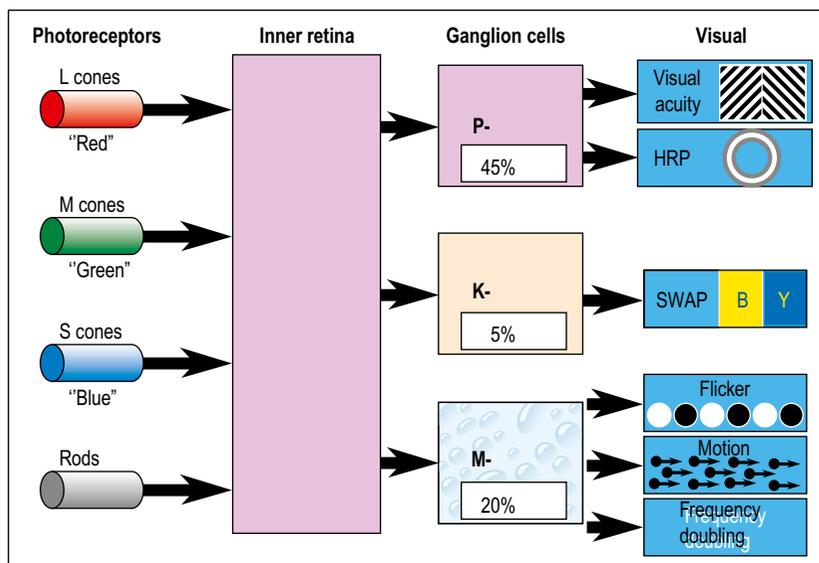


Fig. 11-1 Ganglion cell types and functions. Some visual processing occurs in the retina (bipolar layer, etc.). The ganglion cells probably do not exclusively mediate the function assigned to them but they are largely responsible for carrying it to the brain. HRP, high resolution perimetry; SWAP, short-wavelength automated perimetry. (Courtesy of Chris Johnson.)

and less threshold variability.^{20–22} Since this algorithm is only a few months old as of this writing, experience is limited and little has been published, so most of this section, unless otherwise indicated, will be devoted to what is known about the standard, full-threshold SWAP. The output of the SWAP test is similar to the output of SAP (Fig. 11-3). STATPAC is available for SWAP with a norma-



Fig. 11-2 Short-wavelength automated perimetry test on a Humphrey automated perimeter. In the SWAP test, a blue (usually size V) test object is projected onto a yellow background, therefore isolating the blue-cone koniocellular ganglion cell system. (Courtesy of Chris Johnson.)

tive database that can indicate the probability of abnormality at each tested point. Probably the most useful parameter for detecting early glaucoma with SWAP is the glaucoma hemifield test; it seems to be a sensitive and specific indicator of glaucoma-like damage.

Several independent, longitudinal studies have demonstrated the superiority of SWAP compared to SAP, both in early detection of abnormalities and in earlier detection of progression.^{23–28}

Not all studies have shown that SWAP is more sensitive than SAP.²⁹ On the other hand, abnormal SWAP results correlate with optic nerve abnormalities even when the SAP is normal.^{30,31}

Short-wavelength automated perimetry tests produce lots of noise, especially in naïve subjects, and a learning curve similar but actually longer than that seen for SAP has been demonstrated.³² Long-term fluctuation is greater with SWAP than with SAP.³³ Defects seen on SWAP tend to be steeper and larger than those seen on either SAP or frequency-doubled perimetry.³⁴

Patients with migraine also may show defects on SWAP testing;³⁵ whether this represents a manifestation of independent nerve damage caused by the migrainous process or an association of migraine with glaucoma remains to be determined. Tamoxifen may induce abnormalities in SWAP (but not frequency-doubled perimetry) well before abnormalities are seen on SAP or in the retina.³⁶

For interpretation, a SWAP can be considered abnormal if, on at least two exams, a pattern standard deviation is abnormal at worse

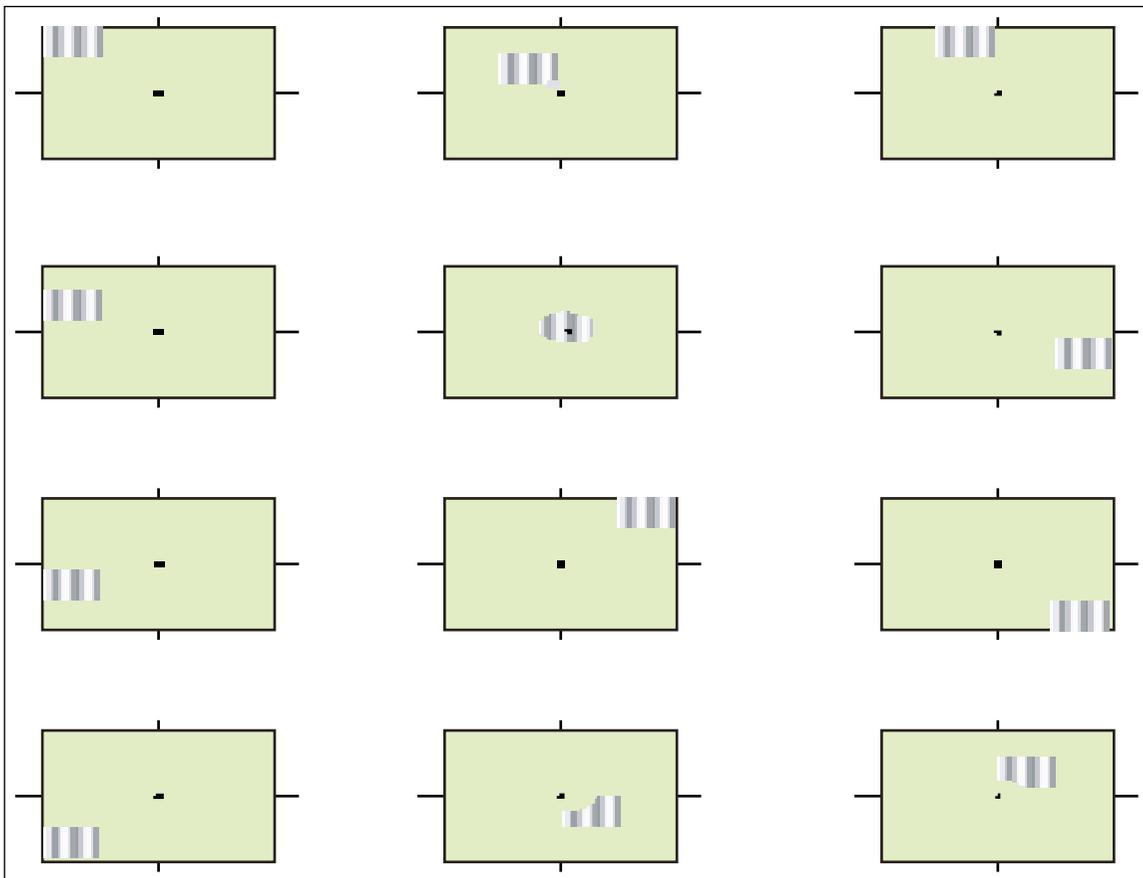


Fig. 11-3 Short-wavelength automated perimetry defect with SAP. Frequency-doubling perimetry from the original device. Alternating dark and light stripes are presented in 17 different parts of the visual field in the original device, and 64 in the Matrix. The contrast between the dark and light stripes is varied to define the threshold.

(Courtesy of Zeiss-Meditec, Inc., Jena, Germany.)

Table 11-1 Advantages and disadvantages of SWAP

Advantages	Disadvantages
Detects glaucoma defects early	Tedious
Can track progression	Takes 20–30 minutes per eye
Most perimeters can be modified to perform	Affected by lens opacities
Familiar format on results	Affected by refractive error
SITA may make it more user friendly	

than the 1% level, the glaucoma hemifield test is outside normal limits, there is one hemifield cluster with sensitivity below the 1% level, there are two hemifield clusters below the 5% level, there are four abnormal (<0.05%) points, or there are five abnormal (<0.05%) points on the pattern deviation plot.³⁷ However, large variations are seen in ocular hypertensives examined with SWAP, and with different definitions of abnormality, large variations in who has abnormalities will be seen, suggesting that we do not yet have the right combination of diagnostic sensitivity and specificity to completely rely at least on a single SWAP test to determine if a true abnormality exists.^{38,39}

In summary, SWAP is likely to detect functional glaucomatous damage and progression before SAP. However, problems with media opacities, length of test, fatigue, tediousness, high long-term fluctuation, and repeatability compared to SAP limit its usefulness, especially in the elderly (Table 11-1).⁴⁰ It may be most useful in relatively young glaucoma suspects with good concentration for whom finding the earliest functional defect may play a role in determining management. As with any test, correlation of the results with other clinical findings is required to determine if the results of any single test or series of tests in a patient are reasonable and fit the clinical picture.⁴¹ The advent of SITA SWAP may reduce the tediousness, duration, and noise level of SWAP, but this remains to be independently verified.

FREQUENCY-DOUBLING PERIMETRY

Frequency-doubling perimetry or technology (FDP, FDT) targets the function of a subset of ganglion cells – the M magnocellular ganglion cells that carry temporal information such as flicker and motion. These cells comprise only 10–15% of the total ganglion cells. There is little redundancy in this subset of cells and it would be expected that malfunction would be relatively easy to detect. In fact, studies have shown that abnormalities in FDP, like those seen with SWAP, often precede those seen in SAP by several years.^{42,43} In this test, a low-frequency sinusoidal grating (0.25 cycles per degree) undergoes rapid reversal of light bars to dark 50 times per second (25 Hertz). The gratings are projected into different parts of the visual field and, at each location, projected at different levels of contrast between the light and dark bars (Fig. 11-4). The lower the contrast at which the grating is seen as a grating, the better is the sensitivity. Although the rapid reversal gives an optical illusion that the number of light and dark bars are twice as many in the same space as are actually present (doubled frequency – hence the name), it is not known if this optical illusion has anything to do

with the diagnostic ability of the test; in fact, the mechanism seems similar to that which detects any flickering stimulus.^{44,45} The original device tested 17 sectors of the central 30°. Subsequent studies showed that even better sensitivity for glaucomatous defects was obtained with smaller gratings that were projected in a pattern similar to the 24–2 and 30–2 of the Humphrey automated perimeter. This latter observation formed the basis for the Humphrey Matrix (Carl Zeiss-Meditec, Dublin, CA) which is the newer, more versatile model. The 24–2 FDP testing strategy performs similarly to the 24–2 SAP in patients suspected of having glaucoma although the correlation is not one to one.⁴⁶ Defects may be present on SAP that are not detected by FDP and vice versa.⁴⁷

There are two general algorithms for testing similar to SAP. The screening mode is a threshold-related suprathreshold test. It is fast (1–2 minutes per eye) but not very useful for a monitoring baseline. The other algorithm is full threshold which takes closer to 10 minutes per eye. It is still faster than full-threshold SAP but no longer practical for screening. New algorithms such as the Zest program, which uses Bayesian logic, can cut the testing time in half without significantly affecting the accuracy.^{48,49} The ZEST program is available with the Matrix device and has made the threshold program with FDP quite practical and useful. The 20–1 threshold program of the FDP takes one-quarter to one-half the time of a SITA SAP without loss of specificity or sensitivity.⁵⁰

In general, the FDP appears to be more sensitive and specific.⁴⁶ Frequency-doubling perimetry has less test–retest variability than SAP, which might make it, theoretically at least, more sensitive at detecting changes over time.⁵¹ As noted above, defects on FDP may precede defects detected by SAP by several years. Furthermore, the defects on FDP in eyes with normal SAP relatively accurately predict the location of future SAP defects.⁵² Longitudinal studies do suggest that FDP is sensitive at detecting glaucomatous progression; however, the SAP and FDP do not always identify the same subset of patients, suggesting that patients may progress in different ways.⁵³

Frequency-doubling perimetry has a faster learning curve than SAP (Table 11-2); furthermore, since the test is faster and the patients more comfortable with identifying the flickering target, fatigue is less of a factor.⁵⁴ In the authors' experience, patients overwhelmingly prefer the FDP to the SAP. While the learning curve is faster with FDP, the first attempt should not be relied upon in naïve subjects; however, the second attempt is usually accurate and stable.⁵⁵ With the threshold programs, immediate retesting should be avoided as fatigue can be a factor after immediate repeat testing.⁵⁶ However, in screening situations where the 2-minute screening program has been used, immediate repeat testing may help to significantly reduce false positives.

Frequency-doubling perimetry can be used reliably in children after 8 years of age^{57,58} but reasonable results may be obtained as young as 5 years of age with proper training and preparation.⁵⁹

From the beginning, it was shown that FDP was sensitive for glaucoma defects.⁶⁰ The results of FDP correlate well with SAP in both high-tension and low-tension glaucoma.^{61,62} Sensitivity and specificity for all glaucoma defects are at about 90% compared to other visual tests for glaucoma.⁶³ In particular, the sensitivity and specificity for moderate to advanced glaucomatous defects are above 97%, which is an enviable record indeed.^{40,64} For early glaucoma, the sensitivity is 85% and the specificity is 90%.⁶⁴ Comparisons with SWAP and SAP are quite favorable for the FDP.⁶⁵

Defects on FDP correlate with thin corneas in ocular hypertensive eyes, adding more evidence that both these parameters may

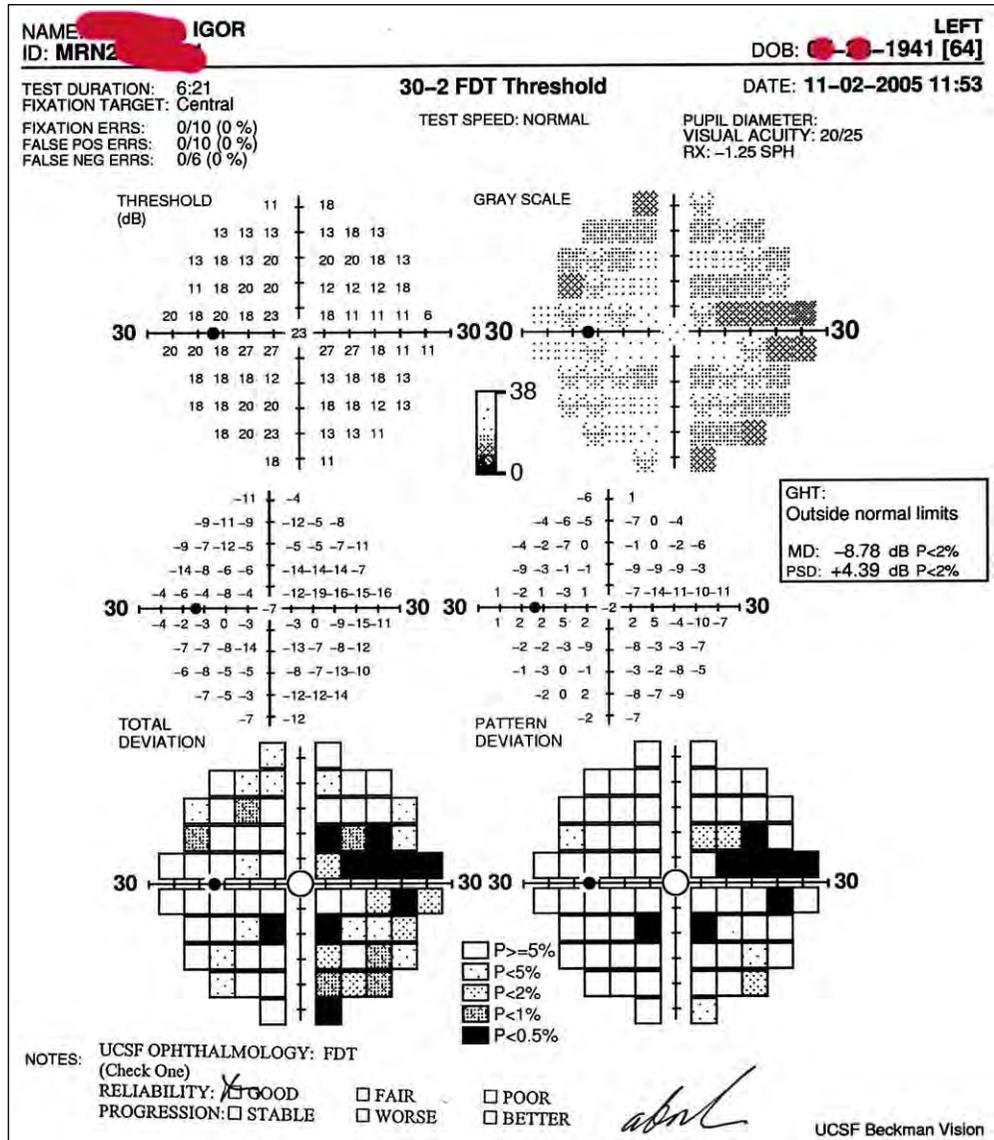


Fig. 11-4 Frequency-doubling perimetry showing nasal step. Note similarity of output to standard threshold achromatic perimetry.

Table 11-2 Advantages and disadvantages of FDP	
Advantages	Disadvantages
Relatively portable	Still somewhat bulky
Can be used in ambient illumination	Affected by media opacity – especially cataract
Relatively insensitive to refractive error	Still subjective
Faster than SAP	False positives possible especially with first field
May pick up glaucomatous changes earlier than SAP	Screening tests do not pick up all glaucomatous defects
Shorter learning curve than SAP	Ability to detect progression not yet proven
Can be used in children	
Reading disabilities have no effect on results	

be risk factors for ultimate development of glaucoma as defined by SAP.⁶⁶ Frequency-doubling perimetry also correlates well with structural abnormalities as defined by laser scanning devices such as the Heidelberg Retinal Tomography (HRT), Ocular Coherence Technology (OCT) and scanning polarimetry.^{67,68} However, the correlation is not perfect suggesting that the structure–function damage is not uniform from patient to patient.⁶⁷

As happens with SAP, the screening programs which forego the careful evaluation of the thresholds are going to be less sensitive at detecting early glaucomatous visual field defects than the threshold strategies.⁶⁹ With FDP, the 54–stimulus 24° field similar to the 20–2 of the Humphrey SAP perimeter (now included with the Matrix version) is somewhat more sensitive than the original 17–stimulus field.⁷⁰ However, the 24–2 seems to be as sensitive as the 30–2 pattern so there is little gain in performing the longer test.⁶⁹

Unlike SAP, FDP is relatively insensitive to refractive errors with up to about 6 diopters of spherical error having little effect on the

results.⁷¹ Nevertheless, for most accurate results, refractive errors should be corrected where possible.⁵⁶ Frequency-doubling perimetry seems to be affected only a little bit by aging;⁷² the small aging effects are incorporated as part of the normative database included with both models of the device. The normative database allows for similar analysis as seen with SAP, including mean deviation, pattern deviation, glaucoma hemifield test and reliability indices. Also, the second eye tested is less sensitive than the first eye tested, and this is also incorporated into the analysis procedures.⁷³

As with SAP, the presence of media opacities or pupil constriction which reduces retinal illumination may confound the results of FDP, causing the expected reduction in mean deviation but also possibly masking some local abnormalities.^{74,75} Removing a cataract generally improves the mean deviation with little effect on the pattern deviation, although, at least in one study, the pattern deviation worsened after cataract surgery suggesting that media opacity may mask some localizing defects.^{76,77}

Because of its relative small size, making it the most portable of threshold devices, FDP has been found to be a very useful device for community screening for glaucoma.^{78–82} In an English-speaking population, the screening C-20 program has only a modest learning effect.^{83,84} The screening algorithm of the FDP has acceptable sensitivity compared to SAP to justify its use in a mass screening to detect moderate to advanced glaucoma.⁸⁵ The FDP in screening mode is superior to the Damato campimeter in both sensitivity and specificity.⁸⁶ However, in a non-English speaking developing country, FDP may not be relied upon as the sole screening device since it has relatively low sensitivity when compared to expert optic nerve evaluation, although specificity can be improved by repeat testing.^{87,88} Children with learning disabilities have significant difficulty with FDP; however, adults with relatively mild reading disabilities have no greater problems performing reliable FDPs than adults without reading disabilities.⁸⁹ The preceding study used college students, so it is unknown whether adults who had reading disabilities that interfered with their ability to attend college would have enough difficulty with FDP that other screening methods for glaucoma would be more effective in this particular population.

While progression of some defects has been shown with FDP, its ability to detect progression as a routine monitoring tool has not been demonstrated.⁹⁰

While no single test has been shown to detect all glaucoma, FDP has become a most useful screening tool for finding glaucoma and detecting it in its relatively early phases.⁹¹ Careful studies have suggested that each of the functional tests detect a subset of early glaucomatous changes and that some combination of functional tests (such as SWAP and FDP) may be better than any single functional test at finding the earliest functional changes in glaucoma.⁹² Usually, structural changes precede the functional ones, and these structural changes, when they finally correlate with functional ones, may affect different ganglion cell populations in different patients.

OTHER PSYCHOPHYSICAL TESTS

HIGH-PASS RESOLUTION PERIMETRY

High-pass resolution perimetry (HRP) was first described by Frisen in 1987 and is the measurement of resolution over the extent of the visual field.⁹³ It appears to be measuring the function of the ganglion cells.^{94,95} In this technique, rings with a bright core and a

dark border of various sizes (although other target types have been used) are projected onto the visual field while the subject fixates on a central target and the subject indicates when the ring is perceived. The process is a modification of acuity perimetry first described by Johnson et al in 1979 and later by Phelps in the 1980s.^{96,97} The smaller the ring that can be perceived at a given location, the higher is the resolution of that part of the retina. While contrast could be varied, in the test described by Frisen, contrast is held constant and the size of the target is varied. As one gets further from fixation, as might be expected, the rings need to be larger in order to be perceived. Furthermore, the bowl screen is only 167 mm away at the center but has a convex curve so that the more peripheral targets are actually further away than the central fixation target. Compare this to SAP where the bowl is at 330 mm and is curved in a concave way so that, in general, the test targets are all equidistant from the retina. The computer, therefore, needs to adjust the targets for both size and shape to maintain constancy of angular size.

The typical test involves 50 locations within the central 30° where the majority of ganglion cells lie and, in that way, is similar to the 30–2 of light-sense perimetry.⁹⁸ Because of the close distance, a six diopter optical correction must be added to the distance correction. The test is easier on subjects because it is quicker and discriminations are more positive than standard automated perimetry, but it is still a subjective test and may be susceptible to many of the errors of any psychophysical test. High-pass resolution perimetry has less variability than SAP.^{98,99} The HRP probably depends on the parvocellular channels, since that appears to be the only system within the ganglion cell family that carries resolution information; parvocellular ganglion cells are the largest group of ganglion cells representing about 80% of the total population.¹⁰⁰ Another study showed a good relationship between HRP and the number of midsize ganglion cells, although the number of patients was quite small.¹⁰¹ However, not all studies support the selective action of HRP.¹⁰²

The technique is not affected by anti-glaucoma medications and seems suitable for both diagnosis and monitoring.¹⁰³

Like SAP, the response to HRP declines with age, but, unlike SAP, this decline is proportional to the 'normal' age-related loss of ganglion cells with a direct correlation with the known age-related ganglion cell loss.¹⁰⁴ In addition to glaucoma, defects are found in intracranial hypertension, optic neuritis, and other neuro-ophthalmologic conditions that affect the visual fields.^{105,106} Also like SAP, HRP is affected by media opacities.¹⁰⁷

High-pass resolution perimetry is most useful in ocular hypertension and glaucoma. There is an overall general reduction in sensitivity as well as location-specific defects.¹⁰⁸ Sensitivity for glaucomatous defects is probably slightly better than or similar to full-threshold SAP.^{98,109} Using age-related probability plots, sensitivity and specificity for early glaucoma were about 85%.¹¹⁰ High-pass resolution perimetry also seems useful in monitoring glaucoma eyes over time.¹¹¹ In fact, one prospective and one cross-sectional study suggested that HRP can detect progression before it is evident on SAP.^{112,113} In another study, the sensitivity and specificity of HRP correlated well with that obtained with FDT.¹¹⁴ High-pass resolution perimetry may be more sensitive to intraocular pressure-induced damage than SAP.^{115,116}

The location of defects correlates well with SAP.¹¹⁷ Abnormalities on HRP correlate well with neuroretinal rim area as well as with other measures of optic nerve structure.^{118,119} High-pass resolution perimetry also correlates well with nerve fiber layer thickness measurements, although there appears better correlation with the higher pressure forms of glaucoma.¹²⁰ The test takes about one-third less

time than full-threshold SAP and seems to generate more repeatable fields.^{98,121} Reliability indices are similar to SAP.¹²² High-pass resolution perimetry seems easier to perform and slightly more reliable than SAP in children.¹²³

In summary, HRP shows great promise as a subjective test that is sensitive, specific, repeatable, short, and patient-friendly. It can be used for screening, diagnosis, and follow-up. Several studies have indicated that it may be superior to full-threshold automated perimetry clinically. Unfortunately, patent disputes have held up its commercialization in the United States. When and if the disputes can be settled, additional studies will be needed to determine its role in glaucoma diagnosis and management.

MOTION DETECTION PERIMETRY

Several visual functions other than light sense are disturbed in glaucoma. One of these functions is motion detection. It has been known for some time that patients with glaucoma detected motion less well than age-matched normals.¹²⁴ This is evident in kinetic perimetry. Motion detection perimetry probably isolates the magnocellular pathway.¹²⁵ With the advent of computerized stimuli, it became possible to embed motion in a series of random dots among other sophisticated stimuli. Studies began appearing to test whether motion detection may be impaired at an earlier stage in glaucoma than SAP or some of the other tests noted above. While it is clear that motion detection is indeed impaired, with current testing capabilities, motion detection does not do as well at picking up glaucomatous damage as FDT and SWAP.^{126,127} Motion detection perimetry was able to successfully identify abnormal quadrants in glaucomatous eyes and in some glaucoma suspect eyes with normal SAP, but not any more reliably than SWAP.¹²⁵ While motion detection perimetry does correlate well with other functional tests, it seems to detect a small subset of abnormal ocular hypertensive eyes that the other tests do not, but its sensitivity and specificity at this point make it less reliable as a test than either FDT or SWAP or both.

ELECTROPHYSIOLOGY

All psychophysical tests have some inherent disadvantages. They are subjective and their performance is subject to the physical and emotional status of the patient. Such conditions as fatigue, emotional upset, anxiety, physical discomfort, extraneous noise, and movement can all adversely affect the results. The search has been on for an objective test that can eliminate or reduce the effect of the above factors. Three approaches utilizing new adaptations of old technology are currently in the investigative stage, one of which has been approved by the US Food and Drug Administration (FDA) and has reached the marketplace. These techniques are pattern electroretinography (PERG), multifocal electroretinography (mfERG) and multifocal visual evoked potentials (mfVEP).

The electroretinogram (ERG)

The ERG has been a part of ophthalmic diagnosis for the past 50 or more years. The ERG uses electrodes on the cornea, usually held in place with a soft contact lens, to pick up the very faint electrical signals emitted by retinal cells following stimulation with light. Because the electrical signal is very faint, the best that could be done until recently has been to measure a mass response, that is, the response of the whole retina. The shape of the massed retinal electrical wave could be analyzed, and if missing one or more of its

components, some general conclusions could be made about the health of the retina as a whole. Most ophthalmologists are at least exposed to this technique during their residency as a diagnostic aid in generalized retinal diseases, such as the hereditary retinal dystrophies, and as a prognostic aid in major trauma to the eye. The faintness of the responses from small areas precluded detecting any merely local areas of retinal dysfunction.

The addition of the computer to this technique allowed rapid stimulation, randomization of location of stimuli, and averaging of the responses from many stimuli. By stimulating different parts of the retina in a random or semi-random sequence and by averaging the responses to several stimuli to a particular part of the retina, the computer can effectively (although only virtually) multiply the amplitude of the faint signal from one part of the retina so it can be detected by the corneal electrode.

The pattern electroretinogram (PERG)

The PERG is similar to the standard bright-flash ERG in that recordings are made from the entire retina; in this case, the stimulus, rather than being just a flash of light, is a reversing checkerboard pattern. The electrical signal from the retina is recorded using corneal electrodes which must be carefully constructed so as not to interfere optically with the image projected onto the central 15° of the retina by the checkerboard pattern.¹²⁸ Using optically neutral corneal electrodes and proper technique, the variability can be minimized and a stable, reproducible series of wave forms generated.¹²⁹ While the flash ERG generates an electrical signal from the retinal rods and/or cones, the signal derived from the PERG seems to come largely from the retinal ganglion cells, although other inner retinal cells such as amacrine and bipolar probably contribute to the signal.¹³⁰ Most likely, based on studies of optic nerve disease, the negative (downward) part of the signal comes from the ganglion cells and the positive (upward) part comes from the amacrine, bipolar and other inner retinal cells.^{131,132} Other mammals besides humans seem to generate similar responses to the PERG.¹³³ In fact, the changes in PERG correlate well with ganglion cell loss in hypertensive rats.¹³⁴ The PERG probably is detecting early diffuse damage to the ganglion cells rather than focal damage.¹²⁸

Early on in the studies of PERG in humans it was noted that the amplitude of the signal was reduced in glaucoma.¹³⁵⁻¹³⁷ Multiple subsequent studies have confirmed a PERG abnormality in open-angle glaucoma.¹²⁸ Similar findings were observed in monkeys made glaucomatous with argon laser treatment to the trabecular meshwork.¹³⁸ Reduced amplitude of the PERG has also been found in some patients with ocular hypertension and in those with highly suspicious optic nerves ("pre-perimetric glaucoma").^{139,140} In one retrospective study, amplitude (bottom of negative to top of positive) was reduced in 87% of confirmed open-angle glaucoma and in 57% of ocular hypertensive eyes.¹⁴¹ Abnormal PERG findings quantitatively correlated with neuroretinal rim area and retinal sensitivity as measured by threshold perimetry.^{142,143}

In one study, over a 1-3 year period, 5 of 12 high-risk ocular hypertensive eyes with abnormal PERG at the beginning of the study developed glaucomatous visual field defects, while none of the eyes with normal PERGs showed any sign of progressing.¹⁴⁴ Bayer and Erb, in a 5-year, prospective study of over 150 glaucomatous eyes, showed that combining PERG with SWAP had an 88% success in predicting future SAP visual field progression.¹⁴⁵ Pattern electroretinography findings correlated well with mfVEP findings, optic nerve cupping and visual field loss in most patients with glaucoma.¹⁴⁶ Abnormalities in the PERG correlate well in ocular hypertensives

with risk factors for the development of glaucoma such as thin corneas, African heritage, positive family history, etc.¹⁴⁷

The PERG has been utilized to assess visual function in glaucoma following experimental treatments.¹⁴⁸ Improvement of the PERG (as well as the mfVEP – see below) was used in one longitudinal, controlled study as an objective measure to assess the effect of citicoline treatment on glaucoma.¹⁴⁹ In another study, comparing eyes with ocular hypertension or glaucoma who were treated with pressure-lowering drops to similar eyes without treatment, showed definite improvement of PERG parameters in many of the eyes in the treated group but not in the untreated group.¹⁵⁰ Thus, PERG may be more sensitive than perimetry in detecting either deterioration or improvement and could be used in the future as an objective way to monitor the effects of treatment.

In summary, the pattern electroretinogram shows promise as an early warning system for glaucomatous damage and possibly to detect those eyes at high risk for progression. Also promising is the possibility that it can be used as an objective method to determine either progression or improvement of glaucomatous damage during treatment. Whether this test paradigm has superiority over any of the others in this chapter remains to be demonstrated.

The multifocal electroretinogram (mfERG)

Based on studies by Sutter, Hare was able to show that monkeys treated with laser to develop elevated intraocular pressure developed evidence on the mfERG of ganglion cell dysfunction which was confirmed by histopathologic correlation.¹⁵¹ Furthermore, this laboratory was able to show an effect of the neuroprotective agent, oral memantine, in protecting components of the mfERG as well as the mfVEP (see below) in monkeys with experimental glaucoma, establishing the usefulness of electrophysiology for monitoring ganglion cell and optic nerve damage in subhuman primates.¹⁵² Raz et al demonstrated that the mfERG is affected both by stimulus contrast and by luminance in monkeys and that wave forms were generated by both inner and outer retinal elements.^{153,154}

Furthermore, they were able to demonstrate a clear difference between normal and glaucomatous monkeys with the mfERG. Other laboratories showed various defects in the mfERG associated with glaucoma in humans.^{155,156} Some of these findings correlate with nerve fiber layer thickness.¹⁵⁷ Although it may be tempting to ascribe the mfERG changes to the ganglion cell layer, some contribution from the inner plexiform layer is probably also present.¹⁵⁸

The multifocal visual-evoked potential (mfVEP)

Like the electroretinogram, the visual evoked potential (VEP) has been around for a long time. The visual evoked potential is basically a localized electroencephalogram – reading the faint electrical signals from the visual cortex using skin electrodes over the back of the head. Like the ERG, the VEP can detect large-scale problems in the visual system from retina to visual cortex (Fig. 11-5). As a general rule, if the retina is at fault or if there is a major interruption in the visual system from optic nerve to visual cortex, the amplitude of the signal is reduced. If the problem is a malfunction of the optic nerve, such as demyelinating disease, the signal is delayed and, perhaps, prolonged causing a prolongation of signal latency. As with the ERG, improvements in stimuli and in averaging of the signals have allowed the stimulation of specific parts of the retina and representation of those specific parts of the retina in the signals measured from the visual cortex.

Klistorner and co-workers used pattern stimulation of different parts of the visual field using multifocal pseudorandomly alternated pattern stimuli that were scaled in size to match their respective

representation in the visual cortex, and were able to identify loss of signal in areas of scotomata as seen on standard automated perimetry.¹⁵⁹ Correlation of histopathologic damage to ganglion cells with the mfVEP in ocular hypertensive monkeys was confirmed by Hare and co-workers.¹⁵¹ A similar correlation was found in humans, where a linear relationship was found between the degree of defect on the mfVEP and the depth and breadth of scotomata on SAP, with both correlating with estimated number of ganglion cells lost.¹⁶⁰ Graham and co-workers stimulated up to 60 sites within the central 25° of visual field and found that defects seen on both amplitude and latency of the mfVEP did correspond with visual field defects in eyes with glaucoma.¹⁶¹ Graham and co-workers further refined their observations by applying asymmetry analysis of both amplitude and latency to improve the detection of early glaucomatous defects in eyes with asymmetrical glaucoma.¹⁶² Hood and co-workers had similar findings.¹⁶³ However, in a recent study, latency delay was modest in proven glaucoma patients and proved less reliable as an indicator of damage than previous studies.¹⁶⁴

In a larger study, Klistorner and Graham demonstrated that the mfVEP could be considered an objective visual field measurement in 60 patients with either suspected or actual glaucoma.¹⁶⁵ Other studies have confirmed that the mfVEP can detect glaucomatous damage early, sometimes even before white-on-white threshold perimetry.¹⁶⁶ The correlation with SAP is quite high – 95% in one study.¹⁶⁷ However, not all studies found a good correlation; Bengsston found considerable overlap between glaucoma eyes and normals using a VEP probability map.¹⁶⁸ Thienprasiddhi et al found that the mfVEP often identified defects in the perimetrically normal hemifield of glaucomatous eyes whose only SAP defect was in the alternate hemifield, suggesting that it does indeed identify some defects before SAP.¹⁶⁹

While there appears to be good correlation between the mfVEP and SAP, in a minority of patients with early glaucoma, defects may appear on one and not the other suggesting that they may not measure exactly the same functions and that some functions may be differentially affected early in the disease.¹⁷⁰ In one recent study, the sensitivity of mfVEP for all glaucoma was 97.5%, and for early glaucoma 95%, with specificity of 92% based on SAP; however, based on masked optic nerve analysis, the sensitivity was equal for SAP and mfVEP with mfVEP having the better specificity.¹⁷¹ Correlation with structural abnormality as evidenced by Heidelberg retinal tomography has been variable.^{172,172b}

Signal-to-noise ratios have been found to be a good proxy for reliability including false positives and negatives.¹⁷³ The higher the signal-to-noise ratio, the more reliable the result. Repeatability has been shown to be at least as good and probably better than SAP in one study;¹⁷⁴ however, in another study, the variability of mfVEP was slightly worse than SAP.¹⁷⁵ Interpretation of the results can be tricky, especially with monocular testing, where not only do the waveforms vary between individuals but may vary across different regions of the visual field; cluster analysis may be the most accurate way of determining defects.^{176,177} A cluster of three abnormal points seems to be a strong indicator of glaucomatous damage.¹⁷⁸

Electrode position is critical in obtaining good signals.¹⁷⁹ The Acumap (Heidelberg Engineering, Heidelberg, Germany) unit uses theinion as a reliable landmark to position the electrodes. Other sources of error include poor contact with the scalp, patient movement, lack of fixation, and significant refractive error (Box 11-2).¹⁸⁰ Even small fixation instability, as little as 3°, may significantly reduce the amplitude of the signal.¹⁸¹ However, other than fixation, little

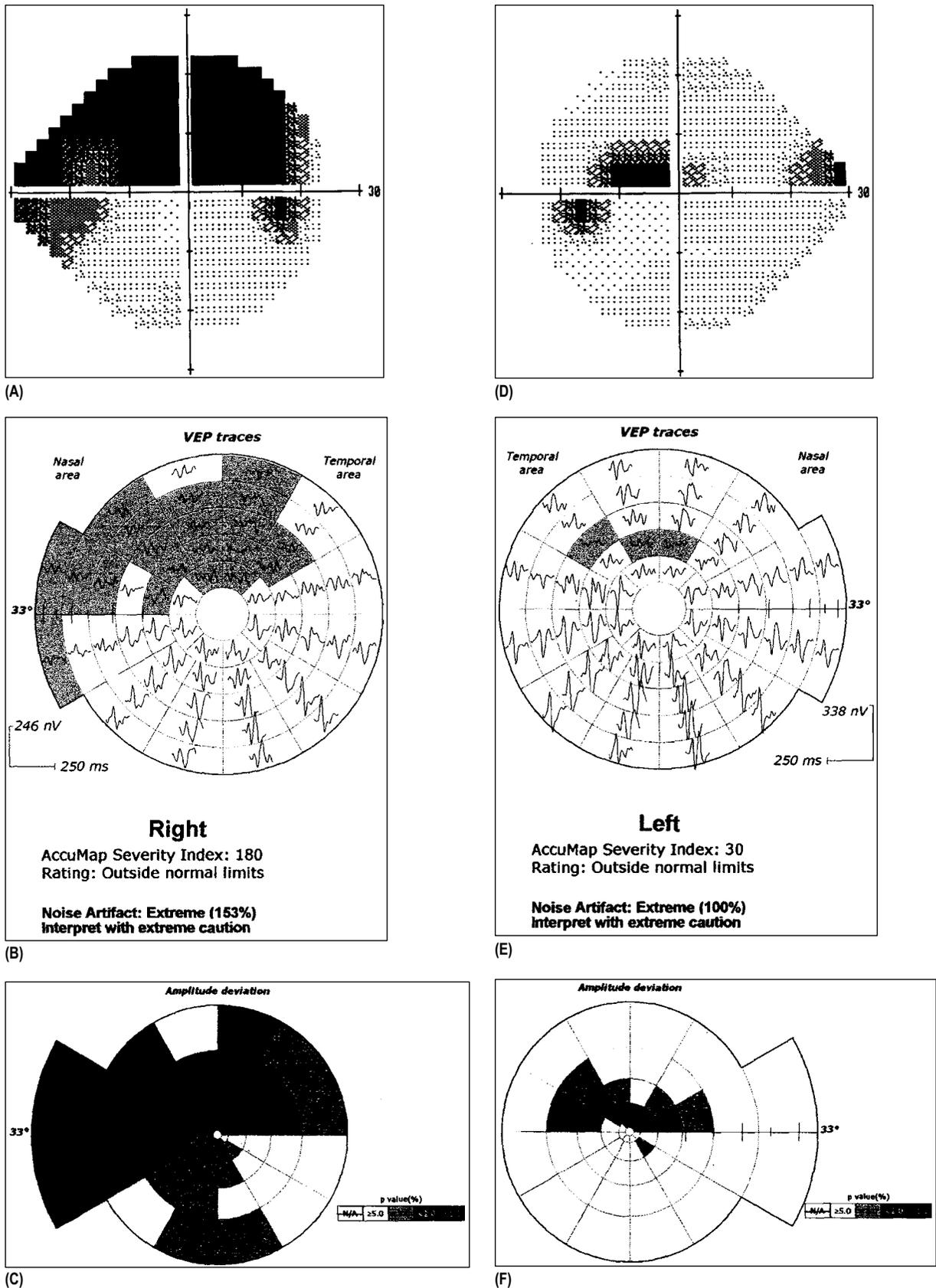


Fig. 11-5 Multifocal visual-evoked potential (mfVEP) and matching SAP. (A) SAP OD showing superior altitudinal defect. (B) mfVEP raw data with superimposed abnormal grey scale showing superior arcuate abnormality. (C) mfVEP amplitude deviation showing superior altitudinal defect. (D) SAP OS showing superior arcuate defect. (E) mfVEP OS raw data with superimposed grey scale showing superior arcuate defect. (F) mfVEP OS amplitude deviation showing superior arcuate defect.

Box 11-2 Sources of error of mfVEP

Electrode position
 Poor electrode contact with scalp
 Refractive error
 Poor fixation
 Eccentric fixation
 Media opacity
 Miosis
 Mydriasis

else is required of the patient so that reliable fields may be obtained on the elderly, those who don't understand how to perform threshold perimetry, and children. The test does take about 20 or so minutes per eye so it takes as much time as a full-threshold SAP and is not practical as a screening instrument. Children as young as 5 years of age can give reliable, repeatable results, although caution must be exercised in interpreting abnormalities as there is an age-related

maturation.¹⁸² Significant media opacities may cause false positive defects to appear on the mfVEP.¹⁸³ Small pupils may reduce the amplitude of the signal whereas dilated pupils may improve latency and mask a borderline abnormal finding.¹⁸⁴

Despite the fact that an FDA-approved, relatively user-friendly device is commercially available, the mfVEP is technology in development. It is currently clinically useful as a functional threshold in some patients who are unable to perform accurate threshold perimetry; these include the very elderly or infirm, children, those unable to concentrate, developmentally disabled, and some others. The mfVEP may detect functional changes before SAP. The mfVEP may also be useful in the assessment of suspected malingering.¹⁸⁵ How it performs compared to SWAP and FDT remains to be determined. Its ability to track and monitor changes over time still awaits longitudinal studies. Future improvements in stimulus algorithms, analytical algorithms, and computer processing should bring improvements in sensitivity and specificity.¹⁷⁶ When that happens, an objective test like this stands a good chance of replacing SAP; until then the mfVEP is a useful adjunct.

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CHAPTER
12

Optic nerve anatomy and pathophysiology

In the past decades, two significant changes have impacted how we contextualize the pathogenic mechanisms of primary open-angle glaucoma. The first change is clinically relevant: the elimination of intraocular pressure (IOP) from the essential definition of the disease.¹⁻³ In other words, glaucomatous optic neuropathy is thought of as an optic nerve disorder in which IOP is one important causative, dose-related risk factor among several others.

The other important shift has been in the conceptual framework for pathogenesis. At one time, theories of glaucomatous pathophysiology were rhetorically confined to a coarse dichotomy, considered from either a ‘mechanical’ or a ‘vasogenic’ basis. Contemporary research has elucidated many intriguing and complementary details both from biomechanical^{3b} and from vasogenic perspectives. And in addition, multiple insights into pathophysiology at the immunologic, cellular, and biochemical levels have begun to elucidate a variety of cascades, which together or separately may manifest in final pathways detectable to us as the clinical features of glaucomatous optic neuropathy.

All glaucomatous atrophy shares the following features⁴: (1) progressive death of retinal ganglion cells, manifesting as (2) characteristic histopathologic alteration of the optic nerve – known as excavation – which is functionally apparent as (3) sequential visual field deterioration in characteristic patterns. Detailed understanding of the microanatomy of the optic nerve is intimately entwined with the current concepts of glaucomatous pathophysiology.

ANATOMY OF THE OPTIC NERVE HEAD

The optic nerve head (ONH) can be divided into four anatomic parts: the surface layer and the prelaminar, laminar, and retrolaminar portions. Each portion of the ONH is made up of axons (nerve fibers) grouped into bundles, blood vessels, and supporting glial tissue.

The superficial nerve fiber layer (SNFL) of the ONH has its most anterior limit at the point where the nerve contacts the vitreous. For histopathologic and clinical purposes, the peripheral edge of the nerve is defined by the anterior limits of the scleral ring. The posterior limit of the SNFL is recognized histologically as the point at which the axon bundles have completed their 90° turn from the plane of the retina and have reached the level of the choroid. The prelaminar portion of the ONH is the indistinct segment of the axons surrounded by the outer retina, choriocapillaris, and choroid; structurally the astroglial component here is considerably increased compared with the SNFL. The laminar portion of the nerve is contained within the lamina cribrosa; here the glial-wrapped axon bundles are confined in the relatively rigid pores of the specialized laminar scleral plates. Posterior to this is the retrolaminar portion of

the optic nerve, where its thickness is doubled by the presence of myelinating oligodendrocytes. These and other eponymic details are illustrated in Figure 12-1.

In the human eye the distribution of the nerve fibers from the peripheral retina toward the optic nerve is such that axons from peripheral ganglion cells are progressively overlaid by axons derived from cell bodies closer to the optic nerve (Fig. 12-2).⁵ These peripheral fibers remain peripheral as they enter the disc; central fibers enter centrally, adjacent to the physiologic cup. This topographic arrangement correlates with the clinical progression of the glaucomatous visual field: paracentral scotomas appear early in the disease as the cup enlarges, and the peripheral field remains until the peripheral axons in the nerve are affected.⁶

The arterial blood supply to the ONH varies among individuals,⁷⁻¹¹ but there is general agreement about its fundamental components (Fig. 12-3).¹² The central retinal artery (CRA) and the short posterior ciliary arteries (SPCAs) all contribute directly or indirectly to a capillary plexus that supplies the ONH. The venous drainage of the ONH is almost entirely through branches of the central retinal vein, although important choroidal collaterals exist; these collaterals may appear as retinociliary shunts in instances of disturbed retinal circulation.

The branches of the CRA supply the SNFL. This is the network responsible for the flame- (splinter-) disc hemorrhages seen clinically, and it is also the vascular bed that appears in fluorescein angiograms of the ONH. The prelaminar ONH is supplied by branches of the SPCAs, which enter the disc substance through the adjacent sclera and posterior to the choroidal bed (see Figs 12-1 and 12-3). With one prolific exception,^{7-10,13,14} most investigators maintain that vessels derived from the peripapillary choroid make only a minor contribution to the blood supply of the anterior ONH.^{11,12,15-21}

The laminar portion is vascularized primarily by centripetal SPCAs, although an axial longitudinal anastomotic capillary bed has been described.¹¹ The ability of that network to provide collateral circulatory support in the event of an arteriolar blockage, however, appears to be limited. The anterior portion of the retrolaminar nerve, however, enjoys both centripetal vascular supply from the pia-meninges and a significant axial vasculature from branches of the CRA.

MECHANISMS OF GLAUCOMATOUS OPTIC NEUROPATHY

A particularly cogent framework for integrating the vast amount of experimental and clinical observations of the various factors contributing to glaucomatous optic neuropathy has been elaborated by Quigley.⁴ His approach poses three queries: (1) What is the primary

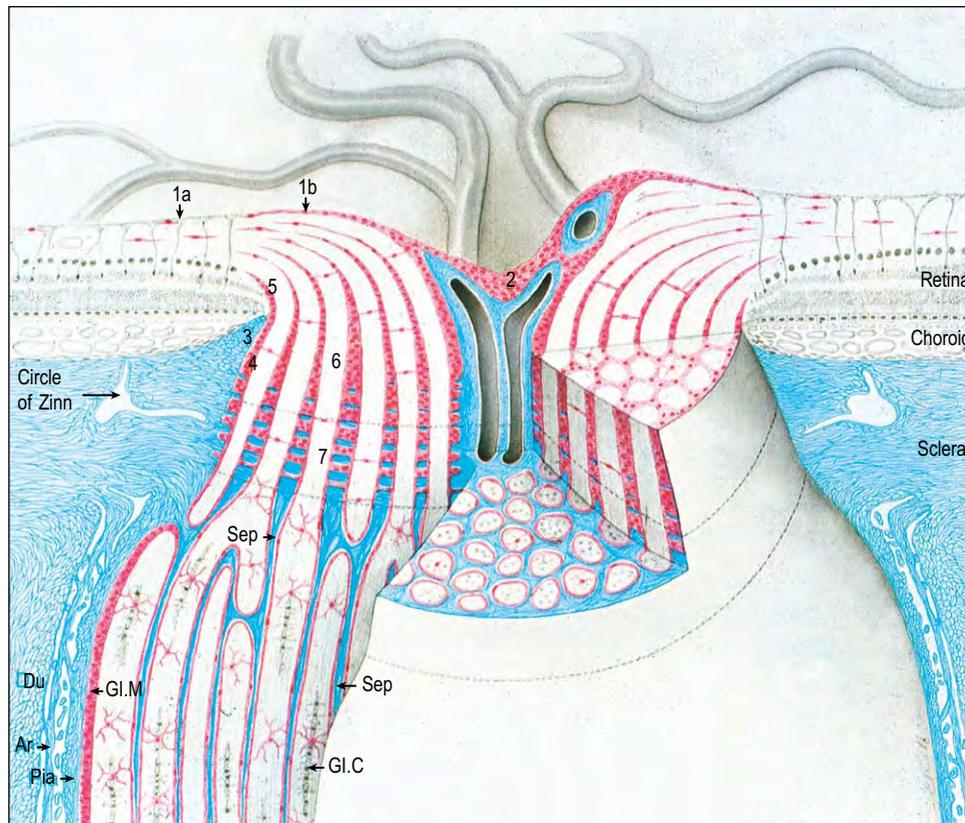


Fig. 12-1 Three-dimensional drawing of the intraocular and part of the orbital optic nerve. Where the retina terminates at the optic disc edge, the Müller cells (1a) are in continuity with the astrocytes, forming the internal limiting membrane of Elschnig (1b). In some specimens, Elschnig's membrane is thickened in the central portion of the disc to form the central meniscus of Kuhnt, (2). At the posterior termination of the choroid on the temporal side, the border tissue of Elschnig (3) lies between the astrocytes surrounding the optic nerve canal (4), and the stroma of the choroid. On the nasal side, the choroidal stroma is directly adjacent to the astrocytes surrounding the nerve. This collection of astrocytes (4) surrounding the canal is known as the border tissue of Jacoby. This is continuous with a similar glial lining called the intermediary tissue of Kuhnt (5), at the termination of the retina. The nerve fibers of the retina are segregated into approximately 1000 bundles, or fascicles, by astrocytes (6). On reaching the lamina cribrosa (upper dotted line), the nerve fascicles (7) and their surrounding astrocytes are separated from each other by connective tissue (blue). This connective tissue is the cribriform plate, which is an extension of scleral collagen and elastic fibers through the nerve. The external choroid also sends some connective tissue to the anterior part of the lamina. At the external part of the lamina cribrosa (lower dotted line), the nerve fibers become myelinated and columns of oligodendrocytes (black and white cells) and a few astrocytes (red-colored cells) are present within the nerve fascicles. The astrocytes surrounding the fascicles form a thinner layer here than in the laminal and prelaminar portion. The bundles continue to be separated by connective tissue all the way to the chiasm (Sep). This connective tissue is derived from the pia mater (Pia) and is known as the septal tissue. A mantle of astrocytes (GLM), continuous anteriorly with the border tissue of Jacoby, surrounds the nerve along its orbital course. The dura (Du), arachnoid (Ar), and pia matter (Pia) are shown. The central retinal vessels are surrounded by a perivascular connective tissue throughout their course in the nerve; this connective tissue blends with the connective tissue of the cribriform plate in the lamina cribrosa; it is called the central supporting connective tissue strand here.

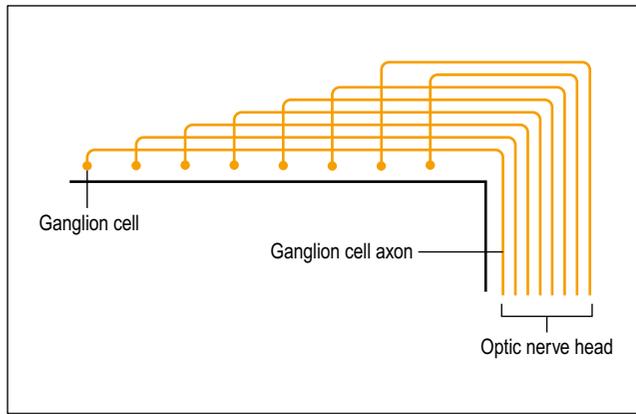
(From Anderson D: Arch Ophthalmol 82:506-530, 1969. Copyright 1969. American Medical Association.)

site of glaucomatous injury? (2) What factors contribute to ganglion/axonal injury? (3) Precisely how do the ganglion cells die? The merit of this scheme is that the multiple factors and pathogenic influences that have been elucidated²²⁻²⁵ can be accommodated without having to embrace the artificial, binary posturing of the mechanical versus vasogenic theories of causation.

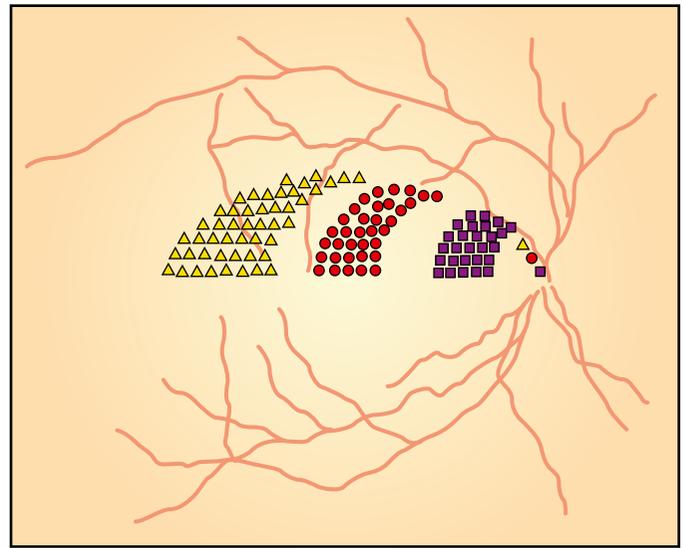
WHERE ARE THE GANGLION CELLS INJURED?

There is consensus that the ONH itself – specifically the sclera lamina of the ONH – is a primary site of glaucomatous axonal injury. This has been observed in a variety of chronic glaucomatous experiments in primates and in enucleated human eyes with primary open-angle glaucoma (POAG).²⁶⁻³⁸ Histologically all orthograde and retrograde structures and systems of intra-axonal

transport are disrupted in this laminar location of the axons' course.^{33,39-44} Retrograde death occurs in the retinal ganglion cell body approximately 4 weeks later, and loss of the distal axon to the brain occurs within 1 week by Wallerian degeneration. Recent studies have also implicated both the venous outflow channels of the lamina cribrosa⁴⁵ and the interplay of the retrolaminar cerebrospinal fluid pressure with the IOP in setting the translaminal tissue pressure.⁴⁶ At a biochemical level, neurotoxic and glial-toxic nitric oxide enzymes have been localized to the ONH as well.^{47,48} Any theory of glaucomatous pathogenesis must therefore account for this site-specific localization to the lamina cribrosa for the earliest signs of axonal injury. Another promising line of research is also focusing on this laminar location, emphasizing its key anatomic position at the converging interface of four pressure compartments: the IOP, the retro-laminar sub-arachnoid space, the intracranial cerebrospinal fluid (CSF) space posteriorly, and the surrounding



(A)



(B)

Fig. 12-2 (A) Schematic diagram of the axonal arrangement in humans shows that the closer the ganglion cell is to the optic nerve, the more superficial its axon is in the nerve fiber layer. Thus axons from cells in the periphery occupy the periphery of the optic nerve, and axons from cells closer to the disc occupy the center of the nerve head. **(B)** Schematic diagram of the horizontal topography of axonal bundles from arcuate areas of the retina as they project into the anterior part of the optic nerve, viewed ophthalmoscopically. Bjerrum areas of disc correspond to approximately the central 30° of the superior and inferior temporal quadrants. Peripherally located ganglion cells project to the peripheral optic nerve (triangles), centrally located ganglion cells to intermediate portions of the nerve (circles), and peripapillary ganglion cells to the central portion of the nerve (squares).

(A) (From Airaksinen PJ, Alanko HI: Graefes Arch Clin Ophthalmol 220:193, 1983.) **(B)** (From Minckler DS: Arch Ophthalmol 98:1635, 1980.)

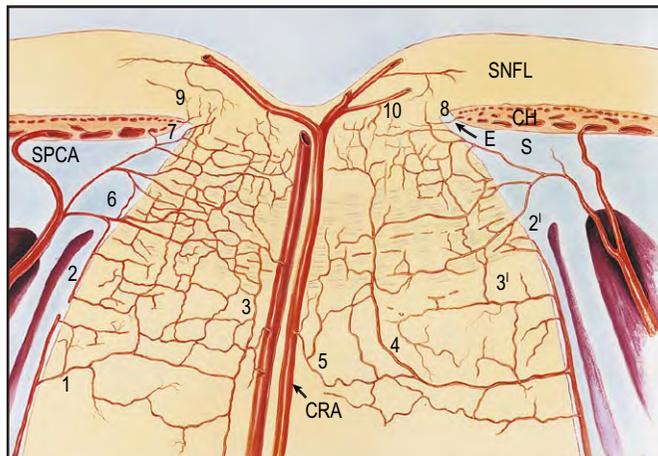


Fig. 12-3 Composite illustration of the various optic nerve vascular arrangements. Venous vessels and the superficial central retinal artery (CRA) plexus are not drawn in full. *Retrolamina*: (1) Pia mater as the source of transverse and longitudinal vessels. (2,2') Recurrent short posterior ciliary artery (SPCA) to the retrolamina and pial vessels to the lamina cribrosa. (3,3') Pial-derived longitudinal arterioles course to and anastomose with the laminal vasculature. (4) Occasionally realized large pial arteriole courses longitudinally through the laminal tissue. (5) Intraneural branching of central retinal artery, with anastomosis to the laminal and retrolaminar systems. *Lamina cribrosa*: (6) Transverse entry of scleral SPCAs that dominate the laminal vasculature and mingle with the longitudinal microcirculation. *Prelamina*: (7) Branch of the SPCA courses through Elschnig's tissue (E) at the level of the choroid (CH) and enters into the nerve. (8) Occasional choroidal vessel to the prelamina; S, sclera. *Superficial nerve fiber layer (SNFL)*: (9) Choriocapillaris 'spurs' capillary anastomoses with other retinal and prelaminar vessels. (10) Both epipapillary and peripapillary branches of the central retinal artery anastomose with prelaminar vessels.

(From Lieberman MF, Maumenee AE, Green WR: Am J Ophthalmol 82:405, 1976.)

intra-orbital space.^{46,48b} Alterations among trans-laminar pressure gradients, as with traumatic CSF leaks, may clinically contribute to glaucomatous progression.^{48c,48d}

Yet the inner retina is apparently another site of damage to both the retinal ganglion cell (RGC) and astroglial populations. It has been hypothesized that intraretinal or intravitreal glutamate levels that are neurotoxic to ganglion cells play a role in glaucoma.^{49–52} Such biochemical specifics suggest possible strategies of neuroprotective intervention.^{53–57} This approach is being actively pursued in other neurologic degenerative conditions such as Parkinson's disease and Alzheimer's disease^{58,59} although equivocal results in large studies caution enthusiasm for effective glaucoma interventions at this time.⁶⁰

The growing appreciation of astroglial roles in CNS neurotransmission^{61,62} significantly expands the scope for research into this heretofore overlooked cellular population's possible role in neurodegenerative diseases, such as glaucoma.^{48,63,64}

Although the role of vascular perfusion remains relevant to elucidating glaucomatous pathophysiology, localization to specific vascular beds within the globe remains problematic.⁶⁵ If generalized vascular insufficiency at the level of the retinal or choroidal circulations were primarily involved in glaucomatous optic atrophy, extensive deleterious effects on other retinal cell types would be expected, but this is not the case in the histopathology of glaucoma.^{66,67} Diffuse vascular insufficiency of an ocular layer, as is reportedly responsible for diffuse inner choroidal thinning in glaucoma,⁶⁸ may contribute to the glaucomatous pathogenesis indirectly or in ways that remain unknown.

WHAT INJURES GANGLION CELLS?

This is a fascinating topic for which the impressive strides of recent glaucoma epidemiology bear directly on histopathologic events.⁶⁹

For example, unequivocal clinical risk factors for developing glaucoma include IOP, increasing age,^{3b} race, high myopia, family history of POAG, and a variety of vascular indexes. These factors should be distinguished from associated clinical findings that reflect early but established glaucomatous damage before manifesting as defects in the visual field. Such associated findings include large cup/disc ratio⁹ (and related indexes from ONH imaging); disc hemorrhages; nerve fiber layer defects; and abnormal psychophysical changes such as short-wavelength (blue–yellow) perimetric defects^{70–75} or altered contrast sensitivity.⁷⁶

Both risk factors and early alterations must necessarily be expressed at the cellular level. Quigley⁴ considers four aspects of potential ganglion cell injury.

Ganglion Cell Susceptibility

There are an average of one million ganglion cells per human eye, with tremendous variability by a factor of three to four.⁷⁷ The size of the optic disc is a marker for axon number: the larger the scleral canal, the more nerve fibers are present.^{78–80} Interestingly, eyes with POAG do not have larger discs than do age-matched normals, and this also holds true for blacks who generally have larger optic discs than do whites.⁸¹ These data exemplify the paradoxical nature of many ‘susceptibility factors’: a larger optic disc would theoretically be more deformable and thus exacerbate axonal loss (see below); yet such large discs have more axons, whose greater numbers might reduce susceptibility to glaucomatous atrophy.

Aging takes a toll on the number of nerve cells throughout the brain, with a loss of approximately 25% over a lifetime, including loss of the retinal cell populations. Any acceleration of this process could manifest as clinical glaucoma. Elevated IOP, even in normal eyes, may be one such accelerant for subclinical axon loss.⁸² Thus increased age and elevated IOP may converge in hastening the natural attrition of ganglion cells.

Susceptibility may also reside in the specific subtype of ganglion cells. There are significant variations of ganglion cell populations among mammalian and primate eyes,⁷⁷ with at least 13 varieties of RGCs reported in primates.^{25,83} The most commonly encountered ganglion cells in the human retina are small (parvo) cells and large (magno) cells, in a ratio of approximately 8:1, respectively. The parvo cells transmit acuity and color data; the magno cells convey motion perception and scotopic information.⁸⁴

The preferential loss of the magnocellular population in early glaucoma, reported by several investigators,²⁴ may reflect one of several scenarios. Perhaps there is a genuine but unexplained intrinsic sensitivity of the magno cells to the (unknown) earliest toxic effects of glaucoma. A likelier explanation is that diffuse damage occurs to all axons in the ONH but manifests as an early magnocellular defect because there are fewer such fibers to begin with, and they tend to congregate in susceptible portions of the lamina cribrosa (see below). This is compatible with reports of early glaucoma damage to both parvocellular pathways (tested by short-wavelength perimetry) and magnocellular pathways (assessed by motion-automated perimetry).⁷⁵ It is important to conceptualize the ‘redundancy’ or abundance of ganglion cells relative to actual clinical visual function. Approximately 25% RGC loss is required for an afferent papillary defect; approximately 35% RGC loss before defects are detected with computerized threshold white-on-white perimetry; and 40% RGC loss before acuity worsens.^{24,25} Clinical tests that can preferentially exploit the early loss of different ganglion cell populations and their functions are actively being pursued.^{85,85b} (See Chapter 11.)

Connective tissue structures within the optic nerve head

Because excavational cupping of the ONH is an essential characteristic of progressive glaucoma, the vulnerability and behavior of the structural elements of the optic nerve are a focus of intense interest. From a clinical perspective, the greater susceptibility of the myopic eye than the emmetropic or hyperopic eye to sustain glaucomatous damage suggests altered scleral rigidity or deformation of the posterior scleral structures as contributory factors.^{69,86} Research on the biomechanics of lamellar and prelaminar tissues implicates the interplay of IOP and aging factors on the development of glaucomatous cupping.^{3b}

Optic disc excavation is the consequence of three related events: (1) loss of neural rim axons; (2) elongation, stretching, and collapse of the lamellar beams and their posterior axial displacement (bowing); and (3) outward, centrifugal rotation of the lamellar insertion into the scleral insertion zone (Fig. 12-4).^{28,87,88} Histopathologically, many cellular and subcellular alterations of the normal lamellar structures^{89,90} have been associated with this distinctive form of optic atrophy. Changes include specific remodeling of the extracellular matrix of the lamellar tissue and astrocytic reactivation,^{64,91–94} variations in elastin, suggestive of decreased compliance,^{95–97} and concomitant loss of the intralaminar microvasculature as the axonal mass is diminished. Combined, these various changes can result in an altered mechanical compliance of the ONH.^{98,99}

Another intriguing characteristic of the lamellar architecture that bears directly on axonal injury in the ONH is the lower density of support in the upper and lower lamellar pores, a finding seen in perhaps as many as 50% of glaucomatous eyes.^{88,100–102} The pores tend to be larger in the superior and inferior areas of the lamina cribrosa; this is thought to allow less support for, and more compressibility of, the arcuate axon bundles (Fig. 12-5).¹⁰³ Such vulnerability would result in their earlier loss in glaucoma in an hourglass configuration, manifesting as the arcuate visual field defects.

These regional anatomic differences of the lamina are the most dramatic demonstrable asymmetric structures that correlate with the clinical patterns of damage seen in glaucoma, but are not exclusive. For example, the finding of extremely thin lamina cribrosa structures in highly myopic eyes has led to the speculation that this could expose the ONH to steeper translaminar pressure gradients between the IOP and cerebrospinal fluid space, accounting for greater sensitivity to glaucomatous damage in such eyes.¹⁰⁴ Variations in astroglial structures within the lamellar region have also been reported.¹⁰⁵

Clearly the clinical risk factors of race and family history could be expressed as genetic aberrations in any one of the myriad cellular and synthetic processes alluded to above. Undiscovered alterations in the production or function of collagen, elastin, extracellular matrix, astrocytes, lamellar architecture, or other structures in the ONH could result singly or jointly in the overall susceptibility of the ONH to excavational damage. Similarly, unknown genetic variations in ganglion cell populations, numbers, or sensitivities could also manifest as clinical disease.

Intraocular pressure level

Although it is unclear which cellular and histologic alterations are primary or secondary, elevation of the IOP is the most consistent and reproducible experimental model for producing pathognomonic glaucomatous excavation of the optic disc.^{35,29,106–108} Physicians have anecdotally observed excavational cupping, similar to that seen with glaucoma, in a variety of circumstances,¹⁰² including arteritic anterior ischemic optic neuropathy,^{109–111} compressive optic neuropathy,^{112,113} and optic nerve infarction. Under laboratory

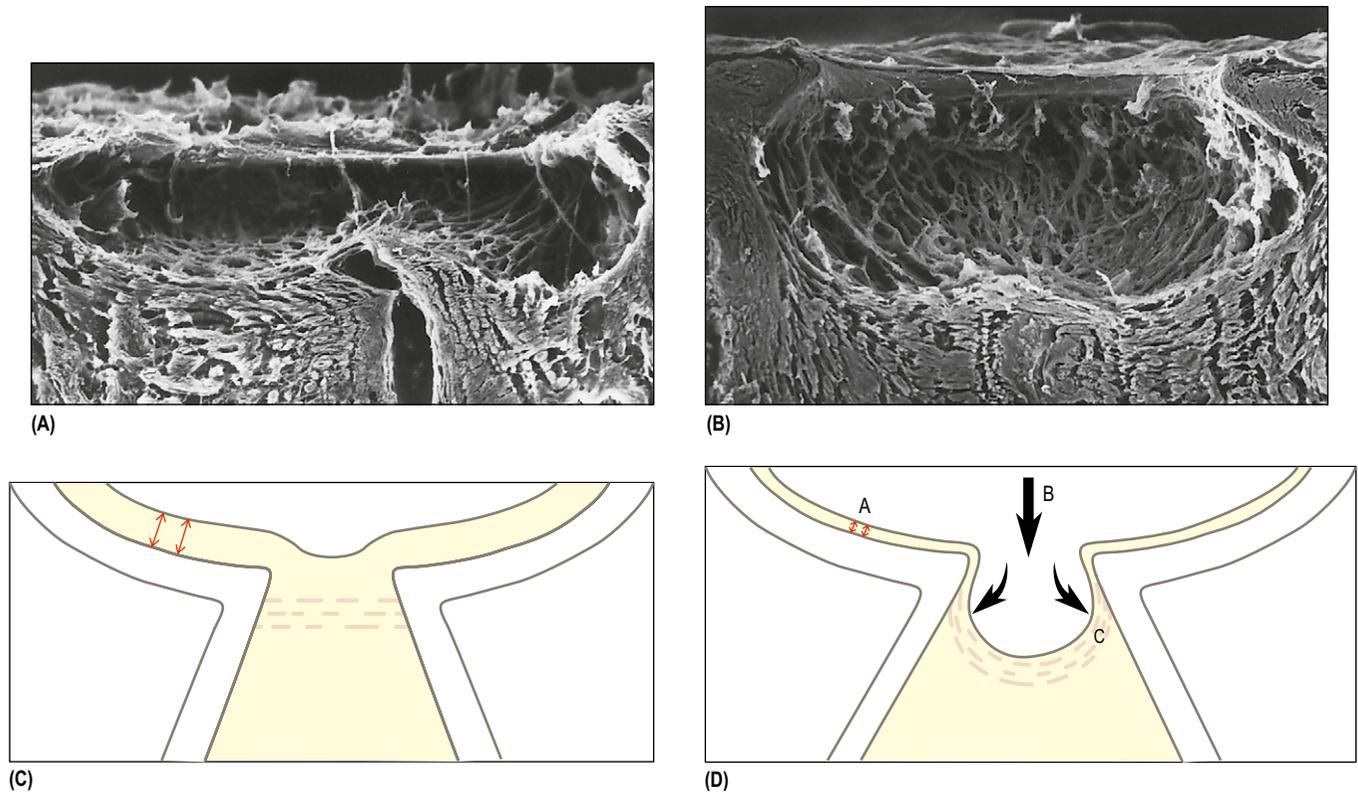


Fig. 12-4 Scanning electron microscopy of human glaucomatous optic nerve heads. As glaucoma excavation occurs, the lamina cribrosa takes on a W shape. **(A)** Moderate glaucomatous damage. **(B)** Advanced glaucomatous damage. Note that the distance from the retinal surface to the posterior surface on the lamina cribrosa increases in severely damaged glaucomatous eyes. **(C)** Schematic representation of a normal optic nerve head, with three noteworthy features: the normally thick retinal nerve fiber layer (NFL; red arrows), minimal central cup, and orientation of the lamina pores aligned with the curve of the posterior scleral wall. **(D)** Three major alterations of glaucomatous damage are the thinning of the retinal NFL (smaller red arrows), posterior excavation and enlargement of the central cup (large black arrow), and posterior outward rotation of the lamina cribrosa with cupping (smaller curved black arrows). **(B)** (From Quigley H et al: *Am J Ophthalmol* 95:673, 1983.)

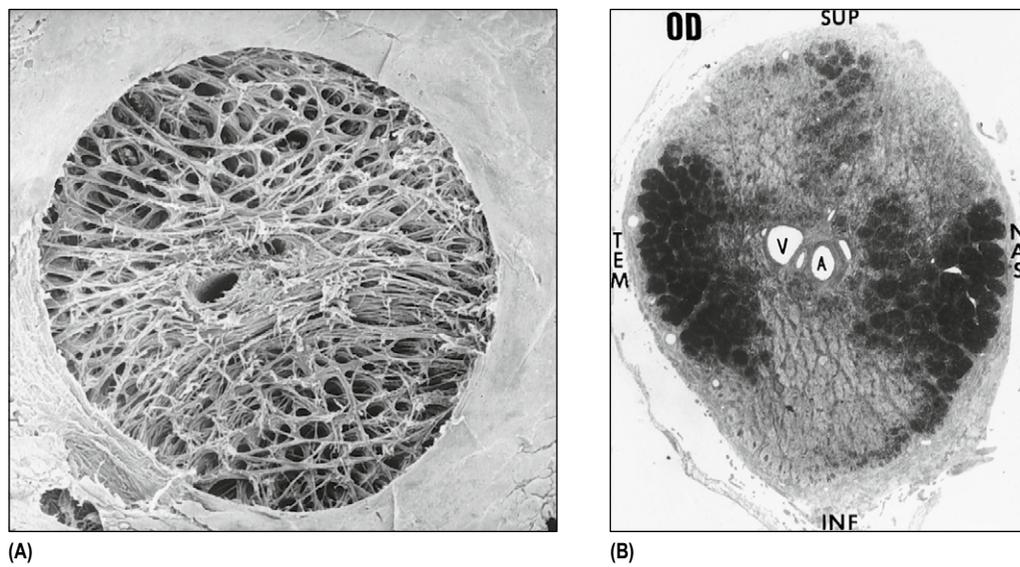


Fig. 12-5 **(A)** After neural digestion, scanning electron microscopy shows the connective tissue structure of a normal human lamina cribrosa. Note the smaller pores and denser collagen struts horizontally in contrast to the larger pores above and below ($\times 40$). **(B)** Cross-section of a glaucomatous human optic nerve. The remaining axons stain dark in the regions of greatest connective tissue density, revealing an 'hourglass' configuration of atrophy above and below ($\times 30$). (Photographs courtesy of HA Quigley, MD.)

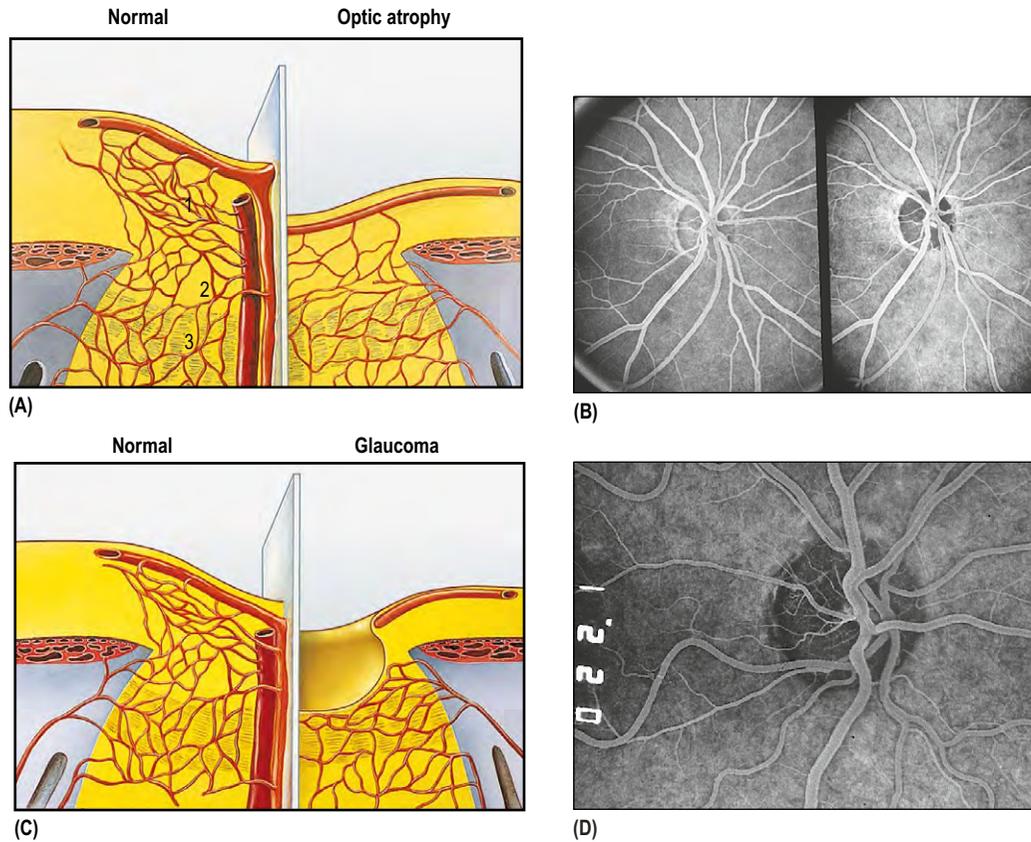


Fig. 12-6 (A) Schematic diagram of decreased optic nerve head (ONH) blood supply in descending optic atrophy. 1, Superficial nerve fiber layer; 2, prelamina; 3, lamina cribrosa. (B) Descending optic atrophy following intraorbital nerve transection. ONH angiograms at 12 seconds (left) and 23 seconds (right) show early focal loci of non-filling and late diffuse hypofluorescence. (C) Schematic diagram of decreased ONH blood supply in glaucomatous optic atrophy; note the characteristic cupping. (D) Advanced open-angle glaucoma ONH angiogram shows diffuse hypofluorescence.

circumstances, however, neither optic nerve transection nor ischemic insults recapitulate the consistent ONH alterations seen both in prolonged experimental IOP elevation and in clinical glaucoma.

Precisely how IOP induces these unique changes remains unclear.¹¹⁴ Clinically it has been well established that there is a continuum of association between IOP and POAG, much as a dose-response curve.^{69,115} In actuality, there is no 'normal' IOP that serves as a fail-safe reading for determining the presence or absence of the risk or progression of glaucoma.¹¹⁶

Some of the ambiguity surrounding the role of IOP is epidemiological: among Japanese or African-Americans, sensitivity to IOP levels for developing glaucomatous atrophy appears greater than in whites,⁴ although non-pressure factors, such as population-specific mean IOP values or the pressure-independent risk of central corneal thickness, may confound our understanding. Some of the ambiguity is technological: for example, pachymetric investigations of the effect of corneal thickness on applanation pressure readings suggest that even the categories of 'ocular hypertensives' and 'low-tension glaucoma eyes' may reflect instrument artifact, with thinner corneas reading lower IOPs and thicker corneas higher IOPs.^{117,118} Similarly, the intriguing possible relationship between IOP and the pressure gradient experienced by the ONH adjacent to the retrolaminar's cerebrospinal fluid pressure remains to be elucidated experimentally and clinically.^{46,48b,119}

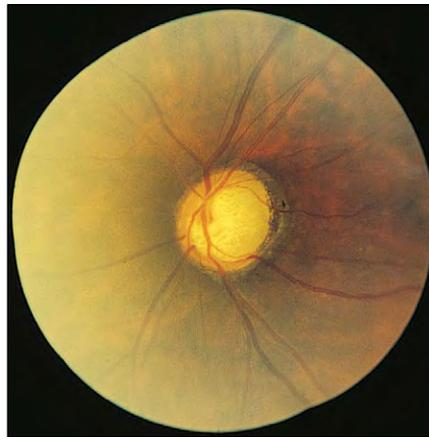
Vascular nutrition of the optic disc

In the search for the other pathogenic factors involved in glaucomatous atrophy, either independent of or in concert with IOP, much has

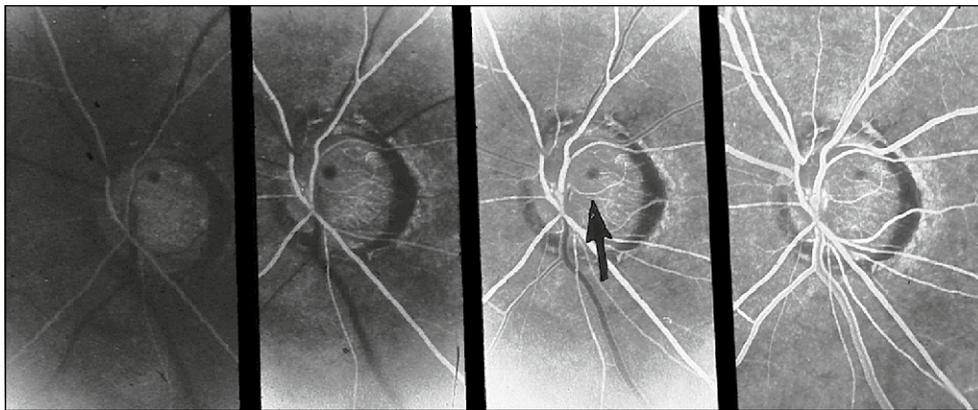
been published regarding the vascular status of the glaucomatous eye and patient. Some clinical reports have observed anecdotal worsening of glaucomatous field defects and the disc with therapeutic or pathologic reduction of the systemic blood pressure¹²⁰⁻¹²⁹; yet there is a contradictory study of glaucomatous patients who sustained severe hypotension without clinical deterioration.¹³⁰ Epidemiologic assessments have revealed a complex relationship between systemic hypertension and glaucoma, involving age as a factor.^{131,132} High blood pressure is relatively protective against glaucoma in younger individuals; in older patients systemic hypertension is a risk factor. Conversely, a low diastolic blood pressure in conjunction with elevated IOP (average 26 mmHg) increases the glaucoma risk eight-fold.¹³²

Thus it may be particularly valuable to evaluate the synergy of risk factors such as blood pressure and IOP together, rather than approaching the problem from either a vasogenic or mechanical hypothesis of causation.⁴ In fact, retrospective multivariate analyses show complicated groupings of various factors.^{133,134}

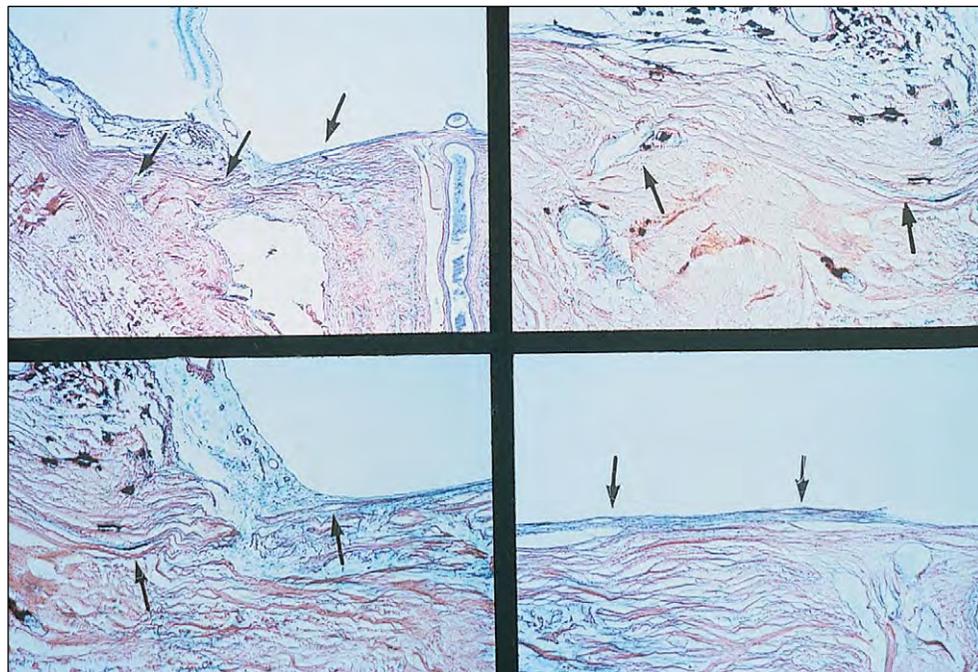
Peripheral vasospasm has been found by some to be associated with low-tension (normal pressure) glaucoma.^{135,136} The hypothesis is that peripheral vasoconstriction, as measured in the finger's nail-bed capillary responses to cold water immersion, correlates with altered endothelial autoregulation of the blood supply of the ONH.¹³⁷ However, correlation with observable parameters such as peripapillary retinal arteriolar narrowing¹³⁸ has not been clinically convincing. Similarly, other vasculopathic diseases such as migraine and diabetes mellitus have been both reported¹³⁹⁻¹⁴¹ and reported not^{132,142,143} to be associated with glaucoma.



(A)



(B)



(C)

Fig. 12-7 (A) Appearance of the disc in advanced low-tension glaucoma. (B) Angiogram of the same low-tension glaucoma ONH. Note the diffuse hypofluorescence. Arrow indicates a discrete prelaminar vessel, seen below. (C) Histologic sections of the same low-tension glaucomatous ONH, with a specific vessel seen in angiogram identified as originating from short posterior ciliary artery. Extensive neural and vascular loss can be seen together.

A fundamental issue of how vascular disorders could affect the ONH is the process of *autoregulation*.^{144,145} The body exercises various control mechanisms to maintain perfusion through myogenic and metabolic feedback loops. These include global control through cardiac output and blood pressure, local control for the regional distribution of flow, and hormonal control for prioritization of various vascular beds. Autoregulation refers to the initiation of a local response to control blood flow within a range of physiologic parameters.²⁰ Such autoregulation is lacking in the choroid but present in both the retina¹⁴⁶ and optic nerve.^{147–149} The extensive intraneural capillary bed in the ONH appears to be primarily responsible for this regulation. Deficient autoregulation has been reported both in the ONH and in the retina of glaucomatous eyes.¹⁵⁰ The specific mechanisms of damage and response, however, remain elusive.

Another vascular phenomenon that has been extensively studied in glaucoma is fluorescein angiography of the disc.^{151–157} Focal areas of ‘filling defects’ can be seen in areas of excavation, but these are almost certainly non-specific, secondary changes due to the loss of capillaries in focal areas of optic nerve atrophy (Figs 12-6 and 12-7).^{4,158–161} Moreover, disc angiograms record the vascular bed of the SNFL, derived from branches of the CRA. As such, little information about vascular events within the lamina cribrosa, where glaucomatous damage first manifests, is apparent.

Related aspects of disc angiography are the patterns of choriocapillaris and choroidal perfusion, which can demonstrate ‘watershed zones’ of relative hypofilling between the end-vessel territories of the lateral and medial posterior ciliary arteries.¹³ Allegedly this accounts for the spectrum of both glaucomatous and anterior ischemic optic neuropathy.^{14,107} A related concept is that of a watershed zone between the ONH and the peripapillary choroid that is potentially vulnerable to ischemia.^{12,19,162} Reservations about the relevance of these angioarchitectural findings for the pathogenesis of glaucoma are based on several grounds, including: (1) the absence of any asymmetric vascular supply that would account for the pathognomonic asymmetric polar excavation of the glaucomatous ONH and arcuate defects respecting the horizontal raphe; (2) the absence of diffuse tissue damage as a result of ischemia; and (3) the virtual absence of clinical syndromes in which a diseased choroid effects glaucoma-like disc and visual field changes and vice versa.

Conversely, investigations using ever-sophisticated new technologies to assess the retrobulbar large vessels are yielding consistent

evidence of vascular abnormalities associated with glaucomatous eyes. Such techniques include disc and choroidal angiography with the scanning laser ophthalmoscope, using either fluorescein or indocyanine green dyes; laser and scanning laser Doppler flowmetry to assess flow velocities of the disc surface and surrounding choroid; and color Doppler imaging of flow in the ophthalmic artery and its branches.^{138,163–177} It is certainly conceivable that poor perfusion can exacerbate other factors for ganglion cell loss.

HOW DO GANGLION CELLS DIE?

Just as the plethora of findings from various areas of investigation are increasing our understanding of how clinical risk factors are expressed at the histopathologic level to cause ganglion cell injury, the final act of how ganglion cells die also is being pieced together. One finding of great interest is that higher levels of glutamate, a neurotoxin usually seen as a result of ischemia, may be present in glaucomatous eyes.^{49–52} The source and pathway of this potent marker have yet to be elucidated.

Currently apoptosis is the most cogent explanation for ganglion cell death in glaucoma. *Apoptosis* refers to the preprogrammed genetic mode for individual cellular suicide; it is one of the ‘pruning’ mechanisms operative embryologically.^{178,179} Electron microscopic and biochemical evidence point to this as one mechanism for cell death in experimental glaucoma^{180–182}; *in-vivo* detection of RGC death by apoptosis-sensitive binding proteins has recently been described.¹⁸³ Clinically speaking, apoptosis is consistent with the total absence of ischemic signs in advancing glaucoma, such as the swollen axons appearing as cotton-wool spots in retinal microangiopathy.

Apoptosis may well be initiated by the loss of the normal retrograde flow of neurotrophic growth factors along the damaged axon due to insults in the lamina. Without such sustaining factors reaching the cell body, the ‘suicide’ program is triggered, as it is in embryologic cells that do not make their central neural connections and subsequently die.

As we have seen, the axons in the ONH are subject to a variety of potentially adverse mechanical, vascular, and biochemical events. Interrupting axonal integrity at this vulnerable anatomical transition zone triggers the death of its retinal-dwelling ganglion cells. The continued elaboration of toxic influences and cascades of injury will hopefully lead to the identity of many more potential areas for therapeutic intervention.

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CHAPTER
13

Clinical evaluation of the optic nerve head

There are several practical consequences of discarding intraocular pressure (IOP) as central to the definition of glaucoma.^{1,2} One is that the clinician *must* become proficient at examining the optic nerve head (ONH) to appreciate the often subtle signs of glaucomatous optic atrophy; neither tonometry nor perimetry alone can be relied on to determine the presence of the disease. In fact, there is increasing evidence that alterations in the ONH are the earliest signs of primary open-angle glaucoma (POAG), and that visual field studies are more useful later in the disease process.^{3–6,6b}

Similarly, instead of using the IOP for classification into ‘normal-tension’ or ‘high-pressure’ glaucoma, various subtypes of glaucomatous disease are postulated based on various appearances of the glaucomatous ONH, with specific disc changes often seen in constellation with associated clinical findings.^{7–13} Although technological advances have been made in imaging and quantifying the three-dimensional features of the ONH, the fact remains that the clinician’s mastery of discriminating ophthalmoscopy is indispensable for the appropriate management of the glaucoma patient.

CLINICAL TECHNIQUES OF EVALUATION

The observer’s ability to *stereoscopically* evaluate the ONH with sufficient magnification is the essence of optic nerve surveillance in glaucoma. This can effectively be done at the slit lamp, using a variety of contact and non-contact lenses. It can also be performed using stereoscopically obtained disc photographs. Comparable information can be obtained from a variety of commercial imaging devices (see Ch. 14).

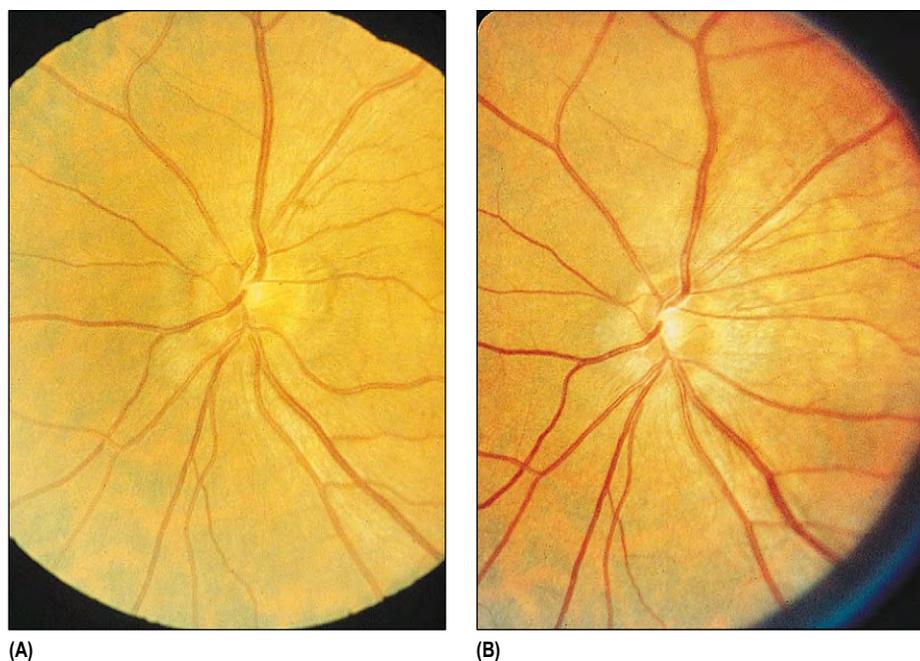
Slit-lamp funduscopy provides a good stereoscopic, direct view of the ONH when the pupil is at least 4 mm in diameter.¹⁴ Direct visualization of an upright image can be performed with a non-contact lens such as the Hruby or high-diopter (78D or 90D) fundus lens, or with contact devices such as the Zeiss four-mirror or Goldmann macular lens. With proper calibration and attention to detail, reliable measures of the optic disc diameter and disc area can be generated with such techniques, whose data are comparable to laborious planimetric measurements.^{15–18} For smaller pupils, a contact lens is often required for stereopsis. Indirect and inverted disc visualization with the 60D, 78D, or 90D fundus lenses can best be obtained when the pupil is dilated. The consistent advantage of high-magnification stereoscopic viewing is that many subtle alterations in the ONH can be detected, such as discrepancies between the cup size based on color criteria and contour criteria. Similarly, the shallow cupping of myopia is more obvious with a narrowed slit-lamp beam, and the disc often can be better seen this way in patients with early cataracts.

Monocular examination of the ONH is done with a hand-held, direct ophthalmoscope. The ease of this method makes it suitable for glaucoma screening and for interval evaluations that seek information on specific disc findings, such as the presence or resolution of a disc hemorrhage. Direct ophthalmoscopy is best thought of as an adjunct to the stereoscopic evaluation, the latter providing the specific three-dimensional details that are then monitored monocularly by parallax viewing and creation of shadows.¹⁹ The halogen bulb in the direct ophthalmoscope provides a brighter view than standard bulbs; when used with a red-free green filter, the nerve fiber layer can be visualized effectively.

If the pupil is small, if the cornea is irregular, or if the eye moves (as in children or patients with nystagmus), the patient can be placed supine, and a smooth-domed Koeppel lens can be applied. This will hold the lids open and help steady the globe, both allowing gonioscopy and providing a clear (but minified) view of the posterior fundus and ONH with the direct ophthalmoscope.

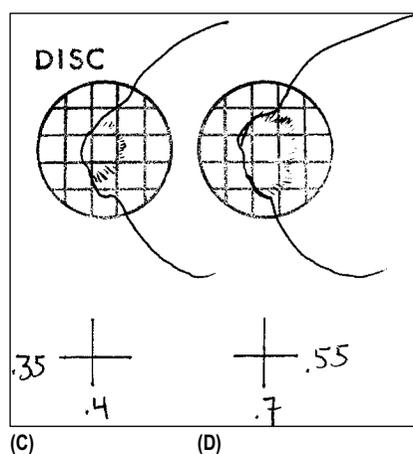
Photographs of the ONH continue to remain an extremely useful technique for documenting change in the disc over time (Fig. 13-1A, B).^{20–23} Precisely because photographic slides are portable, durable and independent of constantly changing technological platforms, they conserve invaluable information for long-term care. For example, they are useful to obtain as a baseline before refractive corneal surgery in young myopes at risk for glaucoma, since the images of their discs allow future comparisons decades hence. Baseline photographs should be taken in glaucoma suspects and glaucoma patients at the time of the initial visit, and then at intervals of every 6–18 months, depending on the patient’s stage of disease and clinical stability.¹ Careful stereo evaluation of these pictures, using commercial viewers or +10 lenses, allows for the appreciation of subtle changes in the contour of the cup and shape of the neuroretinal rim (NRR), changes in the pathway of vessels, subtle disc hemorrhages not clinically appreciated^{23b} or alterations in the peripapillary choroid (Figs. 13-2 and 13-3).

The clinician’s disc drawings are a useful adjunct to disc photographs and should be performed regularly on all patients (see Fig. 13-1C, D). They are valuable for two reasons: they require the clinician to pay attention to subtle details in the ONH, and they are an incentive to *regularly* review previous drawings and photographs to assess disc stability. Likewise, they can potentially be as valuable as disc photographs in determining progression.^{24,25} Various drawing routines have been devised,²⁶ but attention to stereoscopic details – such as the vertical and horizontal demarcation of the cup; the integrity and regularity of the NRR; the configuration of vessels at the disc margins; the appearance of laminar pores or disc hemorrhages; and peripapillary disc changes – can be methodically delineated when attention is given to their diagrammatic rendering.



(A)

(B)



(C)

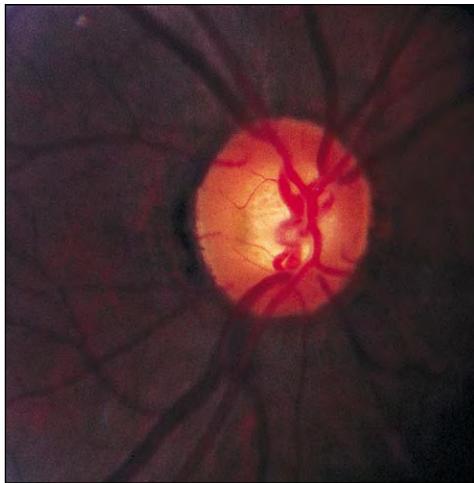
(D)

Fig. 13-1 (A, B) Fundus photographs of a left eye six months apart showing increasing disc cupping during period of uncontrolled intraocular pressure (upper 30s). Note rather uniform enlargement of the disc cup. **(C, D)** Hand-drawn diagrams, as noted in patient's chart, of the same progressive cupping seen in photographs. The accompanying cross indicates estimations of maximal vertical and horizontal dimensions of the cup.

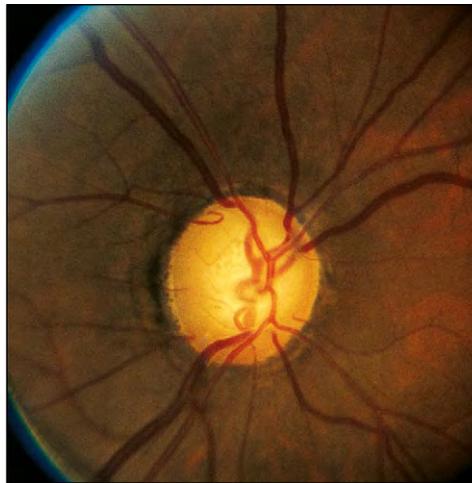


Fig. 13-2 Optic disc pit. The inferior pole of this optic disc has a horizontally elliptical greyish defect into which the inferior vein falls. This is a dramatic optic pit. This eye had a corresponding dense superior visual field defect.

Spaeth and co-workers have proposed an elaborate but reproducible clinical scheme for diagramming and staging the extent of glaucomatous disc damage, using slit-lamp and direct ophthalmoscopic technology.²⁷⁻³⁰ The Disc Damage Likelihood Scale (DDLS) distinguishes 10 stages of progressive glaucomatous changes of the disc, whose clinical significance is discriminated based on whether the disc size is small, average or large. Classification is abetted by a standardized chart with examples (Fig. 13-4).³⁰ First, either a 60D, 66D or 90D lens is used at the slit lamp to estimate the disc size in millimeters with a reticule, and the value multiplied by lens-power-dependent constants: this determines a small, average or large optic nerve size. Next, the neuroretinal rim is assessed at its narrowest point (i.e., the cup axis is discriminated at its largest extent) by direct ophthalmoscopic exam, and notated; the disc is drawn, with careful attention to the NRR. Lastly the DDLS is invoked by integrating



(A)



(B)

Fig. 13-3 (A) The initial photograph of the right optic disc in a patient with primary open-angle glaucoma. **(B)** The patient after a 12-year interval. During this interval, there has been concentric enlargement of the cup. An area of focal thinning of the neural rim can be observed near a cilioretinal vessel in the superotemporal region. The bent portion of this vessel could not be visualized well before the loss of the overlying neural rim tissue. (From Campbell DG, Netland PA: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)

	DDLS Stage	Narrowest rim width (rim/disc ratio) [average disc size: 1.50 - 2.00 mm]	Example
At Risk	1	0.4 or more	
	2	0.3 to 0.39	
	3	0.2 to 0.29	
	4	0.1 to 0.19	
Glaucoma Damage	5	less than 0.1	
	6	0 (extension: less than 45°)	
	7	0 (extension: 46° to 90°)	
Glaucoma Disability	8	0 (extension: 91° to 180°)	
	9	0 (extension: 181° to 270°)	
	10	0 (extension: more than 270°)	

Fig. 13-4 The Disk Damage Likelihood Scale (DDLS) is based on the radial width of the neuroretinal rim measured at its thinnest point. The unit of measurement is the rim/disc ratio, that is, the radial width of the rim compared to the diameter of the disk in the same axis. When there is no rim remaining, the rim/disc ratio is 0. The circumferential extent of rim absence (0 rim/disc ratio) is measured in degrees. Caution must be taken to differentiate the actual absence of rim from sloping of the rim as, for example, can occur temporally in some patients with myopia. A sloping rim is not an absent rim. Because rim width is a function of disk size, disk size must be evaluated prior to attributing a DDLS stage. For small disks (diameter <1.50 mm) the DDLS stage should be increased by 1; for large disks (diameter >2.00 mm) the DDLS stage should be decreased by 1. This is done with a 60D to 90D lens with appropriate corrective factors. The Volk 66D lens minimally underestimates the disk size. Corrective factors for other lenses are: Volk 60D \times .88, 78D \times 1.1, 90D \times 1.33. Nikon 60D \times 1.03, 90D \times 1.63.⁶⁵

the disc diagram, the narrowest rim-to-disc ratio and the nomogram; assume an average size, and adjust afterwards. Two sequential parameters are encountered with progressive disease: the radial width of the NRR at its narrowest point; and in areas of total NRR loss, the circumferential extent (in degrees) of absent rim tissue. The score is determined for each eye, and the quantitative

values assigned have high inter- and intra-observer agreement, as well as good correlation with visual field loss.

OPTIC DISC CHANGES IN GLAUCOMA

In large part because of the prodigious efforts by Jonas and co-workers³¹⁻⁴¹ in meticulously delineating the morphometric and pathogenic details of the ONH in glaucoma and optic atrophy, there is a framework for approaching the massive literature on the features of glaucomatous changes in the ONH derived from clinical observations, investigational imaging, and histopathologic correlations. Eight intrapapillary findings and four associated peripapillary features address the spectrum of glaucomatous alterations of the ONH. Following this, proposed subclassifications of glaucoma based on patterns of ONH appearance are discussed.

INTRAPAPILLARY DISC CHANGES

With meticulous stereoscopic observation of the intrinsic structures of the optic papilla, the clinician can discern two aspects of the optic disc (its size and shape); two aspects of the NRR (its size and shape); three aspects of the optic cup (its size and configuration, and the cup:disc ratio); and the relative position of the central retinal vascular trunk and its branches to the laminar surface and disc architecture.

Optic disc size

The mean area of the optic disc in whites is 2.1–2.8 mm² and is independent of age after the first decade of life.³⁵ Disc size is related to race – it tends to be smaller in whites, intermediate among Asians, and largest among blacks.^{42,43} There are several helpful clinical tools in estimating disc size during routine examination. When the smallest 5° aperture of the Welch Allyn direct ophthalmoscope is projected onto the retina in eyes with a refractive error within $\pm 4D$ of emmetropia, the circular spot has an area of 1.7 mm² – and thus provides a reliable estimation of whether an optic disc is clinically larger or smaller than normal (Fig. 13-5).⁴⁴ Another technique for clinical-research use is the calculation of the disc area based on measuring the horizontal and vertical diameters of the ONH. After adjusting the slit-lamp beam in the vertical (V) and horizontal (H) meridians and multiplying the obtained lengths

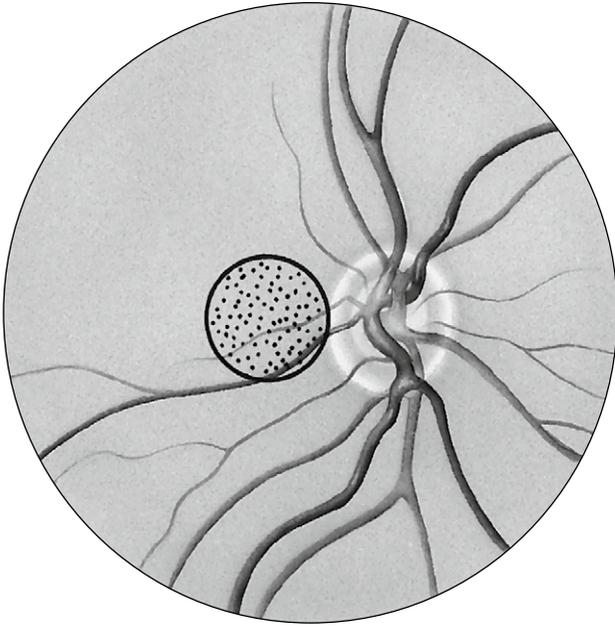


Figure 13.5 Drawing of the light spot projected onto the retina when the fundus is visualized with the small (5°) aperture of the Welch Allyn direct ophthalmoscope. The light spot is normally slightly smaller than the average normal optic disc and provides a convenient clinical technique for estimating optic disc size for eyes within $\pm 4D$ of emmetropia. (From Airaksinen PJ, Tuulonen A, Werner EB: Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn, St Louis, Mosby, 1996.)

by a factor of 1.26, these values are then entered into the modified formula for an ellipse:⁴⁵

$$\text{Area} = \pi/4 \times (H \times V) \text{ in } \text{mm}^2. \text{ } ^{45}$$

Formulas for using different sizes of indirect lenses at the slit lamp to measure the disc have also been generated.^{46,47}

Within the refractive range of -5 to $+5D$, the optic disc size shows little significant variation. Hyperopes over $+5$ show smaller optic discs, and high myopes have larger optic discs.⁴⁸ Jonas has characterized *macrodiscs*, manifesting large areas (over 4.2mm^2), as either primary or secondary.^{48,49} Primary macrodiscs are independent of age and refraction and can be asymptomatic (presumably hereditary) or symptomatic, as in the morning glory syndrome or congenital optic pit.⁵⁰ Secondary macrodiscs include the enlarging ONHs seen with progressive myopia or with uncontrolled congenital glaucoma.

Optic disc size correlates with a variety of morphometric and clinical features. *Small discs* are associated with ONH drusen,⁵¹ pseudopapilledema,⁵² and non-arteritic anterior ischemic optic neuropathy.⁵³ *Large discs* demonstrate greater neuroretinal rim area,³⁵ more axonal fibers,³⁹ larger size and number of lamellar pores,⁵⁴ and other expressions of increased ocular cellular components, such as more retinal pigment epithelial cells and photoreceptors, cilioretinal arteries, and so on.⁵⁵

It is intriguing that *intermediate* disc size is associated with arteritic anterior ischemic optic neuropathy,⁵³ central retinal vein occlusion,⁵⁶ and the most common forms of glaucoma – POAG,^{34,57} juvenile open-angle glaucoma,⁵⁸ age-related ('senile sclerotic') open-angle glaucoma,⁵⁹ and pseudoexfoliation open-angle glaucoma.⁶⁰ Logically, one might deduce that smaller discs,

with relatively smaller axonal numbers (reduced axonal reserves) and a higher ratio of lamellar pores to disc area, might be more susceptible to damage. (In fact, slight enlargement of cupping in small discs is apt to be clinically significant.) Conversely, one might argue that larger discs, despite their greater axonal numbers (reserves?), sustain greater lamellar displacement and are subject to a larger area of lamellar pressure gradients. Compensatory factors, such as comparable connective tissue proportions and pore size distribution in the lamina cribrosa (as seen in black eyes when compared with white eyes), may play a role in minimizing the effect of optic disc size on the cascade of glaucomatous insults in the lamina cribrosa.⁶¹

Optic disc shape

The oval form of the normal optic disc has a vertical dimension approximately 7–10% larger than the horizontal dimension.³⁵ The shape shows no correlation with age, sex, body weight, or height – it only correlates with the extent of corneal astigmatism.³⁸ This relationship is particularly seen with high degrees of astigmatism, with the axis corresponding to the longest axis of the ONH. Recognition of this fundus finding in children may alert the clinician to evaluate the corneas and forestall refractive amblyopia.

In myopes of less than 8D, there is no apparent difference in the optic disc shape from normals.³⁸ Nor is there any correlation between the optic disc shape and the NRR area, perimetric defects, or the susceptibility to glaucoma.³⁸ However, with increasing myopia, and especially in eyes over 12D myopic, there is increasing ovality of the disc. This suggests stretching or tractional vectors are not evenly distributed across the myopic optic disc and that may play a role in the pathogenesis of glaucomatous optic atrophy in these eyes.⁶²

Neuroretinal rim size (NRR)

The NRR is the intrapapillary extension of the nerve fiber layer and is hence a critical parameter for evaluation. The direct correlation with the optic disc size – the larger the disc, the larger the NRR – is reflected in a direct correlation with axonal count and the area and number of lamellar pores.^{39,43,54} This indicates that there is a greater axonal reserve capacity in eyes with larger optic discs. Nevertheless, there is a great deal of inter-individual variability of the NRR size, depending on specific factors such as axonal counts, axonal densities within the ONH, variations in lamellar architecture, and glial cell counts within the disc.³⁹

Neuroretinal rim shape

The characteristic vertical oval shape of the optic disc and the horizontal oval shape of the optic cup contribute to the NRR shape. In descending order, the rim is broadest in the inferior disc, then the superior disc, then the nasal disc, and thinnest in the temporal disc. This asymmetry may reflect in part the fact that the center of the ONH is $0.53 \pm 0.34 \text{mm}$ horizontally above the foveola. Hence a relatively larger number of axons exit the eye through the relatively more cramped inferior portion of the ONH – which would account for the optimal visibility of the retinal nerve fiber layer (RNFL) in the inferotemporal aspect of the disc.³⁷

This gradient of axonal distribution, represented by the variable shape of the NRR in different disc quadrants, also correlates with the morphology of the lamina cribrosa – the largest pores and the least amount of interpore connective tissue are in the inferior and superior poles, compared with the nasal and temporal sectors.⁶¹ Similarly, the thinnest axons are temporal, and the thickest are in the polar regions. These findings all suggest that differential axonal

populations distributed in a structurally non-homogeneous lamina cribrosa may well account for asymmetric cupping of the glaucomatous disc and characteristic visual field loss patterns of the disease.

In progressive glaucoma, the NRR is diffusely lost in all sectors, and its diminution is predictive for subsequent visual field loss.^{63–65} Neuroretinal rim loss manifests earliest in the inferotemporal and superotemporal regions, followed by the temporal sector, and lastly the nasal rim.^{66,67} This is virtually identical to the patterns of visual field damage seen clinically.^{68,69} Also of clinical interest is the observation that the sector of the NRR farthest from the central trunk of retinal vessels may be affected by rim loss earlier than other sectors.³¹

Although some have advocated the evaluation of NRR pallor as a distinctive indicator of early glaucomatous damage,^{70,71} other studies indicate that this color-assessment variable provides little additional information over discrimination of the NRR area itself.⁷² With few exceptions, non-glaucomatous optic atrophy manifests neither with enlargement of the optic cup nor with a

decrease in the NRR area – but rather with increased NRR pallor and attenuation of the peripapillary retinal vessels.⁷³

Optic cup size in relation to optic disc size

The larger the optic disc, the larger the optic cup.^{73b} As with macrodiscs, *macrocup*s have been described and subclassified into primary types (physiologic and fixed after the first year of life) and secondary types (because of either increasing myopic enlargement of the disc⁷⁴ or progressive glaucomatous atrophy).

Special attention must be paid to small optic discs, which usually have virtually no cup.³² Hence the earliest signs of glaucomatous progression may be more easily appreciated by evaluating the RNFL or peripapillary choroid.⁷⁵ Even the development of a small cup in an eye previously without any cupping may indicate early damage in the crowded disc.

Optic cup configuration and depth

There is no standard pattern for the development of glaucomatous cupping of the ONH (Fig. 13-6).^{68,76–79} This cupping may begin as

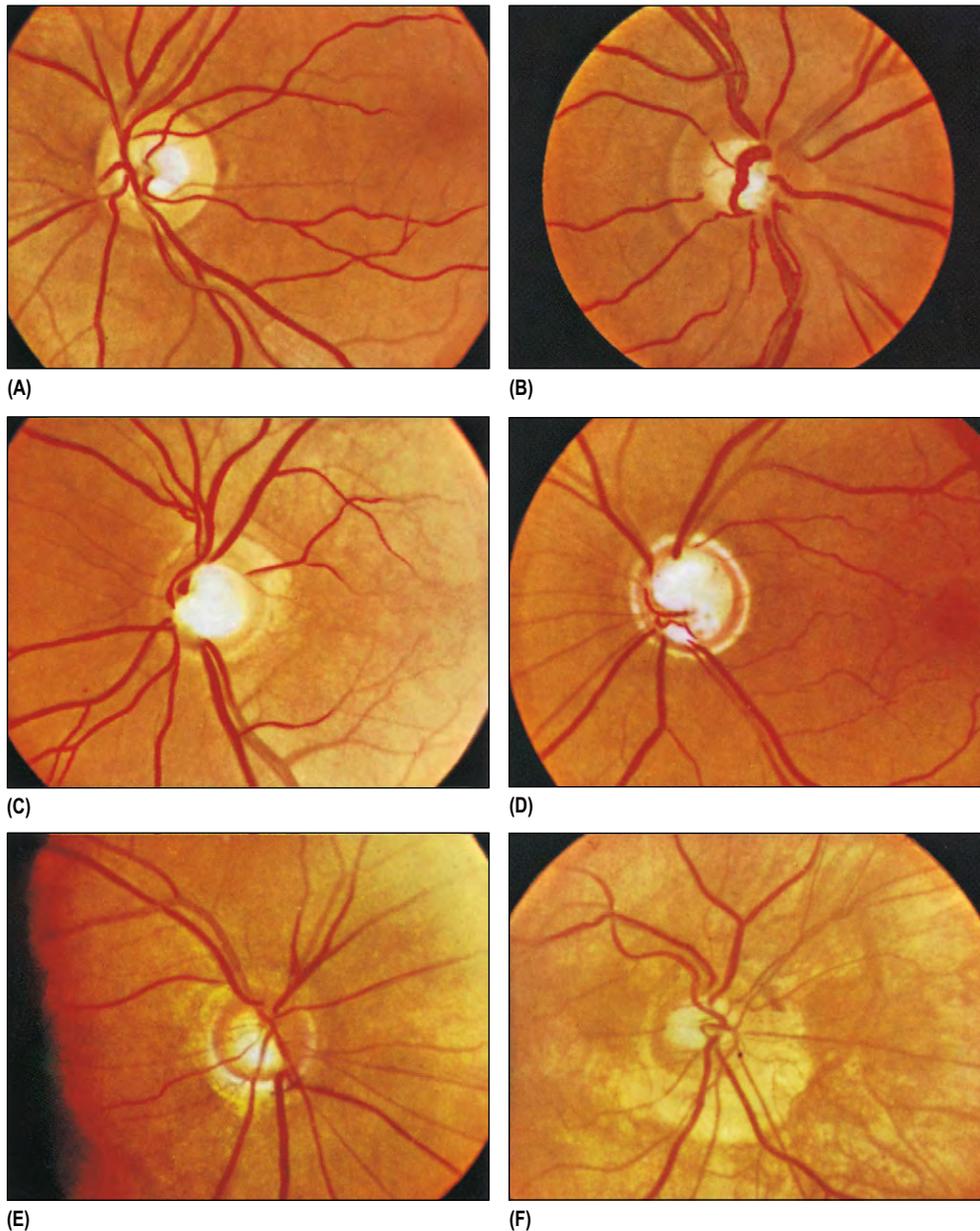


Fig. 13-6 (A) Optic disc with slight physiologic cupping, cup:disc ratio (C/D) 0.4. (B) Optic disc with moderate cupping, C/D 0.5. (C) Optic disc with moderate cupping, C/D 0.8. (D) Optic disc with severe cupping, C/D 0.9. (E) Cupping of lower portion of the optic disc, C/D 0.5–0.6. (F) Slightly cupped myopic disc with peripapillary atrophy. Contact lens ophthalmoscopy demonstrates cupping that extends to the periphery of the disc.

a symmetric enlargement of the physiologic cup, but usually some portion of the rim erodes more rapidly than the rest. In myopic eyes and discs with age-related open-angle glaucoma,⁵⁹ the cup tends to be shallow, especially temporally. In other kinds of glaucoma, NRR thinning can be localized and appear as a notch or, less frequently, as a pit at the disc rim. If notches are present both inferiorly and superiorly, the cup becomes vertically oval like a football.

The slope of the wall of the disc cup generally is steepest nasally and becomes shallowest temporally, with the upper pole having a somewhat steeper slope than the lower pole.

Cupping occurs slowly unless the pressure is very high. We have seen patients with pressure in the 40s develop an increase of 0.2–0.3 in cup:disc ratio in a matter of weeks. In young children and infants, the elastic capacities of the infant nerve allow transient and reversible disc cupping to be produced by pressure on the globe during examination of the patient under anesthesia.

Reversal of glaucomatous disc cupping can be dramatic in young patients following surgical or medical lowering of IOP (Fig. 13-6).^{80,81} Reversal is less dramatic in older patients, presumably because reduced elasticity of the scleral tissue in older patients does not allow the cup to resume its prior configuration. Also, cupping that results from actual loss of nerve tissue is unlikely to reverse.⁸²

Cup:disc ratios

Because of the vertically oval optic disc and the horizontally oval optic cup, cup:disc ratios are usually larger horizontally than vertically in normal eyes; in only 7% of normals is this pattern reversed.³⁵ This is in stark contrast to eyes manifesting early glaucomatous loss, in which the vertical cup:disc ratio increases faster than the horizontal ratio.^{34,48} Appreciation of increasing vertical cupping is clinically very useful.⁸³

Because the cup:disc ratio depends on the highly variable optic disc and optic cup diameters, normal ratios span from 0.0 to 0.8.^{34,48} They are larger in eyes with large optic discs and smaller in eyes with small optic discs. Stereoscopic viewing tends to yield

higher estimations of the cup:disc axes than monocular viewing with a direct ophthalmoscope.

When drawing or noting the cup:disc ratio, it is particularly useful to indicate both the maximal horizontal (H) and the maximal vertical (V) dimensions. Often these are written in one-tenth units (e.g., .5H & .6V); carrying out the estimation one decimal place further (e.g., .55H & .65V) indicates an intermediate estimation rather than the viewer's hyperacuity precision (see Fig. 13-1C and D). Estimations by the same observer may vary by 0.1–0.2 units over time; hence accurate drawings indicating precise landmarks, or stereophotographs, can greatly supplement the clinical record.

To a limited extent, cupping in adult glaucoma is reversible, but not nearly to the extent seen in children (see Fig. 13-7).^{81,82} Compressive lesions of the extrabulbar portion of the optic nerve can cause profound visual field loss that may recover dramatically when the compression is relieved.⁸⁴ In glaucoma, this phenomenon exists to a small degree, in that apparent recovery of visual field loss has occurred following treatment of the glaucoma. Spaeth and co-workers^{12,85} suggest this as one way of recognizing the adequacy of treatment. In our experience, however, this recovery is rarely prominent and is certainly not manifest when defects in the nerve fiber layer have already appeared. As the axons die, they occupy less space in the scleral canal, and the cup enlarges. Quigley⁸⁶ found up to 40% of some nerves' axonal mass could be lost without having any recognizable field defect on Goldmann perimetry. Thus nerve damage can occur and progress with little or no field defect. Despite advances in computerized perimetry and other psychophysical tests for early glaucoma, progressive optic disc cupping without visual field loss remains an early indicator of glaucoma, assuming no other disease process is occurring.³⁻⁶

Position of central retinal vessels and branches

It has been observed that there is local susceptibility to NRR loss in the rim sector farthest from the major trunk of the central retinal vessels.³¹ This specific relationship of glaucomatous loss can be useful to monitor in circumstances with an unusually shaped NRR.

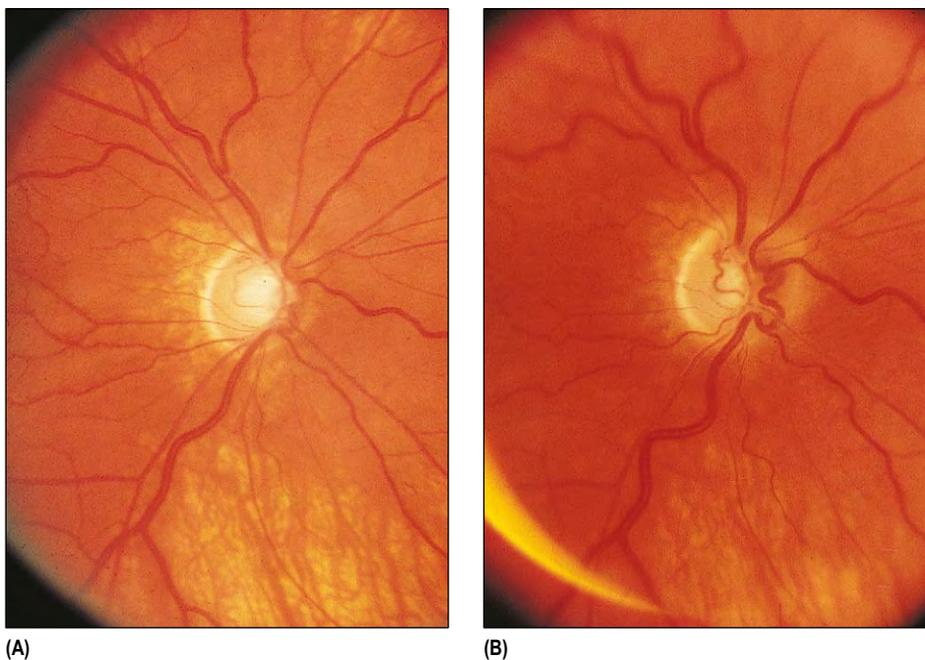


Fig. 13-7 This 5-year-old child underwent two goniotomies. **(A)** The optic nerve before the first goniotomy. **(B)** The optic nerve before the second goniotomy. Note an increasing thickness of the rim with an increasing pinkness of the nerve head as pressure is lowered after each goniotomy.

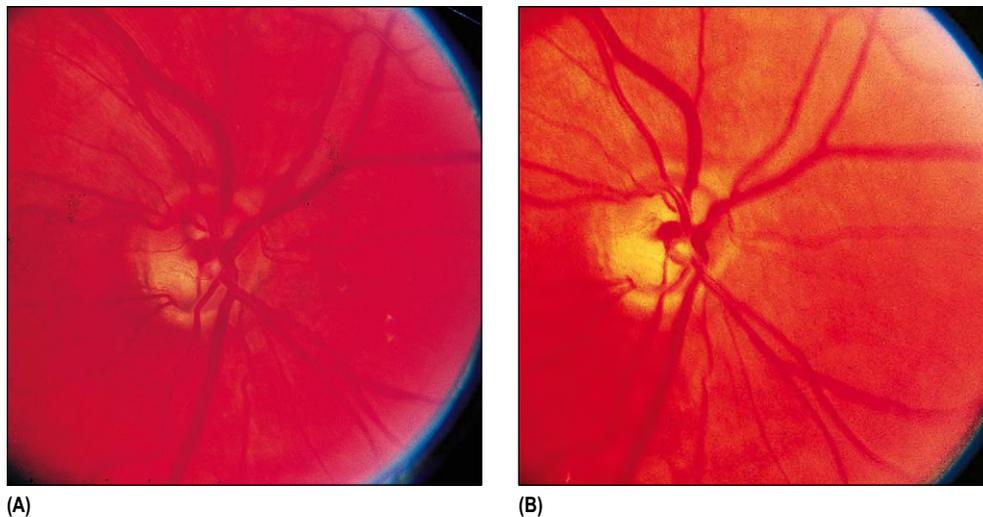


Fig. 13-8 (A) Extension of the cup (notching) inferotemporally. **(B)** Seven years later; note thinning of the neural rim and shifts of the positions of blood vessels. (From Campbell DG, Netland PA: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)

As the cup enlarges, the retinal vessels, which usually pass perpendicularly through the disc tissue to reach the retina, are displaced externally following the receding nasal wall of the cup. Where the vessels shift from a more vertical orientation along the cup wall to a horizontal orientation on the retinal surface, there is a bend in the vessel. Change in the shape or position of that bend, as may be seen when comparing serial photographs, is a sensitive indicator of disc change and can be monitored with disc imaging (Fig. 13-8).⁸⁷

Vessels that pass circumferentially across the temporal aspect of the cup have been called circumlinear vessels. If they pass the exposed depths of the cup, they are 'bared.'⁸⁸ Baring of circumlinear vessels is seen because as the cup recedes, it exposes the vessels. Baring of circumlinear vessels is seen commonly in glaucomatous cups, but it may be seen in normal cups as well.⁸⁹

PERIPAPILLARY DISC CHANGES

By paying attention to alterations in the area immediately surrounding the optic disc, valuable information can be determined about the glaucoma status of the ONH. Four phenomena should be evaluated – optic disc splinter hemorrhages; changes in the RNFL; variations in the diameter of retinal arterioles; and patterns of peripapillary choroidal atrophy (PPCA).^{89b}

Optic disc hemorrhages

Nearly 30 years ago, Drance and co-workers⁹⁰ revived interest in splinter hemorrhages on the ONH in glaucoma patients. These are either flame-shaped or blot hemorrhages that can occur at any location around the disc rim (Fig. 13-9). They usually are located within the nerve fiber layer extending across the disc rim into the retina, but they may occur deep in the disc tissue. They last for a variable interval between 2 and 35 weeks.⁹¹ Because they appear in areas of preserved NRR, they are not usually seen in advanced cases of cupping in which little rim remains.⁴⁰

The literature on optic disc hemorrhage has been dominated by case series and case-controlled studies in eyes under surveillance for glaucoma.⁹² As a result, many assertions about the association of disc hemorrhage with one type of glaucoma (e.g., 'low-tension glaucoma')^{91,93-96} or about the specificity of this finding for predicting glaucomatous loss⁹⁷⁻¹⁰⁰ sometimes reflect this selection



Fig. 13-9 MDisc hemorrhage at the inferior pole of the right optic disc. (From Campbell DG, Netland PA: Stereo atlas of glaucoma, St Louis, 1998, Mosby.)

bias. A comprehensive Australian population-based study, using subjects rather than eyes, provides a more broad-based context for assigning meaning to disc hemorrhages.¹⁰¹

This epidemiologic survey of mostly whites in the Blue Mountains near Sydney used a thorough glaucoma assessment including computerized fields and disc photographs on all participants. An overall prevalence rate of optic disc hemorrhage of 1.4% was found; this was slightly higher than the rates of 0.8%⁹⁷ and 0.9%¹⁰² reported in the only two other population-based studies in the literature. Positive correlation was seen with increasing age and among women; no correlation was identified with a history of vascular events, smoking, aspirin use, or myopia.¹⁰¹ Most remarkable was that 70% of all disc hemorrhages were seen in subjects *without* any definite signs of glaucoma. Only 1 out of 4 patients over 50 years old with a disc hemorrhage demonstrated other disc and visual field signs of glaucoma. Thus the specificity of this sign as a screening tool does not seem particularly good, as reported elsewhere.¹⁰³ Non-glaucomatous factors, such as aspirin use and diabetes, are also associated with such hemorrhages.^{103b}

Nevertheless, among patients known to have glaucoma in this Australian study, disc hemorrhages were decidedly more common (13.8%); for every high-pressure glaucoma eye there were three eyes with 'low-pressure' disease. And when compared with normals, patients with ocular hypertension had twice the frequency of disc hemorrhage.¹⁰¹ Eyes with lower IOPs following filtration surgery showed fewer disc hemorrhages than pre-operatively.^{101b} Others have demonstrated a strong association between disc hemorrhages in glaucomatous eyes with RNFL loss (especially inferotemporally), NRR notching,¹⁰⁴ and discrete visual field loss.^{92,105,106} Such hemorrhages may precede progression of the disease,^{92,105,107–112} with subsequent disc and field changes manifesting between 1 and 7 years later.^{110,112}

Another long-term prospective evaluation, the Ocular Hypertensive Treatment Study,^{23b} made several important observations about disc hemorrhages in selected patients with elevated IOPs. Of note was that only 16% of disc hemorrhages detected on stereophotographs were identified on funduscopic examination. It is of cautionary significance that so many of us clinicians are missing these subtle findings in the vast majority of cases. Another important finding was that though their patients were considered at risk for POAG at the time of their recruitment, after 7 years' follow-up, some 86% of eyes that developed a disc hemorrhage did not manifest POAG according to strict, pre-defined criteria.

Others also report that there may be neither accelerated progression¹¹³ nor apparent functional loss associated with disc hemorrhage.^{97,105,114,115} Interestingly the morphometric parameters of disc size, shape, NRR, peripapillary atrophy (and IOP or visual field loss) show no difference between eyes with unilateral disc hemorrhage.¹¹⁶ Asian eyes requiring filtration surgery for both open-angle and angle-closure glaucoma showed similar rates of disc hemorrhages as reported in white patients.¹¹⁷

Although some of the data are contradictory, a cautionary value can be assigned to this ophthalmic finding. The identification of a disc hemorrhage in any eye compels considerations that glaucoma may be present. In an eye with known glaucoma, such a finding merits increased attention and surveillance.

Though some have proffered an association of disc hemorrhage and specific types of glaucoma – notably the focal type of normal-pressure glaucoma^{91,93,95} – others have noted the sampling problem bias of these assessments and claim that disc hemorrhages can be found in all types of glaucoma.^{40,58–60,103} This controversy reflects our lack of knowledge regarding the pathogenic mechanisms underlying the disc hemorrhage. For example, a higher IOP may stop a hemorrhage earlier, limit its size, and enhance its reabsorption faster than lower IOP. Hence the alleged connection between disc hemorrhage and 'low-pressure glaucoma' may simply reflect persistence of a more obvious bleed, leading to its greater clinical visibility.^{111,118}

Explanations that disc hemorrhages reflect ischemic events in the ONH contributing to glaucomatous progression^{114,119,120} are unconvincing on several grounds. Axonal damage occurs within the lamina cribrosa, and not in the NRR; and the retinal circulation that accounts for the capillary bed responsible for disc hemorrhages is not implicated in glaucomatous disease (see Ch. 12). Perhaps most telling is that disc hemorrhages are *never* associated with cotton-wool spots of the associated nerve fiber layer, as seen in focal ischemic infarction of the retina. On the other hand, explanations that say mechanical shearing of small disc vessels occurs with structural collapse of the progressively cupped disc¹²¹ are not

supported by observations of eyes that have sustained sudden IOP elevations from ocular contusion yet do not manifest disc hemorrhages.¹²² Both the mechanism of disc hemorrhage and the precise vessels involved¹⁰³ – arterioles, veins, or retinal radial peripapillary capillaries – remain unresolved.

Other possible causes of disc hemorrhages include anterior ischemic optic neuropathy, optic nerve drusen, central or branch retinal vein occlusion, diabetic retinopathy, vasculitis, papilledema, anticoagulation therapy, and posterior vitreous detachment. Most of these causes can be recognized by accompanying signs such as disc swelling, more diffuse hemorrhages throughout the retina, or vasculopathy. Posterior vitreous detachment can be diagnosed by recognizing the condensed vitreous ring that is torn away from its attachment at the ONH.

Nerve fiber layer defects

Ophthalmoscopic visible defects in the RNFL, first described by Hoyt and co-workers,¹²³ represent visible loss of optic nerve axons from any form of optic atrophy. Two patterns of nerve fiber loss have been described – localized wedge defects and diffuse loss – which alone or in combination can be recognized in glaucoma patients. Localized loss is more easily and consistently recognized, but is less common.^{86,108,124–129}

Detection of RNFL defects is particularly useful in determining whether a glaucoma suspect has or has not yet manifested the structural changes of early glaucoma. Such RNFL changes can precede the appearance of functional changes in the visual field and thus have great value as early indicators of disease.^{128–131}

Clinical evaluation can be done by a variety of methods: red-free direct ophthalmoscopy,¹²³ or a wide-angle camera with either blue or green filters and high-resolution black-and-white film such as Kodak Panatonic X.^{125,128,129} A photographic survey of the ONH region provides a particularly sensitive method of evaluation that affords more precise and studied assessment than a clinical exam alone of the patient.¹³¹ Specialized imaging techniques for assessing the RNFL have also been developed, such as computer-imaged height measures of the peripapillary nerve fiber layer,^{132–134} scanning laser polarimetry,^{135,136} photogrammetric measurements of RNFL thickness,^{137,138} and optical coherence tomography (see Ch. 14).^{139–141} The clinician should learn the basics of RNFL assessment either by using the slit lamp with a high-plus non-contact or contact lens, or by using red-free direct ophthalmoscopy. The red-free (green) filter combined with precise focusing enhances the appearance of the RNFL. The nerve fibers are seen most easily in the retinal area adjacent to the superior and inferior temporal aspects of the disc (superior and inferior Bjerrum's area), where the RNFL is thickest.¹²⁷ Here the fibers are closely packed and can be recognized by the bright linear reflexes reflected by the bundles.

The RNFL is more obvious in young people with moderately dark fundi and becomes increasingly difficult to see in older patients and in patients with media opacities or lighter fundus pigmentation. Beyond two disc-diameters, distance from the disc, the fibers diverge, and the RNFL thins, leaving normal darker spaces between the bundles. These slit-like spaces must not be confused with true localized slit RNFL defects, which are broader and darker, and extend up to the disc rim.^{86,123,126,127,142}

Localized RNFL defects appear as dark bands that fan outward from or near the disc margin, following the pattern of the nerve fiber layer. Localized loss may occur in conjunction with diffuse or generalized loss. Diffuse loss is more difficult to assess. To evaluate

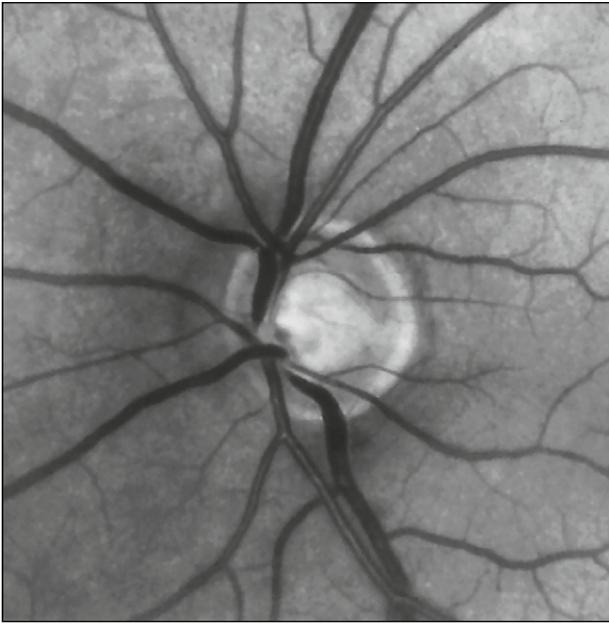


Fig. 13-10 Marked diffuse thinning of the retinal nerve fiber layer (RNFL) in association with a concentrically enlarged optic cup. Note good visibility of vessels, including small capillaries. Atrophy of the RNFL has unmasked the mottled appearance of the retinal pigment epithelium.
(From Airaksinen PJ, Tuulonen A, Werner EB: Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, Krupin T, editors: *The glaucomas*, 2nd edn, St Louis, Mosby, 1996.)

RNFL loss,¹⁶⁷ the examiner must be familiar with the variations in appearance of the normal RNFL and photographic artifacts that can simulate diffuse RNFL loss. Comparing the RNFL appearance of one eye with the fellow eye can be helpful.

Careful observation of the vessels and vascular reflexes can help differentiate a poorly visible RNFL in a normal patient from a thinned or generally atrophic RNFL in a patient with disease. If the retinal vessel reflexes are bright and sharp and smaller branches are easily visualized, generalized atrophy may be present (Fig. 13-10).

Considerable experience is required to master the technique of RNFL evaluation, but it is unquestionably worth the effort. It allowed Quigley and co-workers⁸⁶ to diagnose 84% of glaucoma patients while falsely selecting only 3% of normal patients. Airaksinen and co-workers,¹²⁵ in a similar study, reported a 94% success rate in detecting 51 glaucoma patients by examining the RNFL; however, they noted a 17% false-positive rate. They emphasized that localized and diffuse RNFL defects can occur together in the same eye. In glaucoma suspects with elevated IOP and normal visual fields and optic nerves, Quigley and co-workers⁸⁶ found RNFL changes in 13% of 194 eyes, whereas Airaksinen and co-workers¹²⁵ found them in 52% of 52 patients.

As with any test for a disease, its value is related to its applicability, sensitivity, and specificity. Current techniques allow this test to apply to about 90% of those patients needing it, and its reported sensitivity ranges from 84% to 94%, with a specificity ranging from 3% to 17%. As such, it becomes another tool for early recognition of those patients who require careful observation and may be at great enough risk to warrant early treatment.

Diameter of retinal arterioles

Diffuse narrowing of the retinal vessels on the ONH is a non-specific indicator of optic atrophy, seen both with descending atrophy and non-arteritic anterior ischemic optic neuropathy.^{75,143} Thus it has also been reported in glaucomatous eyes – as the NRR gets smaller, so do the retinal vessels. Such narrowing increases with age but is significantly pronounced in proportion to the degree of optic atrophy.^{144,145} Because of this finding's association with many forms of optic nerve disease, it most likely reflects non-specific vascular responses to decreased demands for peripapillary perfusion with progressive loss of the axonal mass. Because the decreased retinal arteriolar diameter of optic atrophy is independent of PPCA – a characteristic of glaucomatous optic atrophy – retinal arteriolar constriction by itself does not support the idea of diffuse vasospasm of retinal and posterior ciliary vascular beds contributing to glaucomatous damage.¹⁴⁴

Peripapillary chorioidal atrophy

For decades clinicians have observed an increased prominence of PPCA in eyes with advanced glaucomatous optic neuropathy.¹⁴⁶ A variety of imprecise terms have been advanced – scleral lip, peripapillary halo, choriocleral crescent, halo glaucomatosus, and so on. There is agreement that alterations in the peripapillary chorioidal region can be acquired and can progress in conjunction with progressive glaucomatous optic atrophy. It is less certain that distinguishing PPCA either enhances the recognition of glaucoma or presages its progression.

White scleral halos can be found among normal and glaucomatous eyes, but they are more pronounced among the eyes with advanced disc changes.¹⁴⁷ Such a possible focal relationship between localized nerve damage and adjacent peripapillary changes has also been noted in studies by Anderson and co-workers.^{148–153} Because the peripapillary junction with the optic nerve represents an anatomic defect in the blood–brain barrier, it has been hypothesized that PPCA changes possibly reflect a more vulnerable site for potential vasoactive substances to penetrate the adjacent nerve head.¹⁴⁹ Other theories invoke the possible tilt of the optic disc or variations in the vascular tree.¹⁵⁴

The association between PPCA alterations and specific glaucomatous changes appears relational but not necessarily causative. For example, areas of PPCA change correlated with visual field changes in several studies^{148,155,156} and appeared predictive for some ocular hypertensive patients who later developed glaucoma.^{63,154,157,158} On the other hand, contradictory experimental chronic glaucoma studies in monkeys^{159,160} and inconclusive long-term studies correlating NRR loss with PPCA changes¹⁶¹ in ocular hypertensive patients who later developed glaucoma¹³⁰ have also been reported. Histologic studies of glaucomatous eyes reveal inconsistent alterations in choriocapillaris and choroidal vessel densities, making it hard to correlate and interpret the PPCA changes sometimes seen in glaucoma.¹⁶²

Some of the contradictory studies may revolve around the precision of the areas being examined. Jonas and co-workers^{163,164,168} have popularized a classification of PPCA into two different (if not always distinctive) areas. Ophthalmoscopically, the more peripherally *zone alpha* is characterized by irregular hypopigmentation and hyperpigmentation and by thinning of the overlying chorioretinal layer, and it tends to have somewhat nebulous boundaries. *Zone beta* is located closer to the optic disc border and is usually more distinctive because of its visible sclera and visible large choroidal vessels. When both zones are present, zone beta is always internal

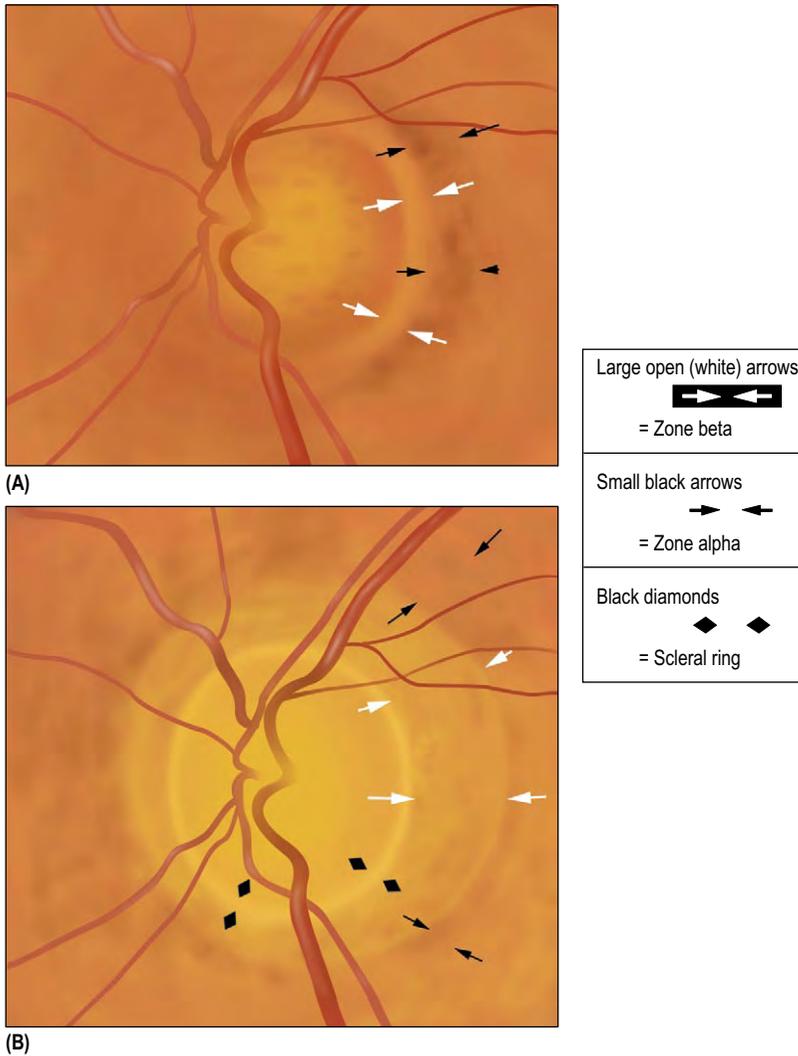


Fig. 13-11 (A) Peripapillary areas can sometimes be distinguished as zone beta (hypopigmented atrophic area that is most prominent temporally and that can correspond to sectors of the greatest disc cupping; large white arrows) and zone alpha (poorly demarcated hyperpigmented region irregularly surrounding zone beta; smaller black arrows). **(B)** Halo glaucomatous. With extensive glaucomatous cupping, zone beta (large white arrows) can surround the entire disc, with indistinct zone alpha (smaller black arrows). Note distinction between the scleral ring (thin white circumferential show of scleral tissue; black diamonds) and zone beta.

to zone alpha; internal to zone beta is the peripapillary scleral ring, which is often exaggerated in highly myopic eyes and with tilted discs. When zone beta completely surrounds the ONH, it has been called the *halo glaucomatosus* (Figs 13-11 through 13-14).

Histologically, zone alpha shows irregularities in the retinal pigment epithelium, consisting of an unequal distribution of melanin granules and partial atrophy of cells. In zone beta, adjacent to the optic disc, Bruch's membrane is bare of retinal pigment epithelium cells, the photoreceptors are markedly reduced in density or completely missing, and the choriocapillaris is severely attenuated.¹⁶⁵ Although there are slight methodological differences in measuring the more clearly distinguished zone beta, the increased area and increased frequency of the discrete locus of PPCA correlate both with variables of increasing severity (such as NRR area loss, loss of RNFL, and correlation with disc hemorrhage) and with progressive field changes in some studies.^{154,157,158,163,166}

Although some maintain that progressive changes in zone beta are independent of IOP and correlate with a relatively non-specific manifestation of advanced glaucomatous disc damage,¹⁵⁷ others have associated pronounced PPCA alterations with two distinctive subtypes of glaucoma – normal-pressure disease¹⁵⁶ and age-related POAG.⁵⁹ Because non-glaucomatous optic atrophy is *not* associated

with PPCA any more than with normal eyes, PPCA recognition may contribute to the clinical discrimination between glaucomatous and other mechanisms of disc damage.¹⁴³

PATTERNS OF OPTIC NERVE CHANGES AND SUBTYPES OF GLAUCOMA

With the wealth of clinical and morphometric studies of the ONH in all stages of glaucoma, a variety of classification schemes has been proposed to clinically distinguish subtypes of glaucoma based on the appearance of the disc.^{7-11,13,58-60,74,169} Although these 'archetypes' are not universally accepted, and there is considerable overlap of features as they appear in clinical practice, their tabulation is useful. Intra- and interobserver correlations for consistent identification have been reasonable.¹⁷⁰ These patterns are summarized and collated in Table 13-1.

HIGH MYOPIA DISC PATTERN

Highly myopic eyes with open-angle glaucoma have larger and often abnormally shaped optic discs (Fig. 13-15), and their

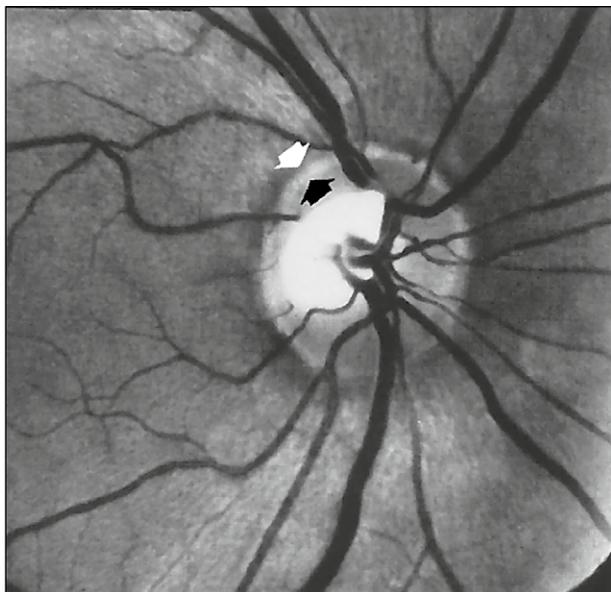


Fig. 13-12 Normal optic disc with physiologic scleral ring surrounding the optic disc. The scleral ring is limited centrally to the edge of the choriocleral canal (black arrow) and peripherally to the edge of the retinal pigment epithelium (white arrow).

(From Airaksinen PJ, Tuulonen A, Werner EB: Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn, St Louis, Mosby, 1996.)

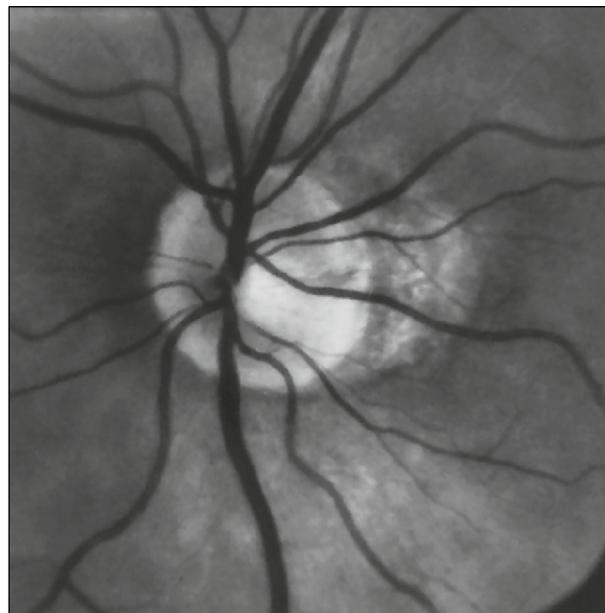


Fig. 13-14 Partial atrophy of peripapillary layers with disorganization, hypopigmentation, and hyperpigmentation of the retinal pigment epithelium, designated zone alpha. A small disc hemorrhage is located at 3 o'clock position. (From Airaksinen PJ, Tuulonen A, Werner EB: Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn, St Louis, Mosby, 1996.)

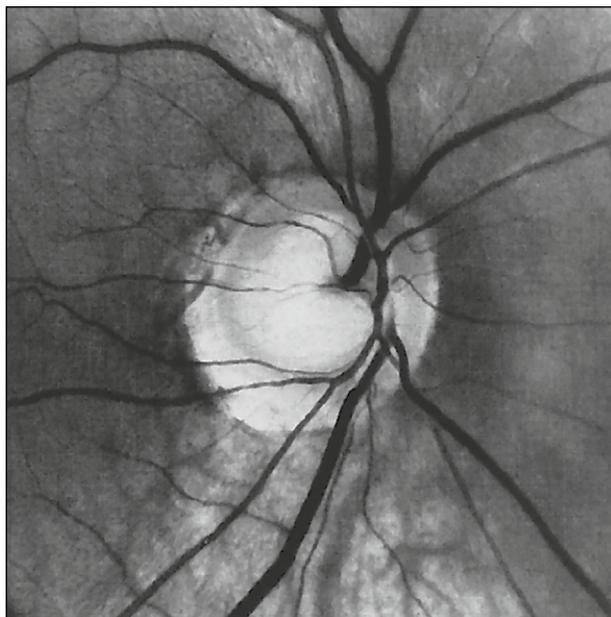


Fig. 13-13 Glaucomatous optic disc with diffuse thinning of the neural rim inferiorly with corresponding total atrophy of the retinal pigment epithelium and choriocapillaris, designated zone beta.

(From Airaksinen PJ, Tuulonen A, Werner EB: Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn, St Louis, Mosby, 1996.)

diagnosis represents a special problem in the management of glaucoma. Many myopic eyes have lost considerable vision from primary or secondary glaucoma before the ophthalmologist becomes aware of the diagnosis. The reasons for this difficulty are three-fold.

First, as Goldmann¹⁷¹ has pointed out, the distance between the level of the lamina cribrosa and the level of the retina is much less than in normal or hyperopic eyes. The average value of this distance in the normal eye is about 0.7 mm,¹⁷² whereas that of the myopic eye is between 0.2 and 0.5 mm. Therefore a completely cupped disc in a myopic eye will have only half the depth of the usual glaucomatous cup – and such a shallow excavation is difficult to clinically appreciate. Furthermore, the myopic ONH is masked by the usual myopic conus, tilting of the disc, and peripapillary atrophy. Often disc photographs are superior to drawings for surveillance of the subtle progression of the shallow cup with associated shifts in vessels or changes in PPCA.

Also, the ocular rigidity usually is lower than that of normal eyes. Therefore Schiötz tensions, using the ordinary conversion tables, are lower than the actual IOP. As described in Chapter 4, applanation tonometry prevents this error. A less well characterized potential artifact is the influence of thin corneas causing falsely lower applanation IOP readings; this may be operative in some myopic eyes.

Staphylomas of the posterior pole or peripheral fundus may produce irregular refractive errors that affect visual field examination. These errors especially affect current methods of perimetry using reduced-intensity static targets. In high myopia, it is best to have patients wear their regular contact lenses during testing. Finally, an enlargement of the blind spot or cecentral changes may be incorrectly attributed to the myopic conus and choroidal atrophy. The astute clinician must be on guard for glaucoma in myopic patients because it occurs more frequently in these patients (Fig. 13-16).⁶²

Table 13-1 Subtypes of glaucoma by optic nerve head appearance

Glaucoma types	Age and sex	Optic disc size and shape	Optic cupping	Disc hemorrhages or rim notches	Focal RNFL defects	Visual field changes	PPCA changes	IOP	Associated systemic anomalies
High myope	Younger than 50 years of age; males more than females	Large	Concentric, shallow, and sloping	Thin superior and inferior rims	No	Dense; focal; superior = inferior	Marked (may overlap with myopic temporal crescents)	Normal-high	-
Focal normal pressure (focal ischemic)	Older than 60 years of age; occurs in women more than in men	Normal	Deep and steep	Frequent disc hemorrhage and polar rim loss	Yes	Dense; focal; near fixation; superior more than inferior	±	Normal-high	Migraine; peripheral vasospasm?
Age-related atrophic POAG (senile sclerotic)	Older than 60 years of age	Normal	Saucerized, shallow, concentric and 'moth-eaten'	No	No	Relative defects with diffuse loss	Frequent; associated with tessellated fundus	Normal-high	Ischemic heart disease ± systemic hypertension
Juvenile OAG	10-40 years of age	Normal	Deep and steep	No	No	-	No	Normal-high	-
POAG (generalized enlargement)	Older than 40 years of age	Normal	Diffuse and round, concentric and symmetric	Rare disc hemorrhage and rare focal rim notch	No	Diffuse	No	High	-

Data from references 7-11, 13, 53, 59, 60, 74, 167-169.
RNFL, Retinal nerve fiber layer; PPCA, peripapillary choroidal atrophy; IOP, intraocular pressure; POAG, primary open-angle glaucoma; OAG, open-angle glaucoma.

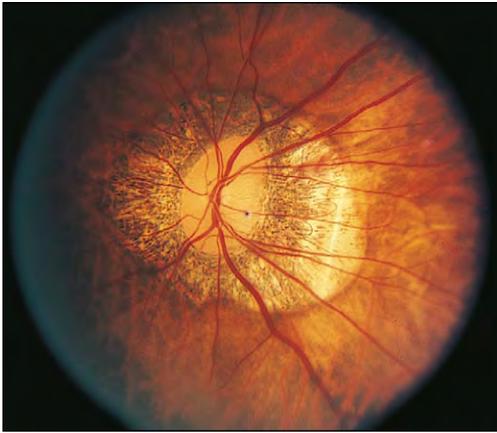
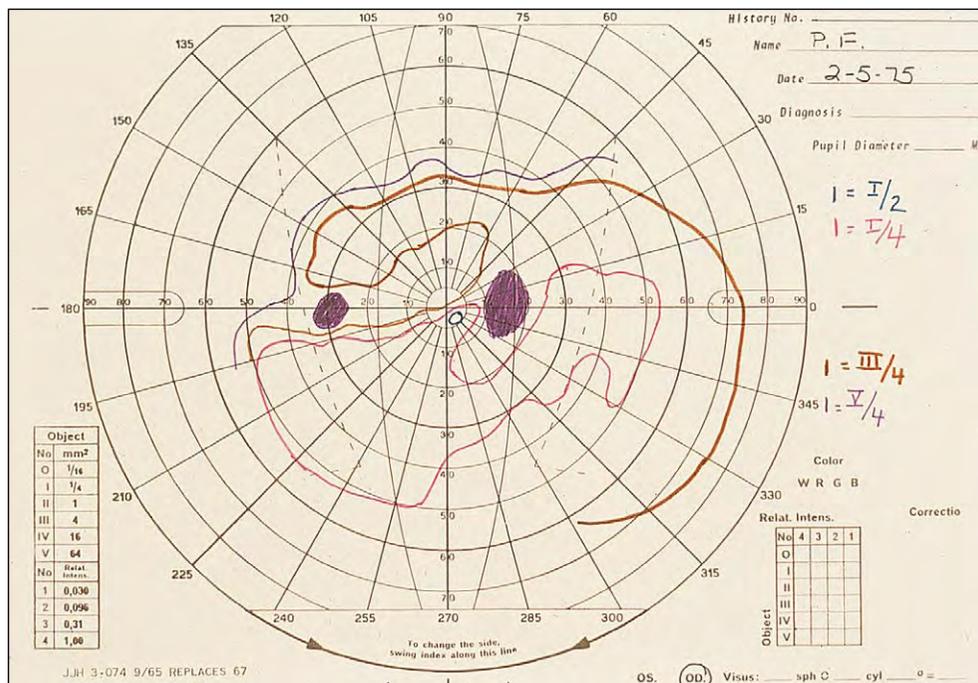


Fig. 13-15 High myopia disc pattern.



(A)



(B)

FOCAL NORMAL-PRESSURE PATTERN (FOCAL ISCHEMIC)

Eyes with the focal type of normal-pressure glaucoma have normally sized and shaped optic discs, but with characteristic cupping (Fig. 13-17).¹³ Often there is a steep and distinct edge to the cup, with the deep cup remaining visible as it vertically progresses to manifest rim notches, disc hemorrhages, and focal RNFL wedge defects.¹⁷³ Despite the polar notching, often the remainder of the rim tissue remains relatively intact.¹¹ Peripapillary choroidal atrophy changes are not particularly prominent.¹⁶⁸

The clinical associations for this disc appearance include a higher frequency among women, scotomas near fixation in the superior visual field,¹⁰ and a positive history for migraine headaches.¹¹ An exhaustive review of many other possibly relevant

Fig. 13-16 (A) The myopic disc can be particularly difficult to interpret for glaucomatous change. In this case, the disc edge is distinguished from the large temporal crescent. Myopic changes in the fundus can contribute to the visual field defects. (B) Visual field from the same patient. There is superior central loss caused by myopic degeneration. Peripheral contraction and apparent superior arcuate defect may be glaucoma related.



Fig. 13-17 Focal normal-pressure pattern (focal ischemic).

findings has been published.⁸ When color Doppler imaging of the retrobulbar circulation was undertaken, *all* of these disc-based categories of glaucoma demonstrated circulatory abnormalities in the orbital vessels, without a discrete pattern being attributable to this particular focal variety.¹⁶⁹ The inclusion of the term ‘ischemic’ is thus based on the clinical impression of frequent disc hemorrhages in these eyes, which rarely demonstrate highly elevated IOPs.

AGE-RELATED ATROPHIC PRIMARY OPEN-ANGLE GLAUCOMA PATTERN (SENILE SCLEROTIC)

Eyes with age-related atrophic primary open-angle glaucoma (Fig. 13-18) are often associated with diffuse fundus changes described as both ‘choroidal sclerosis’ and ‘tessellated fundus’¹¹ – findings that, in combination with the association with older age, account for the term ‘age-related’ or ‘senile sclerotic.’ The discs are of normal size and shape, but PPCA is a prominent finding,⁵⁹ so the edges of the ONH must be carefully distinguished. The cupping is described as shallow and saucerized, even ‘moth-eaten.’¹¹ As the concentric cupping progresses, the neural rim may nevertheless retain a pale but almost normal color.⁶⁸ This anomaly results in a discrepancy between the ‘color cup,’ as estimated on the basis of pallor (often with the monocular view of the direct ophthalmoscope), and the actual geometric, larger shape of the cup, as determined by high-magnification stereoscopic disc evaluation. The clinical appreciation of such *color/cup discrepancy* is important and often explains why visual field loss appears to be greater than the optic disc changes. Overlooking the color/contour discrepancy is a common reason for clinicians to underdiagnose the extent of glaucomatous damage in elderly patients. Focal changes, such as polar notching, disc hemorrhages, or wedge RNFL defects, are uncommon in this form of age-related atrophic cupping.

Often the fundus appearance is striking in its mosaic, or tessellated, pattern of prominent choroidal vessels and mottled orange background. One study⁵⁹ found that subgroups with the highest degree of fundus tessellation showed the most peripapillary atrophy and the lowest mean maximal IOP when compared with other subgroups with the same disc appearance. Other clinical associations have included a tendency toward lower IOPs;⁹ more generalized vascular disease (systemic hypertension and ischemic heart disease);¹¹ visual field loss that was often diffuse;⁵⁸ evidence

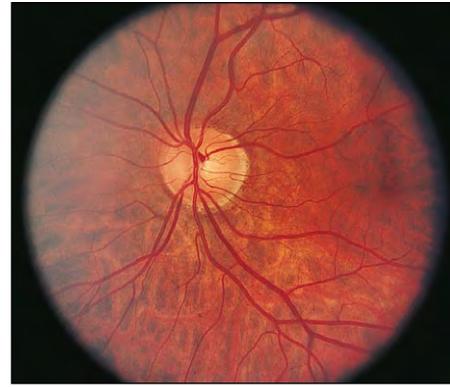


Fig. 13-18 Age-related atrophic primary open-angle glaucoma pattern (senile sclerotic).

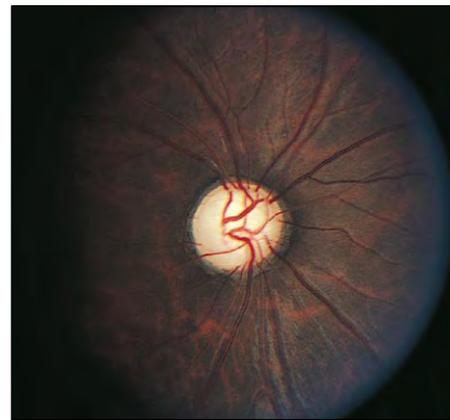


Fig. 13-19 Juvenile open-angle glaucoma pattern.

of pronounced disturbances of orbital blood vessel velocities as determined by color Doppler imaging;¹⁶⁹ and visual field progression less marked than seen with other patterns of disc damage.¹⁷⁴

JUVENILE OPEN-ANGLE GLAUCOMA PATTERN

Disc findings in younger patients with open angles, with or without discrete angle anomalies, share features in common with discs subjected to sustained elevated IOPs from secondary causes (Fig. 13-19).⁵⁸ The nerves are of normal size and shape and thus differ from myopic discs. The cupping is often distinctively steep-edged and deep, exposing the lamellar pores and struts, and it enlarges in a concentric pattern. Focal changes, such as disc hemorrhages, wedge RNFL defects, and signs of PPCA, are infrequent. One comparative study found virtually no distinctive morphologic features between high-IOP juvenile glaucomatous discs and those of older eyes with ‘normal-tension glaucoma.’¹⁷⁵

PRIMARY OPEN-ANGLE GLAUCOMA PATTERN (GENERALIZED ENLARGEMENT)

A distinctive category of disc appearance that is commonly seen in POAG with high IOPs includes a disc of normal size with diffusely enlarged round cups (Fig. 13-20).¹¹ Localized rim defects

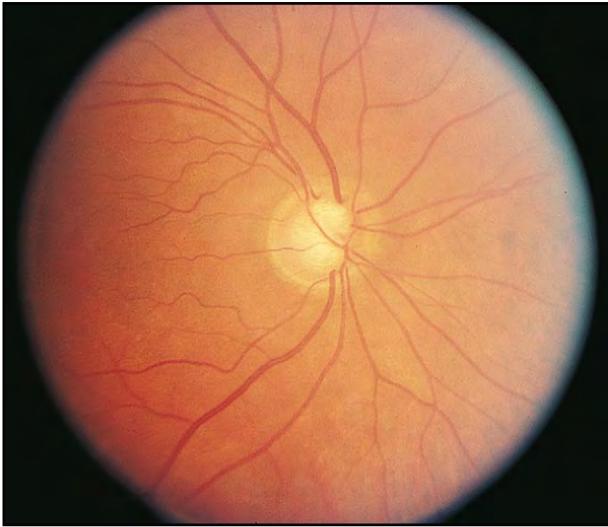


Fig. 13-20 Primary open-angle glaucoma pattern (generalized enlargement).

are uncommon, so abnormality or progression of cup enlargement necessitates comparison with the fellow eye, with serial photographs, or drawings. The cup increase is often biased toward the temporal rim, with gradual attenuation of the neural rim.⁶⁸ Such ‘temporal unfolding’ is a very common scenario in disc change, is difficult to clinically appreciate, and is associated with both diffuse RNFL and visual field loss. Usually the secondary forms of open-angle glaucoma, such as pseudoexfoliation⁶⁰ and pigmentary dispersion, manifest disc changes in a similar pattern.

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CHAPTER
14

Optic nerve imaging

Larissa Camejo and Robert J Noecker

Glaucoma is an optic neuropathy with characteristic optic nerve appearance and visual field loss for which elevated intraocular pressure (IOP) is one of the main risk factors.¹ This characteristic optic nerve appearance results from structural glaucomatous changes which usually precede functional deterioration (visual field loss).^{2,3} Therefore, improvement of the diagnostic methods of structural abnormality and change can result in earlier diagnosis of the disease.

Structural evaluations of the optic nerve head (ONH) and retina are key to the diagnosis and follow-up of glaucoma patients. Imaging tests complement slit-lamp biomicroscopy exam and stereo photos of ONHs. Ophthalmoscopy and even sequential stereo photos are dependent on the expertise and skills of the observer. High intra-observer and inter-observer variability has been demonstrated in several studies.^{4,5} The goal is to diagnose the disease or its progression as early as possible, to increase the probability of preventing visual loss.^{6,7}

There are three predominant imaging technologies currently in use for the diagnosis and evaluation of glaucoma in Europe and the U.S.⁸ These devices are: confocal scanning laser ophthalmoscopy (CSLO) (the most common commercial application is known as Heidelberg retina tomography (HRT)); optical coherence tomography (OCT); and scanning laser polarimetry (SLP), whose commercial application is known as GDX. Scans of the ONH, retinal nerve fiber layer (RNFL) and of the macula have been studied for their relevance to glaucoma. Not all imaging technologies have the capability of imaging all three intraocular structures. The ONH can be scanned with HRT and OCT. The nerve fiber layer can be scanned with GDX and OCT, and the macula can be scanned with OCT. All these technologies work differently and have their own strengths and limitations as well as different measures of reliability. Full comprehension of all of these points will allow the clinician to accurately interpret the data obtained by each one of the imaging tests, as well as their correlation with one another. The ultimate goal is to improve the early diagnosis of glaucoma and detection of glaucomatous progression.

CONFOCAL SCANNING LASER OPTHALMOLOGY (CSLO)

HEIDELBERG RETINA TOMOGRAPHY (HRT)

Confocal scanning laser ophthalmoscopy is the imaging technology and HRT (Heidelberg Engineering, Heidelberg, Germany) is the major commercially available instrument that utilizes this imaging system to study the eye (Fig. 14-1). Heidelberg retina tomography has three generations: HRT, HRT II and HRT 3.

Confocal scanning laser ophthalmoscopy is capable of obtaining three-dimensional images of the optic disc by acquiring high-resolution images, both perpendicular to the optic axis (x - and y -axis) and along the optic axis (z -axis) (Fig. 14-2). It is based on the principle of spot illumination and spot detection. Conjugated pinholes are placed in front of the light source and light detector and allow only light originating from a determined focal plane to reach the detector. Sequential sections are obtained by moving the depth of the focal plane through the whole depth of the tissue being studied; in this case, the optic nerve. The focal plane depth is adjusted by shifting the confocal aperture or pinhole (Fig. 14-3).

Heidelberg retina tomography makes use of a 670 micron diode laser to perform rapid scanning of the fundus. Oscillating mirrors in the HRT device redirect the laser beam to the x - and y -axis, along a plane of focus that is perpendicular to the optic axis (z -axis). A bi-dimensional image (15×15 degrees) is obtained at each focal plane. As the device changes the focal plane, other bi-dimensional images of the optic nerve are obtained. Each one represents an optical section of the optic nerve. A total of 64 sections, each done with 1/16 mm of depth interval, are obtained and used to create a three-dimensional image of the optic nerve. These 64 sections are equivalent to a depth of 4 mm.

Each optical section is composed of 384×384 points compose each optical section. Each one of these points has an x (horizontal),



Fig. 14-1 Heidelberg retina tomography (HRT) II scanning laser ophthalmoscope.

y (vertical) and z (depth) value to locate it in space. The amount of light or 'reflectance' along the z -axis is measured at each scanned point, and the more intense the light is at a given point, the higher (closer to the surface) this is. In this way, the peak distribution of the reflected laser light intensity corresponds to the retinal/ONH surface. The peak intensity along the z -axis is assumed to correspond to the internal limiting membrane that overlies the retina and optic disc. A matrix of retinal height measurements is then created. The result is a topographical map of 384×384 height measurements of retinal and optic nerve surface topography. The light intensity measured at each one of the 384 points and used for the creation of the mean topography map is the result of an average of three scans which are automatically obtained by the newer generations of HRT. The transverse resolution is 10 microns and the axial resolution is 300 microns.

Once the image is taken, the operator delineates the optic nerve contour line over the reflectance or topography image. The

operator places points at the external edge of the disc border and the machine draws a 'best-fit' ellipse linking these points together (Fig. 14-4). Heidelberg retina tomography proceeds to define the reference plane based on the disc contour drawn by the operator. The reference plane is located 50 microns posterior to the mean height along a 6° arc of the contour line at the temporal inferior sector. Structures above the reference plane and within the contour line are considered to be rim. Anything below the reference plane is considered cup (Fig. 14-5). Computation of stereometric parameters, classification of the eye and comparison to previous examinations are then done by the HRT. Classification of the eye is done with Moorefield's regression analysis or other discriminating method in HRT II, or with neural network analysis in HRT 3.

The latest software available, HRT3, can provide ONH stereometric analysis without manual delineation of the disc margin by the operator. After a three-dimensional model of the ONH is constructed, five optic nerve parameters are calculated and then

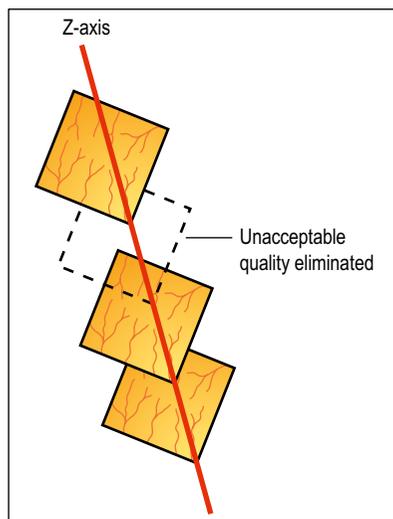


Fig. 14-2 Single images are obtained at different depths along the z -axis and aligned. Poor-quality images are eliminated in the process.

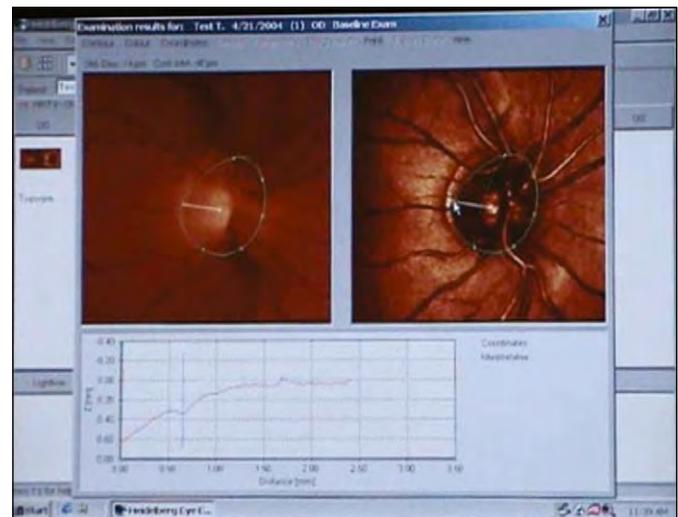


Fig. 14-4 Optic nerve disc delineation by operator.

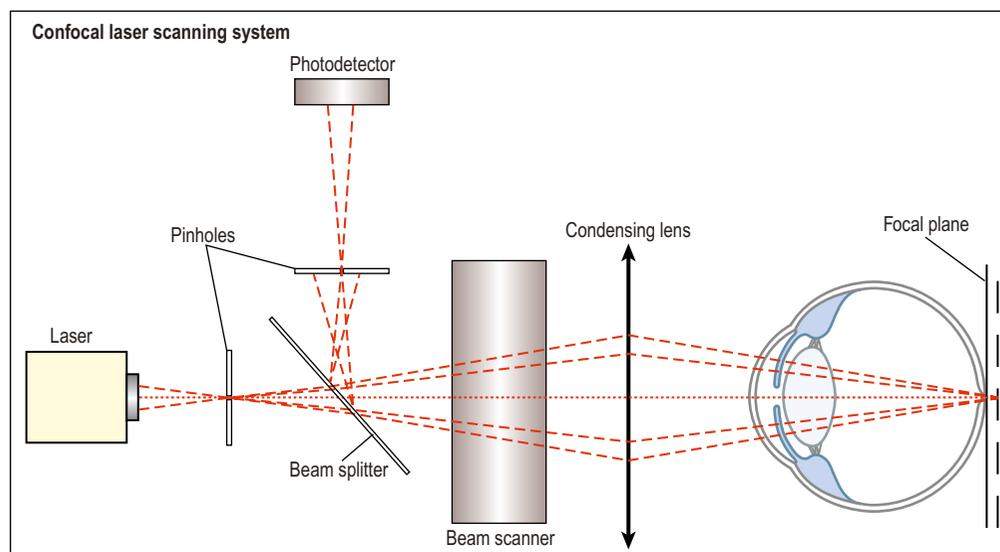


Fig. 14-3 Schematic diagram of a confocal scanning laser system used in HRT. (Adapted from Fingeret M, Flanagan JG, Liebman JM: The essential HRT primer, USA, Heidelberg Engineering, 2005.)⁷

analyzed with an artificial intelligence classifier, the relevance vector machine (RVM). From this analysis, a glaucoma probability score (GPS) is created.

Adjustments are made to the parameters to account for differences in age and disc size by both versions of HRT. However, HRT 3 is equipped with a larger and more diverse normative database than its predecessor. It currently includes large samples of three different ethnicities: Caucasian (>700), African descent (>200) and Indian or south-east Asian (>100). In comparison, the HRT II normative database includes 112 eyes, all from Caucasian subjects.

There are several printout formats currently available: initial report, follow-up report and 'OU report,' among others. Below, the different components of the HRT printout are discussed.

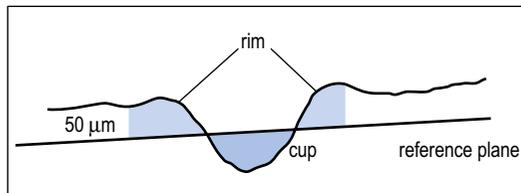


Fig. 14-5 Reference plane as calculated by HRT is based on disc contour delineation. The reference plane is defined as 50 microns posterior to the mean height along 6° of the contour line at the temporal inferior sector. Structures above the reference plane and within the contour line are considered as rim. Structures below the reference plane are considered as cup.

Components of the HRT report

1. *Patient data:* name, sex, date of birth, patient ID, and date of exam are provided here (Figs 14-6 and 14-7).

2. *Topography image:* located on the left upper corner of the printout. It is a false-color image. More superficial areas appear darker and deeper areas appear of a lighter color. Additional colors are added to the map: red indicates the cup (area below the reference plane) and green and blue indicate neuroretinal rim tissue (above the reference plane). Blue indicates sloping rim.

3. *Reflectance image:* located in the right upper corner of the unilateral report or below the topography image on the 'OU report.' It is also a false-color image and is similar to a photograph with the brighter areas representing highest reflectance, like the cup. The reflectance image is overlaid with Moorfields analysis.

4. *Retinal surface height variation graph:* this appears once the disc contour is drawn and accepted. It is the graphical representation of the retinal height along the contour line and of the thickness of the nerve fiber layer. A green line represents the retinal height and a red line represents the reference plane. The graph depicts, from left to right: the thicknesses of the temporal (T); temporal-superior (TS); nasal-superior (NS); nasal (N); nasal-inferior (NI); temporal-inferior (TI); and temporal (T) sectors. Because the thickness of the normal retina is irregular, the contour line will appear as what is known as the 'double-hump.' The hills or 'humps' correspond to the superior and inferior nerve fiber layer, which are normally thicker than the rest of the areas.

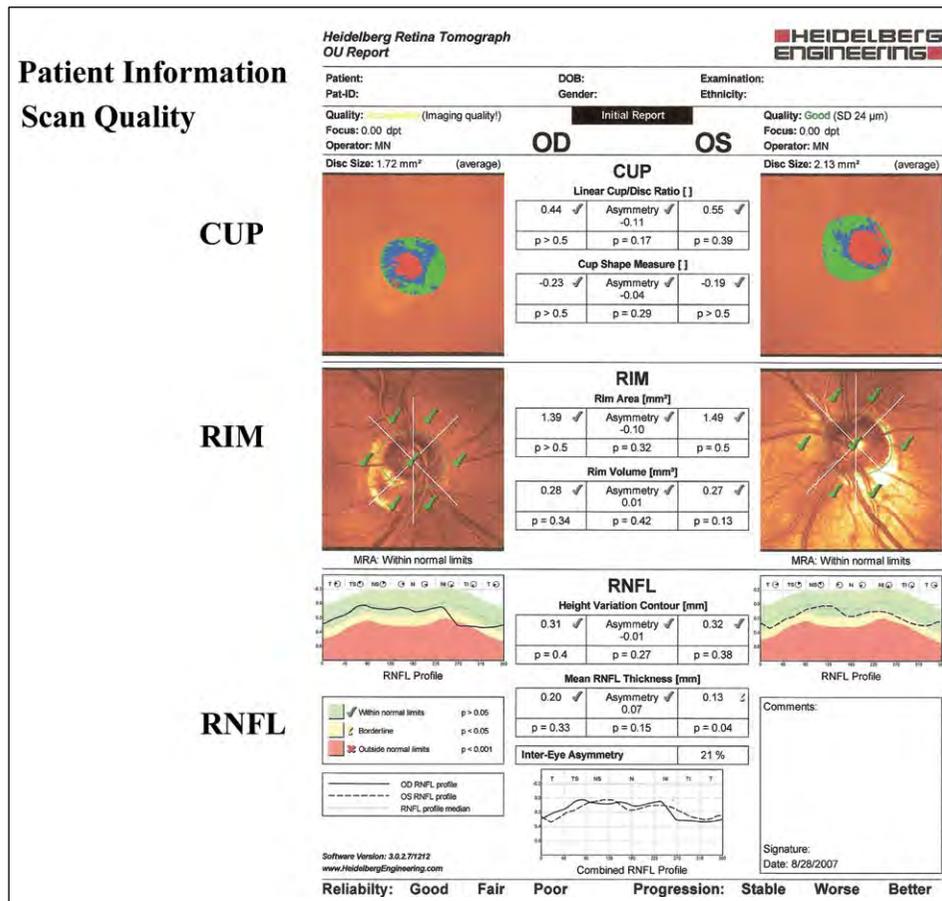


Fig. 14-6 HRT 3 baseline printout. After patient information, a Quality score is provided with classification for quick quality assessment. Scores below 30 represent good quality images. The cup section represents the disc topography. The CUP parameters shown in this row are cup/disc (C/D) area ratio and cup shape measure. The RIM section represents reflectance data with overlay of mean rim area (MRA) classification. The middle column shows rim parameters: rim area and rim volume. The last section contains the RNFL profile graph. It displays the height values at the optic disc margin going around the optic disc from the temporal side, to superior, nasal, inferior, and back to temporal (TSNIT). The green shaded area gives the normal range for that particular age, optic disc size, and ethnicity. Height measures that fall into the yellow zone are borderline, and those that fall into the red zone indicate abnormal values.

Patient Information

Scan Information

Topography

Horizontal (H) cross-section. Vertical (V) cross-section is in between topography and reflectance images. Retinal surface height graph to right.

Stereometric parameters. Moorfields regression graph to right.

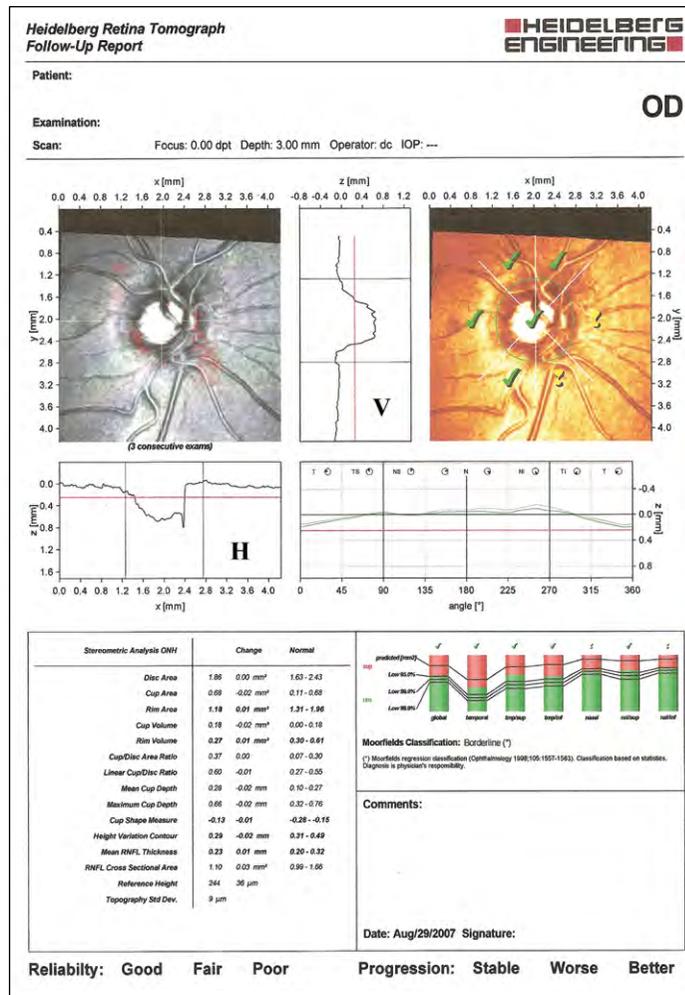


Fig. 14-7 HRT II baseline printout.

5. *Vertical and horizontal interactive analysis:* these are the optic nerve retinal surface height horizontal and vertical cross-sections. A smooth trace as opposed to a 'jagged' trace represents a better quality scan. Observation of the trace can provide information of the disc steepness, presence of sloping, etc.

6. *Stereometric analysis:* HRT II provides a list of 14 nerve parameters. They are: disc, cup and rim area, cup and rim volume, cup/disc area ratio, linear cup/disc ratio, mean cup depth, maximum cup depth, cup shape measure, height variation contour, mean retinal nerve fiber layer (RNFL) thickness, RNFL cross-sectional area and reference height. To the right of the stereometric parameters, a column specifies \pm one standard deviation from the mean of the normative database for each of the parameters. HRT 3 only provides values for 6 stereometric parameters in the 'OU printout.' These are: cup/disc area ratio, cup shape measure, rim area and volume, height variation contour and mean RNFL thickness. Each value is designated as within normal limits, borderline or outside normal limits after comparing to the normative database.

7. *Moorfields regression analysis (MRA):* the MRA is based on a normative database of 112 Caucasian subjects with refractive error $<6D$ and disc size within the range of 1.2–2.8 mm. A predicted rim area/disc area line was obtained after plotting the ratio values among these subjects. Such a predicted line represented the value obtained in 50% of the normal subjects studied. Further classification limits

were obtained. In this way, if the rim area of any segment (global assessment or any of the 6 sectors) is below the 99.9% prediction interval, the nerve is classified as outside normal limits (red x). In other words, 99.9% of 'normals' have a higher rim area/disc area value than that of the nerve being classified as outside normal limits (ONL). If the rim area falls between the 95% and 99.9% prediction lines, it is classified as borderline (yellow checkmark). Rim areas that fall above the 95% prediction level are classified as within normal limits (green checkmark). The Moorfields analysis graph is shown in the printout, indicating the predicted intervals on which the nerve classification is based. Seven different columns representing all sectors are shown and classified as within normal limits (WNL), borderline (BL) or ONL. Green color represents the rim and red represents the cup. Moorfields classification is also shown over the reflectance image as a green checkmark, yellow exclamation point, or a red 'x.' The Moorfields classification of the nerve is written at the bottom of the graph. Moorfields regression analysis classifies discs based on the worst classified sector.

8. *Glaucoma probability score (GPS):* new software included in the HRT 3 generation allows calculation of the GPS. It is based on the construction of a three-dimensional model of the ONL and peripapillary RNFL by using five parameters: cup size, cup depth, rim steepness, and horizontal and vertical RNFL. The complete three-dimensional model is then subjected to analysis by an artificial

intelligence classifier, the relevance vector machine (RVM), that compares it to a predetermined normal and glaucoma model and then derives the probability of glaucoma for the scanned eye:

- Probability $\leq 28\%$ – within normal limits (WNL)
- Probability $> 28\%$ – borderline (BL)
- Probability $\geq 64\%$ – outside normal limits (ONL).

Evaluating scan quality

Only data extracted from a scan of good quality is valuable. Therefore, it is of the utmost importance to know how to identify a poor quality scan. Good quality indicators are even luminance and sharp borders of the topography and reflectance images, as well as good centration of the disc. The standard deviation (SD) is a measurement of variability of the same pixel values among three different scans. The average light intensity for each point is what is used for the RNFL height measurement. The manufacturer has suggested not analyzing scans with a SD value greater than 40. It is important to point out that SD should not be the only parameter to use when assessing quality. A poor quality scan can still have a low SD value if there is small or no variability among the three scans.

The manufacturer's classification of scans by SD values is:

- <10 : excellent
- 11–20: very good
- 21–30: good
- 31–40: acceptable
- 41–50: poor
- >50 : very poor.

Looking at cross-sections can also help determine the degree of noise in the obtained images. The contour cross-sectional trace should be soft and not 'jagged.'

Strengths and limitations

Heidelberg retina tomography allows for rapid and simple operation and for three-dimensional representation of the optic nerve without the need for pupil dilation. Heidelberg retina tomography was used in one of the largest glaucoma clinical trials, the Ocular Hypertensive Treatment Study (OHTS), and therefore a large amount of data is available.^{10,11}

Limitations of the HRT include the use of a reference plane that depends on the contour line drawn by the operator. Measurements might be affected by the blood vessels. The nasal border of the nerve can be difficult to identify given that blood vessels can appear crowded in this area and obscure the disc's edge. *Confocal scanning laser ophthalmoscopy is appropriate for scanning the ONH but not the macula or RNFL.*

Substantial inter-observer variability exists among HRT parameters, depending on the placement of the contour line. The most dependent parameters were rim volume and disk area and the least dependent were mean height contour and cup shape in one study.¹²

Higher rim measurements obtained from HRT optic nerve analysis compared to planimetric evaluation of disc photos are thought to be in part a result of blood vessel inclusion as part of the disc.^{13,14} These limitations are secondary to potential errors in the delineation of the nerve done by the operator. The GPS analysis bypasses this problem. Early studies regarding the reliability of GPS analysis and its comparison with conventional HRT-MRA analysis are available.^{15–17}

Heidelberg retina tomography's capability of discrimination between normal and glaucomatous patients has been tested in the past, and parameters were compared to search for the best discriminating parameters. Among the best parameters were cup

shape measure, rim area and cup volume.^{18,19} Nevertheless, combining parameters can render the strongest discrimination between groups. Different methods have been designed to analyze the data. Mikelberg's discriminating analysis and MRA are part of HRT software. Moorfields regression analysis can discriminate glaucomatous nerves from normals with 84.3% sensitivity and 96.3% specificity.^{20,21} Still, the HRT will occasionally call a severely damaged optic nerve normal or a normal optic nerve abnormal.

Heidelberg retina tomography tends to overestimate rim area in small optic nerves and to underestimate rim area in large nerves. So on either extreme of disc size range, care should be taken when analyzing these scans.

New developments

The latest generation is HRT 3. HRT 3 includes the same MRA classification as HRT II, but it is based on a larger, more diverse normative database. It also assigns a GPS to the optic nerve disc. The GPS is based on three optic disc parameters and two RNFL parameters. A three-dimensional optic nerve is constructed and compared to preconstructed models of normal and glaucomatous nerves and a GPS is assigned to the nerve being tested. This analysis is independent of optic nerve contour delineation.

Testing from the patient's perspective

The patient's experience is similar to that of having a slit-lamp exam and definitely more comfortable than having a fundus photo taken. The luminance of the diode laser is 100 times lower than the luminance of a digital fundus flash camera. The diode laser used in HRT is safe to the eye. A typical imaging session can be completed in less than 7 seconds.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

Optical coherence tomography (Carl Zeiss Meditec, Inc., Jena, Germany), developed in 1991,^{22,23} is an imaging technology that performs high-resolution, cross-sectional imaging of the ONH, RNFL and macula. It measures the intensity and echo time delay of back-scattered and back-reflected light from the scanned tissues (Fig. 14-8). Optical coherence tomography is analogous to ultrasound B-mode imaging, the difference being that the former uses light and the latter uses sound. It is based on the principle of low-coherence interferometry and the ability to differentiate retina layers depending on the different time delay of their reflections.

A super luminescent 820 or 850 nm diode laser beam is the light source directed to a partially reflecting mirror that splits the light into two beams: one is directed towards a mirror placed at a known distance (reference mirror) and the other is directed towards the eye, from where it will reflect back. This back-reflected light will consist of multiple echoes, with information about the distance and thickness of the different intraocular tissues. The back-reflected light from the eye is combined with the back-reflected light from the reference mirror and coherent light is compared. Interference is produced when two light pulses coincide. The reference mirror is then moved so that the time delay of the reference light pulse can change accordingly and therefore other intraocular structures can be measured (Figs 14-9 and 14-10). The laser beam is panned throughout the tissue and a series of scans are obtained in the manner explained above, until a two-dimensional map is created based on the interference signals detected. The map is color coded in a way that white and red represent areas with high reflectivity and

blue and black represent areas with low reflectivity. High reflectivity layers include the nerve fiber layer, retinal pigment epithelium (RPE) and choriocapillaris. Low reflectivity layers or tissues include the photoreceptor layer, choroids and pockets of fluid.

Unlike other machines, OCT has the ability to scan three distinctive ocular structures: the peripapillary RNFL, the optic nerve,

and the macula (Fig. 14-11). Optical coherence tomography has the best axial resolution of all the imaging devices presented here. OCT 3 has a resolution of 8–10 microns and the latest Ultra-high resolution has an impressive axial resolution of 3–4 microns. On the other hand, transverse resolution is limited secondary to the limited number of sampling points obtained by OCT. Different



Fig. 14-8 OCT Stratus.
(Courtesy of Zeiss Meditec, Inc., Jena, Germany.)

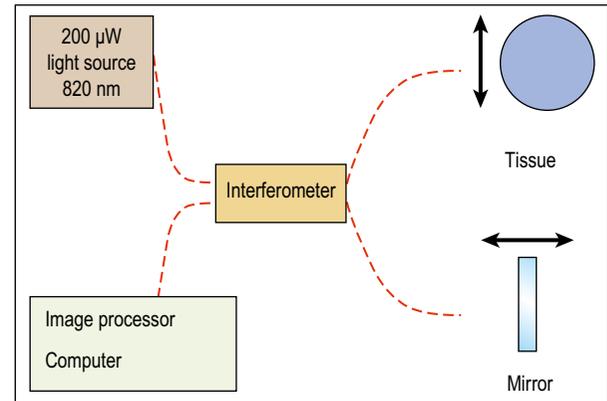


Fig. 14-10 This is a diagram of the fiber-optic interferometer in the OCT imaging system. Low-coherence superluminescent diode is coupled into an optical fiber and directed into an optical fiber coupler (beam splitter), where one fiber forms the measurement path and the other the reference path. The fiber in the measurement path is connected to a clinical imaging device, such as a fundus camera of a slit-lamp biomicroscope. (Adapted from Schuman JS, Puliafito CA, Fujimoto JG: *Everyday OCT: a handbook for clinicians and technicians*, NJ, USA, Slack Inc., 2006.)²⁴

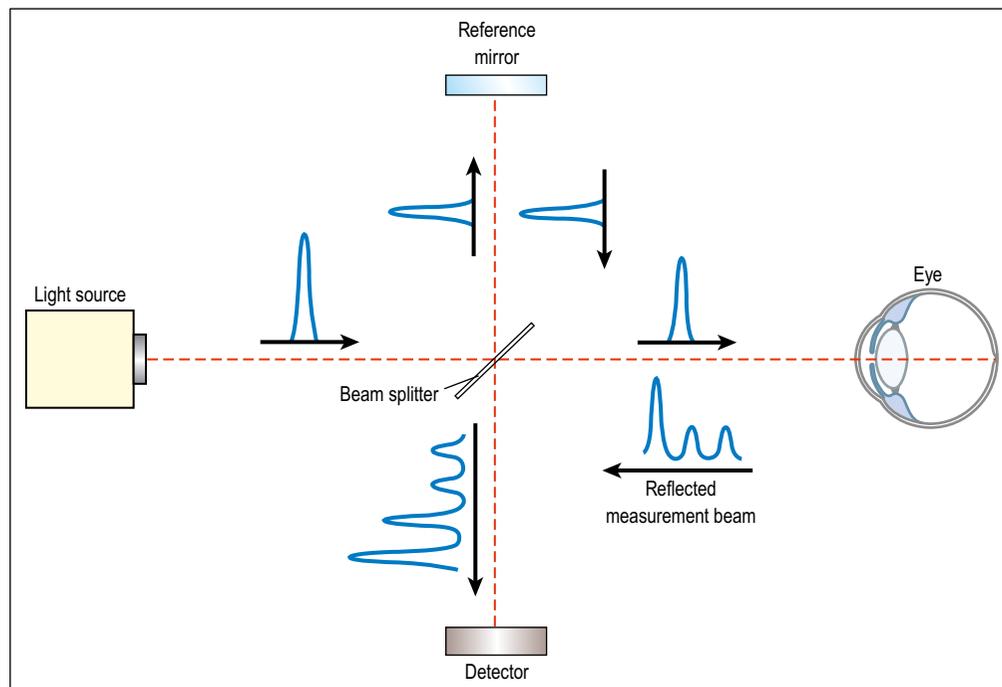


Fig. 14-9 Low-coherence interferometry system used in OCT. A superluminescent 850 nm diode laser beam is directed to a partially reflecting mirror that splits the light into two beams: one is directed towards a mirror placed at a known distance (reference mirror) and the other is directed towards the eye, from where it will reflect back. This back-reflected light will provide information about the distance and thickness of the different intraocular tissues. The back-reflected light from the eye is combined with the back-reflected light from the reference mirror and coherent light is compared. Interference is produced when two light pulses coincide. The reference mirror is then moved so that the time delay of the reference light pulse can change accordingly and therefore other intraocular structures be measured.

(Adapted from Schuman JS, Puliafito CA, Fujimoto JG: *Everyday OCT: a handbook for clinicians and technicians*, NJ, USA, Slack Inc., 2006.)²⁴

generations of OCT exist: OCT 1, OCT 2, OCT 3 or Stratus OCT, and OCT Spectral (Fig. 14-12); Newer technologies include spectral domain and fourier domain OCT; these show higher resolution than previous OCT versions.*

DIFFERENT SCANNING MODALITIES

Peripapillary scan

This consists of a 3.4 mm circular scan that is used to measure the thickness of the RNFL. A RNFL curve is obtained by ‘opening up’ the circular scan. The RNFL curve starts with the temporal quadrant and continues clockwise in the right eye and counterclockwise in the left eye. The RNFL thickness values are provided for the four quadrants (temporal, superior, nasal, and inferior) and for 12 clock hours. Tested optic nerves are classified as within normal limits, borderline or outside normal limits, after comparing their RNFL thickness values to those of the normative database. The outcomes are also color coded. Green means within normal limits, yellow, borderline, and red, outside normal limits. Classification of

RNFL thickness is assigned to all sectors and clock hours of the nerve but an average RNFL is also established.

Macular scan

This consists of six linear scans in a spoke pattern configuration. The linear scans are spaced 30° apart.

The length of the linear scans can be 3 mm or 6 mm. The longer 6 mm scan is more commonly used. The ‘fast macular scan’ utilizes 128 A-scans for each radial linear scan. It is possible to choose 256 and even 512 A-scans. Variability of measurements might decrease by using more sampling points (more A-scans), but the time of the test might increase as well, which could ultimately cause errors in image registration by jeopardizing the patient’s ability to maintain fixation. A color-coded (blue represents thinner retina and yellow-green-red represents thicker retina) macular thickness map and a map with quantitative measurements in nine sectors is derived from the macular scan. The map depicted is a cross-sectional map along one of the six radial scans (a small map will show which axis is being analyzed).

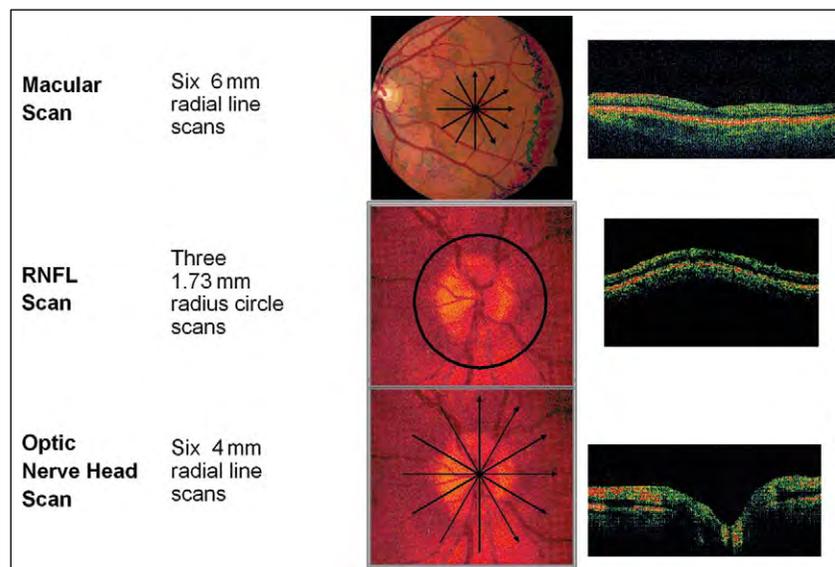
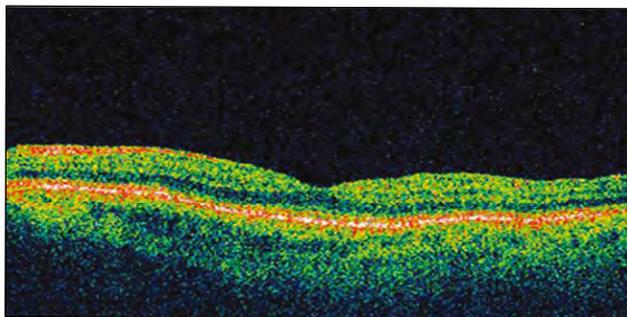


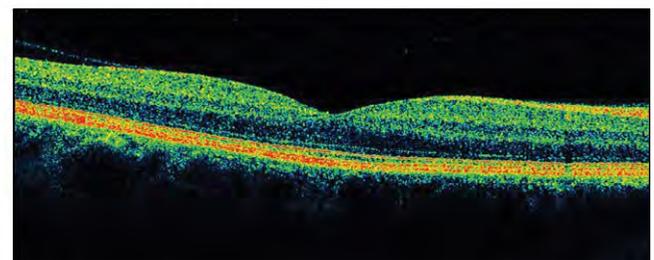
Fig. 14-11 Different OCT scanning modalities. (A) Linear scan used in macular scan; (B) fast macular scan; (C) circular scan of RNFL; (D) linear scan used in ONH scan. (Courtesy of Zeiss-Meditec, Inc., Jena, Germany.)

Stratus OCT



(A)

Spectral Domain (UHR) OCT



(B)

Fig. 14-12 (A) Stratus OCT image of macula area. (B) Spectral domain OCT image of macular area. Note higher resolution and clearer delineation of retinal layers compared to Stratus OCT.

(Courtesy of Zeiss-Meditec, Inc., Jena, Germany.)

*Several new devices from different manufacturers were appearing on the market as this book goes to press. The superiority of these higher resolution devices for clinical purposes remains to be demonstrated.

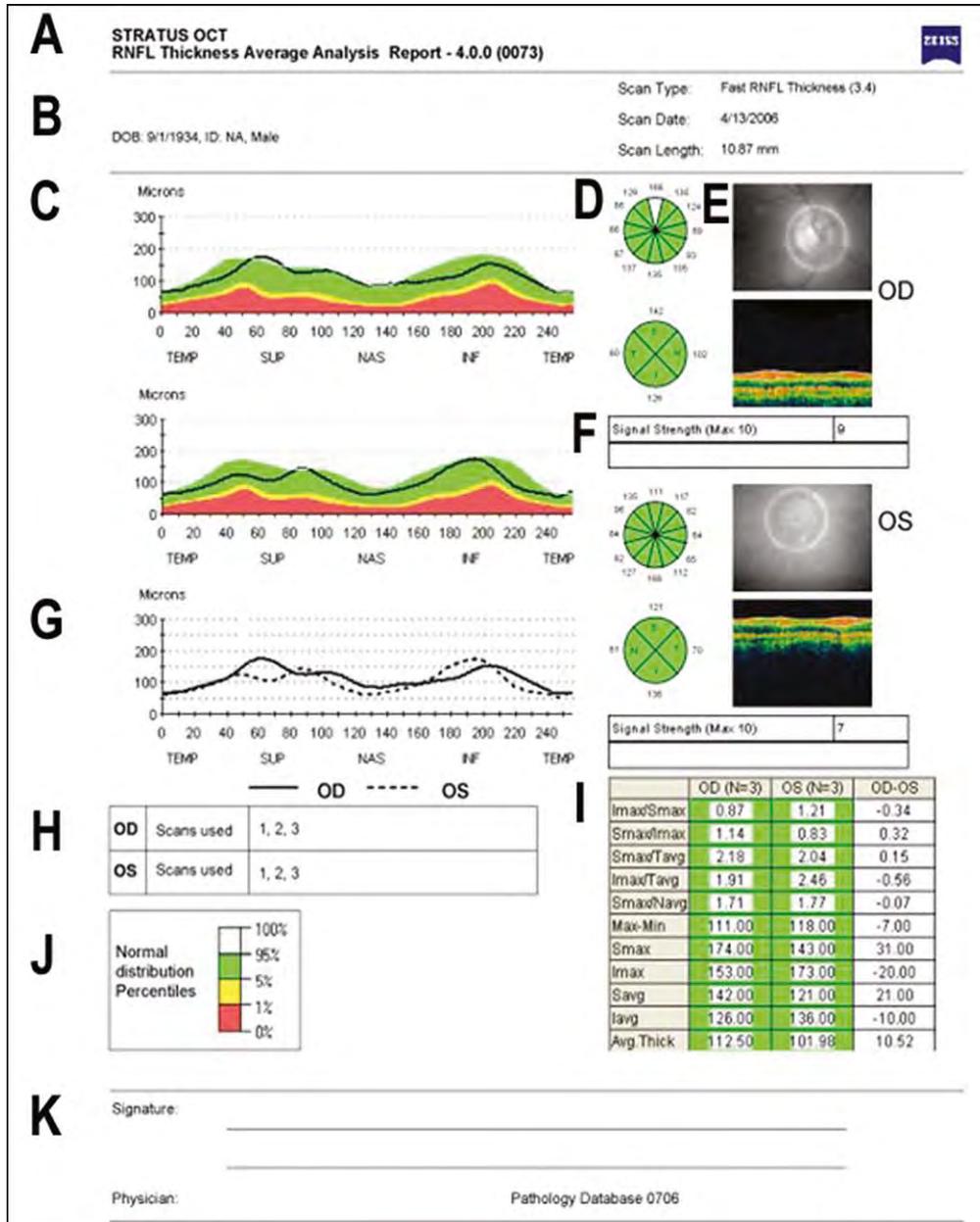


Fig. 14-13 OCT RNFL thickness average analysis report. **(A)** Type of report. **(B)** Patient information. **(C)** RNFL thickness graph with color-coded normative database. **(D)** Clock-hour thickness (top) and quadrant thickness (bottom). **(E)** Fundus image showing scan placement (top) and single OCT scan (bottom). **(F)** Signal strength. **(G)** Overlay graph of RNFL thickness for both eyes. **(H)** Scans included in analysis. **(I)** Measured parameters. **(J)** Percentiles for normal distribution. **(K)** Physician interpretation. (Adapted from Schuman JS, Puliafito CA, Fujimoto JG: Everyday OCT: a handbook for clinicians and technicians. NJ, USA, Slack Inc., 2006.)²⁴

ONH scan

The same 'star' or 'spoke' pattern scan used to scan the macula is also used to scan the ONH. Each line measures 4 mm in this linear scan. Optical coherence tomography automatically defines the ONH margin as the endings of the RPE, which are marked by a blue cross. A straight line is drawn connecting these crosses. A parallel line is drawn 150 microns anterior to this line. This line is analogous to the reference plane described in HRT. Anything above the line is considered rim and anything below is considered cup.

Fast scans

These are available with OCT 3. They are time efficient, obtained in 1.92 seconds. Accuracy of the scan is improved secondary to reduction of error caused by the patient's movement or loss of fixation. Resolution is lower. All three structures (RNFL, macula, and ONH) can be scanned using the 'fast-scan' modality.

Comparison of three scanning areas has been done. Stratus OCT (OCT 3) demonstrated reproducible measurements of RNFL, macular and ONH parameters in one study.²⁵ In a comparison for detection of glaucoma damage, OCT ONH and RNFL parameters proved to be superior than macular parameters in discriminating normal from glaucoma patients.²⁶

COMPONENTS OF THE OCT REPORT

RNFL thickness average analysis

The printout includes RNFL thickness curves for both eyes. The RNFL curve is drawn as a black line on a graph featuring thickness in microns and different areas of the peripapillary RNFL: temporal, superior, nasal, and inferior. The RNFL curve is drawn over a background of color-coded (green means within normal limits, yellow means borderline and red means outside normal limits) shaded

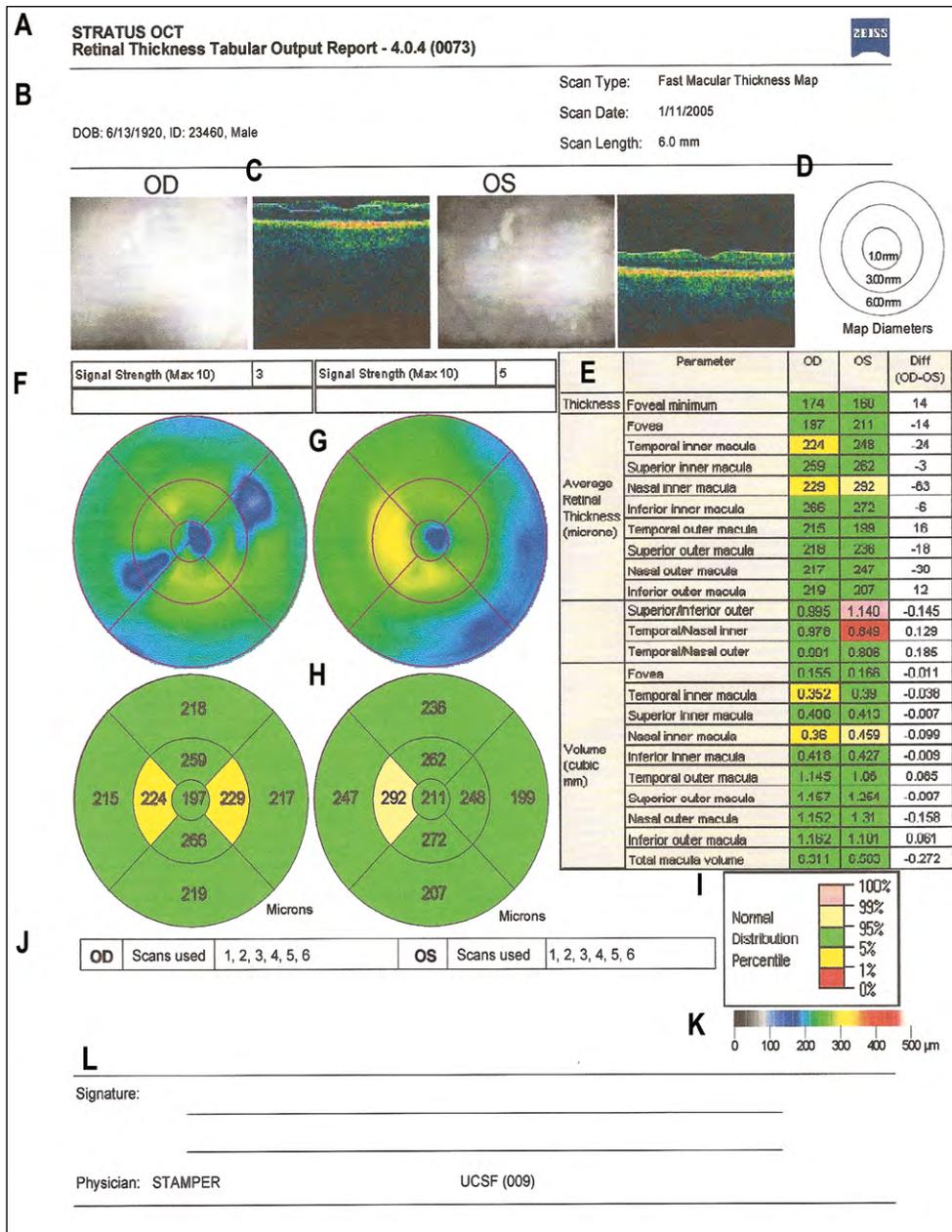


Fig. 14-14 Retinal thickness tabular output report. **(A)** Type of report. **(B)** Patient and scan information. **(C)** Fundus image and single OCT scan. **(D)** Diameters used for thickness map. **(E)** Thickness and volume parameters. **(F)** Signal strength. **(G)** Color-coded thickness map. **(H)** Thickness map with normative data. **(I)** Percentiles for normal distribution. **(J)** Scans included in the analysis. **(K)** Color-coded thickness scale. **(L)** Physician interpretation. (Adapted from Schuman JS, Puliafito CA, Fujimoto JG: Everyday OCT: a handbook for clinicians and technicians, NJ, USA, Slack Inc., 2006.)²⁴

areas representing RNFL thickness classification according to the normative database. A normal RNFL curve will have the characteristic 'double hump' appearance with the superior and inferior RNFL being thicker than the nasal and temporal RNFL. The peripapillary RNFL is divided into 12 clock hours and into four quadrants. All are classified in a color-coded manner. A photo of the retina while the scan was obtained is also shown in the printout. The circular scan appears in the picture and its centration over the ONH can be corroborated. Centration is important for accurate thickness measurements of all quadrants. A false color cross-sectional image is shown for both eyes with signal strengths specified for each image. The average thickness is calculated for both eyes and it appears at the bottom of the thickness measurement table. The thickness values are color coded as well. Studies have been done to assess the reproducibility of these values. Schuman et al.²⁷

found a SD of 10–20 microns for the average RNFL thickness and 15–30 microns for the clock-hour measurements (Fig. 14-13).

Macular analysis

A retinal thickness analysis and a retinal map analysis can be obtained from the macular scan data. The retinal thickness printout provides a cross-sectional image of the retina along a specific axis of scan (indicated in the printout), signal strength, and a thickness chart with background shaded areas representing the normative database. A retinal thickness measurement is also provided. The retinal map analysis also provides a cross-sectional image and includes two maps, one with qualitative and another with quantitative thickness measurements. Measurements for nine macular sectors are shown as well as thickness measurements for the center of the scan and the total macular volume (Fig. 14-14).

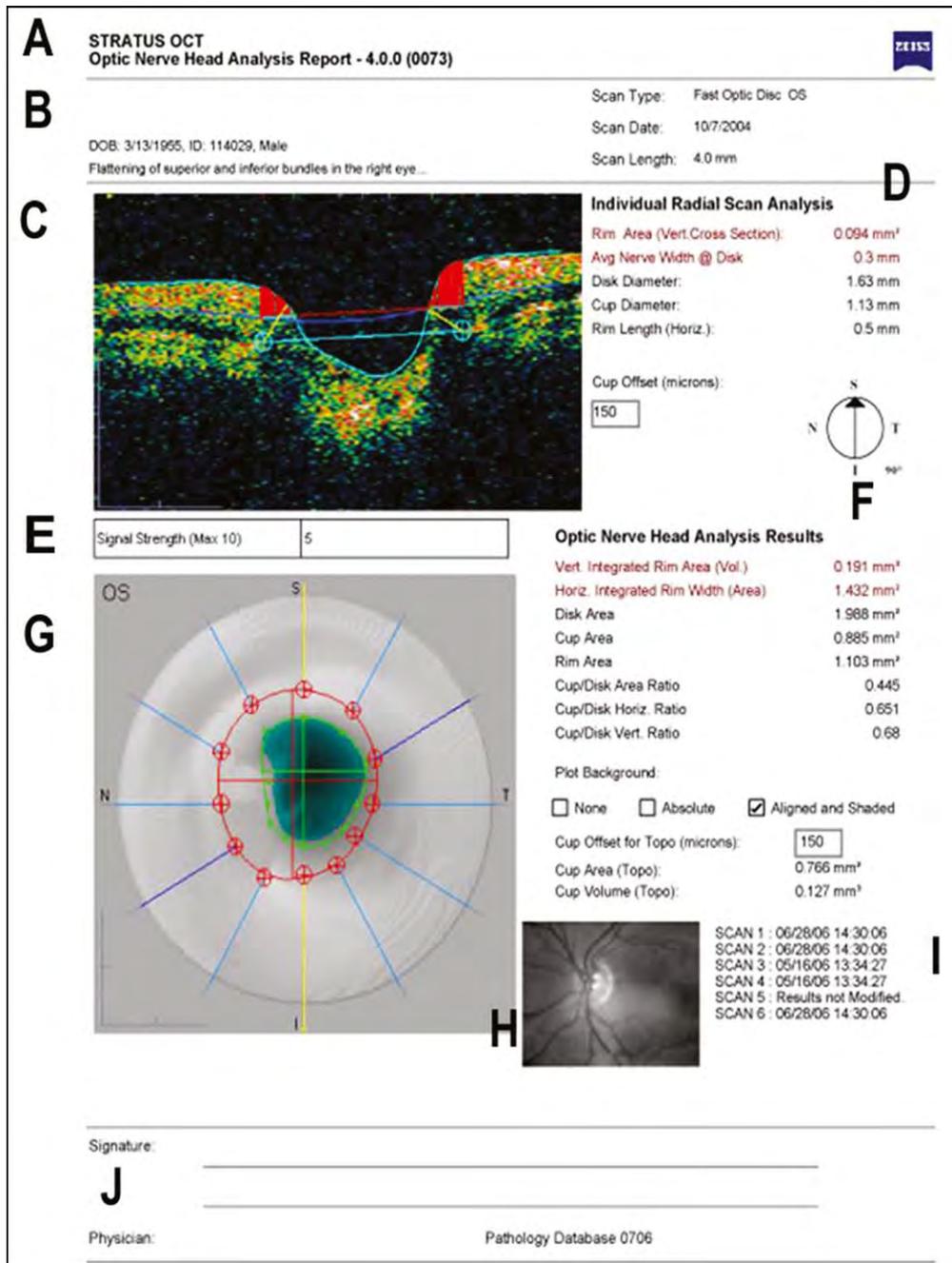


Fig. 14-15 Optic nerve head analysis report. **(A)** Type of report. **(B)** Patient and scan information. **(C)** Single OCT image. **(D)** Single scan analysis parameters. **(E)** Signal strength. **(F)** Overall analysis parameters. **(G)** Plot of radial scans with selected scan indicated by yellow lines. **(H)** Fundus image showing scan placement. **(I)** Times at which the radial scan was last modified. **(J)** Physician interpretation.

(Adapted from Schuman JS, Puliafito CA, Fujimoto JG: Everyday OCT: a handbook for clinicians and technicians. NJ, USA, Slack Inc., 2006.)²⁴

Optic nerve head analysis

A false color cross-sectional image of the optic nerve head is presented and is overlaid with two horizontal lines: one connects the edges of the RPE together and the other represents the reference plane. Tissue located above the reference plane and within the edges of the RPE is considered neuroretinal rim, and tissue below the reference plane and within the edges of the RPE is considered cup. The area corresponding to the rim is colored in red, the contour is traced in green and the edge of the ONH, which is defined automatically by the OCT as the termination of the RPE is traced, in yellow. Such contours of the optic nerve are drawn beside the previous image. Information on all six radial scans is used for the contour of the ONH. One of the radial scans is yellow and it represents the axis of the cross-sectional image in the printout (Fig. 14-15).

QUALITY ASSESSMENT

- *Peripapillary circular scan centration*: decentration of the scan can account for inaccurate measurements of RNFL thickness. For example, if the circle is displaced inferiorly, the superior sector will be thicker than if the scan was centered and the inferior quadrant might be measured thinner than the real thickness. The RNFL that is closer to the disc will be thicker than further away.
- *Signal strength value*: the manufacturer suggests a signal strength not lower than 5. Signal strength equal to or stronger than 6 is considered to indicate good quality.
- *Homogeneity of the RNFL scan*: loss of reflectivity in the scan is less than ideal and can affect the overall quality.
- *OCT algorithm*: the RNFL is usually shown in between two white lines that delineate its anterior and posterior borders.

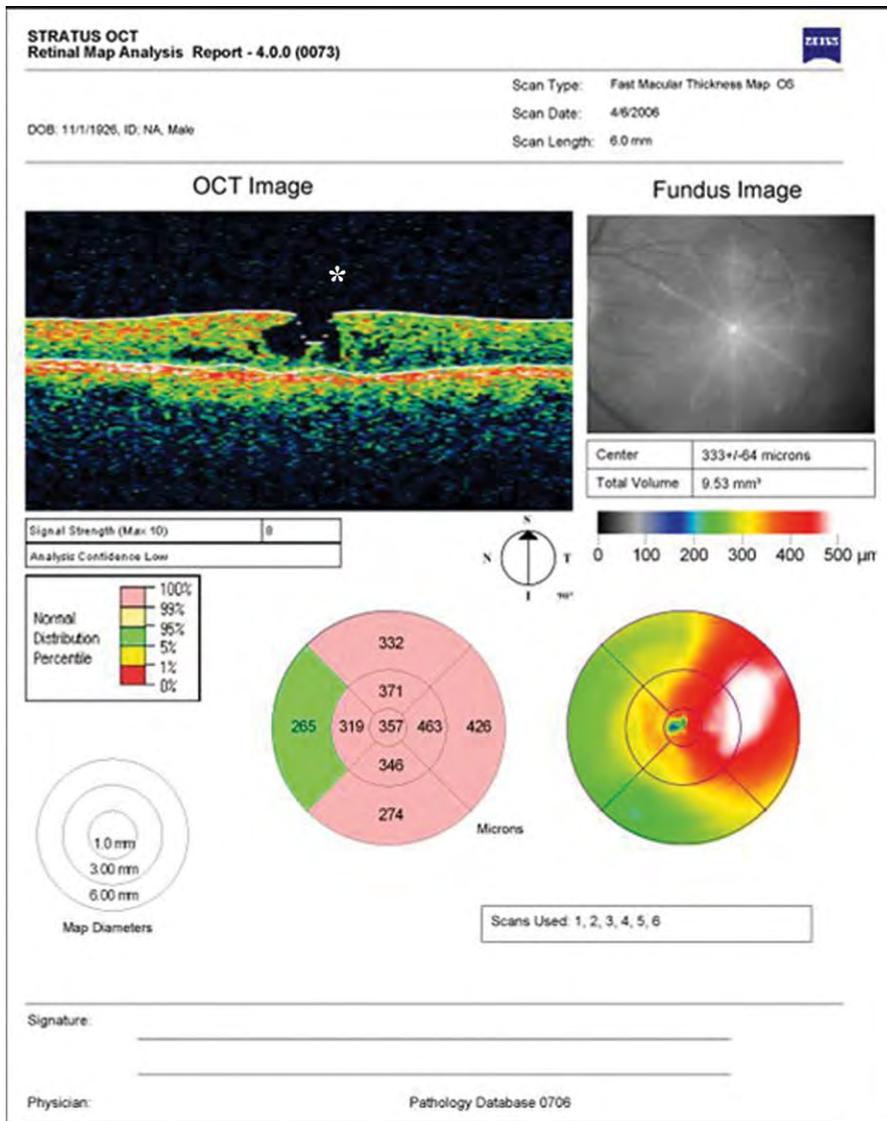


Fig. 14-16 Example of algorithm failure of the macular scan, as evidenced by disrupted image (*). (Courtesy of Zeiss Meditec, Inc., Jena, Germany.)

Sometimes, in poor quality scans, the white lines fail to follow the limits of the RNFL and a 'dropout' is seen in the cross-sectional image (Fig. 14-16).

STRENGTHS AND LIMITATIONS

Optical coherence tomography is the most versatile ancillary imaging test used in ophthalmology. It has the best axial resolution of all imaging devices and provides images of such high resolution that cross-sections of tissues can be compared to histopathology slides. *It is also the only technology capable of imaging the RNFL, macula and ONH.* Compared to HRT, OCT is obtaining thickness measurements and not height measurements. Insofar as OCT macular imaging has opened the doors to a better understanding, diagnosis and follow-up of innumerable retinal pathologies assessment of the macular region by OCT holds promise in detecting early glaucomatous changes as well.^{27b} As with the other devices, it is a machine that is easy to operate, safe and can obtain images without pupillary dilation.

Limitations include its normative database, and its limited sampling density that reduces its transverse resolution. Of note is that a newer generation of OCT (Spectral OCT) will provide higher resolution and three-dimensional images. Another limitation is that OCT data are originated from one set of scans and not a series (three) of sets of scans as in HRT. And unlike the HRT 3, current OCT devices have not yet developed robust programs for the longitudinal evaluation of glaucomatous progression..

TESTING FROM THE PATIENT'S PERSPECTIVE

Patients will be asked to place their chin in the chin rest and forehead against the headrest. Again, the exam feels similar to the slit-lamp exam. The patient will see different light patterns as the OCT comes into position for the scan: glowing red scan pattern, red landmark spot and green fixation target. If the patient has a cataract, he or she may perceive the green light as being white or yellow. There is the option of using an external fixation wand for the fellow eye which is useful when the eye being scanned is blind and cannot hold fixation with the internal light.

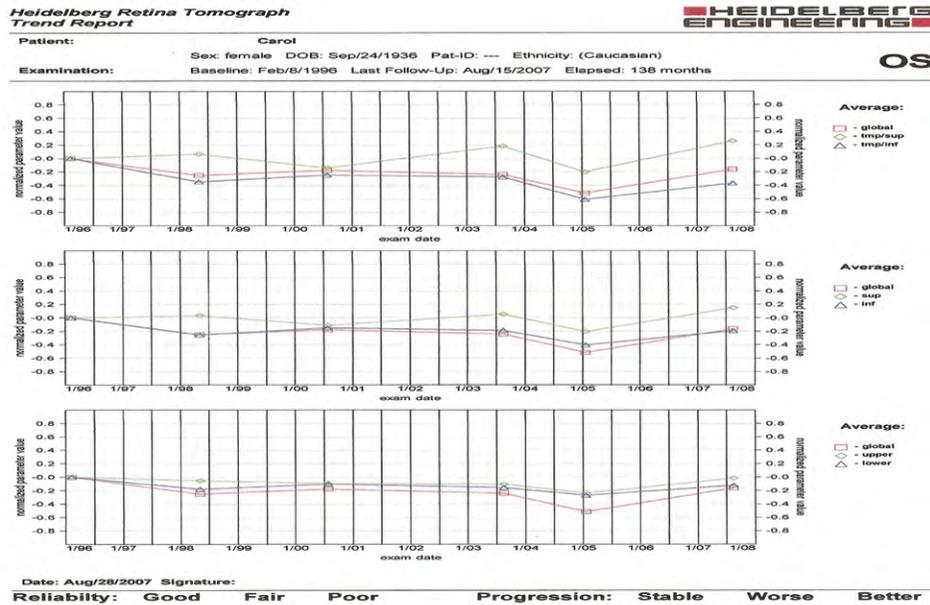
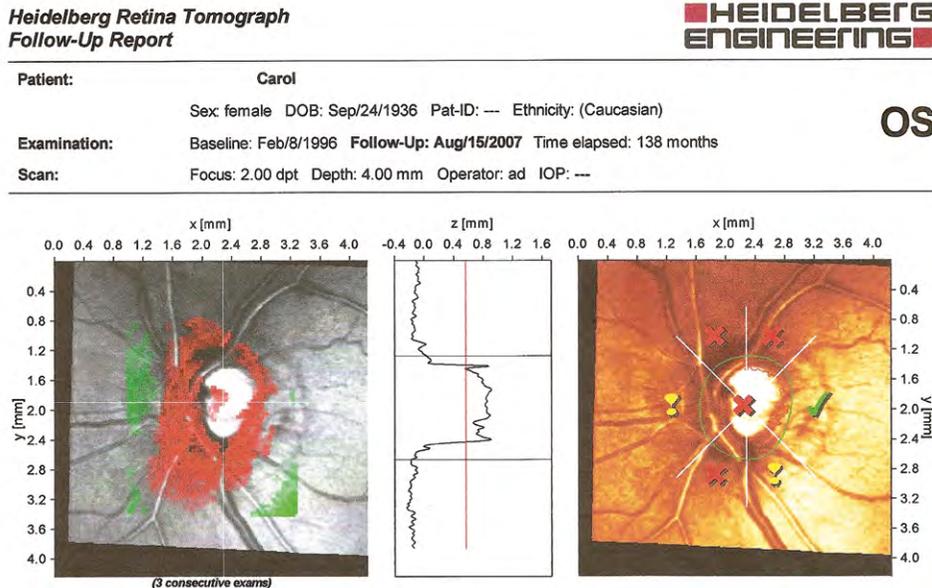
(A) Trend Analysis**(B) Topographic Change Analysis**

Fig. 14-17 Change analysis with HRT. **(A)** Trend analysis: several parameters are plotted over time giving a linear indication of progression. **(B)** Alternatively, topographic change analysis (TCA) can be used to evaluate for glaucoma progression. Change probability maps with red or green over the optic nerve image indicate change in topography having significant P values. Red means depression and green elevation. Note that for the same patient, trend analysis appears stable but rim seems to be depressed.

LONGITUDINAL EVALUATIONS

To assess change over time, HRT uses what is called the topographic change analysis or TCA.²⁸ This is a statistical method to compare topographic values of superpixels over time. It calculates the probability (P value) of the difference in height values between two time points to be caused by chance alone. A high P value ($P > 0.05$) would indicate high probability of the change to be caused by chance, and a low P value ($P < 0.05$) would mean that the change

did not occur by chance. Topographic change analysis is automatically done after the third scan is obtained: one baseline and two follow-up scans. The analysis is made with raw topographic values, so it is independent of disc contour delineation. The display occurs as a change probability map with the reflectivity maps overlaid with color-coded superpixels that had significant P values of change. Red means depression and green means elevation (Fig. 14-17).

The RNFL thickness longitudinal evaluation with OCT has been explored in recent studies. Wollstein et al compared the ability

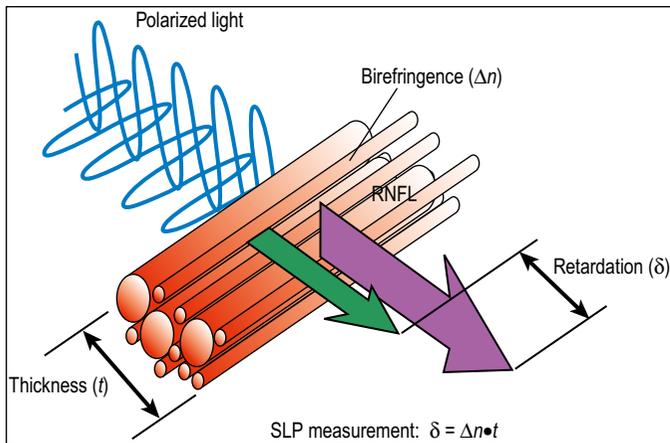


Fig. 14-18 In the retina, the parallel arrangement of the microtubules in retinal ganglion cell axons causes a change in the polarization of light passing through them. The change in the polarization of light is called retardation and it can be quantified. The retardation value is proportionate to the thickness of the RNFL.

of peripapillary RNFL measurements obtained by OCT, visual fields and clinical assessment of detecting progression in glaucoma suspects and glaucoma patients.²⁹ Investigators found that a greater likelihood of glaucomatous progression was identified by OCT versus automated perimetry.

SCANNING LASER POLARIMETRY

GDX

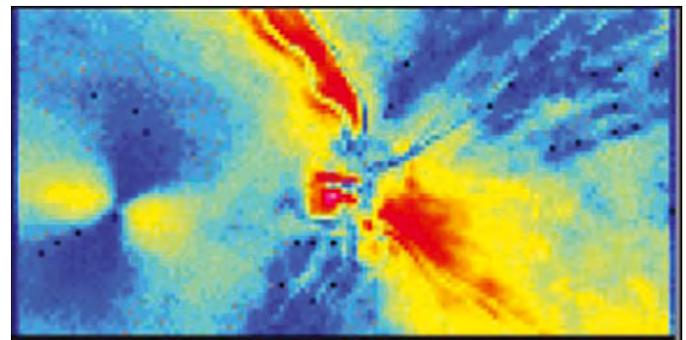
Scanning laser polarimetry is an imaging technology that is utilized to measure peripapillary RNFL thickness. It is based on the principle of birefringence. The main birefringent intraocular tissues are the cornea, lens and the retina. In the retina, the parallel arrangement of the microtubules in retinal ganglion cell axons causes a change in the polarization of light passing through them. The change in the polarization of light is called retardation, which can be quantified. The retardation value is proportionate to the thickness of the RNFL (Fig. 14-18). GDX is the device that utilizes this technology.

The latest generation is the GDX variable corneal compensator (GDX VCC, Carl Zeiss Meditec; Jena, Germany, and Dublin, California) (Fig. 14-19). This device also uses a diode laser (780 nm) to obtain measurements along a 15×15 area of the retina. The scan is obtained by the use of an ellipse that must be centered over the ONH as seen in the reflectance map. Data from the scanned area are displayed as a 256×256 pixel color-coded grid, representing different levels of retardation and therefore RNFL thickness. A retardation map and a deviation map are included in the printout.

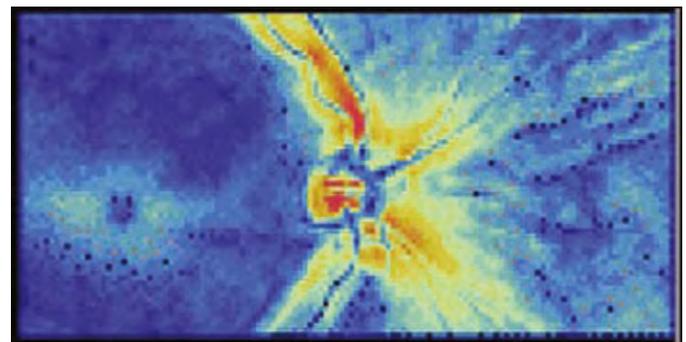
VCC stands for variable corneal compensator, which was created to account for the variable corneal birefringence in patients. It uses the birefringence of Henle's layer in the macula as a control for measurement of corneal birefringence. Birefringence around the fovea is known to be uniform and arises from Henle's layer. Scanning laser polarimetry of the macula with no compensation for the anterior segment gives rise to a non-uniform pattern at the fovea due to birefringence of the cornea, and the hourglass pattern indicates the axis and magnitude of the uncorrected cornea birefringence (Fig. 14-20).



Fig. 14-19 GDX VCC imaging unit.
(Courtesy of Zeiss Meditec, Inc., Jena, Germany.)



(A)



(B)

Fig. 14-20 Birefringence around the fovea is uniform and arises from Henle's layer. When a 'bow-tie' or 'hourglass' shape is seen around the fovea, this represents corneal birefringence. The bow-tie's magnitude and axis is representative of corneal birefringence. (A) Depicts an example of corneal birefringence before compensation, and (B) shows the disappearance of the bow-tie after corneal compensation has been made.

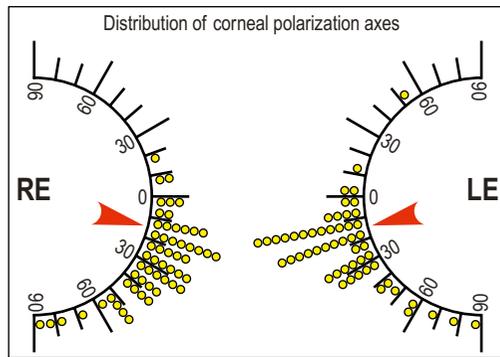


Fig. 14-21 Variability in magnitude and axis of corneal birefringence is significant and therefore there is the advantage of using a variable corneal compensator (VCC) as opposed to the previous fixed corneal compensator.

The VCC was incorporated after noticing a large variability in corneal birefringence among different patients and acknowledging the fact that a fixed generic corneal compensator was not going to suffice (Fig. 14-21).³⁰ An enhanced corneal compensator (ECC) with some improved features over VCC is currently being tested. One recent study reported that ECC significantly reduces the frequency and severity of atypical birefringence patterns compared with VCC and improves the correlation between RNFL measures and visual function.³¹

Components of the GDX report

1. *Patient data and quality score*: the patient's name, date of birth, gender and ethnicity are reported at the top of the printout. An ideal quality score is from 7 to 10 (Fig. 14-22).

2. *Fundus image*: it is a reflectance image of the posterior pole that measures 20° by 20° (Fig. 14-23). GDX VCC obtains more than 16 000 data points to construct this image. During the scanning process, this image serves to evaluate the quality of the scan before moving forward. Also, the operator centers the ellipse over the ONH in this image. The ellipse size is defaulted to a small setting but manipulating the calculation circle can change the size of the ellipse. The calculation circle is the area found between the two concentric circles, which measure the temporal-superior-nasal-inferior-temporal (TSNIT) and nerve fiber indicator (NFI) parameters. By resizing the calculation circle and ellipse, the operator is able to measure beyond a large peripapillary atrophy area, for example (Fig. 14-24).

3. *RNFL thickness map*: this is a color map depicting the different thicknesses of peripapillary RNFL (see Fig. 14-23). It represents the retardation level of the different scanned points. Hot colors like red and yellow mean high retardation or thicker RNFL and cool colors like blue and green mean low retardation or thinner areas. A typical scan pattern is that one with thicker RNFL superiorly and inferiorly, like a vertical bow-tie (Fig. 14-25).

4. *TSNIT graph*: this graph demonstrates the patient's RNFL thickness as a black line drawn over a shaded area of normality based on a normative database of over 500 eyes. This graph is based on data points within the calculation circle.

5. *TSNIT symmetry graph*: this graph overlays the individual TSNIT graphs for the right and left eye.

6. *TSNIT comparison graph and serial analysis graph*: these graphs compare two or more scans of the same eye obtained on different visits. These graphs do not appear on the regular printout.

7. *Deviation from normal map*: this map shows how the patient's RNFL thickness compares with the values derived from the normative database. Color-coded squares indicate the amount of deviation from normal at each given location. A color legend defining statistical significance of deviation from normal appears at the bottom (see Fig. 14-23).

8. *TSNIT parameters*: these are computed from the calculation circle data and are compared to the normative database. They are also color coded based on different *P* values. The parameters are: TSNIT average (average thickness values within the calculation circle), superior average (average of pixels in superior 120° of the calculation circle), inferior average (same as above, but along the inferior 120°), TSNIT standard deviation and inter-eye asymmetry.

9. *Nerve fiber indicator (NFI)*: the NFI is an indicator of the likelihood that an eye has glaucoma. It is a proprietary value, so its exact origin has not been published. Data within and outside the calculation circle are used to generate the NFI value. It is a number between 0 and 100. The higher the NFI, the more likely the patient has glaucoma. The GDX manufacturer offers the following as a guideline on the NFI interpretation:

- <30: low likelihood of glaucoma
- 30–50: glaucoma suspect
- >50: high likelihood of glaucoma.

Quality assessment

- Appropriate focusing and illumination of the retinal area being scanned is necessary.
- The ONH must be inside a black square while obtaining the scan.
- Presence of motion artifacts can decrease the quality of the scan. These are sometimes noticed as black rectangles at the edges of the scans or lines along the vessels.
- The ellipse must be centered over the ONH. Centration is usually more important than adequate size.
- The scan will provide a 'quality score.' A score between 7 and 10 is ideal. The device will also provide 'OK' for alignment, fixation and refraction (Fig. 14-26).
- Presence of atypical scans in the retardation map. A typical scan should have the thicker bundles along the vertical axis, where the RNFL is thicker. The pattern of a normal RNFL should be that of a vertical bow-tie. An atypical scan is one where the overall thickness is increased, where the thickness axis is tilted or where the thickness is along radial lines through the periphery of the scan. An objective way to evaluate atypical scans is with a support vector machine, which assigns a typical scan score.

Strengths and limitations

GDX allows for rapid and simple imaging of peripapillary RNFL. Good interactive features to assess for quality of the image are included in the software. As with the previous technologies, no papillary dilation is necessary. This device can only provide RNFL data. Corneal surgery will induce error in the measurements, but these should be corrected by VCC. On the other hand, macular pathology is likely to impede GDX scanning, given that VCC calculation is dependent on an intact Henle's layer. The NFI or likelihood score for having glaucoma is a proprietary value and cannot be independently validated.

Studies have been published demonstrating GDX reproducibility and use in glaucoma evaluation, but most of the published studies were done with the fixed corneal compensator used in the earlier

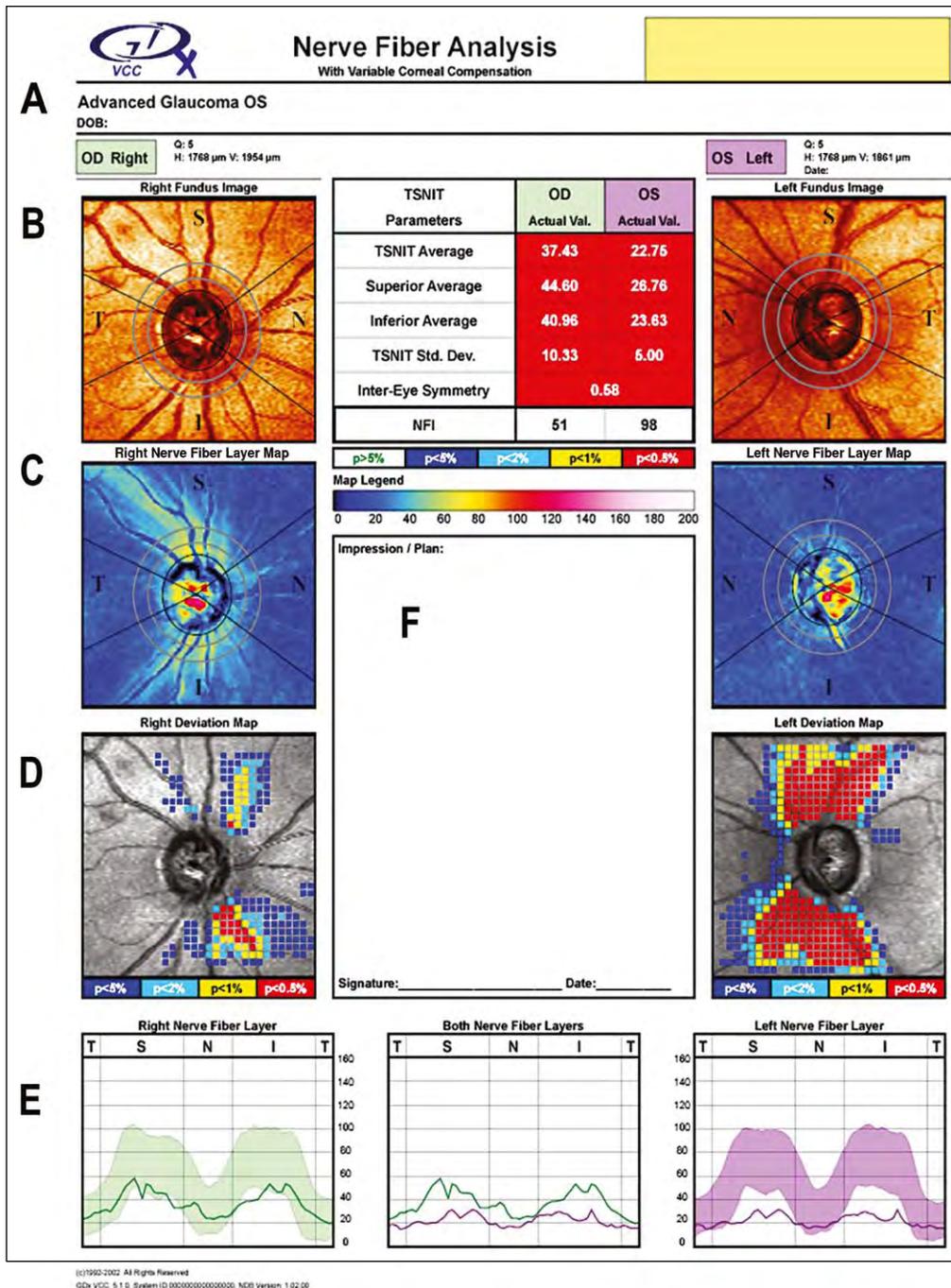


Fig. 14-22 GDx printout **(A)** Patient and quality information. **(B)** This shows the reflectance image and a table with temporal-superior-nasal-inferior-temporal (TSNIT) and nerve fiber indicator (NFI) parameters for each eye. **(C)** This consists of the retardation or RNFL thickness maps, which are color coded with hot colors representing thicker RNFL. **(D)** These are the deviation plot maps. Each small square is color coded and represents deviation from normality. The color represents the *P* value for abnormal points. **(E)** TSNIT and TSNIT symmetry maps show the patient's RNFL curve or curves against a shaded area representing the normative database. **(F)** Space for physician interpretation. Note the asymmetry between right and left eye, with the left eye having a much thinner nerve fiber layer. (Courtesy of Zeiss Meditec, Inc., Jena, Germany.)

generation of GDx.³²⁻³⁴ Reports do exist evaluating GDx VCC in different circumstances, such as presence of peripapillary atrophy³⁵ or in comparison to HRT and OCT.³⁶⁻³⁸

Testing from the patient's perspective

The patient will be asked to place his or her face into the 'mask' of the GDx. The patient will see a field of thin red horizontal lines. On one side of the field, the patient will see short, bright, blinking red horizontal lights similar to an equal sign. That is the patient's fixation target. The scan acquisition takes less than 1 second.

CONCLUSIONS

Glaucomatous changes can affect the optic nerve structure and its function. For the most part, optic nerve structural changes frequently precede functional changes. Thus the ability to detect early glaucomatous structural changes has great potential value in delaying and avoiding progression of the disease. This chapter has reviewed the most important imaging devices currently (2007) used in the evaluation of glaucoma. They have been of enormous value in the comprehension and evaluation of glaucomatous

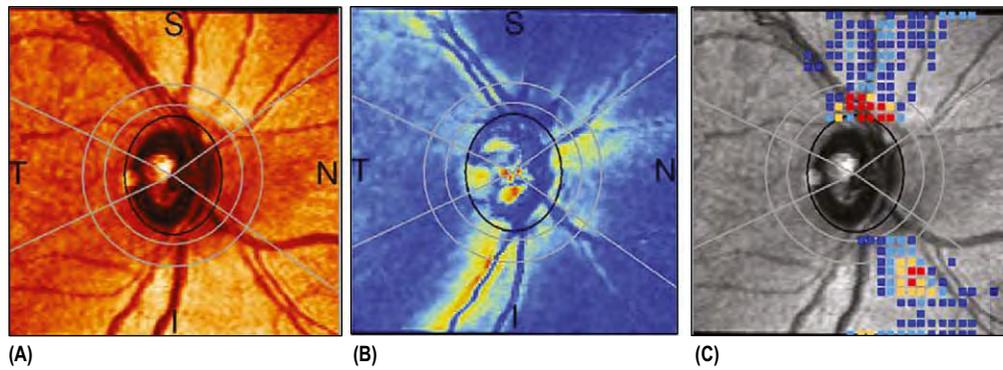


Fig. 14-23 Different peripapillary images in GDX report. From left to right: reflectance image with the ellipse centered on the disc, retardation or RNFL thickness color map and deviation plot.
(Courtesy of Zeiss Meditec, Inc., Jena, Germany.)

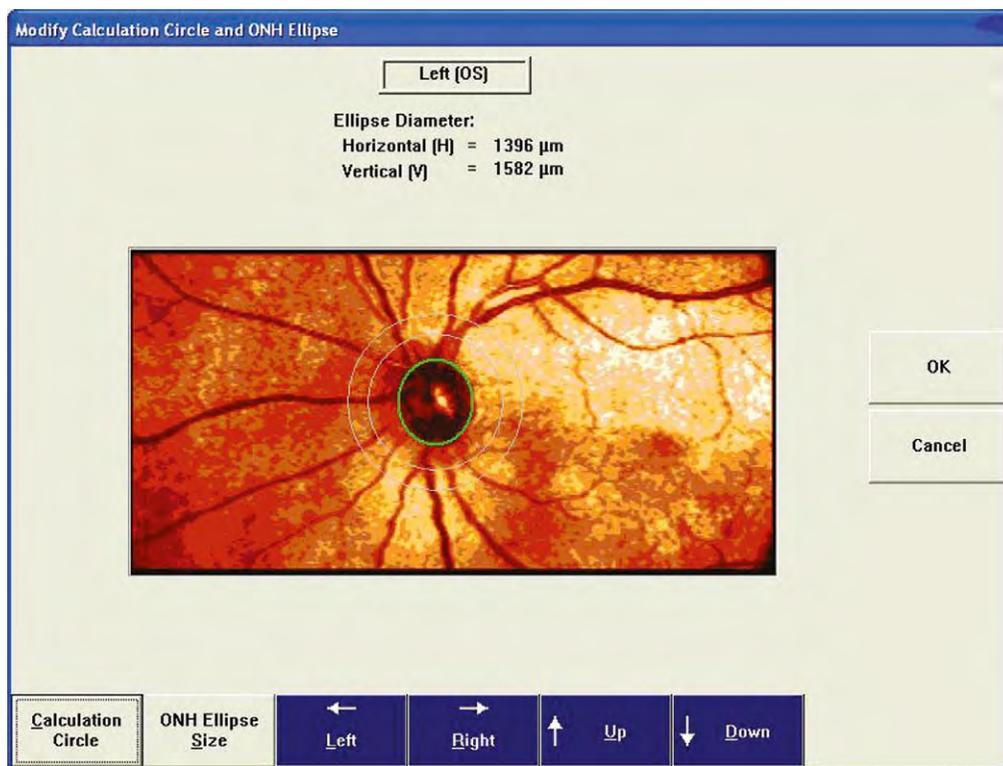


Fig. 14-24 Operator's screen during GDX scanning of a patient. The operator places the ellipse over the ONH. It must be centered appropriately. The calculation circle is the area between the two concentric circles and it can be modified by the operator. Manipulating the calculation circle allows for resizing of the ellipse. TSNIT parameters are derived from measurements of RNFL within the calculation circle and NFI parameters are derived from RNFL inside and outside the calculation circle.
(Courtesy of Zeiss Meditec, Inc., Jena, Germany.)

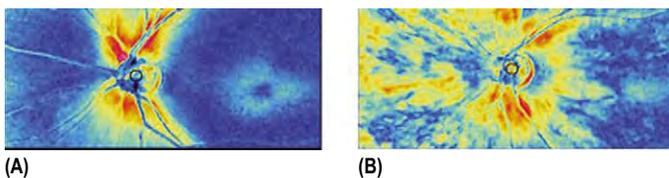


Fig. 14-25 Typical and atypical GDX scans. Typical scans will show a vertical bow-tie, with thicker RNFL (hot colors) superiorly and inferiorly such as the scan seen in (A). (B) is an example of an atypical scan, showing increased overall thickness.

disease during the last couple of decades. Some of these have been used as ancillary tools in relevant clinical trials.

Despite their advantages, there are important limitations. None of these devices has the ability to specifically capture all the nuances of appearance available in stereoscopic photographs of the disc, and which can serially be examined by the clinician with a low-tech light box. Given the rapid and unpredictable innovation in preferred and compatible technologies of optic nerve imaging – which may make earlier studies uninterpretable a decade hence – many clinicians would do well to obtain baseline disc photographs

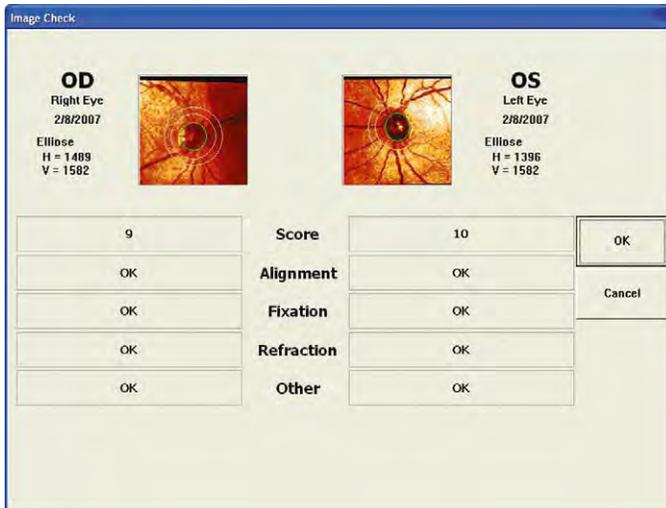


Fig. 14-26 Image quality check screen while scanning a patient with GDX.

on all glaucoma patients. Another unavoidable frustration, besides rapidly changing technologies, is the clinical fact that the most difficult optic discs to interpret in terms of glaucomatous changes – specifically highly myopic and tilted optic discs – are also those discs which optic nerve imaging devices have the greatest limitations in discriminating abnormality from pathology.

Hence these devices should not be regarded as replacing the skilled ophthalmologist's capacity to evaluate all aspects of the patient's diagnosis and disease status but they can definitely aid in the complicated decision-making process that is so commonly involved in glaucoma practice. Imaging technology has made a gigantic contribution to glaucoma by providing objective parameters, but care should be taken in analyzing these tests, remembering that test quality and reliability need to be assessed before interpreting them.

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CHAPTER
15

Primary angle-closure glaucoma

HISTORICAL REVIEW AND CLASSIFICATIONS

The Hippocratic aphorisms include two mentions of blindness, one of which may refer to glaucoma: ‘When headache develops in cases of ophthalmia and accompanies it for a long time, there is a risk of blindness.’¹ Gradually the different causes of blindness were separated, with the most important distinction between cataract (which was treatable by couching) and glaucoma (which was not). Thirteenth century Syrian Salah-ad-din-ibin Yusuf al-kahal bi Hamah described a condition that he called ‘migraine of the eye’ or ‘headache of the pupil’: possibly a description of acute angle-closure glaucoma, with painful hemicrania and dilation of the pupil.¹

Itinerant British oculist Richard Banister published a clear description of end-stage or absolute glaucoma in which he observed that the eye was hard to palpation.² Further descriptions of congestive glaucoma and the firmness of the eye were published by Platner, Guthrie, Beer, and Demours.² Demours also reported halo vision in glaucoma.²

In 1853, von Arlt ascribed the cause of glaucoma to the struggle for a livelihood, grief, weeping, vexation, eyestrain, and a damp dwelling.³ Most other scientists in the eighteenth and nineteenth centuries viewed glaucoma as a disease of the vitreous humor that was associated with iritis and arthritis. Following the development of the ophthalmoscope in 1851 by von Helmholtz, Jacobson, Jaeger, von Graefe, and Weber disproved this theory by noting glaucomatous cupping in eyes with clear vitreous bodies.² The lack of vitreous involvement in glaucomatous eyes was confirmed histopathologically by Mackenzie and Muller.²

Another important step in our understanding of glaucoma came from studies by Leber, Weber, and Knies of the aqueous humor circulation in animal and human eyes.² The association between shallow anterior chambers and acute attacks of angle-closure glaucoma became clear in the late nineteenth century.^{4,5} It was during this time that von Graefe,⁵ in one of the landmark papers of ophthalmology, proposed iridectomy as a treatment for glaucoma. In the 1920s, Curran,⁶ Banziger,⁷ and Raeder⁸ independently put forth theories regarding the mechanism of pupillary block and further proposed that peripheral iridectomy cured angle-closure glaucoma by relieving this block. The efficacy of peripheral iridectomy as a treatment for glaucoma was confirmed by many physicians, including Gifford,⁹ O’Connor,¹⁰ Elschmig,¹¹ Barkan,¹² and Chandler.¹³ With the development of gonioscopy by Trantas, Salzmann, Koeppe, and Troncoso, the mechanism of angle closure was confirmed; and glaucoma was classified in modern terms by Barkan according to the state of the angle.¹⁴ Rosengren’s prescient biometric studies of the anterior segments in the ‘primary glaucomas’

distinguished the symptomatic angle-closure eyes from the asymptomatic open-angle eyes.¹⁵ This classification system was clinically elaborated by Sugar,¹⁶ and later adopted by the American Academy of Ophthalmology in 1949.¹⁷

Today glaucoma continues to be classified into open-angle and angle-closure forms (see Ch. 1). In open-angle glaucoma, there is increased resistance to aqueous humor outflow through the trabecular meshwork–Schlemm’s canal–episcleral venous system by a variety of mechanisms which do not involve *visible* obstruction by the iris. In the angle-closure glaucomas there is increased resistance to outflow because of damage to, or obstruction of, the trabecular meshwork by the peripheral iris, preventing the aqueous humor from reaching the outflow channels.

CLASSIFICATIONS OF ANGLE-CLOSURE DISEASE

Historically the angle-closure glaucoma nomenclature has been confusing: conditions were sometimes classified by the time course of the disease, sometimes by the effects of the angle closure, and sometimes by the presumptive pathophysiology of the angle closure. For example, angle-closure glaucoma has been described by the adjective pairs *congestive/non-congestive* and *compensated/uncompensated*. These terms have been abandoned because they lack specificity. The congestion and corneal decompensation are usually a function of the rapidity with which the pressure rises, or reflect underlying causal phenomena such as uveitis.

Similarly the terms *acute*, *subacute*, and *chronic* have often been used to reflect the time course and/or presence of symptoms. Abrupt and total angle closure is *acute*; recurrent and self-limiting episodes of closure with elevated intraocular pressure (IOP) are *subacute*; and asymptomatic elevated IOP or peripheral anterior synechiae is *chronic*. Although these and similar temporal terms (e.g., ‘latent’ and ‘imminent’) have long had currency, even appearing in an elaborate contemporary classification of European and Inuit angle-closure disease based on high-resolution anterior segment imaging and clinical presentations,¹⁸ this complex scheme is problematic for two reasons. First, it is cumbersome for epidemiologic assessment, and often requires guesswork by the clinician – which makes standardization of diagnoses difficult. Second, these terms add little or no value to clinical strategies for patient care. Such terms explicitly presume correlated clinical signs and symptoms in the presentations of angle-closure glaucoma, with the time course of the patient’s disease retroactively designated by the clinician. Yet in one assessment of worldwide primary angle-closure glaucoma, four-fifths of patients presented entirely without symptoms.¹⁹ We concur with newer diagnostic definitions that discard older time-based terms, because they neither shed light on the natural history of disease progression,

nor contribute to stage-specific management interventions for the disease.²⁰

In large part due to the recent appreciation of the magnitude of glaucoma blindness in the world, a disproportionate part of which occurs in Asians with primary angle-closure disease,^{21,22} consensus meetings among world glaucoma experts were held under the auspices of the Association of International Glaucoma Societies (AIGS) in 2006 to elaborate consistent and clinically applicable sets of definitions for angle-closure glaucoma disease (see Appendix).²³ Based on over a decade's attempts to develop a simplified, clinically relevant classification,^{24–27} this terminology has been endorsed by the American Academy of Ophthalmology, the International Society of Geography and Epidemiology of Ophthalmology (ISGEO), and the Southeast Asia Glaucoma Interest Group. Comparable schemes are now being used in numerous studies throughout the world:²⁸ in Japan,²⁹ Thailand,³⁰ India,^{31–34} Mongolia,³⁵ and among various Chinese populations.^{36–38}

This uniformity of approach has two major merits. Epidemiologically, it greatly facilitates meaningful comparison among population studies, which further helps elucidate risk factors relevant to angle closure, determining clinical markers for progression of disease, distinguishing differential responses and complications of interventions, and discovering clues as to underlying pathogenic mechanisms. And for the individual patient, this scheme of the natural history of primary angle closure addresses both the prognosis for progression, and the stage-appropriate need for treatment.

TWENTY-FIRST CENTURY CONSENSUS CLASSIFICATION

The new classification of primary angle-closure (PAC) disease relies on three simple categories: IOP measurement, gonioscopy, and disc and visual field evaluation. In other words, the presenting patient's *clinical examination alone* determines the staging of the disease, regardless of the presence, absence, or reliability of symptom history, alleged duration, intermittency of problems, etc.

- 1. Primary angle closure SUSPECT (PAC suspect):** greater than 270° of irido-trabecular contact plus absence of peripheral anterior synechiae (PAS) *plus normal IOP, disc, and visual field*. In other words, the suspect eye has normal IOPs, optic nerves and visual fields, i.e., no signs of clinical glaucoma, but whose angle before indentation gonioscopy is graded as a Shaffer grade 2 or less, without PAS on compression. *The angle is at risk.*
- 2. Primary angle CLOSURE (PAC):** greater than 270° of irido-trabecular contact with either elevated IOP and/or PAS plus normal disc and visual field examinations. In other words, angle closure demonstrates irido-trabecular contact in 75% of the angle, with either PAS or elevated IOPs, but without disc and visual field changes. *The angle is abnormal in structure (PAS) or function (elevated IOP).*
- 3. Primary angle-closure GLAUCOMA (PACG):** greater than 270° of irido-trabecular contact plus elevated IOP plus optic nerve and visual field damage. In other words, angle-closure glaucoma manifests the criteria of *closure* above, plus demonstrable disc and/or visual field changes. *The angle is abnormal in structure and function, with optic neuropathy.*

It is important, of course, not to exclude all temporal information in this scheme: *acute* PACG remains a specific observable presentation category of the disease, requiring immediate recognition and intervention.

CLARIFICATIONS AND COMMENTARY

Mastery of indentation (compression) gonioscopy with such devices as the Posner or Zeiss 4-0 mirror goniolens (see Chs 5 and 7) is the indispensable skill required to apply this classification. Since narrow angles are not particularly common – an estimated 2–6% of Caucasian eyes have suspiciously narrow angles (Shaffer grade 2 or less), and 0.6–1.1% have critically narrow angles (grade 1 or less)^{39,40} gonioscopic subtleties can only be learned by its routine practice in the clinic on every new patient, young or old. Irido-trabecular contact needs to be identified as *present* or *absent*, and then discriminated as either *appositional* (by indenting and revealing angle structures) or *synechial*, while documenting the latter's *extent* (in terms of degrees or total clock hours). The use of a goniolens larger than the corneal diameter (e.g., Goldmann or Koeppe lenses) may allow better resolution of angle structures,⁴¹ but successful indentation to view deeper into the angle is usually not possible.

Consistent and competent gonioscopy technique is required, such as conducting all examinations in a dark room, using a small, 1-mm slit-lamp beam away from the pupil, identifying the most anterior point of iris-angle contact, and avoiding inadvertent compression.⁴² It is helpful to characterize PAS as to their *height* (e.g., 'to Schwalbe's line'), *regularity* (e.g., 'symmetric, tented PAS' or 'broad, shaggy PAS') and *circumferential extent* (e.g., 'from 3 to 6 o'clock'). Indirect estimations of angle embarrassment, such as the van Herick method,³⁹ or tangential pen-light examination, are not by themselves sufficient for screening; slit-lamp gonioscopy is indispensable, and preferably with indentation assessment (Figs. 15-1 and 15-2).^{43,44}

The quintessential finding for a PAC suspect is that of irido-trabecular *contact*, a concept with greater specificity than 'anatomically narrow angle' or 'occludable angle' (although the latter term is still used in ICD-9-CM coding). A 'narrow angle' without contact, sometimes characterized as 'occludable', can imply for the clinician a predictive risk for closure which is not, in fact, substantiated by rigorous epidemiologically-derived criteria. The decision to proceed with iridotomy or surveillance requires a variety of factors to be considered: the patient's access to care, whether the lens may soon require cataract surgery for visual reasons, the status of the fellow eye, the patient's age and ethnicity, etc.

In the absence of iris-trabecular touch, it is imperative to estimate the angle depth. Though there are a variety of useful schemes to visually quantify the angle configuration (see Ch. 7), the Shaffer assessment of 20° or less of an irido-trabecular angle appears to be a robust and inclusive benchmark.^{25,26} It is also crucial to emphasize that gonioscopy in any PAC suspect needs to be repeated on a regular and recurrent basis as part of standard ophthalmic care.

Controversy remains regarding the extent of irido-trabecular contact in the definitions used to distinguish between 'suspect' and 'closure'. At issue are the earliest effects and interplay of the two mechanisms, frequently co-existent, that are responsible for damage to the angle structures: (1) intermittent appositional abutment of iris to trabeculum, which can histologically manifest as degeneration of meshwork tissue even in sites remote from PAS;⁴⁵ and (2) PAS, whose extent correlates with levels of IOP elevation.^{46,47}

The implications of precisely defining 'suspect' and 'closure' have real-world impact of great import, highlighting the eminent practicality of this classification and its flexibility for refinement over time. A 'looser' definition (e.g., 180° or less of touch) than the current criterion of 270° of irido-trabecular contact could classify

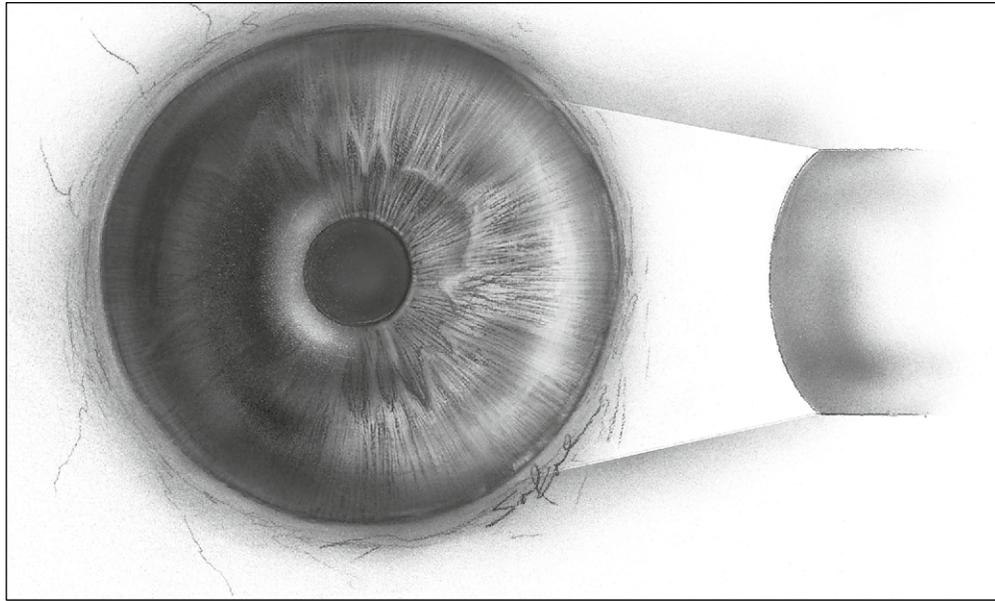


Fig. 15-1 Illumination from the temporal side casts shadow on iris if there is considerable bombé.

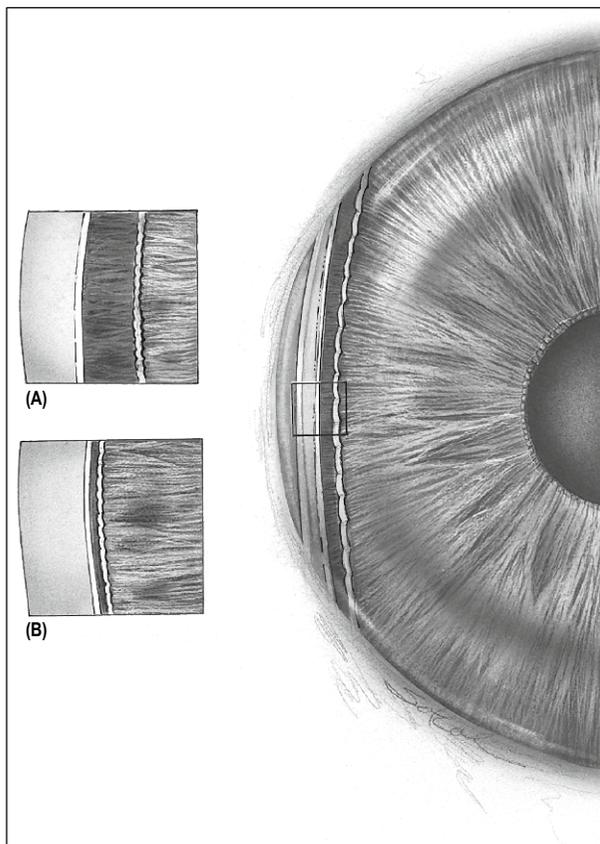


Fig. 15-2 Slit-lamp examination of the peripheral anterior chamber. **(A)** If the distance between the iris surface and the corneal endothelium is equal to the corneal thickness, the angles are likely to be deep. **(B)** Conversely, if the distance is less than one-fourth of the corneal thickness, the angles are likely to be narrow.

(Modified from van Herick W, Shaffer RN, Schwartz A: *Am J Ophthalmol* 68:626, 1969. Published with permission from The American Journal of Ophthalmology. Copyright by the Ophthalmic Publishing Company.)

up to 50% more eyes as diseased, requiring monitoring for PAS or immediate treatment of elevated IOPs; epidemiologically speaking, this could pose an enormous burden.^{20,34} Another aspect of this controversy is that using visible light – as is inherent in clinical gonioscopy – may be minimizing our perception of irido-trabecular contact, by unavoidably constricting the pupil and thus opening the angle to some degree. Hence our current instrumentation for clinically detecting the disease is *underestimating* the likelihood or extent of repetitive appositional iris–trabecular contact, which can cause chronic, cumulative trabecular damage.

There are those, however, who argue for the advantage of a lower threshold for characterizing PAC: by requiring less than 270° of irido-trabecular contact, detection is made more inclusive and attentive to early signs of angle embarrassment. In effect, this view prefers that the clinician be pre-emptive, and categorically assert that a patient does *not* have any stigmata of angle closure rather than, as is now done, tolerate findings that there *is* angle closure already underway. Earlier detection, so this line of thinking goes, might lead to earlier iridotomy treatment before the momentum of progressive disease occurs.⁴⁸

But since we do not precisely know which eyes will progress to actual glaucoma despite early manifestations of narrow angles with or without trabecular dysfunction, the oft-assumed benign nature of laser iridotomy needs to be reconsidered. The first consideration is that laser iridotomy therapy may, to some small extent, affect the lens and predispose to cataract formation.^{49–51} With the shunting of aqueous through a peripheral patent iridotomy, instead of its normal physiologic pathway through the pupil, there may be an adverse impact on overall lenticular metabolism.⁵² Moreover, focal tissue alterations have been seen following laser treatment. Small focal lenticular changes below the anterior capsule following yttrium-aluminum-garnet (YAG) iridotomy may predispose to long-term cataractous visual changes.⁵³ Similarly, in marginally healthy corneas, the focal corneal endothelial loss sometimes seen following argon laser iridotomy may predispose to long-term focal or diffuse corneal decompensation.^{54–67}

Yet another consideration is that a patent iridotomy is not necessarily effective in eliminating irido-trabecular touch,⁶⁸ with one

study finding that over 60% of treated Chinese eyes were still manifesting post-iridotomy irido-trabecular contact, requiring continued glaucoma management.⁶⁹ Moreover, after receiving a patent laser iridotomy for an acute attack, some eyes experience *repeated* acute angle-closure attacks.^{70,71} Thus it appears that the effectiveness of laser intervention may not always be either benign or curative; its effectiveness appears to be stage-specific to the disease, and dependent on underlying mechanisms other than pupillary block.

Consider the implications of the high rates of PACG found in surveys of select Chinese and Indian populations, affecting nearly 2% of individuals over the age of 40 years old: with nearly half of the world's population living in India and China, scores of millions of people potentially require iridotomy.^{22,31,36,72} Because of the major public health ramifications in this context of millions of potentially affected eyes, it is imperative to determine whether laser iridotomy treatment induces even a small percentage of vision impairment when utilized prophylactically. Even a fraction of a per cent of post-iridotomy complications of cataract or corneal changes would affect enormous numbers of people with limited access to address their vision loss. Further research as to the benefits and demerits of each approach – either to recruit eyes with the earliest stigmata for consideration of treatment, or to reach a predetermined threshold or stage-specific criterion before progression – remains to be determined.

The end condition of primary angle-closure *glaucoma* includes the fundamental criteria for any glaucoma: damage to the optic nerve, with concomitant loss of visual field function. Hence the screening strategies for epidemiologically detecting this advanced stage of PACG are identical to those efforts for detecting primary open-angle glaucoma: optic nerve evaluation and, when feasible, perimetric assessment. In circumstances where advanced PACG disease with compromised media prohibits disc and visual field testing, for example cataract or corneal disease, a coarser definition holds for PACG whereby an IOP >24 and/or acuity of <3/60 (20/400), or a history of prior glaucoma surgery, will suffice. The stigmata of prior angle-closure attacks other than PAS – such as glaucomflecken changes in the anterior lens, patches of iris necrosis, etc. – are worth noting, but are not in themselves predictive.²⁵

PRESENTATIONS OF PRIMARY ANGLE-CLOSURE DISEASE

The manifest advantage of the simple tripartite definition of PAC disease, based solely on the findings present at the time of the exam, is essential for epidemiologic and comparative studies. But

for deciding management and follow-up options, the clinician too must determine whether the presenting eye is a PAC suspect, manifests closure, or has PACG itself. This is the first step of management. Next she must then methodically distinguish among a variety of anatomical pathophysiologic mechanisms at play in the presenting eye. Hence a *mechanism-based* scheme complements the *diagnostic* definitions; together they illuminate the natural history and stage-appropriate findings which require intervention.

NEW IMAGING TECHNOLOGIES

As with optic nerve imaging, technological advances have profoundly impacted our understanding of patterns of anatomic alterations underlying angle-closure disease. There are two major devices whose contributions dominate the current clinical literature:

1. *Ultrasonic biomicroscopy* (UBM)⁷³ requires a skilled technician, a supine patient, and a water-bath coupling probe on the eye. With tissue penetration of 4 mm, a UBM's resolution typically includes angle structures as well as imaging of the anterior lens and anterior ciliary processes; images appear as radial slices of one portion of the angle. Because UBM scans are obtained in real time on video, there are resultant advantages (e.g., dynamic capture of anterior segment responses to accommodation, or to dark or light stimulation, etc.) (Fig. 15-3) and disadvantages (e.g., relatively low-resolution images, movement artifact, etc.)
2. *Anterior segment ocular coherent tomography* (AS-OCT) uses infrared light while examining a sitting patient without direct ocular contact; single-frame pictures can be obtained under different lighting conditions. Images comprise a 180°-diameter slice of the anterior segment (Fig. 15-4), currently limited to but a few clock hours (e.g., 3–9 o'clock scan), but dramatically capture the pupil and iris–trabecular configuration in high definition. The limited penetration of the light source restricts resolution to the angles and iris only, without reliable imaging of the anterior ciliary processes or lens. Nevertheless, highly detailed calculations of such parameters as angle opening distance, angle recess area, and the trabecular–iris space area introduce new levels of precision for approaching PAC disease.^{74,75}

Both kinds of instruments propel investigations of subtle changes heretofore invisible to earlier investigators.^{76–98} correlation of gonioscopy and measurable parameters in imaging of the angle;⁹⁹ alterations in angle configuration from laser iridotomies or cataract

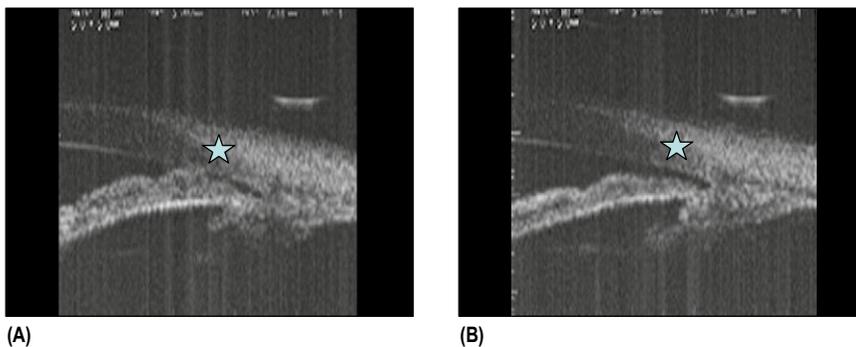


Fig. 15-3 (A) Ultrasonic biomicroscopy of angle closed (star) in darkness-induced dilation. (B) Ultrasonic biomicroscopy of angle opened (star) in light-induced miosis.

(Courtesy of Shan Lin, MD.)

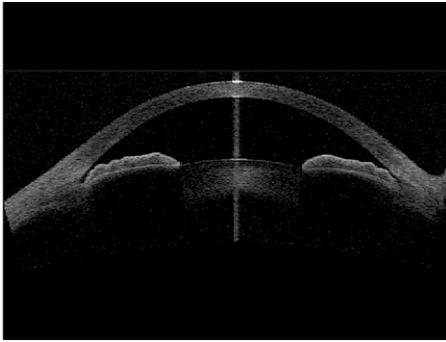


Fig. 15-4 Anterior segment ocular coherent tomography 180° image of narrow angles pre iridotomy. (Courtesy of Mingguang He, MD.)

surgery,^{69,100–102} anomalous anatomical positioning of the ciliary processes in plateau iris,^{103,104} etc. Other instruments extend our abilities to meticulously assess the anterior chamber depth, such as the scanning peripheral anterior chamber (SPAC) depth analyzer^{105,106} and the Pentacam (Oculus Instruments) device incorporating Scheimpflug photography.¹⁰⁷

As a result of the revolutionary technologies of the UBM and AS-OCT studies in particular, specific mechanisms and parameters for comprehending PAC disease are being elaborated. When combined with the classical literature based on clinical observations of subtle variations in disease presentations, a fuller picture of the angle-closure glaucomas results.

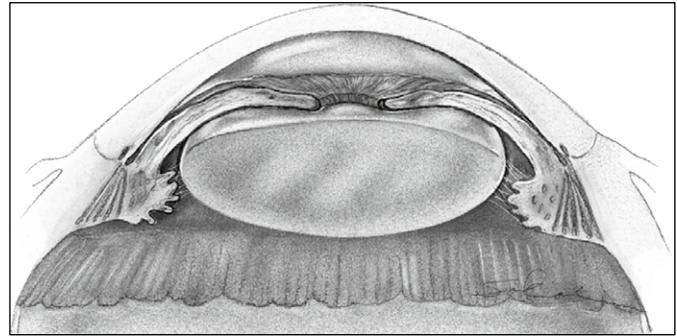
CLASSIFICATION BY MECHANISMS IN THE ANTERIOR SEGMENT

We classify the primary angle-closure mechanisms based on three site-specific disturbances in the *anterior* segment. We group these mechanisms because they share important characteristics in common: (1) all three can, with clinical input, be discriminated by anterior segment imaging; (2) they clinically manifest under similar circumstances, clustering closely in the differential diagnosis of causes of PACG; and (3) they differentially respond to laser iridotomy, which helps discriminate among the underlying mechanisms (Fig. 15.5).^{*} The three pathophysiological mechanisms grouped in the consideration of PACG are:

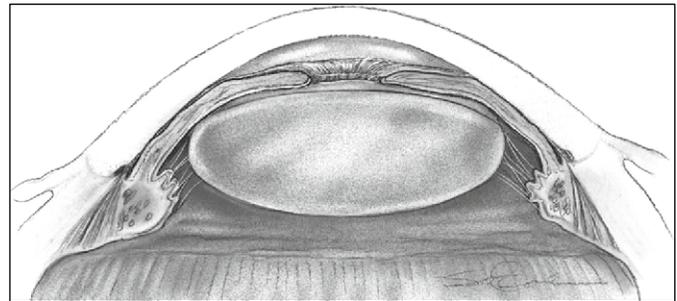
1. pupillary block glaucoma
2. plateau iris: configuration and syndrome (ciliary body anomalies)
3. phacomorphic glaucoma (lens-induced obstruction).

Conditions involving forces involving the mid or posterior segments of the eye, such as ciliary block (malignant) glaucoma or cilio-choroidal detachments, are discussed in the following chapter.

^{*}Although ciliary block ('malignant') glaucoma has been included among the mechanisms at play in the primary angle-closure classification,²⁰ we respectfully dissent and prefer to include it among the *secondary* angle-closure glaucomas. This is because of the rarity of ciliary block glaucoma, because its commonest presentation is postoperative, and because the target anatomical sites of vitreal-hyaloid and zonular-lens interface are not usually clarified by UBM studies (as are the three other mechanisms of PACG).



(A)



(B)

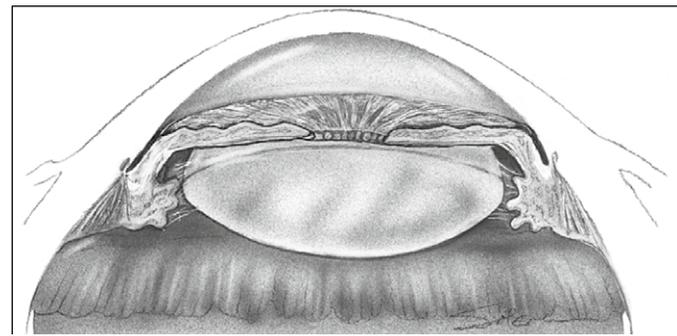


Fig. 15-5 Schematic view of three different mechanisms of PACG.

(A) *Pupillary block* with shallow anterior chamber, both centrally and peripherally, and iris bombé. Posterior chamber is enlarged. (B) *Plateau iris configuration* with relatively deep central anterior chamber and shallow peripheral anterior chamber. The plane of the iris is flat until near its insertion, where it takes a sharp, angled turn. (C) *Anterior displacement of the lens* (phacomorphic) with shallow anterior chamber, both centrally and peripherally; the iris is draped over the lens, and the posterior chamber is compressed.

1. PUPILLARY BLOCK GLAUCOMA

Pupillary block is the fundamental mechanism underlying the spectrum of PAC disease. Its pathophysiology involves: (1) lens-iris apposition at the pupil, with resultant bowing forward of the peripheral iris as aqueous pressure builds up in the posterior chamber; and (2) an anatomically predisposed eye that allows the anterior displaced peripheral iris to occlude the trabecular meshwork. The commonplace distinction between an *acute* attack and *chronic* disease remains important for clinical management decisions.

Epidemiologic studies

Epidemiologic studies address the entire spectrum of PAC disease in its three ‘suspect’, ‘closure’ and ‘glaucoma’ manifestations. The incidence and prevalence of PAC disease in a population are influenced by a number of factors, including the definitions used, and people’s age distribution, gender, racial make-up, range of refraction, and heredity.

Most individuals with narrow angles do not develop angle closure or glaucoma. As mentioned previously, anatomically narrow angles are found in 2–6% of eyes in the United States.^{39,40} In contrast, the prevalence of angle-closure glaucoma in the United States is probably less than 0.2% of the population. This suggests that, at most, only 1 of every 10 American whites with anatomically narrow angles will develop angle-closure glaucoma in his or her lifetime. In a population-based study in Hyderabad, India, Thomas and co-workers showed that, over a 5-year period, the risk of progressing from narrow angles (PAC suspects) to actual angle closure with either elevated IOP or synechiae (PAC) was 22%, but none of their patients actually developed optic nerve damage (PACG).^{108,109} But, of 337 patients from the same population with PAC followed for 5 years, the risk of progressing to actual PACG was 28%.⁴³ In contrast, in one study in Olmsted County, Minnesota, the incidence of angle-closure glaucoma was 8.3 per 100 000 of the population 40 years of age and older.¹¹⁰ In this same study, 14% of participants were blind in at least one eye at the time of diagnosis and a further 4% became monocularly blind over a 5-year follow-up. Thus we see there is tremendous variability in the manifestations of this disease, many of which appear to be both population and disease-specific.

Primary angle-closure glaucoma with pupillary block occurs one-fourth to one-tenth as frequently as does primary open-angle glaucoma (POAG) among white individuals living in the United States and western Europe.^{111,112–115} One study states that PACG occurs in 0.1% of whites older than 40 years of age and comprises about 6% of the total glaucoma cases.¹¹⁶ Within this group, angle-closure glaucoma affects fewer individuals of Mediterranean origin than of northern European origin.¹¹⁷ Primary acute angle-closure glaucoma with pupillary block seems to occur less frequently in individuals of black African ancestry;^{118,119} those who are affected generally have a chronic asymptomatic form of the disease.^{118,120–123}

Acute PACG, with pupillary block, occurs rarely in some east Asian-derived populations, including Pacific islanders and American Indians,^{24,124,125} yet occurs frequently in other populations, including Eskimos (Inuit) in such diverse places as Greenland, Alaska, and northern Canada.^{126–128} Alsbirk¹²⁹ reported that 10% of Eskimo women and 2.1% of Eskimo men over 40 years of age are affected by PACG. In such south Asian countries as India and Sri Lanka, the prevalence of PACG is equal to that of POAG.^{130,131} Primary angle-closure glaucoma appears to be relatively more common among many eastern and south-east Asian peoples, including the Chinese, Malaysian, Burmese, Filipino, and Vietnamese.^{24,132,133} Most of these cases are asymptomatic PACG (so-called ‘creeping angle-closure type’).¹³⁴ Conversely, Japanese and Thai patients seem to have PACG less frequently than do other Asians.^{135–137}

In Taiwan, the prevalence of PACG in a rural population was about 3%, with an additional 2% PAC suspects.¹³⁸ Angle-closure glaucoma is uncommon among those of Hispanic origin, averaging about 0.10%.¹³⁹ In a study of a northern Italian population, a prevalence of PACG of 0.6% was found, but occludable angles were found in over 15%, which is higher than previous studies in Caucasian populations.¹⁴⁰ In south India, there is a relatively low rate of PACG and

suspects with narrow angles (0.7% and 1.4% respectively); but among the PACG eyes, plateau iris was common.^{31,141,142}

In descending order, the entire spectrum of PACG appears most prevalent among Inuit and Eskimos,¹⁴³ then, those of south-east Asian heritage (especially Chinese, Filipino, Vietnamese), less so in those of European descent (although the prevalence varies from country to country), and least among those of African and Hispanic descent. In China and Singapore, for example, PACG is not only very prevalent – representing over one-third of the total glaucoma – but it is the most common cause of bilateral glaucoma blindness, though outnumbered 2:1 by POAG disease.^{39,144–146} Ethnicity apparently also plays a role in the severity of PACG when it clinically presents. For example, Chinese Singaporeans are twice as likely to require hospitalization for PACG than Singaporean Indians or Malaysians, although identical medical resources are available to all three groups.¹⁴⁷

This is a vast amount of information to keep track of, and is constantly evolving. It should be obvious that both PACG’s mechanisms and its natural history comprise a wide spectrum, with specific variations among different ethnic populations.¹⁴⁸ A few salient summary facts are presented in Box 15-1, which highlights key points from this new abundance of epidemiologic data on PAC disease.

Demographic risk factors

Age

Classic reports noted that PACG with pupillary block occurs with greatest frequency in the sixth and seventh decades of life.^{111,150,151}

Box 15-1 Salient points regarding epidemiology of primary angle closure^{19,20,48,72,149}

- PACG is rare compared to occludable angles**
For every 10 ‘occludable angles’ seen, there’s one case of PACG
Gonioscopy (our only tool!) is a POOR predictor
Most ‘occludable’ eyes do NOT get glaucoma!
Are YAG peripheral iridotomies innocuous (cf. reported focal lens changes and endothelial loss)? With a possible long-term complication rate of only 5%, prophylactic iridotomies on 40 million ‘at-risk’ Chinese and Indians *could* still cause >2 million potential problems
- Acute PACG is uncommon compared to chronic PACG**
Expect one acute PACG for every three chronic PACGs: i.e., the *majority* of world glaucoma disease is comprised of both *asymptomatic* chronic PACG and POAG
There are two implications:
Most patients do not know they have disease
The same screening algorithms for assessing IOPs, disc changes and visual fields apply
- Ethnic variabilities of the glaucomas**
POAG: *moderate* variable incidence among Caucasians ≈ Chinese < Hispanics < Africans
PACG: *large* variable incidence among Caucasians < urban Chinese < Mongolians ≈ Inuit
Hence, the *ratio* of POAG to PACG varies:
Euros ≈ Africans ≈ Hispanics – 5 POAG:1 PACG
Urban Chinese – 1 POAG:2 PACG
Mongolians – 1 POAG:3 PACG
- PACG is the major cause of world glaucoma blindness!**
China: >90% glaucoma-blind have PACG, i.e., *10 × more blindness* from PACG than POAG (although their incidence ratio is near parity, with 2 POAG:3 PACG!)
Of 60 million with glaucoma in the world, >1/3 have PACG – but 25% of these patients are *blind* (more than twice the POAG blind)

Several age-associated changes can include progressive relative pupillary block from a combination of increasing lens thickness, more anterior positioning of the lens, and pupillary miosis. It should be emphasized, however, that PACG with pupillary block can occur in patients of any age, and rarely even in children – though the etiologies among the young are almost always developmental or secondary.^{152–155}

Gender

Older studies have reported that PACG with pupillary block occurs 2–3 times more commonly in women than in men.^{36,117,156–159} The increased prevalence of angle closure in women probably reflects the fact that women have shallower anterior chambers;^{96,160} with some 10% less ocular volume than men.¹⁹ One exception to this observation may be in those of black African ancestry, in whom the occurrence of angle-closure glaucoma is apparently comparable among men and women.¹¹⁸

Heredity

Most cases of PACG with pupillary block are sporadic in nature – that is, there is no family history of glaucoma. However, several pedigrees are reported to have a high prevalence of PACG,^{161,162} some with autosomal-dominant and some with autosomal-recessive patterns of inheritance. Shallow anterior chambers and narrow angles have been reported as more common in relatives of patients with PACG than in individuals whose relatives do not have the disorder.^{163–165} Similarly, a recent report observed that plateau iris configuration may aggregate in familial patterns.¹⁶⁶

Fifty years ago, Tornquist^{91,163} suggested that the configuration of the anterior chamber was inherited under polygenic influence, explaining the variable familial occurrence of PACG rather than a specific gene linked to the disease. The intricate developmental details now available regarding the growth of the anterior chamber¹⁶⁷ and the explosive field of molecular genetics may soon elaborate upon these clinical perceptions.

Refractive error

The prevalence of PACG with pupillary block is much higher in individuals with hyperopic eyes, which typically have shallow anterior chambers and short axial lengths.^{96,143} Although rare, angle-closure glaucoma can occur in myopic eyes.¹⁶⁸

Miscellaneous factors

Older reports have suggested that PACG with pupillary block occurs more commonly in the winter months.^{169–171} This was variously attributed to low levels of illumination, increased cloudiness, changeable weather, and low sunspot activity.¹⁷² Central corneal thickness – a recently recognized risk factor for POAG – does not seem to have an association with PACG.¹⁷³

Ocular risk factors and mechanisms

Ocular risk factors cluster around a variety of findings, each of which reflects smaller ocular dimensions:^{19,20,143}

1. Shallow anterior chamber both centrally^{81–83} and peripherally.^{82,84,85} Both Lowe⁸¹ and Alsbirk⁸⁶ found angle-closure glaucoma to be uncommon in eyes with central anterior chamber depths of 2.5 mm or greater (Table 15-1).
2. Decreased anterior chamber volume.⁷⁷
3. Short axial length of the globe.^{76,82}
4. Small corneal diameter.^{84,88}
5. Increased posterior corneal curvature (i.e., decreased radius of posterior corneal curvature).^{89–91}
6. Decreased corneal height.⁸³

Table 15-1 Central anterior chamber depth and angle-closure glaucoma in a group of Eskimos

Prevalence of Angle-Closure Glaucoma (%)	Anterior Chamber Depth (mm)
>2.5	0
2.0–2.49	1
1.5–1.99	20
<1.5	85

Modified from Alsbirk PH: Acta Ophthalmol (Copenh) 53:89, 1975.⁸⁶

7. Anterior position of the lens with respect to the ciliary body.⁸³
8. Increased curvature of the anterior lens surface.⁹²
9. Increased thickness of the lens.^{76,83,92,93,174}
10. More anterior insertion of the iris into the ciliary body, giving a narrower approach to the angle recess, and possible anomalies of iris histology.¹⁷⁵
11. Thinning of the ciliary body is reportedly associated with anterior movement of the lens, increased lens thickness and decreased anterior chamber depth.¹⁷⁶

Three measures in particular show particularly high correlations with angle-closure disease: (1) reduced axial anterior chamber depth and volume; (2) thicker lens; and (3) steeper radii of corneal curvature.^{177,178} The biometric peculiarities of eyes predisposed to angle-closure glaucoma are accentuated by three trends associated with aging. First, the lens grows in thickness throughout life.^{95,96} Second, the lens assumes a more anterior position with age.⁹⁵ Third, the pupil becomes increasingly miotic with age. All of these age-associated changes increase the contact between the iris and lens, potentiate pupillary block, and reduce anterior chamber depth and volume. It is estimated that central anterior chamber depth decreases 0.01 mm/year.⁹⁶

Despite the elaboration of the specific ocular risk factors associated with PACG, the ‘fit’ with the demographic data is not completely congruent: to wit, *population* studies do not support the generalization that ethnic groupings have smaller eyes or ocular dimensions than others.^{19,177,179} Another way of integrating the data in light, for example, of the excessive burden of devastating PACG among Chinese populations, is to state that, statistically, Chinese don’t have smaller eyes – but those with small eyes (e.g., elderly women) are at greater risk for angle-closure disease. This anomaly has generated new hypotheses as to what other specific factors may be at play, such as the possible role of choroidal expansion in both angle-closure glaucoma and in ciliary block (malignant) glaucoma.^{19,180}

Iris bowing and lens-iris channel

Somehow the junction of the lens and iris at the pupillary plane modulates the flow of aqueous from the posterior to the anterior chamber, but it apparently is not a simple matter of direct contact between lens and iris. Part of this mechanism is thought to be due to iris structures: the iris sphincter muscle exerts a posterior vector of force that causes the central iris to ‘hug’ the anterior lens surface,⁷⁸ with a possible contributory interplay with the dilator musculature. Preliminary studies of intra-iris collagen in acute PACG eyes suggest morphological changes may also contribute to abnormal iris mechanics.¹⁷⁵ The flow capacity may also depend on the viscosity and other properties of the aqueous.

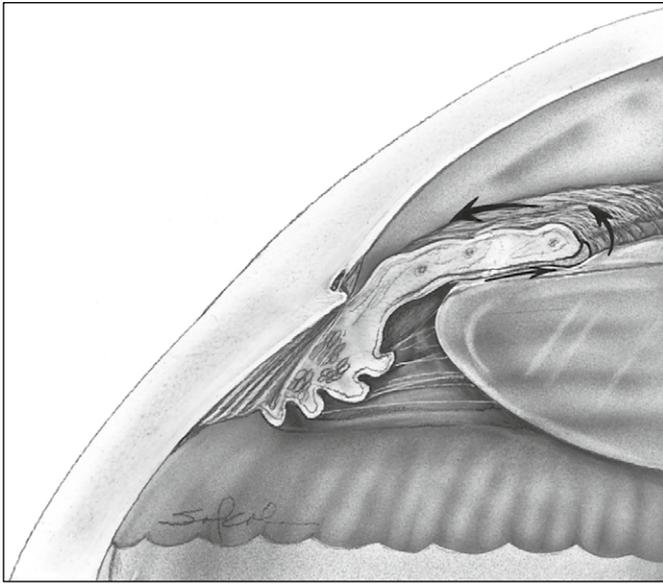


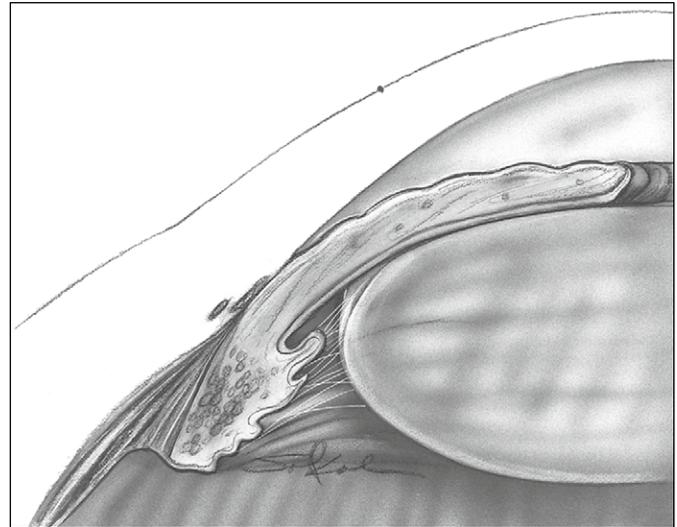
Fig. 15-6 Relative pupillary block.

This important interface has been described as the *iris-lens channel*: an extremely thin (<5 microns), fluid-filled, flat, doughnut-shaped passage between the posterior iris surface and the anterior lens, circumferentially extending beyond the edges of the pupil.¹⁸¹ This dynamic and pulsatile¹⁸² fluid ‘structure’ provides normal resistance to aqueous flow from the posterior to anterior chambers. This thus functions as a relative one-way valve to sustain a minimally higher pressure in the posterior chamber than in the anterior chamber, hence directing anterior flow forward. Though the iris-lens channel is currently below the level of UBM resolution, the lens itself is not thought to *directly* contact the posterior iris, but remains a major variable in determining the configuration of the lens-iris channel, and hence its flow capacity.

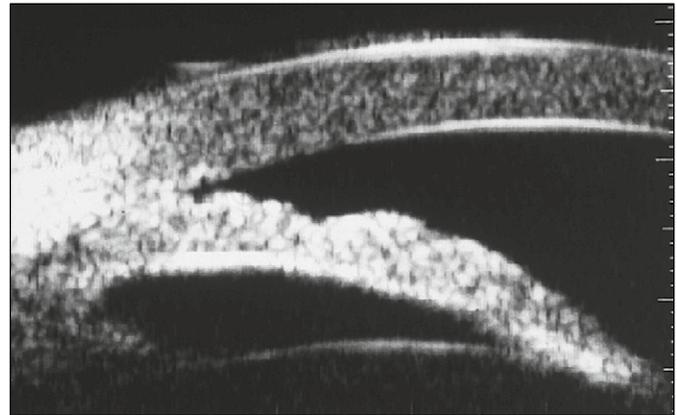
The resistance to flow has classically been referred to as *relative pupillary block* (Fig. 15-6). Under normal circumstances, this pressure differential is of little significance; however, if the pupillary block were to increase, the pressure posterior to the iris could force the peripheral iris to billow forward into the angle. (‘Like a sail full of wind’ is how this is often described to patients in explaining the salutary effect of a peripheral iridotomy’s perforation of the iris.) The increasing anterior bowing of the peripheral iris is maximized both when the anterior lens surface is progressively more anterior relative to the iris root, and when the pupil is in a mid-dilated position. A thicker iris has reduced flexibility which could increase the pressure difference between posterior and anterior chambers through the lens-iris channel.^{19,175,183}

If the peripheral iris bows forward slightly or if the anterior chamber is relatively large, the effect on IOP and anterior chamber dynamics would be inconsequential. However, if the peripheral iris bows forward enough to cover the trabecular meshwork, the normal outflow of aqueous humor from the anterior chamber would be blocked and the IOP could increase⁷⁹ (Fig. 15-7). Angle-closure disease typically occurs in eyes with small anterior segments in which even a relatively small forward bow of the peripheral iris may contact the trabecular meshwork.

Intraocular pressure and outflow facility are normal in eyes with shallow but open angles, no matter how narrow the angle appears. In contrast, when the iris is in contact with the trabecular



(A)



(B)

Fig. 15-7 (A) Pupillary block leading to angle closure. **(B)** Ultrasound biomicroscopic photograph illustrating central posterior iris apposition causing the iris to bow forward and occlude the anterior chamber angle. (Courtesy of Robert Ritch, MD.)

meshwork, IOP rises and outflow facility falls in proportion to the extent of the angle closed; the resultant IOP would depend on the function (outflow facility) of the remaining unobstructed and undamaged angle.

Moderate pupillary dilation is historically the most recognizable cause of increased pupillary block, frequently due to pharmacologic dilation. It is thought that the posterior vector of force of the iris sphincter muscle reaches its maximum when the pupil is moderately dilated to a diameter of 3.0–4.5 mm.^{78,97,183} Furthermore, when the pupil is moderately dilated, the peripheral iris is under less tension and is more easily pushed forward into contact with the trabecular meshwork. Lastly, dilation may also thicken and bunch the peripheral iris in the angle. In contrast, when the pupil is *widely* dilated, there is little or no contact between the lens and the iris and minimum pupillary block. This fact explains why acute angle-closure glaucoma rarely occurs while the pupil is in the actual process of dilating due to mydriatic eye drops: the dilation occurs rapidly enough that pupillary block does not have time to develop. Rather, pupillary block ‘classically’ occurs as the pupil constricts over hours following dilation, presumably because the mid-dilation is prolonged as the mydriatic effect slowly reverses.

Pupillary block can also be increased by marked pupillary miosis. Despite this cautionary apprehension about pharmacologic dilation precipitating acute angle closure, in reality it is quite rare in a general population.⁴³

There exists a rich, anecdotal literature of everyday life ‘triggers’ for precipitating attacks of acute PACG; reports commonly identified emotional upset (e.g., bad news, pain, fear, illness, an accident) or dim illumination (e.g., in a restaurant or theater). Emotional upset is thought to dilate the pupil through increased sympathetic tone to the iris dilator muscle, whereas dim illumination dilates the pupil through decreased cholinergic tone to the iris sphincter muscle. But why precisely an attack is precipitated under one such circumstance, but not by the countless dilations and constrictions of the pupil during a lifetime of quotidian activity and emotional reactivity, is never clear. Similarly, the forward movement of the lens, which occurs in a variety of situations such as reading, changes in body position, and miotic therapy, has been implicated as a trigger. Diurnal variations in the anterior chamber depth with parasympathetic fluctuations and pupillary diameter,⁹⁸ and diurnal variations in aqueous secretion have also been suggested as contributory factors.¹⁸⁴

The pharmacological precipitation of acute PACG in predisposed individuals, by a variety of medications applied topically, systemically, or transdermally, is better documented. These medications include tranquilizers, bronchodilators, antidepressants, vasoconstrictors including common nasal decongestants, appetite suppressants, antiparkinsonian agents, cold preparations, anti-nausea agents, and antispasmodics (Box 15-2).^{185–189} These drugs are thought to dilate the pupil through an anticholinergic effect on the iris sphincter muscle, or a sympathomimetic effect on the iris dilator muscle.

Special attention needs to be drawn to the role of the parasympathomimetic drugs, which constrict the pupil and increase pupillary block. These drugs also contract the ciliary muscle, allowing the zonules to relax and the lens to move forward. Although these changes may not always have clinical relevance, the incontrovertible fact is that angle-closure glaucoma can be precipitated by miotic agents in susceptible eyes with narrow angles. (As discussed below, in considerations for managing the fellow eye after an attack of acute PACG, it is advisable to *avoid* miotics such as pilocarpine in the ‘prevention’ of PACG.) Because of this risk, it is important to repeat gonioscopy when initiating or changing miotic therapy. The strong miotics (e.g., cholinesterase inhibitors) are more likely to produce angle closure because they cause greater constriction of the pupil and induce vascular congestion of the uveal tract.

The proper treatment for miotic-induced angle closure is discontinuing the drug. If the angle remains exceedingly narrow after discontinuing the parasympathomimetic agent or if the patient requires miotic treatment for IOP control, laser iridotomy can be performed

Provocative tests

One goal that remains as elusive as ever has been the ability to predict which eye at risk will proceed towards disease. As recent epidemiologic assessments have demonstrated, most eyes with ‘occludable angles’ do *not* progress towards PACG.⁴³ This was an especially compelling concern before laser iridotomies were available, since surgical iridectomies were not without morbidity, particularly in terms of complications and cataract formation.⁵⁰

Some of the above-mentioned observations on the role of body position and pharmacologic effects have historically generated an array of *provocative tests*: to elevate IOP in conjunction with occlusion of the angle, so as to indicate which eyes ‘at risk’ merit surgical

Box 15-2 Classes of drugs capable of precipitating angle-closure glaucoma in susceptible eyes

Antipsychotic agents
Phenothiazines: e.g., perphenazine (Trilafon), fluphenazine (Prolixin)
Anticonvulsants
e.g., Topiramate (Topomax)
Antidepressants
Tricyclic agents: e.g., amitriptylene (Elavil), imipramine (Tofanil)
Non-tricyclic agents: e.g., fluoxetine (Prozac), paroxetine (Paxil), venlafaxine (Effexor)
Monoamine oxidase (MAO) inhibitors
e.g., Phenylzine (Nardil), tranylcypromine (Parnate)
Antihistamines
e.g., Ethanolamines: e.g., orphenadrine (Norgesic)
Antiparkinsonian agents
e.g., Trihexyphenidryl (Artane)
Antispasmodics
Propantheline (Pro-banthine)
Dicyclomine (Bentyl)
Antibiotics
e.g., Sulfa, quinine
Sympathomimetic agents
Adrenaline (epinephrine), ephedrine
Dipivefrin
Amphetamine, hydroxymphetamine
Tetrahydrozoline
Naphazoline
Mydriatic agents
<i>All:</i> cyclopentolate, tropicamide, atropine, homatropine, scopolamine
Miotics
e.g., Echothiophate (Phospholine Iodide), pilocarpine 2–6%
Botulinum toxin
Cardiac agents
e.g., Disopyramide (Norpace)

Modified from Mandelkorn R. Drug-induced glaucoma. In: Zimmerman TJ, Koener KS, editors: Clinical pathways in glaucoma. New York, Thieme, 2001:333–350.¹⁸⁵

intervention.^{190,191} Most provocative tests were designed to resemble ‘physiologic’ situations, in the hope that the test would mimic the natural history of the condition. Fortunately, two prospective studies have been conducted, and *neither* validates the utility or reliability of such examinations.^{192,193}

A variety of testing strategies have been reported: (1) *mydriatic* stimulation with a weak, short-acting parasympatholytic agent such as tropicamide 0.5% or a weak sympathomimetic such as hydroxymphetamine, to mildly dilate the pupil and either raise the IOP^{194,195} or demonstrate impaired tonographic outflow;¹⁹⁶ (2) *dark room* testing to induce physiologic miosis;^{197,198} (3) a *prone* test with the head resting on one’s arms on a table, arguably shifting the lens anteriorly without dilation;^{199,200} and (4) complex *pharmacologic* provocations, such as applying a mixture of cycloplegics or mydriatics with pilocarpine.^{201,202}

Unfortunately, each of these ‘provocative’ tests produce enough false positives and false negatives to make them unreliable as predictors of true angle closure or angle-closure glaucoma. Most studies indicate that 10–30% of eyes with well-documented histories of angle-closure glaucoma have negative provocative tests.^{195,199,202} Furthermore, approximately 5% of eyes with angle-closure glaucoma have positive provocative tests after peripheral iridectomy.^{191,199,202} Finally, even a small percentage of normal eyes and

of eyes with open-angle glaucoma develop elevated IOP without angle closure during provocative testing.¹⁹⁹ This has been variously attributed to a cycloplegic effect on outflow facility or hypersecretion of aqueous humor.^{199,203} Therefore, the provocative tests from a previous generation of clinical techniques are of little help in predicting a patient's likelihood of developing angle-closure glaucoma. They are no longer either clinically recommended or relevant.

Whether newer efforts integrating a variety of technologies will be more helpful remains to be seen. For example, Congdon and co-workers¹³⁸ found that ultrasonic measurement of the anterior chamber depth combined with tonometry gave an acceptable balance between a sensitivity of 88% and a specificity of 92% in a screening to discover PAC suspects and PAC. While assessing the fellow eyes of patients who presented with acute PACG attacks, using both Scheimpflug photography and ultrasound biomicroscopy, Friedman and co-workers¹⁷⁸ found shallow peripheral anterior chambers, more narrowing of the angle when going from light to dark, and greater opening of the angle after pilocarpine drops compared to controls. Whether these kinds of newer dynamic tests are any more sensitive or specific in indicating which patients are likely to develop angle closure still awaits longitudinal, prospective study.

Clinical presentations of acute PACG with pupillary block

When the outflow capacity of the angle is sufficiently compromised to elevate the IOP, possible irreversible damage to the optic nerve can subsequently ensue. Asymptomatic disease of presumably long duration is much more common than the dramatic symptoms of a precipitous closure of the angle, with rapid deterioration in optic nerve and/or corneal function. *Acute* PACG is a distinctive form of clinical disease, with a constellation of presenting signs and symptoms requiring urgent intervention, as well as preventive measures for the fellow eye.

Signs and symptoms

The typical patient with an acute attack of PACG from pupillary block will have a sudden onset of pain or aching on the side of the affected eye. This pain is accompanied by blurred vision or colored haloes around lights (from the refractive and diffractive changes of corneal edema); ocular congestion; and sometimes nausea, vomiting, and sweating. The pain usually occurs in the trigeminal distribution, and is locally experienced by the patient as in the eye; or it can manifest as referred pain in the orbit, head, ear, sinuses, or teeth. The discomfort may be mild to severe – so severe in fact that the glaucoma attack may masquerade as an acute intracranial process such as an aneurysm.

The eye pain appears to be related more to the rapid *rate of the rise* in IOP than to the absolute level of the pressure itself. The blurred vision occurs at first as a result of distortion of the corneal lamellae, and later as a result of corneal epithelial edema. The corneal edema acts as a diffraction grating that breaks white light into its component colors, causing patients to note colored haloes or rainbows around incandescent lights. During these episodes, the blue-green colors are central and the yellow-red colors are peripheral. In a study of over 5000 Taiwanese patients with angle-closure glaucoma, symptoms of angle closure were present in only 35% of patients.⁸⁰

Autonomic stimulation during an acute attack can result in nausea, vomiting, sweating, and bradycardia. These symptoms are sometimes confused with those caused by a flu-like illness or an acute abdomen; with systemic distress and vomiting, PACG attacks have been mistaken for acute appendicitis. Occasionally systemic

Box 15-3 Physical findings in acute angle-closure glaucoma with pupillary block

Findings during an acute attack of angle-closure glaucoma

Two of the following symptom sets:

- Periorbital or ocular pain
- Diminished vision
- Specific history of rainbow haloes with blurred vision

IOP >21 mmHg plus **three** of the following findings:

- Ciliary flush
- Corneal edema
- Shallow anterior chamber
- Anterior chamber cell and flare
- Mid-dilated and sluggishly reactive pupil
- Closed angle on gonioscopy
- Diminished outflow facility
- Hyperemic and swollen optic disc
- Constricted visual field

Findings suggesting previous episodes of acute angle-closure glaucoma

- Peripheral anterior synechiae
- Posterior synechiae to lens
- Glaukomflecken
- Sector or generalized iris atrophy
- Optic nerve cupping and/or pallor
- Visual field loss
- Diminished outflow facility

Modified from Quigley H, Yamamoto T: Management of acute angle-closure crisis. In: Weinreb R, Friedman D, editors: Angle closure and angle closure glaucoma: reports of 3rd AIGS consensus meeting, Hague, 2006:21–26.²⁰⁷

symptoms such as abdominal or chest pain are predominant and may make diagnosis difficult.²⁰⁴ Acute angle-closure attacks have precipitated under conditions of intense physiological stress, such as pituitary apoplexy²⁰⁵ and childbirth.²⁰⁶

Most attacks of angle-closure glaucoma are unilateral. However, 5–10% of the attacks may affect both eyes simultaneously.¹⁵¹ Patients who develop acute attacks of angle-closure glaucoma may relate that they have had similar but less severe episodes in the past, recalling mild episodes of discomfort or blurring that were relieved by sleep or by exposure to bright light. Such reports have been used to substantiate the terminology of 'subacute' or 'intermittent' angle closure; but they are, strictly speaking, variable and subjective reports, difficult to accurately correlate with actual ocular dysfunction.

Clinical examination

The clinical examination of an eye in acute PACG can reveal a spectrum of physical findings (Boxes 15-3 and 15-4):

1. Diminished visual acuity.
2. Perilimbal conjunctival hyperemia (i.e., 'ciliary flush').
3. Corneal edema, at times involving only the epithelium, but occasionally thickening the stroma and precipitating striae.
4. A shallow anterior chamber both centrally and peripherally.
5. Minimal-to-moderate anterior chamber reaction caused by increased aqueous humor protein concentration.²⁰⁸ Severe or prolonged attacks may produce heavy anterior chamber cell and flare – but keratic precipitates are rarely seen.

Box 15-4 Differential diagnosis of acute angle-closure glaucoma**Evidence of compromised angle on gonioscopy or shallow anterior chamber**

Ciliary block glaucoma (aqueous misdirection or malignant glaucoma)
 Neovascular glaucoma
 Iridocorneal endothelial syndrome
 Plateau iris syndrome with angle closure
 Secondary angle closure with pupillary block (e.g., posterior scleritis)
 Cilio-choroidal detachments (bilateral)

High-pressure open-angle glaucomas masquerading as acute angle closure

Glaucomatocyclitic crisis
 Herpes simplex keratouveitis
 Herpes zoster uveitis
 Sarcoid uveitis
 Pigmentary glaucoma
 Exfoliative glaucoma (may have associated angle closure)
 Post-traumatic glaucoma
 Phacolytic glaucoma
 Steroid-induced glaucoma

Modified from Quigley H, Yamamoto T: Management of acute angle-closure crisis. In: Weinreb R, Friedman D, editors: Angle closure and angle closure glaucoma: reports of 3rd AIGS consensus meeting. Hague, 2006:21–26.²⁰⁷

6. A moderately dilated, vertically oval, sluggish, or nonreactive pupil. The high IOP causes ischemia and paresis of the pupillary sphincter.^{209–211} (It is important to assess for a reverse Marcus Gunn pupillary sign to gauge the extent of optic nerve damage in the symptomatic eye.)
7. Markedly elevated IOP, usually in the range of 35–75 mmHg.
8. A closed angle on gonioscopy, which is *the* critical test for diagnosing angle-closure glaucoma. It is sometimes difficult to evaluate the angle during an acute attack because of corneal edema and hazy media. In this situation, gonioscopy should be repeated after the IOP is reduced by medical treatment, which hopefully permits the cornea to clear (see ‘Treatment of acute PACG’ below). One or two drops of anhydrous glycerin can also be administered to the anesthetized eye to clear the cornea and improve the gonioscopic examination. (Other topical hyperosmotic agents, although less effective, may work if glycerin is not available: these include hypertonic salt solutions and Karo (or other brand) syrups whose sugar content is high enough to provide some osmotic effect.) As discussed below, repetitive corneal indentation at the slit lamp may burp the angle open to reduce both the pressure and corneal obscuration. If the view remains hazy, angle-depth estimation by the van Herick test³⁹ and gonioscopy of the fellow eye can confirm the presence of narrow angles, albeit imprecisely. Ultrasonic biomicroscopy or AS-OCT imaging studies, if available, can be very helpful diagnostically.
9. Sometimes a hyperemic, swollen optic disc. The optic disc is swollen during an attack of angle-closure glaucoma presumably from impaired axoplasmic flow. Or the optic disc may be swollen when hypotony follows an acute attack of angle-closure glaucoma. The disc does not appear pale or cupped during the acute attack unless there have been previous episodes of angle closure or concomitant glaucoma from another cause.²¹²

When IOP was raised to high levels in experimental studies in monkey eyes, the optic discs appeared swollen for 4–5 days and then became pale and cupped.²¹³ The appearance of the optic disc is altered if there is a concomitant central or branch vein occlusion.^{214–216} It is also possible for a central retinal vein occlusion to cause a transient shallowing of the anterior chamber (see Ch. 16).^{217,218}

10. A normal or constricted visual field. (Visual field examinations are generally not performed during acute attacks of angle-closure glaucoma.) Following an attack, visual fields can demonstrate a variety of perimetric defects.^{212,219} Curiously, eyes with *asymptomatic* PACG may have worse visual fields than an eye after an acute attack, possibly reflecting the chronicity of the glaucomatous processes which may be unrecognized by the patient.²²⁰
11. Diminished tonographic outflow facility. The resistance to outflow is directly related to the extent of the angle closure. The resistance also depends on whether the open portions of the angle have been damaged by previous attacks of angle closure.

Recent clinical publications^{149,207} define an acute attack of PACG by the presence of: (1) at least *two symptoms* (such as ocular pain and nausea/vomiting); *plus* (2) an *elevated IOP* > 21 mmHg; *plus* (3) at least *three findings* from the clinical examination, e.g. corneal edema, shallow anterior chamber, gonioscopic confirmation of angle closure, etc. (see Box 15-3). Such explicit criteria of definitions make clinical and research studies significantly more specific and comparable.

A patient examined during an acute attack of PACG with pupillary block may demonstrate stigmata of previous attacks, including PAS, posterior synechiae between the peripupillary iris and lens, anterior subcapsular lens opacities (‘glaukomflecken of Vogt’, sector or generalized atrophy of the iris, pallor and cupping of the optic disc, and visual field loss. The iris atrophy is probably ischemic in origin and is more often located superiorly than inferiorly. This process releases a considerable amount of pigment, which is then deposited on the iris surface, corneal endothelium, and trabecular meshwork. The ischemia may contribute to the severe pain during the acute attack.

Many of the above signs and symptoms could occur as a result of an abrupt and profound rise in IOP regardless of cause. The ophthalmologist must distinguish PACG with pupillary block from secondary forms of angle closure, as well as open-angle glaucoma with sudden markedly high levels of IOP. The differential diagnosis includes neovascular glaucoma, plateau iris syndrome, hypertensive iridocyclitis, aqueous misdirection, post-traumatic recessed angle, exfoliative glaucoma, pigmentary glaucoma, and glaucomatocyclitic crisis (see Box 15-4). A special situation exists with exfoliative syndrome, which can produce very high IOPs in the presence of an open angle. However, exfoliative syndrome is also associated with an increased prevalence of narrow angles and an increased risk of pupillary block PACG.²²¹

These non-PACG entities are usually discriminated by a careful history of the temporal course of events, a slit-lamp examination, and indentation gonioscopy of the involved and the fellow eyes. The examination also serves to detect secondary forms of angle closure that are associated with ciliary block glaucoma, ciliary body swelling, posterior segment tumors, central retinal vein occlusion, nanophthalmos, etc.

It is crucial that *both eyes be examined* in order to determine whether any presenting condition is bilateral, and to assess the potential for the second eye to become involved.

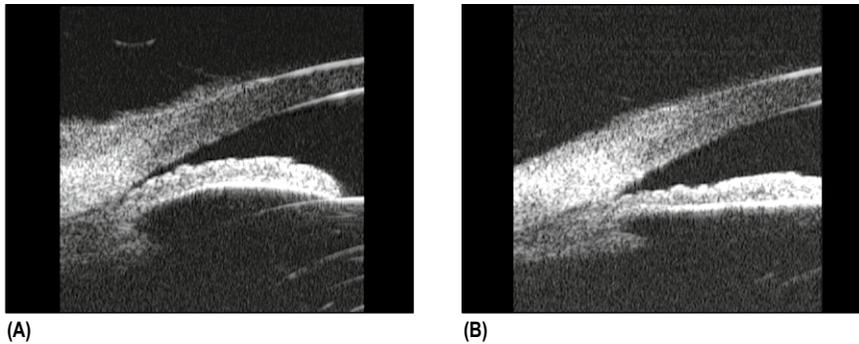


Fig. 15-8 (A) Ultrasonic biomicroscopy of closed angle before peripheral laser iridotomy. **(B)** Ultrasonic biomicroscopy of opened angle after peripheral laser iridotomy.

(Courtesy of Mingguang He, MD.)

Treatment of acute PACG

The treatment of acute PACG with pupillary block can be divided into four stages:

1. *Immediate medical therapy* is required for lowering the IOP, thus enhancing maximal visualization of angle structures for diagnosis and treatment, and interrupting pressure damage to the optic nerve, trabecular meshwork, and lens. Once the IOP has been lowered, and the cornea cleared as a result, a variety of laser interventions can be initiated (see below).
2. *Protection of the fellow eye* is initiated with medical treatment to reduce the IOP, until the acute attack is resolved and a prophylactic iridotomy can be performed. For reasons elaborated below, we emphatically *encourage that chronic miotics not be used to 'prevent' angle closure in the fellow eye.*
3. *Laser iridotomy* in both the involved and fellow eyes can often, but not always, achieve two objectives: (1) to relieve acute pupillary block and open the angle; and (2) eliminate future acute attacks of PACG (Fig. 15-8). Following iridotomy, the central anterior chamber depth may not appreciably deepen by slit-lamp examination, and irido-trabecular contact can be seen to persist (as seen in approximately 60% of Chinese eyes in the Liwan study); in contrast, UBM studies usually demonstrate some opening of the angle.^{69,222} Clinically, iridotomies usually reduce but do not totally eliminate the possibility of future attacks of angle-closure glaucoma.⁷¹ Intriguing new studies that proceed directly to cataract/intraocular lens surgery following an attack of acute PACG may prove, with confirmatory research, to be an appealing alternative to laser iridotomy.²²³ Unless the fellow eye with PAC has visually significant cataract that can be expeditiously addressed, laser iridotomy – *not* prophylactic miotic medical therapy – is imperative. The risk of *not* performing a contralateral iridotomy after an acute attack in the presenting eye is formidable; nearly 50% of such eyes can go on to an acute attack, usually in the first months following the patient's initial presentation, even with the use of pilocarpine.^{224,225}
4. *Long-term glaucoma surveillance and IOP management of both eyes* is obligatory following an attack of acute PACG. Following such an episode, the long-term prognosis for such an eye avoiding visual loss is guarded; cataract as well as the high likelihood of failed medical management frequently require surgery.²²⁶ The potential morbidity of PACG is not to be underestimated: in one long-term follow-up of 4–10 years, more than one out of six of acute-attack eyes were blind, and nearly half had advanced glaucomatous disc and field

damage.¹⁴⁹ Fellow eyes after prophylactic iridotomy fared better in two studies of 4–6 years' follow-up, with single-digit rates of progressive glaucoma developing.^{227,228} In summary, every *acute* PACG eye and its fellow eye are automatically at risk for PACG – the most common cause of glaucomatous blindness in the world.

Medical management of acute PACG

Patient comfort and lowering of the IOP are the first priorities in addressing an acute crisis of PACG. When these aims are achieved, one can proceed to more definitive interventions with the laser, such as iridotomy, pupilloplasty, or iridoplasty. Medications to control pain and emesis should be administered as needed. If the patient presents in great physical distress, a retrobulbar anesthetic (e.g., 4 cc of a 50:50 mixture of 2% lidocaine with 0.75% bupivacaine) can be enormously helpful to both patient and physician: the analgesia and interruption of nausea and vomiting provide welcome relief to the sufferer; and the eye is stable and insensate for ocular manipulations (e.g., paracentesis) and laser treatments. Patients, of course, need to be explicitly told that the loss of vision with the retrobulbar injection is temporary; and the practitioner needs to compensate for the lost ability of the patient to cooperate with different gaze positions during gonioscopy or laser therapy.

The physician should immediately administer some combination of a topical β -adrenergic antagonist (such as timolol or levobunolol),¹¹¹ a topical α -adrenergic agent (such as apraclonidine or brimonidine), a prostaglandin analogue,^{229–231} an oral or parenteral carbonic anhydrase inhibitor (e.g., acetazolamide)²³² and, if necessary, an oral hyperosmotic agent (e.g., glycerin or isosorbide) (Table 15-2). These agents will begin lowering the IOP, alleviating pain, and allowing the cornea to be cleared with a topical hyperosmotic agent for further diagnostic evaluation. Intravenous mannitol may be used if oral agents are unavailable, not tolerated, or contraindicated as in diabetes mellitus.

Assuming there are no contraindications, any of the commonly used topical β -adrenergic antagonists can be administered to the affected eye to reduce aqueous humor formation and IOP. Timolol or levobunolol will begin to take effect within about 20 minutes of administration. Apraclonidine 0.5% or brimonidine (0.15–0.2% formulations), which reduce aqueous formation, are often helpful in reducing IOP rapidly.²³³ Prostaglandin analogues have also proven to be empirically effective, their longer-term pharmacodynamic profiles notwithstanding.²²⁹ Similarly, the carbonic anhydrase inhibitor, acetazolamide, can be given orally in a dose of 500 mg. If the patient is nauseous or vomiting, acetazolamide (250–500 mg) may be administered intravenously.

Table 15-2 Treatment of acute angle-closure glaucoma

Method	Drug and Administration
β-Adrenergic antagonist	Timolol or levobunolol: one drop to affected eye
Prostaglandin analogue	Latanoprost: one drop to affected eye
α-Adrenergic agonist	Apraclonidine or brimonidine: one drop to affected eye
Carbonic anhydrase inhibitor	Dorzolamide: one drop to affected eye; or acetazolamide (500 mg orally, or intravenously if the patient is nauseous)
Hyperosmotic agent	Glycerine 50% or isosorbide 45% (1.5–4 ml/kg orally); mannitol 20% (2–7 ml/kg intravenously if the patient is nauseous or unable to tolerate oral agents)
Limited role of pilocarpine	Pilocarpine 1%: one drop two or three times immediately preceding laser iridotomy
Pain and emesis control can be obviated by retrobulbar anesthesia	

Systemic hyperosmotic agents dehydrate the vitreous and allow the lens–iris diaphragm to move posteriorly; they are often the most effective means of lowering IOP during acute episodes of angle-closure glaucoma and can be a crucial part of therapy for severe attacks. Oral glycerin is administered as a 50% solution in a dose of 1.5–4 ml/kg. In diabetic patients, oral 45% isosorbide solution can be given in a similar dose. Both of these agents may be made more palatable by pouring them over crushed ice and/or adding lemon juice. If the patient is nauseous or vomiting, 20% mannitol is administered in a dose of 2.0–7 ml/kg over 30–45 minutes. If the IOP begins to fall substantially, it is not necessary to administer the entire dose of mannitol. A reduced dose may prevent hypervolemia, which can induce cardiac overload or pulmonary edema, especially in elderly patients with cardiovascular disease. The need for hyperosmotic agents has been reduced by the availability of α-adrenergic agonists. This is fortunate as oral hyperosmotic agents, especially isosorbide, have become difficult to obtain.

To reduce anterior chamber inflammation and the chance of both anterior and posterior synechiae formation, topical steroids may be administered after the acute attack is broken.

The common admonition to apply topical miotics in the management of acute PACG is, in our assessment, an historical anomaly and in fact quite controversial. Miotic agents' alleged utility for managing acute disease, and as preventive therapy for the fellow eye or until an iridotomy can be arranged, is repeated in decades' worth of ophthalmic literature and textbooks. Nevertheless, much of pilocarpine's role is by historical default. For much of the twentieth century (and even now in much of the developing world) it was the only widely available and affordable IOP-lowering agent. Moreover, its seemingly obvious effect of constricting the pupil, which 'retracts' the peripheral iris from its contact with the angle, made its use in angle-closure treatment appealing. But two important but oft overlooked natural history studies of *fellow* eyes in patients presenting with acute PACG reported nearly a 50% acute attack rate in Caucasians within a few months of their initial presentation.^{224,225} This is a much higher rate of acute attacks than expected and suggests, contrary to accepted wisdom, that the use

of 'prophylactic' pilocarpine in these fellow eyes may have been *the precipitating cause* for such extensive morbidity.

These studies' clinical observations are in concert with physiologic assessments and calculations of pilocarpine's intraocular effects on the biomechanics of the lens, ciliary body, and iris – in other words, *pilocarpine exacerbates virtually every parameter involved in angle-closure mechanics*.^{19,234} There are two major intraocular mechanical situations that miotics exacerbate: (1) pilocarpine's effects on ciliary body and zonular responses allow the lens shape to become more convex, while facilitating its anterior movement, thus shallowing the anterior chamber, with peripheral compromise of the irido-trabecular angle; and (2) miotics induce increased convexity of the iris as the lens advances¹⁸³ which, with the simultaneous miotic-induced miosis, predisposes the lens–iris channel to greater resistance to aqueous flow. The result is frequently an inadvertent *worsening of pupillary block*.

We advocate a fresh, critical reappraisal of this tradition-bound medication's true role in managing the angle-closure glaucomas. Pilocarpine and other miotics are useful under specific and circumscribed circumstances: to induce miosis to maximally stretch the peripheral iris in anticipation of an immediate laser iridotomy or iridoplasty; to effect mild miosis in plateau iris angle-closure disease, thus stretching the peripheral iris and helping to open the angle; or to powerfully lower IOP as an adjunct therapy in pseudophakic open-angle glaucoma. Many glaucoma experts use low-dose pilocarpine very sparingly as part of the total regimen to manage an acute attack. Pilocarpine 1% can be used twice or three times after the pressure has been lowered by other means to put the peripheral iris on stretch, thus facilitating peripheral placement of the laser iridotomy. However, other glaucoma experts have given up the use of pilocarpine entirely in managing acute angle closure and instead use other medical agents, paracentesis, and/or laser iridoplasty to bring the pressure down.

In most acute attacks of angle-closure glaucoma with pupillary block, the IOP is so high that the pupillary sphincter muscle is ischemic and unresponsive to topical miotic agents.^{209–211} Therefore, pilocarpine is less useful to bring the high pressure of an acute attack down than it is to improve the ability to perform the best iridotomy. Surgical interventions, such as iridectomies or cataract extraction, remain effective options if laser iridotomy is not feasible or available. It also bears repeating that there is virtually universal consensus among glaucoma specialists that pilocarpine is *definitely not* an alternative to laser iridotomy for the *contralateral eye* following an acute attack, which must be performed as soon as it is feasible.²³⁵

An acute attack of angle-closure glaucoma should not be considered terminated until the IOP is reduced and sustained at the lowest possible levels, and the angle is as open as physically possible on gonioscopy. Obviously, if the angle is irreversibly closed by PAS, then iridotomy will not keep the pressure down. The physician must not be satisfied simply when IOP temporarily falls with medical treatment, because profound hyposecretion and hypotony can follow an acute attack of PACG. Unless the angle is open maximally, IOP will rise again to very high levels over the hours and days, when the ciliary body recovers its secretory function: close clinical surveillance is warranted.

Slit-lamp maneuvers in management of acute PACG

Besides applying a combination of topical and systemic hypotensive drugs, the clinician can use several invaluable *mechanical methods* at the slit lamp to acutely reduce the IOP. Especially after having provided the patient relief with a retrobulbar anesthetic injection,

these maneuvers can often accelerate corneal clarity for gonioscopy and more definitive laser treatments. Such maneuvers include:

1. *Axially depressing the central cornea* with a small gonioprism (e.g., the Zeiss four-mirror lens) or with a blunt instrument (e.g., a muscle hook or moist cotton swab), perpendicular to the corneal apex and parallel to the visual axis. The axial force indenting the cornea is transmitted to the iris, bowing it posteriorly, interrupting pupillary block, and thus displacing aqueous towards the periphery of the anterior chamber, where it can momentarily force open the angle and incrementally reduce IOP (Fig. 15-9).²³⁶ Care must be taken, however, with fragile corneal epithelium in the presence of corneal edema, to not allow the indentation device to slip off eccentrically and thereby shear off a sheet of epithelium.
2. Applying *digital massage* to the globe after retrobulbar anesthesia. This technique is used to dehydrate the vitreous cavity and lower IOP in preparation for cataract surgery, and may be of temporary help.
3. Performing an *anterior chamber paracentesis*, under topical anesthesia, with a small-gauge disposable sterile needle (e.g., #25, #27 or #30 gauge).^{237,238} Though not a maneuver without hazard in an eye with a shallow chamber and possible forward position of the crystalline lens, the technique consists of a slow penetration through the peripheral cornea, barely entering the chamber with the needle point, all the while under direct slit-lamp observation. Some authors advocate a gentle semi-rotation movement back and forth of the bevel of the needle in and out of the puncture site, intermittently 'fish-mouthing' the entry track for visible leakage. Others suggest that with a small #30 gauge needle, penetration into the anterior chamber alone will allow decompression and reliable IOP reduction to 10mmHg through the small bore, with minimal fluid appearing in the shaft of the needle. This carefully performed maneuver can dramatically slow aqueous outflow, decompress the IOP and clear the cornea.

Laser interventions for acute PACG

The window of a lower IOP, afforded by medical and/or mechanical pressure reduction, both interrupts glaucomatous forces on the

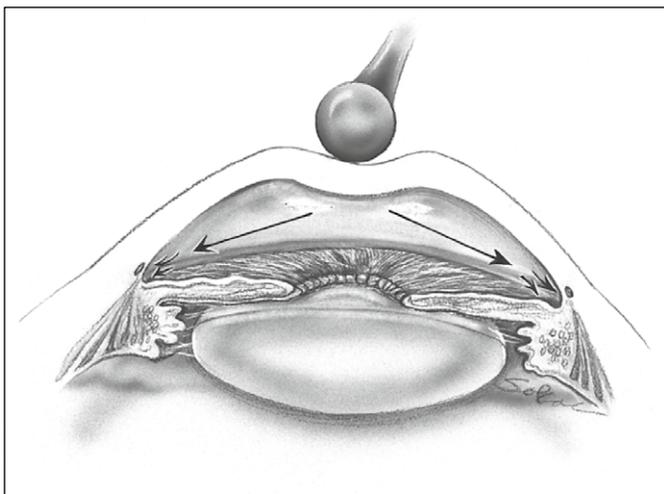


Fig. 15-9 Depressing the central cornea with a blunt instrument forces aqueous humor into the periphery of the anterior chamber where it may open the angle.

optic nerve and simultaneously enhances corneal clarity, so as to proceed with more definitive laser interventions (see Ch. 30 for details on types of devices and treatment parameters):

1. An *iridotomy* can be made with an argon, or a neodymium:yttrium-aluminum-garnet (Nd:YAG), laser. This treatment is indispensable in the management of all forms of PACG, in either their acute or chronic manifestations (Fig. 15-10.)
2. A *peripheral iridoplasty* (gonioplasty) can be performed with an argon laser. Even in the presence of slightly hazy corneal media, it is often possible to flatten the peripheral iris and have it retract centripetally towards the pupil and away from the trabecular meshwork.^{239,240} Argon laser iridoplasty has been reported to be at least as effective as medical therapy in controlling an acute attack.²⁴¹
3. A *pupilloplasty* can be made at the edge of the pupil, using an argon laser and high-density contact lens (e.g., Wise sphincterotomy lens): applications of intense, small bursts, 2–3 mm eccentric to the pupillary margin superiorly create a 'tear-drop' shape enlargement of the pupil towards 12 o'clock, often focally relieving pupillary block.^{239,242}

Laser iridotomy Peripheral laser iridotomy, with Nd:YAG or argon instruments, is the definitive treatment for acute angle-closure glaucoma with pupillary block, with incontrovertible evidence to support its effectiveness.²²⁹ Once free communication exists between the posterior and anterior chambers there is an insufficient pressure differential to push the peripheral iris forward against the trabecular meshwork. The peripheral anterior chamber depth usually increases after iridectomy or iridotomy, in the absence of extensive PAS, whereas the central depth is unchanged.^{81,84,243} Ultrasonic biomicroscopy studies demonstrate the same finding: after iridotomy, the angle opens and markedly reduces the appearance of occludability without deepening the central anterior chamber.²²²

Once PACG's optic nerve damage has been demonstrated, iridotomy alone is unlikely to control the glaucoma, and either further medical therapy or filtering surgery will be required.^{226,244}

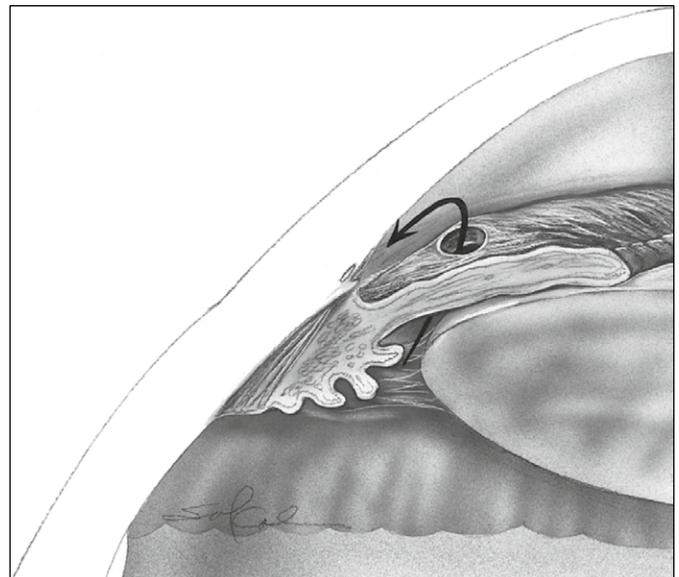


Fig. 15-10 Patent iridectomy reduces pupillary block and equilibrates pressure in the posterior and anterior chambers.

Rarely, acute attacks persist despite a patent iridotomy, nearly always necessitating surgery for cataract extraction and/or filtration.⁷⁰

Argon and Nd:YAG iridotomies have virtually replaced surgical iridectomy as the preferred technique for performing iridectomy.^{245–251} The term *iridotomy* is used to indicate laser-induced openings in the iris, whereas *iridectomy* indicates surgical removal of iris tissue. Although surgical iridectomy is a relatively safe and simple procedure, it is invasive and presents a small but still present risk of intraocular complications such as cataract, bleeding, and endophthalmitis. Surgical iridectomy is now reserved for such infrequent situations such as: the laser fails to produce a patent iridotomy; laser iridotomies repeatedly close; a laser is neither available nor functioning properly; opacities of the cornea interfere with laser treatment; or the patient is uncooperative or unable to sit at the slit lamp.^{194,252–256} Often if the eye comes to filtration, an additional surgical iridectomy may be advisable.

Argon laser iridotomies, in contrast to those performed with a Nd:YAG laser, may close at a later date, subjecting the eye to redevelopment of angle closure.²⁵⁷ Closure of laser iridotomies is usually by regrowth of iris pigment epithelium.²⁵⁸ Fleck²⁵⁷ has calculated that a 15- μm opening is theoretically large enough to prevent pupillary block; however, localized iris edema, pigment epithelial proliferation, and changes in iridotomy size after pupil dilation may obstruct a small opening. Therefore it is recommended that an iridotomy between 150 and 200 μm should be created.

If an acute attack can be terminated by medical means, the physician can proceed directly to laser iridotomy, or wait 1–2 days for the cornea to clear and intraocular inflammation to subside. The physician must observe the IOP and the patient carefully to ensure that a repeat attack does not occur.

Laser iridoplasty (gonioplasty) and pupilloplasty As mentioned above and addressed in Chapter 31, other argon laser interventions have their role in the management of acute PACG. The *peripheral iridoplasty* (also referred to as *gonioplasty*) is a viable treatment in three settings: (1) acute PACG from pupillary block, unresponsive to medical treatment, and where a perforating laser iridotomy is precluded by excessive shallowing of the anterior chamber, inflammation or corneal edema; (2) plateau iris syndrome; and (3) acute phacomorphic angle closure. Though easiest to perform in areas free of PAS, iridoplasty is remarkably effective in the management of acute angle closure, with either 180° or 360° of treatment.^{259,260} This technique has proven to be as effective as intensive medical therapy with pilocarpine, timolol, and acetazolamide.²⁴¹

The role of iridoplasty in managing angle-closure disease caused by plateau iris is discussed more fully below. In brief, by itself it is effective in opening the angle, sometimes for the long term; when combined with, or after,^{261–264} a laser iridotomy, it may well serve as an effective treatment for this condition.²⁶⁵ As mentioned, pupilloplasty refers to laser techniques which can interrupt pupillary block by distorting the pupil into a tear-shaped configuration, focally interrupting decreased flow through the iris–lenticular junction, thus facilitating aqueous egress into the anterior chamber. Both techniques are important components of the laser armamentarium in managing acute angle-closure disease.

Surgical management of PACG

There are slightly different considerations for surgical intervention for the acute and the long-term manifestations of PACG. If IOP elevation persists despite a patent laser iridotomy in acute disease and subsequent medical therapy, there are several compelling surgical options that have been proffered, but not yet universally

embraced: filtering surgery alone; lens extraction alone, with or without goniosynechialysis; combined lens extraction with trabeculectomy; or goniosynechialysis alone.^{266–268} Often pressure reduction is the primary focus in this context, with surgery often made challenging by persistently elevated IOPs, diminished corneal clarity, shallow anterior chamber, and inflammation accompanying the acute crisis. Surgical goals for chronic PACG are comparable to the considerations for operating in eyes with uncontrolled POAG: long-term IOP reduction towards a target range, stabilization of progressive disc and/or visual field deterioration, and addressing the juxtaposition of cataractous visual loss in conjunction with the need for glaucoma surgery. However, most of these procedures have not been evaluated for PACG in a randomized controlled fashion with different populations, and the literature must be approached with caution.

Trabeculectomy with and without antimetabolite seem to be equally valid approaches.^{269–271} One major center in the study of PACG reported a significantly higher rate of trabeculectomy failure (over one-third of cases) and complications in medically uncontrolled PACG eyes than in eyes which were medically controlled, suggesting that filtration surgery may not be the ‘procedure of choice’ in such circumstances.²⁷² Nevertheless, acute PACG eyes in both Asia and the US require filtering surgery between one-third and one-half of the time.²⁷³

Because of the causative role of a large, anteriorly located lens in pupillary block,¹⁷⁴ lens removal and intraocular lens (IOL) implantation is an attractive primary surgical approach: it offers the patient the likelihood of improved vision, and it is a technique that is familiar to many more surgeons throughout the world than is trabeculectomy. Although it has been recommended as a primary intervention²⁷⁴ and appears capable of restoring angle anatomy to a more normal configuration,²⁷⁵ it nevertheless can be a daunting operative procedure in the semi-acute setting, confronting the surgeon with such challenges as a shallow anterior chamber, a convex lens prone to anterior capsular tears, and a flacid iris from ischemic damage.²⁶⁸ A particularly exciting and well-controlled study found phacoemulsification/IOL surgery to be comparable to, and in fact more advantageous than, laser iridotomy in the management of acute PACG.²²³ The applicability of this approach among different populations and its long-term safety and efficacy in the hands of surgeons with various techniques and skill levels remain to be clarified.

The combination procedures of cataract with filtration surgery,²⁷⁶ or cataract with glaucoma shunt have also been described in the context of PACG management.²⁷⁷ But in the absence of data as to the advantages or disadvantages of a one-stage combined versus two-stage procedure for coexistent uncontrolled acute PACG with cataract, the decision as to which approach to follow remains subjective.

Goniosynechialysis refers to the deliberate intra-operative shearing or peeling of synechial adhesions in the angle, either mechanically or with a viscoelastic dissection, for at least 180°.^{266,267} Originally proposed by Campbell and Vela as an intervention appropriate for eyes with PAS documented to be less than a year old, it has since been used in conjunction with cataract surgery.^{278,279} The procedure’s duration of effectiveness is, however, unclear, with UBM studies documenting only a short-term effect of opening the angle.²⁸⁰

Management of the fellow eye

Fellow eyes of an eye presenting with acute PACG require a laser iridotomy. Implicit in the three-stage classification of PAC disease is the clinical reality that many eyes steadily progress through the natural history of the condition, unless that course is interrupted. Although it appears there is considerable ethnic variation among

the rates of disease progression – with Caucasian eyes showing slow conversion to complete angle closure, sometimes after more than 25 or 30 years,^{192,281–288} in contrast to Mongolian and Chinese eyes suffering rapid development of disease²⁸⁹ – it is important to consider a presenting eye in terms of its stage-specific manifestations.

Eyes identified in the early stages of either demonstrating irido-trabecular touch without elevated IOPs (PAC suspects), are less likely than eyes with elevated IOPs and/or PAS yet normal discs and fields (PAC), to benefit from early laser iridotomies.²²⁷ But, as discussed above, we still await long-term controlled studies of specific populations to determine how tight the criteria for angle embarrasment needs to be to obtain maximum benefit from early iridotomies with an acceptably low rate of complications. Elevated IOP is of course seen more commonly in eyes the greater the PAS. However, increased IOP is also found in eyes without synechia, suggesting that transient apposition between the iris and trabecular meshwork can chronically damage the outflow channels, as histologically demonstrated by Sihota and colleagues.⁴⁵ Again the clinical conclusion is the necessity of vigorous surveillance, with periodic gonioscopic, disc, and field assessments.

In contrast, at the other end of the disease spectrum are PACG eyes with demonstrable glaucomatous damage to the disc and field, which by and large *require* laser iridotomy to eliminate the component of pupillary block; yet such an intervention is not always sufficient to completely manage the glaucomatous process, especially in Asian populations.¹⁴⁹ Whether early phacoemulsification/IOL surgery is a viable alternative to laser iridotomy for managing the eye with glaucomatous damage has not been completely determined.

As emphasized previously, miotics alone are *not* considered an appropriate prophylactic measure to forestall PAC progression, since they don't reliably prevent, and may in fact precipitate, acute attacks. Their chronic administration may exacerbate the development of PAS, cataracts, and conjunctival changes detrimental to successful filtration surgery. Similarly, there is *no* evidence to support the reliability of provocative tests in predicting which eyes are at risk of progression or need intervention.

Sequelae of acute PACG

In the early post-iridotomy period, elevated IOP may occur as a result of release of pigment and other debris, incomplete or sealed iridotomy, unrecognized plateau iris syndrome, inflammation, extensive PAS, or corticosteroid administration.^{290,291} Elevated IOP can also occur months to years later and has been reported in 24–72% of eyes following surgical iridectomy for angle-closure glaucoma.^{194,247,249,252–255} Though these older studies lack the consistent criteria now in use for staging PAC disease, their findings reflect the need for vigorous surveillance. Patients must be explicitly warned of the need for lifelong care even when iridotomy has apparently 'cured' their acute glaucoma.

In Chinese patients, over 50% of eyes with acute PACG after iridotomy develop elevated IOPs, most within 6 months.⁴⁸ Furthermore, as many as 17% of such patients become blind in an eye with an acute attack within 6 or so years; therefore, close monitoring is *mandatory*, even with successful breaking of the attack and after iridotomy.¹⁴⁹ It is commonplace to recognize that once optic nerve damage can be demonstrated after an acute attack – i.e., PACG is manifest – iridotomy won't sufficiently control pressure, and supplemental medical therapy or surgery is required.⁴⁷

The treatment of the PACG after iridotomy is similar to that for open-angle glaucoma, with a stepwise escalation of medical therapy and filtering surgery as needed, but with more frequent gonioscopy.

Some researchers have reported that synechial closure may be alleviated by argon laser iridoplasty (gonioplasty), enhancing visualization of the trabecular meshwork and giving access to perform trabeculoplasty if needed.^{262–264} However, its long-term effectiveness for pressure control has not yet been established, with synechia often reappearing over time.

While typical glaucomatous visual field loss following an acute attack of PACG occurs in the minority of eyes (about 40%), nerve fiber layer loss can be demonstrated in most patients whose attack's duration was longer than 48 hours.^{292–294} The severity of visual field loss is directly correlated with the level of IOP during the attack.²⁹⁵ The characteristics of field loss after an acute attack vary in different accounts: some report a predilection for broad arcuate damage;²⁹⁶ others note generalized perimetric defects;²⁹⁷ and yet others remark on the vulnerability of the nasal field.²⁹⁸

The development of visually significant cataract is a relatively common occurrence following acute-angle attacks (nearly all of whom were treated with iridotomies), reported in nearly a third of such eyes.¹⁴⁹ Cataract rates after surgical iridectomies were even higher.⁵³ The distinction between cause and effect, however, is unclear. Large, cataractous lenses are often a contributor to pupillary block, so many patients already have some lens opacity when the attack occurs. Most investigators believe that surgical iridectomy accelerates the development of lens changes. Although argon laser can produce localized lens changes, no data exist yet to prove laser iridotomy as a cause of generalized lens opacity. A review of patients treated with argon laser peripheral iridotomy showed no statistically significant differences from age- and sex-matched controls in the development or severity of cataract development.⁵¹

Corneal damage can occur both from the acute attack itself and, to a limited extent, from the laser iridotomy treatment. A decrease in central corneal endothelial cell density has been reported following acute attacks of angle-closure glaucoma.^{54–56} The decrease in cell density correlates with the duration of the attack; in fact, longer attacks may cause as much as 77% endothelial cell loss.^{56,86} The loss of endothelial cells also correlates with other indicators of ocular damage, including visual field loss and optic disc cupping.⁵⁷ Occasionally corneal decompensation requiring penetrating keratoplasty occurs after an acute attack. Patients with Fuchs' endothelial dystrophy have shallower anterior chamber depths, shorter axial lengths, and a greater propensity for increased IOP after penetrating keratoplasty.⁵⁸

At the corneal surface, the argon laser can cause superficial burns, especially if a contact lens is not used during iridotomy; such burns, however, usually disappear within a few days. Deeper but mild endothelial loss after laser iridotomy has been noted.⁶⁷ The Nd:YAG laser can cause a localized area of denuded corneal endothelial cells, especially if a contact lens is not used⁵⁹ or if the treated iris is very close to the corneal endothelium.^{60,61} However, there is usually no generalized decrease in endothelial cell density with clinical sequelae following iridotomy.^{62–66} However, patients with pre-existing endothelial dystrophy who suffer an acute angle-closure attack may be more susceptible to the effects of laser iridotomy, developing corneal decompensation after treatment.^{61,63}

Correlating older and newer terminologies for angle closure

The following section is an attempt to accommodate the rich clinical literature of angle-closure disease within the newer structural classification used today. Since the gonioscopic estimation of the

extent of PAS, in conjunction with the absence or presence of elevated IOPs, disc, and field changes, constitutes the parameters for PAC suspects, PAC and PACG, not all published accounts discriminate these findings, making precise correlation difficult.

For example, reference to *subacute* PACG with pupillary block in the literature has also been referred to by the terms *prodromal*, *intermittent*, and *subclinical glaucoma*.^{248,299} This is a milder form of angle closure in which symptoms may be modest or absent. Patients often report that they have experienced mild episodes of discomfort, blurred vision more often at night or with dim illumination, and their halo vision was often relieved by sleep or exposure to bright light. (By history alone it is possible to confuse subacute angle closure with transient ischemic attacks or other neurologic causes of intermittent visual loss.³⁰⁰)

Between episodes of subacute angle closure, IOP and outflow facility are generally normal and no PAS are present. This latter finding suggests that some of these eyes have 'narrow' or 'occludable' angles, with or without reaching the threshold of 270° of irido-trabecular touch which currently defines a PAC suspect. On rare occasions, subacute angle-closure glaucoma is seen as intermittent ocular hypertension.³⁰¹ Patients with subacute angle-closure glaucoma may progress to either an acute attack or chronic angle-closure glaucoma; this suggests that the progressive embarrassment of the angle by PAS was not observed as the eye progressed into PAC or frank PACG.

The next category in common usage is *chronic PACG* with pupillary block, also referred to as *creeping angle closure*.^{191,302,303} This entity is often misdiagnosed because it closely resembles PACG: patients are asymptomatic and have quiet eyes, yet manifest cupping and atrophy of the optic discs, and corresponding visual field loss. Intraocular pressure is moderately elevated, but often poorly responsive to medical treatment.³⁰³ Gonioscopy is the key to the diagnosis of chronic angle-closure glaucoma, revealing a very narrow angle with apposition between the iris and the trabecular meshwork over most of the circumference of the angle. Therefore, gonioscopy remains an indispensable element in the evaluation of any eye with elevated IOP, cupping, or visual field loss.

The apposition usually begins in the superior angle and progresses in both directions toward the 6 o'clock position.^{14,304,305} In Chinese patients, the superior and temporal aspects of the angle are most likely to develop synechiae early.³⁰⁶ When approximately two-thirds of the angle is occluded, IOP rises substantially. As a general rule, the more extensive the synechial closure, the higher the IOP and the more optic nerve damage there will be on presentation.³⁰⁷ The height of the IOP depends on both the extent of synechial closure and on the competency of the remaining unoccluded trabecular meshwork.

This category of 'chronic PACG' is virtually congruent with the current definition of PACG itself, with the designation *chronic* for the most part indicating that symptoms are rare. This is in fact the commonest presentation of PACG in the world.

2. PLATEAU IRIS

Barkan³⁰⁸ noted that 20% of eyes with 'noncongestive' forms of angle-closure glaucoma were atypical in that they had normal central anterior chamber depths, little bombé, and minimal pupillary block. This unusual anterior segment configuration was further detailed and given the name *plateau iris* by Shaffer and Chandler.^{309,310} Wand and co-workers³¹¹ then divided plateau iris into two entities that they called 'plateau iris configuration' and 'plateau iris syndrome'.

Plateau iris *syndrome* refers to the development of angle closure, either spontaneously or after pharmacologic dilation, in an eye with a patent iridotomy; plateau iris *configuration* refers to an anteriorly displaced peripheral iris compromising the angle.²⁰

Though this entity, with merit, has been classified as an 'angle-closure glaucoma without pupillary block' due to a 'pushing mechanism', it is now included as one of three basic PACG mechanisms, along with 'pupillary block' and 'phacomorphic' glaucomas. All three are part of a closely related differential diagnosis at the time of clinical presentation, and all three are amenable to the new anterior segment imaging technologies of UBM and/or AS-OCT, which can often help differentiate among them.

Plateau iris configuration

Plateau iris configuration consists of narrow angles or angle closure in an eye with a 'normal' central anterior chamber depth on slit-lamp examination, and a flat iris plane from pupil to periphery (as opposed to the peripheral forward bow of pupillary block (see Fig. 15-5B)). On gonioscopy, the iris appears flat from the pupillary margin to the periphery – a shape that Tornquist termed 'plateau'³¹² – at which point it takes a sharp turn posteriorly before inserting into the ciliary body. This sharp turn creates a narrow angle recess and the potential for angle closure. The iris root is usually anteriorly displaced. In many cases the iris periphery has redundant folds with a particularly prominent roll by the iris insertion: the *double hump* or *S-sign* of a peripherally elevated roll of iris may be seen on gonioscopy.

This anterior segment configuration differs from the shallow central anterior chamber and iris bombé seen typically with pupillary block (see Fig. 15-5A). The double hump sign is best seen with Koepe gonioscopy, where the forwardly positioned ciliary processes prevent the peripheral iris from falling backward in the supine position; it can also be demonstrated with the on-off indentation maneuver of compression gonioscopy at the slit lamp. Ultrasound biomicroscopy reveals anteriorly displaced ciliary processes that crowd or push the peripheral iris forward and thus prevent the peripheral iris from falling back after iridotomy.³¹³ When the pupil dilates spontaneously or in response to pharmacologic agents, the iris can crowd into the angle and occlude the trabecular meshwork. If this happens often enough or over a wide enough portion of the angle, elevated IOP and/or PAS may result, with the potential to progress into PAC or PACG.

A recent ultrasound study of anterior chamber depth challenges the long-held clinical perspective that the central anterior chamber depth is normal with the plateau iris configuration. This study found that, surprisingly, the anterior chamber depth of eyes with plateau iris was abnormally shallow; not only when compared to normal eyes, but also in comparison to eyes with pupillary block glaucoma.³¹⁴

Plateau iris configuration is more common than recognized, although the condition is probably not common per se. It is one of the more frequent causes of otherwise rare angle closure in older children or young adults.³¹⁵

In many cases, plateau iris configuration is accompanied by some degree of pupillary block, which exacerbates the problem. Therefore, it is often not possible on clinical grounds to differentiate between a pupillary block PAC and a plateau iris configuration embarrassing the angle until after an iridotomy has been performed. In conditions precipitated by pupillary block, iridotomy will cause the iris to fall back and the peripheral chamber to deepen; whereas in plateau iris, the peripheral angle remains unchanged. However, iridotomy often can prevent the development of, or progression of,

elevated IOP with its potential for progressive PAC or glaucoma; this suggests that pupillary block, indeed, does play at least some role in some cases in the development of this angle closure. If iridotomy does not widen the angle substantially following iridotomy it is assumed there was only minimal pupillary block preoperatively.

After the iridotomy, these eyes should be examined periodically for signs of elevated IOP, peripheral synechiae and glaucomatous damage. Pupillary dilation should be undertaken with care, even after iridotomy. Mydriasis is best accomplished with one drop of either 0.5% tropicamide or 2.5% phenylephrine (unless examination of the retinal periphery is mandatory), since the effects of these agents can be readily reversed with dipiperazole. It is probably best to use dipiperazole (if available) routinely after dilation in these cases.

Patients with plateau iris configuration (and plateau iris syndrome) should be warned to avoid agents which have a potential for dilating the pupil (see Box 15-2). These include any medication with anticholinergic activity such as antihistamines, phenothiazine antianxiety agents, antidepressants, and drugs used for incontinence and for diarrhea.³¹⁶⁻³¹⁹

Plateau iris syndrome

Plateau iris syndrome is defined as angle closure in the presence of plateau iris configuration following a patent iridotomy. Whereas earlier studies implicated a peculiar anatomic configuration of the peripheral iris which allowed it to bunch in the angle and occlude the trabecular meshwork with pupillary dilation, it is now understood that angle closure occurs because the ciliary processes are rotated forward,^{320,321} as amply demonstrated on UBM (Fig. 15-11). (Note the inherent limitation of AS-OCT, which cannot consistently image tissue behind the iris plane – hence UBM is the mainstay technology for diagnosing this condition.) Ultrasound biomicroscopy has also revealed several patients with multiple ciliary body cysts associated with plateau iris syndrome – now called *pseudoplateau iris* (see below).³²²

Plateau iris syndrome is often seen in young patients aged 30–40 years old, and occurs equally among men and women. This syndrome presents with or without symptoms occurring days, weeks, months, or years after iridotomy or other intraocular surgery. This can occur spontaneously or after pharmacologic dilation of the pupil. If not diagnosed and treated properly, repeated episodes of angle closure can progress to PAC or PACG: increasing numbers of PAS, persistent elevation of IOP, and ultimate glaucomatous damage.³²³

Lowe and Ritch³²⁴ proposed an ‘incomplete’ type of plateau iris syndrome that is more common than the ‘complete’ form of the syndrome. In the incomplete plateau iris syndrome, the iris is not as far forward as in the complete syndrome; in these patients,

the IOP does not rise with dilation, but PAS may form over time. Gonioscopy and ultrasound show large and/or anteriorly positioned ciliary processes that seem to push the iris against the trabecular meshwork.^{325,326} Such a configuration has also been detected with an absent ciliary sulcus and long ciliary processes.¹⁰³

Earlier investigators thought that plateau iris syndrome was relatively common, occurring in 6–20% of eyes with angle closure.^{327,328} However, these estimates were based on post-iridectomy provocative tests that were done without gonioscopic documentation of angle closure. Plateau iris syndrome is apparently seen in most populations; but ethnic variability, as with all the PACGs, is apparent. For example, in Samoans, plateau iris may be relatively common.³²⁹ And in a series of PACG eyes from India, evidence of plateau iris was found by UBM in 40% of eyes whose angles opened after iridotomy, and in two-thirds of eyes whose angle did not open after iridotomy.³³⁰

Although it is possible to identify plateau iris before iridotomy by noting on gonioscopy the typical configuration of a peripherally flat and anterior iris insertion yielding little angle detail with compression, the diagnosis is usually not made until after a successful iridotomy; at that point, little significant opening of the chamber angle and elevated IOP (especially after pharmacologic dilation) may signal its presence. Therefore, gonioscopy should always be performed after peripheral iridotomy. Obviously, if there are extensive PAS, then the diagnosis cannot be substantiated by this criterion. A UBM study is usually definitive in making the diagnosis.

The differential diagnosis of plateau iris syndrome includes extensive PAS due to any cause; imperforate or occluded iridotomy with persistent pupillary block; multiple cysts of the iris or ciliary body; ciliary block glaucoma (aqueous misdirection or malignant glaucoma); open-angle glaucoma with anatomically narrow angles (as with increasing cataract formation); and the effect of chronic topical corticosteroids or cycloplegic agents.

The sequence of laser procedures for plateau iris syndrome is not fixed. Usually the first treatment for plateau iris syndrome is a laser iridotomy. However, if UBM imaging is available, a peripheral iridoplasty may be the initial treatment, since iridotomy often does not change the anterior segment anatomy.³³¹ In practice though, because of the possibility of some component of pupillary block, an iridotomy is eventually performed.

In a common treatment scenario, once the syndrome is confirmed post-iridotomy, several miotic agents can be tried to minimize pupillary dilation (e.g., pilocarpine 1–2% 2–4 times a day, or pilocarpine 4% ophthalmic ointment (Pilogel™) at bedtime). Argon laser peripheral iridoplasty (gonioplasty) can also be undertaken (see Ch. 31 for details). If the response to miotics is inadequate, or if the patient is unable or unwilling to use them long term,

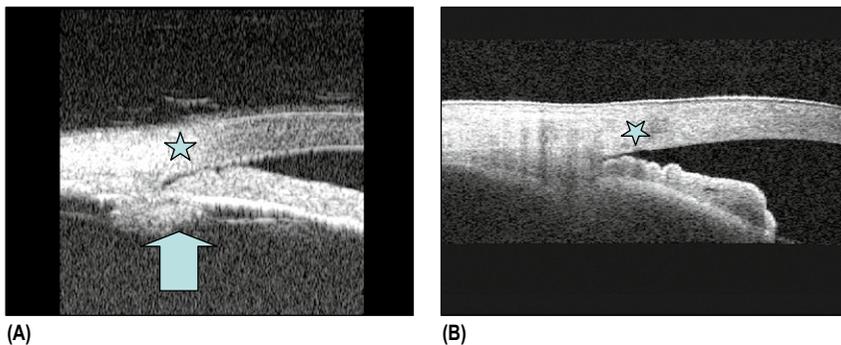


Fig. 15-11 (A) Ultrasonic biomicroscopy of plateau iris configuration, with anteriorly rotated ciliary process (arrow) pushing angle closed (star). **(B)** Anterior segment ocular coherent tomography of plateau iris configuration shows narrow angle (star), but no ciliary body image is captured.

(Courtesy of Shan Lin, MD.)

argon laser peripheral iridoplasty should be performed to widen the angle.^{263,332} Long-term follow-up in patients with plateau iris syndrome suggests that peripheral iridoplasty is quite effective in both opening the angle and preventing progression; however, some patients may require retreatment, so long-term monitoring is necessary.²⁶⁵ If iridoplasty plus medical therapy cannot control the IOP adequately, then trabeculectomy, other filtration surgery, or glaucoma drainage devices should be considered; care is needed, as these patients are at risk for ciliary block glaucoma (aqueous misdirection syndrome). Cataract extraction with IOL implant has also been described as effective in allowing the ciliary processes to move posteriorly and improve pressure control,³³³ but apposition has been documented to persist even after lens removal.¹⁰⁴

Pseudoplateau iris (cysts of the iris and ciliary body)

Primary cysts of the iris and ciliary body usually arise from the epithelial layers. The cysts can be single or multiple and involve one or both eyes. In most cases the cysts remain stationary and cause no harm.³³⁴ In rare cases the cysts are sufficient in size and number to lift the iris forward and cause angle-closure glaucoma without pupillary block.^{335,336} As noted above, this condition appears clinically identical to plateau iris but is caused by peripheral iris or ciliary body pigment epithelial cysts (or rarely a ciliary body tumor) pushing the peripheral iris forward causing angle closure and potential glaucoma.³²² The syndrome of iris cysts and angle-closure glaucoma has been reported in a few families in whom it is inherited in an autosomal dominant pattern.³³⁷

Iris cysts are usually dark brown and may be visible through an iridectomy or at the pupillary margin, especially when the pupil is dilated. Ciliary body cysts are often less pigmented and are difficult to see unless they are quite large. The presence of the cysts gives the iris surface an undulating or irregular appearance. The anterior chamber is uneven in depth, and the angle is variable in width. The diagnosis of pseudoplateau iris or angle closure caused by iris or ciliary body cysts can only be confirmed by UBM. Peripheral iridoplasty has been described as sometimes effective.³³⁸

Once diagnosed, angle-closure glaucoma associated with cysts of the iris or ciliary body may be found to manifest an acute or chronic time course. If the cysts causing angle closure are visible, they can be punctured with an argon or Nd:YAG laser. Argon laser settings of 50–100 μm, 0.1–0.2 seconds, and 200–1000 mW are used to collapse the cysts and free their fluid (which is well tolerated by the eye). Nd:YAG settings are similar to iridotomy. It may be necessary to repeat the laser treatment if the cysts reform.³³⁹ If the cysts are not visible at the pupillary margin, it is possible to puncture them by first doing a laser iridotomy over the involved area, especially if UBM has identified their location.³⁴⁰ This technique is suitable when a few large cysts cause angle closure; it would not be suitable when multiple small cysts are present. Nonpigmented cysts of the ciliary body can be punctured with the Nd:YAG laser. Medical therapy may be required after cyst puncture if extensive PAS are present. In a few cases the cysts cannot be treated with a laser, and filtering surgery is necessary.

Secondary cysts of the iris and ciliary body may be caused by trauma, tumors, or congenital syphilis.³⁴¹ The cysts may cause glaucoma by the mechanism described above, or they may be associated with glaucoma on the basis of inflammation or neovascularization.

3. PHACOMORPHIC GLAUCOMA

This third category of PACG mechanisms embraces a variety of situations where an abnormal lens either compromises the lens-iris

channel (pupillary block) or mechanically pushes the peripheral iris forward into the angle structures. Though the term *phacomorphic glaucoma* is often reserved for intumescent cataracts which crowd the anterior segment, technically the Greek etymology refers to ‘lens-shape’ or ‘lens-form’, the common denominator among several lens-related angle-closure glaucomas. (Pupillary block from secondary causes, such as uveitis, are not *per se* related to anomalous lens structure or positioning, and are addressed in Ch. 16.) Such distinctive conditions of an aberrant lens – from swelling, dislocation or subluxation – often require a laser iridotomy in an attempt to eliminate any pupillary block component, and can be imaged with UBM to clarify the anomalous anatomy.

Intumescent and swollen lens

Increased pupillary block can develop slowly with an age-related cataract or rapidly with a traumatic, swollen cataract. Pupillary block may not be the sole mechanism of angle closure because the enlarging lens may also push the peripheral iris forward into the angle.³⁴² Phacomorphic glaucoma is often seen in eyes that were traumatized in the past and that have limited vision. This condition is usually unilateral and resembles PACG, except for the presence of an intumescent lens and a normal anterior chamber depth in the fellow eye.

The immediate medical treatment for phacomorphic glaucoma is identical to that outlined earlier in this chapter for managing PACG. The goals of medical treatment are to open the angle and reduce the IOP to a level that permits corneal clarity for laser, or to lower pressures for safer incisional surgery. The definitive treatment for this condition is cataract extraction. If cataract extraction is not possible because of extenuating circumstances (e.g., gravely ill patient) or must be delayed, iridotomy should be performed. Iridotomy may not be curative in all cases, especially those in which direct pressure from the lens is playing a greater role than is pupillary block. Yet one study showed excellent effectiveness of Nd:YAG iridotomy in breaking the acute attack of angle-closure glaucoma and allowing the inflammation to improve prior to cataract surgery.³⁴³

Angle-closure glaucoma from a *swollen lens* has been described as an idiosyncratic response to a variety of systemic medications, including the sulfonamide drugs and their derivatives, the carbonic anhydrase inhibitors,^{344–346} thiazide diuretics,³⁴⁷ tetracycline,³⁴⁸ prochlorperazine,³⁴⁹ spironolactone,³⁵⁰ phenformin, acetylsalicylic acid,³⁵¹ and the anticonvulsant topiramate (Topamax).³⁵² This clinical situation has a distinctive presentation: affected patients complain of blurred vision at distance, and are noted to have *acquired bilateral myopia*, with shallow anterior chambers and angle closure. This condition is thought to be caused by swelling of the lens,^{243,353,354} although some authorities suggest that forward lens movement also plays a role. The myopia and induced angle closure disappear a few days after the drug is discontinued. During this time, the patient can be treated with one or more hypotensive drops: β-adrenergic antagonist, prostaglandin analogue, or α-adrenergic agonist. A topical carbonic anhydrase inhibitor can also be added (assuming sulfa-based systemic drugs did not precipitate the problem), as can pilocarpine and a hyperosmotic agent if necessary. Cycloplegic agents are thought to be ineffective in this condition.³⁵⁵ Surgical intervention should be avoided, because the lens swelling improves spontaneously.^{188,355}

Although such condition as dislocated and subluxed lenses, from ectopia lentis or microspherophakia, are included in Chapter 16, their clinical diagnosis and treatment are comparable to the clinical management of the senile enlarged lens in phacomorphic PACG.

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CHAPTER
16Secondary angle-closure
glaucoma

OVERVIEW OF TERMS AND MECHANISMS

The diseases discussed in this chapter share a final common pathway of angle closure and obstruction of outflow, but they are associated with contributory or causative conditions beyond the parameters elaborated in the previous chapter for the spectrum of primary angle-closure glaucoma (PACG). They are thus distinct from PACG, the most common cause of glaucoma blindness in the world. When a related or identifiable ophthalmic condition is known to be present with the onset of angle closure, it is referred to as *secondary*. We propose that this definition now subsumes and replaces the category of ‘combined (mixed) mechanism glaucoma’ as well. It is important for clinicians to be familiar with these secondary angle-closure conditions, not because they are common causes of glaucoma, but rather because they are capable of producing severe elevations of intraocular pressure (IOP) and marked loss of vision.

Historically, ‘combined (or mixed) mechanism glaucomas’ referred to eyes with more than one diagnosis, identified either coincidentally or sequentially. Their angles are not usually seen as closed, yet they present with compromised outflow. In some cases the existence of two types of glaucoma in one eye appears to be a chance occurrence; for example, an eye with exfoliation syndrome suffers trauma and develops uveitis with secondary angle-closure glaucoma. In other cases the treatment of one form of glaucoma produces a second form of the disease; for example, a filtering procedure for juvenile open-angle glaucoma is complicated by a flat anterior chamber, extensive peripheral anterior synechiae (PAS), and progressive glaucoma which is now due to angle closure. It seems unnecessary to perpetuate the anecdotal and highly idiosyncratic nomenclature of the ‘combined mechanism’ categories. When discrete causative factors are known – such as PAS following laser trabeculoplasty for primary open-angle glaucoma (POAG)^{1,2} – such cases can be conceptualized as ‘secondary angle-closure glaucomas’, and etiologic mechanisms identified according to the explanatory model elaborated below.

It is easiest to conceptualize the secondary angle-closure glaucomas as occurring through two different fundamental mechanisms: an *anterior pulling mechanism* and a *posterior pushing mechanism*.^{1–3} With the anterior pulling mechanism, the peripheral iris is pulled forward onto the trabecular meshwork by the contraction of a membrane, inflammatory exudate, or fibrous band (Fig. 16–1). Examples of this mechanism include neovascular glaucoma and the iridocorneal endothelial (ICE) syndrome. As the membrane, band, or inflammatory material contracts, it acts like a zipper to form permanent PAS, which can be spotty and irregular or diffuse and quite regular. Pupillary block plays little or no role in this mechanism.

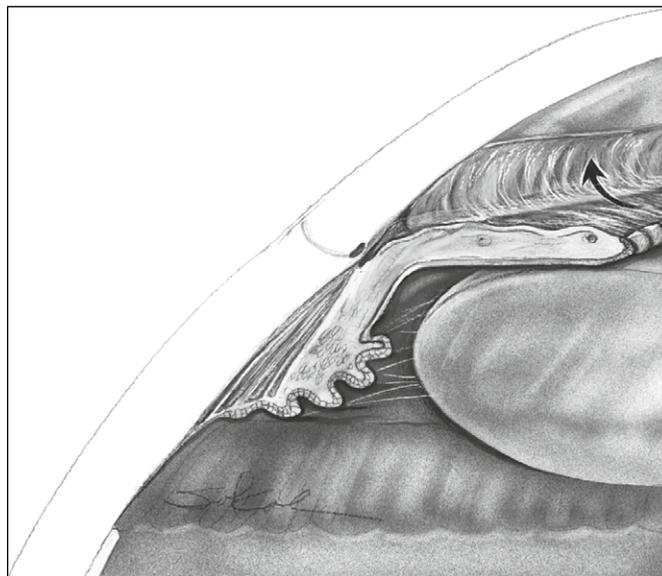


Fig. 16–1 Schematic view of anterior pulling mechanism of angle-closure glaucoma without pupillary block. A membrane, exudate, or band contracts in the angle, pulling the peripheral iris into contact with the trabecular meshwork.

With the posterior pushing mechanism, the peripheral iris is displaced forward by the lens, vitreous, or ciliary body (Fig. 16–2). An example of this mechanism occurs when gas is injected into the vitreous cavity to repair a retinal detachment, displacing the lens–iris diaphragm sufficiently forward to close the angle. This can happen despite the presence of a patent iridotomy.

The degree of *pupillary block* in the secondary angle-closure glaucoma is, by definition, not the primary and exclusive event.⁴ The posterior pushing mechanism in particular can be accompanied by varying degrees of pupillary block. In some conditions, such as ciliary block glaucoma (aqueous misdirection or malignant glaucoma) or in retinopathy of prematurity, pupillary block needs to be eliminated with iridotomy for both diagnostic and therapeutic reasons (Fig. 16–3).

ANTERIOR PULLING MECHANISM

NEOVASCULAR GLAUCOMA

Neovascular glaucoma is caused by a fibrovascular membrane that develops on the surface of the iris and the angle. At first the membrane merely covers the angle structures, but then it contracts to form PAS.

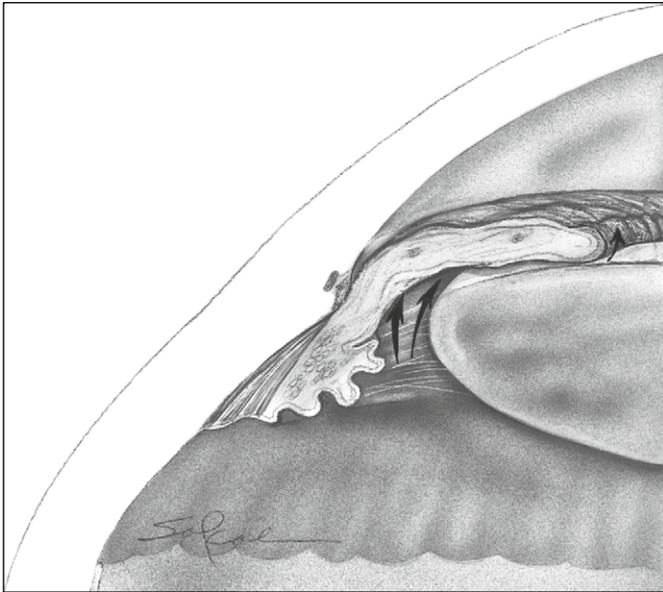


Fig. 16-2 Schematic view of posterior pushing mechanism of angle-closure glaucoma without pupillary block. The peripheral iris is displaced forward by the lens, vitreous, or ciliary body.

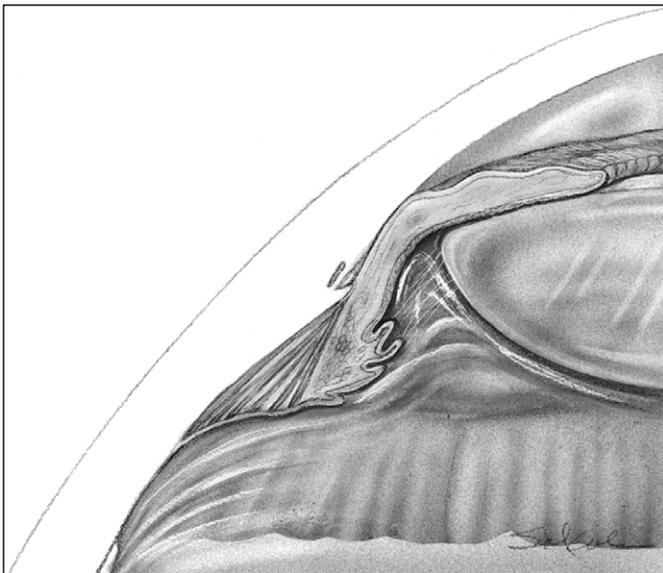


Fig. 16-3 Schematic drawing of proposed mechanism of ciliary block glaucoma. Thickened, less permeable vitreous face is in contact with lens, iris and ciliary body. Lens and iris are displaced forward.

Neovascular glaucoma is virtually always associated with other ophthalmic abnormalities, most commonly some form of ocular ischemia. Neovascular glaucoma is an important entity because it often causes great morbidity and visual loss. A variety of other terms have been used to describe this condition, including thrombotic glaucoma, hemorrhagic glaucoma, diabetic hemorrhagic glaucoma, congestive glaucoma, and rubeotic glaucoma. The term *neovascular glaucoma* is used here because it includes all glaucoma caused by or related to a fibrovascular membrane on the iris and/or angle.⁵ It is important to distinguish the terms *neovascular glaucoma* and *rubeosis iridis*. Rubeosis iridis refers to new vessels on the surface of the iris regardless of the state of the angle or the presence of glaucoma.

Neovascular glaucoma was first described in 1866 following central retinal vein occlusion.⁶ Additional descriptions were provided by various observers in the latter part of the nineteenth century and early twentieth century, including Coates in 1906.⁷ Nettleship⁸ and Salus⁹ noted the association of neovascular glaucoma and diabetes mellitus. Kurz¹⁰ described the gonioscopic appearance of new vessels in the angle and postulated that this fibrovascular tissue contracted to form PAS. Until 1963, the condition was known mostly as ‘hemorrhagic glaucoma’, based on the occasional association with hyphema; the term ‘neovascular glaucoma’ was proposed by Weiss and co-workers,^{11,12} and because this term better fits with the pathophysiology of the condition, it has become the accepted one.

Histopathology

Histopathologic examination of eyes with neovascular glaucoma, regardless of etiology, reveals that the new vessels arise from the microvascular bed (capillaries or venules) in the iris and ciliary body.¹³ The new vessels appear first as endothelial buds from capillaries of the minor arterial circle; new buds may then appear from vessels anywhere in the iris. Changes occur within the microstructure of the endothelial cells and in the extracellular matrix surrounding them.¹⁴ The buds then become vascular tufts not unlike tiny glomeruli. The new vessels have thin walls with irregular endothelia and pericytes.^{15,16} The junctions between the endothelial cells appear to be open, which accounts for their leakiness on angiography.¹⁷

With time, a clinically invisible fibrous membrane develops along the vessels. The membrane contains myofibroblasts that have contractile properties. The contraction of the myofibroblasts pulls the posterior pigment layer of the iris epithelium anteriorly, producing ectropion uveae, and pulls the peripheral iris into the chamber angle, producing PAS.¹⁸ There is one report that new vessels developing after central retinal vein occlusion are larger in diameter and more irregular than those associated with diabetes mellitus.¹⁹

Despite the variety of underlying diseases, the clinical appearance and histopathologic findings of neovascular glaucoma do not vary greatly.²⁰ However, there may be some variation in the acuteness of the onset and the rate of progression, depending on the underlying condition. For example, neovascular glaucoma associated with central retinal vein occlusion may progress more rapidly than that associated with diabetes mellitus,^{21,22} and often depends on the predominance of either an ischemic or hemorrhagic retinal insult.

Pathogenesis

The pathogenesis of neovascular glaucoma is that retinal ischemia liberates angiogenic factors that diffuse forward and induce new vessel formation on the iris and in the angle.^{23–25} Capillary occlusion or ischemia appears to be the initiating event in this process, which seems to be similar to the production of an angiogenic factor or factors by solid tumors.^{26,27} Angiogenic substances (or substance) from tumors implanted in the eye but at a distance from the retina and iris have been shown to cause neovascularization of both.²⁸ Angiogenic factors are produced by hypoxic retinal tissue *in vitro*.²⁹ Angiogenic factors have been detected in mammalian retina and in aqueous humor samples from patients with neovascular glaucoma.³⁰ In laboratory experiments, this factor (or factors) is capable of stimulating capillary endothelial proliferation, corneal neovascularization,³¹ and retinal neovascularization.³² Vasoproliferative factors have been detected in increased amounts in the eyes of both animal models and patients with neovascular glaucoma.^{33–35} And most recently is the impressive regression of new vessels induced by molecular-specific antiangiogenic factors, such as bevacizumab.³⁶

Historically, a number of substances have been proposed as the angiogenic factor. Some of the families of compounds having angiogenic activity include fibroblast growth factor, vascular endothelial growth factor (VEGF), angiogenin, platelet-derived endothelial cell growth factor, transforming growth factor- α , transforming growth factor- β , and tumor necrosis factor- α . Vascular endothelial growth factor is thought to be a primary culprit. It is found in concentrations 40–100 times normal in the aqueous humor of patients with neovascular glaucoma.³⁷ Tolentino and co-workers³⁸ showed that intravitreal injection of VEGF can produce iris neovascularization and neovascular glaucoma in primates. Some consider that angiogenesis is most likely a process (not unlike the clotting or inflammatory cascades) involving several families of agents, including polypeptides, amines, lipids, and other low molecular weight compounds.

The above theory explains many observations about neovascular glaucoma. Diffusible molecules from the retina enter the anterior chamber through the pupil, with their highest concentration near this site. This may explain the initial appearance of rubeosis iridis at the pupillary margin. This mechanism also accounts for why rubeosis iridis and neovascular glaucoma are more common after cataract extraction with capsular disruption and after vitrectomy in eyes with vascular retinopathy. The lens and vitreous may serve as mechanical barriers to the diffusion of an angiogenic substance.^{39–43} Furthermore, the vitreous humor apparently also contains an endogenous inhibitor of angiogenesis.⁴⁴ Finally, vitrectomy and cataract surgery cause inflammation, which may further serve as a stimulus to neovascularization. Lastly, this theory explains the efficacy of panretinal photocoagulation or retinal cryoablation in neovascular glaucoma, treatments which destroy ischemic retina that had been synthesizing the angiogenic factor(s). Aiello and co-workers⁴⁵ have found a marked decrease in VEGF in the vitreous of patients after panretinal photocoagulation. These treatments may also liberate inhibitory factors that counteract the vasoproliferative stimulus.^{46,47}

Conditions and diseases commonly associated with neovascular glaucoma

Neovascular glaucoma is associated with a large number of diseases and conditions (Box 16–1). As noted above, most of these conditions have some relation to either retinal or ocular ischemia

Box 16–1 Diseases and conditions associated with neovascularization of the iris and neovascular glaucoma

Ocular vascular disease

- Central retinal vein occlusion
- Central retinal artery occlusion
- Branch retinal vein occlusion
- Branch retinal artery occlusion
- Sturge-Weber syndrome with choroidal hemangioma
- Leber's miliary aneurysms
- Sickle cell retinopathy
- Diabetes mellitus

Extraocular disease

- Carotid artery disease/ligation
- Ocular ischemia
- Aortic arch syndrome
- Carotid-cavernous fistula
- Giant cell arteritis
- Pulseless disease

Assorted ocular diseases

- Retinal detachment
- Eales' disease
- Coats' disease
- Retinopathy of prematurity
- Persistence and hyperplasia of the primary vitreous
- Retinoschisis
- Glaucoma
 - Open-angle
 - Angle-closure
 - Secondary
- Norrie's disease
- Stickler's syndrome

Trauma

- Essential iris atrophy
- Neurofibromatosis
- Lupus erythematosus
- Marfan's syndrome
- Recurrent hemorrhages
- Vitreous wick syndrome

Ocular neoplasms

- Malignant melanoma
- Retinoblastoma
- Optic nerve glioma associated with venous stasis
- Metastatic carcinoma
- Reticulum cell sarcoma
- Medulloepithelioma
- Squamous cell carcinoma conjunctiva
- Angiomatosis retinae

Ocular inflammatory disease

- Chronic uveitis
- Endophthalmitis
- Sympathetic ophthalmia
- Syphilitic retinitis
- Vogt-Koyanagi-Harada syndrome

Ocular therapy

- Cataract excision (especially in diabetics)
- Vitrectomy (especially in diabetics)
- Retinal detachment surgery
- Radiation
- Laser coreoplasty

Modified from Gartner S, Henkind P: Neovascularization of the iris (rubeosis iridis). *Surv Ophthalmol* 22:291;⁴⁸ 1978 and Wand M: Neovascular glaucoma. In: Ritch R, Shields MB, Krupin T, editors: *The glaucomas*. 2nd edn., St Louis, Mosby, 1982.⁴⁹

or to chronic inflammation. In a large comprehensive survey, diabetes mellitus was associated with about one-third of the cases of neovascular glaucoma; central retinal vein occlusion with another third; and a variety of conditions with the last third – with carotid occlusive disease being the most common in the last group.⁵⁰ The discussion here is limited to a few of the more common entities, such as central retinal vein occlusion and diabetes mellitus, from among a wide variety of predisposing conditions.^{48,49,51}

Diabetes mellitus

Diabetes mellitus is one of the most common causes of neovascular glaucoma,⁵² accounting for approximately one-third of the cases. Neovascular glaucoma is usually seen in eyes with proliferative

diabetic retinopathy, but it can be seen in eyes with nonproliferative retinopathy if there are large areas of capillary nonperfusion.⁵³ The prevalence of neovascular glaucoma is related to the duration of diabetes and may also be influenced by the presence of other vascular diseases such as hypertension. It is common for neovascular glaucoma to appear within 6 months of vitrectomy in diabetic patients,^{54–58} especially in aphakic eyes,^{59–61} in eyes with proliferative retinopathy, and in eyes with pre-existing rubeosis iridis. In similar fashion, diabetic neovascular glaucoma is a common occurrence after intracapsular cataract extraction, whether performed alone^{39,62} or in combination with vitrectomy. There is evidence that diabetic neovascular glaucoma is less common after extracapsular cataract extraction than after intracapsular cataract extraction,⁶³ unless the capsule is ruptured, or zonular support is lost with exposure of vitreous (as seen with lax capsular support in pseudoexfoliation.) As noted previously, the lens and vitreous may act as mechanical barriers to the forward movement of angiogenic factors elaborated by the retina. The vitreous may also serve as an endogenous inhibitor of angiogenic stimuli.

It is especially important to emphasize the distinction between rubeosis iridis and neovascular glaucoma in diabetic eyes. Rubeosis iridis is said to occur in 1–17% of diabetic eyes,^{64–66} and in 33–64% of eyes with proliferative diabetic retinopathy.^{67,68} Clearly, the prevalence of rubeosis iridis is much higher than the prevalence of neovascular glaucoma. Rubeosis iridis may progress to neovascular glaucoma in some diabetic patients, but in others the condition remains stationary for long periods of time or even regresses.⁶⁹ The rate of progression is much lower if the retina is treated with photocoagulation. If neovascular glaucoma develops in one eye of a diabetic patient, the fellow eye is at high risk if adequate retinal photocoagulation is not applied.

Central retinal vein occlusion

Central retinal vein occlusion is among the commonest cause of neovascular glaucoma. It is estimated that about 30% of patients who suffer a central retinal vein occlusion develop neovascular glaucoma. More comprehensive investigations have done much to clarify this association. Hayreh^{70,71} has carefully discriminated central retinal vein occlusion into two types – ischemic and non-ischemic (venous stasis retinopathy). Approximately three-quarters of central retinal vein occlusions are non-ischemic, and one-quarter are ischemic.⁷² Yet neovascular glaucoma occurs in 18–86% of eyes with ischemic vein occlusions, as opposed to 0–4% of eyes with non-ischemic occlusions.^{73–77} According to a large study, about 40% of patients with ischemic central retinal vein occlusion will develop neovascular glaucoma.⁷⁸ The distinction between ischemic and non-ischemic vein occlusions is usually made by judging the degree of retinal capillary non-perfusion (capillary dropout) on fluorescein angiography.^{79,80} Other signs of ischemia include 10 or more cotton wool spots in the retina, an absent perifoveal capillary network on fluorescein angiography, arteriovenous transit time greater than 20 seconds, leaky iris vessels on angiography, and a reduced B:A wave ratio on electroretinography. Eyes with ischemic central retinal vein occlusions should receive panretinal photocoagulation (or cryoablation if no laser is available) to reduce the incidence of neovascular glaucoma. Careful follow-up is mandated even in those with the non-ischemic type because of the observation that one-third of eyes with central retinal vein occlusion and good perfusion at the onset show signs of ischemia by 3 years.⁸¹

Neovascular glaucoma may present anywhere from 2 weeks to 2 years following a central retinal vein occlusion.⁸² However, the condition often presents about 3 months after central retinal vein

occlusion: hence its reputation as the ‘100-day glaucoma’. Younger patients with central retinal vein occlusions often have associated vascular diseases, such as hypertension or one of the collagen vascular disorders.

Older patients with central retinal vein occlusions often have associated glaucoma or elevated IOP. Elevated IOP or glaucoma has been reported in 10–23% of eyes that developed a central retinal vein occlusion.^{83,84} In most cases the underlying glaucoma is open angle or exfoliative in type, but there have been a few reports of central retinal vein occlusion following angle-closure glaucoma.⁸⁵ The underlying glaucoma is often masked because these eyes may have a low IOP for weeks to months following vein occlusion.⁸⁶ In addition, the low IOP may reflect transient poor perfusion of the ciliary body. The presence of pre-existing POAG increases the risk of neovascular glaucoma after central retinal vein occlusion despite adequate prophylactic laser treatment: adequate treatment of the pre-existing glaucoma does not prevent the onset of neovascularization. Furthermore, pre-existing open-angle glaucoma may make any subsequent neovascular glaucoma more refractory to treatment.⁸⁷ It is also common for fellow eyes to have elevated IOP or to develop it at a later time. Although a true causative role for elevated IOP in central retinal vein occlusion has not been established, it is probably wise to treat fellow eyes with elevated IOP with ocular hypotensive agents. One case-control study does support elevated IOP as a risk factor in central retinal vein occlusion along with systemic hypertension and male gender.⁸⁸ Green and co-workers⁸⁹ proposed that posterior bowing of the lamina cribrosa in glaucoma creates a mechanical obstruction that impedes the venous outflow and contributes to venous stasis and/or occlusion.

Carotid occlusive disease

Carotid artery disease is considered the third most common cause of neovascular glaucoma. Neovascular glaucoma has been reported after carotid artery ligation^{90,91} and idiopathic carotid artery obstruction. The obstruction can be unilateral or bilateral and can involve the common carotid artery or the internal carotid artery.^{92–95} Carotid artery obstruction does not cause neovascular glaucoma in all cases because there is usually sufficient collateral flow to prevent widespread retinal ischemia. Carotid artery palpation and auscultation should be performed in all cases of central retinal vein occlusion. Neovascular glaucoma associated with carotid artery disease often has a confusing presentation and a variable course. If anterior segment ischemia is severe, the vessels on the iris may be less visible, and the IOP may be normal or even low despite extensive neovascular closure of the angle. These eyes often suffer wide swings in IOP, depending on the perfusion to the ciliary body.⁹⁶ Patients who undergo surgery to relieve or bypass carotid artery obstruction may experience a dramatic rise in IOP when the ciliary body blood supply improves and aqueous humor formation increases. Panretinal photocoagulation may be less successful in eliminating iris neovascularization in patients with carotid artery obstruction because the anterior segment of these eyes is also ischemic and is not affected by retinal ablation techniques.

Ocular ischemic syndrome

Several authors have described a condition called chronic ocular ischemic syndrome that includes signs of transient ischemic attacks; ocular motor disturbances; midperipheral retinal hemorrhages; neovascularization of the iris; and, late in its course, corneal striae and hypotony.^{97,98} Although the term was initially used to describe obstruction of the carotid artery, extracarotid causes have also been identified, including abnormalities of carotid flow without

stenosis, cranial arteritis, and coronary artery disease.^{99,100} Carotid artery obstruction accounts for about 75% of these patients, with other risk factors being diabetes mellitus, systemic hypertension, and a history of cerebrovascular accident.¹⁰¹ Doppler imaging of the carotids should be considered if any of the symptoms or signs associated with the ocular ischemic syndrome are manifest. Treatment proposals have included oral verapamil, panretinal photocoagulation, and carotid endarterectomy, although the latter intervention does not always effect a significant clinical improvement.^{102,103}

Central retinal artery occlusion

Other vascular occlusive diseases of the eye may also be associated with neovascular glaucoma. Seven per cent to 15% of patients with a central retinal artery occlusion will develop neovascular glaucoma.^{104,105} Some, but not all, have concomitant carotid artery occlusive disease.¹⁰⁶ Again, the preponderance of ischemic and disrupted retina is felt to be causative. Although panretinal photocoagulation may have some effect in reducing the incidence of neovascular glaucoma, it is not as effective as in retinal vein occlusion or diabetes mellitus.¹⁰⁷

Miscellaneous

Neovascular glaucoma occurs after a variety of therapeutic interventions, including radiotherapy,^{108,109} microwave thermoradiotherapy,¹¹⁰ and retinal detachment surgery.¹¹¹ Neovascular glaucoma occurs after radiation therapy for uveal melanoma between 8.5% and 25% of the time and is dose and time dependent.¹¹² Cataract extraction in eyes that have had radiation is a risk factor for the acceleration of neovascular glaucoma, as it is in eyes with diabetes.¹¹³ Clearly, many of the eyes requiring these therapies have underlying diseases producing ischemia of the retina or tumors capable of producing vasoproliferative factors. Intraocular tumors also can be associated with neovascular glaucoma.¹¹⁴

Clinical presentation

Neovascular glaucoma often presents with an acute onset of pain, tearing, redness, and blurred vision. In some cases, depending on the underlying disease, patients report diminished vision for weeks to months before the onset of the pain and redness. When first seen, an affected eye may have ciliary injection, a hazy cornea from epithelial edema, a deep anterior chamber with moderate flare, a hyphema, a small pupil, and new vessels on the iris and in the angle. The first sign of rubeosis iridis is increased permeability of the blood vessels at the pupillary margin as detected by fluorescein angiography or fluorophotometry.¹¹⁵ Clinically the new vessels are first detected as small tufts at the pupillary margin. Occasionally new vessels are seen first in the angle if the tufts near the pupil are obscured by dark iris pigment (Fig. 16–4A). The neovascularization progresses over the iris surface and into the angle. The new vessels extend from the iris root across the ciliary body and scleral spur, where they arborize over the trabecular meshwork^{117–119} (Fig. 16–4B). At times it may be difficult to distinguish new vessels from normal iris vessels, especially in inflamed eyes. Normal iris vessels have a uniform size and a radial course, and they do not branch within the iris. In contrast, new vessels have an irregular size and an irregular course, and they branch frequently. New vessels also lie on the iris surface rather than in the stroma as normal vessels do.

When the fibrovascular membrane covers a substantial portion of the trabecular meshwork, outflow facility falls and IOP rises. With time, the membrane pulls the peripheral iris up into the angle (Fig. 16–4C). The rate at which this occurs is quite variable, ranging from days to years.

In the late stages of neovascular glaucoma the eye is painful with bullous keratopathy, a sealed angle, and intractable glaucoma. Traction from the fibrovascular membrane lifts the iris anteriorly, gives the stroma a compacted appearance, and produces ectropion

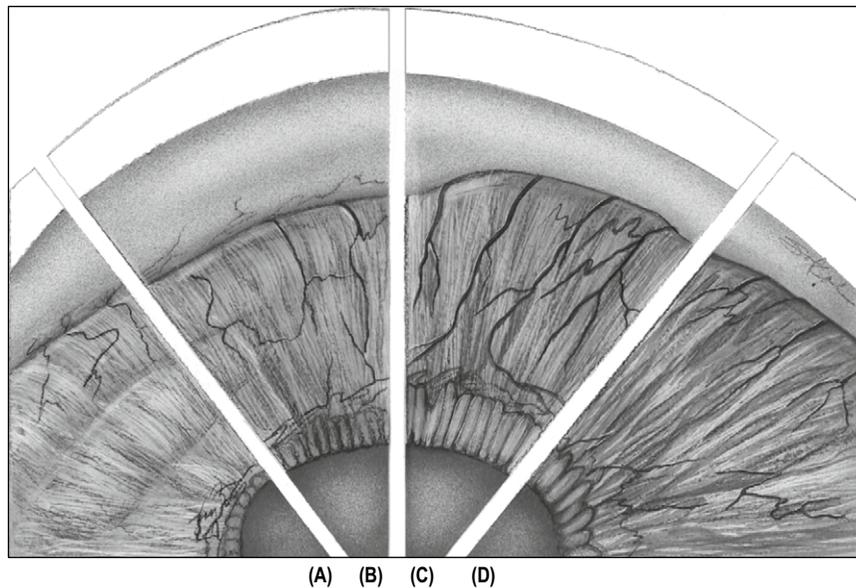


Fig. 16–4 Stages of neovascular glaucoma. **(A)** Pre-glaucoma stage with new vessels appearing at pupillary margin and in angle. **(B)** Open-angle glaucoma stage with new vessels spreading and fibrovascular tissue covering angle. **(C)** Heavy neovascularization and extensive peripheral anterior synechiae. **(D)** Regression stage with angle sealed and vessels less visible.

(Modified from Hoskins HD Jr: *Trans Am Acad Ophthalmol Otolaryngol* 78:330, 1974.¹¹⁶)

uveae and a fixed, dilated pupil. At this stage, the new vessels may be much less visible, especially those in the angle (Fig. 16–4D).

Treatment

Historically, eyes with neovascular glaucoma had a poor prognosis, and enucleation for chronic pain was a frequent outcome. This dismal picture has changed remarkably over the past several decades, and in many instances neovascular glaucoma can be prevented or treated satisfactorily in terms of patient comfort, although restoration of visual function is uncommon.

Despite recent improvements in therapy, it is always far more effective to prevent neovascular glaucoma than to treat the disease once it is established. We have already mentioned the use of prophylactic panretinal photocoagulation (or retinal cryoablation) to deter neovascular glaucoma following ischemic central retinal vein occlusion. In similar fashion, photocoagulation can prevent neovascular glaucoma in eyes with proliferative diabetic retinopathy or non-proliferative retinopathy and large areas of capillary non-perfusion. Immediate panretinal photocoagulation may also prevent rubeosis iridis from progressing to neovascular glaucoma.

When a patient is seen with an acute episode of neovascular glaucoma, including markedly elevated IOP, the initial treatment consists of maximal IOP-reduction medical therapy, atropine for relief and to maximally dilate the pupil before iris mobility is lost, and corticosteroid. In this situation, miotic agents, prostaglandins, and adrenaline (epinephrine) are usually ineffective in lowering IOP, and may exacerbate pain and conjunctival injection.¹²⁰ In most cases it is important to proceed rapidly with panretinal photocoagulation or retinal cryoablation to prevent total angle closure.^{121–124} Following this treatment, new vessels in the angle begin to regress within a few days to a few weeks. Depending on the extent of the PAS, the retinal treatment may abort the glaucoma, or leave a stable form of residual angle closure that may be responsive to medical therapy or surgery.¹²⁵

If extensive PAS are present after retinal ablation, and if IOP is not controlled by medical treatment, the clinician's choice of therapy is usually based on the visual potential of the eye. If the eye has good visual potential, and if the neovascular membrane has regressed, filtering surgery can be successful, especially when augmented with antimetabolites.^{126,127} Wet field cautery or underwater diathermy to the sclera and iris may be useful to reduce intraoperative bleeding,^{128,129} but particularly helpful is preoperative intravitreal bevacizumab.^{36,130} Postoperatively, these eyes are often inflamed and require extensive topical, periocular, and systemic corticosteroid treatment.

Other authorities believe that there is a high failure rate of standard filtering surgery in eyes with neovascular glaucoma, even after the angiogenic stimulus has been reduced or eliminated, and despite antimetabolite agents. Today, many clinicians attempt to control the glaucoma with some type of posterior glaucoma drainage device.^{131–137} Glaucoma drainage implants appear to be successful in controlling pressures and preserving vision in approximately two-thirds of patients with neovascular glaucoma, dramatically reducing the need for enucleation in these otherwise doomed eyes.¹³⁸ In aphakic eyes it is possible to implant the tube through the pars plana, so long as the anterior vitreal skirt has been removed by pars plana vitrectomy.¹³⁹

There are a number of therapeutic options for eyes with neovascular glaucoma and poor visual potential. Eyes with limited or no vision can often be made comfortable using cycloplegic agents and topical corticosteroids regardless of the IOP.¹⁴⁰ Cyclodestructive

procedures may be appropriate if the patient is too infirm for surgery, has too little visual potential to proceed with filtration or tube surgery, or requires immediate pain relief. The history of attempting to reduce aqueous production by means of ciliary destruction is a long one.

Cyclocryotherapy often reduces IOP and makes patients more comfortable after an initial period of pain lasting 1–7 days, but this treatment is less effective in maintaining vision.^{141–144} Cyclocryotherapy is usually applied at -60°C to -80°C , using a large-tip probe with its anterior edge 2.5 mm posterior to the limbus. Six to eight 60-second freezes are placed over half of the circumference of the ciliary body. Frequent complications of this treatment include iridocyclitis, hypotony, pain, cataract, and phthisis bulbi. If cyclocryotherapy fails to reduce IOP, the treatment can be repeated over the same quadrants of the ciliary body and extended slightly. At least one-quarter of the ciliary body should remain untouched to reduce the incidence of phthisis bulbi. In the past, cyclodiathermy was used for the same purpose as cyclocryotherapy.^{145,146} Cyclodiathermy was largely abandoned and replaced by cryotherapy, which had a higher rate of success and a lower rate of complications. More recently, cyclocryotherapy itself has been replaced by either trans-scleral laser cyclophotocoagulation or endocyclophotocoagulation.^{147–154} One can expect approximately 65% success after 1 year in controlling pressures and pain with this modality. The results seem comparable with those achieved with posterior glaucoma drainage device implantation. In our hands, diode laser cyclodestruction with a contact delivery probe is a relatively safe and effective procedure for patients with poor vision or poor visual prognosis and for those for whom a glaucoma drainage device operation may be inadvisable (e.g., previous encircling band, poor physical condition). Retrobulbar alcohol injections and enucleation are appropriate treatments for eyes either with no useful vision or with intractable pain that does not respond to medical therapy and ciliodestructive procedures.

Some have advocated direct laser treatment to new vessels in the angle, a technique referred to as goniotocoagulation, if neovascularization of the iris is encountered before PAS have formed.¹⁵⁵ Low-energy argon laser treatments (0.2 seconds, 50–100 μm , 100–200 mW) are applied to the neovascular tufts as they cross the scleral spur. The laser therapy often must be repeated because these vessels may re-open minutes to days after treatment. Although goniotocoagulation is inadequate treatment for neovascular glaucoma by itself, it may be a useful adjunct to panretinal photocoagulation in certain situations. For example, goniotocoagulation can reduce angle neovascularization and synechia formation temporarily while panretinal photocoagulation takes effect and reduces the angiogenic stimulus. Finally, goniotocoagulation can be applied when full panretinal photocoagulation is not totally successful in reducing the angiogenic stimulus. Its efficacy, however, is perhaps less than that of intravitreal angiogenic inhibitors; both modalities, however, may provide only temporary relief of weeks to months.

In neovascular glaucoma eyes secondary to central retinal vein occlusion, clinicians recommend intravitreal bevacizumab (1.25 mg/0.05 ml) (Avastin) to be administered through the pars plana 24–78 hours preceding surgery, with near total regression of iris neovascularization within 48 hours and some IOP lowering, an effect lasting for some weeks. This rapid regression of new vessels allows both for panretinal photocoagulation and glaucoma surgery with reduced risk of bleeding.^{36,130} Similarly focal laser or intraocular surgery can be enhanced with temporary regression of new vessels by such intervention. When used with combined surgical

approaches such as pars plana vitrectomy with panretinal endolaser and filtration surgery,¹⁵⁶ the outlook for greater surgical success in treating neovascular glaucoma in the short-to-medium term appears brighter.

IRIDOCORNEAL ENDOTHELIAL SYNDROME

The iridocorneal endothelial (ICE) syndrome takes many clinical forms but usually includes some combination of iris atrophy, corneal edema, and secondary angle-closure glaucoma without pupillary block. This syndrome is caused by an abnormal corneal endothelium that forms a membrane over the anterior surface of the iris and the angle structures. When this membrane contracts, it distorts the iris and closes the angle (Fig. 16–5).¹⁵⁸

Histopathology

Histopathologic examination of eyes affected by the ICE syndrome reveals a thin, abnormal corneal endothelium and Descemet's membrane separated by a thick accumulation of collagen.^{159–161} These tissues form a multilayered membrane that covers the angle and extends onto the anterior surface of the iris.^{162–165} The endothelial cells develop the epithelial-like characteristics of desmosomes, microvilli, tonofilaments (contractile elements), and proliferation – none of which occur in normal corneal endothelium.^{166,167} Most authorities believe this to be a metaplasia of endothelium into cells with epithelial characteristics, from an unknown trigger.¹⁶⁸ These histopathologic changes are manifest on clinical examination by a 'beaten silver' appearance to the endothelium on slit-lamp examination; a loss of the normal, regular endothelial mosaic on specular reflection; and alterations in the size and shape of endothelial cells on specular microscopy.¹⁶⁹ The size and shape of endothelial cells show great variation – some may be necrotic, and the findings are often patchy in the early stages of the condition. Even with the variation in clinical presentation, the endothelial findings are usually there if looked for carefully enough.

Pathogenesis

The most commonly accepted theory on the pathogenesis of the ICE syndrome proposes that the fundamental defect is in the corneal endothelium, whose dysfunction results in corneal edema. Furthermore, the corneal endothelium in this condition elaborates a membrane which causes a secondary angle closure. When the membrane contracts, it forms PAS leading to glaucoma, as well as iris defects such as corectopia, 'stretch holes', and iris nodules. Ischemia may be a secondary phenomenon producing 'melt holes.' At present we do not understand what causes the corneal endothelium to behave in this unusual manner. A few investigators^{170,171} postulate that there is an abnormal proliferation of neural crest cells or a fetal crest of epithelial cells.¹⁷² Other authorities¹⁷³ suggest the endothelium proliferates because of inflammation. Electron micrographic, immunohistochemical, and serologic studies have suggested herpes simplex virus¹⁷⁴ and, in another laboratory, Epstein-Barr virus.¹⁷⁵ The viral theory is attractive and might explain the unilaterality of this syndrome in the vast majority of patients. In the past it was proposed that the ICE syndrome was a primary iris defect or that the disease occurred because of vascular insufficiency.^{176,177} These latter theories no longer seem tenable.

Clinical presentation

The PAS are more extensive in the quadrant toward which the pupil is displaced. The iris in the opposite quadrant has thinner stroma and full-thickness holes in some cases. In the Cogan-Reese

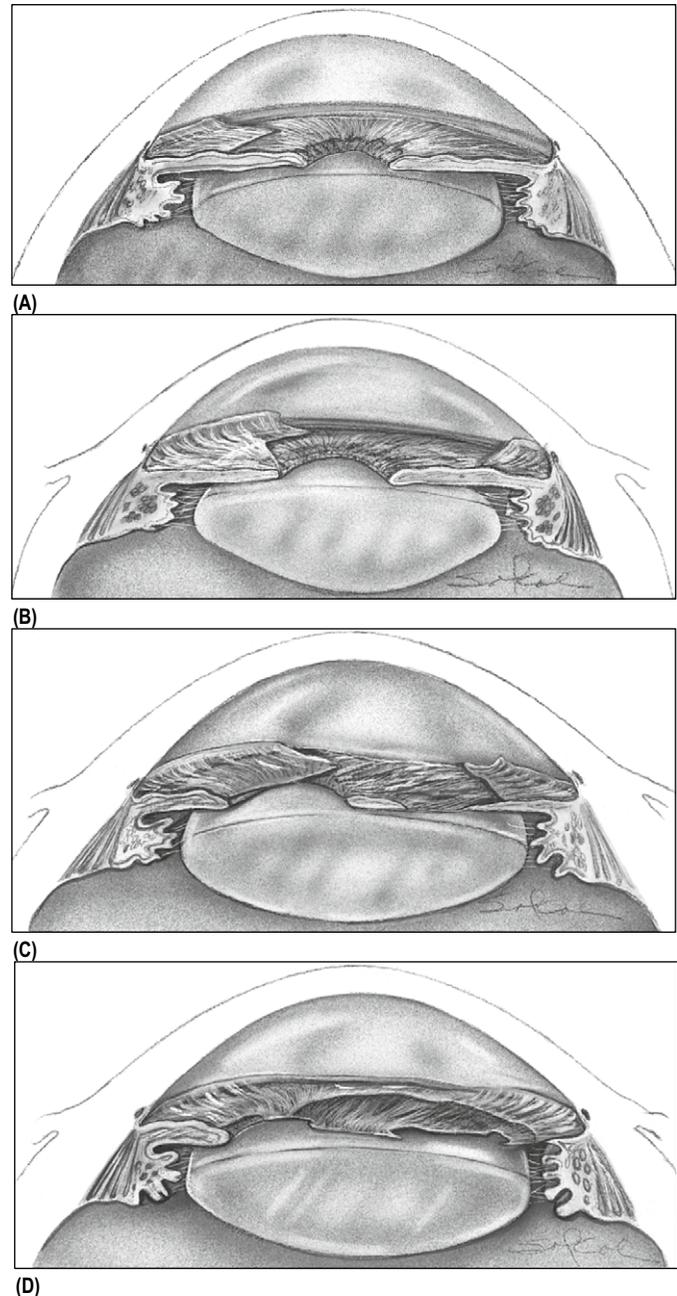


Fig. 16–5 Schematic view of iridocorneal endothelial syndrome.

(A) Membrane forms in one area of angle. **(B)** Additional areas of angle are involved, and contraction of membrane displaces pupil. **(C)** As membrane contracts, iris thins and peripheral anterior synechiae form. **(D)** Almost total closure of angle with thinning of iris, pupillary displacement, and hole formation.

(Modified from Shields MB: *Surv Ophthalmol* 24:3, 1979.¹⁵⁷)

syndrome, pigmented lesions project anteriorly from the iris surface and are surrounded by the multilayered membrane. The nodules are actually small portions of iris stroma that have been pinched off by the membrane.

Within the spectrum of the ICE syndrome there are three well-characterized clinical entities – progressive iris atrophy, Chandler's syndrome, and Cogan-Reese syndrome – as well as a variety of intermediate forms.¹⁵⁷ All of the variants of this syndrome appear



(A)



(B)

Fig. 16-6 (A) Early essential iris atrophy. (B) Goniophotograph of characteristic peripheral anterior synechia associated with iridocorneal endothelial syndrome.

in early to mid adult life,¹⁷⁸⁻¹⁸⁰ occur in whites more often than blacks, and affect women more commonly than men.¹⁸¹ The patients usually are seen after noticing a change in the appearance of their iris or pupil, a disturbance in their vision, or mild ocular discomfort. Although there are a few reports of familial cases,¹⁸² in most individuals the medical and family histories are unrevealing. The ICE syndrome almost always involves one eye, although the fellow eye may have subclinical abnormalities of the iris or corneal endothelium.^{183,184} Furthermore, there have been a few well-documented reports of individuals with bilateral involvement.¹⁸⁵⁻¹⁸⁸ Some degree of corneal endothelial abnormality is usually seen on slit-lamp examination in most patients with abnormal specular microscopy in all.

Progressive (essential) iris atrophy

In progressive iris atrophy (known as *essential iris atrophy* in the past) the clinical picture is dominated by corectopia and progressive dissolution of the iris (Fig. 16-6).¹⁸⁹ The iris dissolution begins as a patchy disappearance of the stroma and progresses to full-thickness holes (Fig. 16-7). Some of the holes occur in quadrants away from the direction of pupillary displacement and are thought to be caused by traction ('stretch holes'). Other holes occur without corectopia and are ischemic in nature ('melt holes'), as demonstrated on fluorescein angiography of the iris. Broad patchy PAS

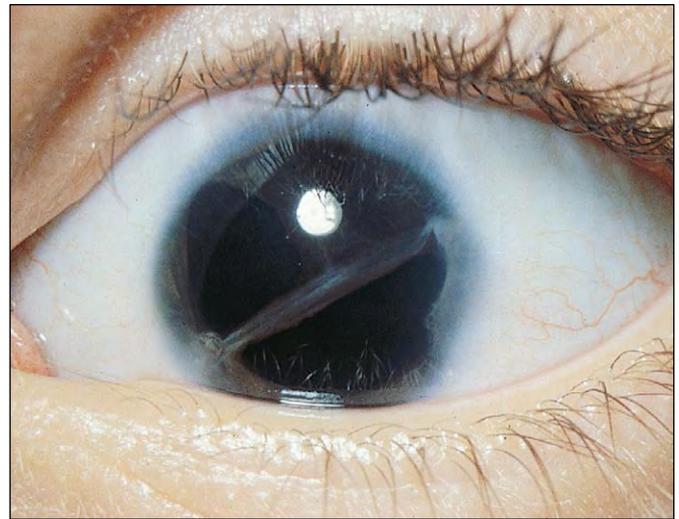


Fig. 16-7 Advanced essential iris atrophy with polycoria.

form attachments anterior to Schwalbe's line. The synechiae lift the iris off the surface of the lens, and also produce ectopion uveae and corectopia. Depending on the distribution of the synechiae, the pupil can be displaced to one side or pulled into a pear, oval, or slit shape. As the PAS become more extensive, IOP rises. The severity of the glaucoma is usually related to the extent of the synechiae. On occasion, elevated IOP is noted despite open angles; in this situation the membrane has covered the angle but not yet contracted to form permanent adhesions. The corneal endothelium may appear normal but more often has the appearance of tiny guttata. The cornea may become edematous when IOP is elevated.

Chandler's syndrome

Chandler's syndrome is the most common variant of the ICE syndrome. The most prominent features of Chandler's syndrome are corneal endothelial dysfunction and corneal edema.¹⁹⁰ The endothelium has a hammered silver appearance that is similar to, but less coarse than, the abnormalities seen in Fuchs' dystrophy. On specular microscopy the endothelial cells appear pleomorphic with dark cytoplasmic areas and loss of the normal hexagonal patterns.^{191,192} Early in the course of the disease specular microscopy may demonstrate normal and abnormal endothelial areas. With time, the normal areas diminish in size.^{193,194} Specular microscopy also helps to distinguish early Chandler's syndrome from posterior polymorphous dystrophy, which has some clinical similarities.¹⁹⁵ The corneal endothelium becomes so dysfunctional that epithelial edema develops at normal or only slightly elevated IOPs. In contrast to the marked corneal changes, the iris involvement is generally mild and limited to superficial stromal dissolution. Corectopia is minimal or absent. Peripheral anterior synechiae form, but they are not as diffuse and do not extend as far anteriorly as in progressive iris atrophy. For this reason glaucoma is often mild.

Cogan-Reese syndrome

The Cogan-Reese, or iris nevus, syndrome is differentiated from progressive iris atrophy and Chandler's syndrome by the occurrence of pigmented lesions of the iris.¹⁹⁶ Some eyes have pedunculated iris nodules,^{197,198} other eyes have diffuse pigmented lesions, and still others have both. The pigmented iris lesions may appear years after the other features of the syndrome and then may disappear spontaneously.¹⁹⁹ These are definitively not nevi: instead, they

are islands of normal iris pinched by the contracting endothelial membrane. The iris may have any degree of dissolution from mild to severe. A similar variability is noted in the degree of corneal edema and the severity of the angle-closure glaucoma. Especially in the early stages, characteristics of both progressive iris atrophy and iris nevus syndrome may be seen in the same iris.

The differential diagnosis of the ICE syndrome is very large because the clinical features of the syndrome are so variable. Included are corneal conditions such as posterior polymorphous dystrophy and Fuchs' dystrophy, iris abnormalities such as iridoschisis and malignant melanoma, developmental disorders such as Rieger's syndrome and aniridia, and miscellaneous conditions such as neurofibromatosis and anterior uveitis with nodules. The diagnosis is often missed early because the corneal and iris signs may be subtle.²⁰⁰ Most of the conditions in the differential diagnosis are bilateral, so a unilateral condition should raise the possibility of the ICE syndrome.

Treatment

The treatment of the ICE syndrome is as variable as the clinical picture. If corneal edema produces pain or reduced vision, the patient may be helped by hypertonic solutions or soft contact lenses. In many cases corneal edema is improved if IOP is reduced by medical or surgical therapy. Some patients with the ICE syndrome eventually require penetrating keratoplasty.^{201–203}

Glaucoma is initially treated with the full range of medical therapy. Laser trabeculoplasty offers no help in this condition because most of the angle is covered by a membrane or sealed with synechiae. Short-term success has been reported with a goniotomy procedure.²⁰⁴ But as the entire angle is progressively covered by a membrane or sealed by synechiae, medical therapy or angle surgery eventually fail because of relentless angle closure. Filtering surgery or glaucoma drainage devices are often required to control glaucoma in patients with the ICE syndrome. However, clinicians should be aware that functioning filtering blebs often fail after 2–5 years, perhaps related to proliferation of a membrane over the internal opening of the sclerostomy, despite the use of adjunctive antimetabolite therapy.²⁰⁵ In such cases, some would attempt a repeat trabeculectomy with mitomycin application²⁰⁶ or tube operation. In most cases, corneal edema clears after successful filtering surgery; in other cases, edema persists, presumably because of corneal endothelial dysfunction.²⁰⁷ At one time it was proposed that eyes with the ICE syndrome undergo a wide basal iridectomy to prevent total closure of the angle by PAS.^{208,209} This approach has not proved to be useful.²¹⁰ Ultimately, the discovery of the stimulus to epithelialization of the corneal endothelium will lead to inhibitors, and possibly prevent this difficult angle-closure disease.

POSTERIOR POLYMORPHOUS DYSTROPHY

Posterior polymorphous dystrophy is a disease of the corneal endothelium that is sometimes associated with glaucoma. This condition affects both eyes and is usually inherited as an autosomal dominant trait, although autosomal recessive patterns have been reported. Association with an abnormality on the long arm of chromosome 20 has been reported for at least one large pedigree.²¹¹ Posterior polymorphous dystrophy occurs without known racial or sexual predilections,²¹² although several Thai families have been reported with this condition in association with Alport's syndrome.²¹³

Histopathology

Histopathologic study of eyes from individuals with posterior polymorphous dystrophy reveals a thin Descemet's membrane covered

by multiple layers of collagen.²¹⁴ This is lined by a layer of cells that various investigators have stated resembles endothelium,^{97,98,107,126} epithelium,^{20,208} or fibroblasts.^{98,126,211} In some cases a membrane has been noted in the angle and on the anterior surface of the iris.²¹¹

Pathogenesis

The cause of posterior polymorphous dystrophy remains controversial. Analogous to the ICE syndrome, some investigators postulate that a dysplastic corneal endothelium produces a basement membrane-like material that extends into the angle and onto the iris. When the membrane contracts, it causes iris atrophy, corectopia, and iridocorneal adhesions.⁴⁹ Most authorities believe posterior polymorphous dystrophy is a developmental disorder; a few authorities have postulated that a viral infection, perhaps herpes simplex, causes metaplasia of the corneal endothelium. Perhaps several different stimuli can produce similar epithelialization of endothelium.

Clinical presentation

Although the clinical picture of posterior polymorphous dystrophy is quite variable,²¹⁴ the most typical physical finding is a cluster or linear arrangement of vesicles in the posterior cornea surrounded by a gray haze.²¹⁵ The deep corneal stroma and Descemet's membrane may also have band-like thickenings, white patches, *peau d'orange* appearance, or excrescences that project into the anterior chamber. Posterior polymorphous dystrophy may also have associated corneal edema, iris atrophy, mild corectopia, and iridocorneal adhesions.²¹⁶ Most cases of this syndrome are non-progressive, and the individuals affected maintain good vision throughout their lives. These eyes are often asymptomatic. The diagnosis is made on routine examination or because other members of the family have been affected.

A minority of the individuals with posterior polymorphous dystrophy develop progressive corneal changes including corneal edema. Glaucoma occurs in 10–15% of patients with this disorder. In some cases glaucoma occurs in eyes with iris atrophy, corectopia, and iridocorneal adhesions.²¹⁷ However, in other cases glaucoma occurs in eyes with open angles and an anterior insertion of the iris into the ciliary body, which resembles congenital glaucoma.²¹⁸

The differential diagnosis of posterior polymorphous dystrophy includes Fuchs' corneal dystrophy, congenital hereditary corneal dystrophy, Axenfeld's syndrome or Rieger's syndrome, and congenital glaucoma. These conditions should be distinguished readily by slit-lamp examination. The Haab's striae of congenital glaucoma are thin areas surrounded by a thickened, retracted Descemet's membrane. In contrast, the corneal involvement of posterior polymorphous dystrophy consists of thickened areas without breaks in Descemet's membrane.

Treatment

Most cases of posterior polymorphous dystrophy require no treatment. If the cornea becomes edematous, the patient should be treated with hypertonic solutions, soft contact lenses, and penetrating keratoplasty as needed. The presence of iridocorneal adhesions is a risk factor for failure of keratoplasty. Eyes with glaucoma are treated with medication and then filtering surgery as necessary.

EPITHELIAL DOWNGROWTH

Pathophysiology

Epithelial downgrowth (also called epithelial ingrowth) occurs when an epithelial membrane enters an eye through a wound and

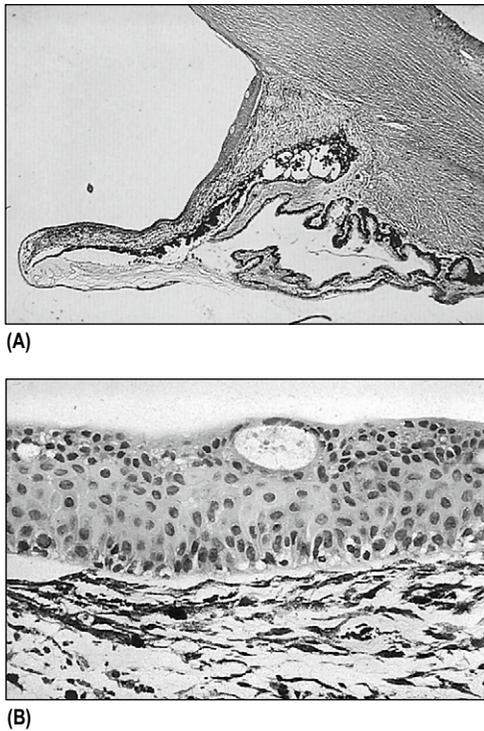


Fig. 16-8 (A) Epithelialization of anterior chamber angle. **(B)** High-power view. (Courtesy of Ramesh C Tripathi, MD, PhD and Brenda J Tripathi, PhD, Chicago, Ill.)

then proliferates over the corneal endothelium, trabecular meshwork, anterior iris surface, and vitreous face (Fig. 16-8). The epithelial membrane in the angle contracts, producing PAS and severe angle-closure glaucoma without pupillary block.

Cataract surgery is the most common cause of epithelial downgrowth. In the past it was estimated that this complication occurred in about 1 in 1000 ICCE cataract operations.^{219,220} A relatively recent review cites a 0.12% incidence decreasing to 0.08% in the decade of the 1980s.²²¹ Furthermore, epithelial downgrowth was found in 8–26% of eyes enucleated for complications of cataract surgery.^{222–224} In recent years epithelial downgrowth has been encountered less commonly because of the wide adoption of microsurgery and better techniques of cataract extraction. Epithelial downgrowth has also been reported after penetrating keratoplasty,^{225,226} glaucoma surgery, penetrating trauma, and unsuccessful removal of epithelial cysts of the anterior segment.^{227,228}

In most cases the epithelium invades the eye through a fistula or a wound gape;²²⁹ fistulas have been detected in 23–50% of such eyes.²³⁰ It is also possible that epithelium can grow into a suture tract,^{231,232} or it can be introduced into an eye at the time of surgery or trauma.^{233,234} Epithelial downgrowth can occur after uncomplicated surgery but is more likely to occur if surgery is associated with hemorrhage, inflammation, vitreous loss, or incarcerated tissue.²³⁵ Other factors seem to be endothelial damage and stromal vascularization. In the past it was observed that epithelial downgrowth occurred more frequently when cataract surgery was performed with a corneal section rather than with a limbal section. Furthermore, many authorities believed that epithelial downgrowth was less common when the cataract wound was covered with a limbus-based conjunctival flap rather than with a fornix-based conjunctival flap. These observations came from uncontrolled

studies, and their significance is not clear. Furthermore, modern cataract extraction techniques have markedly reduced the incidence but have not eliminated the problem.^{236–238}

Histopathology

Histopathologic study of biopsy specimens and enucleated globes reveals the presence of stratified squamous epithelium on the corneal endothelium, iris, and angle structures.^{239–241} The epithelium, which resembles conjunctival epithelium, is one to three cells thick except at the advancing corneal edge, where it may be five cells thick. However, the epithelium may also originate from cornea.²⁴² The epithelial membrane passes posteriorly in some eyes to cover the ciliary processes, pars plana, and retina.²⁴³ If a fistula is present, it is also lined by stratified squamous epithelium.²⁴⁴

Clinical presentation

Epithelial downgrowth usually is seen as a low-grade persistent postoperative inflammation, including conjunctival injection, photophobia, discomfort, and aqueous humor cells.²⁴⁵ Careful examination may reveal large whitish cells floating in the anterior chamber. Affected eyes often have some evidence of current or past wound leak and are hypotonic if the fistula is still functional. The key to diagnosing this condition is finding a grayish white membrane with a scalloped, thickened leading edge on the posterosuperior corneal surface. The cornea overlying the membrane may be edematous, and the iris may be drawn up to the old wound or incision. The anterior surface of the iris often appears compacted, with loss of its normal architecture. In advanced cases the eye is painful with bullous keratopathy and intractable glaucoma.

The diagnosis of epithelial downgrowth is usually made on clinical grounds as indicated above. Specular microscopy may be helpful in some cases, but this technique requires a clear cornea overlying the membrane.^{246,247} Involvement of the iris is dramatically demonstrated when it is treated with large, low-energy argon laser burns (200–500 μm , 100–400 mW, 0.1 second), which turn the epithelial membrane white. (Normal iris does not respond this way.) Because of the gravity of the situation, it is usually desirable to confirm the diagnosis histopathologically. Aqueous humor can be aspirated, passed through a Millipore filter, and then examined to identify epithelial cells. An alternative approach is to obtain a specimen by scraping a small portion of the posterior cornea with a blunt spatula. If these approaches are unfeasible or inadequate, biopsies should be taken of the posterior cornea and iris.

Most cases of epithelial downgrowth are associated with severe glaucoma. Usually the glaucoma is caused by a membrane that lines the angle and contracts to form PAS. Other factors contributing to the glaucoma include chronic inflammation, pupillary block, and obstruction of the trabecular meshwork by desquamating epithelial cells.²⁴⁸

Treatment

The treatment of epithelial downgrowth is often difficult and unrewarding. All of the techniques in current use attempt to close the fistula and then to excise or destroy the epithelium in the eye. It is common to determine the extent of iris involvement using the argon laser as described above. The corneal portion of the membrane can then be destroyed with cryotherapy or chemical cauterization. The affected iris can be excised, and cryotherapy can be applied to any remaining membrane on the ciliary body and retina.²⁴⁹ An alternative approach is to do an *en-bloc* excision of all involved tissues.²⁵⁰ Others have excised the involved iris and vitreous with a vitrectomy instrument and destroyed any remaining

membrane with cryotherapy after the eye has been filled with air. Yet another approach involves excision of involved tissues, a penetrating keratoplasty, and implantation of a glaucoma shunt.²⁵¹ One case report using adjunctive 5-fluorouracil, both for glaucoma control and in an attempt to control the epithelialization, was unsuccessful. Many other techniques have been described in the past for treating epithelial ingrowth, including X-radiation, beta-irradiation, curettage with alcohol, and photocoagulation.^{252–254} These have been largely abandoned as ineffective. Immunotoxin has been shown to inhibit epithelial proliferation in tissue culture;²⁵⁵ perhaps an agent like this may find some use in the future in this very frustrating condition.

All of the current techniques have been reported to salvage some eyes with epithelial downgrowth and even to maintain good vision in a few cases. However, recurrences of the downgrowth are common, and surgery is frequently associated with complications that include corneal edema, chronic inflammation, macular edema, and phthisis bulbi. The results of treatment are better if the condition is diagnosed early. However, it must be stressed that *preventing* epithelial downgrowth is far more effective than treating established disease. Surgical and traumatic wounds must be cleaned of epithelial tissue fragments and foreign material and then sutured meticulously.

FIBROVASCULAR INGROWTH

Fibrovascular tissue can grow into an eye if there is an open wound after penetrating trauma or surgery. Fibrovascular ingrowth occurs more frequently if the trauma or surgery is associated with hemorrhage, inflammation, or incarcerated tissue.^{256–258} Fibrovascular ingrowth can occur from pars plana incisions, as well as from more anterior ones.²⁵⁹ In some cases the ingrowth resembles a vascular stalk that enters the eye through an old wound and then fans out over the anterior segment. In other cases the ingrowth forms a gray-white membrane posterior to the corneal endothelium, without an obvious entry site or a vascular stalk. The membrane may have an interlacing pattern of gray fibers that has been compared to woven cloth.²⁶⁰ Various authorities have attributed the invading fibroblasts to the subconjunctival connective tissue, corneal stroma, limbal tissue,²⁶¹ and metaplastic endothelium.²⁶² The invading fibrovascular tissue grows over the corneal endothelium, anterior iris surface, vitreous face, and angle, where it contracts to form PAS. On occasion the membrane can also attach to the retina and cause a traction detachment.

Fibrovascular ingrowth usually causes glaucoma when the membrane covers the angle and then contracts to form peripheral anterior synechiae. Other factors contributing to the glaucoma include uveitis, pupillary block, and underlying trauma. In many ways, fibrovascular ingrowth resembles epithelial downgrowth, although it is less virulent in its course.²⁶³

It is far better to prevent fibrovascular ingrowth than to treat the condition once established. In the past this condition was a common finding in eyes enucleated after cataract surgery or trauma.²⁶⁴ With current microsurgical techniques, fibrovascular ingrowth is encountered far less often.

The glaucoma associated with fibrovascular ingrowth is usually managed by medical therapy. In some cases posterior glaucoma drainage device implantation or cyclophotocoagulation is required to control IOP. On occasion it is possible to excise the fibrovascular tissue, including the fistula at the old wound. However, this approach is not suitable for most eyes with fibrovascular ingrowth because the involvement of the anterior segment is too extensive.

Furthermore, the poor visual prognosis usually does not warrant such aggressive surgery in most cases. Cyclodestructive procedures can often alleviate painfully high IOPs.

Glaucoma has been reported from proliferation of iris melanocytes across the angle and the remainder of the anterior segment.²⁶⁵ This type of glaucoma is extremely rare.

FLAT ANTERIOR CHAMBER

A flat anterior chamber after penetrating trauma or surgery can lead to the formation of PAS and secondary angle-closure glaucoma without pupillary block (Table 16–1; Fig. 16–9). The development of synechiae is related to the duration of the flat anterior chamber and the degree of inflammation of the eye. There are a number of reports on delayed re-formation of the anterior chamber after cataract extraction. In most of these studies secondary angle-closure glaucoma was common if the anterior chamber was flat for 5 days or longer.^{267–269} Flat anterior chambers are encountered far less often with modern microsurgical cataract techniques. However, flat anterior chambers occur not uncommonly after filtering operations, and they are often allowed to persist for a few to several days before re-formation is attempted. Flat anterior chambers also may occur in association with malignant glaucoma and penetrating keratoplasty.

Following re-formation of a flat anterior chamber, the residual secondary angle-closure glaucoma is treated with standard medical therapy. Often patients respond better to medical treatment than would have been predicted by the extent of the angle closure. This suggests that some of the trabecular meshwork is functional behind the apparent PAS; that is, the synechiae are bridging rather than closing the angle if the duration of tissue approximation is short enough. If medical treatment is inadequate, a laser trabeculoplasty can be considered if at least one-third to one-half of the angle is open. However, the clinician must be aware that a sustained post-laser IOP rise may necessitate filtering surgery. Other alternatives include filtering operations, cyclodestructive procedures, and surgical goniosynechialysis of the PAS.²⁷⁰

INFLAMMATION

Inflammation can produce glaucoma through a variety of mechanisms, including increased viscosity of the aqueous humor, obstruction of the trabecular meshwork by inflammatory cells and debris, scarring of the outflow channels, elevated episcleral venous pressure, forward displacement of the lens–iris diaphragm, and pupillary block from posterior synechiae. Inflammation can also produce angle-closure glaucoma without pupillary block when the peripheral iris swells as a result of the inflammatory process, when precipitates or exudates in the angle contract to form PAS, or when there is forward rotation of the ciliary body. These can occur after surgery or trauma, in idiopathic inflammatory conditions, or with specific uveitis entities such as interstitial keratitis,²⁷¹ sarcoidosis,²⁷² ankylosing spondylitis,^{273,274} pars planitis,²⁷⁵ and juvenile rheumatoid arthritis, particularly the pauciarticular variety.^{276–279} Peripheral anterior synechiae form more readily in eyes with shallow anterior chambers and in eyes afflicted with chronic granulomatous inflammatory disease.

Secondary angle-closure glaucoma without pupillary block is usually managed with medical therapy. It is crucial that residual inflammation be suppressed with corticosteroids. However, the ophthalmologist must keep in mind the possibility of inducing corticosteroid glaucoma. Patients are often more comfortable

Table 16-1 Differential diagnosis of the postoperative flat anterior chamber

	Malignant Glaucoma	Choroidal Detachment	Pupillary Block	Suprachoroidal Hemorrhage	Wound Leak
Central anterior chamber	Flat or shallow	Shallow	May be normal	Flat or shallow	Flat or shallow
Intraocular pressure	Normal or elevated	Low	Normal or elevated	Normal or elevated	Low
Fundus appearance	Usually normal	Large, smooth, brown mass	Usually normal	Dark brown or dark red elevation	Choroidals may be present
Suprachoroidal fluid	Absent	Present	Absent	Present	Absent
Relief by drainage of suprachoroidal fluid	No	Yes	No	Yes	No
Relief by iridectomy	No	No	Yes	No	No
Patent iridectomy	Yes	Yes	No	Yes	Yes
Onset	Usually within days, but may be months	Usually within first week	Anytime	Immediately or within first few days	Usually within first few days but may be late with adjunctive antimetabolites
Seidel test	Negative	Negative	Negative	Negative	Positive

Modified from Simmons RJ, Maestre FA: Malignant glaucoma. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn. St Louis, Mosby, 1996.²⁶⁶



Fig. 16-9 Histopathology of anterior synechia formation following postoperative flat anterior chamber. (Courtesy of William H Spencer, MD.)

with the addition of cycloplegic agents which may, by dilating the pupil, prevent pupillary block from posterior synechia formation. Virtually all topical glaucoma agents are used to control IOP, with two guarded exceptions. Miotics may be helpful in the pseudophakic eye if it is quiet, but they are usually counterproductive in the presence of persistent inflammation. Similarly, prostaglandins should be used with caution because they may occasionally precipitate an inflammatory reaction.²⁸⁰ Hyperosmotic agents are administered on occasion for acute elevations of IOP.

If medical therapy fails to control IOP, filtering surgery must be considered. Because standard filtering surgery is less likely to be successful in inflamed eyes (and these patients are often young people), filtering surgery with adjunctive antimetabolite therapy or glaucoma drainage devices such as the Molteno, Baerveldt, or Ahmed implants should be performed. In children with inflammatory

disease the prospects for successful filtering surgery are further reduced by rapid healing, low scleral rigidity, and the increased thickness of Tenon's capsule.²⁸¹ A few authorities have used a modified goniotomy procedure – trabeculodialysis – to treat children with inflammation and glaucoma. A goniotomy knife is used to depress the iris and lyse any PAS present. The trabecular meshwork is then incised below Schwalbe's line, and the trabecular tissues are retracted further.^{282,283}

PENETRATING KERATOPLASTY

Angle-closure glaucoma can develop after penetrating keratoplasty, from mechanisms including pupillary block, postoperative inflammation, or a flat anterior chamber from a wound leak. The severity of the glaucoma is generally related to the extent of the synechial closure. The incidence of postkeratoplasty angle closure is reduced by performing one or more iridectomies, closing the wound meticulously, using a graft slightly larger than the recipient bed, and administering corticosteroids postoperatively.^{284–286} However, in some cases the iris becomes attached to the corneal wound, and it is pulled forward in progressive fashion. Glaucoma of one sort or another is a complication in about 20% of penetrating keratoplasties.²⁸⁷

Most cases of postkeratoplasty angle-closure glaucoma without pupillary block can be managed with standard medical treatment. Many of these eyes are aphakic and respond well to cholinesterase inhibitors, β -blockers, α -adrenergic agonists, prostaglandins, and carbonic anhydrase inhibitors. If pupillary block is contributing to the glaucoma, a laser iridotomy should be performed. Laser trabeculoplasty may be helpful, provided that at least one-third to one-half of the angle is open.²⁸⁸ When medical treatment fails to control the glaucoma, filtering surgery with mitomycin-C can be successful if conjunctiva is not heavily scarred.²⁸⁹ However, the surgeon must proceed with care to avoid damage to the corneal graft. Filtering surgery alone often fails.²⁹⁰ A posterior glaucoma drainage device

may also be very useful in these situations, though special care must be taken to place the tube within the anterior chamber far from the new graft tissue.^{291,292} Cyclocryotherapy and other ciliary body destructive procedures are used commonly to control IOP before or after penetrating keratoplasty.^{293,294} The pressure reduction is often temporary, but the procedure can be repeated as required.

IRIDOSCHISIS

Iridoschisis is a patchy dissolution of the iris in which the anterior stroma separates from the posterior stroma and muscle layer. The anterior stroma then splits into strands that project into the anterior chamber and sometimes touch the cornea. Iridoschisis is usually bilateral and tends to involve the lower iris quadrants. This condition usually occurs in older individuals but has been reported in children.²⁹⁵ Many patients have a pre-existing chronic ocular disease such as uveitis. Glaucoma occurs in about 50% of the patients and is usually related to the development of PAS in the region of the iris strands.^{296,297} Pupillary block and the release of pigment and debris may also contribute to the glaucoma in some cases.²⁹⁸ The cornea overlying the iris strands may develop bullous keratopathy. Angle closure may occur from forward bowing of the anterior iris stroma.²⁹⁹ One report suggests that angle-closure glaucoma may actually cause iridoschisis and that any patient with the condition should have primary angle-closure glaucoma ruled out as an underlying condition.³⁰⁰

Elevated IOP and iridoschisis are usually managed by medical therapy. If pupillary block is playing a substantial role, a laser iridotomy should be performed. In some cases filtering surgery is required to control the glaucoma.

ANIRIDIA

Aniridia produces angle-closure glaucoma without pupillary block. This is discussed in the section devoted to glaucoma in infants and children in Chapter 23.

POSTERIOR PUSHING (OR ROTATIONAL) MECHANISM

As discussed earlier, it is possible to conceptualize secondary angle-closure glaucoma without pupillary block as occurring through two major mechanisms: by anterior pulling or by posterior pushing, or rotation. In the anterior pulling mechanism, a membrane, exudate, or fibrous band in the angle contracts and pulls the iris forward into contact with the trabecular meshwork. In the posterior pushing mechanism, the peripheral iris is displaced by the lens, vitreous, or ciliary body (see Fig. 16–2). The posterior pushing mechanism is often accompanied by swelling and anterior rotation of the ciliary body, which further acts to close the angle. When the ciliary body swells, it rotates forward about its attachment at the scleral spur and diminishes the diameter of the ciliary ring. Both of these factors reduce the tension on the zonules and allow the lens to move forward.

Several mechanisms, often overlapping, have been proposed to explain the role of the ciliary body in ‘pushing’ forms of secondary angle-closure glaucoma:

1. When the anterior uveal tract swells from inflammation or vascular congestion, the ciliary ring is narrowed, which reduces

tension on the zonules, permits the lens to come forward, and displaces the peripheral iris.

2. When the ciliary body swells, it also rotates forward about its attachment to the scleral spur, which again loosens the zonules and displaces the root of the iris. The ciliary body is like a fan that opens about its attachment at the scleral spur as it swells.³⁰¹
3. Finally, ciliary body swelling is often accompanied by the accumulation of suprachoroidal and supraciliary fluid, which further rotates the ciliary body and iris root into the angle.

CILIARY BLOCK GLAUCOMA (AQUEOUS MISDIRECTION OR MALIGNANT GLAUCOMA)

In 1869 von Graefe described an uncommon complication of ocular surgery consisting of a postoperative flat or shallow anterior chamber and elevated IOP. He named this condition ‘malignant’ glaucoma because it relentlessly worsened despite conventional therapy.³⁰² The term ‘malignant glaucoma’ is not related to the pathophysiology of the condition and is often frightening to patients who believe they have a malignancy of the eye. This text’s original author, Dr Robert Shaffer, strongly felt that the term *malignant glaucoma* should be replaced by the term *ciliary block glaucoma*.^{303,304}

The term *ciliary block* or *malignant glaucoma* refers to a spectrum of atypical angle-closure glaucomas that share several essential features.^{266,305,306} Other terms have been proposed for this condition, many of which purportedly point to the underlying pathophysiology. These terms include *aqueous misdirection*, *hyaloid block glaucoma* and *posterior aqueous entrapment*. Historically, this condition was commonly appreciated as a complication of a filtering procedure in eyes with pre-existing angle-closure glaucoma or shallow anterior chambers, although anomalous ‘triggers’ for its presentation³⁰⁷ have been reported, such as laser iridotomy,^{308,309} miotic usage,³¹⁰ infectious endophthalmitis,^{311,312} retinal conditions,^{313–315} and hyperplastic ciliary processes.³¹⁶

There is good agreement in the literature about several essential features of this condition, but other features are more controversial.³¹⁷ Clinically, ciliary block glaucoma is suspected in the presence of a Spaeth grade 1 or 2 shallow anterior chamber, with the prominent axial shallowing of the peripheral and central anterior chambers simultaneously. The pressure is usually higher than expected; in the early postoperative period it may simply be between 15 and 20 mmHg despite the appearance of what would seem to be an otherwise adequate bleb; in other cases the pressure can be quite high indeed.

To diagnose ciliary block glaucoma, it is *essential to eliminate the possibility of pupillary block*; hence a patent iridectomy must be established before this diagnosis can be considered. Sometimes the diagnosis is made only in retrospect, after evaluating the eye’s response to several interventions. For example, cycloplegics can ameliorate malignant glaucoma and miotics can exacerbate the situation. If surgical intervention is necessary, disrupting the hyaloid face or collapsing the vitreous is usually curative; some use aggressive vitrectomy/lensectomy to form a unicameral eye creating easy passage for fluid from the vitreous cavity into the anterior chamber.

Other aspects that are sometimes seen with ciliary block glaucoma include the rarity of spontaneous resolution – and hence its ‘malignant’ designation. It is usually bilateral in predisposition, and it is often worsened by conventional glaucoma surgery such as iridectomy or filtration procedures. The clinical presentation of ciliary block glaucoma is similar to that of other conditions, notably angle-closure glaucoma with ciliary choroidal detachment syndrome.

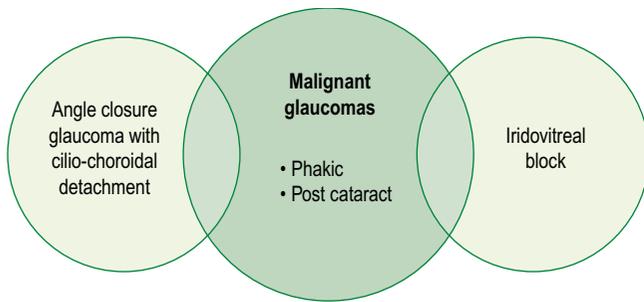


Fig. 16–10 Overlapping of clinical syndromes sharing features with malignant glaucoma.

(From Lieberman MF, Lee DA: Diagnosis and management of malignant glaucoma. In: Higginbotham EJ, Lee DA, editors: Clinical guide to glaucoma management, Woburn, MA, Butterworth-Heinemann/Elsevier, 2004.³⁰⁵)

This specific condition is usually bilateral in its presentation, with identifiable choroidal detachments associated with other diseases, such as HIV (Fig. 16–10).^{318–320}

Though not well described in the classical literature on malignant glaucoma, recent authors have observed the accumulation of fluid in the suprachoroidal space in some cases of ciliary block glaucoma,^{305,321} which can frequently be confirmed by ultrasonic biomicroscopy (UBM) (Fig. 16–11).³²² This finding has been incorporated into a model that proposes the common denominator of choroidal effusion as underlying several of the angle-closure glaucomas (see below).

Other situations that may overlap with the appearance of ciliary block glaucoma include eyes that have undergone cataract extraction, with or without lens implantation, with sequestration of aqueous behind the iris plane. These conditions have been referred to as ‘iridovitreal block’³²³ and ‘retrocapsular aqueous misdirection’.³²⁴

The pathophysiologic sequence of ciliary block glaucoma is thought to be as follows.^{325,326} After some initiating event (e.g., shallowing of the chamber during trabeculectomy) there is cause for misdirection of the aqueous to circulate into or behind the vitreous body.³²⁷ This apparently leads to an alteration of the vitreous volume and its compaction, with a cycle of increasing vitreous swelling and reduced conductivity of aqueous anteriorly. The enlarging vitreous body is unable to exchange aqueous across the hyaloid face at the junction of the zonules, vitreous face, and ciliary processes. This progressive vitreal engorgement results in shallowing both axially and peripherally in the anterior chamber, with increasing apposition of the peripheral iris into the angle, setting up a further cycle of angle-closure glaucoma.^{325,326,328} A recent model^{328b} proposes that choroidal expansion (proposed as an initiating event in acute angle closure as well) may also be a contributory event for anterior vitreal movement in malignant glaucoma, and hence its frequent clinical association with primary angle-closure glaucoma.^{326,329}

The management of ciliary block glaucoma needs to be sequential, and specific to the anatomy of the presenting eye. It is *essential* to eliminate the possibility of pupillary block glaucoma by verifying or creating a patent iridectomy. Miotic medications should be discontinued, and vigorous cycloplegia³³⁰ (atropine 1% twice daily plus phenylephrine 2.5% four times daily) as well as the use of topical steroids (prednisolone 1% six times daily) should be instituted. Other agents to reduce aqueous production, such as topical α -adrenergic agonists, β -blockers, carbonic anhydrase inhibitors, prostaglandins, or osmotic agents, can be used to reduce the pressure.

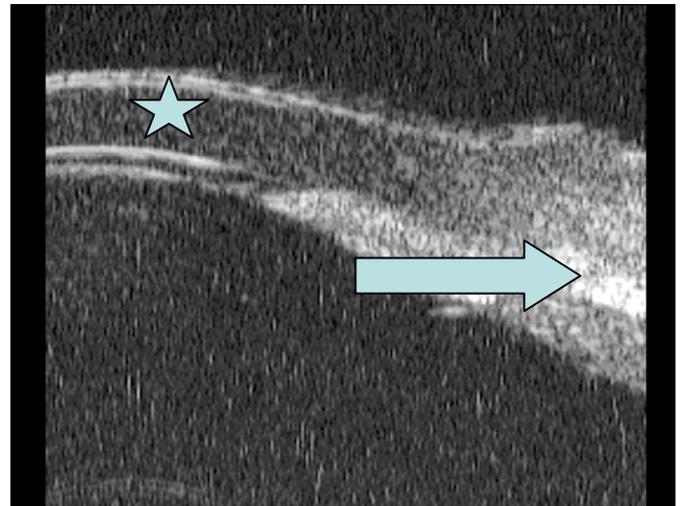


Fig. 16–11 Shallow ciliary effusion seen anteriorly by UBM. Note flat anterior chamber (star) from malignant glaucoma, with anterior suprachoroidal effusion (arrow). (Courtesy of Shan Lin, MD.)

A waiting period of approximately 5 days has been advised, if feasible, with an intensive medical regimen^{330,331} to see if there is resolution, with as many as half of the cases resolving during this interval.³³²

In the event that surgical intervention is necessary, the status of the lens largely determines which non-medical options are available. Either a needle aspiration of vitreous through the pars plana³³³ or pars plana vitrectomy^{334,335} can be curative in *phakic* eyes (see Fig. 36–15). Eyes that have had cataract extraction – with or without a lens implant – and a retained posterior capsule permit the frequently curative intervention of the Nd:YAG laser* for direct incision of the hyaloid face.^{336–338} (This may be the mechanism of argon laser shrinkage of visible ciliary processes:^{339,340} peripheral disruption of the hyaloid–ciliary interface.) In an eye with a *retained posterior capsule*, as with a posterior chamber intraocular lens,^{341–343} (see Fig. 36–16), it is necessary to sequentially eliminate pupillary block, retrocapsular block, and hyaloid block by respectively laser-ing through the iris, posterior capsule, and hyaloid face.³⁰⁵ In the *acapsular* eye (e.g., aphakia) (see Fig. 36–17), hyaloidectomy centrally and peripherally³⁴⁴ can be undertaken with the Nd:YAG laser or with incisional surgery.

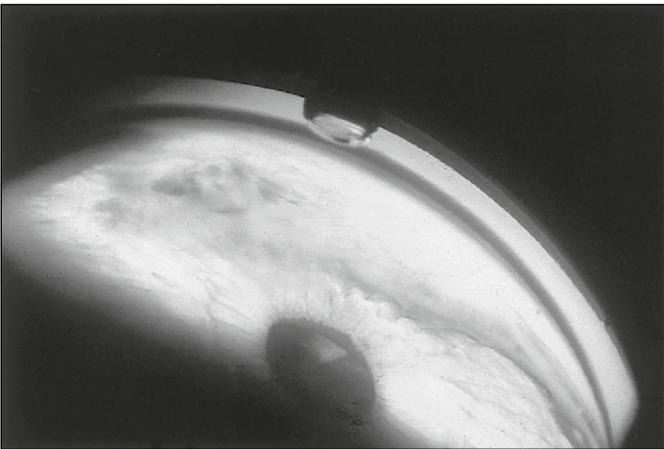
Vigorous surveillance is still necessary in all malignant glaucoma eyes, even after laser or surgery, because recurrent cases of ciliary block glaucoma have been reported. This has been seen particularly after vitreous aspiration or vitrectomy,^{345–348} which may not have been sufficiently anterior in the phakic eye to access and interrupt the obstruction of the anterior hyaloid face, so close to the lens. In such instances it may be necessary to sacrifice the lens to access the hyaloid itself. Chronic atropine drops may be needed; and great attention should be paid to the fellow eye, which is at a high risk for recapitulating the events of the first eye’s ciliary block glaucoma attack.

INTRAOCULAR TUMORS

Ocular malignant melanoma is frequently associated with glaucoma through a variety of mechanisms, including direct extension of the tumor into the trabecular meshwork, seeding of tumor cells



(A)



(B)

Fig. 16-12 (A) Iris melanoma. (B) Invading angle.

into the outflow channels, obstruction of the meshwork by pigment or pigment-laden macrophages,³⁴⁹⁻³⁵² neovascularization, PAS,³⁵³ iridocyclitis, and hyphema.^{354,355} Benign iris and ciliary cysts³⁵⁶⁻³⁶⁰ have been associated with glaucoma, presenting in ways similar to the plateau iris mechanism. Melanomas of the choroid and ciliary body can also displace the lens-iris diaphragm and produce angle-closure glaucoma without pupillary block.^{349-355,361-365} In most cases, glaucoma occurs when the melanoma is already large, and enucleation is the appropriate therapy. There have been a few reports of surgery for angle-closure glaucoma in eyes that were determined later to harbor undetected melanomas.³⁶³⁻³⁶⁵ At times, iris melanomas invade the angle and cause secondary angle closure without pupillary block (Fig. 16-12). Generally these eyes have good vision, and the glaucoma is managed by medical treatment.

Other intraocular tumors such as adenomas and leiomyomas may push the iris forward and cause angle-closure glaucoma. One such example, a leiomyoma, is shown pushing the iris forward in Figure 16-13.

*Only rarely, in the days of large surgical iridectomies, was adequate visualization possible of the ciliary processes or hyaloid to attempt either YAG or argon laser therapy in phakic eyes.

**Fig. 16-13** Leiomyoma pushing the peripheral iris forward and closing off the chamber angle.

(Courtesy of William H Spencer, MD.)

Metastatic tumors to the eye are frequently associated with glaucoma, especially when the tumor involves the anterior segment of the globe.^{366,367} Glaucoma occurs through a variety of mechanisms, including direct extension of the tumor into the trabecular meshwork, iridocyclitis, hyphema, neovascularization, and PAS. Metastatic tumor can also serve as a rapidly developing posterior mass that displaces the lens-iris diaphragm and causes angle-closure glaucoma without pupillary block.^{366,367} If the diagnosis of metastatic disease is uncertain, a paracentesis can be performed, and the cells can be examined histologically. In most cases enucleation is not warranted for metastatic disease, and medical treatment is instituted to control IOP and relieve the patient's symptoms. Some metastatic tumors are responsive to radiation therapy.

Retinoblastoma is frequently associated with glaucoma through the mechanisms of neovascularization, angle seeding, iridocyclitis, and hyphema.³⁶⁸ A retinoblastoma can also act as a rapidly developing posterior mass that displaces the lens-iris diaphragm and leads to angle-closure glaucoma without pupillary block. In fact, this is the mechanism in 27% of cases with elevated IOP.

NANOPHTHALMOS

The term *nanophthalmos* refers to an eye that is normal in shape but small in size. This abnormality can occur sporadically or can be inherited in an autosomal dominant or an autosomal recessive pattern.³⁶⁹⁻³⁷¹ Nanophthalmos is a bilateral condition, and men and women are affected in equal numbers.³⁷²⁻³⁷⁴ The prevalence has been calculated to be between 0.06% and 0.1%. Nanophthalmic eyes have a short anteroposterior length (<20 mm) and a small corneal diameter (Table 16-2). In contrast, the lens is normal, or even somewhat large, in size, so the ratio of the volume of the lens to the volume of the eye is 10-25% instead of the normal 3-4%. Other findings in nanophthalmic eyes include a shallow anterior chamber both centrally and peripherally, an anteriorly displaced iris, high hyperopia, thick sclera, spontaneous and postoperative uveal effusions,^{375,376} and a wide pulse pressure. A subset of patients with familial, recessive nanophthalmos also have a pigmented retinal degeneration.^{377,378}

Nanophthalmic eyes frequently develop angle-closure glaucoma in the fourth to sixth decades of life. This can progress to total synechial closure. Histopathologic examination of these globes reveals

Table 16-2 Ocular dimensions of nanophthalmic eyes

	Mean	Range
Corneal diameter (mm)	10.3	9.5–11.0
Anterior chamber depth (mm)	15	10–27
Refractive error (D)	+13.6	+7.25–+ 20.00
Axial length (mm)	17.0	14.5–20.5
Lens thickness (mm)	5.2	4.2–7.3
Volume lens/volume eye (%)	12.2	4–25
Combined thickness sclera and choroid (mm)	1.2	0.8–4.0

Modified from Singh OS, and others: *Ophthalmology* 89:1006, 1982.³⁷⁴
Published courtesy of *Ophthalmology*.

a thickened sclera with abnormal sclerocytes, an abnormal arrangement of collagen, an abnormal glycosaminoglycan metabolism, and an accumulation of proteoglycans.^{379–382}

Because these are already very small eyes, they have little anatomic reserve against any condition that will further compress the angle. Pupillary block related to age and to lens swelling is a factor in some. However, pupillary block does not play an important role in all nanophthalmic eyes because many do not respond favorably to laser iridotomy. In other nanophthalmic eyes, angle closure is probably precipitated by the development of a choroidal effusion. The effusion rotates the ciliary body anteriorly, displaces the peripheral iris, and loosens the zonules, allowing the lens to move forward. (This sequence has been proposed to be an underlying mechanism of many angle-closure glaucomas.³⁸³) The thick sclera may produce choroidal effusion by obstructing flow through the vortex veins.

Nanophthalmic eyes with normal IOPs and open angles should be followed carefully for signs of progressive angle narrowing. If narrowing occurs, a laser iridectomy should be performed to eliminate any element of pupillary block. If the angle does not deepen, or if it becomes progressively shallower after iridotomy, laser goniotomy is recommended. One or two quadrants can be treated in a session, and the treatment can be repeated if the effect diminishes with time. Topical β -adrenergic antagonists, α_2 -adrenergic agonists, prostaglandins and topical carbonic anhydrase inhibitors are prescribed for elevated IOP. Because these patients often tend to be young, oral carbonic anhydrase inhibitors are often not tolerated well. Miotic agents lower IOP in some nanophthalmic eyes but raise pressure in others, presumably by allowing the lens to move forward; it is best to avoid them here. Systemic corticosteroids have little effect on the uveal effusions occurring in this syndrome.³⁸⁴ If laser and medical treatments are inadequate to control angle-closure glaucoma, some authorities recommend surgically unroofing at least two vortex veins to relieve venous obstruction. Other authorities recommend creating permanent drainage sites for suprachoroidal fluid in two to four quadrants.

It is important to emphasize that intraocular surgery should be avoided in nanophthalmic eyes unless absolutely necessary. Surgery is often accompanied by intraoperative and postoperative disastrous complications, including choroidal effusion, non-rhegmatogenous retinal detachment, cataract, and flat anterior chamber. Standard intraocular surgery reduces IOP to atmospheric pressure, which promotes uveal effusion and retinal detachment; hence an intraoperative anterior chamber maintainer (e.g., Lewicke cannula) should be inserted and connected to balanced salt solution, with great attention to preventing even the slightest hypotony during

the procedure. If filtering surgery is required in nanophthalmic eyes, prophylactic sclerotomies should be performed in both lower quadrants, and the sclera should be left unsutured and even unroofed to allow continued drainage of suprachoroidal fluid. An alternative to trabeculectomy would be a glaucoma shunt procedure, prophylactically using either an anterior chamber maintainer or intracameral viscoelastic to forestall any low IOPs.

A recent study³⁸⁵ of 19 eyes with bilateral uveal effusion syndrome identified three subtypes: nanophthalmic eyes; short but normal eyes (average axial length of 21 mm); and normal eyes. The first two types displayed abnormal scleral structures, with disorganized collagen bundles and intramatrix proteoglycans; these types alone responded to subscleral sclerotomies.

SUPRACHOROIDAL HEMORRHAGE

A non-expulsive suprachoroidal hemorrhage can act as a rapidly developing posterior mass and produce angle-closure glaucoma without pupillary block. This entity is most often seen after filtering operations in aphakic eyes and is discussed in the section on complications of glaucoma surgery in Chapter 37.³⁸⁶

POSTERIOR SEGMENT INFLAMMATORY DISEASE

Posterior scleritis is associated with increased IOP in 12–46% of cases.^{387–389} This occurs through a variety of mechanisms, including increased viscosity of the aqueous humor; inflammation of the outflow channels; obstruction of the trabecular meshwork by inflammatory cells and debris; PAS; neovascularization; and elevated episcleral venous pressure.³⁹⁰ Posterior scleritis can also be associated with choroidal effusion and secondary angle-closure glaucoma without pupillary block.^{391–393} The effusion acts as an acutely developing posterior mass that displaces the lens-iris diaphragm, possibly by trans-vitreous pressure.^{328b} In addition, the scleritis is associated with swelling and anterior rotation of the ciliary body. When examined, these eyes demonstrate a shallow anterior chamber both centrally and peripherally, partial to total angle closure, and a sectorial or circumferential choroidal effusion. The IOP may be normal, high, or even low depending on the rate of aqueous humor production. The other ocular findings depend on both the underlying disease and whether the scleritis involves the anterior segment (Box 16–2).

Treatment

The medical management of scleritis includes systemic non-steroidal anti-inflammatory agents, topical cycloplegic agents, and topical and systemic corticosteroids as needed. Topical β -adrenergic antagonists, α_2 -adrenergic agonists, and topical carbonic anhydrase inhibitors are administered to control IOP. Systemic carbonic anhydrase inhibitors and hyperosmotic agents may be given for short-term treatment of markedly elevated IOP. Miotics are of little value in this situation. Topical prostaglandin agents can be administered, with careful attention to whether or not inflammation is being exacerbated.²⁸⁰ The anterior chamber deepens spontaneously when the inflammation and the effusion subside. However, the scleritis can produce extensive PAS and chronic angle-closure glaucoma.

In similar fashion, any inflammatory disease of the posterior segment can cause choroidal effusion, swelling, and anterior rotation of the ciliary body, as well as secondary angle-closure glaucoma without pupillary block. Angle closure occurs not uncommonly in the Vogt-Koyanagi-Harada syndrome.^{394,395}

Box 16–2 Ophthalmic causes of uveal effusion

- I. Idiopathic (e.g., uveal effusion syndrome)
- II. Inflammatory
 - A. Uveitis
 1. Sympathetic ophthalmia
 2. Vogt-Koyanagi-Harada syndrome
 3. Pars planitis³²⁰
 - B. Scleritis
 1. Herpes zoster¹²³
 2. Collagen vascular disorders
 3. Acquired immunodeficiency syndrome¹²⁴
 - C. Infected scleral buckle
 - D. Thyroid disease
- III. Increased choroidal vascular pressure
 - A. Venous obstruction
 1. Nanophthalmos
 2. Hypoplastic vortex veins
 3. Scleral buckling procedure
 4. Panretinal photocoagulation¹²⁵
 - B. Arterial communication
 1. Sturge-Weber syndrome
 2. Arteriovenous fistula¹²⁶
- IV. Hypotony
 - A. Glaucoma surgery
 - B. Possibly mitomycin induced¹²⁷
 - C. Cataract surgery
- V. Infiltrative
 - A. Tumors
 1. Melanoma
 2. Metastatic disease
 3. Leukemia
 4. Lymphoma
 - B. Lymphocytic hyperplasia

Modified from Brockhurst RJ: Arch Ophthalmology 98:1987, 1980,³⁷⁶ Gass JDM, Jallow S: Ophthalmology 89:1018, 1982.³⁸⁴

CENTRAL RETINAL VEIN OCCLUSION

A central retinal vein occlusion is sometimes followed by a shallow anterior chamber and angle-closure glaucoma.^{396,397} It may be difficult to determine the exact sequence of events in all patients because angle-closure glaucoma can also precipitate a central retinal vein occlusion. Most cases of angle closure following central retinal vein occlusion abate spontaneously over a few days to several weeks. However, a few eyes develop sufficient PAS and damage to the trabecular meshwork to leave them with residual angle-closure glaucoma.

The anterior chamber usually shallows within 1–3 days after a central retinal vein occlusion, although a few delayed cases have been reported. The patients may be asymptomatic or may complain of pain and blurred vision. Besides the findings of the central retinal vein occlusion, examination reveals corneal epithelial edema, a shallow anterior chamber both centrally and peripherally, an IOP in the range of 25–45 mmHg, and partial to total angle closure.

The mechanism of angle closure after a central retinal vein occlusion appears to be similar to that of scleral buckling and panretinal photocoagulation. The vein occlusion interferes with the venous drainage of the uveal tract, causing swelling and anterior rotation of the ciliary body. The central retinal vein occlusion also causes

a transudation of fluid into the choroid, retina, and vitreous. The fluid acts like an acutely developing posterior mass that displaces the lens–iris diaphragm.³⁹⁸ In some cases this pushing mechanism of pupillary block contributes to the development of glaucoma.

Most cases of angle closure following central retinal vein occlusion are managed with medical treatment. The patients are given cycloplegic agents, topical corticosteroids, β -adrenergic antagonists, topical α_2 -adrenergic agonists, topical carbonic anhydrase inhibitors, and hyperosmotic agents as necessary.³⁹⁹ Although there are a few reports that pilocarpine is helpful in this condition, it is wise to try cycloplegic agents as the initial therapy. If medical therapy is insufficient to protect the optic nerve and prevent widespread PAS, laser gonioplasty should be considered. If pupillary block is playing a role, a laser iridectomy should be performed. It is important for the clinician to determine whether the central retinal vein occlusion is associated with retinal ischemia. If ischemia is present, retinal ablation should be performed after the anterior chamber deepens (see the section on neovascular glaucoma, p. 212).

SCLERAL BUCKLING PROCEDURE

After a scleral buckling procedure, it is common for the anterior chamber to be shallow for a few days.^{400–402} In 1–2% of eyes, this condition progresses to angle-closure glaucoma without pupillary block.^{403–405} The anterior chamber deepens spontaneously over days to weeks, but PAS may be formed during this period, creating residual angle-closure glaucoma.

Many patients with postscleral buckling angle-closure glaucoma are not recognized because either they are asymptomatic or the symptoms are misinterpreted as those ‘normally’ seen after scleral buckle procedures. Some patients are detected only when a hazy view of the retina suggests corneal edema. A few patients with markedly elevated IOPs are seen with ocular pain, nausea, vomiting, and chemosis. Examination reveals a shallow anterior chamber both centrally and peripherally, corneal edema, and total angle closure. Intraocular pressure is usually in the range of 25–50 mmHg but can be higher on occasion. A serous or bloody choroidal detachment is a frequent finding in this situation.⁴⁰⁶

There are several factors that contribute to the development of angle-closure glaucoma after scleral buckling procedures. The buckle itself displaces the lens, iris, and vitreous.⁴⁰⁷ However, this cannot be the sole mechanism of angle closure because the buckle persists, and yet the anterior chamber deepens spontaneously, over time. It is postulated that the encircling band causes a temporary interference with the venous drainage of the uveal tract, which leads to swelling and anterior rotation of the ciliary body and accumulation of supraciliary and suprachoroidal fluid. On occasion, a buckle may directly compress one or more vortex veins, leading to vascular congestion and angle-closure glaucoma. This mechanism has been confirmed experimentally in monkey eyes.⁴⁰⁸ In some eyes, pupillary block contributes to the glaucoma.⁴⁰⁹ However, in most eyes, pupillary block plays little role, as evidenced by the lack of iris bombé, the occurrence of this condition in aphakic eyes with patent iridectomies, and the lack of effectiveness of iridectomy.

Most cases of postscleral buckle angle-closure glaucoma can be treated medically until the anterior chamber deepens spontaneously over a few days to a few weeks. The patients are given cycloplegic agents, topical corticosteroids, topical β -adrenergic antagonists, topical α_2 -adrenergic agonists, topical carbonic anhydrase inhibitors, and hyperosmotic agents as needed. Some authorities recommend systemic corticosteroids to reduce inflammation and to speed resorption

of suprachoroidal fluid. In this situation, adrenaline (epinephrine) is generally ineffective in lowering IOP, and miotics should be avoided because they worsen the condition. Because angle closure following scleral buckling is a temporary condition, modest elevations of IOP are usually tolerated well. However, if the IOP is very high, if pre-existing cupping is extensive, if the optic nerve circulation is embarrassed, or if extensive PAS are forming, argon laser goniotomy should be attempted.⁴¹⁰ This is usually a suitable but conservative approach. If pupillary block is contributing to angle closure, a laser iridectomy should be performed; however, this is a rather unlikely event. In an occasional case, it may be necessary to drain the suprachoroidal fluid and re-form the anterior chamber. In the rare situation in which one or more vortex veins are compressed, the buckle should be revised to relieve the obstruction.

Air or other gases may be injected into the vitreous cavity to repair some retinal detachments. The gas bubble can expand sufficiently to displace the peripheral iris and produce angle-closure glaucoma.^{411–412} The medical management of this situation is similar to that outlined previously. If the IOP elevation threatens the optic nerve, some of the gas should be removed, and the anterior chamber should be re-formed.⁴¹⁵ It is important that clinicians realize that some tonometers may give misleading results in eyes filled with air or other gasses. In this situation the applanation tonometer gives accurate readings, whereas the Schiøtz and air puff tonometers may not.^{416,417}

PANRETINAL PHOTOCOAGULATION

Panretinal photocoagulation (PRP) is often followed by a shallow anterior chamber and angle closure.^{319,418–421} In one study, 14 of 45 eyes (31.1%) developed angle closure within 3 days of PRP. Most of the reported cases have occurred in diabetic patients; it is unclear whether diabetes mellitus plays a direct role in this entity, or whether diabetic patients simply form the vast majority of individuals undergoing such therapy. Angle closure is more common in eyes with pre-existing shallow angles but can occur in eyes that had deep anterior chambers before treatment.

Most individuals with angle closure after PRP are asymptomatic, although an occasional patient complains of ocular discomfort or headache. Examination of these patients reveals corneal epithelial edema, a shallow anterior chamber both centrally and peripherally, a myopic shift in refraction, a choroidal detachment, an IOP in the range of 20–50 mmHg, and partial to total angle closure. The anterior chamber usually deepens spontaneously over a few days to a few weeks.

The mechanism of angle closure after PRP is thought to be interference with the venous drainage of the uveal tract, leading to choroidal detachment and swelling and anterior rotation of the ciliary body. This theory is supported by ultrasound studies demonstrating ciliary body thickening after PRP. Photocoagulation may break the blood–ocular barriers and cause a transudation of fluid into the retina, choroid, and vitreous. This fluid may act as an acutely developing mass and displace the lens–iris diaphragm forward. Pupillary block may contribute to the development of glaucoma in some cases.

Angle closure following PRP is usually managed with medical therapy. The patients are given cycloplegic agents, topical corticosteroids, prostaglandins, topical β -adrenergic antagonists, topical α_2 -adrenergic agonists, and topical carbonic anhydrase inhibitors as needed. Because this is a temporary condition, medical treatment is usually sufficient to protect the optic nerve until the anterior

chamber deepens spontaneously. If the IOP elevation threatens the optic nerve or if PAS are forming rapidly, laser peripheral iridoplasty should be performed. If pupillary block is contributing to the glaucoma, a laser iridectomy should be created. If lesser methods fail, the definitive treatment for this condition is drainage of suprachoroidal fluid and re-formation of the anterior chamber.

It should be emphasized that many patients develop elevated IOP after PRP and yet have wide open angles. In most such cases the trabecular meshwork is plugged by protein-rich fluid, debris, and inflammatory cells. Panretinal photocoagulation may also theoretically interfere with uveoscleral flow, reduce ciliary muscle tone, and release prostaglandins.

RETINOPATHY OF PREMATURETY

Angle-closure glaucoma can occur in patients with retinopathy of prematurity. The mechanisms are varied and include neovascularization, pupillary block, and pushing forward of the lens–iris diaphragm.⁴²² In known cases of retinopathy of prematurity, periodic gonioscopy is indicated and the pupil should be dilated with care. If pupillary block appears to be part of the mechanism, a laser peripheral iridotomy should be performed. If a narrow angle is encountered in a young individual, retinopathy of prematurity as well as ectopia lentis and microspherophakia should be considered. This is further discussed in the section on secondary glaucoma in infants and children in Chapter 20.

PUPILLARY BLOCK MECHANISMS

When pupillary block is the major mechanism in the presence of a stable, and essentially normal, lens, the peripheral iris is pushed forward by aqueous humor in the posterior chamber, which is under greater pressure than the fluid in the anterior chamber. Pupillary block is relieved by iridotomy, or by extensive pupillary dilation: either maneuver allows the pressures in the two chambers to equilibrate so that the peripheral iris is no longer bowed forward into contact with the trabecular meshwork. This is in distinct contrast to the posterior pushing mechanism without pupillary block, whereby the peripheral iris is displaced forward by direct pressure from the lens, ciliary body, vitreous, or mass lesion in the posterior segment. This latter mechanism is not relieved by iridotomy or pupillary dilation because there is no back pressure from aqueous humor trapped in the posterior chamber. In fact, in this situation, the posterior chamber is usually compressed or obliterated.⁴²³

Secondary pupillary block glaucoma: iris–lens adhesions

Inflammation is one of the commonest such causes of secondary pupillary block. The iris can adhere to the lens in a number of conditions, including chronic inflammation, flat anterior chamber, and long-term miotic administration. Extensive posterior synechiae can interfere with the circulation of aqueous humor from the posterior chamber to the anterior chamber. In this situation, if the peripheral iris is mobile, it billows forward in a marked bombé configuration (Fig. 16–14). If the iris has patches of adherence, the surface appears irregular or lumpy with alternating flat (e.g., adherent) and convex (e.g., bombé configuration) portions. The initial treatment for extensive posterior synechiae is to dilate the pupil vigorously to free a portion of the iris and reduce pupillary block. Any concomitant inflammation should be treated with topical corticosteroids. Many of these eyes require laser iridotomy

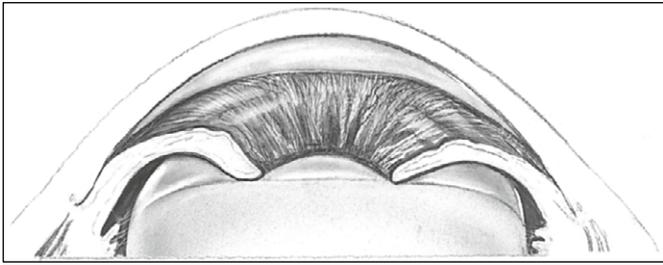


Fig. 16-14 Posterior synechiae and iris bombé.

to prevent recurrence of pupillary block – which in this context of inflammation may mean that the iridotomies will close and need to be repeated. Close clinical surveillance is required, and surgical iridectomy may become necessary. If the source of inflammation has been controlled, and the onset of PAS documented to be recent, surgical goniosynechialysis may be useful.⁴²⁴

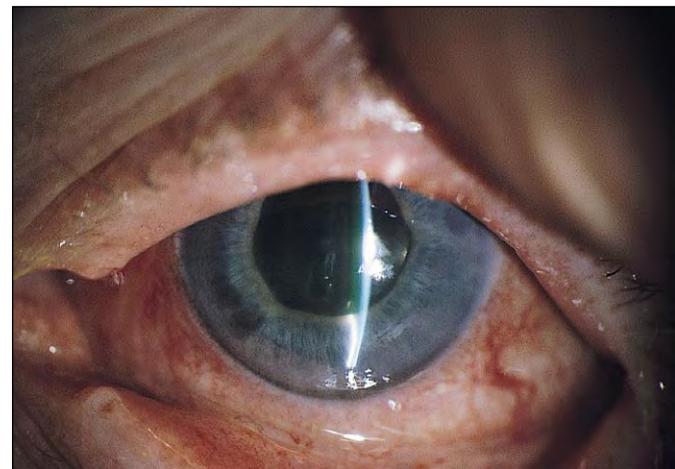
Extensive adhesions of the iris to the vitreous face can also produce pupillary block and secondary angle-closure glaucoma.^{425–428} This occurs in aphakic and pseudophakic eyes, especially those in which the iridectomy is not patent, occluded, or omitted. Pupillary block and secondary glaucoma can also result from adherence of the iris to an intraocular lens (IOL). This occurs most often with anterior chamber lenses, but can be seen with posterior chamber and iris-supported lenses as well, especially in eyes in which the iridectomy was omitted or occluded (Figs 16-15 and 16-16).^{429–431}

With anterior chamber lenses the optic may form a ball valve-type seal over the pupil while the haptic covers the iridectomy.⁴³² Some cases of pseudophakic pupillary block can be managed by vigorous pupillary dilation to break the posterior synechiae. If this is inadequate, pupillary dilation can be augmented by laser photomydriasis (pupilloplasty),⁴³³ where multiple intense, focused argon laser applications are applied to the 12 o'clock margin of the pupil radially for 2–3 mm, thereby stretching the pupil into a 'tear-drop' shape and often breaking the block. Iridotomy is the most effective treatment but, especially with some anterior chamber lenses, it may have to be performed in one to four quadrants to relieve the pupillary block.^{434,435} With anterior chamber lenses it is important that the iridectomies be spaced far enough apart to prevent the haptics from occluding the openings even if the pseudophakos rotates. In the absence of a pre-existing iridectomy (e.g., following filtration surgery) it is strongly advised to perform iridectomy at the time of an anterior chamber IOL placement, or to soon perform a laser iridotomy prophylactically. This precaution has bearing as well with the advent of phakic lens implants for refractive purposes, where pupillary block angle closure is a possible complication of the procedure. Postoperative gonioscopy should be performed routinely in these patients to identify those at risk.⁴³⁶

Although pseudophakic pupillary block with a posterior chamber lens implant is rare in an otherwise normal eye,⁴³⁷ the eyes of diabetic patients and those with current or past history of ocular inflammation are at particular risk for this problem.⁴³⁸ In these cases, a peripheral surgical iridectomy should be strongly considered at the time of cataract surgery. The ultrasound biomicroscope may be helpful in the differential diagnosis of angle closure occurring in a pseudophakic eye.⁴³⁹ In some eyes, a wound leak may be the precipitating factor for a sequence of events that includes shallow anterior chamber, occluded iridectomy, and pupillary block. Other contributing factors include postoperative inflammation,



(A)



(B)

Fig. 16-15 Pupillary block with anterior chamber intraocular lens.



Fig. 16-16 Pupillary block with a posterior chamber lens.

retained air or viscocohesive (Healon-5™) in the anterior or posterior chamber, or residual lens material.

The treatment for aphakic and pseudophakic pupillary block is the same as that outlined earlier for phakic eyes. In some aphakic and pseudophakic eyes, fluid appears to be loculated in the posterior chamber. It may be necessary to perform iridotomies

in two to four quadrants to relieve the pupillary block in this situation. Topical hyperosmotic agents may be helpful to clear the cornea and allow the iridotomies. If one or more patent iridotomies do not cause the iris to fall back and the IOP to decrease, malignant glaucoma or a ciliochoroidal detachment with angle closure may be operative. In these latter situations, miotics are contraindicated.

Although the emphasis in this section is on iris–lens adhesions, it needs to be remembered that iritis produces a secondary angle closure not only by pupillary block, but also by inducing synechial closure of the angle itself. The iris may be pulled into the trabecular meshwork by fibrinous exudates in the angle that turn to fibrous tissue and then contract, resulting in PAS. Thus, the glaucoma caused by this condition is often severe and difficult to control. The underlying inflammatory condition often results both in recurrence of PAS following iridoplasty or goniosynechialysis procedures to the angle, just as it causes closing of laser iridotomies much more frequently than is seen in non-inflamed eyes.⁴⁴⁰

Dislocated and subluxed lens

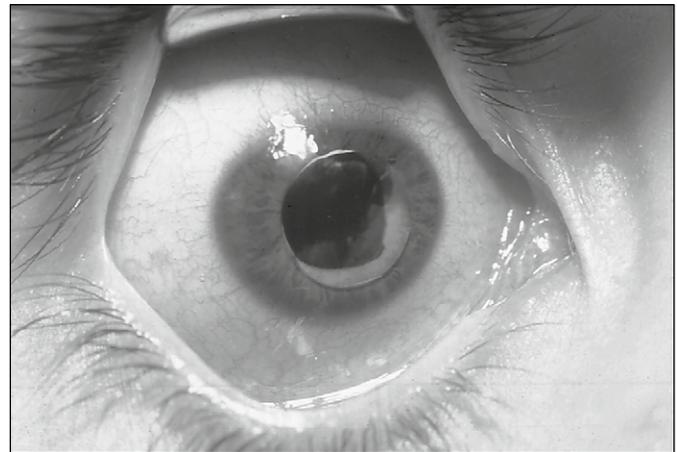
A wide variety of diseases (e.g., syphilis) and predisposing conditions have been implicated in the loss of zonular support, allowing the lens to either sublux or to dislocate anteriorly, inducing a pupillary block by virtue of its aberrant position. Blunt trauma is perhaps the most common condition, though it may precipitate glaucoma from a variety of sequelae: hyphema and late PAS; angle recession; intravitreal hemorrhage; uveitis; and lens dislocation. Pseudoexfoliation's frequent manifestation of zonular laxity (an intraoperative challenge for cataract surgeons) can also lead to anterior displacement of the lens and resultant pupillary block.

Ectopia lentis

Subluxation or dislocation of the lens can also occur as an isolated congenital anomaly, or as part of a generalized condition such as Marfan syndrome, homocystinuria, Weill–Marchesani syndrome, Ehlers–Danlos syndrome, hyperlysinemia, or sulfite oxidase deficiency. Ectopia lentis is also associated with a number of ocular conditions such as aniridia, buphthalmos, and megalocornea.

An ectopic lens can cause severe pupillary block if it comes forward into the pupil or anterior chamber (Fig. 16–17).^{441,442} Dislocation of the lens may also allow the vitreous face to come forward and obstruct the pupil. Other possible causes of glaucoma associated with ectopic lenses include uveitis, trauma, and phacolytic reaction. In most cases of ectopia lentis with pupillary block, the patient is given a systemic hyperosmotic agent, a topical β -adrenergic antagonist, α -adrenergic agonist, prostaglandin analogue and, if necessary, an oral carbonic anhydrase inhibitor to reduce IOP. The use of systemic hyperosmotic agents also shrinks the vitreous, allowing the lens to move posteriorly.

If the lens is caught in the pupil or anterior chamber, weak mydriatic agents are administered. If the zonules are known to be intact, a cycloplegic drug may be used to pull the lens posteriorly. Once the lens is in the posterior chamber, the pupil is constricted by miotic agents and an iridotomy is performed. The iridotomy should be placed in such a position that the lens will not occlude the opening. The patient is then treated long term with miotic agents to prevent forward migration of the dislocated or subluxated lens. There are a few situations in which a dislocated or subluxated lens should be removed, including the inability to reposit it in the posterior chamber; severe diplopia; reduction of visual acuity related to cataract or high astigmatism; phacolytic glaucoma; corneal decompensation; or intractable uveitis. The choice between



(A)



(B)

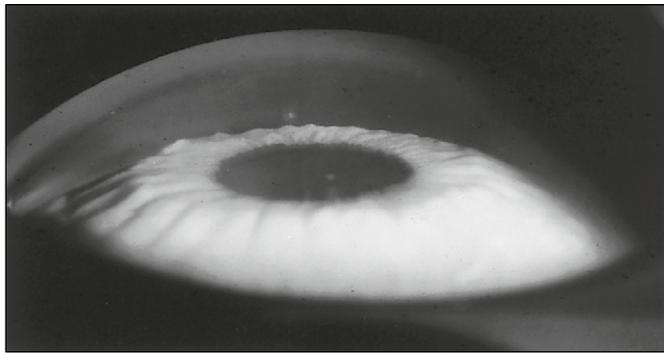
Fig. 16–17 (A) Lens prolapsed into pupil and anterior chamber. **(B)** Light micrograph of crystalline lens dislocated into the anterior chamber. (Courtesy of William H Spencer, MD.)

anterior cataract extraction and lensectomy through the pars plana depends on the position and condition of the lens. Intraocular surgery in these situations is associated with a high rate of complications, in part caused by the condition of the eyes and in part caused by the associated systemic diseases (e.g., homocystinuria).

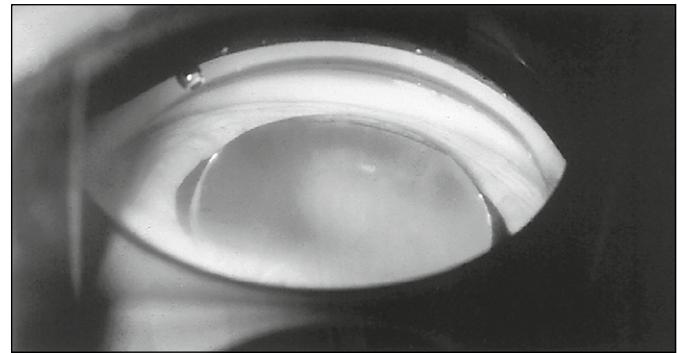
Microspherophakia

Microspherophakia (i.e., a small round lens), ectopia lentis, and glaucoma may occur as an isolated familial condition⁴⁴³ or may be associated with a variety of diseases, including Marfan syndrome, homocystinuria,⁴⁴⁴ Klinefelter's syndrome,⁴⁴⁵ mandibulofacial dysostosis,⁴⁴⁶ and Alport's syndrome.⁴⁴⁷ Most commonly, however, microspherophakia is associated with the Weill–Marchesani syndrome, which is characterized by short, stocky habitus, short fingers and toes, brachycephaly, and limited finger and wrist mobility. In microspherophakia, the equatorial diameter of the lens is decreased while the thickness is increased, giving it a spheric or globular shape (Fig. 16–18A).^{448–451}

When the pupil is dilated, the entire circumference of the lens is visible at the slit lamp (Fig. 16–18B). Dislocation of the lens is common and often occurs at a relatively young age. Pupillary block and glaucoma occur through one of two mechanisms: either the lens dislocates into the pupil and anterior chamber or long zonules



(A)



(B)

Fig. 16–18 (A) Gonioscopic view of a spherophakic lens displacing the iris and shallowing the anterior chamber. **(B)** Gonioscopic view after pupillary dilation showing the entire circumference of the lens in the pupil.

allow the lens to come forward into the pupil. The physician should be suspicious of microspherophakia when angle-closure glaucoma occurs in young myopic individuals or when a myopic individual has a shallow anterior chamber.

When an acute episode of glaucoma occurs in an individual with Weill-Marchesani syndrome, the status of the zonules is usually unknown. If the physician knows that the zonules are intact, a cycloplegic agent should be administered to pull the lens posteriorly. If the zonules are not intact, however, dilating the pupil allows the lens to come forward into the anterior chamber. Miotic agents often aggravate pupillary block in spherophakia.⁴⁵²

The safest approach is to avoid both miotics and cycloplegics and to administer hyperosmotic agents, carbonic anhydrase inhibitors,

and topical hypotensive agents, and to place the patient in the supine position. The hyperosmotic drugs shrink the vitreous and allow the lens to move posteriorly, thereby reducing pupillary block, where it can be ‘captured’ with a miotic. An argon or Nd:YAG iridotomy can then be performed in both eyes. Laser iridotomy is preferable to surgical iridectomy because the latter is associated with a high rate of complications. Ritch and Wand⁴⁵³ have suggested that prophylactic iridotomies be performed in all individuals with the Weill-Marchesani syndrome. However, in the event that an iridotomy and medications are inadequate to forestall progressive glaucoma damage, complex surgery including lensectomy, vitrectomy, sutured posterior IOL and a glaucoma shunt has been described.⁴⁵⁴

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CHAPTER
17

Primary open angle glaucoma

Primary open-angle glaucoma (POAG) can be considered a chronic, progressive, anterior optic neuropathy that is accompanied by a characteristic cupping and atrophy of the optic disc, visual field loss, open angles, and no obvious causative ocular or systemic conditions. In the majority, but by no means all, cases the intraocular pressure (IOP) is elevated above the statistically 'normal' range, reflecting a reduced aqueous humor outflow facility. Although elevated IOP is not the cause of all damage in POAG, it is the major risk factor. The issue of IOP has been complicated by the rediscovery of the importance of corneal thickness as both a parameter that may cause inaccurate readings with applanation tonometry and an independent factor that may change the risk of developing open angle glaucoma.¹ The mechanism by which elevated IOP damages the optic nerve is not clear, but ischemia of the optic disc or nerve fiber layer, direct mechanical compression of axons, local toxicity, or some combination of these has been implicated.

Primary open-angle glaucoma may be more than one disease with a final common pathway of damage to the ganglion cells and optic nerve; at present, we are unable to clearly distinguish any subclassification, although attempts have been made to divide POAG into 'IOP sensitive' and 'IOP insensitive' forms. Given our lack of knowledge on this subject, we will continue to discuss POAG as if it were a single disease. Primary open-angle glaucoma is referred to by a variety of other names, including open-angle glaucoma, chronic open-angle glaucoma, chronic simple glaucoma, and open-angle glaucoma with damage.

Primary open-angle glaucoma is the most common form of glaucoma in many countries and accounts for 60–70% of the cases seen in the United States. By the year 2000, it was estimated that there were approximately 2.5 million cases of POAG in the United States (about 1.9 million white Americans and 0.6 million black Americans).² The Dana Center in Baltimore estimates that 45 million people worldwide will have open-angle glaucoma by the year 2010, of which 4.5 million will be bilaterally blind.³ This disease has a hereditary component and becomes more prevalent with age. Because POAG is very slowly progressive, it is usually asymptomatic until late in its course; affected individuals can develop severe damage before they seek professional help. Most cases of POAG are discovered through screening programs or on routine ocular examinations.^{4,5} Population-based screening programs may have a small yield and may not be cost effective; however, screening programs directed towards those at higher risk (e.g. the elderly, people of African descent) may be more productive.⁶

In a minority of white patients but a majority of Japanese patients, optic nerve cupping and visual field loss develop without recorded IOPs above the statistical norm. This condition is called *normal-tension glaucoma* (normal-pressure glaucoma, low-tension glaucoma,

or low-pressure glaucoma). Many individuals have IOPs above the statistically 'normal' range (>2 standard deviations from the mean, or 21 mmHg), but only a very small percentage of these ever develop optic nerve damage. Those individuals with 'elevated' IOPs who also have normal optic nerves, normal visual fields, and no known ocular or systemic condition accounting for the increased pressure are said to have *ocular hypertension*. These individuals are at increased risk (compared with those with 'normal' IOP) of developing true glaucoma. The Ocular Hypertension Treatment Study (OHTS) showed that many of those with above 'normal' IOP have thick corneas and are at low risk for development of actual glaucoma.⁷

The existence of normal-tension glaucoma and ocular hypertension implies that some optic nerves are quite sensitive to the effects of IOP, whereas others are quite resistant. As noted previously, ischemia, mechanical factors, and neurotoxic agents have been cited, but, unfortunately, we are unable to formally identify those clinical factors leading to optic nerve damage. Although we know about some risk factors, it is impossible to determine with any degree of confidence which of those individuals with 'elevated' IOPs will ultimately develop actual optic nerve damage (although we can estimate risk). Nor can we determine the 'safe' level of IOP for any given individual.

EPIDEMIOLOGY

The study of epidemiology (the distribution of a disease in a population, and the identifiable conditions that are associated with it) helps us understand some of the factors that alter the risk of glaucoma, its progression, and its sequelae. The understanding of POAG has been significantly improved in recent years by the application of epidemiologic principles. From reviews of various sources of data, it can be estimated that 2.25 million Americans 40 years of age and older have POAG.⁸ In Australia, the prevalence of definite glaucoma ranges from 2.1 to 2.5% of those over 50 years old and the number of people with glaucoma is expected to double by the year 2030.⁹ Worldwide, over 2 million people develop this condition every year. Between 84 000 and 116 000 persons are estimated to be bilaterally blind (visual acuity <20/200) in the United States. Worldwide, more than 3 million people are bilaterally blind because of POAG.¹⁰

PREVALENCE

In most studies performed in western Europe and in the United States, the prevalence of POAG¹¹ is 0.5–1% of the population

above age 40 (Table 17-1). Various studies have reported different prevalences depending on the population sampled, the ages of the individuals studied, the techniques of examination, and the definitions of glaucoma used. The most recent US study using rigorous definitions estimated the overall prevalence of open-angle glaucoma at about 1.9% of those over 40, with blacks having three times the prevalence of whites.²⁷ A similar overall prevalence was found for definite POAG in those over age 40 in Spain.²⁸ Many previous studies found higher prevalence rates because the investigators diagnosed glaucoma by elevated IOP or abnormal aqueous humor dynamics instead of visual field loss and optic disc cupping.

However, even more recent studies, using strict criteria for optic nerve damage, have shown a surprisingly high prevalence, especially among those of black African ancestry and among those over 70 years of age (see Ch. 1). Recent studies have emphasized the differences among various racial and ethnic groups vis-à-vis the prevalence of glaucoma. For example, in southern India, the prevalence of open-angle glaucoma is 1.6% of the population with greater than 98% unaware that they have the disease.²⁹ In Japan, glaucoma is quite common compared to other Asian and Caucasian societies. In the Tajima study, 3.9% of those over 40 years old had POAG and the vast majority had IOPs below 21 mmHg.³⁰ Among Singapore Chinese, the prevalence of POAG in those over 40 years of age is about 1.6%.³¹ The prevalence of open-angle glaucoma also appears to be relatively high in a population study in Bangladesh (about 2% in people over 40).³² However, the highest prevalence is still in those of west African origin; for example, in Ghana, the prevalence of open-angle glaucoma is over 8% in those over 40.³³ In South Africa, the prevalence of glaucoma in general was almost 3% among black South Africans over 40; surprisingly, 16% of these had exfoliative glaucoma.³⁴ However, even some Caucasian populations may have a high prevalence of glaucoma; for example, in Iceland, the prevalence of glaucoma (including exfoliative) in those over 50 is 4%.³⁵ In another example, Greeks seem to have an unusually high prevalence: >4% compared to other European groups.³⁶ Australians also have a relatively high prevalence of glaucoma (3%), with women having a higher prevalence than men and the prevalence increasing 'exponentially' with age.³⁷

INCIDENCE

Few studies determining the true incidence of POAG in the general population have been undertaken. A study of this type requires a large population-based sample with long-term follow-up. Such a study has been performed in Barbados over 4 years. In this population of largely black African ancestry, the 4-year incidence of glaucoma over 40 years of age is 2.2%, with higher rates for males, those of African ancestry, those with high IOPs, and those with suspicious discs at enrollment.³⁸ Incident rates increased from 1.2% in the 40–49 age group to 4.2% in those over 70.³⁹ Using data from the Framingham study, Podgor and co-workers⁴⁰ have estimated that the incidence of POAG rises from 0.2% at age 55 to 1.1% at age 70; that is, the incidence of POAG is 2 cases per 1000 people per year from age 55 to 60 years, and 11 cases per 1000 people per year from age 70 to 75 years. The Rotterdam study showed that the incidence of glaucoma over 6.5 years in those over 55 years of age was 1.2% for probable open-angle glaucoma and 0.6% for definite open-angle glaucoma.⁴¹ The incidence increased with age so that at age 60, the incidence was about 1% and it rose to 3% at age 80. As in most other studies, most of the patients with incident glaucoma were unaware of their disease. In Australia, the overall 5-year incidence of definite glaucoma in those over 40 was 0.5% and of definite and probable glaucoma 1.1%; the incidence ranges from near 0 at 40 to over 4% at age 80.⁴² A similar increase in incidence has been found in Minnesota.⁴³

INTRAOCULAR PRESSURE

There is general agreement that IOP is the most important known risk factor for open-angle glaucoma development. Evidence clearly indicates that elevated IOP can cause glaucomatous optic nerve changes in experimental animals.^{44,45} Even in normal-pressure glaucoma, asymmetric IOP has been noted to correlate with asymmetric cupping and field loss, with the greater damage most often occurring on the side with higher pressure.^{46,47} Population surveys also support the increase in prevalence of open-angle glaucoma with

Table 17-1 Prevalence of open-angle glaucoma

Investigator	Site	Ages (years)	No. examined	Diagnostic criteria	Prevalence (%)
Stromberg ¹²	Skovde, Sweden	>40	7275	Disc and field changes	0.41
Hollows & Graham ¹³	Wales	40–74	4231	Disc and field changes	0.47
Bankes et al ¹⁴	England	>40	5941	Disc and field changes	0.76
Armaly ¹⁵	Iowa	20–89	2325	Arcuate scotoma	4.08
Kahn & Milton ^{16,17}	Framingham, Mass	52–85	2433	Visual field changes	1.43
Bengtsson ¹⁸	Dalby, Sweden	55–70	1511	Disc and field changes	0.86
Mason et al ¹⁹	St Lucia, West Indies	30–86	1679	Disc and field changes	8.8
Tielsch et al ²⁰	Baltimore, Maryland (white)	>40	2913	Disc and field changes	1.29
Tielsch et al ²⁰	Baltimore, Maryland (black)	>40	2395	Disc and field changes (black)	4.74
Shiose et al ²¹	Japan	≥40	8126	Disc and field changes	2.6
Klein et al ²²	Beaver Dam, Wisc	43–84	4926	Disc and field changes	2.1
Coffey et al ²³	Ireland	≥50	2186	Disc and field changes	1.9
Leske et al ²⁴	Barbados, West Indies	40–84	4709	Disc and field changes	6.6
Dielmans et al ²⁵	Rotterdam, Netherlands	≥55	3062	Disc and field changes	1.1
Mitchell et al ²⁶	Blue Mountain, Australia	≥49	3654	Disc and field changes	3.1
Friedman et al ²⁷	Estimate US	>40	Meta-analysis	Disc and field changes	1.9

Modified from Leske MC: Am J Epidemiol 118:166, 1983; Wilson MR, Martone JF: Epidemiology of chronic open-angle glaucoma. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn, St Louis, Mosby, 1996.

increasing IOP.^{13,48,49} Among those with elevated IOP without evidence of glaucomatous damage (ocular hypertensives), the OHTS study shows that the higher the IOP, the more likely that glaucomatous damage will develop.⁵⁰ Because many individuals with 'elevated' IOP never develop glaucoma, and because many people with glaucoma have 'normal' IOPs, IOP obviously cannot be the only risk factor.

AGE

The prevalence of POAG increases with age (Table 17-2).^{13,20,22,48,51} However, one should not infer from this statement that the disease is limited to middle-aged and older individuals; it occurs in children and young adults as well.⁵²⁻⁵⁴ The effect of age on the prevalence of POAG holds true even after compensating for the relationship between increasing age and increasing IOP.⁵⁵ Even in Japan where IOP does not increase with age, open-angle glaucoma does increase in prevalence with age.³⁰ Age is also a risk factor for the conversion from ocular hypertension to open-angle glaucoma.⁵⁰

GENDER

Conflicting information exists about the effect of gender on the prevalence of POAG. In several studies, males had a higher prevalence of glaucoma.^{16,24,25,56} In the Barbados study, POAG was associated with older men, high IOP, positive family history, lean body mass, and low blood pressure to IOP ratio.⁵⁷

RACE

As noted above, POAG is more prevalent in blacks than in whites.^{20,58} Furthermore, the disease seems to develop at an earlier age and has a more rapid progression in black patients.^{40,59-62} It is estimated that the incidence and the prevalence of blindness from glaucoma are 8-10 times higher in black patients than in white patients in the United States.^{20,63} The OHTS study showed black race to be a risk factor for the development of open-angle glaucoma from ocular hypertension using univariate analysis; however, race drops out of the risk factors in the multivariate analysis because blacks have significantly thinner corneas than other racial groups and the thin corneas become the predominant risk factor.⁵⁰ Some have proposed that optic nerve ischemia from sickle cell anemia contributes to the high prevalence of POAG in blacks. However, this theory

was not supported by one study, which found that only 2 of 40 black patients requiring filtering surgery had a positive test for sickle cell trait.⁶⁴ Black patients seem to respond to some treatment modes less favorably than do whites;⁶⁵⁻⁶⁸ whether this explains the more virulent course has not been answered. Furthermore, some black patients may not have access to the same quality of treatment as white patients have. When compared with whites, blacks have higher levels of IOP⁶⁹⁻⁷¹ and larger cup-to-disc diameter ratios.⁷² In the USA, in those of Hispanic (admittedly a very mixed group) background, the prevalence of open-angle glaucoma is midway between that of blacks and whites with a more rapid rise in prevalence as the population ages.⁷³ Latinos of Mexican background living in Los Angeles also have a higher prevalence of open-angle glaucoma that is nearly 5% in those over 40; the prevalence is therefore somewhere between those of European ancestry and those of African ancestry.⁷⁴

Data on the prevalence of POAG in other ethnic and racial groups are less complete. It is stated that POAG is rare in Pacific Islanders,⁷⁵ some Asians,⁷⁶⁻⁷⁸ and certain Native American tribes. In Mongolia, the prevalence of open-angle glaucoma was found to be quite low (0.5%) with angle-closure glaucoma having a prevalence of 1.4%.⁷⁹ In Japan, the prevalence of POAG is 0.58%, with normal-pressure glaucoma having a prevalence of 2.04%.²¹ In an English study, the prevalence of open-angle glaucoma was found to be similar in those of European descent and in those of Asian descent.⁸⁰ However, it is unlikely that this population living in England is representative of all Asian groups. In Tunisia, the overall prevalence of open-angle glaucoma in a population over 40 years of age was 2.7%. This is similar to that found in Europeans but lower than that found in those of black African descent.⁸¹ In southern India (mostly Tamil), as noted above, the prevalence of open-angle glaucoma is 1.6% in those over 40.²⁹ Further surveys using standardized techniques and definitions are needed in many population groups.

SOCIOECONOMIC FACTORS

Very few studies have been performed on the relationship between socioeconomic variables and the prevalence of POAG. In different reports, manual laborers have an increased⁸² and a decreased⁸³ prevalence of POAG. The Baltimore Eye Study suggested that socioeconomic factors played some role in the increased prevalence and severity of open-angle glaucoma in those of black African descent, but only a small part compared with racial factors.²⁰ A retrospective study from England looking for parameters contributing to blindness

Table 17-2 Prevalence of primary open-angle glaucoma by age (%)

Age (years)	Wales (Hollands and Graham) ¹³	Framingham, Mass. (Liebowitz and Co-workers) ⁵¹	Baltimore White (Tielsch and Co-workers)* ²⁰	Baltimore Black (Tielsch and Co-workers)* ²⁰
40-49	NR	NR	0.92	1.23
50-54	0.3	NR		
55-59	0.9	0.5	0.41	4.05
60-64	0.5	0.7		
65-69	1.1	0.9	0.88	5.51
70-74	1.3	1.7		
75-79	NR	2.0	2.89	9.15
80-85	NR	4.4	2.16	11.26

Modified from Leske MC: *Am J Epidemiol* 118:166, 1983; Tielsch JM, and others: *JAMA* 266:369, 1991.

*Reported in decades (e.g., 50-59)

NR, not reported

from glaucoma found that lower socioeconomic status was indeed one of the risk factors despite universal health care in that country.⁸⁴

Little is known about the effect of lifestyle, vocation, geography, diet, and nutrition on glaucoma. Moderate exercise has been shown to decrease IOP in both normal volunteers and in patients with POAG.^{85,86} Furthermore, moderate exercise has been shown to increase choroidal blood flow, although with some limits.⁸⁷ However, whether regular exercise results in better long-term IOP control or improved ganglion cell survival has not been demonstrated. One study showed little effect of caffeine on IOP but a more recent study did implicate caffeine use as being related to increased IOP and to having glaucoma.^{88,89} It may be difficult in these kind of studies to separate out the effects of a substance like caffeine and the effects of the total fluid volume associated with the intake.

REFRACTIVE ERROR

Myopia has been associated with POAG in many studies.^{90–94} It is not clear whether myopia has a direct influence on the prevalence of the disease or whether it acts through its known associations with increased IOP and larger cup-to-disc ratios.^{95,96} It is often difficult to diagnose glaucoma in myopic individuals because they have (1) broad, shallow optic cups with less distinct margins; (2) baring of the blind spot or other refractive scotomata on visual field testing; (3) low ocular rigidity, which makes Schiøtz tonometer readings inaccurate, and (4) thin corneas and sclera which may give falsely low readings on Goldmann tonometry.

CORNEAL THICKNESS

As noted previously, a thin cornea is a risk factor for conversion from ocular hypertension to open-angle glaucoma.¹ Race as a risk factor in itself disappeared when corneal thickness was taken into account; that is, those of African ancestry had thinner corneas and this accounted for all of the increased risk for conversion to open-angle glaucoma among blacks with ocular hypertension. A thin cornea also seems to be a marker and possible risk factor for advanced glaucoma on diagnosis.⁹⁷ A thin cornea will cause Goldmann tonometry to underestimate the IOP. In the OHTS study cited above, the increased risk related to thin corneas could not be explained solely by the underestimation of IOP. Therefore, thin corneas may be a marker for increased susceptibility of the optic nerve. Perhaps, people with thin corneas have less support tissue in the optic nerve making it more liable to pressure-induced and/or vascular damage.

HEREDITY

Primary open-angle glaucoma appears to have a genetic or familial component. Over the years, autosomal dominant,^{52,98} autosomal recessive,^{99,100} and sex-linked¹⁰¹ inheritance patterns have been reported. Currently, most authorities believe that the genetic influence occurs through polygenic or multifactorial transmission. It is reported that 5–50% of cases of POAG are hereditary, with the best estimate being 20–25%.¹⁰² The risk of developing POAG in first-degree relatives is 4–16%.^{102–107} The Rotterdam study found that relatives of patients with POAG were 10 times more likely to have or develop glaucoma than relatives of those without glaucoma.¹⁰⁸ In Australia, the odds ratio for first-degree relatives is 3.1 and a positive family history was the strongest risk factor for development of glaucoma.¹⁰⁹ A monozygotic and dizygotic twin study estimated the inheritability to be 13%.¹¹⁰ In a carefully done study of

laboratory-confirmed monozygotic twins and their spouses in Iceland, the concordance for open-angle glaucoma in the twins was 98%, much higher than in the spouse pairs.¹¹¹ In one study, the association was higher with a sibling affected than with a parent or child.¹¹² In the Barbados study, 25% of the siblings of patients with POAG had either POAG or were suspect for POAG.¹¹¹ Siblings of those individuals with glaucoma are more likely to have a higher IOP and a larger cup-to-disc ratio than siblings of those without glaucoma.^{113,114} Two longitudinal studies – one population-based and the other over 18 years in length – demonstrated a strong association between the development of glaucoma and positive family history.^{58,115}

Recently, studies have identified one gene (GLC1A) that is associated with juvenile-onset open-angle glaucoma and some (about 3–4%) cases of POAG in adults.^{116,117} This gene is located on chromosome 1 in the q23–25 region.¹¹⁸ Three different mutations of this gene have been identified in about 4% of patients with POAG.¹¹⁹ One particular mutation seems to account for most of the abnormal genes found in a population of glaucoma patients in India.¹²⁰ This mutation was only present in about 5% of the total glaucoma population. Yet another mutation has been identified in a Chinese family with juvenile-onset open-angle glaucoma.¹²¹ Another gene that has been associated with adult-onset open-angle glaucoma is located on chromosome 2 (GLC1B).¹²² Both of these genes associated with POAG in adults seem to be related to an early-onset type. Some well-established pedigrees have had abnormalities in neither of these genes (see Ch. 20). Allingham and co-workers have identified a mutation on chromosome 15 that accounts for a relatively large subset (17%) of early, but not childhood-onset, glaucoma.¹²³ Junemann and co-workers found a relatively high prevalence of polymorphisms in the methylenetetrahydrofolate reductase gene in POAG patients but not in exfoliative glaucoma patients in Germany.¹²⁴ A group from Australia identified a novel gene abnormality on chromosome 3 which occurs in a large Tasmanian family with early-onset open-angle glaucoma, one-third of whom have mutations in the myocilin gene and others with glaucoma show mutations on chromosome 3.¹²⁵ Another study found an association between an endothelial nitric oxide synthase gene and open-angle glaucoma accompanied by migraine.¹²⁶

All these studies open an exciting frontier and suggest that open-angle glaucoma may be associated with several different genes, each of which may produce a different time of onset and, perhaps, clinical course; furthermore, similar phenotypes can be seen with different mutations of different chromosomes even within the same family. The next few years should see some clarity in this area.

Several ocular factors associated with POAG – including IOP, outflow facility, and cup-to-disc ratio – appear to be genetically determined.^{127,128} For example, children and siblings of glaucoma patients are far more likely to have abnormal aqueous humor dynamics than are first-degree relatives of normal individuals.¹²⁹ Thus some of the polygenic inheritance of POAG may occur indirectly through these associated factors rather than directly through the disease itself.

SYSTEMIC FACTORS

Primary open-angle glaucoma has been linked to a variety of endocrine and vascular disorders. Several studies have shown a high prevalence of diabetes mellitus in patients with POAG, as well as a high prevalence of POAG in patients with diabetes.^{130–134} Although neither the Baltimore Eye Study nor the Diabetes Audit and Research in Tayside Study (DARTS) in the United Kingdom were able to find

an association of open-angle glaucoma with diabetes mellitus,^{135,136} but the most recent population studies strongly support an association with diabetes mellitus. These include the Blue Mountains Eye Study in Australia,¹³⁷ the Rotterdam Study,¹³⁸ and the Beaver Dam Eye Study in Wisconsin.¹³⁹ The explanation for this relationship remains obscure, but some investigators have proposed that diabetes affects the small blood vessels supplying the optic nerve, thereby rendering it more susceptible to glaucomatous damage.

Other investigators have proposed a relationship between POAG and thyroid disease.^{140–142} In one study, open-angle glaucoma was associated with chronic thyroid orbitopathy.¹⁴³ A more recent study confirmed the association of Graves' disease with not only open-angle glaucoma but also normal-tension glaucoma and ocular hypertension (not surprising as the IOP can be raised with restrictive muscle conditions).¹⁴⁴ However, not all studies have shown this association.^{145,145a} In the Veteran's Hospital in Birmingham, Alabama, an association was found between males with open-angle glaucoma and hypothyroidism.¹⁴⁶

Corticosteroid function and systemic vascular disease, and their relationships to POAG, are discussed in greater detail later in this chapter. Having open-angle glaucoma does not seem to influence mortality; this is an important observation since decisions about the intensity of treatment can be made against the background of typical life expectancy for age.^{147,148}

Vascular disease has long been suspected of contributing to glaucomatous damage. In the Barbados study, baseline systemic hypertension seemed actually to reduce the risk of incident open-angle glaucoma while low blood pressure (or more accurately, low perfusion pressure) seemed to increase the risk.¹⁴⁹ Studies of blood flow in and around the eye in the laboratory strongly suggest that blood flow is reduced or disordered in glaucoma.¹⁵⁰ However, whether this abnormal blood flow is a primary causal phenomenon or secondary to the optic atrophy has not been shown. One study of American veterans suggests that long-term oral statin or other anticholesterol use is associated with a lower risk of open-angle glaucoma.¹⁵¹ A subsequent study in a broader population has confirmed this observation.¹⁵² The Blue Mountains Eye Study suggests an association between open-angle glaucoma and migraine.¹⁵³

A few studies have linked primary open-angle glaucoma with sleep apnea.^{154–156} The mechanism of this is not clear but may relate to the respiratory disturbance leading to transient nocturnal episodes of hypoxia, which may increase the propensity of the optic nerve to damage.¹⁵⁷ However, not all studies have been able to confirm this association.¹⁵⁸

The Rotterdam study produced an unexpected and as yet unexplained association between early menopause and glaucoma.¹⁵⁹

PATHOPHYSIOLOGY

A detailed discussion of POAG must address two fundamental issues: (1) the mechanism(s) of IOP elevation, and (2) the mechanism(s) of progressive optic nerve cupping and atrophy.

DIMINISHED AQUEOUS HUMOR OUTFLOW FACILITY

It is generally accepted that the increased IOP seen in most cases of POAG is caused by a decreased facility of aqueous humor outflow. Although there have been a few reports of patients with

hypersecretion of aqueous humor, these reports were based on tonographic estimates of aqueous humor production rather than on direct measurements such as fluorophotometry. If the entity of hypersecretion exists, it must be exceedingly rare and therefore will not be discussed further here.

In enucleated normal human eyes, Grant¹⁶⁰ demonstrated that incising the entire trabecular meshwork reduced the resistance to outflow by 75%. This finding was confirmed by Peterson and co-workers.¹⁶¹ From this observation, most investigators inferred that the increased resistance to outflow seen in glaucoma must also lie between the anterior chamber and the lumen of Schlemm's canal.¹⁶² The main site of resistance to outflow is probably in juxtacanalicular tissue,¹⁶³ where the greatest concentration of mucopolysaccharides and the greatest phagocytic activity reside.¹⁶⁴ This was further confirmed by careful microcannulation and pressure measurements at various locations within the trabecular meshwork area; the resistance was found in a region 7–14 mm internal to the inner wall of Schlemm's canal.¹⁶⁵

It should be emphasized that not all authorities accept this hypothesis. Others have also proposed that outflow facility is reduced because the trabecular meshwork prolapses into Schlemm's canal, thus occluding the lumen and preventing circumferential flow of aqueous humor to the collector channels.^{166–169} The argument against this theory is that Schlemm's canal only collapses at very high levels of IOP. No evidence exists to show that the canal is occluded when IOP is in the range of 25–35 mmHg,¹⁶⁹ which is the situation in most eyes with POAG.

The decreased outflow facility in glaucoma has also been ascribed to an obstruction of the intrascleral collector channels. This obstruction could be caused by an accumulation of glycosaminoglycans in the adjacent sclera.^{170–173} Krasnov has proposed that POAG is really several different diseases with different sites of resistance.¹⁷⁴ He believes that obstruction in the collector channels accounts for approximately 50% of the cases of POAG. This theory was partially refuted by experiments that demonstrated that unroofing Schlemm's canal did not reduce resistance to outflow in glaucomatous eyes until the canal was entered; that is, no scleral blockage was noted.¹⁷⁵

If the hypothesis is accepted that the trabecular meshwork or the endothelium of Schlemm's canal is the site of the increased resistance to outflow in POAG, the question of what process interferes with normal aqueous elimination must be asked. Several theories have been proposed to explain this phenomenon, including those that follow:

1. An obstruction of the trabecular meshwork by foreign material. Several investigators have noted the accumulation of foreign material in the trabecular meshwork and juxtacanalicular tissue, including pigment, red blood cells, glycosaminoglycans,^{176,177} amorphous material,^{178,179} extracellular lysosomes,¹⁸⁰ plaque-like material,^{181–183} and protein.¹⁸⁴ Lütjen-Drecol and Rohen have postulated that the electron-dense material consists of collagen and elastin and that these materials are responsible for the increased resistance to aqueous outflow.¹⁸⁵ It is also possible that a normal constituent that is catabolized insufficiently or synthesized excessively obstructs the meshwork.

2. A loss of trabecular endothelial cells. Glaucomatous eyes have fewer endothelial cells than normal eyes, although the rate of decline in the two is similar.^{186,187} This suggests a premature aging process in glaucomatous eyes.¹⁸⁶ A loss of endothelial cells would interfere with various important trabecular functions, including

phagocytosis and synthesis and degradation of macromolecules. The lack of a complete endothelial covering could allow the trabecular beams to fuse.

3. A reduction in pore density and size in the inner wall endothelium of Schlemm's canal. The endothelium lining the inner wall of Schlemm's canal accounts for 10–20% of the total resistance.^{163,188} Ultramicroscopic pores can be found in the endothelium of the inner wall of Schlemm's canal, and they seem to be reduced in both size and density in open-angle glaucoma.¹⁸⁹

4. A loss of giant vacuoles in the inner wall endothelium of Schlemm's canal. Giant vacuoles may play a crucial role in moving fluid from the meshwork into the lumen of Schlemm's canal.^{179,190} A reduction in the number and size of these microstructures is seen in glaucoma. Alvarado and Murphy¹⁹¹ found a reduction in the area of 'cul-de-sacs' in the juxtacanalicular tissue in glaucomatous eyes; this reduction could account for the increased resistance to outflow.

5. A loss of normal phagocytic activity. Phagocytosis occurs in the trabecular meshwork continuously and represents the self-cleaning filter of the meshwork. It has been postulated that the trabecular endothelial cells lose their normal phagocytic activity or are overwhelmed by foreign material, which leads to cell death or migration from the beams.^{192,193}

6. Disturbance of neurologic feedback mechanisms. Nerves, whose function is unknown, have been found in the trabecular meshwork.¹⁹⁴ Nerve endings, some of which could be mechanoreceptors, have been located in the scleral spur of humans.¹⁹⁵ It has been speculated that these nerves could function to slow down aqueous formation or speed outflow when IOP is elevated. Theoretically, some interference with this feedback mechanism could lead to unchecked elevation of IOP.

Histopathologic study of the conventional aqueous drainage system from patients with POAG reveals a number of abnormalities, including those that follow (Fig. 17-1):

1. Alterations in the trabecular beams, including fragmentation of collagen, increased curly and long-spacing collagen, and coiling of fiber bundles^{170,196}
2. Thickened basement membranes
3. Narrowed intertrabecular spaces^{173,197,198}
4. Fused trabecular beams¹⁹⁹
5. Decreased number of trabecular endothelial cells^{186,199}
6. Reduced actin filaments²⁰⁰
7. Accumulation of foreign material^{179,181}
8. Decreased number of giant vacuoles
9. Narrowing of collector channels¹⁹⁹
10. Closure of Schlemm's canal^{199,201}
11. Thickened scleral spur.

However, these histopathologic changes must be interpreted with caution. Most of the glaucoma specimens are obtained at surgery; thus artifacts are common, and it is impossible to fix the tissues at their normal IOP levels. In addition, the specimens generally come from eyes with advanced damage. Furthermore, it is difficult to know whether the changes seen are primary phenomena or secondary to the effects of increased IOP or medical and surgical treatment. Finally many of the histopathologic alterations are also seen in older, normal eyes. In fact, some researchers have proposed that the outflow changes of POAG could be an acceleration of the normal aging process.¹⁸⁶



Fig. 17-1 Sagittal section through trabecular meshwork in open-angle glaucoma (trabeculectomy specimen). Basement membranes are thickened, trabecular sheets are widened, and curly collagen has accumulated (arrows). BM, Basement membrane; EL, elastic fibers; N, nuclei ($\times 7500$; inset $\times 15\,000$). (From Rohen JW, Witmer R: Graefes Arch Clin Ophthalmol 183:251, 1972.)

Although it is impossible to be sure of the fundamental defect of aqueous humor outflow in POAG, the balance of the evidence favors the trabecular meshwork or the endothelium of Schlemm's canal as the site of the increased resistance. If we accept this hypothesis, we must still ask why outflow facility is reduced in POAG. Various investigators have linked the increased resistance to outflow with altered corticosteroid metabolism, dysfunctional adrenergic control, abnormal immunologic processes, and oxidative damage.

Altered corticosteroid metabolism

Soon after the early descriptions of corticosteroid-induced IOP elevations, Armaly²⁰² and Becker and Hahn²⁰³ noted that patients with POAG were quite responsive to topical glucocorticoids. These researchers proposed that the IOP response to topical corticosteroids was inherited and that this inheritance was either the same as, or closely linked to, the inheritance of POAG.^{202,203} The corticosteroid hypothesis was then extended to include a generalized sensitivity to the effects of glucocorticoids in patients with POAG.

Various investigators noted patients with POAG had (1) increased plasma levels of cortisol;²⁰⁴ (2) increased suppression of plasma cortisol with different doses of exogenous dexamethasone;²⁰⁵ (3) continued suppression of plasma cortisol by dexamethasone despite concomitant administration of diphenylhydantoin (phenytoin);^{206,207} (4) disturbed pituitary adrenal axis function,²⁰⁸ and (5) increased inhibition of mitogen-stimulated lymphocyte transformation by glucocorticoids.^{209,210} Researchers postulated that endogenous corticosteroids affected trabecular function by altering prostaglandin metabolism, glycosaminoglycan catabolism, release of lysosomal enzymes,¹⁷⁶ synthesis of cyclic adenosine monophosphate,²¹¹ or inhibition of phagocytosis.²⁰⁹

The corticosteroid hypothesis came under attack as subsequent studies in glaucomatous patients failed to confirm the increased sensitivity of non-ocular tissues to the effects of glucocorticoids.^{212–216} In addition, the IOP response to topical corticosteroids was shown to lack reproducibility²¹⁷ and to be less controlled by inheritance than previously thought.^{218–220}

Recent data have re-opened the corticosteroid issue. Trabecular endothelial cells from patients with POAG have an abnormal metabolism of glucocorticoids, with increased levels of delta-4 reductase and reduced levels of 3-oxidoreductase.²²¹ The importance of this observation, and whether it represents a primary or a secondary change in the tissue, is unclear at present. Most recently, a gene mutation (GLC1A) has been associated with juvenile-onset glaucoma and a small fraction of adult-onset POAG.²²² Mutations of this gene (trabecular meshwork-inducible glucocorticoid response (TIGR)) are associated with the production of an abnormal glucocorticoid-inducible stress-response protein (myocilin) in the trabecular meshwork that may affect glycosaminoglycan and other glycoprotein metabolism, as well as cell-surface properties.²²³ In addition to giving a genetic basis for some types of glaucoma, the TIGR gene could tie in a possible role for corticosteroids in the glaucomatous process. Furthermore, patients who respond to topical steroids with a very high IOP are more likely to develop visual field loss than moderate responders.²²⁴ In this study, none of those who were low responders developed visual field loss.

Dysfunctional adrenergic control

In analogous fashion to the corticosteroid theory, others have proposed that the diminished outflow facility in patients with POAG could be explained by an increased sensitivity to adrenergic agonists. Various reports indicated that patients with POAG had (1) a greater IOP reduction after the administration of topical adrenaline (epinephrine);²²⁵ (2) a greater response to adrenaline (epinephrine) or theophylline in inhibiting mitogen-stimulated lymphocyte transformation,^{226,227} and (3) more frequent premature ventricular contractions after topical administration of adrenaline (epinephrine).²²⁵ Furthermore, ocular hypertensive subjects who demonstrated a fall in IOP greater than 5 mmHg after topical adrenaline (epinephrine) administration had a higher rate of developing visual field loss.²²⁸ However, additional studies have generally failed to confirm an increased sensitivity to adrenergic agonists in patients with POAG.²²⁹

Abnormal immunologic processes

Other investigators have explained the diminished aqueous humor outflow in POAG by abnormal immune responses. Increased levels of γ -globulin and plasma cells have been detected in the trabecular meshwork of patients with POAG.^{230,231} Furthermore, glaucoma patients were noted to have a high prevalence of antinuclear antibodies.^{232,233} However, subsequent, more detailed studies have

failed to confirm these findings.^{234–236} An association between POAG and certain human lymphocyte antigens was reported²³⁷ and then refuted by multiple studies.^{238–240} Endothelin-like immunoreactivity has been noted to be increased in the aqueous of glaucoma patients, suggesting a role for this molecule in IOP regulation.²⁴¹ Antibodies to heat shock protein, an indicator of cell stress, have been noted to be increased in the serum of glaucoma patients.²⁴² Evidence for immunologic factors in open-angle glaucoma, especially in the retinal ganglion cell layer, have led some to propose vaccination as a potential neuroprotecting treatment in glaucoma.²⁴³

Oxidative damage

Interest has developed in the question of whether the trabecular meshwork could be damaged by oxidative insult. The meshwork contains glutathione, which may protect the endothelial cells from the effects of hydrogen peroxide (H_2O_2) and other oxidants. This interesting hypothesis is still the subject of active research.^{244,245}

Other toxic influences

Lütjen-Drecoll has postulated that transforming growth factor (TGF) beta2 may be involved in the pathogenesis of open-angle glaucoma.²⁴⁶ Dan and co-workers have shown that there is a three-fold increase in the levels of plasminogen activator inhibitor in the aqueous humor of glaucoma patients compared to cataract patients without glaucoma.²⁴⁷ These findings suggest that this protein may play some role in the pathogenesis of increased IOP.

In summary, the cause of the trabecular dysfunction in POAG is unclear at present. To date, no single theory explains the pathophysiology.

OPTIC NERVE CUPPING AND ATROPHY

The second major issue to be addressed in the pathogenesis of POAG is the cause of the optic disc cupping and atrophy. This topic is dealt with in detail in Chapter 12. Cupping consists of backward bowing of the lamina cribrosa, elongation of the lamellar beams, and loss of the ganglion cell axons in the rim of neural tissue.²⁴⁸ Cupping is the hallmark of glaucomatous damage, although it is seen occasionally in ischemic states and compressive lesions in the posterior optic nerve and chiasm. Histologic studies indicate that optic nerve cupping includes the loss of all three elements of the disc – axons, blood vessels, and glial cells. Glial cells appear to atrophy as a secondary phenomenon, and some glial cells are present even in advanced stages of glaucomatous optic atrophy.^{249,250} Other investigators have reported selective loss of capillaries in the disc substance^{251,252} or in the peripapillary retina.^{253,254} These findings have not been confirmed, however and blood vessels actually seem to be lost in proportion to the loss of axons.^{249,255} A recent study of the submicroscopic histopathology and immunohistochemistry of the optic nerve showed fibrosis, arteriosclerotic changes and loss of capillaries in glaucomatous optic nerves compared to non-glaucomatous ones.²⁵⁶ These changes were not present in the higher IOP eyes with pseudoexfoliative glaucoma.

Most authorities believe that the lamina cribrosa is the site of glaucomatous optic nerve damage.^{255,257} The lamina is a relatively rigid structure that surrounds the densely packed axons. Furthermore, the lamina is the tissue that divides the higher IOP space from the lower subarachnoid pressure space. Early in glaucoma, the lamina is compressed. In the later stages of the disease, the lamellar sheets become fused, and the entire lamina bows backward.²⁵⁸

It is commonly accepted that increased IOP either directly or indirectly causes optic nerve cupping. The evidence for this can be summarized as follows:

1. Most patients with POAG have increased IOP, which generally predates by years the development of cupping and visual field loss.
2. Elevated IOP is a major risk factor for the development of POAG in glaucoma suspects.
3. Elevated IOP is the only known common element to a wide variety of secondary glaucomas.
4. In all animal models of glaucoma, elevated IOP precedes optic nerve damage and visual loss.²⁴⁸
5. Even in normal-pressure glaucoma, in which IOPs do not exceed the statistically 'normal' range, the degree of cupping is related to the level of IOP.^{46,47,259}
6. Mechanical changes in the topography of the optic nerve and in the lamina cribrosa are seen early in experimental glaucoma with elevated IOP in monkeys and are not seen in other forms of optic nerve damage.^{260,261}

Although IOP is certainly one risk factor, most investigators point to other factors that also affect glaucomatous cupping.^{248,262,263} They point to the observations that (1) a significant per cent of patients develop optic nerve cupping and visual field loss at normal levels of IOP; (2) some patients maintain normal optic nerves and visual function despite elevated IOP, and (3) the level of IOP does not correlate well with the progression of established POAG. However, these observations do not refute a linkage between IOP and optic nerve damage; rather they imply variable resistance of the optic nerve to pressure-induced damage. That is, some nerves are more sensitive to pressure than are others.

More than 130 years ago, Mueller²⁶⁴ proposed that elevated IOP led to direct compression and death of axons, whereas von Jaeger²⁶⁵ stated that ischemia was the cause of progressive glaucomatous cupping. Yamazaki and Drance reported abnormal retrobulbar circulation by color Doppler imaging in eyes with progressively worsening normal-tension glaucoma compared to those with stable glaucoma.²⁶⁶ Other studies have supported some abnormality in ocular circulation in patients with primary open-angle glaucoma and normal-tension glaucoma compared to secondary glaucomas. Although the debate over the role of mechanical versus circulatory factors continues to the present, most would agree that no one theory explains all of the observed phenomena and that each plays some role in at least some patients. The optic nerve damage from glaucoma is multifactorial and, at different times and in different eyes, may involve genetic susceptibility factors, mechanical forces, ischemia, loss of neurotrophic factors, and neurotoxicity. It also may be that actual ganglion cell death depends on the inability of astroglial cells to prevent or repair injury to the cell or its extracellular matrix regardless of the source of the initial trauma.²⁶⁷

CLINICAL FEATURES

SYMPTOMS

Primary open-angle glaucoma is usually described as an insidious, slowly progressive, bilateral condition. The adjective 'insidious' is appropriate because most patients are asymptomatic until the late stages of the disease. The few exceptions to this rule include

the occasional patient who notices a scotoma when performing a monocular visual task and the young patient who has sudden, severe elevations in IOP that cause corneal edema, halo vision, and discomfort. If patients are not diagnosed until they develop extensive glaucomatous damage, they become symptomatic from loss of fixation in one or both eyes or from loss of peripheral vision, which interferes with activities such as driving. The early stages of POAG usually develop slowly over months to years. As glaucoma advances, however, the pace accelerates. In a recent study from Melbourne, Australia, the prevalence of glaucoma increased from 0.1% in the 40- to 49-year-old age group to 9.7% in the 80- to 89-year-old age group; 50% of those found to have glaucoma were previously undiagnosed.²⁶⁸ Untreated open-angle glaucoma can and does lead to significant vision loss and blindness. The 10-year incidence, in an untreated Afro-Caribbean population, of unilateral blindness was 16% and of bilateral blindness was 11%.²⁶⁹ In another study of a treated Afro-Caribbean population, open-angle glaucoma was responsible for approximately one-fifth of the prevalent blindness.²⁷⁰

Quality of life is generally not affected early in glaucoma, but as the disease progresses or as treatment becomes more aggressive, quality of life may be impacted.²⁷¹ In fact, patients with glaucoma also tend to have other medical conditions which directly or indirectly through the required treatment may affect quality of life and even the ability to apply glaucoma medications;²⁷² this situation should be kept in mind when prescribing additional glaucoma medications.

FINDINGS

Primary open-angle glaucoma is generally a bilateral disease of adult onset; however, a juvenile-onset type is seen that is indistinguishable from the adult-onset variety except for a stronger genetic factor and a more aggressive course. At least one eye should have either characteristic damage to the optic nerve or retinal nerve fiber layer or characteristic visual field changes, open angles with no obvious abnormality, and absence of any other condition known to cause glaucoma. Primary open-angle glaucoma often is asymmetric on presentation, however, so that one eye may have moderate or advanced damage, whereas the fellow eye may have minimal or no detectable damage. In this situation, the clinician must not be fooled and mistakenly conclude that the patient has a unilateral secondary glaucoma.

Most patients of European or African ancestry with POAG have elevated IOPs in the range of 22–40 mmHg. A few patients may have much higher pressures, which occasionally reach levels of 60 or even 80 mmHg. Some patients will never have IOPs over 18 mmHg. These patients are said to have normal-tension glaucoma (low-tension glaucoma). It is important to remember that IOP fluctuates throughout the day and that patients with glaucoma undergo wider fluctuations than do normal individuals. Although most people reach their highest IOPs in the morning, others may reach their peaks in the afternoon or evening or follow no consistent pattern. Diurnal IOP measurements may be useful in some situations, including diagnosing POAG, explaining progressive damage despite apparent good pressure control, evaluating the efficacy of therapy, and distinguishing normal-tension glaucoma from POAG.

Most individuals have fairly symmetric IOP readings although asymmetric POAG does occur reasonably frequently. When pressure is higher in one eye, that eye usually has a larger cup and a more damaged visual field than the fellow eye. Marked differences in IOPs between the two eyes should raise suspicion of exfoliative syndrome or another form of secondary glaucoma.

A reduced outflow facility is the fundamental abnormality of aqueous humor dynamics in POAG.²⁷³ As glaucoma progresses, outflow facility declines progressively. Measurements of outflow facility by tonography are not part of the routine clinical assessment of glaucoma today. Single measurements of outflow facility do not help much in the diagnosis of POAG or in the assessment of the efficacy of treatment.

An *afferent pupillary defect* can be seen in patients with asymmetric or unilateral glaucoma. This finding, which is also referred to as *Marcus Gunn's sign*, is elicited by the swinging flashlight test. It has even been noted in patients with asymmetric cupping and normal kinetic visual fields.²⁷⁴

The angles are open in patients with POAG. The angles can be narrow, but there can be no peripheral anterior synechiae (unless caused by prior laser treatment or surgery), no apposition between the iris and the trabecular meshwork, and no developmental abnormalities of the angle. Moderate pigmentation of the meshwork is often present in proportion to the patient's age and race. Heavy pigmentation is suggestive of other disorders, including pigmentary glaucoma, exfoliative syndrome, trauma, and uveitis.

The crucial clinical findings in POAG are those that occur in the optic disc and visual field. Defects in the nerve fiber layer are also seen in most patients. These matters are presented in detail in Chapters 10 and 13 and are not discussed further here. Other findings include impairment of contrast sensitivity, temporal contrast sensitivity, loss of color perception, and other psychophysical impairments as outlined in Chapter 11.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of POAG includes conditions that can mimic any of the cardinal features of the disease, such as elevated IOP, cupping and atrophy of the optic disc, and visual field loss. Primary open-angle glaucoma must be distinguished from a variety of secondary and developmental glaucomas. These include exfoliative syndrome, pigmentary dispersion, trauma, anterior segment inflammation, subacute or chronic angle closure, elevated episcleral venous pressure, Axenfeld's and Rieger's syndromes, and corticosteroid administration. These conditions are usually distinguished from POAG by a careful history and clinical examination.

Optic disc cupping is typical but not pathognomonic of glaucoma. Cupping has been reported in association with arteritic and non-arteritic anterior ischemic optic neuropathy,²⁷⁵ as well as with compressive optic nerve lesions.²⁷⁶ At times, pits or colobomas of the optic nerve can be mistaken for enlarged cups,^{277,278} although the glaucomatous process can produce a pit-like appearance of the optic nerve.^{279,280} As a general rule, glaucoma causes more optic disc cupping than pallor, whereas the opposite occurs for most neurologic or ischemic diseases.²⁸¹⁻²⁸³

Many conditions can cause visual field loss that has an arcuate or nerve fiber bundle appearance.²⁸⁴⁻²⁸⁵ Box 17-1 lists some of these conditions.

TREATMENT

INDICATIONS

Generally the ophthalmologist institutes treatment when the patient either has the classic glaucoma triad of visual field loss,

Box 17-1 Differential diagnosis of arcuate scotoma

Chorioretinal lesions

- Myopic degeneration
- Atypical retinitis pigmentosa^{286,287}
- Photoreceptor degeneration^{288,289}
- Branch vein occlusion
- Branch artery occlusion
- Juxtapapillary chorioretinitis²⁹⁰

Optic disc lesions

- Drusen²⁹¹
- Pits
- Colobomas
- Papillitis
- Chronic papilledema²⁹²

Optic nerve lesions

- Arteritic and non-arteritic ischemic optic neuropathy
- Retrobulbar neuritis
- Exophthalmos
- Pituitary tumors
- Meningiomas
- Aneurysms
- Chiasmatic arachnoiditis

optic nerve cupping, and elevated IOP, or is at high risk of developing them. Other indications for treatment include progressive cupping without detectable visual field loss, the development of visual field loss, episodes of corneal edema caused by elevated IOP, and a vascular occlusion associated with increased IOP. In patients with asymmetric POAG (i.e., bilateral elevated IOP with unilateral optic nerve cupping and unilateral visual field loss), the other eye usually is treated aggressively because it has at least a 40% chance of developing visual field loss over a 5-year period.²⁹³

GOALS

The major goal of glaucoma treatment is to preserve good visual function for the patient's lifetime and prevent interference, in so far as is possible, with the quality of life. This is accomplished by lowering the IOP (until a better treatment comes along) to a level that will stop, or at least slow, the progression of optic nerve damage and its consequent vision loss. The treatment should maximize good visual function and comfort, as well as preserve a reasonable quality of life for the patient by minimizing the side effects from the treatment itself, the risk of vision loss and, in many cases, the costs associated with treatment.

For some years, doubt existed regarding the efficacy of pressure lowering for glaucoma. However, a spate of randomized, prospective clinical trials over the past decade have left no doubt that pressure lowering is effective both in slowing or stopping the progression of actual glaucoma and in reducing the risk of conversion from ocular hypertension to frank glaucoma.²⁹⁴ While at this point in history, we have many choices of pressure-lowering therapy, including medications, laser surgery and incisional surgery, no curative therapy exists for POAG, so one can only aim at controlling the disease. We can lower the IOP but as yet cannot directly protect the optic nerve or enable regeneration of damaged or dead ganglion cells. Although some improvement in optic nerve parameters can be expected in a minority of patients treated for glaucoma,

it is rare that substantive anatomic or functional improvement occurs after satisfactory pressure lowering.²⁹⁵ Medications that may stabilize or slow the progression of glaucomatous damage independent of pressure lowering are currently being developed but are not yet available for clinical use. Some medications may have neuroprotective properties in the laboratory but none has been absolutely proven clinically. Perhaps, by the time the next edition of this book is published, neuroprotective agents will have been shown effective and will be available for clinical use.

It is impossible to determine *a priori* what level of IOP is necessary to stabilize the patient's disease. Some patients suffer progressive damage at 16mmHg, whereas others tolerate IOPs of 40mmHg for long periods. A general rule is, however, that the higher the IOP, the greater the likelihood of progressive damage. The Advanced Glaucoma Intervention Study (AGIS) strongly suggested that patients with open-angle glaucoma need pressure lowering both in amount and consistently over time. Progressive damage is an indication that more aggressive therapy is needed to lower IOP. The decision to pursue more aggressive therapy is complicated because it must reflect not only the rate of progression and the state of the disease but also the patient's beliefs, preferences, age, general health, and life expectancy. Costs also need to be considered in many cases.

Target pressure

The current practice is to estimate the pressure level (range) below which further damage to the optic nerve is unlikely to occur (target pressure) and then aim to keep the IOPs consistently below this level or, at least, within the estimated range. The target pressure is estimated by noting the untreated level of IOP; the degree of optic nerve cupping and visual field loss; the family history of glaucoma;

the presence of any other aggravating conditions such as diabetes mellitus or arteriosclerotic vascular disease, and the rate of progression if known. In the average patient, the clinician should aim for a pressure 20–30% below the initial untreated pressure. With greater optic nerve damage (e.g., 0.8 disc diameter cupping or more), increasing age, and more risk factors, the target pressure should be lowered. The target pressure should be reassessed periodically and lowered if progression, optic nerve hemorrhage, or increase in risk factors occurs (see Chapter 22). One should also keep in mind that in the AGIS, not only was lack of progression associated with a low average IOP but also with no IOPs exceeding 18mmHg during the entire 6 years of the study.²⁹⁶ So, maintaining the IOP consistently below 18mmHg in the average glaucoma patient and lower yet in the patient with advanced disease seems like a reasonable goal. While lowering pressure definitely slows or stops progression in most patients, it does not do so in all patients and it is difficult to identify those who will progress or reliably determine target pressure from any baseline characteristics.²⁹⁷

TYPES OF TREATMENT

The usual progression of treatment in POAG is medical therapy, followed by laser trabeculoplasty, then filtering surgery. Several large, prospective controlled trials of glaucoma treatment have been completed (Table 17-3). In general, the studies show that lower IOPs tend to preserve vision better, and filtering surgery seems to achieve that best of the three modalities. Laser trabeculoplasty seems to be as effective as timolol for initial treatment of glaucoma. A few studies have been done comparing medical therapy and filtering surgery. Generally these trials have shown that filtering surgery is more

Table 17-3 Prospective, controlled clinical trials of initial therapy in primary open-angle glaucoma

Study	Target group	Purpose	Patients (n)	Follow-up (years)	Findings
Scottish Glaucoma Trial ²⁹⁸	Newly diagnosed primary open-angle glaucoma (POAG)	Medication vs. trabeculectomy	99	3.5	Trabeculectomy lowered IOP more than medication and protected better against further visual field loss
Moorfields Primary Treatment Trial ²⁹⁹	Newly diagnosed POAG	Medication vs. laser trabeculoplasty vs. trabeculectomy	168	5+	Trabeculectomy lowered IOP the most, laser trabeculoplasty (ALT) next and medication least. Medical treatment and ALT groups showed more visual field loss than trabeculectomy
Glaucoma Laser Trial (GLT) ³⁰⁰	Newly diagnosed POAG	Medication versus ALT	271	2.5–5.5	Initial ALT at least as effective as timolol in reducing IOP and preserving vision
Glaucoma Laser Follow-up Study ³⁰⁰	Newly diagnosed POAG	Medication versus ALT (long-term follow-up)	203	6–9	Initial ALT at least as effective as timolol in reducing IOP and preserving vision over 6–9 years
Early Manifest Glaucoma Trial (EMGT) ³⁰¹	Newly diagnosed POAG	ALT plus medication vs. observation	255	6	Treatment halved the rate of progression (53% vs. 26%). Lower IOP associated with less progression
Collaborative Initial Glaucoma Treatment Study (CGITS) ³⁰²	Newly diagnosed POAG	Medication versus trabeculectomy	607	5	Both medication and surgery had same visual field results at 5 years. Visual acuity worse early in study for trabeculectomy but same at 5 years

Modified from American Academy of Ophthalmology Preferred Practice Pattern: Primary open-angle glaucoma, 1996.

effective than medical therapy in preserving visual field but is associated with a greater loss of visual acuity and a higher incidence of cataract,^{303,304} although glaucoma itself as well as topical medical treatment are risk factors for cataract formation.³⁰⁵

Despite the findings of these controlled clinical trials, most experts, at least in the United States, continue to use medical therapy as the first-line approach in POAG (see Chs 21 through 28). The reasons for this approach include the relatively short effectiveness of laser treatment and even surgery as measured against the lifetime needs of the glaucoma patient and the relative safety of medical treatment. Trabeculectomy has the risk of profound visual loss or other significant complications. Although the side effects of medical therapy can be protean, they are rarely permanent and usually disappear after cessation of the particular offending treatment. In Europe, with the advent of the more potent antiglaucoma drugs, glaucoma surgery as primary treatment has declined.³⁰⁶ In general, the clinician should prescribe the safest drug or drugs for the patient in the lowest doses necessary to control the IOP at the desired level. It is important to measure IOP at different times of the day and at different intervals after drug administration to determine the response to therapy. The failure of medical treatment is usually judged by inadequate control of IOP, progressive visual field loss or optic nerve cupping, the appearance of an optic nerve hemorrhage, intolerable side effects of medication, or demonstrated (or admitted) poor compliance with therapy.

The clinician should use the patient's previous course in both eyes as a guide for judging the adequacy of therapy. For example, if an individual has progressive damage in either eye when IOP was in the range of 20 mmHg, and the pressure is at that level again, more aggressive treatment is probably indicated rather than waiting for further damage. Studies have shown that from a societal point of view (as well as the patient's), treating the disease adequately to prevent progression is more cost effective than trying to manage more advanced disease.³⁰⁷

In developed countries like the US and western Europe, the prostaglandin analogues are the usual first medications to try since their once a day regimen makes compliance easier and their side effects are relatively benign. The non-selective β -blockers are also popular because they can be given once or twice a day and have infrequent ocular side effects, although significant systemic side effects often occur after months of treatment. These two classes of medications represent the most effective for monotherapy.³⁰⁸ Wide variations occur in treatment patterns in the US and women are often treated less aggressively than men.³⁰⁹ When one medication lowers the IOP but not enough, a second medication can be added. However, if the first fails to lower the IOP a significant amount, then substitution is preferable. When a second or third medication becomes necessary, the use of combination drops may help compliance. Studies on compliance and persistence suggest that neither are achieved anywhere near the rate that doctors think.³¹⁰ Nevertheless, over 90% of patients can be expected to be controlled with medications over their lifetime. For the typical glaucoma patient, two or three medications would be the maximum suggested before resorting to laser or incisional surgery. At present, maximum medical therapy consists of a prostaglandin-like agent, a β -adrenergic antagonist, a topical carbonic anhydrase inhibitor, and an α -agonist. Most ophthalmologists recommend laser trabeculoplasty before resorting to miotics (except in aphakic or pseudophakic eyes), although these agents should not be forgotten as potential therapy. Systemic carbonic anhydrase inhibitors are rarely used unless surgery is not feasible or has failed.

When medical treatment fails or when at least two topical agents have been found wanting, argon or selective laser trabeculoplasty is the next therapeutic option for most individuals with POAG, as well as being the primary treatment for those unable or unlikely to use medical therapy (see Ch. 32). This technique reduces IOP substantially in 70–80% of patients. Most individuals continue to require at least some medical therapy after laser trabeculoplasty, although it is possible to reduce the number of medications in a significant percentage of patients.³¹¹ Unfortunately, in many patients, IOP rises again months to years after laser treatment. There seems little difference in the long-term outcome between argon and selective laser trabeculoplasty.³¹²

If medical treatment and laser surgery are inadequate to control POAG, filtering surgery is the next appropriate step. Filtering surgery controls IOP in approximately 80–90% of patients with POAG. Approximately one-third of Caucasian patients with POAG go on to filtration surgery according to one retrospective study in Minnesota.³¹³ Racial differences exist in the response to laser surgery and filtering surgery; for example, the AGIS showed that whites responded better to filtering surgery first compared to blacks who responded better to argon laser trabeculoplasty first.³¹⁴ Economics and the results of the Collaborative Initial Glaucoma Treatment Study (CIGTS), where surgical and medical therapy in newly diagnosed glaucoma patients were found to be equally effective at long-term pressure control, probably justify filtering surgery as the primary treatment in developing countries.³¹⁵

If one drainage procedure fails to control IOP or if the risk factors for failure are high (e.g., black African ancestry, youth, secondary glaucoma), many ophthalmologists repeat filtering surgery with an inhibitor of wound healing, such as 5-fluorouracil or mitomycin C. On the other hand, many use topical application or injection of these agents even in primary filtering operations. If two or more filtering surgeries have failed despite antifibrosis agents or there is a high likelihood of failure after a single filtering operation fails, a tube-shunt (glaucoma drainage) device such as a Molteno, Baerveldt, or Ahmed implant can be used. A recently concluded randomized controlled trial suggests that non-valved implants such as the Molteno or Baerveldt are as good if not somewhat better at controlling IOP at 1 year than a trabeculectomy in a previously operated eye. So, some would consider a tube-shunt procedure after the first trabeculectomy (or similar) fails.³¹⁶ It is also possible to reduce aqueous humor formation by treating the ciliary body with trans-scleral cyclophotocoagulation or endocyclophotocoagulation, although these are usually reserved for end-stage cases.

PROGNOSIS

The prognosis in POAG is determined by (1) the degree of optic nerve damage;^{317–320} (2) the height of the IOP;^{317,318,320–325} (3) the vulnerability of the disc tissue;³²⁶ (4) the presence of systemic vascular disease;³²⁷ (5) the compliance with treatment,³²⁸ and (6) the timeliness and appropriateness of treatment. Age is also a factor, as the older one gets the more likely the disease is to progress.³²⁹ Few prospective studies exist on the prognosis of untreated open-angle glaucoma. One such study, done on the island of St Lucia in the Caribbean, noted progression to end-stage disease over a 10-year period in about 35% of untreated eyes, with about 55% of eyes progressing.³³⁰ Generally, treated open-angle glaucoma progresses relatively slowly. In one study, approximately one-third of patients with open-angle glaucoma became worse over 9 years.³³¹ In another retrospective study done in Iowa on mostly Caucasian patients, 68%

of patients progressed over at least 8-years follow-up, as detected by visual field tests, with an average loss of about 1.5% per year.³³² Progression of optic cupping in treated patients as measured by stereo photography was about 0.0068 linear cup-to-disk ratio units per year; higher treated IOP were associated with more rapid progression.³³³ In Olmsted County, Minnesota, a retrospective study of all newly diagnosed glaucoma patients (mostly white) found the risk of less than 20/200 vision or less than 20° of visual field in one eye to be 27% over 20 years, and in both eyes, 9%.³³⁴ In another study with about 20 years of follow-up, only 20% remained stable and 80% progressed with about 17% becoming legally blind; about 40% of the blindness was caused by glaucoma.³³⁵ These two studies seem to have found about the same rates of blindness. In a retrospective study like this, many patients could have remained stable but died and therefore were not counted. On the other hand, bilateral blindness is uncommon in treated open-angle glaucoma and many of the unilaterally blind are blind at diagnosis.³³⁶ In the Barbados Eye Studies, the incidence of progression due to glaucoma alone over 4 years in treated eyes was about 1% to low vision (20/40–20/100) and 0.3% to blindness (20/200 or less).³³⁷ In this same group, those over 70 at the initial visit had a 22% chance of reaching 20/40 or less and a 7% chance of becoming blind; about one-fifth of these were due to glaucoma alone. These figures probably accurately represent the incidence of significant visual loss in an Afro-Caribbean population whose glaucoma is likely to be more severe at diagnosis and more progressive than that in patients of European descent.

In the Early Manifest Glaucoma Trial study where patients with early glaucoma were randomly assigned to treatment or no treatment, over 53% progressed during the 6 years of the study.³³⁸ Treatment halved the rate of progression and a 10% reduction in the rate of progression was manifest for each mmHg lowering of IOP achieved. As a general rule, the two eyes tend to react similarly so progression in one eye of someone with symmetrical glaucoma suggests that treatment should be more aggressive in both eyes.³³⁹ The greater the degree of visual field loss, the more progression is likely to occur.³⁴⁰

Several clinicians have noted that patients with advanced optic nerve cupping generally have a worse prognosis.^{317–320,341,342} Some authorities have explained this observation by stating that a damaged disc is more susceptible to further damage. An alternative explanation is that a disc with advanced damage has very few remaining axons, so that each nerve fiber lost is of greater importance. Some authorities propose that eyes with advanced damage require low-normal or even subnormal levels of IOP to stabilize the disease.^{319,343,344} One retrospective study demonstrated that patients having trabeculectomy in advanced medically uncontrolled glaucoma had about a 45% chance of becoming legally blind over 10 years, which means that over 50% were prevented from becoming blind by this treatment.³⁴⁵ Once again, as in previous studies, the more advanced the disease, the more likely the patient was to progress to legal blindness despite surgery.

In a recent 4-year prospective study of relatively large numbers (total >500) of patients with open-angle glaucoma – most with high pressures, some with low pressures, and some with secondary glaucoma – the risk factors for progression in those with high pressures were older age, advanced perimetric damage, smaller neuroretinal rim, and larger zone beta of parapapillary atrophy.³⁴⁶ Those with low IOPs showed only presence of disk hemorrhages at baseline as a risk factor. There were no differences between those with primary glaucoma and those with secondary glaucoma in the risk factors for progression.

As mentioned previously, some eyes can tolerate elevated IOPs for long periods, whereas others suffer progressive damage at

apparently normal levels of pressure. This phenomenon is usually explained by variable resistance of the optic disc to pressure-induced damage. Other factors that may be important include variable vascular perfusion to the optic nerve and differing compliance with treatment. Correlation between low blood flow velocity in the retinal artery circulation and progression has been noted.³⁴⁷ Although a very few clinicians believe that the natural history of POAG is not altered by treatment,²⁶³ the vast majority believe – based on several controlled studies – that control of IOP stabilizes the disease or slows its course in most patients.^{299,300,321,325,348,349}

One should not infer from this statement, however, that successful reduction of IOP can be equated with stabilization of the disease. Some patients have progressive visual field loss despite marked reductions of IOP by medical therapy, argon laser trabeculectomy, or filtering surgery.^{320,350–352} However, the overwhelming preponderance of evidence favors lowering IOP as the best current treatment that provides for both stabilization of the disease and the most cost-effective approach.³⁵³ It is important that patients realize the need for periodic follow-up for the remainder of their lives, even after treatment has reduced IOP. Clinicians must distinguish progressive glaucomatous damage from short- and long-term fluctuations in visual function, as well as from the slow decline in visual function that occurs with age.

Other prognostic factors stated to be important in POAG include the presence of an optic disc hemorrhage and a family history of glaucoma.^{322,354} Aung and co-workers noted that normal-tension glaucoma patients with the E50K mutation in the optineurin gene were three times as likely to progress as those without the mutation.³⁵⁵ Several studies have noted nocturnal drops in arterial blood pressure to be associated with progressive optic nerve damage.^{356,357} Patients with a poor life expectancy also are more likely to progress.³⁵⁸ Myopia was found to be associated with a better prognosis in one study.³⁵⁹

THE GLAUCOMA SUSPECT AND OCULAR HYPERTENSION

A patient may be considered a POAG suspect (i.e., more likely to develop glaucoma than the average person) on the basis of family history of the disease, a suspicious-appearing optic disc, or an elevated IOP. An individual who has a first-degree relative with POAG has approximately an eight-fold greater risk of developing the disease.^{360,361} Not all studies have confirmed this strong a relationship to family history.¹¹² However, prudence dictates that anyone with a first-degree relative (parent, sibling, or child) with POAG should have regular ocular examinations, including tonometry and ophthalmoscopy, every 1 or 2 years up to age 60, with increasing frequency over age 60. If additional risk factors exist, such as elevated IOP, thin corneas and/or black African ancestry, then more frequent examinations are in order. An individual with a suspicious-appearing optic disc (e.g., a large cup-to-disc ratio, slight asymmetry of the cups, slight irregularity of the rim, questionable nerve fiber layer dropout) requires a careful examination that includes tonometry, perimetry, and some method of recording the appearance of the optic nerve and nerve fiber layer such as photography or other imaging. Gonioscopy is also in order. The frequency of follow-up for such a person depends on the clinician's level of suspicion. The most common reason to consider a patient a glaucoma suspect is because of elevated IOP on routine examination or screening. This subject is discussed in the next section.

EPIDEMIOLOGY OF OCULAR HYPERTENSION

Individuals with IOPs of 21 mmHg (the statistical upper end of the 'normal' range) or greater, normal visual fields, normal optic discs, open angles, and absence of any ocular or systemic disorders contributing to the elevated IOPs are referred to as having *ocular hypertension*. Some clinicians prefer other names for this group, including glaucoma suspect, open-angle glaucoma without damage, and early glaucoma. The term used is not important as long as clinicians realize that they are dealing with individuals who are at greater risk of developing POAG but have not yet shown definitive evidence of the disease.

The concept of ocular hypertension is important because this set of findings occurs in 4–10% of the population over age 40.^{13,14,51,362} Ocular hypertension is present in up to 18.4% of people over 40 years old of black African descent compared with 13.6% of those of mixed race and only 4.6% of whites in the same age groups.³⁶³ In both Australia and Pakistan, IOPs over 21 mmHg occur in about 3.5% of the population.^{364,365} Ocular hypertension is clearly far more prevalent than POAG (Table 17-4). In the past, it was common to equate elevated IOP with POAG; that is, individuals with

increased IOP would develop glaucoma if they lived long enough. It is now clear that only about 0.5–1% of ocular hypertensive patients per year develop visual field loss as detected by kinetic perimetry (Table 17-5).^{367,369,370,372,376,377} Although threshold perimetry may be more sensitive than kinetic,³⁷⁸ it is unlikely that the number of ocular hypertensive patients converting to open-angle glaucoma would exceed 2% per year.

The Ocular Hypertension Treatment Study (OHTS), which randomly assigned 1600+ patients with IOPs between 24 and 32 mmHg and without visual field defects to observation or medical treatment that lowered IOP at least 20%, found that, at the end of 5 years, 9.5% of the observation group developed a glaucoma 'end point' whereas only 4.4% of the treated group did.³⁷⁹ The numbers were almost double when the African-Americans were considered separately, with 16% developing a glaucoma end point in the observation group and 8.4% in the treated group.³⁸⁰ This creates a dilemma about what to do with these individuals who are at increased risk for developing POAG. On the one hand, ophthalmologists want to intervene as early as possible to prevent optic nerve cupping and visual field loss. On the other hand, most ocular hypertensive individuals will complete their lives without developing substantial visual loss.

Thus, instituting treatment in all patients does not seem reasonable, taking into consideration the low incidence of conversion from ocular hypertension to frank open-angle glaucoma, as well as the cost, inconvenience, side effects, and frequent non-compliance. Note that even 4% of the total and 8.4% of the African-American treated patients in the OHTS study went on to develop progressive optic nerve change or visual field damage.^{379,380} This debate has been sharpened by recent studies showing that ocular hypertensive patients can lose as many as 40% or even 50% of their optic nerve axons despite having normal kinetic visual fields,³⁴⁴ or as many as 35% of their ganglion cells despite normal automated threshold perimetry.³⁸¹ Despite this finding, the current recommendation is that most ocular hypertensive individuals do not require medical therapy. Treatment should be reserved for those patients who demonstrate early damage and for those who are thought to be at high risk for developing glaucoma (see below). Newer modalities such as short-wavelength automated perimetry, frequency-doubling perimetry, and confocal laser ophthalmoscopy appear to be able to detect optic nerve functional damage and anatomic damage before they are seen with clinical examination or with standard threshold static

Table 17-4 Prevalence of abnormal intraocular pressure and glaucoma

Population	Prevalence of abnormal intraocular pressure (%)	Prevalence of open-angle glaucoma with visual field loss (%)
Ferndale, Wales ¹³	7.1	0.47
Bedford, England ¹⁴	3.0	0.76
Skovde, Sweden ¹²	3.3	0.41
Des Moines, Iowa ¹⁵	12.7	1.3
Blue Mountain, Australia ³⁶⁴	3.7	3.0*
Barbados, West Indies ^{24,363}	18.4	7.0
(black population)		
Barbados, West Indies ^{24,363}	4.6	0.8
(white population)		

Modified from Anderson DR: *Surv Ophthalmol* 212:479, 1977.
*Includes normal-pressure glaucoma.

Table 17-5 Prospective follow-up of ocular hypertensive subjects without treatment

Reference	Intraocular pressure	Follow-up (years)	Patients (n)	Per cent developing open-angle glaucoma
Sorenson ³⁶⁶	>20	15	55	7.4
Kitazawa ³⁶⁷	>21	9.5 (mean)	75	9.3
Linner & Stromberg ³⁶²	22–26	5	152	2.0
Graham ³⁶⁸	>21	4	195	0.5
Armaly ¹⁵	>23	5	198	0.5
Wilensky ³⁶⁹	>21	5–14	50	6.0
Linner ³⁷⁰	22–26	10	92	0.0
Lundberg ³⁷¹	>21	20	41	3.4
Perkins ³⁷²	>21	5–7	124	3.2
Schappert-Kimmijser ³⁷³	22–30	5	94	12.8
Hovding & Aasved ¹¹⁵	>21	20	29	27.6
Walker ³⁷⁴	>21	10	109	10.1
Coleman ³⁷⁵	24–32	5	818	9.5%

Box 17-2 Risk factors in ocular hypertension**Prospectively proven risk factors**

Thin corneas (<535 microns)
 Elevated intraocular pressures
 Increasing age
 Vertical cupping of the optic nerve (>0.6)
 Increased pattern standard deviation on threshold perimetry
 Abnormalities in the optic nerve with the scanning laser ophthalmoscope
 Pseudoexfoliation

Putative risk factors

- I. Sociodemographic factors
 - a. Gender (women)
 - b. Race (blacks and Hispanics)
- II. First-degree relative with open-angle glaucoma
- III. General medical status
 - a. Cardiovascular disease
 - i. Coronary artery disease
 - ii. Atherosclerosis
 - iii. Cerebrovascular disease
 - iv. Peripheral vascular disease
 - v. Abnormal cold pressor test
 - vi. Hypertension
 - vii. Aggressive antihypertensive therapy
 - viii. Hypotension
 - ix. Hemodynamic crisis
 - b. Endocrine disease
 - i. Thyroid disease
 - ii. Diabetes (some studies say a risk, others a protective factor)
 - iii. Acromegaly
 - iv. Cushing disease
- IV. Aqueous humor dynamics
 - a. Large diurnal variation in IOP
 - b. Rising IOP with time
 - c. Increased IOP in supine position
- V. Optic disc
 - a. Large cup-to-disc diameter ratio
 - b. Optic disc hemorrhage
 - c. Filling defects on fluorescein angiography
 - d. Parapapillary atrophy
- VI. Miscellaneous ocular findings
 - a. Myopia
 - b. Pigment dispersion
 - c. Central retinal vein occlusion

perimetry.^{382–385} The question of what constitutes early optic disc and visual field changes is addressed in detail in Chapters 10 and 13.

RISK FACTORS FOR DEVELOPMENT OF OPEN-ANGLE GLAUCOMA

The OHTS, which may be our best modern study of the fate of treated versus untreated ocular hypertensives, showed that 9.5% of untreated ocular hypertensives will go on to develop open-angle glaucoma as manifest by optic nerve changes or visual field changes in 5 years.^{7,50} Roughly 10% of ocular hypertensive eyes will develop evidence of visual field loss as measured by threshold perimetry over a 9–10-year period.³³¹ Another study in Sweden followed ocular hypertensives for a mean of almost 9 years and found a conversion rate for those without (pseudo)exfoliation of 27% based only on visual field measurements.³⁸⁶ Many parameters have been stated to be risk factors for the development of POAG (Box 17-2).

Unfortunately, no parameter taken alone has proven to be a useful risk factor because of the following reasons:

1. Most of the studies on risk factors dealt with one parameter in isolation. This type of univariate analysis is unlikely to shed light on a disease as complex as POAG.
2. In many studies, the investigators assumed that parameters that separated a group of glaucomatous eyes from a group of normal eyes were risk factors. Retrospective separation of groups is very different from prospective predictions.
3. Many putative risk factors were identified in retrospective or cross-sectional studies rather than in prospective studies. This makes it difficult to distinguish factors that have prognostic value (because they occur early in the disease process) from factors that are not helpful (because they occur late in the disease course).
4. Different studies used different populations, definitions, and examination techniques.

Intraocular pressure is the most obvious example of a single risk factor that fails to predict the development of POAG. Most ophthalmologists accept the link between elevated IOP and POAG. However, only 10% or so of the patients with elevated IOP have glaucomatous visual field loss.^{12–15,387} In addition, one-third of the persons detected with glaucomatous visual field loss have normal IOPs during their initial screening examination.^{12,14,15} Finally, many individuals can maintain normal visual function for long periods despite elevated IOP.^{115,366–372,388} Thus, although elevated IOP is associated with POAG, it is neither necessary nor sufficient for development of the disease.

Some investigators (Table 17-6) have carried out a more detailed multivariate analysis of risk factors. These researchers have identified elevated IOP, optic disc abnormalities, increasing age, family history of glaucoma, decreased outflow facility, and systemic vascular disease as the factors that best predict the development of POAG. In a retrospective study, Hart and co-workers³⁹² identified 96% of the eyes that developed POAG and 79% of the eyes that did not. In a prospective study, Drance and co-workers³⁹⁰ predicted 79% of the eyes that developed POAG and 74% of the eyes that did not. Once again, the OHTS study has come to the rescue. Using multivariate analysis, the OHTS team found that the risk factors for conversion from ocular hypertension to manifest glaucoma are thin corneas, older age, larger vertical and horizontal cup-to-disc ratio, larger pattern standard deviation, and higher IOP.³⁷⁵ Of all the risk factors, thin central corneal thickness was the most powerful.^{7,50} Note that when thin corneas are taken into account, being of African descent drops out as a risk factor. A second retrospective study has confirmed the importance of thin corneas as an important risk factor.³⁹⁴ The Swedish long-term study noted above randomized ocular hypertensives to either treatment with timolol or placebo for up to 10 years and found risk factors that were similar to the OHTS study (although they did not measure corneal thickness); the risk factors for conversion to open-angle glaucoma in this study were suspicious disk, older age, and higher IOP.³⁸⁹

Nerve fiber layer defects have been shown to precede visual field defects in ocular hypertensive eyes converting to open-angle glaucoma by as much as 4–5 years.^{395,396} Fluorescein angiographic filling defects in the optic nerve may precede development of visual field loss in ocular hypertensive patients.³⁹⁷ Other tests that have shown in longitudinal studies to predict those who have already developed early glaucoma or who will develop it in the future include blue-yellow perimetry,^{383,398} motion detection perimetry,^{399,400} pattern electroretinogram,⁴⁰¹ and optic nerve changes by scanning laser ophthalmoscopy.⁴⁰² Nerve fiber layer assessment by

Table 17-6 Risk factors for the development of primary open-angle glaucoma from studies employing multivariate analysis

Factor	OHTS ³⁷⁵	Bengtsson & Heijl ³⁸⁹	Drance et al ³⁹⁰	Kitazawa ³⁹¹	Hart et al ³⁹²	Armaly et al ³⁹³
Elevated IOP	Yes	Yes	Yes	Yes	Yes	Yes
Cupping of optic disc	Yes (vertical)	Yes	Yes	Yes	Yes	Yes
Increasing age	Yes	Yes	No	Yes	Yes	Yes
Thin cornea	Yes	NT	NT	NT	NT	NT
Family history of glaucoma	No	No	NA	Yes	Yes	Yes
Decreased outflow facility	NT	NT	NT	Yes	No	Yes
Diabetes	Protective	No	Yes	No	No	NT
Vascular disease	No	No	Yes	Yes	No	No
Poor visual acuity	No (excluded)	No	No	Yes	No	No
Increased pattern standard deviation	Yes	No	NT	Yes	NT	NT

Modified from Kass MA, and others: *Surv Ophthalmol* 25:155, 1980.
NA not applicable; NT not tested.

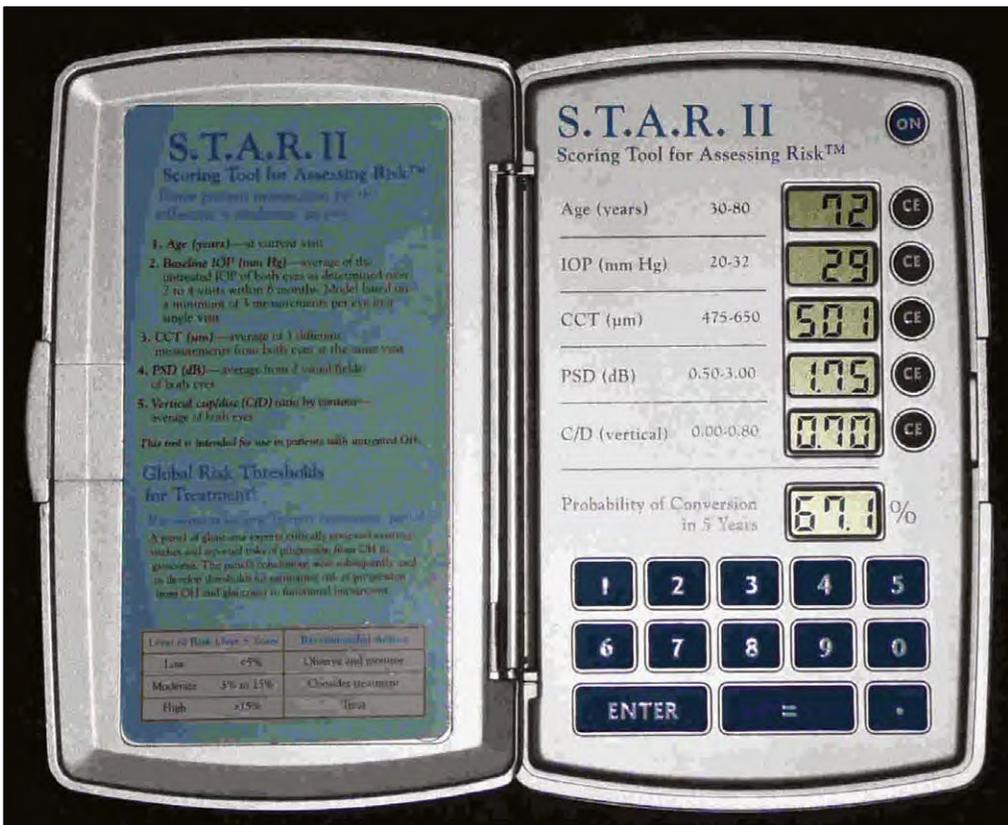


Fig. 17-2 The S.T.A.R. II Risk Calculator. In this illustration, a 72-year-old open-angle glaucoma suspect with an IOP of 29mmHg, a corneal thickness of 501 microns, a pattern standard deviation on threshold perimetry of 1.75 and a cup-to-disc ratio of 0.7 has a 67% chance of developing frank open-angle glaucoma within 5 years.

scanning laser polarimetry shows reduced nerve fiber layer levels in ocular hypertensive patients compared with normals;⁴⁰³ some think this may indicate very early neural damage. Tezel and co-workers⁴⁰⁴ retrospectively evaluated 175 ocular hypertensive patients over 10 years. Ninety eight of 350 eyes developed actual glaucoma over a 10-year follow-up period as measured by visual field changes, optic nerve damage, or both. Parapapillary atrophy, as well as larger vertical cup-to-disc ratio, and small neural retinal rim area-to-disc area ratio were associated with progression. Age, positive family history, and elevated IOPs were also correlated with progression. An enlarging area of parapapillary atrophy was also correlated with development of glaucoma.⁴⁰⁵ In a small subset of the OHTS patients who had scanning laser ophthalmoscopy during their

follow-up, abnormalities in some of the parameters as well as in the overall classification and the Moorfields' regression classification were identified as risk factors for progression to glaucoma.⁴⁰⁶ The cardiologists have been well ahead of the ophthalmologists in being able to assess risks of disease development. Fortunately, ophthalmology is catching up. Using the OHTS results, Medeiros and colleagues have developed a risk calculator for ocular hypertensives that can be helpful in predicting the relative risk for actual glaucoma development.⁴⁰⁷ They have validated this model in a prospective study independent of the OHTS group of patients. A scoring tool based on this model has been published by Pfizer Corporation (STARRII Risk Calculator) and, as of this writing, has been provided to ophthalmologists and others free of charge (Fig. 17-2).

Table 17-7 Prevalence of optic nerve and/or visual field damage at different levels of ocular hypertension

Reference	Intraocular pressure (mmHg)	Eyes (n)	Percentage with damage
Graham and Hollows ⁴⁰⁸	20–25	814	7
	26–30	291	12
	>30	53	28
Pohjanpelto and Palva ⁴⁰⁹	20–24	NA	–
	25–29	229	69
	30–34	71	11
	35–39	22	27
	40–44	10	7
	45–49	5	40
	50–54	2	100
Armaly ¹⁵	25–29	50	8
	30–34	4	25
	35–40	1	–
	>60	3	33
Stromberg ¹²	20–30	200	0.5
	30–36	14	29
	>36	29	72

Modified from Anderson DR: *Surv Ophthalmol* 21:479, 1977.
NA, Not applicable.

TREATMENT

An ocular hypertensive individual requires periodic examinations, including tonometry, perimetry, and optic disc assessment. Blue-yellow perimetry or frequency-doubled perimetry may be helpful in identifying the earliest glaucomatous visual field defects, although these techniques may have a more significant noise level that reduces specificity. Stereoscopic optic disc photographs provide baseline information against which one can determine changes in the optic nerve over time. Nerve fiber layer photographs may also be useful. Other, newer digital imaging tests such as confocal scanning laser ophthalmoscopy, ocular coherence tomography, and/or scanning laser polarimetry are just beginning to show evidence of detecting early optic nerve damage and change.⁴⁰⁶ Therapy should be instituted if early damage is detected or if the patient appears to be at high risk for developing POAG based on the risk factors identified above. Many clinicians institute medical treatments if the IOP is 30mmHg or greater, noting that the prevalence of glaucoma at this pressure level is 11–29% (Table 17-7).^{12,15,408,409} It may also be appropriate to recommend therapy for individuals with IOPs in the middle-to-upper 20s who also have one or more risk factors (Box 17-3). Following are other possible indications for treatment:

1. A one-eyed patient. Many clinicians are more aggressive in treating one-eyed patients.
2. A young patient. Some ophthalmologists prescribe medical treatment more rapidly for young patients who will be exposed to high pressure for many years. This may be questionable reasoning because, often, young optic nerves are more resistant to the effects of elevated IOP than are older ones.
3. Unreliable visual fields or optic disc assessment. The entire concept of following ocular hypertensive patients without

Box 17-3 Differential diagnosis of normal-tension glaucoma

- I. Glaucoma
 - A. Elevated intraocular pressure (IOP) not detected
 1. Undetected wide diurnal variation
 2. Low scleral rigidity
 3. Systemic medication that may mask elevated IOP (e.g., recent β -blocker treatment)
 4. Past systemic medication that may have elevated IOP
 5. Elevation of IOP in supine position only
 - B. Glaucoma in remission
 1. Past corticosteroid administration
 2. Pigmentary glaucoma⁴¹⁰
 3. Associated with past uveitis or trauma
 4. Glaucomatocyclitic crisis
 5. Burned-out primary open-angle glaucoma
- II. Optic nerve damage
 - A. Congenital optic nerve conditions⁴⁵
 1. Pits
 2. Colobomas
 3. Tilted discs
 - B. Ischemic optic neuropathy
 1. Arteritic
 2. Non-arteritic
 - C. Compressed lesions
 1. Tumors
 2. Aneurysms
 3. Cysts
 4. Chiasmatic arachnoiditis
 - D. Optic nerve drusen
 - E. Demyelinating conditions
 - F. Inflammatory diseases
 - G. Hereditary optic atrophy
 - H. Toxic drugs or chemicals
- III. Ocular disorders
 - A. Myopia
 - B. Retinal degeneration
 - C. Myelinated nerve fibers
 - D. Branch vascular occlusions
 - E. Choroidal nevus or melanoma
 - F. Choroidal rupture
 - G. Retinoschisis
 - H. Chorioretinal disease
- IV. Systemic vascular conditions
 - A. Anemia
 - B. Carotid artery obstruction
 - C. Acute blood loss
 - D. Arrhythmia
 - E. Hypotensive episodes
- V. Miscellaneous
 - A. Hysteria
 - B. Artifact of visual field testing

treatment rests on the clinician's ability to detect early damage. If this is not possible, treatment is indicated.

4. A patient who is content with treatment initiated by another physician and who is tolerating the medication well.
5. An ocular hypertensive patient who desires treatment.
6. An ocular hypertensive patient who has developed a vascular occlusion in either eye.

Regardless of the risk factors and the actual risks of developing open-angle glaucoma, the clinician should remember that these patients do not yet have disease, so their own thoughts and concepts

regarding treatment as well as the loss of the tiny amount of vision necessary to prove real disease, life expectancy and quality of life issues such as cost and potential for side effects can and should play a significant role in the decision of whether or not to treat; escalation of therapy into that which may have significant risks to vision, quality of life, or general health is only occasionally justifiable.

If a decision is made to initiate treatment, medication should be started as a therapeutic trial in one eye. Suitable agents include β -adrenergic antagonists, brimonidine, latanoprost, and topical carbonic anhydrase inhibitors. Monotherapy is desirable with a maximum of two medications most of the time. If common medical agents are not effective in lowering IOP or are not well tolerated, argon or selective laser trabeculoplasty can be considered or the patient can be followed closely without treatment; more aggressive therapy should have a very strong rationale before employment. Thus, miotics, systemic carbonic anhydrase inhibitors, and filtering surgery are rarely used in ocular hypertensive patients.

NORMAL-TENSION GLAUCOMA

The term *normal-tension glaucoma* refers to typical glaucomatous optic disc cupping and visual field loss in eyes that have normal IOP, open angles, and the absence of any contributing ocular or specific systemic disorders. This entity is often called 'low-tension glaucoma,' which is a misnomer because the IOP is usually at the upper end of the normal range and rarely low. Normal-tension glaucoma has long fascinated ophthalmologists because it can be a baffling clinical problem and also challenges traditional theories on the causal relationship between elevated IOP and optic nerve damage. Much has been written about possible differences between normal-tension glaucoma and POAG. However, it is still not clear if they are subtypes of the same disease, distinct entities, or separate conditions that have overlapping characteristics. It is likely that normal-tension glaucoma is not one but several different conditions with similar clinical appearance.

The definition of normal-tension glaucoma used in this chapter excludes cases of 'high-pressure' POAG that progress despite apparent good control of IOP.

PATHOGENESIS

Great controversy surrounds the pathogenesis of normal-tension glaucoma. Some authorities believe normal-tension glaucoma is a variant of POAG in which the optic discs demonstrate greater vulnerability to the effects of IOP.⁴¹¹ Other authorities believe normal-tension glaucoma and POAG have different etiologies.⁴¹¹⁻⁴¹³ Patients with normal-tension glaucoma have been noted to have a higher prevalence of hemodynamic crises,⁴¹⁴ hypercoagulability;^{411,415} abnormal ophthalmodynamometry;^{411,416,417} hypertension; hypotension;^{411,417,418} increased blood viscosity; elevated blood cholesterol and lipids;⁴¹⁹ carotid artery disease;⁴²⁰⁻⁴²² slowed parapapillary, choroidal, and retinal circulations;^{423,424} peripheral vasospasm,⁴²⁵ and migraine.⁴²⁶⁻⁴²⁸ However, many similar studies have found no difference in the prevalences of vascular disease in normal-tension glaucoma and POAG.⁴²⁹⁻⁴³⁵ Even if vascular disease occurs somewhat more frequently in normal-tension glaucoma, it does not imply different pathogeneses of the two conditions. Vascular disease may only reduce optic nerve resistance to pressure-induced damage. Thus, at present, no convincing evidence

shows that normal-tension glaucoma differs in its pathogenesis from POAG. Of course, both normal-tension glaucoma and POAG may be heterogeneous entities that include conditions with different etiologies.

It might be tempting to blame normal-tension glaucoma on errors from tonometry due to thin corneas.^{436,437} While this may be the culprit in some cases of normal-tension glaucoma, it is unlikely to explain the bulk of them. For example, a study of Japanese patients with normal-tension glaucoma failed to find that thin corneas play any role in the normal-tension glaucoma there.⁴³⁸

Multiple studies have shown abnormalities in local optic nerve or peripapillary blood flow in normal-tension glaucoma as measured by Doppler or laser flowmeters;⁴³⁹⁻⁴⁴² one such study was able to correlate local optic nerve blood flow abnormalities with functional deficits on the visual field.⁴⁴² It is difficult to know if these observations are related to cause or are secondary phenomena as a result of optic nerve atrophy or ganglion cell death. Pulsatile ocular blood flow, a possible measurement of ocular perfusion, was found to be reduced in normal-tension glaucoma compared to normals.⁴⁴³ Ophthalmic pulse amplitude, a related measurement, may be a marker for general ophthalmic blood flow; this parameter was found to be reduced in normal-tension glaucoma patients compared to normals and those with high-tension glaucoma.⁴⁴⁴ Nocturnal systemic hypotension or changes in blood flow may be related to progression of normal-tension glaucoma.^{445,446}

Several ocular and systemic characteristics have been associated with normal-pressure glaucoma. These include abnormal immunoproteins such as anti-Ro/SS-A positivity and heat shock protein antibodies indicating a possible autoimmune mechanism.⁴⁴⁷ Elevated plasma C-reactive protein levels as an indicator of vascular inflammation have been found in normal-tension glaucoma patients compared to normal ones.⁴⁴⁸ One study showed that almost 50% of Japanese patients with normal-tension glaucoma were found to have a normal internal carotid artery compressing the optic nerve compared to 30% of normal patients; the authors wonder if carotid compression could play some pathogenetic role in the condition.⁴⁴⁹ Normal-tension glaucoma patients may have a cerebral ischemic pattern like Alzheimer disease indicating a possible common pathway for the two conditions.⁴⁵⁰

Silent myocardial ischemia and ventricular extrasystoles occur more frequently in normal-tension glaucoma patients (45%), compared with 26% of patients with open-angle glaucoma and 12% of those with cataract (only slightly greater than age-adjusted normal rate).⁴⁵¹ Sleep disorders have been found to be associated with normal-tension glaucoma and could be considered a risk factor.⁴⁵²

Recently, mutations in the optineurin gene have been associated with normal-pressure glaucoma.⁴⁵³ Mutations and polymorphisms in this gene located on chromosome 10 seem to be present in about 15% of Japanese patients with normal-pressure glaucoma compared to 5% in the 'normal' population.⁴⁵⁴ Normal-tension glaucoma patients with the E50K mutation in the optineurin gene seemed to have a more severe disease and progressive course than normal-tension glaucoma patients without this mutation.⁴⁵⁵ Polymorphisms in the OPA1 gene mutations of which have been associated with dominant optic atrophy have been found in patients with normal-tension glaucoma, leading some to conjecture that normal-tension glaucoma may be a variant of dominant optic atrophy.^{456,457} However, a study of over 100 normal-tension glaucoma patients failed to find any clinical differences between those with and those without polymorphisms of the OPA1 gene.⁴⁵⁸ This issue remains to be resolved.

CLINICAL FEATURES

The clinical features of normal-tension glaucoma resemble POAG except for the absence of elevated IOP. In most cases, the IOPs cluster at the upper end of the normal range; that is, IOPs are more often 18 or 19 mmHg than 10 or 11 mmHg.^{429,459} Patients affected with this condition often have borderline or low facilities of outflow and wide diurnal and postural fluctuations of IOP.⁴³⁰ Some studies have shown peaks of IOP during the night or early morning – times that do not lend themselves to pressure measurements in the doctor's office.⁴⁶⁰ In one study, patients whose visual fields and optic nerves progressed during a 2.5-year follow-up were subject to higher mean and maximum IOPs than those who were stable.⁴⁶¹ In a prospective study, Shirai and co-workers showed that eyes with IOPs higher than 15 mmHg were twice as likely to progress over a 2-year period as those with IOPs below 15 mmHg.⁴⁶² Patients with wide variation in 24-hour IOP and with disc hemorrhage are at greater risk of progression.⁴⁶³

Some authorities believe the visual field and optic disc changes are identical in normal-tension glaucoma and POAG, whereas others state that subtle differences exist between the findings of the two conditions. Several researchers have reported that visual field defects are denser, steeper, and closer to fixation in normal-tension glaucoma than in POAG.^{303,304,464} However, other investigators have been unable to confirm this difference.^{424,465} Similarly, some authorities believe that the optic discs are more cupped in normal-tension glaucoma,^{103,413,466,467} whereas others believe the appearance of the optic discs is the same in the two disorders.^{411,468–470} Neither Tezel and co-workers⁴⁷⁰ nor Jonas⁴⁷¹ were able to find differences in the zones of peripapillary atrophy in normal-pressure glaucoma compared with those in POAG.

These varying opinions probably reflect the different ways in which the two diseases (if they are truly separate diseases) are detected. Most cases of POAG are detected because of elevated IOP. In contrast, most cases of normal-tension glaucoma are detected because of optic disc cupping. Because it is easier to detect a suspicious IOP than a suspicious optic disc, most cases of normal-tension glaucoma are diagnosed at a later stage of the disease process. When eyes with normal-tension glaucoma and those with POAG are matched for the degree of cupping, the pattern of visual field loss is identical.⁴⁷² Similarly, when eyes with normal-tension glaucoma and those with POAG are matched for the degree of visual field loss, the cupping is identical.

Patients with normal-tension glaucoma demonstrate several abnormalities on fluorescein angiography, including diffuse and focal hypofluorescence of the disc and abnormal transit time.^{473–476} These abnormalities are similar to those seen in POAG. Splinter hemorrhages are noted with greater frequency in patients with normal-tension glaucoma.^{411,477} Patients with normal-tension glaucoma show increased resistance of the ophthalmic artery compared with those with open-angle glaucoma as measured by a variety of indirect methods, including Doppler velocity.⁴⁷⁸

Some cases of normal-tension glaucoma are progressive, whereas others appear to be stable over long periods. Drance and co-workers^{414,479,480} have emphasized that the stable cases are often associated with previous hemodynamic crises, such as episodes of acute blood loss, arrhythmia, and hypotension. These patients are not likely to develop further visual loss unless they experience additional hemodynamic crises. This same group has suggested that there are two groups of glaucoma patients – one associated with vasospasm (migraine or Raynaud's phenomenon) and higher IOP,

and one associated with disturbed coagulation, biochemistry suggestive of vascular disease, and little association with IOP.⁴⁸¹ Others have identified a subgroup of normal-tension glaucoma patients (approximately one-third) who have focal 'ischemic' changes in the optic nerve and who are also more likely to have hypertension and other cardiovascular problems than those with 'typical' high-pressure open-angle glaucoma.⁴⁸² The Collaborative Normal-Tension Glaucoma Study in which patients with progressive normal-tension glaucoma were randomly assigned to observation or treatment showed that approximately one-third of patients progress at 3 years and about one-half at 5–7 years; in those who progressed, the progression was usually quite slow.⁴⁸³ This same study showed that risk factors for progression of untreated normal-tension glaucoma are migraine, female gender, and African ancestry.⁴⁸⁴ Age, level of IOP, and family history were surprisingly *not* risk factors for progression.

In most population-based studies that use perimetry and ophthalmoscopy, between one-third and one-half of the patients with glaucomatous visual field loss have normal IOPs on initial examination.^{13,14,21,22,96,372,485} Some of these individuals demonstrate elevated IOP on repeat examination and are then classified as having POAG.^{372,486,487} The relative prevalences of POAG and normal-tension glaucoma depend on the definition of normal IOP and the number of pressure measurements made.

As a rule, normal-tension glaucoma is seen in older individuals, especially those over age 60, although it is possible to see rare cases in those under the age of 50.^{22,488–490} The disease appears to occur more often in women than in men.^{411,489,491} A relatively high prevalence of normal-tension glaucoma is present in the Japanese population as compared with other racial groups.²¹ The Japanese population seems to be the only ethnic/racial group with such a high prevalence of normal-tension glaucoma.¹³ No clear association exists between normal-tension glaucoma and refractive error.¹³ Although there have been a few descriptions of families with normal-tension glaucoma,⁴⁹² most cases appear to be sporadic. However, a family history of some form of glaucoma is reasonably common in patients with normal-tension glaucoma.⁴⁹⁰

DIFFERENTIAL DIAGNOSIS

Many conditions can produce visual field loss and an abnormal appearance of the optic disc without an elevated IOP (see Box 17-3). Some clinicians refer to these conditions as 'pseudoglaucoma' or even include them under the heading of normal-tension glaucoma. This seems needlessly confusing, and as mentioned previously, the definition of normal-tension glaucoma used here excludes known ocular or systemic causes of visual loss. The term *pseudoglaucoma* should be abandoned because it adds little to our understanding of the disease process. Following are the most common entities in the differential diagnosis of normal-tension glaucoma:

1. Glaucoma. Intraocular pressure readings can be misleading because of diurnal variation, low scleral rigidity, thin corneas,⁴⁹³ or systemic medications that reduce pressure. Some patients demonstrate elevated IOP only in the supine position.^{494,495} Elevated IOP may have caused damage in the past and now may be in remission because of hyposecretion of aqueous humor that may occur in aged and diseased eyes.^{410,496,497} Intraocular pressure may be increased at times when the patient is not evaluated.⁴⁹⁸ The patient may be compliant with medications only on the days when he or she is seen by the ophthalmologist.

2. Congenital defects of the optic disc, including pits and colobomas.
3. Ischemic optic neuropathy.
4. Compressive lesions of the optic nerve, including tumors, aneurysms, and cysts.⁴⁹⁹
5. Retinal diseases, including retinitis pigmentosa and branch vascular occlusion.

WORK-UP

A careful history is the most important part of the work-up for normal-tension glaucoma. This should include questions about previous elevations of IOP, ocular trauma or inflammation, present and past medication use, exposure to toxins, and present and past health. It is especially important to ask about corticosteroid administration systemically, to the eye, the nasal passages, or the skin. Patients must be queried about hemodynamic crises, including blood loss, anemia, arrhythmias, transfusions, and hypotensive episodes. The ocular examination should include measurements of IOP at different times of the day and evening and in the sitting and supine positions. The slit-lamp examination should rule out (in so far as possible) pigmentary dispersion, exfoliative disease, recession of the chamber angle – conditions associated with wide swings in IOP. Auscultation and palpation of the carotid arteries may reveal obstructive disease. Depending on the results of the history and physical examination, some patients should receive a general medical work-up, a neurologic examination, serologic tests for syphilis, an erythrocyte sedimentation rate, measurement of hematocrit and hemoglobin levels, antinuclear antibodies, magnetic resonance imaging, Doppler imaging of the carotid arteries, and/or carotid angiography. Visual fields should be carefully perused and both right and left fields viewed simultaneously to find any evidence of respect of the vertical meridians. Even if one or two fields that may respect the vertical are found, a magnetic resonance image is indicated. However, if the history and physical examinations are unremarkable, routine computed tomography scans or magnetic resonance imaging is rarely of benefit. Generally speaking, extensive systemic work-ups should be reserved for those patients who are under 60 years of age, whose optic discs show more pallor than cupping, whose findings are atypical, whose IOPs are under 17 mmHg before treatment, or whose course is rapidly progressive despite apparently adequate treatment.

TREATMENT

Most clinicians believe that lowering IOP is the main thrust of treatment of progressive normal-pressure glaucoma. In a recent multicenter, prospective, randomization study comparing IOP reduction of 30% or more to non-treatment of progressive normal-tension glaucoma, pressure lowering significantly reduced the incidence of future progression.⁵⁰⁰ The survival curves began to diverge at about 1 year. Cataracts were significantly more common in the treated group, presumably because of filtering surgery. Not all patients progressed.⁵⁰¹ Therefore, patients with the stable form of the disease probably require no treatment. Based on this study, pressure-lowering treatment is clearly indicated in any patient with documented progression or with threatened fixation. Disorders such as anemia, arrhythmia, and congestive heart failure should be treated to prevent ischemia of the optic nerve.⁴¹² In patients with the progressive form of the disease, most clinicians advocate medication, argon or selective laser trabeculoplasty, and filtering surgery as needed to reduce IOP. Many of the traditional medications

such as miotics and β -blocking agents may not produce striking reductions of IOP because the baseline pressure levels are often 15–19 mmHg. In one study, these agents only produced an average 12–13% reduction.⁴⁹⁰ Topical agents including β -blockers, latanoprost, brimonidine, carbonic anhydrase inhibitors, and miotics may be used in whatever combination reduces pressure to below the target without side effects that significantly affect the patient's quality of life. Trabeculectomy does lower pressure and seems to slow but not necessarily stop the progression of the condition.^{502–504} Patients who have had successful trabeculectomy seem to do better if they also receive systemic calcium channel blocking agents.⁵⁰⁵

When beginning therapy, it is wise to determine a target pressure. The process is similar to that in high-pressure POAG. If the untreated pressures are in the high teens, then a target of 15 mmHg or less seems a reasonable place to start. If the untreated pressures are in the mid teens, then one should aim for pressures in the 10–12 mmHg range. It is unlikely that medical therapy can attain pressures much lower than this, although newer agents such as latanoprost and apraclonidine may produce a profound reduction of IOPs, occasionally even into the single-digit range.^{506,507} Once the target has been achieved, it might be wise to perform tonometry at different times of the day to be sure that IOPs are not spiking. This is especially important if visual fields or optic nerves appear to be progressing despite achieving target pressure levels. If this occurs and IOPs are not spiking, then lowering of the target pressure is in order.

Lowering pressure alone may not be the only factor because medications with similar pressure reduction capability may have different abilities to protect against visual field loss. In one study, dipivefrin was superior to timolol in preventing visual field progression despite similar pressure-lowering effects.⁵⁰⁸ A similar positive effect was noted for betaxolol compared with timolol, even though timolol had a more profound pressure-lowering effect.⁵⁰⁹ Betaxolol has also been shown to have some direct neuroprotective characteristics, as well as to produce increased blood circulation around the optic nerve.^{510,511} Brimonidine seems to have some neuroprotective effects independent of its pressure-lowering ability.⁵¹² Dorzolamide has also been shown to improve the blood-flow velocity in the vicinity of the optic nerve.^{513,514} Although the clinical significance of these studies has not been established, betaxolol, brimonidine, and dorzolamide seem to be reasonable agents to consider in low-tension glaucoma, especially if visual field loss or optic nerve damage is progressing with good IOPs.

Many clinicians believe medical therapy is not very helpful in halting the progression of normal-tension glaucoma.^{411,412,489} It is not clear if this opinion arose because the medications available previously were not as good as those we have now (so pressures were not lowered aggressively enough), or if the hypothesis is correct. The Collaborative Normal-Tension Glaucoma Study has clearly shown a beneficial effect of lowering IOP in this condition, at least for some patients.^{500,501} Hopefully, future studies will help us determine which patients are helped by pressure lowering and which are not.

Argon laser trabeculoplasty has been reported to lower IOP in normal-tension glaucoma.^{344,515} As with medical treatment, however, many patients do not respond dramatically. Other studies fail to find a clinically significant effect for laser trabeculoplasty in this condition.^{490,516,517} The bulk of the evidence suggests that argon laser trabeculoplasty is of limited benefit in normal-tension glaucoma but may be worth trying in patients who are reluctant to

undergo, or are high-risk candidates for, surgical intervention. Selective laser trabeculoplasty may be of benefit in patients with normal-tension glaucoma although large-scale studies are lacking. It seems worth trying as the risks are low.

Most clinicians believe that reductions of IOP to low-normal or even subnormal levels are necessary to stabilize progressive normal-tension glaucoma.^{344,489,497,518} The best way to achieve IOPs of 6–10 mmHg is through a full-thickness filtering procedure³⁴⁴ or through a guarded procedure such as trabeculectomy augmented by antifibrosis therapy in the perioperative period. Guarded procedures such as trabeculectomy without adjunct antimetabolite treatment often do not lower IOP below the level of 14–18 mmHg. Full-thickness filtering surgery is said to be most beneficial in those patients whose baseline IOPs are in the upper teens.⁴⁸⁹ Studies by de Jong and co-workers and Geijessen confirm that pressures in the range under 10 mmHg are possible with filtering surgery and that pressures in this range seem to stabilize the disease for most patients.^{490,519} The authors recommend that patients who continue to progress despite maximum tolerated medical therapy and argon laser trabeculoplasty undergo a trabeculectomy with adjunctive mitomycin C or 5-fluorouracil. If surgery stabilizes the situation, the fellow eye may be a candidate for filtration in the future.

Despite best efforts, and even with profound lowering of the IOPs, some patients still progress. Kitazawa and co-workers reported that 6 of 14 patients with normal-pressure glaucoma progressed even with IOPs below 11 mmHg. Risk factors for progression in this group included diabetes mellitus, positive family history, female gender, disc hemorrhage, prolonged cold recovery, increased systolic blood pressure, and history of systemic hemorrhage.⁵²⁰ Patients with advanced optic nerve damage also seem to be at greater risk of progression despite significant pressure-lowering treatment.⁵²¹

Recently, attention has turned to agents that might stabilize or improve normal-tension glaucoma by improving blood flow to the optic nerve or by improving nerve function. The serotonin antagonist naftidrofuryl has been reported to actually improve visual acuity and visual field performance in normal-tension glaucoma.⁵²² However, no confirmatory studies have been published.

Calcium channel blocking agents may increase optic nerve function and improve blood flow to the nerve.⁵²³ Netland and co-workers⁵²⁴ retrospectively studied patients with glaucoma who were taking calcium channel blocking agents for systemic conditions; the mean follow-up was 3.5 years. Fewer patients who were taking calcium channel blocking agents with normal-pressure glaucoma progressed than those not taking calcium channel blockers. This effect did not hold for POAG patients. Two studies have shown improvement in contrast sensitivity after systemic calcium channel blocker treatment, and in one study, some improvement of indirect measures of blood flow was shown in those patients displaying improvement in contrast sensitivity.^{525,526} Nilvadipine, a calcium channel blocker, improved blood flow around the optic nerve in patients with normal-tension glaucoma.⁵²⁷

Sawada and co-workers have shown prevention of visual field progression using brovincamine, a nimodipine-like agent, compared with placebo.⁵²⁸ A second study confirmed the apparent slowing of visual field loss in patients with very low IOP in association with brovincamine therapy.⁵²⁹ Unfortunately, calcium channel blocking agents have a high rate of significant systemic side effects such as flushing and orthostatic hypertension. Furthermore, several other studies have failed to show a positive effect of calcium channel blocking agents on the disease.^{530–532} Based on the data we have available at this time, it would seem that calcium channel blockers should be reserved for the patient whose glaucoma is deteriorating despite traditional topical agents and surgery.

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CHAPTER
18

Secondary open angle glaucoma

PIGMENTARY GLAUCOMA

Pigmentary glaucoma is a secondary form of open-angle glaucoma produced by pigment dispersion in the anterior segment of the eye.^{1,2} This condition constitutes 1.0–2.5% of the glaucomas seen in many Western countries.³ Pigmentary glaucoma generally occurs in young adults but has been described in adolescents and older individuals as well.^{1,4} The disease preferentially involves men, and the women affected usually are a decade older than the men.^{4–6} Pigmentary glaucoma occurs most often in white individuals; it is diagnosed rarely in blacks and Asians.^{1,5,6} There is a strong association between pigmentary glaucoma and myopia: the typical pigmentary glaucoma patient is a myopic white man in his twenties or thirties. One study of black patients found that the average age of onset was 73 years, and the patients were more often hyperopic than myopic, indicating that there may be a different mechanism of disease in this subgroup.⁷ Although there have been a few reports of familial pigmentary glaucoma,^{1,6,8} most cases appear to be sporadic.

Pigmentary glaucoma is characterized by the release of pigment particles from the pigment epithelium of the iris. These particles are carried by the aqueous humor convection currents and then deposited on a variety of tissues in the anterior segment of the eye, including the corneal endothelium (Fig. 18-1), trabecular meshwork (Fig. 18-2), anterior iris surface, zonules (Fig. 18-3), and lens. The loss of pigment from the iris is detected as a series of radial, spokelike, midperipheral transillumination defects. These defects can range in number from 1 or 2 to 65 or 70 and can be thin slits

or coalescent areas. They are best seen in a darkened room by a dark-adapted observer. The defects can be highlighted by shining a small slit beam through the pupil with the light perpendicular to the plane of the iris. On rare occasions, transillumination defects are hidden by very heavy iris pigmentation. Patients with pigmentary glaucoma have very deep anterior chambers, a concave appearance of the peripheral iris, and mild iridodonesis.^{9–11}

The deposition of pigment on the corneal endothelium generally takes the form of a vertically oriented spindle called *Krukenberg's*



Fig. 18-2 Goniophotograph of dense pigment in the anterior chamber angle.

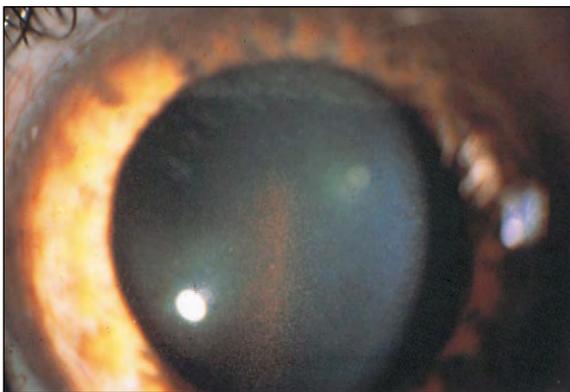


Fig. 18-1 Deposition of pigment on the corneal endothelium, referred to as *Krukenberg's spindle*.
(From Alward WLM: Color atlas of gonioscopy, St Louis, Mosby, 1994.)



Fig. 18-3 Pigment deposit on the zonules.
(From Campbell DG, Netland PN: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)

spindle (see Fig. 18-1), which can range in appearance from faint to striking. The spindle is neither pathognomonic of the disease nor invariably present, but it is a very useful sign. The spindle consists of extracellular as well as intracellular pigment granules phago-cytized by the corneal endothelium.^{12,13} Pigment also accumulates in the trabecular meshwork. In early cases of pigmentary glaucoma, the trabecular meshwork is moderately pigmented, with pigments varying from one portion of the meshwork to another. In advanced cases, the trabecular meshwork appears as a dark-brown velvet band that extends uniformly about the circumference of the angle (see Fig. 18-2). The pigment can cover the entire width of the angle from the ciliary face to the peripheral cornea; a pigment line anterior to Schwalbe's line is often referred to as *Sampaolesi's line*.

Pigment is also deposited on the zonules, posterior lens surface (Zentmayer's ring or Scheie's line), and anterior iris surface. The pigment on the anterior iris surface accumulates in the circumferential folds and can be sufficient to give a dull or even a heterochromic appearance if the pigment dispersion is asymmetric in the two eyes.⁵

The anterior chamber is very deep and the peripheral iris has a concave configuration when viewed at the slit lamp or with gonioscopy (Fig. 18-4). With the exception of pigmentary dispersion, pigmentary glaucoma resembles primary open-angle glaucoma (POAG) in most aspects, including elevated intraocular pressure (IOP), decreased outflow facility, optic nerve cupping, and visual field loss. Large diurnal IOP fluctuations are thought to occur more often in pigmentary glaucoma and can be sufficient to cause corneal edema, blurring, and halo vision. Patients with pigmentary glaucoma can have a sudden release of pigment with severe IOP elevations after pupillary dilation or exercise.¹⁴⁻¹⁸ At times, this release of pigment can be confused with active anterior segment inflammation. Pigment release and marked IOP elevation after exercise can be blocked by topical pilocarpine therapy.¹⁹

Several reports have indicated that pigment dispersion lessens with time so that Krukenberg's spindles and trabecular pigmentation become less prominent.^{4,5} In some cases, this is accompanied by an improvement in aqueous humor dynamics. Ritch has proposed that this disappearance of pigment may explain some non-progressive cases of normal-tension glaucoma.²⁰ That is, a patient who has optic nerve cupping, visual field loss, and normal IOP may have had pigmentary glaucoma and elevated IOP in the past.

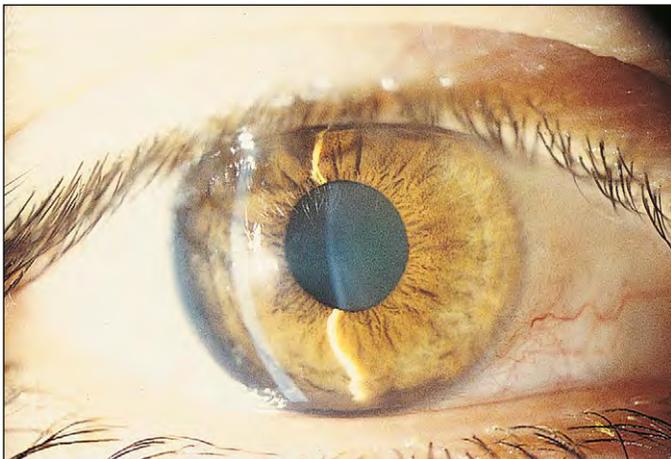


Fig. 18-4 Concave peripheral iris illustrated by an inferior slit beam in a patient with pigmentary glaucoma.

Remission of pigmentary dispersion also has been reported after glaucoma surgery⁶ and lens subluxation.²¹

The differential diagnosis of pigmentary glaucoma includes any condition that produces pigmentation of the trabecular meshwork. These include normal eyes with aging, POAG, uveitis, cysts of the iris and ciliary body, pigmented intraocular tumors, previous surgery (including laser surgery), trauma, angle-closure glaucoma, amyloidosis, diabetes mellitus, herpes zoster, megalocornea, radiation, siderosis, and hemosiderosis. These conditions should be readily distinguished from pigmentary glaucoma by the history and physical examination. The condition most likely to be confused with pigmentary glaucoma is exfoliation syndrome. However, the pattern of iris atrophy in exfoliation syndrome is usually central and geographic, and the pigment accumulation in the trabecular meshwork consists of larger particles that are unevenly distributed about the angle.

It is important to emphasize that many individuals have pigment dispersion without glaucoma or abnormal aqueous humor dynamics.²² Pigment dispersion syndrome (PDS) was found in 2.45% of 934 patients undergoing glaucoma screening,²³ and is thus much more common than pigmentary glaucoma, which results from a decreased facility of outflow following pigment deposition in the trabecular meshwork in a subset of patients with PDS. Pigment dispersion syndrome can be asymptomatic, and have varying levels of expression, and is therefore likely to be overlooked or underdiagnosed. The true prevalence of PDS in the population is not known; most cases of mild pigment dispersion are probably never detected. Pigment dispersion appears to be at least as common as pigmentary glaucoma and occurs with equal frequency in both sexes. In some cases, pigment dispersion progresses to pigmentary glaucoma over time, which can be as long as 12–20 years.¹ However, most individuals with PDS maintain normal visual fields and aqueous humor dynamics, even on long-term follow-up. This good prognosis is especially likely if the patient has a normal tonographic outflow facility when first seen.¹⁶ Generally the degree of pigment dispersion does not correlate well with the presence or future development of glaucoma.⁸ Patients with PDS and normal IOPs should receive a careful initial examination, including visual field examinations and optic nerve photographs. These individuals should then be followed up periodically without treatment.

Any theory about the pathogenesis of pigmentary glaucoma must explain two phenomena: pigment release and diminished outflow facility. Campbell has proposed a mechanical theory to explain pigment dispersion.⁹ He postulated that the concave shape of the peripheral iris allows it to rub against the zonules, causing pigment release and dispersion. Campbell noted that the pattern of iris transillumination defects corresponds with the arrangement of the anterior zonular packets.⁹ He also noted that the number and extent of the iris transillumination defects correlate with the progression of pigmentary glaucoma.⁹ When patients receive miotic treatment, the ensuing pupillary block lifts the peripheral iris off the zonules and allows the transillumination defects to fill in and even disappear. Lord and colleagues measured refraction, keratometry, and axial length of 13 patients with pigmentary glaucoma and 17 controls.²⁴ They found that the pigmentary glaucoma and PDS patients had flatter keratometry than myopic controls, suggesting a difference in their anterior segment architecture.

Not all patients with a diagnosis of pigmentary glaucoma show iridozonular contact on ultrasound biomicroscopy. Pillunat and colleagues studied 28 eyes of 28 patients with pigmentary glaucoma and found that iridozonular contact was present in only 10.²⁵ In these 10 eyes, laser peripheral iridectomy predictably relieved the

characteristic reverse pupillary block, and interestingly led to a 25% decrease in IOP (from a pretreatment mean of 24.6mmHg to a post-treatment mean of 18.3). In the 18 eyes without iridozonular contact, the pressure dropped only slightly, from 25.1 to 23.1. These findings differ from our experience in that we have had no success in lowering pressures in patients with pigmentary glaucoma and ultrasonically confirmed iridozonular contact. Perhaps iridectomy may help during phases of the syndrome when pigment granules are being liberated actively, but iridectomy seems unlikely to benefit established cases when the damage has been done. Richter and colleagues observed active pigment dispersion in 31 of 55 PDS and pigmentary glaucoma patients followed for between 6 and 43 months (mean 27 months).²⁶ Active pigment dispersion was defined as an increase in transillumination, an increase in corneal pigmentation, or the presence of pigment granules on the surface of the lens in the pupil. There were no differences in frequency of active dispersion or worsening of glaucoma in patients less than 44 years old, between 45 and 64, or over 65. Although we have not seen pressure lowering in pigmentary glaucoma patients following laser peripheral iridectomy, iridectomy may have prevented or limited future pressure rise.

In addition to the mechanical theory of pigment dispersion, Anderson and colleagues found that DBA/2J(D2) mice develop a form of pigmentary glaucoma involving pigment dispersion and iris stromal atrophy.²⁷ Using high-resolution mapping techniques, sequencing, and functional genetic tests, they showed that these conditions resulted from mutations in genes encoding melanosomal proteins. They postulate that pigment production and mutant melanosomal protein genes may contribute to human pigmentary glaucoma. Further study is needed to confirm this hypothesis.

When iris pigment is infused into animal or enucleated human eyes, outflow facility decreases and IOP increases.^{16,28} Repeated infusions of pigment, however, do not produce chronic glaucoma in animal eyes.²⁹ Some authorities believe that patients with pigmentary glaucoma must have an underlying developmental abnormality of the outflow channels. As evidence for this theory, they cite (1) the high prevalence of prominent iris processes in patients with pigmentary glaucoma;⁵ (2) patients with pigmentary glaucoma who have angles that resemble infantile glaucoma, and (3) families who have some members with pigmentary glaucoma and other members with congenital glaucoma.

Other authorities propose that pigmentary glaucoma is a variant of POAG. These investigators point to families that have members with both pigmentary glaucoma and POAG.⁵ However, patients with pigmentary glaucoma do not resemble those with POAG when corticosteroid testing is considered.³⁰

Histopathologic examination of specimens from eyes with pigmentary glaucoma demonstrates pigment and debris in the trabecular meshwork cells.^{31–33} With advanced disease, the trabecular cells degenerate and wander from their beams, allowing sclerosis and eventual fusion of the trabecular meshwork.^{31,33} Some propose that excessive phagocytosis of foreign material damages the trabecular endothelial cells and causes them to migrate.³⁴

The treatment of pigmentary glaucoma resembles that of POAG in that the usual progression is from medical therapy to argon laser trabeculoplasty (ALT) to filtering surgery. β -Adrenergic antagonists, adrenaline (epinephrine), dipivefrin, and carbonic anhydrase inhibitors (CAIs) are useful in the management of pigmentary glaucoma. Miotic agents reduce IOP in pigmentary glaucoma and are theoretically appealing because they increase pupillary block and lift the peripheral iris from the zonules. However, cholinergic drugs are generally poorly tolerated by these young patients. Some reports

also indicate that patients with pigmentary glaucoma have a high incidence of retinal detachment,⁶ thus a careful peripheral retinal examination is mandatory before cholinergic agents can be prescribed. Thymoxamine, an α -adrenergic antagonist, might be useful in this situation because it constricts the pupil without inducing a myopic shift in refraction.³⁵

The most intriguing therapy for pigmentary glaucoma is peripheral iridectomy to cure the 'reverse' pupillary block that is responsible for the characteristic peripheral iris concavity.³⁶ Ultrasonic biomicroscopy is helpful in indicating those eyes that are most likely to benefit from iridectomy.¹¹ In eyes with deep peripheral concavity, the effects of peripheral iridectomy are almost immediate. Within seconds of completing the iridectomy the peripheral iris moves forward and assumes a more normal configuration (Fig. 18-5). The long-term effects of peripheral iridectomy are unclear. Ideally peripheral iridectomy would provide effective prophylaxis for patients with PDS before they develop glaucomatous visual field loss. Although it is impossible to determine exactly which patients with pigmentary dispersion syndrome will develop glaucoma,³⁷ it may be most appropriate to treat patients at the first sign of significant IOP elevation. Patients who show elevation following exercise may also be good candidates for peripheral iridectomy.¹⁸ Pilocarpine and other miotics can reduce exercise-induced pressure rises, but parasympathetics routinely cause significant ocular side effects in the young adults most likely to have pigmentary glaucoma. Peripheral iridectomy has the same beneficial effects and is well tolerated by patients of all ages.

If medical management does not control IOP, ALT should be performed.³⁸ Because of the heavy pigmentation of the angle, ALT is done with relatively low energy settings in the range of 200–600 mW. Selective laser trabeculoplasty also works.

Many individuals with pigmentary glaucoma eventually require filtering surgery. Despite the young age of these patients, the results of surgery are generally successful.

As mentioned previously, pigment dispersion may diminish with age. Some patients require less medical therapy and eventually discontinue therapy as they reach 60 or 70 years of age. This does not occur invariably, however, and some individuals with pigmentary glaucoma require life-long treatment.

There have been several reports of pigment dispersion and secondary glaucoma from posterior chamber intraocular lenses (IOLs). This subject is discussed in the section on glaucoma after cataract surgery, p. 273.

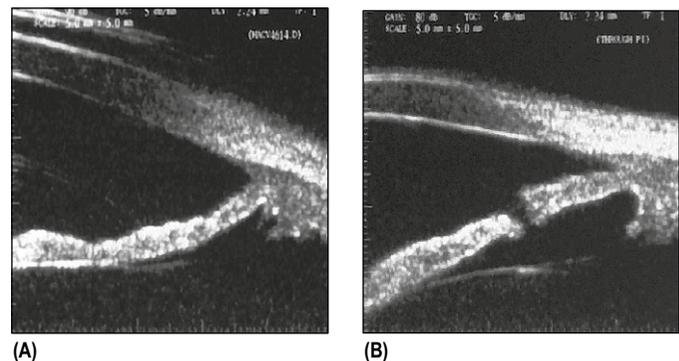


Fig. 18-5 Ultrasonic biomicroscopy of the anterior segment showing the iris before (A) and after (B) peripheral iridectomy in the same patient as in Figure 18-1. The iris configuration changes from concave to slightly convex.

EXFOLIATION SYNDROME (PSEUDOEXFOLIATION SYNDROME)

Exfoliative syndrome (previously or classically known as pseudoexfoliation syndrome) occurs when several ocular tissues synthesize an abnormal protein. This protein may obstruct the trabecular meshwork and cause glaucoma. Exfoliation syndrome and its associated glaucoma are known by a variety of other names, including pseudoexfoliation, senile exfoliation, senile uveal exfoliation, glaucoma capsulare, and iridociliary exfoliation.³⁹ At one time, most cases of exfoliation syndrome were diagnosed in Scandinavia. Although it is now clear that this condition occurs throughout the world, some areas seem to have a higher prevalence of the disease than do others, with particularly high rates in Scandinavia and parts of Africa.^{40,41} It is, however, difficult to compare the published prevalence of exfoliation syndrome precisely because various studies used different techniques and definitions and did not match the patients for age. The prevalence of exfoliation syndrome is closely linked to age, reaching a maximum in the seventh to ninth decades of life.⁴²⁻⁴⁴ The prevalence of exfoliation syndrome in the Framingham study was 0.6% in patients younger than 65 years of age, 2.6% in patients 65-74 years of age and 5.0% in patients 75-85 years of age.⁴⁵ Others have reported that exfoliation syndrome occurs in 3-28% of patients with open-angle glaucoma in the United States, with most estimates in the range of 3-10%.^{42-44,46} In the Blue Mountains Eye Study, the exfoliation syndrome prevalence was 2.7% of the entire population of 3645 that participated.⁴⁷ The prevalence of glaucoma among exfoliation syndrome patients was 14.7%. In contrast, in some areas of Scandinavia, more than 50% of patients with open-angle glaucoma have evidence of exfoliation. Exfoliation syndrome appears to be common among Russian immigrants to the U.S.A.

Exfoliation syndrome is more common in women than in men, but the combination of exfoliation syndrome and glaucoma occurs equally in both sexes.⁴⁸ Most cases appear to be sporadic, but Allingham and associates found a series of Icelandic families in which there appears to be an X-linked inheritance pattern.⁴⁹ In their study, Allingham and colleagues identified six Icelandic families that met the entry criteria of having at least three members over 70 years of age, at least one of whom had exfoliation syndrome. In each of these families, at least one person in the next generation had pseudoexfoliation and glaucoma. In all cases in which a parent and child were found to have exfoliation syndrome, the parent was always the mother.^{40,49}

Recently, a polymorphism in exon 1 of the LOXL1 gene has been found to be highly associated with exfoliative syndrome in Iceland and in Sweden where the prevalence of exfoliative syndrome is very high. The same polymorphisms have been confirmed in populations with exfoliative syndrome in other parts of Europe, India, the United States, Australia, and Japan.⁵¹⁻⁵⁶ These same polymorphisms are NOT associated with POAG and appear to be specific for exfoliative syndrome and glaucoma.⁵⁷ Unfortunately, the polymorphisms can not be used for diagnostic purposes since they appear quite frequently in the 'normal' population.⁵⁸ Whether these polymorphisms in normal individuals are truly markers for future development of exfoliative syndrome or glaucoma or whether some other genetic or environmental facilitator must be present to generate the syndrome remains unknown at this time. That some 'second hit', either genetic or environmental, must be present is hinted at by the study of Hewitt and co-workers⁵⁵ which suggests that Australians of European extraction have a much lower penetrance from the polymorphisms than in the

Nordic peoples. The LOXL1 family of proteins is associated with extracellular matrix formation and stability so it is not surprising that formation of abnormal proteins by genetic variants might affect trabecular outflow and the lens epithelium, among other structures.⁵⁹ Inhibitors of matrix metalloproteinases have been found to be upregulated and actual matrix metalloproteins have been found to be downregulated in the aqueous humor of eyes with exfoliative syndrome compared to eyes without.⁶⁰

One-third to one-half of the cases of exfoliation syndrome are unilateral at detection, but 14-43% of these cases become bilateral over 5-10 years.^{48,61} The prevalence of glaucoma in exfoliation syndrome is reportedly 0-93%.⁴⁸ However, many of these studies diagnosed glaucoma on the basis of elevated IOP or even abnormal provocative tests. Using strict definitions, recent studies detected glaucoma in 6-7% of patients with exfoliation syndrome and detected elevated IOP in an additional 15%.^{48,62,63} In patients who had exfoliation syndrome and normal IOPs at diagnosis, glaucoma developed in 3-15% over 3-15 years.^{41,48,61} In the Ocular Hypertension Treatment Study, the rate of new glaucoma among untreated ocular hypertensive patients was approximately 2% per year.

Exfoliation syndrome is not associated with any known systemic disorder. However, a retrospective study suggests that patients with exfoliative syndrome have a higher risk of developing acute cerebrovascular diseases and chronic cerebral conditions such as Alzheimer disease than those with POAG.⁶⁴ However, this same group was unable to show any overall increase in mortality associated with exfoliative syndrome except as related to use of acetazolamide.⁶⁵

Another study showed higher levels of plasma homocysteine in exfoliative patients compared to those with normal-tension glaucoma.⁶⁶ Increased levels of plasma homocysteine have been associated with increased risk of cardiovascular disease. It is clear that prospective longitudinal studies are needed to determine if these associations noted in retrospective and cross-sectional studies are truly clinically important.

The clinical presentation of exfoliation syndrome includes a classic pattern on the anterior lens surface consisting of a central translucent disc surrounded by a clear zone, which in turn is surrounded by a granular grey-white ring with scalloped edges (Fig. 18-6). This is best appreciated when the lens is examined with the slit lamp after pupillary dilation; if the pupil is not dilated, many cases can be missed because the characteristic ring may not be visible within a small pupil. The central and peripheral zones can be entirely separate or can be joined by bridges of material. It has

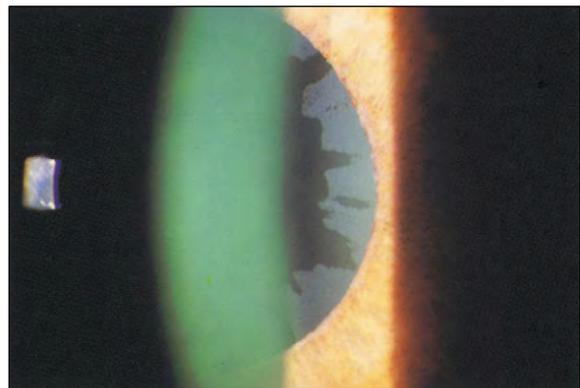


Fig. 18-6 Exfoliation material on the lens.
(From Alward WLM: Color atlas of gonioscopy, San Francisco, 2000, Foundation of American Academy of Ophthalmology.)

been postulated that the movement of the central iris polishes the lens and produces the clear zone. In some cases, the central disc is not present. The peripheral zone may have radial striations and raised edges. Dandruff-like flakes of exfoliation material are deposited on the corneal endothelium, trabecular meshwork, anterior and posterior iris, pupillary margin, zonules, and ciliary processes as well as the anterior hyaloid face in aphakic eyes. The peripupillary iris has an irregular, moth-eaten pattern of transillumination. This is often the finding that alerts the examiner to the possibility of exfoliation syndrome. The pigment released from the iris is deposited in the trabecular meshwork, in the anterior iris, and to a lesser extent on the corneal endothelium. The angle pigmentation is moderate to heavy in amount and somewhat patchy in distribution. A wavy pigmented line (Sampaolesi's line) may be seen anterior to Schwalbe's line. When the pupil is dilated, a shower of pigment may be released. Fluorescein angiography of the iris reveals a decreased number of vessels, neovascularization, and leakage from the vessels that remain.^{67,68}

The treatment of glaucoma associated with exfoliation syndrome is similar to that of POAG. Intraocular pressure is usually higher in exfoliation syndrome, however, and the response to medical treatment is less favorable.⁶⁹ Argon laser trabeculoplasty has its greatest pressure-lowering effect in exfoliation syndrome.^{70,71} Somewhat paradoxically, however, the ultimate success rate of ALT in patients with exfoliation syndrome may be lower than that in other conditions because the initial pressures are higher and because adjunctive medical therapy is less effective. Further, in many successfully treated eyes, the IOP rises again in 12–36 months. Filtering surgery has a high rate of success in this condition.⁶³ Jacobi and colleagues have suggested trabecular aspiration, a non-filtering procedure performed with a suction canula, to clear debris from the trabecular meshwork in cases of exfoliation syndrome.⁷² Short-term follow-up has been encouraging, but longer term follow-up has not been encouraging; a larger multicenter trial will be necessary to determine if this procedure is a viable alternative to intensive conventional therapy.⁷² Several authors reported that eyes with exfoliation syndrome have fragile zonules and a greater incidence of zonular rupture and vitreous loss during cataract surgery.^{73–75}

On microscopy the exfoliation material appears as a fibrillar protein arranged in an irregular meshwork.^{76,77} Evidence of exfoliation syndrome is widely distributed in the ocular tissues and may affect the rigidity of the lamina cribrosa.⁷⁸ This material has been compared to zonules, basement membrane,^{79–81} microtubular constituents,^{82,83} and amyloid.^{76,84} At one time, many thought that all of the exfoliation material came from the lens capsule and epithelium. However, the material has a multifocal origin and has been found in the iris, ciliary epithelium, and conjunctiva as well as in ocular and orbital blood vessels.^{80,84–88} Exfoliative material has been found in the skin of the eyelid in patients with the syndrome.⁸⁹

Schlötzer-Schredhardt and associates found an abnormal relationship between matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitor of metalloproteinases (TIMPs).⁹⁰ They postulate that this abnormal relationship leads to the development and precipitation of the exfoliative material in exfoliation syndrome.⁹⁰ Pseudoexfoliation syndrome with glaucoma appears to be a secondary glaucoma in which exfoliation material and pigment obstruct the trabecular meshwork.^{32,91–93} Ho and colleagues confirmed the finding of inhibitors of matrix metalloproteinases in the aqueous humor of eyes with exfoliation syndrome.⁹⁴ They conclude that there is downregulation of proteolytic activity in the trabecular meshwork leading to clogging. A few authorities have

postulated an underlying defect of the outflow channels and supported this theory by finding a few patients with unilateral exfoliation and bilateral glaucoma.^{42–44,92} However, many patients with apparent unilateral disease have bilateral pseudoexfoliation that can be demonstrated by conjunctival biopsy.⁹⁵ In addition, most patients with unilateral pseudoexfoliation syndrome have more abnormal aqueous humor dynamics in the affected eye.⁹⁶ Finally, patients with exfoliation syndrome and glaucoma resemble the normal population rather than patients with POAG in their corticosteroid responsiveness. One investigator has postulated a developmental defect in eyes with pseudoexfoliation syndrome and glaucoma,⁹⁷ but this has not been confirmed.

CORTICOSTEROID GLAUCOMA

Corticosteroid administration can produce a clinical picture that closely resembles that of POAG, with elevated IOP, decreased outflow facility, open angles, and eventually optic nerve cupping and visual field loss. Classic studies by Armaly^{98,99} and Becker¹⁰⁰ indicate that 5–6% of normals develop marked IOP rises after 4–6 weeks of topical dexamethasone or betamethasone administration. However, an even higher percentage of normal individuals develop substantially increased IOPs if the glucocorticoid is administered in greater frequency, at higher doses or for a longer period. Certain groups in the population are particularly susceptible to the pressure-raising effects of glucocorticoids. These groups include patients with POAG,^{98,101,102} their first-degree relatives,^{100,103,104} diabetic patients,¹⁰⁵ and highly myopic individuals.

Patients who experience a transient or sustained pressure rise after corticosteroid instillation are referred to as steroid responders; if glaucomatous damage ensues as manifested in the optic nerve or on visual field testing, then they truly can be said to have steroid glaucoma. Steroid-induced ocular hypertension would be a more accurate designation in most cases.

Most cases of corticosteroid ocular hypertension or glaucoma are caused by drops or ointments instilled in the eye for therapeutic purposes. However, glucocorticoid creams, lotions, and ointments applied to the face or eyelids may reach the eye in sufficient quantity to raise IOP,^{106,107} as may systemically-administered corticosteroids.^{108–110} This latter category includes glucocorticoids used topically on the skin that may be absorbed and produce systemic and ocular effects.^{111,112}

In addition, periocular corticosteroid injections, especially those involving repository or 'depot' preparations, are capable of raising IOP.^{113–115} Sometimes, the IOP rise occurs months after the injection; if not monitored, optic nerve damage could occur.¹¹⁶ If IOP elevation persists and/or optic nerve damage does occur following a periocular injection of depot corticosteroid, removal of the repository of periocular steroid often allows the IOP to return to non-dangerous levels.¹¹⁷

Recently, intravitreal injection of triamcinolone acetonide has become popular as a treatment for diabetic macular edema, macular edema associated with retinal vein occlusion, and various posterior pole inflammatory diseases. Approximately 30% of eyes having this treatment will show a transient IOP rise.¹¹⁸ In some patients, the IOP rise persists and may require topical medication, laser trabeculoplasty or even trabeculectomy to lower the pressure and prevent optic nerve damage or progression of optic nerve damage.^{119,120} Patients with pre-existing glaucoma, younger age, increased dose of

triamcinolone, higher baseline IOP, uveitis, and repeat injections are risk factors for elevated IOP in the post-injection period.^{121,122}

There have been several case reports of increased IOP following use of a corticosteroid inhaler for asthma,^{123,124} and we have seen at least two cases in which intractable IOP elevation followed the use of a corticosteroid nasal spray for allergic rhinitis. Corticosteroids used in nasal sprays get into the bloodstream in sufficient quantities over the long term to be associated with central serous retinopathy in susceptible patients;¹²⁵ it is reasonable to assume that something similar happens in those susceptible to steroid-induced elevated IOP. In rare cases, glaucoma is produced by endogenous glucocorticoids associated with adrenal hyperplasia or adenoma.^{126,127}

The rise in IOP from corticosteroids may occur within a week of initiating treatment or may be delayed for years. Patients undergoing long-term glucocorticoid treatment must be examined periodically because no time limit exists for this problem. Tragically, many cases of corticosteroid glaucoma are produced by treatment for trivial conditions such as contact lens discomfort or red eyes. In part because of their widespread availability and general effectiveness, combination steroid-antibiotic eyedrops are prescribed routinely by the general medical community for red eyes. In many such cases, the IOP is neither measured nor followed. The overwhelming majority of patients tolerate a short course of these medications quite well, but a small percentage are unusually susceptible to steroid-induced pressure elevation. Other patients are inappropriately allowed to refill steroid drops for an extended period of time. These patients are at significant risk of developing a dangerous elevation of IOP.

There have been several reports of moderate to severe IOP elevation in patients treated with corticosteroid eyedrops following laser-assisted in-situ keratomileusis (LASIK).¹²⁸⁻¹³⁰ The elevated pressure can cause vision-threatening corneal opacity. These cases can be particularly challenging because of the difficulty in obtaining an accurate measurement of the true IOP in the postoperative period (or, in fact, anytime after LASIK because of the subsequent very thin cornea).

As stated, corticosteroid glaucoma usually resembles POAG. However, the clinical picture may be altered by the age of the patient. Infants treated with corticosteroids may develop a condition that resembles congenital glaucoma.¹³¹⁻¹³³ In contrast, elderly patients who received corticosteroid treatment in the past may have normal-tension glaucoma. The clinical picture of corticosteroid glaucoma may also be confounded by the presence of other ocular diseases. For example, a patient with shallow anterior chambers and corticosteroid glaucoma may appear to have chronic angle-closure glaucoma.

Glucocorticoids raise IOP by lowering outflow facility through an unknown mechanism.⁹⁸ The most common explanation for this phenomenon has been that glucocorticoids cause an accumulation of glycosaminoglycans in the trabecular meshwork,¹³⁴ perhaps by stabilizing lysosomal membranes and inhibiting the release of catabolic enzymes. Cultured human trabecular cells secrete a wide variety of substances that contribute to the extracellular matrix. Treating cultured trabecular cells with steroid induces the secretion of elastin, which may have a role in trabecular obstruction *in vivo*.¹³⁵ Other explanations for corticosteroid glaucoma include an inhibition of the phagocytosis of foreign matter by trabecular endothelial cells¹³⁶ and decreased synthesis of prostaglandins that regulate aqueous humor outflow.¹³⁷ Southren and co-workers^{138,139} and Weinstein and co-workers¹⁴⁰ found abnormal glucocorticoid metabolism in trabecular tissue from patients with POAG. This finding may explain the increased susceptibility of patients with POAG to the ocular hypertensive effects of glucocorticoids. Alternatively, if

steroids cause changes that would tend to result in a reduced outflow facility in most or all human eyes, those individuals with marginal or compromised outflow facility to begin with would be expected to show the greatest rise in IOP.

Cultured human trabecular meshwork cells secrete increased amounts of laminin and integrin when exposed to dexamethasone, and a similar mechanism may be operative *in vivo*.¹⁴¹ Other changes include thickening of the trabecular beams, alteration in F-actin architecture, increased cross-linked actin and induction of myocilin protein.^{142,143} Which of these changes plays a role in the corticosteroid-induced elevation of IOP is unknown.

The first step in managing corticosteroid glaucoma is to discontinue the drug. In most cases, IOP returns to normal over a few days to several weeks. During this period, antiglaucoma medications may be used to control IOP.¹⁴⁴ If medication is unsuccessful in controlling IOP and the optic nerve is threatened, laser trabeculoplasty or filtering surgery should be considered.^{145,146} Caution should be exercised, however, before performing an irreversible procedure in what is usually a time-limited condition. It may be most appropriate to confirm progression in glaucomatous damage on maximal tolerated medical therapy before operating.

If glucocorticoid treatment is necessary for the patient's life or well-being, therapy should be altered to the weakest possible drug at the lowest possible dose. The residual glaucoma is then treated in the same fashion as is POAG. In the cases that require topical ocular corticosteroid therapy, the patient should be treated if possible with drugs such as medrysone or fluorometholone because these drugs have less of a tendency to raise IOP.

In rare cases, IOP remains elevated months to years after the corticosteroid has been discontinued.¹⁴⁷ In these situations, it may be impossible to determine whether this is a residual effect of glucocorticoid treatment or whether the patient has had underlying open-angle glaucoma unmasked by the treatment. In either case, the patient is treated in similar fashion. If IOP is elevated because of a periocular glucocorticoid injection and medical therapy is unsuccessful in controlling the pressure and protecting the optic nerve, the repository material should be excised.¹¹³

Topical corticosteroids can increase IOP even in the face of a functioning filtering bleb or tube-shunt procedure (glaucoma drainage device).^{148,149} Therefore, if IOP rises in the mid to late postoperative period, corticosteroid use should be discontinued before assuming that the glaucoma procedure has failed.

LENS-INDUCED GLAUCOMA

There are a variety of lens-induced glaucomas. In the past, great controversy surrounded the pathogenesis and nomenclature of these disorders. This chapter uses the following classification system:¹⁵⁰

1. *Phacomorphic glaucoma*: a swollen lens causes increased pupillary block and secondary angle closure.
2. *Dislocated lens*: a dislocated lens causes increased pupillary block and secondary angle closure.
3. *Phacolytic glaucoma*: lens protein leaks from an intact cataract and obstructs the trabecular meshwork.
4. *Lens-particle glaucoma*: lens material liberated by trauma or surgery obstructs the outflow channels.
5. *Phacoanaphylaxis*: sensitization to lens protein produces granulomatous inflammation and occasionally secondary glaucoma.

Phacomorphic glaucoma and dislocated lens are discussed in Chapter 15. The remainder of this section is devoted to the other three conditions.

PHACOLYTIC GLAUCOMA

Lens protein is normally sequestered within the lens capsule. With age and the development of cataract, the protein composition of the lens is altered to components with heavier molecular weight.¹⁵¹ If these soluble molecules leak through what grossly appears to be an intact capsule, they can obstruct the trabecular meshwork.^{152,153} The lens protein also stimulates inflammation and a macrophage response. The macrophages engulf the lens protein and may further obstruct the outflow channels (Fig. 18-7).¹⁵⁴ Protein of heavy molecular weight is not seen in infants and children, possibly explaining the absence of phacolytic glaucoma in young patients with cataract.

Phacolytic glaucoma is usually seen in older patients, who usually have a history of poor vision in the eye for months or years. The patients we have seen with this condition have often been from areas with little access to health care such as inner cities or developing nations. The disease typically appears with an acute onset of monocular pain, redness, and perhaps a further decrease in vision. Examination reveals a severe IOP elevation, corneal edema, ciliary injection, open angles, and heavy cell and flare. The cells appear larger than white blood cells and somewhat iridescent. The cells may precipitate on the corneal endothelium, but no true keratic precipitates or hypopyon is seen. Ultrastructural analysis of aqueous humor and trabeculectomy specimens in phacolytic glaucoma have revealed melanin-laden macrophages, red blood cells (RBCs), ghost RBCs, macrophages showing erythrophagocytosis, and free cell debris in addition to the lens material-laden macrophages that are traditionally associated with this condition.¹⁵⁵ The flare may be so heavy that the aqueous humor appears yellow. An important physical finding is the appearance of white particles on the anterior lens surface and in the aqueous; these particles are thought to be cellular aggregates or clumps of insoluble lens protein. Visual acuity is reduced in this condition, sometimes to the level of inaccurate light perception. The lens has a mature, hypermature,

or even Morgagnian cataract (Fig. 18-8).¹⁵⁶ Rarely this disease is produced by an immature cataract with a zone of liquefied cortex.

On rare occasions, phacolytic glaucoma has a subacute course, with intermittent leakage of protein producing recurrent episodes of glaucoma, hyperemia, and inflammation. This appearance is more likely if the cataract has been dislocated into the vitreous. The diagnosis of phacolytic glaucoma is usually made on clinical grounds. If the diagnosis is in doubt, an anterior chamber paracentesis should be performed to detect macrophages engorged with lens material. Aqueous humor is examined by phase-contrast microscopy or Millipore filtration and staining.

Cataract extraction is the definitive treatment for phacolytic glaucoma.¹⁵⁷ Before surgery, IOP and inflammation should be reduced by medical treatment, including hyperosmotic agents, topical adrenergic agents, CAIs, cycloplegic drugs, and topical corticosteroids. Traditionally most surgeons have removed these cataracts by an intracapsular technique. Microscopic examination of the lens reveals characteristic calcium oxalate crystals (Figs 18-9 and 18-10). Because the lens capsule is quite fragile, a sector iridectomy and α -chymotrypsin are employed. If the capsule ruptures during delivery, the anterior chamber should be irrigated copiously to remove any residual protein. Other surgeons have used extracapsular cataract

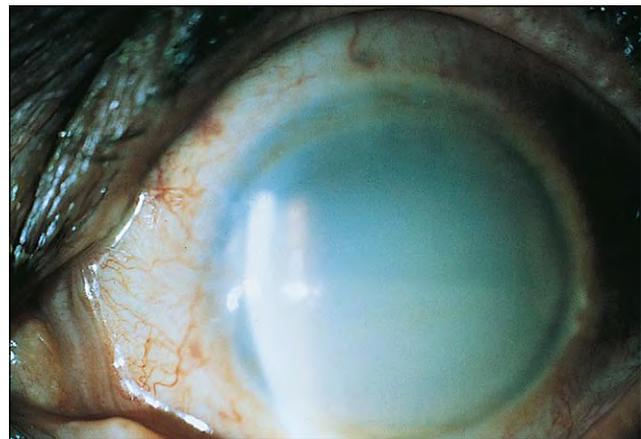


Fig. 18-8 Hypermature cataract.



Fig. 18-7 Phacolytic glaucoma with bloated macrophages and lens material obstructing the trabecular meshwork.

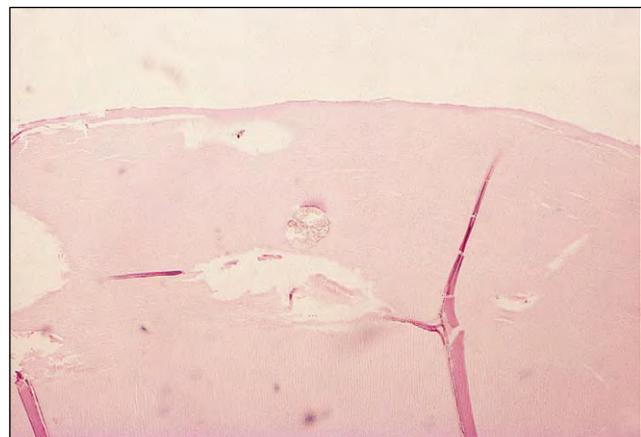


Fig. 18-9 Calcium oxalate crystal in the lens of a patient with glaucoma associated with hypermature cataract. (Hematoxylin and eosin stain.)



Fig. 18-10 In the same lens as Figure 18-9, the calcium oxalate crystal is birefringent when viewed through polarized light.

extraction in patients with this condition with good results.¹⁵⁸⁻¹⁶⁰ Because of the friability of the zonules and the brittleness of the capsule, the anterior capsulorrhexis may be performed by Vannas scissors or some other means that minimizes zonular and capsular stress. Lens delivery and residual cortical aspiration are also performed in an unusually delicate manner. In successful cases, posterior chamber IOL placement is possible and yields excellent results. As the last generation of surgeons trained in intracapsular surgery ages, the extracapsular technique will most likely replace the intracapsular approach. Regardless of approach, most patients have good visual acuity postoperatively and total remission of the glaucoma.

If phacolytic glaucoma is caused by a dislocated lens, the lens should be removed by vitrectomy instruments. Occasionally a dislocated lens can be floated into the anterior chamber with a stream of irrigation fluid and then removed through a limbal incision.

In the rare situation when phacolytic glaucoma is caused by an immature cataract and the eye has good vision, attempts should be made to control IOP and inflammation by medical means. If this fails, the lens should be removed.

LENS-PARTICLE GLAUCOMA

Disruption of the lens capsule by penetrating trauma or surgery liberates lens material, which can obstruct the trabecular meshwork. The resulting glaucoma depends on the amount of lens material liberated, the inflammatory response of the eye, and the ability of the trabecular meshwork to clear the foreign matter.^{152,153} Generally the glaucoma has its onset a few days after the precipitating event. In rare cases, the lens material can be released long after surgery or trauma.^{161,162}

Patients with lens-particle glaucoma usually have significant pain, redness, and decreased vision. Examination reveals corneal edema, elevated IOP, open angles, heavy cell and flare, and chunky white particles in the aqueous humor. A hypopyon may be present, as may fluffy cortical material. If the condition has existed for some time, peripheral anterior synechiae and posterior synechiae may be present.

Generally the diagnosis of lens-particle glaucoma is suggested by the sequence of events. It is more difficult to diagnose delayed cases or cases with spontaneous rupture of the lens capsule, which may be confused with phacolytic glaucoma, phacoanaphylactic glaucoma,

or other conditions. Anterior chamber paracentesis in this condition reveals macrophages and free lens material.¹⁵⁰

The elevated IOP and inflammation associated with lens-particle glaucoma are treated medically in the same fashion as phacolytic glaucoma. If this is not adequate, the residual lens material should be removed. Although fluffy cortical material can be aspirated easily, it is more difficult to remove solid lens material trapped in membranes behind the iris. Sometimes the entire lens mass can be teased from the eye after intracameral infusion of α -chymotrypsin. Lens particles in the vitreous can be removed with vitrectomy instruments. Surgery should not be delayed unduly in this disease or complications may occur, including posterior synechiae, peripheral anterior synechiae, cystoid macular edema, retinal detachment, and corneal decompensation.

PHACOANAPHYLAXIS

Phacoanaphylaxis is an uncommon condition that is thought to occur when patients become sensitized to their own lens protein. Phacoanaphylaxis typically develops after penetrating trauma or extracapsular cataract extraction.^{163,164} Histopathologically, these eyes have a granulomatous inflammation of the lens with polymorphonuclear leukocytes, lymphocytes, epithelioid cells, and giant cells. Occasionally the inflammation involves the trabecular meshwork and leads to a rise in IOP.

Phacoanaphylaxis is treated with medication to reduce inflammation and control IOP. If this is unsuccessful, residual lens material should be removed.

GLAUCOMA AFTER CATARACT SURGERY

Elevated IOP often occurs after cataract surgery through a variety of mechanisms (Box 18-1). Many of these clinical problems are presented elsewhere, so the discussion here is restricted to the entities that are peculiar to cataract surgery.

A transient rise in IOP has been reported in 33% to almost 100% of eyes after cataract extraction, depending on the method of extraction and the surgeon involved.¹⁶⁵ This pressure rise may be undetected because it occurs several hours after surgery, and the pressure may return to near-normal levels by the next morning or whenever the patient is seen for the first postoperative visit. The ocular hypertension may be sufficient to cause pain, nausea and vomiting, corneal edema, and optic nerve damage, especially in patients with pre-existing glaucoma. The elevated IOP usually abates spontaneously over 2-4 days. During this period the patients are treated with topical and systemic antiglaucoma medications, including hyperosmotic agents as needed to control IOP. The mechanism of the IOP rise appears to be complex and includes the following:

1. Inflammation with the release of active substances, including prostaglandins and the formation of secondary aqueous humor.
2. A watertight wound closure with multiple fine sutures limiting the 'safety valve' leak of aqueous humor.
3. Deformation of the limbal area, reducing trabecular outflow. On gonioscopy, Kirsch and co-workers¹⁶⁶ noted a white ridge internal to limbal cataract wounds. This ridge, attributed to tight sutures¹⁶⁷ and to operative edema and swelling, is associated with reduced trabecular function.
4. Obstruction of the trabecular meshwork by pigment, blood, lens particles, inflammatory cells, and viscoelastic substances.

Box 18-1 Glaucoma in aphakic and pseudophakic eyes

- I. Open-angle glaucoma
 - A. Early onset (within first postoperative week)
 1. Pre-existing chronic open-angle glaucoma
 2. α -Chymotrypsin-induced glaucoma
 3. Hyphema/debris
 4. Viscoelastic material
 5. Idiopathic pressure elevation
 - B. Intermediate onset (after first postoperative week)
 1. Pre-existing chronic open-angle glaucoma
 2. Vitreous in the anterior chamber
 3. Hyphema
 4. Inflammation
 5. Lens particle glaucoma
 6. Corticosteroid-induced glaucoma
 7. Ghost-cell glaucoma
 - C. Late onset (more than 2 months postoperatively)
 1. Pre-existing chronic open-angle glaucoma
 2. Ghost-cell glaucoma
 3. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy
 4. Vitreous in the anterior chamber
 5. Late-occurring hemorrhage
 6. Chronic inflammation
- II. Angle-closure glaucoma
 - A. With pupillary block
 1. Anterior hyaloid face
 2. Posterior lens capsule
 3. Intraocular lens
 4. Posterior synechiae
 5. Silicone oil
 - B. Aqueous misdirection (malignant glaucoma)
 - C. Without pupillary block
 1. Pre-existing angle-closure glaucoma
 2. Inflammation/hyphema
 3. Prolonged anterior chamber shallowing
 4. Iris incarceration in cataract incision
 5. Intraocular lens haptics
 6. Neovascular glaucoma
 7. Epithelial ingrowth
 8. Fibrous ingrowth
 9. Endothelial proliferation
 10. Proliferation of iris melanocytes across the trabecular meshwork

Modified from Tomey KF, Traverso CE: Glaucoma associated with aphakia and pseudophakia. In: Ritch R, Shields MB, Krupin T: *The glaucomas*, 2nd edn, St Louis, Mosby, 1996.

 α -CHYMOTRYPSIN GLAUCOMA

α -Chymotrypsin fragments zonules and was used widely to facilitate intracapsular cataract extraction. However, elevated IOP often occurred within 1–5 days after using this drug.^{168–170} When examined, these eyes had open angles, decreased outflow facility,¹⁶⁸ and increased IOP, which could be sufficient to cause corneal edema, wound disruption, and optic nerve damage. This entity is self-limited, lasting for 2–4 days and leaving no permanent abnormalities of aqueous humor dynamics.¹⁷¹

The generally accepted mechanism for α -chymotrypsin glaucoma is that zonular fragments obstruct the outflow channels. This theory is supported by scanning electron microscopy, which

shows zonular fragments in the trabecular meshwork, and by experimental studies in monkeys (Fig. 18-11).^{172–174} A few investigators have proposed alternative mechanisms for the glaucoma, including inflammation or a direct toxic effect on the meshwork, but direct infusion of α -chymotrypsin into the anterior chamber of monkeys actually produced an increase in outflow facility.¹⁷⁵ During the period of elevated IOP, patients are treated with topical and systemic glaucoma medications as needed. Patients with pre-existing optic nerve damage must be watched very closely because the pressure may rise to extremely high levels. The incidence and severity of the pressure rise can be reduced by using a lesser concentration of the drug (1:10 000 instead of 1:5000) in a lower volume (0.25–0.5 ml instead of 2 ml).^{169,176} The anterior chamber should be irrigated before lens extraction to remove zonular fragments. Prophylactic treatment with a variety of agents has generally failed to block this IOP rise,¹⁶⁸ although one group found prophylactic timolol and acetazolamide useful in this situation. α -Chymotrypsin-associated IOP elevation is seen quite rarely today because intracapsular cataract extraction with α -chymotrypsin is rarely performed.

GLAUCOMA FROM VISCOELASTIC SUBSTANCES

Viscoelastic substances often are employed in cataract surgery to protect the corneal endothelium and to facilitate intraocular lens (IOL) insertion. Sodium hyaluronate, the agent with perhaps the widest clinical use, frequently causes marked postoperative IOP elevations.^{177–181} When examined, these eyes demonstrate elevated IOP, deep anterior chambers, and corneal edema. Cellular and particulate matter in the aqueous humor may appear suspended and almost immobile if large amounts of viscoelastic remain in the anterior chamber, but IOP elevations may occur even in the absence of clinically detectable viscoelastic. It is sometimes possible to see tiny ruby-like globs of hemorrhage on the iris surface or suspended in the anterior chamber. These isolated blood droplets indicate the

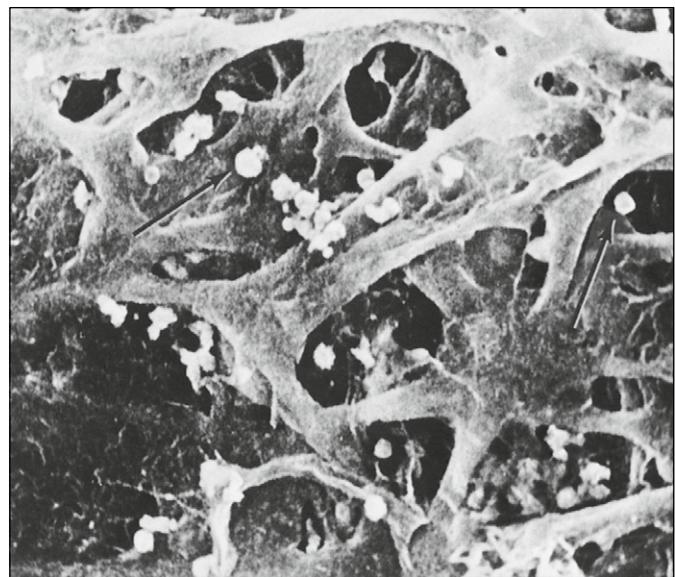


Fig. 18-11 Scanning electron micrograph of the zonular fragments obstructing the trabecular meshwork after α -chymotrypsin administration. (Courtesy of Douglas Anderson, Miami.)

presence of retained viscoelastic. The IOP reaches a maximum in 12–16 hours and then abates spontaneously over the next 72 hours. During this period, patients are treated with topical and systemic glaucoma medications and hyperosmotic agents as needed to control IOP. The postoperative IOP rise can apparently be limited by removing as much of the sodium hyaluronate as possible at the end of the surgery,¹⁷⁹ although some studies have failed to show a significant difference in IOP between eyes that have had the viscoelastic removed and those in which it was left in place at the end of surgery.^{182,183} Because it is difficult to standardize all of the variables that can affect the pressure rise in a given patient, it has been difficult to determine the effectiveness of various prophylactic treatment regimens on preventing the postoperative IOP rise seen after viscoelastic use. Some of these variables include the viscoelastic agent used, the surgeon, the surgical technique, the completeness of viscoelastic removal at the end of the procedure, and the rate at which the patient's eye clears itself of retained viscoelastic.

It is postulated that viscoelastic substances obstruct the trabecular meshwork. This theory is supported by experiments showing that sodium hyaluronate causes elevated IOP in animal eyes¹⁸⁴ and reduces outflow facility in enucleated human eyes.¹⁸⁵ The latter is reversed by intracameral infusion of hyaluronidase. Hyaluronidase is normally present in the anterior segment of the eye but not in sufficient quantity to metabolize the large volume of sodium hyaluronate infused at surgery, at least in the short haul. Obstruction of the trabecular meshwork depends on more than the drug's viscosity because low-viscosity sodium hyaluronate produces a greater rise in IOP in monkey eyes than does high-viscosity sodium hyaluronate.^{186,187}

Other viscoelastic substances have been evaluated for cataract surgery. Viscoat (a mixture of sodium hyaluronate and sodium chondroitin sulfate) produced similar IOP increases in one study, and marginally higher pressures in another.^{177,188} Chondroitin sulfate and methylcellulose may be less likely to elevate IOP.^{189–191}

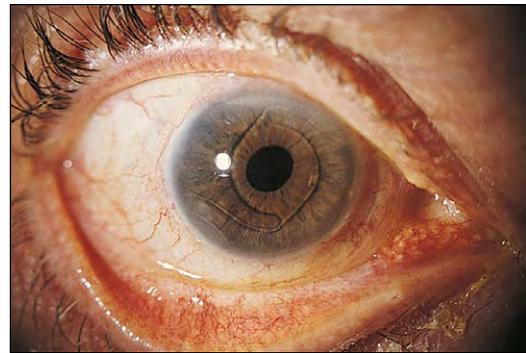
GLAUCOMA WITH PIGMENT DISPERSION FROM INTRAOCULAR LENSES

Pigment dispersion and elevated IOP have been described with posterior chamber IOLs and, in a few cases, with iris fixation lenses.^{192–198} In most instances, the lenses have been decentered, tilted, excessively mobile, too small, or reversed in position, creating excess friction between the optic or haptic and the iris pigment epithelium. The pigment epithelial loss is geographic, and the iris may have a grey atrophic appearance.¹⁹³ The pigment particles rubbed off the iris accumulate in the trabecular meshwork, where they obstruct aqueous humor outflow in a manner analogous to pigmentary glaucoma. Intraocular pressure rises days to months after cataract surgery but may improve spontaneously.

Patients with this entity are responsive to standard medical treatment for glaucoma and to ALT. In some cases, pupillary dilation or constriction may reduce the pigment dispersion. If IOP cannot be controlled, the IOL should be replaced or stabilized. This entity can be distinguished from pigmentary glaucoma by the temporal relation to cataract surgery, the unilateral state, and the absence of a typical Krukenberg's spindle and radial transillumination defects.

UVEITIS-GLAUCOMA-HYPHEMA SYNDROME

The uveitis–glaucoma–hyphema (UGH) syndrome has been described with iris-supported, with posterior chamber,^{199,200} and most often



(A)



(B)

Fig. 18-12 Uveitis–glaucoma–hyphema syndrome. **(A)** Inflamed eye of a patient following anterior chamber intraocular lens insertion. **(B)** Goniophotograph shows the footplate of the lens protruding posteriorly through the iridectomy and brushing against the ciliary processes.

with anterior chamber IOLs.^{201,202} The patients affected by this syndrome often have a history of uncomplicated cataract extraction but then develop elevated IOP, iridocyclitis, and recurrent hyphemas weeks to months after surgery (Fig. 18-12).²⁰³ Ultrasonic biomicroscopy and aqueous humor analysis can aid in confirming the diagnosis.^{198,204} The patients may complain of recurrent episodes of extreme blurring (whiteout), presumably related to the hyphemas. The UGH syndrome is caused by excessive chafing of the iris by the pseudophakos because the lenses are too mobile,²⁰⁵ are poorly designed, or have poor finishing characteristics.^{201,202} Most of the lenses removed from these eyes show sharp or serrated edges capable of traumatizing iris tissue. Although some patients with a mild form of UGH syndrome respond to corticosteroid treatment and standard antiglaucoma therapy, in most cases the lens should be removed to prevent corneal decompensation and optic nerve damage. In a report of 101 IOLs explanted for a variety of reasons, patients with UGH syndrome had relatively poor visual outcomes, with 7 of 9 patients achieving a final visual acuity of less than 20/200. However, explantation did result in a decrease in pain and inflammation and better glaucoma control.²⁰⁶

GLAUCOMA AFTER NEODYMIUM:YTTTRIUM-ALUMINUM-GARNET LASER POSTERIOR CAPSULOTOMY

Intraocular pressure often rises after neodymium:yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy and

can reach levels of 60–80 mmHg.^{207–213} The IOP elevation usually occurs within 2–4 hours of the laser treatment and then abates spontaneously over the next 24 hours.²¹⁴ However, in some patients, the pressure elevations can be delayed, can last for days to weeks,²⁰⁸ or can be severe enough to produce visual loss.²⁰⁹ Extreme IOP elevations are seen more often in eyes with pre-existing glaucoma²⁰⁸ and in eyes that do not have posterior chamber IOLs.^{207,214} There is some controversy about whether higher energy levels and larger capsulotomies are more likely to produce pressure rises, but most studies find little correlation. Intraocular pressure measurements should be taken 2–4 hours, 1 day, and 7 days after Nd:YAG laser capsulotomy. Pretreatment with apraclonidine 1% 1 hour prior to surgery and one drop 1 hour after surgery has been shown to decrease the number and severity of postoperative pressure spikes.^{215,216} The duration of the IOP rise may exceed the duration of action of the medication in some cases, and the pressure may be elevated the next day even after being measured as normal an hour or two after surgery.²¹⁷ We generally give our patients an additional dose of apraclonidine to take just before bedtime on the night of surgery. This will theoretically help protect against a dangerous pressure rise in the very early morning hours. Patients who still have a substantial rise in IOP should be treated with a topical β -adrenergic antagonist, topical, or, if necessary, a systemic CAI, an α -adrenergic agonist, and hyperosmotic agents as needed to control IOP. Topical corticosteroids may be administered to reduce inflammation. There have been sporadic cases reported of Latanoprost-associated cystoid macular edema in pseudophakic eyes following posterior capsulotomy, but these are rare occurrences and the causal relationship remains obscure.^{218,219}

The pressure rise occurring after Nd:YAG laser capsulotomy is usually associated with particulate debris clogging the trabecular meshwork. Altamirano and co-workers²²⁰ used a flare-cell meter to prospectively measure the level of flare and the amount of particulate matter in the anterior chamber following Nd:YAG laser capsulotomy in 65 eyes of 58 patients. They found that the amount of particulate matter correlated strongly ($P < 0.001$) with postoperative pressure rises. The amount of flare also correlated with pressure rises, but not as strongly ($P < 0.037$).²²⁰ Others have found that following Nd:YAG laser capsulotomy in experimental animals, the aqueous humor contains fibrin, lens material, inflammatory cells, macrophages, and RBCs in sufficient quantity to obstruct the trabecular meshwork.²²¹

In a few patients, the vitreous moves forward and causes pupillary block. In other cases, Nd:YAG laser surgery causes sufficient bleeding or inflammation to obstruct outflow. More often, however, the outflow facility is reduced in the absence of severe inflammation or hemorrhage.^{210,213} Some have proposed that Nd:YAG laser surgery releases a dialyzable factor from the vitreous that blocks the outflow channels.²²²

GLAUCOMA FROM VITREOUS IN THE ANTERIOR CHAMBER

Vitreous in the anterior chamber is a rare cause of open-angle glaucoma in aphakic eyes. The glaucoma usually begins within weeks after cataract surgery but may be delayed for months. In most cases, the vitreous reaches the anterior chamber after a spontaneous rupture of the hyaloid face or after an extensive posterior vitreous detachment. In a few cases, vitreous is left in the anterior chamber at the time of cataract extraction. When examined, these eyes demonstrate elevated IOP and open angles. Vitreous fills the

anterior chamber and appears to be in contact with the trabecular meshwork.^{223–225} It should be emphasized that in many cases, confirming this contact by clinical examination is impossible.

The mechanism of the glaucoma in this entity is not clear because vitreous is present in the anterior chamber of many aphakic eyes without causing problems. It is postulated that glaucoma occurs when a large bolus of vitreous comes into contact with a major portion of the trabecular meshwork and obstructs the outflow system. Grant infused vitreous into enucleated human eyes and found a diminished outflow facility that was reversed by hyaluronidase.²²³ In some cases, the mechanism of the glaucoma is more complicated and includes inflammation, pupillary block, and the formation of peripheral anterior synechiae.

Glaucoma caused by vitreous in the anterior chamber is usually a self-limited condition. The vitreous often retracts with time, and then IOP decreases. During this period, topical and systemic pressure-lowering medications are employed to control IOP. The response to miotics is unpredictable in this condition, with some patients helped and others not. Many patients respond better to cycloplegic drugs than to miotics. In unresponsive patients in whom the optic nerve is threatened, vitrectomy should be considered.

GLAUCOMA AFTER TRAUMA

CHEMICAL BURNS

Chemical burns are often associated with a complex pattern of IOP alterations that include an immediate IOP rise followed by a period of hypotony, which in turn is followed by an elevation in the intermediate or late phases of the disease process. Glaucoma is more common after alkali burns but can also be seen after severe acid burns.²²⁶ The diagnosis of glaucoma is often difficult in patients with chemical injuries because opacities of the media may interfere with optic nerve and visual field assessment. Also, external swelling, scarring, and corneal irregularity may interfere with standard methods of tonometry. Intraocular pressure measurements may be more accurate with the pneumatic or MacKay-Marg tonometers than with the Goldmann applanation tonometer.²²⁷

Intraocular pressure elevations in the early phase of disease are caused by scleral shrinkage and release of active substances, including prostaglandins.^{228,229} This situation is managed by topical and systemic medications, including β -adrenergic antagonists, α -adrenergic agonists, CAIs, and hyperosmotic agents as needed.

Elevated IOP in the intermediate phase is usually caused by inflammation.²³⁰ These eyes are treated with aqueous suppressants, hyperosmotic agents, and cycloplegic drugs. Topical and systemic corticosteroids are also used, but the patients must be monitored closely to avoid corneal melting. At times, sufficient posterior synechiae form to produce pupillary block, which requires vigorous pupillary dilation and/or iridectomy. Acute lens swelling can also produce pupillary block.²³⁰

Late elevations of IOP are usually caused by trabecular damage and formation of peripheral anterior synechiae or other intraocular scarring.²³¹ This situation is usually managed by standard medical therapy. Filtering surgery may be required but can be technically difficult if there is extensive scarring of the conjunctiva and episcleral tissues. If extensive scarring is present, a cyclodestructive procedure or a glaucoma drainage device procedure such as an Ahmed or Molteno valve should be considered.^{232–236}

ELECTRIC SHOCK

Transient IOP elevations have been reported after electric injury, cardioversion, and electroshock therapy. Various investigators have attributed the pressure rise to venous dilation, contraction of the extraocular muscles, and pigment dispersion.^{237–239} Because the IOP elevation is usually transient, no therapy is administered.

RADIATION

Radiation can cause elevated IOP through a variety of mechanisms, including neovascularization, open-angle glaucoma associated with diffuse conjunctival telangiectasia, and ghost-cell glaucoma associated with radiation retinopathy and vitreous hemorrhage.²⁴⁰ In many cases, the widespread ocular disease and radiation damage indicate a poor prognosis.

PENETRATING INJURIES

Penetrating injuries can produce elevated IOP through various mechanisms, including flat anterior chamber with formation of peripheral anterior synechiae; inflammation, including sympathetic ophthalmia; intraocular hemorrhage, including hyphema and ghost-cell glaucoma; lens swelling with pupillary block; lens subluxation with pupillary block; lens-particle glaucoma; phacoanaphylaxis; posterior synechiae with pupillary block; epithelial downgrowth, and fibrous ingrowth. When penetrating trauma includes retained organic material, severe inflammation and secondary glaucoma often follow. When blunt and penetrating trauma are combined, angle recession or other forms of direct trabecular damage may produce elevated IOP.

Retained metallic foreign bodies can produce open-angle glaucoma months to years after the injury. It is postulated that iron released from the foreign body is toxic to several ocular tissues, including the retina and the trabecular meshwork. This condition, known as *siderosis*, is similar to hemosiderosis, which results from the release of iron from blood. When examined, eyes with siderosis demonstrate heterochromia, mydriasis, elevated IOP, decreased outflow facility, and a diminished electroretinogram.²⁴¹ The deep cornea, trabecular meshwork, and anterior subcapsular region of the lens all have a rust-brown color. In some eyes, a previous corneal scar and an iris transillumination defect indicate the path of injury.

Prevention is the key to treating ocular siderosis. Traumatized eyes must be examined carefully with indirect ophthalmoscopy, gonioscopy, ultrasound, radiography, and computed tomography (CT) studies to detect metallic foreign bodies.²⁴² Whenever possible, the foreign bodies should be removed to prevent this occurrence. Once glaucoma is present, the foreign body may be so encapsulated that standard extraction techniques may not be possible.²⁴³ Furthermore, at this stage, the prognosis may be limited by extensive retinal damage. Standard medical and surgical means are used to treat the glaucoma. Glaucoma and retinal changes are also seen in chalcosis, which is caused by copper-containing foreign bodies.

CONTUSION INJURIES

Contusion injuries occur most frequently in young men^{244,245} and can cause hyphema, iridocyclitis, iris sphincter tears, iridodilation, cyclodialysis, lens subluxation, retinal tear or dialysis, retinal detachment, vitreous hemorrhage, choroidal rupture, and glaucoma. Postcontusion glaucoma can occur immediately after the injury or

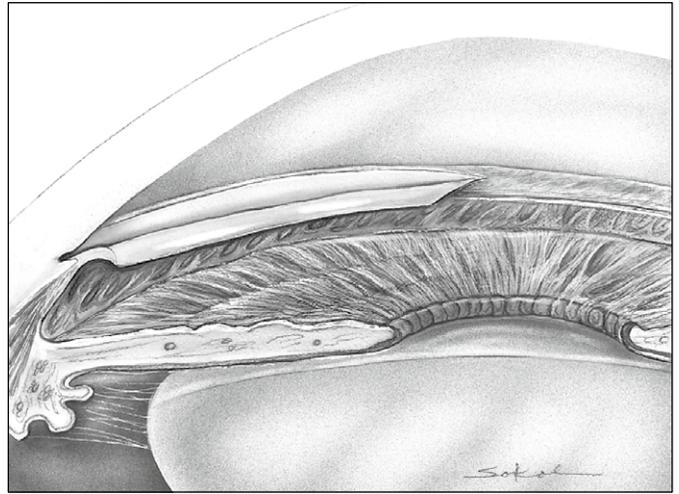


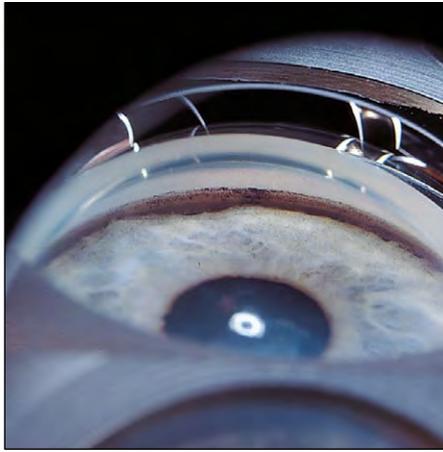
Fig. 18-13 Drawing of an acute flap tear in the trabecular meshwork following ocular trauma.

be delayed for months to years.^{246,247} Uveal effusion and angle closure can occur rarely after blunt trauma.²⁴⁸

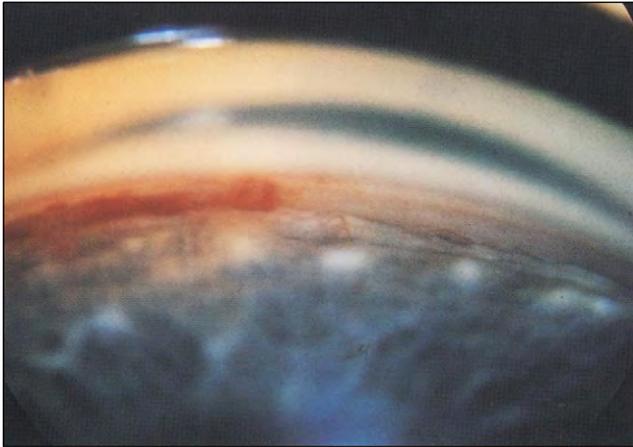
The pressure rise that occurs immediately after non-penetrating trauma can be severe but is usually limited in duration to days or weeks. During this period, patients are treated with topical β -adrenergic antagonists, CAIs, and hyperosmotic agents as needed to control IOP. The cause of the early pressure elevation is often complex and includes trauma to the trabecular meshwork as well as obstruction of the outflow channels by RBCs, leukocytes, pigment, and inflammatory debris. Tears in the trabecular meshwork typically occur after contusions but often are not recognized because gonioscopy is not performed routinely (Fig. 18-13). The tears have the appearance of a hinged flap, with the cut edge posterior to Schwalbe's line. The tear in the meshwork heals within several weeks to months, leaving an area of scarring that is sometimes combined with peripheral anterior synechiae.

In some cases, IOP is low after trauma and then becomes elevated weeks to months later. The likely explanation for this phenomenon is that both outflow facility and aqueous production are reduced immediately after trauma, and then aqueous production recovers first. An alternative explanation is the closing of a tear in the trabecular meshwork or a traumatic cyclodialysis cleft. The IOP elevation that occurs during this period can be very severe and may require filtering surgery if medical treatment fails.

Glaucoma can also occur years or even decades after blunt trauma. Most patients with postcontusion glaucoma have unilateral increased IOP, decreased outflow facility, open angles, and quiet eyes. Many patients have no memory of ocular trauma, whereas others only recall the injury after being questioned by a physician. Other patients will deny a specific history of ocular trauma but fail to consider a routine sports-related injury such as that which occurs during boxing matches or other similar activities. The key finding is a previous tear in the ciliary muscle, called an *angle recession* (Fig. 18-14).²⁴⁹ This may be present in the entire circumference of the angle or only in scattered areas. The recession is usually recognized gonioscopically as an irregular widening of the ciliary band. At times, the angle recession is very subtle. In these cases, it is only diagnosed by comparing one eye with the fellow eye or one part of the angle with the remaining parts. Other clues of angle



(A)



(B)

Fig. 18-14 (A) Goniophotograph of a recessed angle. The angle recess and the width of the ciliary body band vary from area to area. **(B)** Blood in the angle following traumatic angle recession. Jugular compression resulted in discharge of blood from Schlemm's canal into the anterior chamber in this patient who suffered angle recession some months previously. The patient had experienced periodic blurring of vision with pressure elevation as a result of this blood in the anterior chamber. It was resolved with laser applied to the bleeding point.

(From Campbell DG, Netland PN: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)

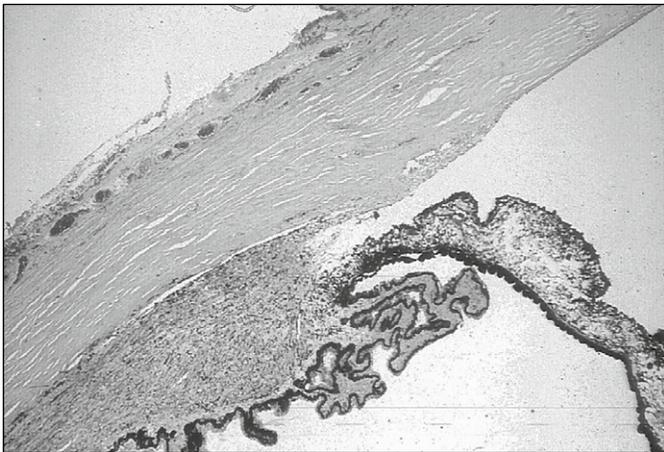


Fig. 18-15 Histopathology of a previous tear into the ciliary face showing the root of the iris recessed posterior to Schlemm's canal.

recession include absent or torn iris processes, posterior attachment of the iris root (Fig. 18-15), an anterior chamber deeper than in the fellow eye, and increased visibility and width of the scleral spur. Late glaucoma is more frequent if the recession involves three-quarters or more of the angle but can occur even with recessions of 1 clock hour or less. The angle recession is not the cause of the glaucoma, but rather it is an indicator of previous trauma. Late glaucoma occurs in an estimated 2–10% of eyes after contusion injuries.^{250–252}

It is thought that eyes with an underlying tendency to develop open-angle glaucoma are more likely to develop late increased IOP after blunt trauma. This theory is supported by the observation that many of the supposedly normal, untraumatized fellow eyes have spontaneous IOP elevations. Furthermore, the normal fellow eyes respond to topical corticosteroids, similar to eyes with POAG.²⁵³

The unifying theory is that eyes with marginal outflow facility are more likely to develop pathologic pressure elevations with trabecular injury than are eyes with excess or reserve outflow facility. Because the outflow facility tends to be about equal in the two eyes, a patient with angle recession and glaucoma might well be expected to have poor outflow in the fellow eye.

Histopathologic study of eyes with post-traumatic glaucoma may reveal a cuticular membrane covering the trabecular meshwork. However, it is not clear whether this membrane is the cause of the glaucoma.¹²

The treatment of late postcontusion glaucoma usually consists of the full antiglaucoma regimen, including miotics.^{254–258} Argon laser trabeculoplasty is often disappointing in this condition but should be considered before proceeding to filtering surgery. It should be emphasized again that the untraumatized fellow eyes should be watched closely for elevated IOP.

GLAUCOMA ASSOCIATED WITH INTRAOCULAR HEMORRHAGE

GHOST-CELL GLAUCOMA

Ghost-cell glaucoma is an uncommon condition that occurs in association with intraocular hemorrhage.²⁵⁹ In this entity, RBCs degenerate in the vitreous, migrate forward to the anterior chamber through a disrupted anterior hyaloid face, and then obstruct the trabecular meshwork.²⁶⁰ The vitreous hemorrhage is usually caused by retinal disease, trauma, or surgery; a recent case report associated ghost-cell glaucoma with snake poisoning injury.²⁶¹ Generally the anterior hyaloid face has been disrupted by vitrectomy, cataract surgery, or trauma,^{262,263} but ghost-cell glaucoma has been reported in non-traumatized phakic eyes as well.²⁶⁴ The RBCs in the vitreous degenerate to tan-colored spheres (ghost cells), which appear empty except for clumps of denatured hemoglobin called *Heinz bodies*. The ghost cells are more rigid than are normal RBCs and thus are less able to pass through the trabecular meshwork.²⁵⁹ This proposed mechanism is supported by animal experiments in which infusion of fixed RBCs produced elevated IOP.²⁶⁵

When examined, patients with ghost-cell glaucoma have elevated IOP, which may be sufficient to cause pain and corneal edema. Slit-lamp examination shows tiny, tan-colored cells in the vitreous, aqueous, and trabecular meshwork. Sometimes the cells in the anterior chamber are so numerous that they settle into a pseudohypopyon.^{259,266} The diagnosis of ghost-cell glaucoma is confirmed

by anterior chamber paracentesis. The anterior chamber aspirates can be passed through a Millipore filter and then stained,²⁶⁷ or the fluid can be examined by phase-contrast microscopy.^{266,268}

Ghost-cell glaucoma is a transient condition that can last for weeks or months depending on the volume of blood in the vitreous and the ability of the trabecular meshwork to clear the degenerated cells. Many cases are controlled by standard medical therapy, including topical β -adrenergic antagonists, α agonists, topical CAIs (oral if necessary), and hyperosmotic agents. Resistant cases are treated with anterior chamber washouts, which can be repeated as needed. If IOP cannot be controlled by repeated anterior chamber lavage, a vitrectomy should be performed to remove as much of the blood as possible.^{269,270}

HEMOLYTIC GLAUCOMA

Hemolytic glaucoma is a rare form of glaucoma associated with intraocular hemorrhage. It resembles ghost-cell glaucoma, except that in hemolytic glaucoma macrophages phagocytize RBC debris and then occlude the trabecular meshwork.²⁷¹ When examined, these eyes demonstrate elevated IOP, reddish cells in the aqueous humor, open angles, and increased pigmentation of the trabecular meshwork.²⁷² The diagnosis is confirmed by anterior chamber paracentesis, which reveals pigment-containing macrophages rather than khaki-colored ghost cells. Microscopic study of eyes with hemolytic glaucoma shows the trabecular meshwork to be occluded by RBCs, debris, and macrophages laden with pigment.²⁷³ Hemolytic glaucoma is usually a self-limited condition that responds to management with topical and systemic pressure-lowering medications. If IOP is not controlled, an anterior chamber washout should be performed. If this is not successful, a filtration or cyclodestructive procedure may be indicated.

HEMOSIDEROSIS

Hemosiderotic glaucoma is a rare entity associated with intraocular hemorrhage. Hemosiderosis is similar to siderosis, except that the source of iron in hemosiderosis is degenerating RBCs rather than a retained foreign body. Hemoglobin released by degenerated RBCs is phagocytized by trabecular endothelial cells. The iron liberated from the hemoglobin causes siderosis and discoloration of the meshwork.^{225,274}

HYPHEMA

Blunt trauma to the globe can produce a tear in the ciliary face and bleeding into the anterior chamber. Traumatic hyphemas can occur in patients of any age or either gender but are typically seen in young men.^{275,276} Patients with hyphemas complain of redness and blurred vision; if IOP is elevated, patients may also complain of pain, nausea, and vomiting. The history of the injury reveals trauma that seems severe in some cases and trivial in others. In all cases, however, the object causing the trauma must have been small enough or sufficiently deformable to fit inside the rim of the orbit in order to strike the globe.

When examined, patients with hyphemas demonstrate diminished vision, conjunctival injection, RBCs floating in the aqueous humor, a variable amount of blood settled to the bottom of the anterior chamber, and normal or low IOPs. Children with traumatic hyphemas often appear somnolent. In most patients, the blood clears spontaneously in a few days with no immediate

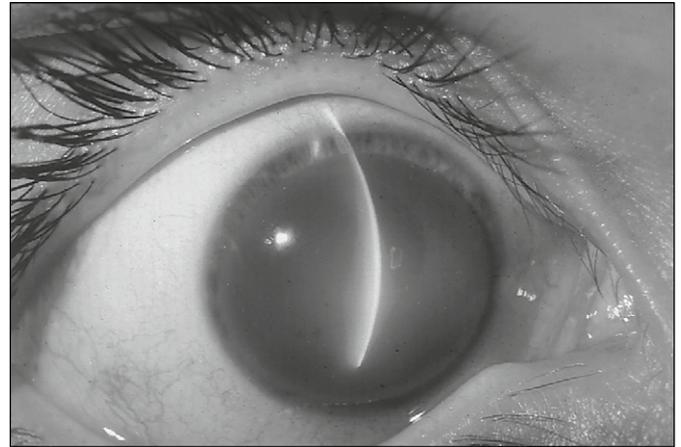


Fig. 18-16 Blood staining of a cornea that is beginning to clear in the periphery.

complications. A few weeks after the injury, these patients should have a careful dilated examination to search for retinal tears, retinal dialyses, and choroidal ruptures. They should also undergo gonioscopy to determine whether angle recession is present.

Unfortunately some patients with traumatic hyphemas have recurrent episodes of hemorrhage into the anterior chamber, or re-bleeds. Most episodes of re-bleeding occur within a few days of the trauma. It is postulated that additional bleeding occurs when the blood clot closing the vessel torn in the original injury undergoes lysis and retraction.²⁷⁷ Reports indicate that re-bleeding after traumatic hyphema occurs in 4–35% of patients.^{277–287} There is reasonable evidence linking aspirin use to re-bleeding.^{279,288,289} Some authorities also believe that re-bleeding is more common in blacks and in individuals with larger hyphemas and hypotony.^{282,285}

Re-bleeding is important because it is often associated with complications, including corneal blood staining (Fig. 18-16), optic atrophy, and elevated IOP. In most cases, elevated IOP is caused by RBCs obstructing the trabecular meshwork.²⁹⁰ Less often, the blood clot may produce pupillary block. Glaucoma is more frequent when the hyphema is total. A total hyphema changing color from red to black (*black-ball* or *eightball hyphema*) is an ominous sign of impending complications. The exact reason for this is obscure, but it is assumed that the underlying injury is more severe in many eyes with eightball hyphema compared with eyes with subtotal hyphema.

The management of traumatic hyphema has been controversial.²⁹¹ Typical practice in the past was to hospitalize all patients for bed rest, sedation, and bilateral patching. However, there is evidence that bed rest and patching are not necessary and that equally good results can be obtained by limiting activity.^{280,284,292} If there is a stable family situation, some patients can be managed at home and checked daily in the physician's office. Despite widespread use, no evidence suggests that either cycloplegics or miotics facilitate the clearing of blood.^{293,294} The antifibrinolytic agents epsilon-aminocaproic acid (Amicar) and tranexamic acid have been found to decrease the incidence of rebleeding.^{277,278,283,295–300} The reported track record of tranexamic acid remains fairly good, although its use is not entirely without risk. The effectiveness of aminocaproic acid has been questioned by some investigators, who found no significant difference in re-bleed rates between patients treated with aminocaproic acid and those treated with either corticosteroids or placebo.^{301–304}

This has been a difficult issue to study.²⁰⁵ The re-bleed rate of the control groups in these studies ranges from less than 5% to over 25%.³⁰⁶ In several cases, the patients in the study group were collected over periods of 10 years or more, and it is difficult to be certain that identical diagnostic criteria and treatment regimens were employed. For the most part, the studies with high rates of re-bleeding in the control group found the medications helpful.^{307–309} Other studies with seemingly similar entry criteria and treatment plans had low re-bleed rates in the control group and showed no benefit from aminocaproic acid.³⁰³ Some authorities recommend that all patients with traumatic hyphemas be treated with an anti-fibrinolytic agent, assuming no contraindication.^{279,284,299} Other authorities use these agents only after severe trauma or in patients with large initial hyphemas. The best available data support using these agents in circumstances in which the re-bleed rate is likely to exceed about 10%. If this is the case in the experience of a particular hospital or practice, it would also seem prudent to carefully review the entire treatment regimen as well as the circumstances and extent of the injury causing the hyphema and the support services available to the patient during convalescence.³¹⁰ A few reports indicate that systemic corticosteroids reduce the rate of rebleeding,³¹¹ although this was not confirmed in other studies.^{285,312,313} Again, patient demographics, the circumstances of injury, and other critical factors are difficult to compare. Elevated IOP associated with a traumatic hyphema is managed by topical and systemic glaucoma medications as needed. Topical corticosteroids are administered if the eye is significantly inflamed, independent of any potential positive effect on re-bleeding rates.

Non-clearing total or subtotal hyphema is a serious condition. In addition to other damage to the eye caused by the event that produced the hyphema, the hyphema itself can cause corneal blood staining, persistent inflammation, and dramatically elevated IOP. Tissue plasminogen activator (t-PA) is a fibrin-specific fibrinolytic agent that has shown promise in experimental³¹⁴ and limited clinical use.^{315,316} Current experience remains limited, at least partially because appropriate cases are rare. Early case reports have been favorable, however.

Surgical removal of blood from the anterior chamber is indicated for persistent pain, corneal blood staining, or IOP elevations threatening the optic nerve. It is difficult to know what IOP level will be tolerated by young healthy patients who have no pre-existing optic nerve disease. One proposed guideline is that an IOP of 60 mmHg for 2 days, 50 mmHg for 5 days, or 35 mmHg for 7 days requires intervention.²⁸⁴ If possible, evacuation of blood should be delayed until the fourth day because, at this time, the clot is somewhat retracted and less adherent to the surrounding tissues. Sometimes, a simple paracentesis allows the clot to retract enough from the chamber angle to allow drainage to occur. Removal of blood also can be done as a washout through a peripheral corneal puncture using saline or a fibrinolytic agent such as urokinase,^{244,317,318} fibrinolysin, or, when available, t-PA. Liquid blood is irrigated from the eye during this maneuver; it is neither necessary nor wise to remove the entire clot. If the anterior chamber remains shallow and a large clot persists, the surgeon may consider performing an iridectomy to relieve pupillary block.

Some surgeons recommend treating the hyphema through a larger limbal incision using manual expression, ultrasonic emulsification, cryoextraction, or vitrectomy instruments.³¹⁹ Other experts recommend a trabeculectomy procedure with or without evacuation.^{320,321}

Patients with sickle cell trait are at great risk of developing IOP elevations and optic nerve damage after traumatic hyphemas. The

abnormal RBCs in the anterior chamber develop sickle deformity so they are less able to pass through the trabecular meshwork.^{322–327} Furthermore, increased IOP may reduce the perfusion pressure to the optic nerve and retina and lead to sickling of RBCs within the vessels of these tissues. Accordingly, more aggressive treatment is indicated in patients with sickle cell trait. Unfortunately patients with sickle cell trait may respond adversely to a variety of medications, including hyperosmotic agents, adrenaline (epinephrine), and acetazolamide.³²⁸ However, these individuals generally tolerate topical β -adrenergic antagonists and methazolamide. It has been suggested that mean IOPs greater than 25 mmHg or pressure spikes higher than 30 mmHg indicate the need for surgery in patients with sickle cell trait and traumatic hyphema.^{322,328} One report states that hyperbaric oxygen reduces sickling of RBCs in the anterior chamber of rabbits.³²⁹

Not all hyphemas arise from contusion injuries. Intraocular bleeding can also occur with penetrating trauma, surgery, neovascularization of the iris or a previous wound, IOLs, tumors, or vascular tufts at the pupillary margin.³³⁰ Elevated IOP is managed with medical therapy and with washout if necessary.

RETINAL DETACHMENT AND GLAUCOMA

Retinal detachment and glaucoma are associated in a variety of ways, including the following:

1. *Chance occurrence:* because glaucoma and retinal detachment are both common diseases, they occur together by chance.

2. *Genetic linkage:* in one series, 4% of the eyes with retinal detachment had open-angle glaucoma.³³¹ This is a much higher prevalence of glaucoma than in the general population. Patients with retinal detachments have larger cup-to-disc diameter ratios and a higher prevalence of corticosteroid responsiveness than would be expected in the general population.³³² Myopia is also associated with glaucoma and retinal detachment. Patients with pigmentary glaucoma also have an increased incidence of retinal detachment.³³³

3. *Common underlying mechanism:* retinal detachment and glaucoma can be associated through a common underlying mechanism such as trauma, cataract surgery with vitreous loss, proliferative retinopathy, or retinopathy of prematurity.

4. *Treatment for retinal detachment may cause glaucoma:* therapeutic agents and interventions such as corticosteroids, scleral buckling procedures, extensive retinal photocoagulation, and vitrectomy are all capable of producing glaucoma. In one study, the IOP was measured directly using a canula in patients undergoing scleral buckling surgery. The highest recorded IOP was 211 mmHg! The mean elevation was 112 mmHg for a mean duration of 118 seconds.³³⁴ Glaucoma does not interfere with the reattachment of detached retinas but may limit the visual outcome.^{331,335} Repair of retinal detachment may reduce scleral rigidity, so it is necessary to use applanation rather than Schiøtz tonometry for postoperative pressure measurements.³³⁶

5. *Treatment of glaucoma may cause retinal detachment:* strong miotic agents are capable of inducing retinal tears, vitreous hemorrhage, and retinal detachment. There is suggestive evidence that standard cholinergic drugs can also cause retinal detachment.^{337,338} Glaucoma patients should have periodic peripheral retinal examinations, especially before starting miotic therapy. Ophthalmologists should question glaucoma patients about flashes, floaters, and curtains in their vision and should be suspicious of any sudden decrease in IOP.

In most cases of newly diagnosed retinal detachment, IOP is low. However, glaucoma may become apparent later or may be detected in the fellow eye. It is postulated that retinal detachment lowers IOP by inducing inflammation and reducing aqueous humor formation. It is also possible that aqueous humor may be eliminated by flowing through the retinal hole into the subretinal space.^{338,340} Campbell has described an extreme example of this phenomenon, which he calls the *iris retraction syndrome*.³⁴¹ In this syndrome, a patient with a rhegmatogenous retinal detachment, secluded pupil, iris bombé, and angle-closure glaucoma develops hypotony and iris retraction when aqueous formation is reduced pharmacologically. Campbell postulates that the induced reduction in aqueous formation allows most of the aqueous humor to go posteriorly through the retinal hole.

SCHWARTZ SYNDROME

In a minority of cases, retinal detachment causes a peculiar increase in IOP that is referred to as *Schwartz syndrome*.³⁴² In this syndrome, rhegmatogenous retinal detachment is associated with elevated IOP, diminished outflow facility, open angles, and cell and flare in the aqueous humor.³⁴³ When the retinal detachment is repaired, the IOP and outflow facility return to normal.³⁴² It has been postulated that the glaucoma is related to angle recession,^{333,342,344} inflammation, pigment granules released by the retinal pigment epithelium,³⁴⁴ and glycosaminoglycans synthesized by the photoreceptors.³⁴⁵ One additional suggestion is that photoreceptor outer segments migrate through the retinal hole and obstruct the trabecular meshwork. The IOP can vary from mildly elevated to very high, and medical treatment is rarely successful in controlling the condition. Schwartz syndrome must be distinguished from glaucoma and non-rhegmatogenous retinal detachment caused by an undetected malignant melanoma.

GLAUCOMA AFTER VITRECTOMY

Elevated IOP has been reported in 20–26% of eyes after vitrectomy.^{346,347} This occurs through a variety of mechanisms (Box 18-2). Because most of these entities are discussed in detail elsewhere in this book, only a few general remarks are offered here.

It is important to monitor IOP postoperatively by applanation tonometry because the accuracy of indentation tonometers is affected by scleral surgery. In addition, intraocular gas may interfere with pressure measurements using a Schiøtz tonometer.

Liquid silicone is sometimes injected into the vitreous cavity in cases of complicated retinal detachment. The silicone and macrophages laden with silicone may obstruct the trabecular meshwork.^{348,349} The silicone may also cause pupillary block, which can be prevented by an inferior iridectomy at the time of surgery.^{350,351} The iridectomy has a somewhat greater chance of closing in these cases; t-PA helped keep the peripheral iridectomy open in a case reported by MacCumber and co-workers.³⁵² In many cases of intra-vitreous silicone injection, IOP is depressed by persistent inflammation, hyposecretion, retinal detachment, or cyclitic membrane formation.

GLAUCOMA WITH UVEITIS

Inflammation can produce glaucoma through a variety of mechanisms, including (1) increased viscosity of aqueous humor;

(2) obstruction of the trabecular meshwork by inflammatory cells and debris; (3) swelling and dysfunction of the trabecular meshwork; (4) liberation of active substances such as prostaglandins; (5) scarring of the outflow channels; (6) development of a cuticular endothelial membrane over the angle; (7) neovascularization; (8) elevation of episcleral venous pressure; (9) forward displacement of the lens-iris diaphragm (uveal effusion); (10) pupillary block, and (11) formation of peripheral anterior synechiae. Elevated IOP can occur with any type of ocular inflammatory disease but is more common in the chronic forms than in the acute forms. In most ocular inflammatory diseases, aqueous humor formation is reduced and IOP is low.³⁵³ If outflow facility is reduced as well, however, IOP can be elevated. Because of this dual involvement of aqueous humor inflow and outflow, eyes with active inflammatory disease often suffer wide swings of IOP, and glaucoma may be missed if only occasional pressure measurements are made. Additionally, these patients can be extremely sensitive to medications (e.g., acetazolamide) that decrease aqueous production. In sensitive patients, the pressure can drop from over 50 mmHg to under 5 mmHg with a single dose. Careful individual titration is needed to arrive at the proper medication regimen.

The treatment of glaucoma associated with ocular inflammatory disease depends on the underlying condition, but in most situations, inflammation is suppressed by some combination of topical, systemic, and periocular corticosteroids. During this treatment the ophthalmologist must be aware of the possibility of corticosteroid-induced IOP elevations. Steroid glaucoma is a particular problem in patients on long-term corticosteroid therapy for chronic or recurrent uveitis. A variety of other medications may be employed to reduce inflammation, including cycloplegic agents, non-steroidal anti-inflammatory drugs, and immunomodulators such as methotrexate, azathioprine, and chlorambucil. Elevated IOP is generally managed

Box 18-2 Glaucoma after vitrectomy

Pre-existing glaucoma

- Angle recession
- Ghost cell
- Primary open-angle glaucoma
- Pigmentary glaucoma

Associated with intraocular hemorrhage

- Hyphema
- Ghost cell
- Hemolytic
- Hemosiderosis

Related to lens material

- Phacolytic
- Lens particle
- Phacoanaphylactic

Neovascular

Inflammatory

Corticosteroid induced

Intraocular gas or liquid

- Air
- Viscoelastic substances
- Perfluorocarbons
- Silicone

Modified from Wilensky JT, Goldberg MF, Alward P: Glaucoma after pars plana vitrectomy. *Trans Am Acad Ophthalmol Otolaryngol* 83:114, 1977.

by topical and systemic glaucoma medications as needed. Miotics are usually avoided because they increase pain and congestion and may promote the development of posterior synechiae. Prostaglandins such as latanoprost are used with caution in uveitic patients because they could theoretically exacerbate signs and symptoms that might be confused with the underlying inflammatory condition.

Argon laser trabeculoplasty (ALT) is not very helpful in eyes with active inflammation. It may cause a mild acute anterior uveitis in some patients and may also lead to peripheral anterior synechiae. For this and other reasons, most surgeons avoid ALT in patients with uveitis. Surgery should be avoided in eyes with active inflammation, but if a filtering procedure is required, inflammation should be suppressed as much as possible by topical and systemic corticosteroid treatment. Inhibitors of scarring such as mitomycin-C³⁵⁴ or 5-fluorouracil (5-FU)³⁵⁵ are often useful in this situation, as are tube-shunt devices such as the Ahmed²³⁴ or Molteno valve.³⁵⁴ In a young individual with uveitis and secondary glaucoma, an Ahmed, Molteno, or Baerveldt implant may be the preferred first procedure since trabeculectomy, even with antifibrosis agents, is unlikely to work. Eyes with active inflammation sometimes require cyclodestructive procedures, although the risk of exacerbating inflammation makes this option worrisome.³⁵⁶

A wide variety of inflammatory diseases are associated with secondary open-angle glaucoma. This section discusses a few of the more common entities

FUCHS' HETEROCHROMIC IRIDOCYCLITIS

Fuchs' heterochromic iridocyclitis is a chronic but relatively mild form of anterior uveitis associated with cataract and glaucoma.^{357–360} Approximately 90% of the cases are unilateral, and the disease has its onset in the third and fourth decades of life.³⁶¹ Men and women are affected in equal numbers. Patients are generally asymptomatic until they develop cataract or vitreous opacities. The physical findings in this syndrome include minimal cell and flare, fine round or stellate keratic precipitates, fine filaments on the endothelium between the keratic precipitates, a patchy loss of the iris pigment epithelium, hypochromia, grey-white nodules on the anterior iris, a few opacities in the anterior vitreous, and chorioretinal scars that resemble toxoplasmosis.^{361–364} Heterochromia may be seen in about 70% of Caucasian eyes.³⁶⁵ However, if the iris is dark in color, heterochromia may be present in only 25% and the diagnosis may rest on the keratic precipitates and areas of iris atrophy.³⁶⁶ Gonioscopy reveals fine vessels that bridge the angle and can bleed with minimal trauma, such as paracentesis.³⁶⁷ Fluorescein angiography of the iris demonstrates ischemia, leakage, neovascularization, and delayed filling of the vessels.^{368,369}

No specific cause has been identified although toxocarasis and toxoplasmosis have both been implicated by associated antibody findings.^{370–372} Rubella virus and antibodies against rubella virus have been found in the aqueous humor of young patients with Fuchs' heterochromic iridocyclitis. Furthermore, the incidence in the United States has significantly declined since the advent of the rubella vaccination program.³⁷³ This evidence strongly suggests that rubella infection plays a role in at least some cases of Fuchs'.

Increased IOP has been reported in 13–59% of patients with Fuchs' heterochromic iridocyclitis.^{364,374} One study, albeit with fairly small numbers, reported an increased glaucoma prevalence among black patients, with 38% (5 of 13) of blacks having glaucoma compared with only 11% (6 of 54) of whites.³⁷⁵ The cause of the glaucoma is not clear, but the angle is open and no peripheral anterior

synechiae are seen. It is postulated that the inflammation eventually produces scarring and dysfunction of the outflow channels. Histologic examination of a few surgical specimens has confirmed the inflammation and scarring of the trabecular meshwork and revealed an inflammatory membrane over the angle.^{376,377}

Glaucoma may also be seen following cataract surgery, neovascularization, or over-zealous treatment with corticosteroids. The inflammatory component of Fuchs' heterochromic iridocyclitis is generally unresponsive to corticosteroid treatment, part of which may be explained by a possible infectious etiology. Elevated IOP is treated with medical therapy, but the results are often disappointing, with only about a quarter of patients achieving satisfactory control.³⁷⁸ In the past, the results of conventional filtration surgery were also poor, with less than half of patients achieving control.^{364,379} Use of wound-healing retardants such as 5-FU and mitomycin-C has improved surgical outcomes considerably, with success rates as high as 72%.³⁷⁸ Cataract surgery with in-the-bag intraocular lens implantation is usually successful.^{380,381}

GLAUCOMATOCYCLITIC CRISIS

Glaucomatocyclitic crisis, also called the *Posner-Schlossman syndrome*, is usually seen in young to middle-aged adults and consists of recurrent episodes of mild anterior uveitis and marked elevations of IOP.^{382–387} Generally this condition is unilateral, but both eyes can be affected at different times.³⁸⁵ Patients have relatively few symptoms considering the height of their IOPs, but they may complain of slight discomfort, slight blurring of vision, or halo vision. The prevalence of this condition is low; for example, in Finland, glaucomatocyclitic crisis represents 0.4% of all uveitis seen in one clinic.³⁸⁸

The physical findings during an episode of glaucomatocyclitic crisis include mild ciliary flush, a dilated or sluggishly reactive pupil, corneal epithelial edema, IOP in the range of 40–60 mmHg, decreased outflow facility, open angles, faint flare, and 1–20 fine keratic precipitates. The keratic precipitates may not appear for 2 or 3 days after the IOP has risen, which may obscure the diagnosis. It is postulated that the elevated IOP is caused by inflammation of the trabecular meshwork, perhaps mediated by prostaglandins.³⁸⁹ There is also evidence of an association between herpes simplex virus and glaucomatocyclitic crisis, but the significance of this association is unknown.³⁹⁰ The crises last several hours to a few weeks. Some patients experience one or two episodes in their lives, whereas other patients experience recurrent crises for many years. As a rule, the frequency of recurrences diminishes with age.

For many years it was accepted that glaucomatocyclitic crisis never caused optic nerve cupping or visual field loss and that aqueous humor dynamics were normal between episodes. It is now clear, however, that some patients with glaucomatocyclitic crisis have abnormal aqueous humor dynamics between episodes and that some have underlying POAG.^{385,387} Furthermore, some patients develop optic nerve cupping and visual field loss because of repeated crises or underlying POAG.^{384,385,387} Indeed, some patients develop glaucomatous damage years after initial symptoms appear; therefore, all patients should be monitored indefinitely.³⁹¹

Glaucomatocyclitic crisis is usually treated with topical corticosteroids and topical and systemic glaucoma medications. As with all types of uveitis, miotics are avoided. Apraclonidine 1% has been found to be particularly effective.³⁹² Some authorities recommend the administration of systemic or topical non-steroidal anti-inflammatory agents because of increased aqueous humor prostaglandin levels. Because the episodes are self-limited, moderate

elevations of IOP should be well tolerated. An occasional patient requires filtering surgery because of progressive cupping and visual field loss.³⁹³ Successful filtering surgery prevents IOP elevations but does not prevent recurrent episodes of inflammation.

PRECIPITATES ON THE TRABECULAR MESHWORK

Inflammatory precipitates on the trabecular meshwork can cause a clinical picture that is easily mistaken for POAG. In this condition, the eyes are white and quiet, and the only signs of inflammation are a few gray or slightly yellow precipitates on the trabecular meshwork associated with irregular peripheral anterior synechiae. Most of these patients have idiopathic disorders, although some later develop a recognizable inflammatory condition such as sarcoidosis, rheumatoid arthritis, or ankylosing spondylitis.³⁹⁴ The precipitates and the elevated IOP are responsive to topical corticosteroid treatment. While waiting for this effect, aqueous humor suppressants may be useful to control IOP. This uncommon condition may be recurrent and asymptomatic, and these patients should be examined periodically to monitor IOP. Inflammatory precipitates have been reported as a cause of increased IOP following ALT.³⁹⁵ As with idiopathic cases, this condition responded to treatment with topical corticosteroids.

HERPES SIMPLEX

Elevated IOP is common when herpes simplex causes iridocyclitis, disciform keratitis, or stromal ulcer.³⁹⁶ The increased IOP is caused by inflammation, swelling, and obstruction of the trabecular meshwork. Herpetic keratouveitis is usually treated with antiviral agents, cycloplegics, and topical corticosteroids. The IOP is controlled with aqueous humor suppressants. Glaucoma may be quite severe in these cases and filtration surgery with wound-healing retardants such as 5-FU or mitomycin-C may be necessary to control pressure.³⁹⁷ Argon laser trabeculoplasty has been implicated as a trigger for recurrent herpes simplex keratitis in at least one case and thus is not an attractive treatment option.³⁹⁸ Cyclodestructive procedures have been attempted in many cases, but serious complications have occurred in several eyes and these procedures are best considered as a last resort.³⁹⁹

HERPES ZOSTER

When herpes zoster involves the ophthalmic division of the trigeminal nerve, especially the nasociliary branch, there is often associated keratitis, iridocyclitis, and secondary glaucoma. The anterior uveitis can be severe, and secondary open-angle glaucoma occurs in 11–25% of patients.⁴⁰⁰ The inflammation is treated with systemic antiviral agents⁴⁰¹ and cycloplegic agents; the IOP is controlled by aqueous humor suppressants.⁴⁰² Topical steroids are used routinely, although there are differences of opinion regarding the optimum timing and intensity of steroid treatment.^{403,404} Surgery in actively inflamed eyes is challenging, although some authors have reported excellent results.⁴⁰⁵ Mitomycin-C- and/or 5-FU-enhanced filtering operations are the procedures of choice,⁴⁰⁶ although if the inflammation is severe or active, a tube shunt could be considered.

SARCOIDOSIS

Approximately 10% of patients with sarcoidosis develop elevated IOP.⁴⁰⁷ This occurs through a variety of mechanisms, including swelling and dysfunction of the trabecular meshwork, obstruction of the trabecular meshwork by inflammatory cells and debris,

peripheral anterior synechiae, posterior synechiae with pupillary block, and neovascular glaucoma.^{394,408,409} These cases can be extremely difficult to manage because of the continual battle between therapy aimed at controlling the underlying pathology and that used to control the glaucoma.⁴¹⁰ Patients with ocular sarcoidosis frequently develop thick, broad-based peripheral anterior synechiae that can lead to a scarred and dysfunctional anterior segment well after the inflammatory episode is over. Tube-shunt procedures, valved or non-valved (e.g., Ahmed, Molteno, Baerveldt) implantation with adjunctive 5-FU or mitomycin-C may be necessary to control severe cases. HLA typing suggests a molecular basis for some of the clinical heterogeneity seen in sarcoid patients.^{411,412}

JUVENILE RHEUMATOID ARTHRITIS

Severe acute and chronic eye disease is an unfortunate but common component of juvenile rheumatoid arthritis.^{413–415} Elevated IOP can occur in any of the forms of juvenile rheumatoid arthritis but is most common in young girls with iridocyclitis and monoarticular or pauciarticular involvement.^{416,417} Glaucoma can result from posterior synechiae and pupillary block or inflammation of the trabecular meshwork.^{418–421} The response to medical treatment and filtering surgery is often disappointing in this condition. A few physicians have reported long-term IOP reductions in these children with a modified goniotomy procedure called *trabeculodialysis*.^{418,419,422} Treating these patients is often complicated further by concomitant visually significant pathology as well as a host of psychosocial issues related to treating children with a painful chronic systemic disease.^{423,424} Close ophthalmic follow-up and prompt treatment of ocular pathology are important in maintaining vision. Genetic typing may allow more precise and earlier diagnosis, which should facilitate early intervention in select cases.^{425–428}

SYPHILIS

Glaucoma often occurs in individuals with congenital or acquired syphilis. Secondary open-angle glaucoma can occur in any of the active inflammatory phases of the disease, including acute interstitial keratitis. Iridoschisis occurs rarely but may be associated with glaucoma in 50% of cases.^{429–431}

A late form of secondary open-angle glaucoma occurs in 15–20% of patients.⁴³² In these cases, gonioscopy reveals occasional peripheral anterior synechiae and irregular pigmentation of the trabecular meshwork.^{433,434} These patients respond poorly to medical treatment, and it is postulated that there may be an endothelial membrane covering the angle.^{435,436} Filtering surgery with wound-healing retardants or drainage valve implantation is often required for this condition.

Syphilis is also associated with angle-closure glaucoma. Some patients with congenital syphilis have small anterior segments and develop acute or chronic angle closure in later years. Elevated IOP has also been reported in association with other inflammatory conditions, including ankylosing spondylitis, pars planitis,³⁴⁹ Behçet's syndrome, sympathetic ophthalmia,⁴³⁷ onchocerciasis,^{438,439} leprosy,⁴⁴⁰ and mumps.⁴⁴¹

INTRAOCULAR TUMORS AND GLAUCOMA

A variety of ocular tumors can produce glaucoma through various mechanisms. Because the tumors producing glaucoma in children

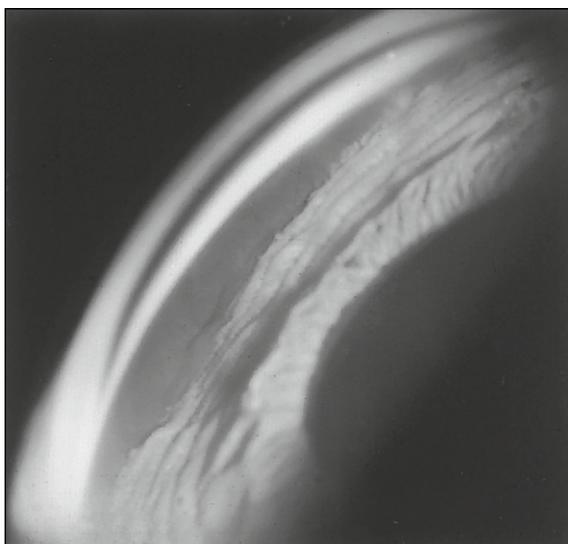


Fig. 18-17 Choroidal melanoma invading the ciliary body and angle.

are presented in Chapter 19, the discussion here is limited to tumors in adults.

Malignant melanoma can be associated with normal, elevated, or depressed IOP. Elevated IOP is reported more frequently with melanomas of the anterior uveal tract than with choroidal melanomas.⁴⁴² Glaucoma can occur through several mechanisms, including the following: (1) direct extension of the tumor into the trabecular meshwork (Fig. 18-17); (2) seeding of tumor cells into the outflow channels; (3) pigment dispersion; (4) inflammation; (5) hemorrhage, inducing hemolytic glaucoma, and suprachoroidal hemorrhage, leading to angle closure; (6) neovascularization of the angle; (7) angle closure from anterior displacement of the lens–iris diaphragm, peripheral anterior synechiae, or posterior synechiae, and (8) obstruction of the trabecular meshwork by macrophages containing melanin released by a necrotic tumor (melanomalytic glaucoma).

Most eyes with advanced melanomas are treated with enucleation or radiation.^{443–449} In some cases, local excisional surgery may be a viable option.^{450,451} If the eye is retained, medical therapy is used to attempt to control IOP. Unfortunately many irradiated eyes develop neovascular glaucoma. In a 5-year study of helium ion irradiation, for example, Decker and co-workers found that 43% of patients developed neovascularization.⁴⁴⁵ Neovascular glaucoma was often not responsive to treatment and was a prominent contributing factor in the subsequent decision to perform enucleation. Metastatic tumors to the eye may cause glaucoma, especially if the metastasis involves the anterior segment.^{452–454} The mechanisms producing glaucoma are similar to those described for malignant melanoma. There is one report of a metastatic tumor invading Schlemm's canal and the collector channels.⁴⁵⁵ Many metastatic tumors are treated with radiation and/or chemotherapy. Medical treatment for glaucoma is indicated to retain vision and reduce discomfort.

Intraocular lymphoma and leukemia can produce glaucoma by seeding the outflow channels or by producing angle closure.⁴⁵⁴ Several benign ocular tumors can also produce glaucoma. Melanocytomas of the iris can invade the angle⁴⁵⁶ or cause sufficient pigment dispersion to obstruct the trabecular meshwork.⁴⁵⁴ Pigment dispersion and glaucoma are also reported with adenomas of the pigment epithelium,^{344,457} melanosis oculi,⁴⁵⁸ and nevus of Ota.^{459–461} These conditions generally respond well to medical

therapy or to ALT. Medulloepithelioma can displace the lens–iris diaphragm or produce neovascularization of the angle.⁴⁴²

AMYLOIDOSIS

The hereditary systemic amyloidoses are a group of diseases in which amyloid is deposited in tissues throughout the body, leading to cardiovascular, renal, endocrine, muscular, gastrointestinal, and neurologic deficits. The ocular findings include vitreous opacification, proptosis, lid abnormalities, extraocular muscle weakness, anisocoria, internal ophthalmoplegia, and retinal vasculitis.^{462,463}

Secondary open-angle glaucoma develops in approximately 25% of the patients with the hereditary systemic amyloidoses. The glaucoma somewhat resembles pigmentary glaucoma because modest pigment exists in the trabecular meshwork and on the corneal endothelium. There is also a resemblance to the exfoliation syndrome because white flecks are seen on the iris near the pupil and on the anterior lens capsule.⁴⁶⁴ Histologic examination of these eyes reveals heavy accumulation of amyloid in the trabecular meshwork.⁴⁶³ Anatomic changes and amyloid deposition involve the ciliary body as well.⁴⁶⁵ This accumulation most likely causes glaucoma by obstructing aqueous humor outflow.⁴⁶⁶ Glaucoma can also be caused by elevated episcleral venous pressure.⁴⁶⁷

Another form of familial systemic amyloidosis and secondary open-angle glaucoma has been reported that includes lattice dystrophy of the cornea, cranial neuropathy, and no vitreous opacities.⁴⁶⁸ These patients may require multiple penetrating keratoplasties over the years, and unresponsive glaucoma is a frequent sequela.⁴⁶⁹ There is also a report of non-familial systemic amyloidosis associated with secondary open-angle glaucoma.⁴⁷⁰

The treatment of glaucoma in amyloidosis is similar to the treatment of POAG.⁴⁶⁷ It has been reported that filtering surgery is successful initially but that the blebs fail over several months to a few years because of the accumulation of amyloid material.⁴⁷¹

ELEVATED EPISCLERAL VENOUS PRESSURE

Any condition that raises episcleral venous pressure also raises IOP by obstructing the post-trabecular flow of aqueous humor. In acute experiments, when a pressure cuff is placed around a patient's neck and episcleral venous pressure is raised 1 mmHg, IOP increases approximately 0.8 mmHg.^{472,473} In a study of IOP and episcleral venous pressure in patients who were placed in a vertically inverted posture (i.e., upside down), Friberg and co-workers found that when the episcleral venous pressure increased 0.83 ± 0.21 mmHg, the IOP rose 1 mmHg.⁴⁷⁴ The difference between these pressure increases has been attributed to fluid being forced from the eye⁴⁷⁵ or to *pseudofacility* (i.e., a pressure-related reduction in aqueous humor formation).⁴⁷³ Recently, however, the concept of pseudofacility has been questioned. It is difficult to interpret acute experiments such as the one just described because IOP, outflow facility, and episcleral venous pressure never reach steady state. Animal models can measure episcleral venous pressure and IOP changes reproducibly in acute experimental settings,^{476,477} but these findings do not necessarily mimic the clinical situation of chronically elevated episcleral venous pressure in the human. For example, acute elevations of episcleral venous pressure increase the total outflow facility,⁴⁷⁵ whereas chronic elevations often decrease outflow facility.⁴⁷⁸ Thus it is difficult to

predict accurately the change in IOP that will accompany a specific rise in episcleral venous pressure. The two pressure changes are often of similar magnitude, but the IOP may be less than or even greater than the rise in episcleral venous pressure.⁴⁷⁹

The physical signs of elevated episcleral venous pressure depend on the underlying disease or condition and include chemosis, proptosis, orbital bruit, and pulsating exophthalmos. Generally the episcleral veins are dilated, tortuous, and have a corkscrew appearance, although this can vary from mild to severe.⁴⁸⁰ The retinal veins are usually not dilated because the rise in venous pressure is counterbalanced by a rise in IOP. The angles are open, and blood is often present in Schlemm's canal. The elevated IOP may produce typical glaucomatous optic nerve cupping and visual field loss. Outflow facility is normal in most cases of elevated episcleral venous pressure. In longstanding cases, however, secondary changes in the trabecular meshwork may reduce outflow facility.⁴⁷⁸

Elevated episcleral venous pressure can be confused with any condition that produces dilated extraocular vessels, including conjunctivitis, episcleritis, scleritis, and general orbital inflammation. Usually the venous pressure is normal in these inflammatory conditions. Furthermore, the most common of these entities, conjunctivitis, affects the superficial vessels and spares the deeper episcleral vessels. This distinction can be made by observing the vessels during slit-lamp examination while moving the conjunctiva with a moist swab. In addition, dilated superficial vessels constrict in response to topical agents such as phenylephrine 2.5%, whereas deeper vessels do not.

Many conditions can produce elevated episcleral venous pressure. These conditions are usually divided into three major categories: obstruction of venous drainage, arteriovenous fistulas, and idiopathic elevations (Box 18-3). The discussion here is restricted to the more common entities.

SUPERIOR VENA CAVA OBSTRUCTIONS

Various conditions can obstruct the superior vena cava, including tumors, aortic aneurysms, mediastinal masses, hilar adenopathy, and intrathoracic goiter.⁴⁸¹⁻⁴⁸³ This obstruction produces edema and

cyanosis of the face and neck (pumpkinhead appearance) as well as dilated vessels in the head, neck, chest, and upper extremities.⁴⁸⁴ Obstruction of the superior vena cava increases intracranial pressure, which leads to headache, stupor, vertigo, seizures, and mental changes. The associated ocular findings include exophthalmos, papilledema, and prominent blood vessels in the conjunctiva, episclera, and retina. Intraocular pressure is elevated, and the IOP increase is greater when the patient is in the supine position.⁴⁸⁵ There is a clinical impression that glaucomatous cupping occurs infrequently with superior vena cava obstruction despite the elevated IOP. Some researchers propose that cupping does not occur because the IOP is counterbalanced by elevated intracranial pressure.⁴⁸⁶ Therapy in this situation is directed toward relieving the obstruction.⁴⁸⁷ During this period, the IOP elevation is treated primarily with medications that decrease aqueous production, such as β -blockers and topical or systemic CAIs; α agonists may also be helpful.

THYROID EYE DISEASE

Thyroid eye disease is known by a variety of names, including endocrine exophthalmos, thyrotropic exophthalmos, and Graves' disease. The hormonal defect of this condition is unclear, and patients can be hypothyroid, euthyroid, or hyperthyroid when their eye problems begin.^{488,489} The physical findings are variable and include exophthalmos, chemosis, lid retraction, lid lag, a staring or startled appearance, dilated conjunctival and episcleral vessels, corneal exposure, restriction of ocular motility, optic atrophy, and diminished retropulsion of the globe.⁴⁹⁰ Intraocular pressure can be increased for several reasons, including elevated episcleral venous pressure. Ocular rigidity is reduced in thyroid eye disease, and thus IOP measurements should be taken with applanation rather than Schiötz tonometry. In addition, because of restricted ocular motility, pressure measurements should be taken with the patient gazing down slightly to minimize a potential transient IOP rise.⁴⁹¹

Ocular hypertension and open-angle glaucoma occur relatively frequently in thyroid-related immune orbitopathy with a prevalence of 8.5% and 2.5% respectively in one study – a prevalence which is significantly higher than controls.⁴⁹² In another study, the prevalence of glaucoma was as high as 14%.⁴⁹³

When glaucoma occurs in the setting of thyroid eye disease, elevated IOP is treated with topical aqueous humor suppressants; topical prostaglandins and α agonists may also be useful. Corticosteroids, radiation, and surgical decompression have been employed to protect the optic nerve, limit corneal exposure, and improve cosmetic appearance.⁴⁹⁴⁻⁵⁰⁰ In addition to thyroid eye disease, in which signs and symptoms of thyroid disease (usually hyperthyroidism) have direct ocular manifestations, long-term study indicates an association between open-angle glaucoma and a history of treatment for thyroid disease, including hypothyroidism.⁵⁰¹

ARTERIOVENOUS FISTULAS

Carotid-cavernous fistulas provide a free communication between the internal carotid artery and the surrounding cavernous sinus, resulting in high blood flow and high mean pressure in the shunt.⁵⁰² The reversal of blood flow in the vessels leads to congestion of the orbital veins and soft tissues. The shunting of the blood may produce ocular ischemia⁵⁰³ and may transmit arterial pulsations to the globe. Patients with carotid-cavernous fistulas often give a history of previous trauma.^{504,505} Many of these patients have

Box 18-3 Etiology of elevated episcleral venous pressure

- I. Obstruction of venous drainage
 - A. Episcleral
 1. Chemical burns
 2. Radiation
 - B. Orbital
 1. Retrobulbar tumors
 2. Thyroid eye disease
 3. Pseudotumor
 4. Phlebitis
 - C. Cavernous sinus thrombosis
 - D. Jugular vein obstruction
 - E. Superior vena cava obstruction
 - F. Pulmonary venous obstruction
- II. Arteriovenous fistulas
 - A. Orbital
 - B. Intracranial
 1. Carotid-cavernous fistula
 2. Dural fistula
 3. Venous varix
 4. Sturge-Weber syndrome
- III. Idiopathic



Fig. 18-18 Carotid-cavernous fistula.
(Courtesy of Randall T Higashida, MD, UCSF Medical Center, San Francisco.)

a dramatic appearance, with pulsating exophthalmos, chemosis, lid edema, vascular engorgement, and restriction of ocular motility (Fig. 18-18).^{506,507} The conjunctival and episcleral veins have a tortuous, corkscrew appearance.⁴⁸⁰ The physical findings usually occur on the same side as the fistula. Because of the connections between the cavernous sinuses, however, the findings may be bilateral or even alternating.^{508,509} Patients with carotid-cavernous fistula often complain of a noise in their head or ears; a bruit is often present over the frontal or temporal regions or over the globe. Intraocular pressure is elevated in the majority of patients because of increased episcleral venous pressure, although angle-closure and neovascular glaucoma have also been reported.⁵¹⁰⁻⁵¹² Skull and orbital radiography, ultrasonography, and CT or magnetic resonance imaging (MRI) confirm the diagnosis, but arteriography provides the most detailed information about the fistula.⁵⁰⁸ Treatment of these fistulas can be difficult and is usually reserved for individuals who have severe pain, incapacitating bruit, progressive glaucomatous visual loss, or other serious complications. A variety of embolization and balloon catheter techniques have been employed with increasing success.⁵¹³⁻⁵¹⁸

Dural fistulas are communications between the cavernous sinus and an extradural branch of the external or internal carotid artery. These fistulas generally have lower blood flow and lower mean pressure.⁵¹⁹⁻⁵²² The clinical appearance of these patients is far less dramatic than that of patients with carotid-cavernous fistulas (Fig. 18-19). Patients with dural fistulas lack bruits and have variable exophthalmos and variable limitation of ocular motility. The conjunctival and episcleral vessels have the same corkscrew, arterialized appearance, and IOP is elevated. This condition is often seen in elderly women who have no history of trauma.⁵²³ At times, the findings are so subtle that only the dilated vessels distinguish this entity from POAG. This condition has been referred to as the 'red-eyed shunt syndrome' by Phelps and co-workers.⁵²² Low-flow or dural fistulas can close spontaneously and may not require treatment. High-flow shunts respond well to interventional approaches in experienced hands.⁵¹⁶ Elevated IOP generally responds to topical β -adrenergic antagonists and CAIs. Although sometimes effective, topical prostaglandins and α -adrenergic agonists often exacerbate the hyperemia associated with the fistula. Choroidal effusion has been reported associated with topical prostaglandin use in a patient with elevated episcleral venous pressure.⁵²³ Glaucoma associated with neovascularization may respond to local laser treatment.⁵²⁴



Fig. 18-19 Dural shunt with engorged vessels.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome is a rare oculocutaneous disorder that produces increased IOP through a variety of mechanisms, including elevated episcleral venous pressure and, possibly, maldevelopment of the chamber angle.⁵²⁵⁻⁵³⁰ Glaucoma that is often resistant to medical therapy occurs in about 40% of patients with the syndrome. Often the glaucoma in these children (and adults) is very challenging to manage.⁵³¹ This condition is discussed in Chapter 19.

IDIOPATHIC ELEVATIONS

Several cases of unexplained or idiopathic elevations of episcleral venous pressure and IOP have been described.^{411,532-537} This condition can be unilateral or bilateral and sporadic or familial. The IOP elevations can lead to glaucomatous cupping and visual field loss. The treatment of elevated episcleral venous pressure depends greatly on the underlying condition. Elevated IOP is treated with topical and systemic medications to reduce aqueous production.

Cholinergic agents may be useful, especially in patients with reduced outflow facility. Argon laser trabeculoplasty may also be helpful in these patients. One study reports lowering IOP with the topical administration of vasodilators.⁵³⁸

Many of these patients eventually require filtering surgery, but ophthalmologists must be aware of the increased possibility of complications. The high venous pressure favors the development of intraoperative choroidal effusion, expulsive hemorrhage, and flat anterior chamber.^{534,539,540} It is recommended that prophylactic sclerotomies be made in one or two inferior quadrants at the beginning of filtering surgery. The sclerotomies are then left open at the end of surgery and covered only by conjunctiva to allow continued drainage of suprachoroidal fluid.⁵³⁹

Staged trabeculectomy is another alternative which is intended to reduce the risks of surgical complications by decompressing the eye more gradually.⁵⁴¹

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CHAPTER
19

Developmental and childhood glaucoma

The developmental glaucomas are a group of disorders characterized by improper development of the eye's aqueous outflow system, usually manifesting in infancy and childhood. Glaucoma in the infant is an uncommon disease, but the impact on visual development can be significant. Early recognition of and appropriate therapy for the glaucoma can significantly improve a child's visual future. Preservation of any vision during a child's formative years is important, even if, in severe cases, the vision is ultimately lost.

The childhood glaucomas are divided into three major categories: (1) primary congenital glaucoma, in which the developmental anomaly is restricted to a maldevelopment of the trabecular meshwork; (2) glaucoma associated with specific ocular or systemic congenital anomalies, and (3) glaucoma secondary to miscellaneous pediatric conditions involving the eye, such as inflammation, trauma, or tumors.

TERMINOLOGY

Previously, the terminology of the glaucomas affecting infants was inconsistent and, at times, confusing. More precise terminology has arisen with developments in the field and should be used whenever possible.

The term *developmental glaucoma* refers to those glaucomas associated with developmental anomalies that are present at birth, including primary congenital glaucoma and secondary glaucomas associated with other developmental anomalies, either ocular or systemic.

- *Congenital glaucoma* is a term synonymous with developmental glaucoma. Secondary glaucoma in infants refers to glaucoma resulting from acquired ocular diseases.
- *Primary congenital glaucoma* is a specific term referring to eyes that have an isolated maldevelopment of the trabecular meshwork without other developmental ocular anomalies or diseases that can raise intraocular pressure (IOP).
- *Infantile glaucoma* is a term that has been used in a variety of contexts. Some use this term as a synonym for primary congenital glaucoma, whereas others apply it to any glaucoma occurring during the first several years of life. Its meaning, therefore, should be specified or its use avoided. Primary infantile glaucoma is synonymous with primary congenital glaucoma.
- *Juvenile glaucoma* is a non-specific term referring to any type of glaucoma occurring later in childhood (after 5 years of age) and through the third to fourth decades. Sometimes a syndrome is

implied and is associated with myopia, autosomal dominance with penetrance as high as 80%, and characteristic clinical course; this condition has been linked to the short arm of the first (1q) human chromosome, coding for the myocilin gene.^{1,2}

- *Buphthalmos* and *hydrophthalmia* are archaic descriptive terms. Buphthalmos literally means 'ox eye' and refers to the marked enlargement that can result from any type of uncontrolled glaucoma presenting in early childhood. Hydrophthalmia refers to the high fluid content of buphthalmic eyes (Fig. 19-1).

CLASSIFICATION

SYNDROME CLASSIFICATION

The developmental glaucomas have been classified in various ways (Box 19-1).¹⁻⁸ The Shaffer-Weiss classification is based on syndromes that divide patients into those with primary congenital glaucoma, glaucoma associated with other congenital ocular or systemic anomalies, and secondary glaucomas in infants.¹



Fig. 19-1 Advanced developmental glaucoma with extensive enlargement and scarring of the cornea. The anterior segment structures are not visible. This is classic buphthalmos.

Box 19-1 Syndrome classification of congenital glaucoma

- I. Primary glaucoma
 - A. Congenital open-angle glaucoma
 1. Presenting age: 0–5 years
 2. Later recognized
 - B. Autosomal dominant juvenile glaucoma
 - C. Glaucoma associated with systemic abnormalities
 1. Axenfeld–Rieger syndrome
 2. Chromosomal disorders
 3. Congenital rubella
 4. Fetal alcohol syndrome
 5. Mucopolysaccharidosis
 6. Neurofibromatosis
 7. Oculocerebrorenal (Lowe) syndrome
 8. Hepatocerebrorenal (Zellweger) syndrome
 9. Oculodermal vascular malformations
 - a. Sturge–Weber syndrome
 - b. Klippel–Trenaunay–Weber syndrome
 - c. Oculodermal melanocytosis
 - d. Phakomatosis pigmentovascularis
 - e. Cutis marmorata telangiectasia congenita
 10. Prader–Willi syndrome
 11. Rubenstein–Taybi (broad-thumb) syndrome
 12. Pierre Robin and Stickler syndromes
 13. Skeletal dysplastic syndromes
 - a. Kniest syndrome
 - b. Michel syndrome
 - c. Oculodentodigital syndrome
 - D. Glaucoma associated with ocular abnormalities
 1. Aniridia
 2. Axenfeld–Rieger syndrome
 3. Congenital ectropion uveae
 4. Congenital hereditary endothelial dystrophy
 5. Microcornea syndromes
 6. Familial iris hypoplasia
 7. Peters syndrome
 8. Posterior polymorphous dystrophy
 9. Sclerocornea
- II. Secondary glaucoma
 - A. Traumatic glaucoma
 1. Acute onset
 - a. Hyphema and angle recession
 - b. Lens debris or vitreal blockade of trabeculum
 - B. Glaucoma secondary to intraocular neoplasm
 1. Retinoblastoma
 2. Juvenile xanthogranuloma
 3. Leukemia
 4. Iris rhabdomyosarcoma
 - C. Uveitic glaucoma
 1. Open angle
 2. Angle closure
 - a. Synechial closure
 - b. Iris bombé with pupillary block
 - D. Lens-induced glaucoma
 1. Subluxation – dislocation with pupillary block
 - a. Marfan syndrome
 - b. Homocystinuria
 2. Spherophakia with pupillary block
 - a. Weill–Marchesani syndrome (autosomal recessive)
 - b. GEMSS syndrome (autosomal dominant)
 - E. Glaucoma after congenital cataract surgery
 1. Chronic open-angle (aphakic or pseudophakic)
 2. Lens debris or uveitic blockade of trabeculum
 3. Pupillary blockade
 - F. Steroid-induced glaucoma
 - G. Neovascular glaucoma
 1. Retinoblastoma
 2. Coats' disease
 3. Medulloepithelioma
 4. Familial exudative vitreoretinopathy
 - H. Secondary angle-closure glaucoma
 1. Retinopathy of prematurity
 2. Microphthalmos
 3. Nanophthalmos
 4. Retinoblastoma
 5. Persistent hyperplastic primary vitreous
 6. Congenital papillary–iris lens membrane
 7. Aniridia
 8. Iridoschisis
 9. Cornea plana
 - I. Glaucoma with increased episcleral venous pressure
 1. Sturge–Weber syndrome
 2. Idiopathic or familial elevated episcleral venous pressure
 3. Orbital vascular malformations
 - J. Glaucoma secondary to intraocular infections
 1. Acute recurrent toxoplasmosis
 2. Acute herpetic iritis
 3. Opportunistic infections seen with AIDS
 4. Congenital rubella

Data from Shaffer RN, Weiss DI: Congenital and pediatric glaucomas. St Louis, Mosby, 1970 and Walton DS: Childhood glaucoma. In: Roy FH, editor: Master techniques in ophthalmic surgery. Baltimore, Williams Wilkins, 1995.

PRIMARY GLAUCOMA

Because not all cases fit precisely into a specific syndrome, an anatomic classification of these glaucomas has been developed.^{4,5} These findings have been grouped according to their clinical manifestations rather than to categories based on pathogenetic mechanisms or genetic linkage.⁹

CLINICAL ANATOMIC CLASSIFICATION

Maldevelopment of the anterior segment is present in all forms of congenital glaucoma. Clinically, gonioscopy and biomicroscopy of

the anterior segment provide the crucial information to determine the therapy and prognosis for the infant.^{10,11} Maldevelopment of the anterior segment may involve the trabecular meshwork alone or the trabecular meshwork in combination with the iris, cornea, or both. The following classification is based solely on empirical clinical observations and does not imply pathogenetic mechanisms (Box 19-2).

Isolated trabeculodysgenesis

In approximately 50% of infants and juvenile patients with glaucoma, isolated trabeculodysgenesis is the only developmental ocular anomaly found. This is the classic defect found in primary congenital glaucoma (Fig. 19-2).⁴ These eyes have no developmental

Box 19-2 Clinical anatomic classification of developmental glaucoma

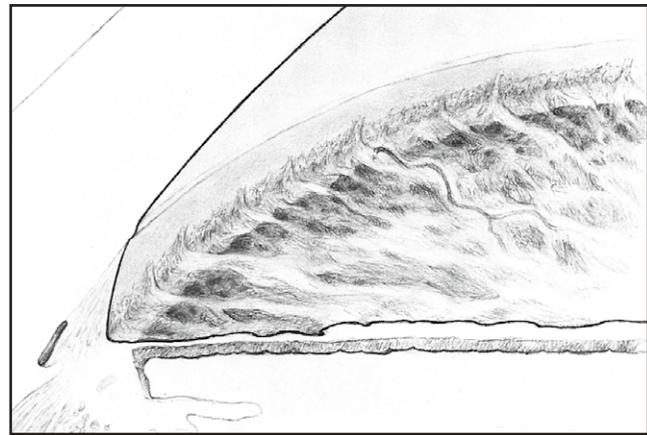
- I. Isolated trabeculodysgenesis (malformation of trabecular meshwork in the absence of iris or corneal anomalies)
 - A. Flat iris insertion
 1. Anterior insertion
 2. Posterior insertion
 3. Mixed insertion
 - B. Concave (wrap-around) iris insertion
 - C. Unclassified
- II. Iridodysgenesis (iris anomalies are usually seen with trabeculodysgenesis)
 - A. Anterior stromal defects
 1. Hypoplasia
 2. Hyperplasia
 - B. Anomalous iris vessels
 1. Persistence of tunica vasculosa lentis
 2. Anomalous superficial vessels
 - C. Structural anomalies
 1. Holes
 2. Colobomata
 3. Aniridia
- III. Corneodysgenesis (corneal anomalies are usually seen with iridodysgenesis)
 - A. Peripheral
 - B. Midperipheral
 - C. Central
 - D. Corneal size
 1. Macrocornea
 2. Microcornea



Fig. 19-2 Anterior segment photograph of a patient with primary congenital glaucoma with an enlarged, clear cornea. A U-shaped Haab's striae extends from the 9 o'clock to the 1 o'clock position. The slightly rolled edges of the original break in Descemet's membrane parallel each other. (From Campbell DG, Netland PN: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)

anomalies of the iris or cornea, except for an abnormal insertion of the iris into the angle wall. The iris and cornea may demonstrate secondary changes as a result of elevated IOP.

This maldevelopment of the trabecular meshwork is present in one of two forms. In the most common form, the iris inserts flatly into the trabecular meshwork either at or anterior to the scleral spur (Fig. 19-3). The ciliary body is usually obscured by this insertion,



Anterior Iris Insertion

Fig. 19-3 Gonioscopic drawing of isolated trabeculodysgenesis with flat anterior iris insertion.

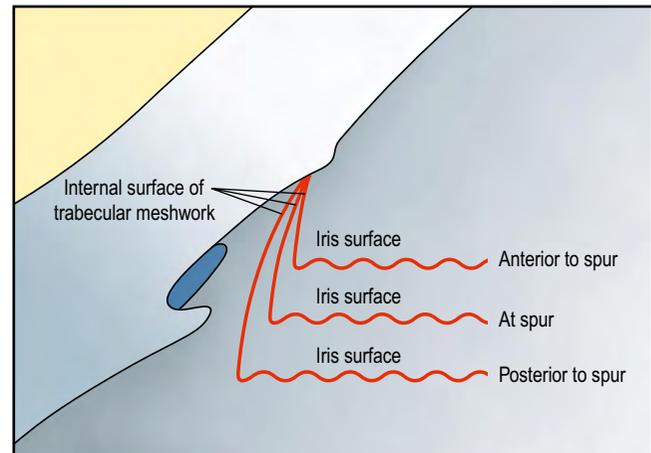


Fig. 19-4 In isolated trabeculodysgenesis with flat insertion, the iris may insert behind, at, or anterior to the scleral spur. In this type of disease, the iris most commonly inserts anterior to the spur.

although the anterior ciliary body may be seen through thick trabecular meshwork if the angle is viewed obliquely from above. The invisibility of the angle recess and ciliary body in the eye with glaucomatous trabeculodysgenesis is a key distinction from the normal infant angle.¹² The iris insertion level may vary along the chamber angle, with some portions of the iris inserting anterior to the scleral spur and other areas inserting at the spur or even posterior to the spur (Fig. 19-4). The surface of the trabecular meshwork may have a stippled, orange peel appearance. The peripheral iris stroma may appear thinned and expose radial blood vessels, as are seen in the immature iris of normal infants. More pronounced iris thinning can occur if the eye enlarges.

In the second form of isolated trabeculodysgenesis, the iris inserts concavely into the chamber angle wall. The plane of the iris is posterior to the scleral spur, but the anterior stroma sweeps upward over the trabecular meshwork obscuring the scleral spur and inserting into the upper portion of the trabecular meshwork just posterior to Schwalbe's line. Thus the iris sweeps around the angle, forming a concave or 'wrap-around' insertion. This conformation is recognized most easily in brown irides and is less commonly seen in children than the flat iris insertion (Fig. 19-5).

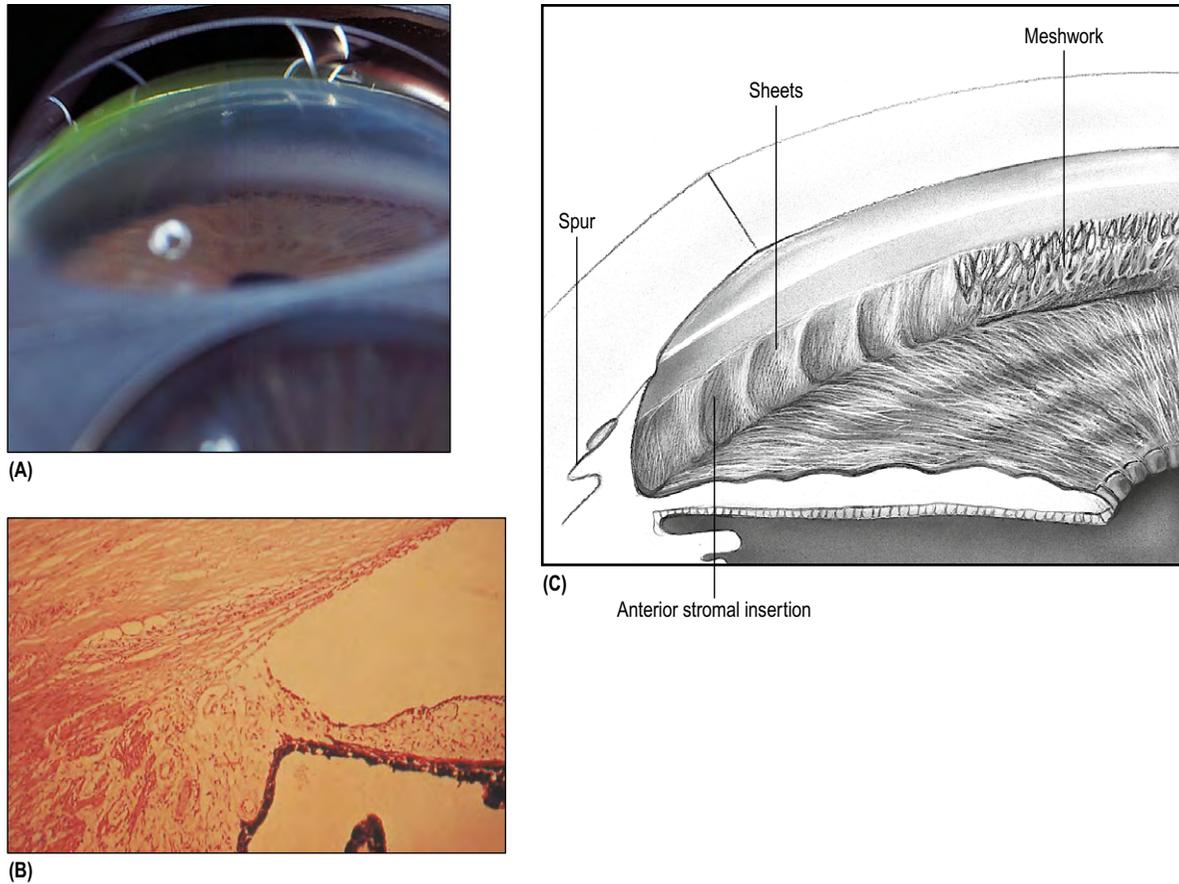


Fig. 19-5 (A) Goniophotograph of a young patient with primary congenital glaucoma revealing a flat iris with peripheral thinning and peripheral radial vessels. A high insertion to the level of the scleral spur is not visible above but is visible below. The trabecular meshwork is slightly greyish, and there is no definition to Schwalbe's line. There is no pigmentation within the trabecular meshwork, which is normal for young people. (B) Histopathology of primary infantile glaucoma. The iris and anterior ciliary body cover the scleral spur and posterior trabecular meshwork. The intratrabecular spaces are compacted. (C) Concave iris insertion in isolated trabeculodysgenesis. The iris may sweep up over the trabecular meshwork as a dense sheet or loose syncytium. Glaucoma associated with this type of iris insertion will respond to goniotomy in infants. (A from Campbell DG, Netland PN: Stereo atlas of glaucoma, St Louis, Mosby, 1998. B from Armed Forces Institute of Pathology. In: Alward WLM: Color atlas of gonioscopy, San Francisco, Foundation of American Academy of Ophthalmology, 2000.)

Both the anterior flat iris insertion and the 'wrap-around' configuration may appear in later 'juvenile' forms of open-angle glaucoma through the third or fourth decade of life.¹³

Isolated trabeculodysgenesis must be differentiated from the gonioscopic appearance of the anterior chamber angle in a normal newborn eye. In a normal newborn, a flat insertion of the iris into the angle wall just posterior to the scleral spur is present. The normal angle recess forms during the first 6–12 months of life. The ciliary body is seen as a distinct band anterior to this iris insertion. The more narrow the ciliary body band, the more developmentally immature is the angle.¹⁴

Isolated trabeculodysgenesis usually presents with symptoms of elevated IOP after the first month of life. A key point in the surgical management of glaucoma infants: if examination reveals isolated trabeculodysgenesis, a prompt goniotomy is highly successful.¹⁵

Iridodysgenesis

Congenital anomalies of the iris are associated with maldevelopment of the trabecular meshwork, the anterior stroma, the full thickness of the iris, the iris vessels, or any combination of these structures.^{15a,15b} In these disorders, the appearance of the trabecular

meshwork may be similar to that found in isolated trabeculodysgenesis. In some cases, additional changes may be seen in the angle, such as irregular clumping of tissue, abnormal vessels, or irido-corneal adhesions.

Anterior stromal defects

Hypoplasia of the anterior iris stroma is the most common iris defect associated with developmental glaucoma. True hypoplasia of the anterior stroma, as opposed to atrophy or thinning, is diagnosed only when there is clear malformation of the collarette with absence or marked reduction of the crypts. This condition is to be distinguished from the stretching of the iris from elevated IOP, which can thin the anterior stroma. The pupillary sphincter may be quite prominent and can have a distinct ring appearance or a 'feathered' outer border (Fig. 19-6; also see Fig. 19-32).

Iris hyperplasia causes a thickened, velvety, pebbled appearance of the anterior iris stroma. Hyperplasia is uncommon and is sometimes seen in association with Sturge-Weber syndrome.

Developmental anomalies of the iris vasculature can occur as a persistent tunica vasculosa lentis or as irregularly wandering superficial iris vessels. In persistence of the tunica vasculosa lentis



Fig. 19-6 Anterior segment photograph of a patient with Axenfeld's anomaly showing a prominent, centrally displaced Schwalbe's ring with peripheral iris attachments. There is iris hypoplasia with loss of iris stroma. (From Campbell DG, Netland PN: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)



Fig. 19-7 Persistence of tunica vasculosa lentis. Blood vessels extend from peripheral iris and ciliary body to envelop the equator of lens.

(Fig. 19-7), a regular arrangement of vessels is seen looping into the pupillary axis either in front of or behind the lens. Over time, attenuation and involution of the vascular veil occur, and continued clinical surveillance is usually sufficient.

Superficial anomalous iris vessels wander irregularly over the iris surface (Fig. 19-8) and do not conform to the normal radial configuration of the iris vasculature. The pupil is usually distorted, and the iris surface has a whorled appearance, often with areas of hypoplastic anterior iris stroma. Present at birth, it is unclear whether these vessels represent an earlier onset of primary congenital glaucoma or an entirely different syndrome. Eyes with this condition have a grave prognosis and usually require multiple surgeries.

Structural iris defects

A structural iris defect (Fig. 19-9) may be seen as a small hole through the iris with no involvement of the sphincter muscle or as a full-thickness coloboma involving the sphincter. The most severe structural iris defect is aniridia, in which only a peripheral stump of iris remains.

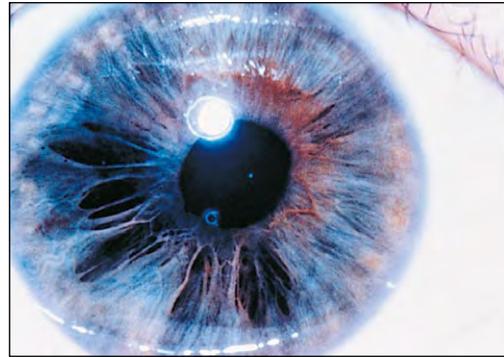


Fig. 19-8 Anomalous superficial vessels course irregularly over the anterior stroma of the iris. The anterior stroma is distorted, and the pupil may be irregularly shaped.



Fig. 19-9 Structural iris defects may be of a variety of configurations, all of which are demonstrated in this single iris. Total absence of sphincter may occur, as shown in the nasal side of this iris. Elliptic openings may penetrate the anterior stroma or full iris thickness, as seen in the temporal side of this iris.

Corneodysgenesis

The corneal stretching and clouding that occur as a result of elevated IOP are acquired, not congenital, defects. Congenital corneal defects may involve the peripheral, midperipheral, or central cornea, or they may appear as abnormalities of corneal size that exist regardless of whether the IOP is elevated. In most cases, associated congenital iris abnormalities exist.

In peripheral corneodysgenesis, a condition exists in which bridging iris filaments or bands attach to a prominent cord-like Schwalbe's line (posterior embryotoxin) (see Figs 19-31 and 19-32). These peripheral abnormalities extend no more than 2mm into the clear cornea and usually involve the entire corneal circumference. Axenfeld's anomaly is the classic disorder demonstrating these abnormalities; however, in the absence of other associated anomalous defects of the angle, posterior embryotoxin alone is not associated with glaucoma and can be seen in as many as 8% of normal eyes.¹⁶

Midperipheral lesions are found in addition to the peripheral abnormalities in patients with Rieger's anomaly.¹⁷ The iris is attached to the cornea in broad areas of apposition that extend out toward the center of the cornea, and pupillary anomalies and holes of the iris are common. The cornea is usually opacified in the areas of the iris adhesions (see Fig. 19-35).

Central corneal anomalies may show evidence of adhesions between the collarette of the iris and the posterior aspect of the central cornea. The cornea usually is opacified centrally and may be thinned. Occasionally a corneal fistula forms. An area of clear cornea between the central defect and the corneal scleral limbus is common. These corneal defects have been called a variety of names, including Peter's anomaly, posterior ulcer of von Hippel, and posterior keratoconus (see Fig. 19-36). Often distinctions among corneal opacifications can be made clinically with high-resolution ultrasound biomicroscopy.¹⁸

Abnormalities of corneal size may occur as microcornea or macrocornea. *Microcornea* may be seen in a variety of congenital anomalies, including microphthalmos, nanophthalmos, Rieger's anomaly, persistent hyperplastic primary vitreous, and congenital rubella syndrome. *Macrocornea* is seen in patients with Axenfeld's syndrome or in X-linked recessive megalocornea. It is distinguished from the corneal stretching resulting from increased IOP by the absence of tears in Descemet's membrane. The prognosis for control of glaucoma in eyes with corneodysgenesis is considerably worse than in eyes with isolated trabeculodysgenesis.

CLINICAL PRESENTATION

As compared with older children and adults, the infant with glaucoma has unique signs and symptoms, including epiphora, photophobia, and blepharospasm, which are present regardless of the cause of the glaucoma and are due to irritation that accompanies corneal epithelial edema caused by elevated IOP. A hazy appearance of the cornea can be intermittent in the early stages and can precede breaks in Descemet's membrane (Fig. 19-10).

Enlargement of these eyes occurs under the influence of elevated IOP, with enlargement mainly at the corneoscleral junction. As the cornea stretches, ruptures of Descemet's membrane allow influx of aqueous into the corneal stroma and epithelium, causing a sudden increase in edema and haze and an increase of tearing and photophobia. The child may become irritable. Large eyes often are not a concern to parents because they are believed to enhance the beauty of the child. But to the ophthalmologist, large eyes are a warning sign.

The breaks in Descemet's membrane (Haab's striae) are single or multiple and appear as glassy parallel ridges ('railroad tracks') on the posterior cornea. The breaks may present in the peripheral cornea concentric with the limbus or in various orientations near or across the central visual axis (Fig. 19-11). The corneal endothelium will migrate over the defect, allowing the edema to clear; however, irregular astigmatism may persist and interfere with vision.

If IOP is uncontrolled, tearing, photophobia, and blepharospasm worsen. Continued enlargement of the cornea from tears of Descemet's membrane may lead to corneal scarring, erosions, and ulcerations. Stretching and ruptures of the zonules can cause lens subluxation. Blunt trauma in these enlarged eyes may result in hyphema and rupture of the globe. Phthisis bulbi may be the final outcome.

After the child is approximately 3–4 years of age, continued enlargement of the globe is less common. The posterior sclera, however, still may be elastic enough to cause a progressive myopia as a result of elevated IOP. Increasing myopia is common in children, but in conjunction with large corneas, suspicious pressures, or discs, it should prompt consideration of glaucoma.

Occasionally, the older child will experience pain with glaucoma, but this is unusual. Most commonly, there are no symptoms



Fig. 19-10 This child has subtle clouding and enlargement of the right cornea. At this point, there are no breaks in Descemet's membrane. Although pressures are elevated in this case of developmental glaucoma, photophobia is minimal.

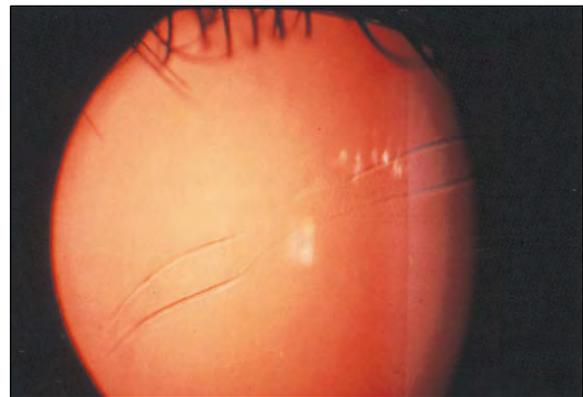


Fig. 19-11 Haab's striae in primary infantile glaucoma. These breaks in Descemet's membrane are usually oriented horizontally (as seen here) or circumferentially. Vertical breaks may be seen in obstetric injuries following forceps deliveries. (From Atward WLM: Color atlas of gonioscopy, San Francisco, 2000, Foundation of American Academy of Ophthalmology.)

until visual field defects become symptomatic. Because diagnosis before symptoms appear is desirable, routine examination of the optic nerve should be performed in all children during preschool examination.

Tonometry should be performed in children who can cooperate (Fig. 19-12). When pacified, nursing infants can often be topically anesthetized and undergo non-contact (e.g., Keeler Pulsair) or contact (e.g., TonoPen, pneumotonometer) tonometry; the non-contact tonometer can be used as a 'game' in children under 6 years of age.¹⁹ In children who cannot cooperate for tonometry, further evaluation with the aid of sedation or general anesthesia is warranted. With or without sedation, examination of the optic nerve is needed to reveal suspected or significant damage from elevated IOP.

EXAMINATION

Office examination

Depending on the age and level of cooperation of the patient, general anesthesia may be required to evaluate the child with glaucoma.^{20,21}



(A)



(B)

Fig. 19-12 (A) Parents of this child used a blue flashlight to prepare the child at home to undergo applanation tonometry and **(B)** ophthalmoscopy. By age of 2½ the child was able to cooperate for examinations in the office.

A complete ocular examination, including slit-lamp examination, applanation tonometry, pachymetry, gonioscopy, optic nerve evaluation, and retinoscopy, can be performed in the office in children older than 5 years of age and, with some training, in children as young as 3. If necessary, the child can be given a mild sedative, such as chloral hydrate syrup (100 mg/kg of body weight to a maximum dose of 3 g in normal, healthy, full-term infants 1 month of age or older).²² Chloral hydrate does not affect IOP readings.²³

Many children after age 5 years can undergo kinetic Goldmann visual field testing with the assistance of a patient and encouraging perimetrist. Pediatric glaucomatous visual field defects duplicate the spectrum of field defects seen in adult primary open-angle glaucoma.²⁴ A gross confrontation visual field examination can be performed on children by holding a toy in the peripheral fields and either moving the toy or shining a light within the toy. Older and more cooperative children will provide a more detailed examination. By the age of 8–10 years, some children can cooperate for a full quantitative visual field examination.

Sometimes a reasonably good office examination can be performed on infants younger than 3 months using the infant diagnostic lens of Richardson and Shaffer (Fig. 19-13). The lens allows examination of the anterior segment, the angle, and the optic nerve head and is well tolerated when placed in the eye with topical anesthesia. Using a direct ophthalmoscope, the examiner can obtain a good view of the posterior pole even if the child has small pupils and mild corneal haze.

Examination under anesthesia

General anesthesia usually is required for a thorough examination of children under the age of 5. With a healthy child and an anesthesiologist experienced in dealing with infants, there is little risk. Surgery has been performed on numerous children under 7 days of age.

A standardized routine for evaluations under anesthesia (EUA) is important, with an assistant simultaneously noting clinical findings



Fig. 19-13 Richardson-Shaffer lens (left) is a small version of the Koeppel lens (right) that fits into the lid aperture of infants. It is useful for examining the anterior segment, as well as the fundus.

determined by the examining physician. All of the essential information regarding the presence and type of glaucoma, the extent of damage, associated findings, and the appropriate surgical options should be established in a prompt, methodical fashion.²¹ The sequential components of the EUA consist of measuring the IOP, assessing the corneal thickness and diameters, gonioscopy, and ophthalmoscopy; additionally, axial length measurements, ultrasonic biomicroscopy, or cycloplegic retinoscopy may also be performed.

Intraocular pressure measurement

There are many variables to consider when assessing a child's IOP: the child's age; the patient's level of activity or sedation; effects of anesthetics; corneal thickness and health; diurnal variations, and, perhaps most importantly, the choice of measuring instrument. The clinician can choose among a variety of tonometers based on

Table 19-1 Intraocular pressures (mmHg) among normal awake children using different tonometers

Age	Pulsair (SD)*	Perkins (SD)†	Pneumotonometer (SD)‡
Premature (26–37 weeks)	10.2‡	18.3§	–
0–1 year	10.6 (3.1)	4.6 (0.5)	14.5 (0.5)
1–2 years	12.0 (3.2)	4.9 (0.5)	14.6 (0.6)
2–3 years	12.6 (1.5)	5.8 (1.0)	15.3 (1.4)
3–4 years	13.7 (2.1)	6.4 (1.8)	14.5 (0.9)
4–5 years	13.6 (2.0)	7.9 (1.3)	14.8 (2.0)
5–6 years	14.4 (2.0)	–	–
6–7 years	14.2 (2.3)	–	–
7–8 years	14.0 (2.5)	–	–
8–9 years	14.3 (1.7)	–	–
9–10 years	14.0 (2.7)	–	–
15–16 years	15.2 (2.4)	13.2	16.42 (2.2)

*Data from Pensiero et al.²⁵;
†Jaafar & Kazi²⁶;
‡Spierer et al.²⁷;
§Musarella & Morin.²⁸

various measuring principles: applanation (Goldmann or hand-held Perkins); indentation (Schiotz); indentation-applanation hybrid (pneumotonometer); non-contact air-puff (Keeler Pulsair), or electronic (TonoPen or Mackay-Marg). Results among instruments vary.

In a large series of unanesthetized healthy children from birth through age 16 measured with the Pulsair device, three different phases of the IOP were identified:

1. *Neonatal phase.* Up to age 1, the average IOP was 10 mmHg, without gender differences, and unrelated to gestational age or birth weight.

2. *Phase of increased IOP values.* An exponential curve of rising IOPs up to age 7–8, rising faster in boys until age 4 and continuing more slowly in girls to age 9 was seen.

3. *Phase of steady IOPs.* From age 8 onward, females had higher IOPs than males, with 'adult' values obtained by mid adolescence.²⁵ Different instrumentation yielded similar trends but with wide variability (Table 19-1).

When validated by intraoperative manometry under anesthesia, the Perkins applanation device tended to underestimate IOP (especially in the supine position), the TonoPen slightly overestimated IOP, and the pneumotonometer was most accurate.²⁹ In another study of children under anesthesia,³⁰ the Schiotz tonometer gave the highest readings; moreover, it is also subject to many artifacts affecting its reliability, such as altered scleral rigidity, small corneal size, or surface abnormalities. Although only one tonometer is indispensable for examinations under anesthesia, another device or two is advisable to double check the measurement and confirm a tendency toward elevation or asymmetry with respect to the fellow eye.

General anesthetics lower IOP to variable amounts and at variable times after administration (Table 19-2).³¹ Intraocular pressure measurements should be taken as soon as the child is quiet, and the precise interval in minutes between onset of anesthesia and the pressure measurements should be noted. Laryngeal mask anesthesia

Table 19-2 Effect of anesthetics and sedatives on intraocular pressure

Anesthetic agent	Route of administration	Usual effect on IOP
Chloral hydrate	Oral or rectal	Nil
Midazolam	Rectal, intramuscular (IM), intravenous (IV)	± Decrease
Methohexital (Brevital)	Rectal, IM, IV	± Decrease
Nitrous oxide	Inhalation	Mild decrease
Oxygen	Inhalation	Mild decrease
Inhaled fluorocarbons (e.g., halothane, enflurane)	Inhalation	Mild–significant decrease
Ketamine	IM	Modest elevation
Succinylcholine	IV	Significant elevation
Compared to endotracheal intubation	–	Significant elevation

Data from Freedman & Walton⁸; Murphy³²; Watcha et al.³³; Lamb et al.³⁴; Barclay et al.³⁵

is a valuable alternative to tracheal intubation,³⁶ with the added feature of causing significantly less IOP elevation at the time of extubation in both normal and glaucomatous eyes.^{34,35,37,38} The laryngeal mask is particularly useful in EUAs with children because it simultaneously protects the patient's airway and allows the examiner unhindered access to both eyes for complete evaluation, such as Koeppel gonioscopy. A mask with an oral airway is also adequate and safe for short examinations. Intramuscular ketamine can be administered in younger children when examination is for diagnosis only; intravenous administration may raise the IOP slightly.

As in the management of adult primary open-angle glaucoma, it is best to place the measured IOP into a clinical context, giving special weight to trends or to asymmetric measurements between two eyes. The diagnosis of glaucoma depends on several factors, only one of which is the pressure level. Elevated IOP by itself, unless extreme, is insufficient to confirm the diagnosis of glaucoma.

To confirm a diagnosis of glaucoma and justify surgery, it is necessary to verify other signs, such as increased corneal diameter, corneal haze, increased cup-to-disc ratio, evidence of anterior segment dysgenesis, or glaucoma in the fellow eye. Otherwise, it is better to re-examine the child in 4–6 weeks to confirm the diagnosis before performing surgery.

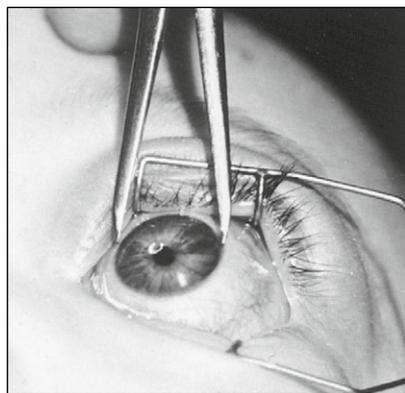
Corneal measurements: diameter and central thickness

As with IOP, there is no absolute normal limit for the corneal diameter among children, although growth trends are evident (Table 19-3). Measuring the corneal diameters, both horizontally and vertically, is a fundamental part of childhood glaucoma assessment (Fig. 19-14). A good baseline measurement is required both for initial diagnosis and for detection of subsequent corneal enlargement. An effective measurement of the corneal diameter can be obtained using calipers to measure the horizontal diameter from the first appearance of the white scleral fibers at the limbus on one

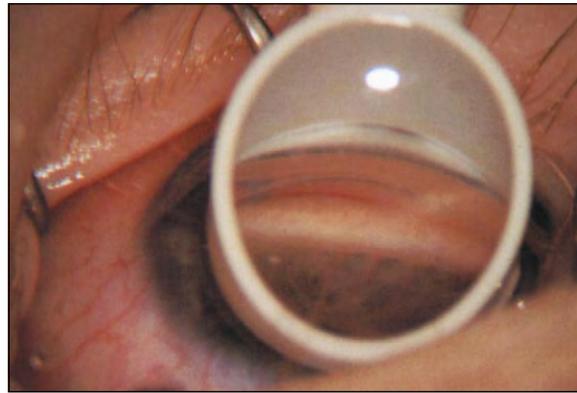
Table 19-3 Corneal diameters and axial lengths among normal eyes and eyes suspicious for glaucoma

Age	Corneal diameters (mm)		Axial length (mm)	
	Normal	Possible glaucoma	Normal	Possible glaucoma
Newborns	9.5–10.5	11.5–12.0	16–17	>20
1 year	10–11.5	12.0–12.5	20.1	>22.5
2 years	11.5–12	12.5–13.0	21.3	>23
3 years	–	–	22.1	>24
>3 years	12	13.0–14.0	23	>25

Data from Morin¹²; Kiskis et al³⁹; Sampaolesi & Caruso R⁴⁰; Fledelius & Christensen.⁴¹



(A)



(B)

Fig. 19-14 Congenital glaucoma examination series. **(A)** Corneal measurement. **(B)** View through a Swan-Jacobs lens into the angle of a child with primary infantile glaucoma. (B from Atward WLM: Color atlas of gonioscopy, San Francisco, 2000, Foundation of American Academy of Ophthalmology.)

side to the same point on the other side, from the 9 o'clock to 3 o'clock positions. This is then repeated vertically from 6 o'clock to 12 o'clock. The measurement is accurate to approximately 0.5 mm; therefore with this technique, changes of less than 0.5 mm should not be considered significant. Some authors prefer customized templates in increments of 0.25 mm for greater precision.²⁸

The measurement of the central corneal thickness (CCT) of adult eyes with primary open-angle glaucoma has a major impact on the clinician's assessment for two reasons: (1) applanation IOP readings are profoundly affected by the CCT (*viz.*, thicker CCTs 'overestimate' and thinner CCTs 'underestimate' true IOPs), and (2) there is a significant risk factor for developing glaucoma damage, independent of IOP corrections, with thinner CCTs.^{1–25,28–31,34–38,42–47} One confounding factor in applying CCT findings in children with glaucoma is the apparent slight thickening of the infant cornea until adult values are reached between age 5–9 years old.⁴⁸

Nevertheless, the clinical effect of CCT measures on the IOP in children is similar to that seen in adults, with thicker corneas seen with ocular hypertension and thinner CCTs on average among black children than in whites.^{49,49a,49b} One large study comparing children under 3 years old – those status-post-congenital glaucoma surgery versus age-related normals undergoing nasolacrimal dilation – demonstrated thinner CCT measurements in glaucomatous eyes, which positively correlated with their larger corneal diameters and longer axial lengths.^{50,50a} On the other hand, thick CCTs are expected in eyes with significant corneal edema from elevated IOP,

and have been reported in eyes with glaucoma with aniridia^{4,51} and in eyes status-post-congenital cataract surgery.^{5,52} Although examinations under anesthesia often require specula to pry the lids for several minutes, with some possible corneal drying, the clinical impact on CCT measures is negligible.^{6,53} The value of pachymetric measures of CCT in infantile glaucoma, though not completely clarified, is nevertheless useful.

When examining the cornea, the ophthalmologist must look for corneal haziness and tears of Descemet's membrane. Tears involving the visual axis, as evident during retinoscopy, must be noted because they can adversely affect a child's visual acuity and contribute to developing amblyopia.

Axial length measurement

The measurement of axial length by A-scan ultrasonography has been recommended by some investigators for routine use in the diagnosis and follow-up of congenital glaucoma, contending that it is a sensitive and reversible measure of disease.^{40,54–56} Others assert that the corneal diameter measurement, besides being easier to measure using simpler equipment, is the most significant clinical feature in detecting congenital glaucoma.^{39,57} One retrospective study suggests that the major contribution of both axial measures and corneal diameters is in the initial diagnostic stages of glaucoma management, but neither parameter distinguished which patients would require re-operation, especially after the age of 2 years.⁵⁸



Fig. 19-15 Bilateral lens insertion of Koeppel lenses to reveal angle abnormalities better seen by comparing both eyes.

Gonioscopy

In the operating room, Koeppel equipment can be used under clean but non-sterile conditions, such as during EUA (Fig. 19-15). Gonioscopy has classically been performed with a smooth-domed Koeppel 14- to 16-mm lens, with a Barkan light and hand-held binocular microscope. If marked corneal clouding exists, the view may be improved by applying topical anhydrous glycerin, or, if necessary, removing the epithelium with a blade or with a solution of 70% alcohol or 10% cocaine on a cotton-tipped applicator. The Koeppel lens also can aid in the visualization of the iris, the crystalline lens, vitreous, and fundus. The lens neutralizes irregular corneal reflexes and improves the view through a small pupil, even allowing disc photography through a relatively small pupil. Thus the examiner sees the entire optic nerve head (albeit minified) in one field. Contemporary four-mirror lenses, whose corneal surface is less than 12mm, can alternatively be used in conjunction with an operating microscope.

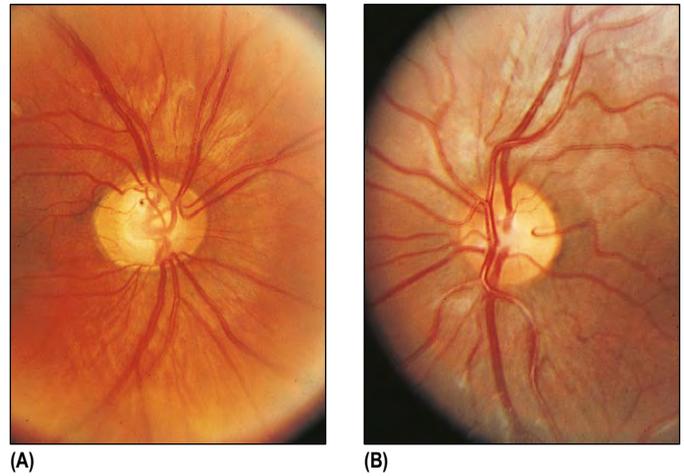
During surgery under the operating microscope, the surgeon can use either a sterile Barkan operating lens (a truncated Koeppel lens) for tangential viewing during insertion of a gonio-knife, or a gas-sterilized four-mirror Sussman or Zeiss lens viewed perpendicularly through the microscope.

Ophthalmoscopy

Cupping of the optic nerve is an early sign of increased pressure and occurs much more quickly and at lower pressures in infants than in older children and adults (Fig. 19-16). This characteristic of dramatically enlarging – and after surgery, reversible – cup size in children reflects the greater amount of elastin amidst the connective tissue of the infantile optic nerve head, allowing an elastic response to fluctuation in IOP (Fig. 19-17; see Fig. 13-6).⁵⁹ Decreased cupping can occur rapidly after IOP reduction and is the single most confirmatory sign that the glaucoma has been surgically stabilized or reversed.

Cup-to-disc ratios greater than 0.3mm are rare in healthy infants and should cause suspicion of glaucoma (Table 19-4).^{5,61,62} Inequality of optic nerve cupping greater than 0.2 cup-to-disc ratio is also suggestive of glaucoma.⁶¹

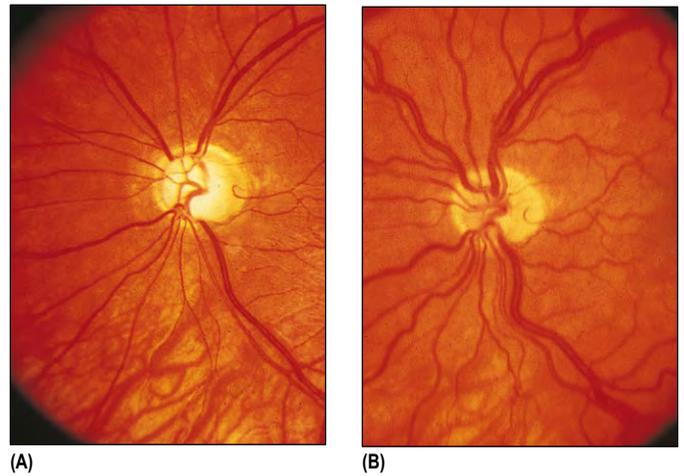
In infancy, the glaucomatous cup can be oval but is more often round, steep-walled, and central, with notable circumferential



(A)

(B)

Fig. 19-16 Asymmetric disc cupping in a child with developmental glaucoma. (A) Note steep-walled cup. This is typical of glaucomatous cupping in the elastic infant eye. (B) The left eye has no cupping.



(A)

(B)

Fig. 19-17 Child with isolated trabeculodysgenesis. (A) Before goniotomy. (B) After goniotomy. Note the reduction in cup size, which is common following successful surgery during the first 1-2 years of life.

Table 19-4 Horizontal cup-to-disc ratios at birth to 3 years

Glaucomatous eyes		Normal eyes	
Cup-to-disc ratio	Seen (n = 95) (%)	Cup-to-disc ratio	Seen (n = 46) (%)
0.1-0.3	5	0.1-0.3	87
0.4-0.5	25	0.4-0.5	13
0.6-0.7	32	-	-
0.8-0.9	38	-	-

Data from Hoskins et al.⁶⁰

Table 19-5 Changes in the cup-to-disc ratio after control of intraocular pressure

Result	Age at surgery	
	<1 year	>1 year
No improvement in cup-to-disc ratio	28	12
Reduction in cup-to-disc ratio of 0.1	15	3
Reduction in cup-to-disc ratio of 0.2	15	0
Reduction in cup-to-disc ratio > 0.2	28	0
Total eyes	86	15

Data from Hoskins et al.⁶⁰

enlargement. *With successful control of the IOP, the cup will either remain stable or its size will decrease.*^{6,59,63} An increased cup size is indicative of uncontrolled glaucoma, and the ophthalmologist must make careful drawings or take photographs with a hand-held camera for future comparison. With normalization of IOP, a reduction in cup size is especially evident in infants less than 1 year of age (Table 19-5).^{5,64}

Other than the reversibility of cupping, the alterations of the optic nerve in infantile glaucoma are comparable to the disc changes seen in adults.²⁴ For example, vertical notching at the inferior and superior poles of the disc appears less often than concentric cupping, as do nerve fiber slit defects. These findings suggest that other than the elastic properties of the infant's disc, the child's optic nerve is subject to similar effects that cause disc cupping in adult glaucoma.

Cycloplegic refraction

After therapeutic normalization of IOP, cycloplegic refraction should be performed to correct significant differences in refractive errors between the two eyes. The importance of refractive surveillance of these eyes cannot be overstressed. Anisometropic and strabismic amblyopia, as well as myopic astigmatism, are prominent causes of visual loss among these children, especially in unilateral cases. Vigorous amblyopia management is as important as adequate glaucoma control by surgery or medication.

Systemic evaluation

A thorough systemic evaluation is also warranted in these children, both to check for any signs of syndromes that may be associated with glaucoma and to ensure the safety of general anesthesia. The coordination of the child's assessment with a pediatrician or specialist in genetics is invaluable.

PRIMARY CONGENITAL GLAUCOMA

INCIDENCE

Although primary congenital glaucoma is the most common glaucoma seen in infancy, it is still an uncommon disease. A general ophthalmologist is unlikely to see more than one new case in several years. Its incidence is approximately 1 in 10 000 live births, though there is tremendous geographic variability, with some reports of 1 case in 1250 Slovakian Gypsy offspring and 1 in 2500 Saudi children.^{1,65} The disease is bilateral in approximately 75% of cases. Males have a higher incidence of the disease, comprising approximately 65% of all cases. More than 80% of primary congenital glaucoma is evident before the first year of life; after age 3 years, classic signs, such as corneal or ocular enlargement, do not occur.

GENETICS AND HEREDITY

Most cases of primary congenital glaucoma occur sporadically.^{66,67} In approximately 10% of cases, an autosomal recessive hereditary pattern is evident. In this situation, both parents usually are heterozygous carriers but do not have the disease. By simple Mendelian genetics, if these parents have four children, one child would be homozygous for primary congenital glaucoma and would manifest the disease, two children would be heterozygous carriers, and one child would be homozygous normal. The actual situation, however, is more complex. Most researchers find a variable penetrance of 40–80%, although penetrance in certain families has been as high as 90–100%. In families with low penetrance, the number of affected children will be less than the expected 25%.

Other researchers believe that primary congenital glaucoma can be inherited through a polygenetic pattern.⁶⁷ This is based on the high percentage of males affected and a rate of involvement of siblings of 3–11% (i.e., the chance of a second child showing the disease) versus the expected 25% if the inheritance were purely recessive. In practical terms, if a second child in a family does manifest infantile glaucoma, the chance for a subsequent sibling with the disease approaches one of four.⁶⁶ It is likely that more than one mode of inheritance exists.

The presence of an affected child should alert the clinician to examine other children in the family. Parents of affected children naturally are concerned about the possibility of other siblings being affected. Some have reported that there is a 4–5% likelihood of occurrence in siblings or offspring of a single affected child. Others have identified the significance of gender on the phenotype's expression. Approximately 3% of siblings may be affected if the affected child is male, and close to 0% if the child is female.⁶⁸

There are, however, families in whom glaucoma appears frequently, and with the advent of molecular genetics, the at-risk members may one day routinely be identified.⁹ This area is among the fastest growing in modern medicine.^{9a,9b} The Human Genome Organization/Genome Database has allocated the following nomenclature for glaucoma genes: *GLC* is the general symbol for glaucoma; 1, 2, and 3, respectively, stand for open-angle, angle-closure, and congenital glaucoma; and *A, B, C*, and so forth refer to the sequential mapping of the first, second, and third genes in that subgroup. By longstanding convention, chromosomes are identified by Arabic numbers (e.g., 1, 2, 3); the long arm and short arm of the chromosome are designated by *q* and *p*, respectively; and further localization by Arabic number appears thereafter. By 2008, scores of loci have been linked to glaucoma and genes identified.^{70,71}

Elucidating the causal chain of events is an ongoing research endeavor. Once 1 of the 26 human chromosomes has been identified as the locus of the genetic defect, the human genome has some 100 000 human genes comprised of 3 billion base pairs. One solitary defective base pair can manifest as a disease; moreover, there is remarkable phenotypic heterogeneity and expression of genetic alterations, as well as clinical overlap of different genetic mutations.^{9,9b,72} For example, it has been estimated that 3% of adult primary open-angle glaucoma patients in the United States manifest a mutation in the *trabecular induction glucocorticoid regulator (TIGR)*, or myocilin, gene.⁷²⁻⁷⁴ But there are at least three known kinds of mutation in this *GLC1A* gene, with variable expressions of glaucoma. The precise manner in which a defectively coded protein participates in the cascade of events that manifest as clinical glaucoma also remains to be elucidated.

Clinical implementation of such technical information is a complex task, embracing a wide range of ethical, legal, and social issues. A particularly helpful compilation, underwritten by the Human Genome Project, addresses such dilemmas as predictive testing for adult-onset disease and alternative models for genetic counseling; non-directiveness in genetic counseling; morally relevant features of defining genetic maladies and genetic testing; abortion and the new

genetics, and ethics of gene therapy.⁷⁵ An example of but one ethical issue in genetic screening for familial glaucoma (and, in fact, all medical diseases) is the uncertainty that a positive screening result will actually clinically manifest, combined with the unknown risk of clinical disease manifesting despite a negative gene screen battery. Clinical wisdom simply dictates that patients and their families at risk continue to undergo regular clinical surveillance until the predictive reliability of human genetic screening is more established.

PATHOPHYSIOLOGY

Anderson described the normal development of the infant angle using scanning electron microscopy, transmission electron microscopy, and phase contrast light microscopy.⁷⁶ The anterior surface of the iris meets the corneal endothelium at 5 months of gestation to form the peripheral aspect of the anterior chamber. Slightly posterior to this junction are cells forming the developing trabecular meshwork. Ciliary muscle and ciliary processes overlap the trabecular meshwork, being separated by loose connective tissue. The trabecular meshwork later becomes exposed to the anterior chamber as the angle recess deepens and moves posteriorly (Fig. 19-18).

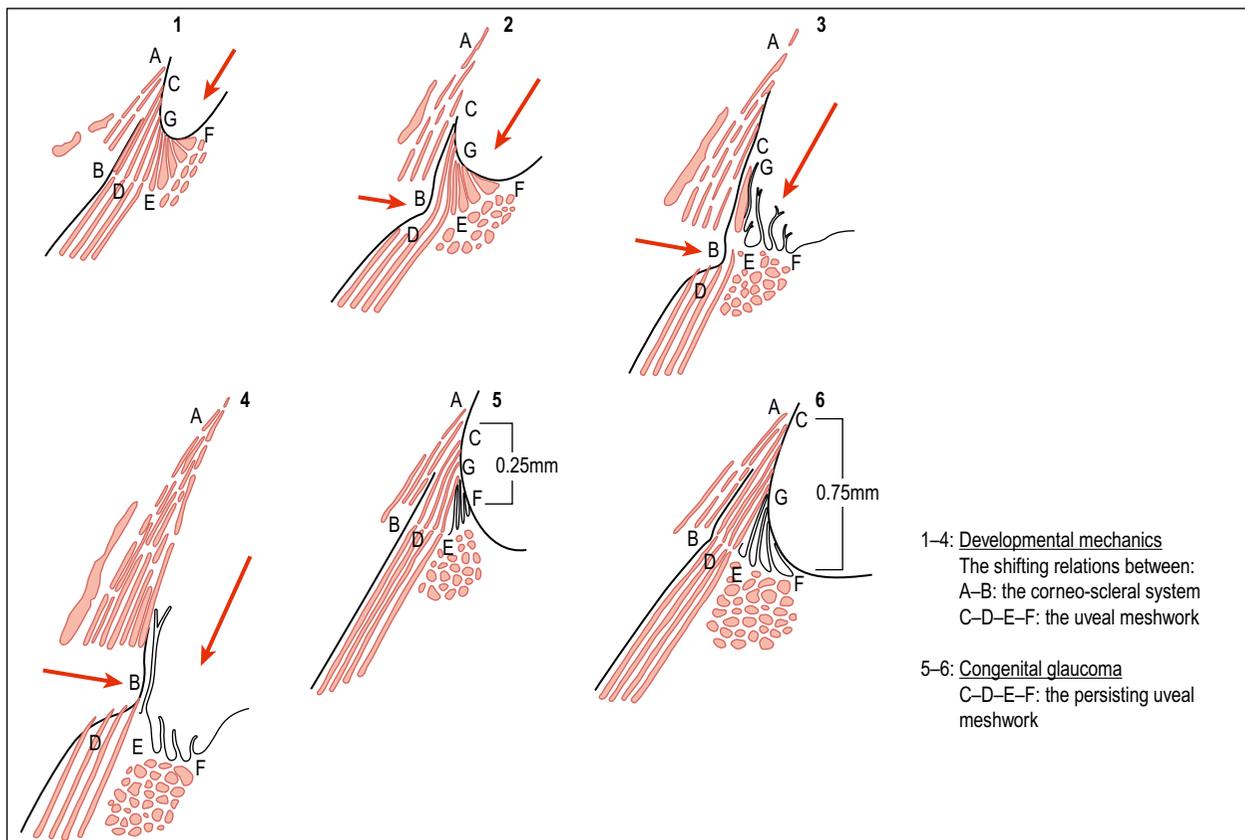


Fig. 19-18 Developmental mechanics of chamber angle. In stage 1, the corneoscleral system forms a purely scleral structure, and the uveal system, consisting of ciliary muscle and its fetal tendon (pectinate ligament or uveal meshwork) is virtually independent from it. Continued development of the chamber angle involves two directions of growth: ingrowing scleral spur (horizontal arrow) gradually invades receding uveal meshwork (vertical arrow). The final stage is the total shift of the insertion of longitudinal muscle from fetal pectinate ligament into scleral spur. During this process, fetal uveal meshwork disappears except for a few fine residual iris processes. In the case of fetal retardation, this developmental process is arrested at an earlier stage, leading to persistence of the uveal meshwork and production of congenital glaucoma.

(From Worst JGF: The pathogenesis of congenital glaucoma: an embryological and goniosurgical study, Assen, The Netherlands, Van Gorcum BV, 1966.)

Various explanations have been proposed to explain how this deepening process occurs.^{16,66} One such mechanism suggests that atrophy and absorption of tissue are responsible.⁷⁷ Another theory proposes that the angle is formed by a process of cleavage between two separate cell types, one of which forms a trabecular meshwork and the second of which forms the root of the iris and ciliary body.⁷⁸ Anderson believes the trabecular meshwork becomes exposed to the anterior chamber by means of posterior sliding of the iris, ciliary muscle, and ciliary processes.⁷⁶

Embryologically the source of cells for the angle structures are mesenchymal, migrating, and differentiating from the neural crest.^{79–81} Although the major developments that lead to the iridocorneal angle unfold in the third trimester, embryonic insults in the first 3–5 weeks following fertilization can also manifest as anterior segment dysgenesis.⁸²

In the normal newborn eye, the iris and ciliary body have usually recessed to at least the level of, and usually posterior to, the scleral spur. Thus during gonioscopy of a normal newborn eye, the insertion of the iris into the angle wall will be seen posterior to the scleral spur, in most cases with the anterior extension of the ciliary body seen as a distinct band anterior to the iris insertion. The iris insertion into the angle wall is rather flat because the angle recess has not yet formed.⁸³ Continued posterior sliding of uveal tissue occurs during the first 6–12 months of life and appears gonioscopically as formation of the angle recess and the apparent posterior insertion of the iris root into the ciliary body. The visibility of the angle recess and ciliary body in fact is a distinguishing feature of the normal infant eye and is conspicuously absent in eyes with trabeculodysgenesis.¹⁴

Anderson's studies have shown that the iris and ciliary body in primary congenital glaucoma appear like an eye that is in the seventh or eighth month of gestation rather than one at full-term development.⁷⁶ The iris and ciliary body have failed to recede posteriorly, and thus the iris insertion and anterior ciliary body overlap the posterior portion of the trabecular meshwork.

Furthermore, histologic studies by Maumenee found an anterior insertion of the ciliary body muscle.^{63,84} He noted that the longitudinal and circular fibers of the ciliary muscle insert into the trabecular meshwork rather than the scleral spur. He also noted that the root of the iris can insert directly into the trabecular meshwork.

Histologic abnormalities found in the trabecular meshwork itself include a thickening of the trabecular beams, thickened cords of the uveal meshwork, and compression of the meshwork with a resultant decrease of trabecular spaces (Fig. 19-19).

Barkan^{83,85} and Worst^{86,87} proposed that the surface of the trabecular meshwork is covered by a thin membrane (Barkan's membrane). Despite extensive histologic examination by Anderson,⁷⁶ Maumenee,^{88,89} and others, however, this membrane has not been found.

Anderson suggests that the apparent membrane was made up of thickened, compact trabecular beams in the area of the meshwork adjacent to the anterior chamber.⁷⁶ This formation gives the appearance of a membrane at the relatively low magnification of gonioscopy and the operating microscope.

Schlemm's canal is open in early cases of primary congenital glaucoma. It may be obliterated in advanced cases, but this is believed to be a secondary alteration caused by the effect of pressure elevation on the ocular tissues. A thickening of the juxtacanalicular connective tissue has been noted, as has an amorphous material in the sub-endothelial area of the internal wall of Schlemm's canal.⁹⁰ It may be that thickened cords of uveal meshwork hold the iris anteriorly,



Fig. 19-19 Specimen from an infant with isolated trabeculodysgenesis. Note that uveal meshwork (U), has no impermeable membrane. Trabecular sheets are somewhat compressed together. Iris inserts well anteriorly onto scleral spur (arrow). Incision of uveal meshwork via goniotomy allows the iris to drop posteriorly and allows trabecular sheets to separate. (Courtesy of Jorge Alvarado, MD, University of California, San Francisco.)

possibly preventing the scleral spur from rotating posteriorly and preventing the trabecular sheets from separating normally.

Clinical evidence supports the theory that the obstruction to aqueous flow is located at the trabecular sheets. Incision into the trabecular sheets by goniotomy relieves the obstruction and normalizes the IOP in most cases. The goniotomy incision may work by allowing the iris to fall posteriorly, which relieves compaction of the trabecular sheets and allows the intertrabecular spaces to open.¹¹ Surgical success is achieved by making a superficial incision into the trabecular meshwork; incisions at various heights along the meshwork seem to be equally effective.

DIFFERENTIAL DIAGNOSIS

There are a variety of conditions that should be considered in differentiating primary congenital glaucoma from other similar clinical presentations (Box 19-3).

Other glaucomas

Primary congenital glaucoma is diagnosed when glaucoma is found in a child with isolated trabeculodysgenesis but with no other ocular or systemic anomalies of development and no other ocular diseases that could result in an increase in IOP. Complete general physical and ocular examinations must be performed. Isolated trabeculodysgenesis may also be the ocular anomaly producing glaucoma in Rubinstein-Taybi syndrome, Sturge-Weber syndrome in infancy, trisomies 13–15, Lowe syndrome, and rubella.

Other causes of corneal enlargement or clouding

Megalocornea is a condition of marked corneal enlargement, often to diameters of 14–16mm. Other signs of congenital glaucoma are absent. These eyes have deep anterior chambers and may have

Box 19-3 Differential diagnosis of primary congenital glaucoma

- I. Other glaucomas
 - A. Glaucoma associated with congenital anomalies
 - B. Secondary glaucoma
- II. Other causes of corneal enlargement or clouding
 - A. Megalocornea
 - B. Sclerocornea
 - C. High myopia
 - D. Metabolic diseases
 1. Cystinosis
 2. Mucopolysaccharidoses
 - a. MPS I H = Hurler's syndrome
 - b. MPS I S = Scheie's syndrome
 - c. MPS II = Hunter's syndrome
 - d. MPS IV = Morquio's syndrome
 - e. MPS VI = Maroteaux-Lamy syndrome
 - f. MPS VII = β -Glucuronidase deficiency
 3. Hand-Schüller-Christian disease (histiocytosis)
 4. Acrodermatitis enteropathica
 5. Peroxismal disorders
 6. Zellweger syndrome
 - E. Posterior polymorphous dystrophy
 - F. Congenital hereditary endothelial dystrophy
 - G. Obstetric trauma
 - H. Inflammation (keratitis, iridocyclitis)
- III. Other causes of epiphora or photophobia
 - A. Nasolacrimal duct obstruction
 - B. Conjunctivitis
 - C. Corneal abrasion
 - D. Meesman's corneal dystrophy
 - E. Reis-Buckler's dystrophy
- IV. Other causes of optic nerve abnormalities
 - A. Pit
 - B. Coloboma
 - C. Hypoplasia
 - D. Tilted disc
 - E. Large physiologic cup

iridodonesis secondary to stretched zonules and a loose lens. On gonioscopic examination, the examiner may find a normal angle, prominent iris processes, or a broad, densely pigmented trabeculum. A high degree of axial myopia is part of the differential diagnosis of megalocornea, as determined by retinoscopy and axial measurements.

Ninety per cent of megalocornea cases occur in males with sex-linked inheritance (Fig. 19-20). Families can have some members with megalocornea and others with primary congenital glaucoma; autosomal dominant congenital miosis can also be seen with megalocornea.⁹¹ This variety of anterior segment disorders is felt to be a manifestation of germ-line mosaicism, with similar embryogenic neural crest cells expressing phenotypic diversity.⁹² Some clinical observers relate that megalocornea may be a spontaneously arrested form of congenital glaucoma.⁹³ Individuals with megalocornea and their families must therefore be periodically checked for the development of glaucoma as well as for cataracts, which can form in this condition.

Sclerocornea is a condition in which extensions of opaque scleral tissue course into the cornea, usually bilaterally, in both autosomal dominant and recessive pedigrees.^{94,95} Vessels usually penetrate deeply and superficially into the cornea. It is sometimes seen in conjunction with cornea plana, Ehlers-Danlos syndrome type VI, and microcornea.⁹⁶⁻⁹⁸

Numerous metabolic diseases can cause corneal haze, including the infantile form of cystinosis, six mucopolysaccharidoses, and the mucopolidoses.

Posterior polymorphous dystrophy occasionally can be present in infancy with corneal edema and without corneal enlargement. It is a dominantly inherited, bilateral disease characterized by peripheral anterior synechiae and polymorphous opacities, typically vesicular, at the level of Descemet's membrane. The associated glaucoma can be either an open-angle or synechial-closure type and usually appears later in life.⁹⁹ By corneal specular microscopy, it can be distinguished from the iridocorneal endothelial syndrome.¹⁰⁰

Congenital hereditary endothelial dystrophy can be present at birth or in the first 1–2 years of life and is seen as a diffuse, bilateral, symmetric corneal edema with photophobia.¹⁰¹ Stromal thickness can be three times the normal level, and clouding can vary from a mild haze to a milky, ground glass opacification (Fig. 19-21). Although usually distinct from congenital glaucoma, cases have been reported that histologically demonstrated congenital hereditary endothelial dystrophy at the time of penetrating keratoplasty, following prior glaucoma surgery.^{102,103}

Obstetric trauma, such as forceps injury that ruptures Descemet's membrane, can result in corneal edema and corneal clouding. These ruptures often are vertical but may run in any direction. There is no corneal enlargement, and the optic nerve is normal. Intraocular pressure typically is normal but may be elevated, usually transiently. The condition is usually unilateral and affects the left eye because of the higher incidence of left anterior occiput presentation at birth. Frequently, periorbital tissues exhibit signs of trauma as well, at least in the perinatal period.

A host of inflammatory diseases – such as viral keratitis (e.g., adenovirus serotype 10) or viral iridocyclitis (e.g., Herpes family) – can cause corneal edema and clouding. Rubella keratitis is particularly suspect in the newborn. Syphilitic keratitis is often seen with secondary iridoschisis and angle closure.¹⁰⁴⁻¹⁰⁶ Other conditions to be considered include human immunodeficiency virus and phlyctenular disease.¹⁰⁷

Other causes of epiphora or photophobia

Diseases presented in the section on corneal clouding, such as inflammation and congenital hereditary endothelial dystrophy, can cause epiphora and photophobia. Some of the disorders discussed in this section, particularly the corneal dystrophies, can result in opacification of the cornea.

The most common cause of epiphora is obstruction of the nasolacrimal duct. Photophobia is not associated with this problem. A chronic mucopurulent discharge may be evident.

Any of several causes of conjunctivitis in the infant can present with redness and tearing. Chemical conjunctivitis caused by silver nitrate prophylaxis is a common cause in the newborn. Bacterial and chlamydial infections are usually associated with a mucoid or mucopurulent discharge and must be ruled out. Viral conjunctivitis must also be suspected. Corneal abrasions are also frequent causes of acute ocular irritation in children and are diagnosed from history and fluorescein examination.

Meesman's corneal dystrophy usually is present in the first several months of life. Patients exhibit ocular irritation, and examination reveals multiple clear to gray-white punctate opacities of the corneal epithelium that are intraepithelial cysts. The condition is bilateral, dominantly inherited, and is the probable equivalent of Stocker-Holt dystrophy.



(A)



(B)

Fig. 19-20 Megalocornea. Front (A) and lateral (B) views of a 4-month-old boy with large eyes since birth. Corneal diameters were 14.5 mm, and intraocular pressures were 13 mmHg in each eye. Gonioscopy demonstrated normal infant angles, and optic discs were healthy with 0.2 cup-to-disc ratios. An uncle had megalocornea with normal intraocular pressures.

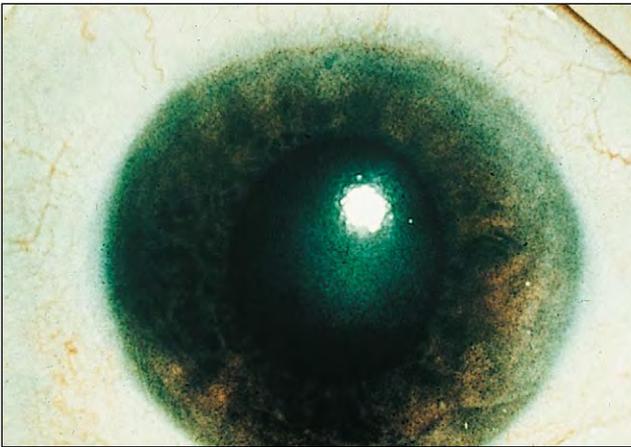


Fig. 19-21 Congenital hereditary endothelial dystrophy. This cornea is markedly edematous but has no enlargement. Intraocular pressure was normal. Patient has since undergone corneal transplantation with excellent results.

Reis-Buckler dystrophy can be present in the first few years of life, with ocular pain resulting from recurrent epithelial erosions. Examination reveals irregular patches of opacity in the region of Bowman's layers that progress to a diffuse reticular pattern associated with an anterior stromal haze.

Other optic nerve abnormalities

Congenital malformations of the disc must be distinguished from disc changes caused by glaucoma. Congenital malformations include congenital pits, colobomata, and optic nerve hypoplasia.

Axial myopia can be associated with a tilted disc and accompanying scleral crescent, which is usually located inferiorly or temporally. This condition can give the optic nerve a 'chopped-off' appearance.

Large physiologic cups also must be distinguished from pathologic cupping caused by glaucoma. Making the distinction is not a common problem in an infant who has accompanying signs and symptoms. Problems can arise in older children in whom changes resulting from globe elasticity are not as evident and yet who are too young for precise visual field testing. Careful examination of all ocular parameters is essential, and follow-up examinations may be required before a definitive diagnosis can be made. Examination of family members can be helpful because several members may reveal a pattern of large discs with prominent cupping. Photographic documentation of the child's optic discs, if available, is invaluable for subsequent comparison, and should be performed at the EUA or in the office if the child can cooperate.

MANAGEMENT

Primary congenital glaucoma is essentially treated with surgery (see Ch. 38 – Childhood glaucoma procedures). Goniotomy is recommended once or twice in children younger than 2–3 years of age if the cornea is clear. Trabeculotomy is recommended in children older than 2–3 years of age and in those of all ages in whom corneal clouding prevents adequate visualization of the angle. If either of these procedures fails, combined trabeculotomy with trabeculectomy and antimetabolites, or a glaucoma valve–shunt, can be attempted. In the event of repeated surgical failure, cyclodestructive procedures with laser can be used. In the current clinical climate where evidence-based interventions are highly valued, it should be noted that these

recommendations are entirely derived from observational data, often from retrospective studies, with virtually no well-controlled randomized comparisons in the literature among alternative procedures.⁶⁵

Surgery is preferred because of problems with medication compliance, a lack of knowledge concerning the cumulative and systemic effects of medications in the infant, and the generally poor response of infants to medications. Surgery has a high success rate and a low incidence of complications.

Early surgery is essential. Damage is increasingly likely the longer the elevated IOP is maintained. Further, it appears that prompt surgery may improve the chances of success by lowering IOP before high pressures can cause permanent compression and adhesion of the trabecular sheets. Surgery is advisable as soon as possible after making the diagnosis and is often performed on the second or third day of life in patients with glaucoma present at birth.

In an infant in whom glaucoma is the presumptive diagnosis, it is best to have the initial EUA performed by the operating ophthalmologist to minimize the pretreatment period and avoid unnecessary anesthesia. Goniotomy and trabeculotomy should be performed by experienced surgeons only. Both require exacting technique to be successful and to minimize complications. The first operation has the greatest chance of success. If complications such as hemorrhage or flat chamber occur, an opportunity to cure this child may be lost.

Preoperative management

Parents of these patients are usually anxious and may have significant feelings of guilt. They should be advised that the disease has occurred because of factors that are beyond their control. The future of long-term surveillance and collaboration between physician and family should be emphasized, as well as the need for frequent follow-up examinations (often with general anesthesia), possible repeat surgeries, chronic medication use, and amblyopia management for visual rehabilitation. With bilateral glaucoma, early referral to rehabilitation specialists may maximize a child's adjustment to limited vision in the early preschool and school years. Families will need a good deal of support, and facilitating contact with support groups of families similarly affected is particularly helpful.

Surgery should not be delayed. Medications are used briefly in the preoperative period only to permit clearing of the corneal edema and improve visualization at the time of diagnostic examination and surgery.

Although there is a wide variety of medications that reduce IOP, studies and dosage profiles for optimal administration in infants and children are usually lacking.^{107a} β -Blockers, such as timolol 0.25% or betaxolol suspension 0.25%, may be administered (1 drop every 12 hours); other commercially available drugs of the same class, such as levobunolol, metipranolol and carteolol, may be equally efficacious. Prostaglandin analogs are usually well tolerated, without demonstrable toxicity in pregnant mothers or children.^{108,109} Although these drugs have not yet been approved for use in children by the Food and Drug Administration, studies have shown that a minimum of side effects developed from short-term use of timolol.^{110,111} Parents should be cautioned to discontinue the medications if any side effects, such as asthmatic symptoms, develop. Apneic spells have been reported in a neonate receiving timolol, and caution is advised in infants of low gestational age.¹¹² The anesthesiologist should be told that the patient is taking a β -adrenergic blocking agent.

Other topical agents approved for adult glaucoma can also be cautiously used in combination with a β -blocker, with special attention to side effects. Eyedrop preparations of adrenergic agonists

(e.g., dipivefrin, apraclonidine), prostaglandins (e.g., latanaprost), or topical carbonic anhydrase inhibitors (dorzolamide) can be used 1 drop every 12 hours. *Brimonidine should be avoided*, as it may produce bradycardia, hypotension, hypothermia, and apnea in infants (manufacturer's package insert, 1998). For short-term use, acetazolamide (5–10 mg/kg body weight every 6–8 hours) orally in suspension form may be considered. Because of the local congestive effects on the conjunctiva and the availability of other drugs, miotics (e.g., pilocarpine 1–2% every 6 hours) are less useful than in the past.

Initial surgery

In a series of 287 eyes, Shaffer reported that one to two goniotomies cured 94% of cases diagnosed between the ages of 1 and 24 months.¹¹³ Because this is the age of occurrence of most primary congenital glaucomas, this statistic is encouraging.

In patients in whom the onset of glaucoma occurred before 1 month of age, the success rate of 26% was poorer. Some of these patients had significant hypoplasia and increased vascularity of the iris and thus are classified now as cases of iridodysgenesis with anomalous iris vessels rather than cases of isolated trabeculodysgenesis. It is unclear whether these cases of early onset are truly primary congenital glaucoma or a more severe syndrome.

Patients with the onset of the disease after 2 years of age show poorer control with goniotomy; Shaffer reported a 38% control rate with one or two goniotomies.¹¹³

A large retrospective study of a dozen reports in the world literature showed equally good results: goniotomies were most successful in children under 1 year of age, achieving successful results more than 75% of the time.⁶⁶ Recent studies^{114,115} continue to confirm this, although relapses have been reported as late as 15 years following surgery.¹¹⁶ Life-long glaucoma surveillance is mandatory for these children.

Goniotomy is a safe procedure when performed skillfully.¹¹⁷ Analysis of 695 goniotomies performed without the use of intracameral viscoelastic revealed only one complication of severe visual loss, an eight-ball hemorrhage with blood staining of the cornea. There were no infections and no lens injuries. There were a few small iridodialyses (4 cases), small cyclodialyses (2 cases), and shallow anterior chambers lasting 1–2 days (5 cases) that had no sequelae. The most common complication was a cardiopulmonary event of concern to the anesthesiologist during anesthesia (6 cases).¹¹⁷ Although all patients recovered, we perform bilateral goniotomies when indicated to avoid the risks involved with an additional anesthesia and to avoid any delay in required surgery.

In patients diagnosed between 1 and 3 years of age, our approach to management is to perform two goniotomies before proceeding to trabeculotomy or trabeculectomy (Fig. 19-22). Many prefer goniotomy^{118–120} rather than a primary trabeculotomy for several reasons: it does not disturb the conjunctiva, which may be needed for later filtering surgery; it is performed with direct visualization of the trabecular meshwork, often engaging quadrants of the angle untouched by trabeculectomy or trabeculotomy, and it incises only those tissues, the superficial trabecular tissues, that are necessary to cure this disease.^{85,121}

Some investigators prefer trabeculotomy *ab externo* as the initial surgical procedure,^{64,122–124} whereas others cite no superiority or preference between the two procedures.¹²⁵ Trabeculotomy also has a high success rate; most studies cite 80–90% success.^{66,126,127} Long-term results for trabeculotomy are excellent.¹²⁸ Significant complications are infrequent, but may include persistent hyphemas, tears in Descemet's membrane, cyclodialysis, synechiae, and staphyloma formation.

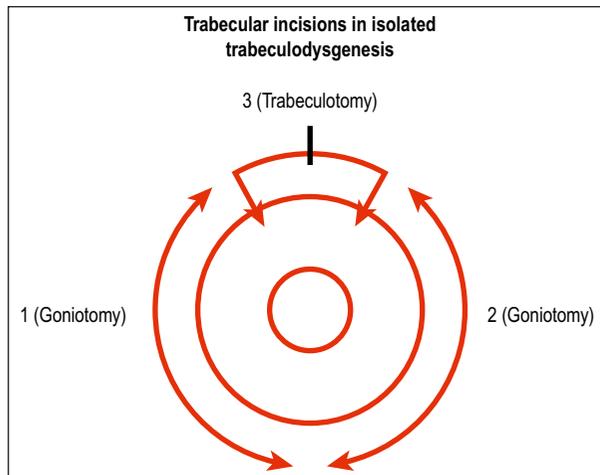


Fig. 19-22 In isolated trabeculodysgenesis, goniotomies are fairly easy to perform in the inferior quadrants. The first procedure usually is placed nasally, and the second procedure, if required, is placed temporally. If these fail, the third procedure could be a trabeculotomy placed superiorly.

A more elaborate ‘purse-string’ 360° trabeculotomy has been described as a successful treatment of childhood glaucomas, with excellent long-term results.^{129,130} After unroofing and identifying the canal of Schlemm, a #6-0 Prolene suture is threaded 360° around, and after reappearing from the opposite direction at the initial surgical site, is drawn like a purse string, rupturing the entire canal in a centripetal fashion. In the event that the canal of Schlemm is impatent, an additional scleral flap is prepared, the canal is unroofed at the site of obstruction, and the Prolene suture is re-threaded back on its course.

Follow-up evaluations

The patient is usually re-examined 4–6 weeks postoperatively, undergoing the same evaluation process as in the initial examination. Again, the examiner must keep in mind the pressure-lowering effects of general anesthesia.

If well controlled, the patient’s symptoms of epiphora, photophobia, and blepharospasm will be reduced, but the symptoms may persist to some degree for many months. Examination will reveal no increase in the corneal diameters and no increase in disc cupping. In fact, disc cupping often decreases.

If the child seems to be doing well, re-examinations are performed in 3–4 months, then every 6 months for 1 year, and then annually. For most children, examination can be performed in the office, beginning at approximately 3 years of age.

If corneal edema worsens, repeat surgery may be performed as soon as 3 weeks after the initial procedure. Re-operating sooner may not give the initial procedure adequate time to function.

Filtering surgery

If goniotomy, trabeculotomy, or both fail to control the glaucoma, the prognosis for ultimate success is poor. Large long-term studies of a combined trabeculectomy-with-trabeculotomy, without antimetabolite, have reported excellent, safe results when performed bilaterally with one general anesthesia, in infants under 6 months of age, and even in infants under one month of age.^{131–135a} Others have suggested a role for trabeculectomy as a primary procedure, with or without mitomycin-C.^{136–139} A recent series found no advantage in using mitomycin-C with trabeculectomy in children, but was too short-term to detect a hypothetical cumulative rate of late bleb

complications, such as leak or infection.¹⁴⁰ One report finds that trabeculectomy without antimetabolite is less effective than primary trabeculotomy.¹⁴¹ Older filtering procedures, such as iridencleisis or the unguarded full-thickness Scheie operation, have an unacceptably high complication rate and are rarely used today.

Synthetic drainage devices

Synthetic drainage devices may be inserted subconjunctivally to provide an opening between the anterior chamber and the subconjunctival space. The Molteno implant is the prototype for a successful device, and it and the implants it has inspired have proven useful in difficult glaucomas unresponsive to trabecular incision or filtering surgery.^{142–146b} One study found that either Ahmed or Baerveldt glaucoma shunts were more effective than trabeculectomy with mitomycin-C in infants under 2 years old, though complications requiring surgical intervention arose.¹⁴⁷ In a study evaluating the long-term results on 48 children under age 16 who received the Baerveldt glaucoma shunt for a wide variety of pediatric glaucomas, the devices were deemed successful for IOP control for a mean period of 5.6 years.¹⁴⁸

Cyclodestructive procedures

Although cryotherapy is widely available and inexpensive, it often causes severe pain in children and frequently must be repeated. It is successful in approximately one of three cases.¹⁴⁹ Long-term complications are considerable and include phthisis, hypotony, chronic uveitis, and cataract. The results in children of an older technique of therapeutic ultrasound have also been disappointing.^{150,151}

Newer and more focused applications of trans-scleral cyclophotocoagulation with lasers have been developed. The non-contact neodymium:yttrium-aluminum-garnet (Nd:YAG) procedures, though well documented in adults,^{152–154} have little application in managing pediatric glaucoma because they are performed with retrobulbar anesthesia and with the patient sitting at a slit-lamp delivery system. Contact YAG laser and contact diode laser techniques deliver energy via a pencil-like probe placed directly over the ciliary body, and thus these procedures are suitable for the supine child with glaucoma in the operating room. An early report identified a pressure reduction of up to 50% in approximately 40–50% of treated pediatric patients, with second and even third repeat procedures commonly needed.¹⁵⁵ Recent studies similarly found eyes with congenital or juvenile glaucoma only partially responsive to laser cyclodestruction or in need of repeat treatment.^{156,157} This experience is comparable to that reported in adult eyes.¹⁵⁸ When the trans-scleral laser is compared with cryotherapy, the pressure reduction is similar but with fewer complications.¹⁵⁹

A more elaborate intraocular procedure of endoscopic photocoagulation, either through the limbus or through the pars plana with vitrectomy, has also been described as effective.^{160–162} A theoretical advantage of direct visualization of the ciliary processes during cyclodestruction is that in congenital glaucoma, the ciliary processes may be rotated in a posterior orientation and not aligned with standard scleral landmarks used for placing a contact laser probe.¹⁶³

Because of their fewer side effects, these lasers for ciliodestruction are preferable to cryotherapy as an end-stage treatment; but before these approaches can be applied earlier in the therapeutic regimen, important issues, such as significant reduction in vision in up to 40% of eyes, should be further clarified.^{152,153,164}

Long-term follow-up, management, and prognosis

An important feature in the management of these patients is the treatment of amblyopia that can result from tears of Descemet’s

membrane involving the visual axis and anisometropia. Although the amount of myopia that is induced by the stretching of the infant globe can be neutralized by the flattening of the cornea, this myopia is often significant. Irregular astigmatism also is evident in many cases. A cycloplegic refraction should be performed as soon as possible and should be followed by frequent adjustments in lens power as the anisometropia changes. Appropriate occlusion therapy must be started as soon as amblyopia is recognized. Even brief periods of corneal clouding can cause deprivation amblyopia. Thus coordination of eye care with ophthalmologists interested in pediatric management can often maximize the child's visual rehabilitation.

Long-term medical therapy in children can be difficult to maintain because of side effects and compliance problems. Moreover, few antiglaucoma medications have been studied in children, and they are mostly used either in a presurgical context or as an adjunct to partially successful surgery.

β -Blockers, such as timolol 0.25%, are well tolerated in most patients who do not have asthma or heart disease.^{110,111} Selective β_1 -adrenergic antagonists, such as betaxolol, may further decrease the incidence of pulmonary side effects. Newer topical agents, such as the α agonists, prostaglandins, and topical carbonic anhydrase inhibitors, can also be used, but possible side effects must be monitored. As noted above, *brimonidine should be avoided in children under 5 years of age*. Coordination of the glaucoma medical regimen with the child's pediatrician is advised. Generally, if an increasing number of topical drops is required for IOP control, further surgery may be indicated.

Patients with primary congenital glaucoma require regular examinations throughout life. Increases in IOP, corneal edema, and retinal detachment^{165,166} can occur at any time and must be detected as soon as possible and treated appropriately. The long-term prognosis for IOP control in successfully treated cases of primary congenital glaucoma appears excellent,^{113,167} although late relapses have been observed up to 15 years later.¹¹⁶ Most patients with primary congenital glaucoma successfully treated in infancy have maintained good pressure control with stable optic nerves and fully functional visual fields into adulthood.

Late developing primary congenital glaucoma

Late developing primary congenital glaucoma occurs in children whose IOP becomes elevated after the age of approximately 3, when corneal enlargement or significant symptoms no longer occur. The angle may have the appearance of isolated trabeculodysgenesis with a flat or concave insertion, or the angle anomaly may be indefinite with a partial development of the angle recess. Some authors group this presentation of glaucoma in the 'juvenile' category.¹³ This disorder may be difficult to distinguish from early developing primary open-angle glaucoma.

Initially, medical treatment should be attempted. Innovative laser treatments of the angle have been described,^{168,169} but they are not widely available. In the event that surgery is required, a trabeculotomy *ab externo* is the initial surgical procedure of choice in children this age.

GLAUCOMA ASSOCIATED WITH OTHER CONGENITAL ANOMALIES

FAMILIAL HYPOPLASIA OF THE IRIS WITH GLAUCOMA

Familial hypoplasia of the iris with glaucoma (Fig. 19-23)^{170,171} is characterized by hypoplasia of the anterior iris stroma, a prominent

pupillary sphincter, trabeculodysgenesis, and glaucoma; this has also been referred to as iridogoniodysgenesis. The anterior stroma of the iris is markedly hypoplastic, and the pupillary sphincter is obvious as a tan distinct ring around the pupil. Glaucoma may occur at any time from birth until late adulthood; the striking iris appearance correlates with eventual glaucoma in 100% of cases. Childhood cases respond well to goniotomy or trabeculotomy. Cases with later onset have been managed successfully with medical therapy, argon laser trabeculoplasty, trabeculotomy, or trabeculectomy.

Its hereditary pattern is autosomal dominant.¹⁷² Early studies had found genetic linkage of iris hypoplasia to the Rieger's syndrome locus at 4q25,¹⁷³ but others considered this association inconsistent.¹⁷⁴ A recent comprehensive review of the literature identifies a total of three causative loci (4q25, 6p25, and 13q14) and persuasively argues for retaining the broader clinical term 'Axenfeld-Rieger syndrome' to embrace a wide range of phenotypic subtypes (*viz.*, Axenfeld anomaly, Rieger anomaly, Rieger syndrome, iridogoniodysgenesis anomaly, iridogoniodysgenesis syndrome, iris hypoplasia, and familial glaucoma iridogoniodysgenesis).¹⁷⁵ This illustrates that there may be a significant difference in the *clinical* classification of the developmental glaucomas (i.e., autosomal dominant iris hypoplasia and autosomal dominant juvenile glaucoma share a common clinical presentation but different chromosomal defects) and the *genetic* associations discovered by molecular biology (i.e., iris hypoplasia and Rieger's syndrome are linked on chromosome 4, but may appear very different from one another).⁹ From the patient's vantage, any of these genetic aberrations or phenotypic expressions confer a 50% greater chance of developing glaucoma than would otherwise be recognized.

DEVELOPMENTAL GLAUCOMA WITH ANOMALOUS SUPERFICIAL IRIS VESSELS

Irregularly wandering superficial iris vessels with distortion or absence of the superficial iris stroma and distortion of the pupil are commonly seen in newborn children with glaucoma (see Fig. 19-8). The cornea usually is hazy, and the vessels may be difficult to see. These vessels can be differentiated easily from the normal radial

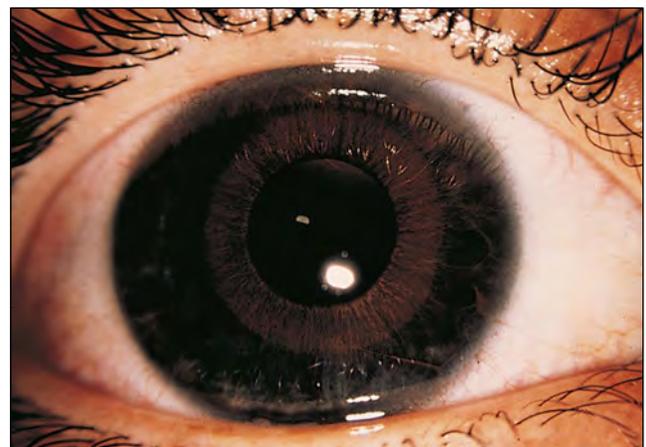


Fig. 19-23 Familial hypoplasia of iris with glaucoma. This patient's mother and son have the same iris appearance and glaucoma. Anterior iris stroma is absent with the exception of a few strands nasally. The sphincter is a prominent ring contrasted against the dark slate-gray appearance of the peripheral iris.



Fig. 19-24 Edge of lens seen in aniridia shows absence of iris. Epithelial keratopathy is clearly visible in lower nasal portion, and a dense cataract is dislocated superiorly.

iris vessels, which are straight and have no associated distortion of the iris tissue. The normal radial iris vessels frequently are visible at birth, before the anterior stroma and its pigmentation have developed completely.

Superficial anomalous iris vessels in children are usually bilateral and resistant to therapy. Early trabeculotomy offers the most hope. Goniotomy can be performed in the least cloudy eye during the same surgery. If the cornea has not cleared dramatically, trabeculotomy or goniotomy should be repeated after 3 or 4 weeks.

Most of these eyes require multiple surgeries and long-term medical therapy. With aggressive management, many can be saved, although vision is rarely normal.

ANIRIDIA

Aniridia (Fig. 19-24) is a bilateral congenital anomaly in which there is profound hypoplasia of the iris in frequent association with multiple ocular anomalies, such as peripheral corneal pannus and keratopathy, foveal hypoplasia, diffuse retinal dysfunction as seen on electroretinography, impaired acuity with nystagmus, cataract and ectopia lentis, and optic nerve hypoplasia.¹⁷⁶ Recent studies using ultrasonic biomicroscopy have also documented ciliary body hypoplasia.¹⁷⁷ The combination of these defects usually causes a formidable barrier to normal visual function. In addition, 50–75% of aniridics develop glaucoma.¹⁷⁸

Two-thirds of patients with aniridia have an affected parent (autosomal dominant form) and one-third represent isolated new mutations.⁹ The autosomal dominant form without systemic abnormalities accounts for nearly 85% of cases. In the sporadic cases, approximately 20% of patients have been found to have Wilms tumor as part of the multisystem WAGR syndrome (Wilms' tumor + aniridia + genitourinary anomalies + retardation).¹⁷³ Thus aniridic children without a family history require co-management with a pediatrician for surveillance of neoplasm and other complications.

The genetic locus of this syndrome for both the sporadic and familial forms is a mutation of the PAX6 gene on the 11p13 chromosome.^{179,180} Curiously this is the same defective gene seen in one case of Peter's anomaly, although the two clinical syndromes are usually distinct and show little overlap.^{9,181}

Although the defective iris is readily apparent at birth, in most cases glaucoma does not develop until later childhood or early

adulthood, and sometimes does not develop at all.¹⁸² In the less frequent infantile-onset cases, the glaucoma is thought to be due to a trabeculodysgenic anomaly of the anterior chamber angle. Because large corneas are rarely seen in aniridic glaucoma, the IOP elevation is presumed to occur at a later developmental stage, usually after age 5 and often into adolescence. Walton¹⁷⁸ directly correlates the severity of the glaucoma with the extent of progressive synechial angle closure by the pulled-up residual iris stump.¹⁸³

The iris is never completely absent; it may vary from being fairly well developed in some areas to being only a rudimentary stump in others. Most commonly, the anterior stroma sweeps up and over the meshwork like concave trabeculodysgenesis.

Corneal dystrophy initially presents as a circumferential and peripheral opacification of the epithelial and subepithelial layers, with vessels advancing into these areas from the limbus. Over many years, this pannus can extend centrally and eventually completely opacify the cornea.

Cataracts develop in most aniridic patients; and the lens may be displaced, with a segmental absence of zonules. Foveal hypoplasia is present in most cases and is clinically appreciated by the appearance of meandering small retinal vessels in what should be the normal avascular zone of the macular region. Vision is usually limited to no better than 20/200, with an accompanying pendular nystagmus. Cases of families with aniridia but normal macular development, no nystagmus, and good vision do occur, implying that the foveal hypoplasia is genetically determined rather than acquired as a result of light damage from lack of iris tissue.¹⁸⁴

If aniridic glaucoma occurs in infancy, a trabeculotomy is the procedure of choice because goniotomies are usually unsuccessful if applied after the onset of glaucomatous IOP elevation.¹⁷⁸ Encouraging results with trabeculotomy alone,¹⁸⁵ trabeculectomy with or without antimetabolites,^{186–188} or a combination of both procedures have been reported.¹⁸⁹ In mice and in some humans, one of the defects associated with a Pax 6 mutation is absence of Schemm's canal.^{189a} We have seen one such infant in which Schemm's canal could not be found either clinically or by high resolution ultrasound biomicroscopy.^{189b} This has significant implications for performing trabeculotomy. In older children, medical therapy is indicated as the initial treatment. Surgical complications include direct lens injury and lens or vitreous incarceration in filtration sites; these problems are considerably reduced with the use of intracameral viscoelastic at the time of surgery.

Preventive goniotomy to prevent progressive adherence of the peripheral iris to the trabecular meshwork has been proposed by Walton.¹⁹⁰ With a follow-up of over 9 years in 55 eyes which underwent one or more goniotomies at age 3, 90% had normal IOPs without medications – in contrast to the 50% of untreated aniridic eyes expected to develop glaucoma in this time frame.¹⁹¹ This uniquely innovative approach, with its demands for impeccable prophylactic surgery and meticulous follow-up, has yet to be duplicated by other centers.

In cases of failed trabecular surgery, glaucoma implants (e.g., Ahmed)¹⁹² or ciliodestructive procedures have been used, often with more than two procedures per eye required.^{146b,193}

The cornea may become sufficiently opaque so that penetrating keratoplasty is needed, although the visual results are marginal (one to two lines of improvement in Snellen acuity).¹⁹⁴ Lens opacification may require cataract extraction. Before operating, however, the ophthalmologist should attempt refraction through the aphakic portion of the pupil if the lens is subluxated. Either extracapsular or phacoemulsification surgery may be used, depending on

the stability of the zonules. Cataract extraction can be difficult and often is accompanied by vitreous loss or further deterioration of the cornea. The use of intraocular lens (IOL) implants in children is an evolving field,¹⁹⁵ and whether their alleged 'protective effect' in forestalling the additional burden of aphakic glaucoma¹⁹⁶ in these aniridic eyes has yet to be determined.

STURGE-WEBER SYNDROME (ENCEPHALOFACIAL ANGIOMATOSIS, ENCEPHALOTRIGEMINAL ANGIOMATOSIS)

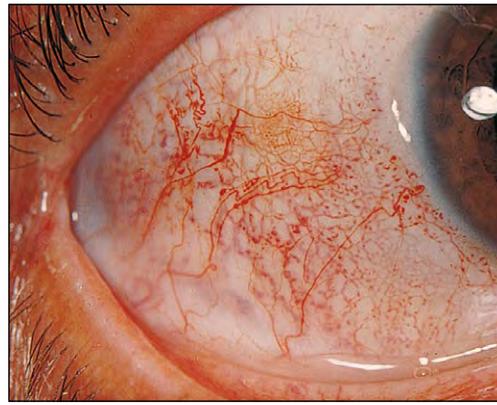
Sturge-Weber syndrome^{197,198} is characterized by a flat facial hemangioma which follows the distribution of the fifth cranial nerve (Fig. 19-25). The genetic transmission of this disease is unclear. Intracranial abnormalities can produce a spectrum of neurological problems, including seizure disorders in the child.¹⁹⁹ For example, the classic meningial hemangioma may be associated with calcification seen on skull X-ray; other more subtle findings can be neuroimaged with a variety of new techniques.²⁰⁰ The facial hemangioma is usually unilateral but occasionally may be bilateral. Choroidal hemangiomas and episcleral hemangiomas are commonly seen, and leakage from the choroidal hemangioma may cause retinal edema (Fig. 19-26). Such ocular abnormalities can be seen with indocyanine green angiography.^{201,202}

Whereas pediatric glaucoma in aniridia can occur as an infantile trabeculodysgenesis but is more likely to occur later as a secondary glaucoma (progressive angle closure), the glaucoma associated with Sturge-Weber syndrome is more likely to appear in infancy and less often manifests in late childhood or adolescence. Sturge-Weber glaucoma is present when the facial hemangioma involves the lids or conjunctiva. Two different mechanisms are thought to be involved. If the glaucoma occurs in infancy, an isolated trabeculodysgenesis type of angle anomaly usually is assumed, described in one case as due to abnormalities in the canal of Schlemm and juxtacanalicular tissue.²⁰³ Some claim that this is sometimes responsive to goniotomy,^{204,205} with more than one procedure frequently required. Medical therapy effectively controls the glaucoma in but a third of pediatric cases.²⁰⁶

Other authors prefer trabeculotomies,^{178,207} combined trabeculectomy/trabeculotomy,²⁰⁸ or glaucoma tubes, such as an Ahmed valve^{209,210} or a two-staged Baerveldt procedure.²¹¹ As the child ages, the elevated IOP is due to an elevation of episcleral venous pressure that occurs as a result of arteriovenous shunts through the episcleral hemangiomas (Fig. 19-27).^{212,213} In older children, medical therapy may be better tolerated and effective, with fewer side effects. If medical therapy is unsuccessful, either filtration or tube surgeries can be used.¹² In the face of surgical failure, cyclodestructive procedures – cryotherapy,²¹⁴ diode laser cyclophotocoagulation,^{157,215,216} or



(A)



(B)

Fig. 19-25 Sturge-Weber manifestation on face (A) and as a vascular congestion of the episclera (B).



Fig. 19-26 Hemangioma of the choroid is almost always present in eyes with Sturge-Weber syndrome. In this case, leakage reduced macular acuity.

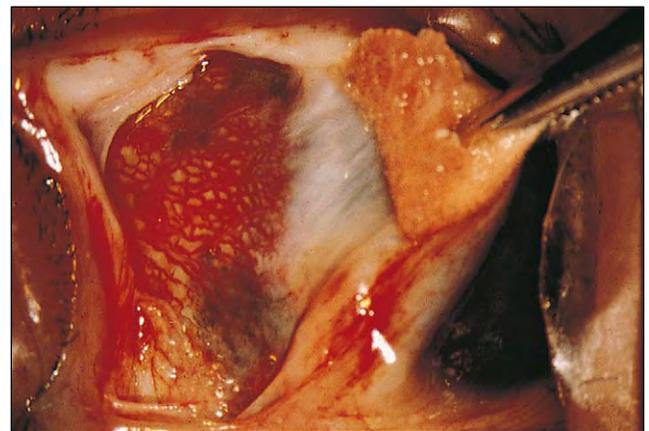


Fig. 19-27 Note the dense episcleral anastomosis found in surgery. These were not visible until Tenon's capsule was elevated. Anastomoses can be cauterized easily and usually do not represent a significant bleeding problem at surgery.

endocyclophotocoagulation²¹⁷ – can be performed, although more than one intervention is usually required, as is the case in many such difficult pediatric glaucomas.²¹⁸

In approximately 20% of procedures which penetrate the anterior chamber, such as trabeculectomy, intraoperative or early postoperative choroidal detachment can occur from a rapid expansion of the choroidal hemangioma with effusion of fluid into the suprachoroidal and subretinal spaces (Fig. 19-28).²¹⁶ Careful attention to maintaining a normal to high IOP during and after surgery – through the use of an anterior chamber maintainer cannula for constant infusion, generous amounts of viscoelastic, and meticulous wound closure – may forestall intra- and perioperative complications. Fortunately, such an event is usually not encountered,²⁰⁸ and prophylactic sclerostomies need not be routinely performed.²¹⁹ However, the surgeon needs to anticipate such a precipitous event of sudden anterior chamber flattening, which may be impossible to re-form through the surgical site or paracentesis site. Posterior sclerotomy followed by anterior chamber reformation should be performed in an attempt to drain fluid from the suprachoroidal space. Extreme caution is advised: the choroid must not be penetrated, to avoid a catastrophic hemorrhage.

If these efforts are not fully successful, usually in a few days, the expansion subsides as the IOP increases. Repeat filtering surgery can be reconsidered at a later time because the choroidal hemangioma may scar, sometimes enabling the surgeon to successfully perform the procedure without recurrence of the expansion. In such reoperative circumstances, two or three posterior sclerotomies should be preplaced, to prevent this anticipated expansion. Alternatively, a glaucoma valve or shunt, inserting the tube into an eye in which IOP has been carefully maintained by an anterior chamber full of viscoelastic, may be considered after a failed filtering surgery.

There is a classification of neural crest disorders that involve episcleral vascular malformations plus ocular hyperpigmentation groups together the Sturge-Weber syndrome, Klippel-Trénaunay-Weber syndrome, oculodermal melanocytosis (nevus of Ota), and phakomatosis pigmentovascularis (a combination of oculodermal melanocytosis and nevus flammeus that is found almost exclusively in Asians).²²⁰ When oculodermal melanocytosis and nevus flammeus (phakomatosis pigmentovascularis) occur together, with each extensively involving the globe, there is a strong predisposition for congenital glaucoma. When one or both are present with only

partial globe involvement, elevated IOP could develop later in life, and long-term glaucoma surveillance is advised. The vascular malformations appear to play a more important role in the predisposition to glaucoma than the oculodermal melanocytosis.

A related syndrome called cutis marmorata telangiectatica congenita involves periocular vascular anomalies associated either with regional or generalized cutaneous marbling.²²¹ It has also been associated with infantile trabeculodysgenic glaucoma^{222–225} and, in one report, with intraoperative suprachoroidal hemorrhage.¹⁹⁴

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

Neurofibromatosis (Fig. 19-29) is an autosomal dominant disorder with variable expressivity, affecting as many as 1 in 3000 people,²²⁶ and manifesting as anomalies of the neuroectoderm and the development of active hamartomas throughout the body.²²⁷ The most common form, neurofibromatosis type 1 (NF-1) (von Recklinghausen's disease), has seven possible manifestations, requiring two for diagnosis: six or more large café-au-lait macules; plexiform neurofibromata; inguinal or axillary freckling; optic glioma; Lisch nodules (melanocytic hamartomas of the iris); distinctive osseous lesions of the sphenoid or long bones; and a first-degree relative with NF-1. (Curiously there is a report of a monozygotic twin with NF-1 and congenital glaucoma – indicating the complexity of genetic manifestation in the disease.)²²⁸

Neurofibromatosis type 2 (NF-2) is a rarer disorder associated with bilateral acoustic neuromas or other neural proliferative lesions, such as meningioma, schwannoma, and glioma. Although NF-2's defining diagnostic criteria are in flux,²²⁹ the disease has a very high mortality by the third decade.²³⁰

The extensive literature on the ocular findings of NF-1 includes neurofibromatous nodules on the iris and eyelids, with ectropion uvea,²³¹ optic nerve gliomas in as many as 15% of asymptomatic children under age 6,²³² and a variety of complications resulting from mass-occupying lesions in the orbit, such as pulsating exophthalmos to sphenoid bone maldevelopment, herniation of brain tissue into the orbit, or proptosis resulting from optic nerve gliomas. Multiple retinal tumors can be seen, including large retinal astrocytic hamartomas, multiple retinal capillary hemangiomas and corkscrew anomalies,²³³ and combined hamartomas of the retina

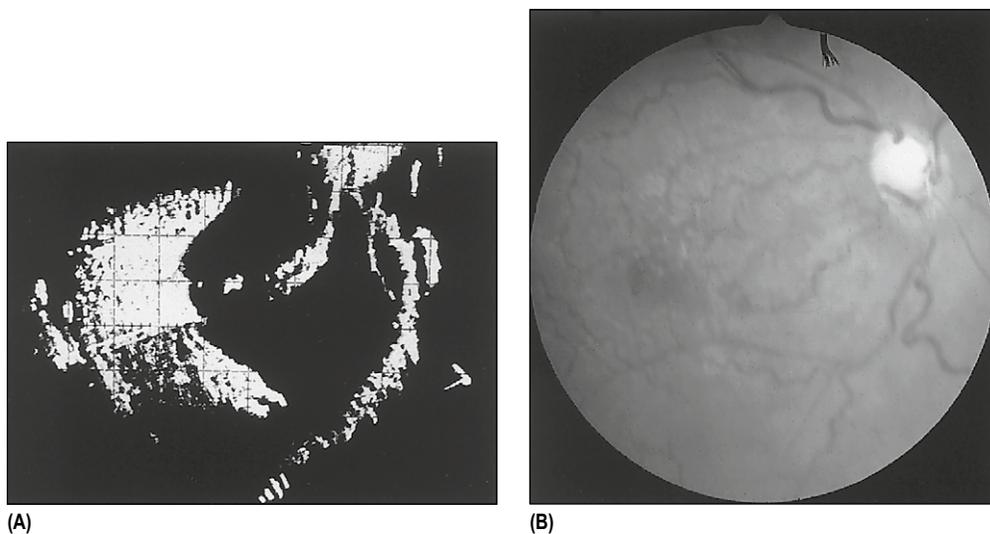


Fig. 19-28 (A) On opening this eye for trabeculectomy, the anterior chamber collapsed and could not be reformed by injection of balanced salt solution. The flap was closed. Postoperative ultrasonography revealed this large choroidal elevation extending almost to the optic nerve posteriorly. **(B)** Serous retinal detachment overlying choroidal expansion in a Sturge-Weber patient following postsurgical choroidal expansion. There was no retinal hole in this patient and the detachment resolved spontaneously.

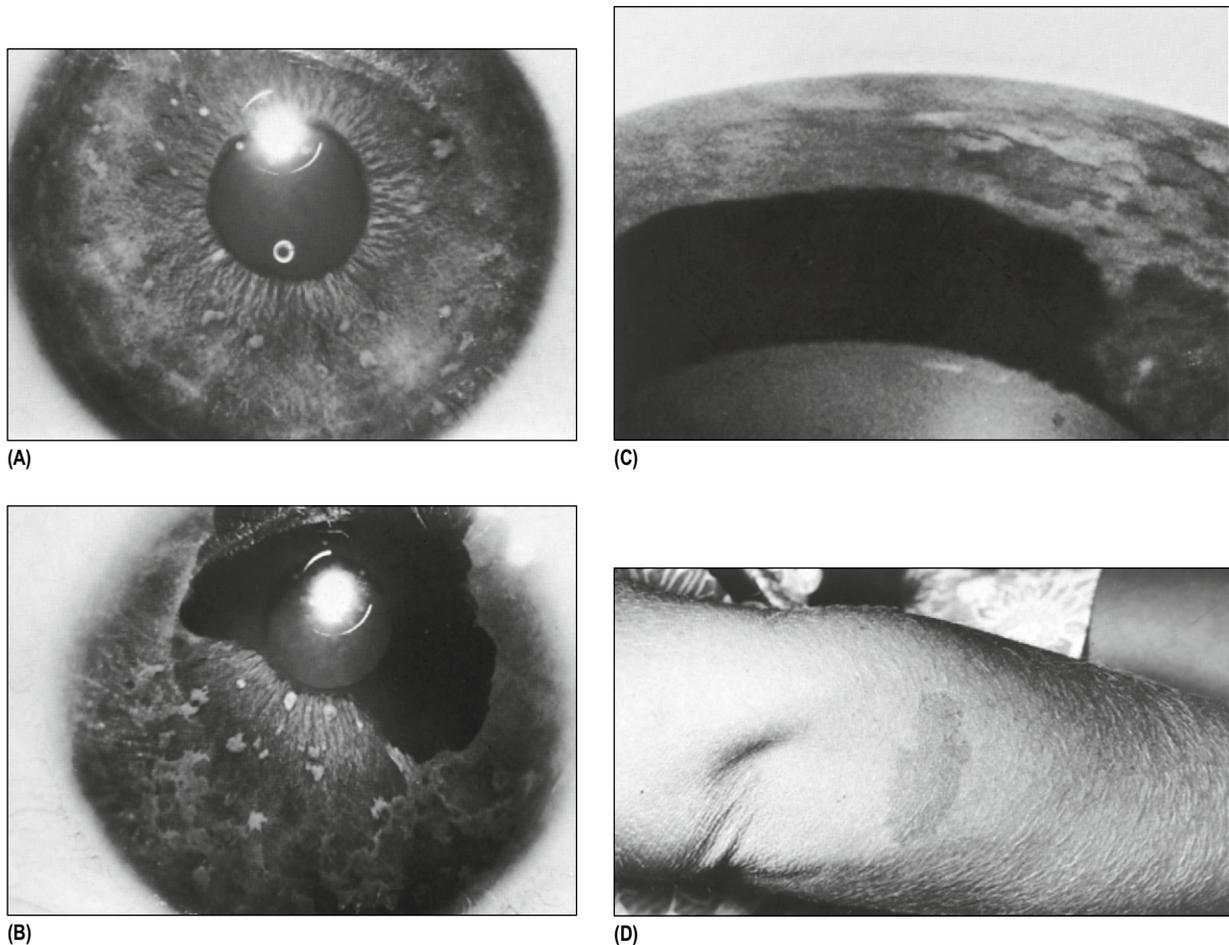


Fig. 19-29 A 22-year-old patient with neurofibromatosis. **(A)** External appearance of iris nodules. **(B)** External view of abnormally pigmented iris. **(C)** Goniophotograph. Note the round pupil, absence of angle recess, and high iris insertion. **(D)** Café-au-lait spot.

and retinal pigment epithelium, resulting in rubeotic glaucoma, vitreous hemorrhage, and retinal detachment.²³⁴

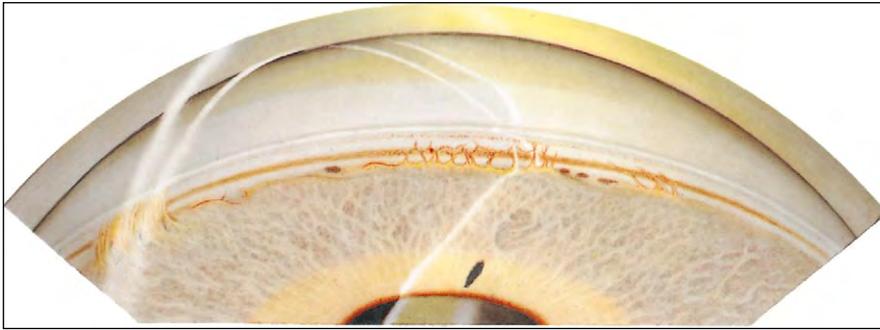
A ‘real world’ context for what a general clinician might encounter, however, was suggested by a study of 211 NF-1 patients, whose diagnosis excluded ophthalmologic criteria, and who were then assessed by anamnesticly masked observers, to determine the frequency of ophthalmic findings. The most common lesions, often together, were Lisch nodules (88%) and choroidal hamartomas (29%); but enlarged corneal nerves, plexiform neurofibromas, and symptomatic optic nerve gliomas were found in less than 5% of cases.²³⁵

Glaucoma may appear up to 50% of the time when neurofibromas involve the upper eyelid or the eye itself (Fig. 19-30). The anterior chamber angle may take on several appearances.²³⁶ Isolated trabeculodysgenesis may be evident. Synechial closure caused by neurofibromatous tissue posterior to the iris or neurofibromatous infiltration of the angle itself, which may be accompanied by synechial closure, may be present. A sheet of avascular, opaque, dense tissue may arise from the periphery of the iris and extend anteriorly into the angle. Later onset glaucoma in neurofibromatosis can be associated with unilateral ectropion uvea at the pupillary margin.^{178,237,238} Usually there is accompanying unilateral ptosis without a palpable neurofibroma; the pupil appears larger due to the static iris hyperplasia of the central iris pigment epithelium. This form of iris ectropion glaucoma may also appear as a distinct form, independent of NF-1 or other anterior segment anomalies.²³⁹



Fig. 19-30 Plexiform neuroma of the upper lid in this patient with neurofibromatosis. Eye beneath plexiform neuroma had severe glaucoma that had not been diagnosed.

The preferred treatment in infants is usually goniotomy, with trabeculotomy recommended if iris adhesions are prominent. In older children, medical therapy should be tried first, followed by the surgeon’s choice of surgical interventions: trabeculotomy,



(A)



(B)

Fig. 19-31 (A) Axenfeld's anomaly. Multiple iris processes have formed between the iris and a prominent Schwalbe's line. There is a broad area of iris adhesion to Schwalbe's line (left). **(B)** Axenfeld's anomaly with dense iris adhesions that almost completely cover the trabecular meshwork. Particles of pigment are deposited along a very prominent Schwalbe's ring. (From Hermann M, and others: Published courtesy of Arch Ophthalmol 53:767, 1955. Copyright the American Medical Association, 1955.)

combination trabeculotomy/trabeculectomy, trabeculectomy with antimetabolites, or glaucoma tube procedure.

PIERRE ROBIN AND STICKLER SYNDROMES

Pierre Robin syndrome was originally characterized by micrognathia, glossoptosis, cleft palate, and cardiac and ocular anomalies.²⁴⁰ Recent studies emphasize the triad of retrognathia, cleft palate, and respiratory distress both from airway and brainstem abnormalities.²⁴¹ Ocular disorders manifest as developmental glaucoma, cataracts, high myopia, retinal detachments, and occasional microphthalmos. There is significant overlap of symptoms with Stickler syndrome,^{242,243} an autosomal dominant disorder characterized by progressive arthropathy, midfacial flattening, Pierre Robin anomaly or cleft palate, sensorineural hearing loss, progressive myopia, pathognomonic vitreoretinal degeneration, and retinal detachment.^{244,245} Recent molecular studies have distinguished two gene loci, expressed as Stickler syndrome with and without non-ocular features.²⁴⁶ The glaucoma in both Stickler and Pierre Robin syndromes is due to isolated trabeculodysgenesis, and goniotomy is the preferred initial procedure.

SKELETAL DYSPLASTIC SYNDROMES

This category embraces an enormous variety of systemic abnormalities with variable ocular manifestations that can include trabeculodysgenic infantile glaucoma. Such disorders include Kniest syndrome,^{247,248,249,250} Michel syndrome,²⁵¹ and the oculodigital (ODD) syndrome.²⁵² The latter syndrome, an autosomal dominant disorder with phenotypic overlap with the Hallermann-Streiff and Meyer-Schwickerath syndromes,^{253,254} also manifests with a variety of neurological findings.²⁵⁵

CORNEODYSGENESIS

Axenfeld's anomaly and Rieger's anomaly and syndrome involve corneodysgenesis of the peripheral (Axenfeld's) and midperipheral (Rieger's) cornea and iris. These disorders appear to represent a spectrum of developmental variations with genetic mutations in common,^{15b,175,256–259} rather than distinctive diseases.^{17,260} Despite abnormalities in the cornea and/or iris in these syndromes, the trabecular meshwork in these disorders is histopathologically indistinguishable from that which is seen in primary congenital glaucoma.²⁶¹

Axenfeld's anomaly

Axenfeld's anomaly (Figs 19-31 and 19-32) is characterized by a prominent anteriorly displaced Schwalbe's line termed *posterior embryotoxon*. This finding differs from isolated posterior embryotoxon, which can be seen in normal eyes; in Axenfeld's anomaly the bands of iris tissue extend across the anterior chamber angle and attach to a thickened Schwalbe's line. Some patients have mild hypoplasia of the anterior iris stroma, but more severe defects of the iris are not present. The disease usually is bilateral, and the inheritance pattern is autosomal dominant.

Approximately 50% of patients with Axenfeld's anomaly develop glaucoma. The glaucoma may occur in infancy and responds to goniotomy or trabeculotomy. If it occurs in later childhood, medical therapy should be tried initially, with trabeculotomy or trabeculectomy considered as surgical procedures.

Rieger's anomaly and syndrome

Rieger's anomaly (Figs 19-33 and 19-34A) may or may not have posterior embryotoxon with adherent iris strands, as in Axenfeld's anomaly. However, midperipheral iris adhesions to the cornea are present in addition to significant iris abnormalities, which can include marked hypoplasia of the anterior iris stroma as well as

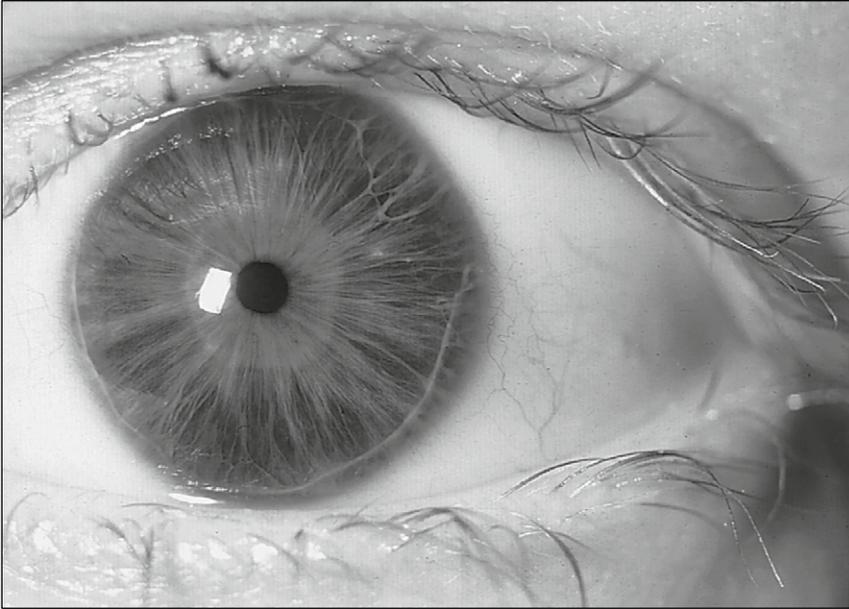


Fig. 19-32 Axenfeld's syndrome with peripheral posterior embryotoxon and hypoplasia of anterior stroma. Note the prominent sphincter present with hypoplasia.

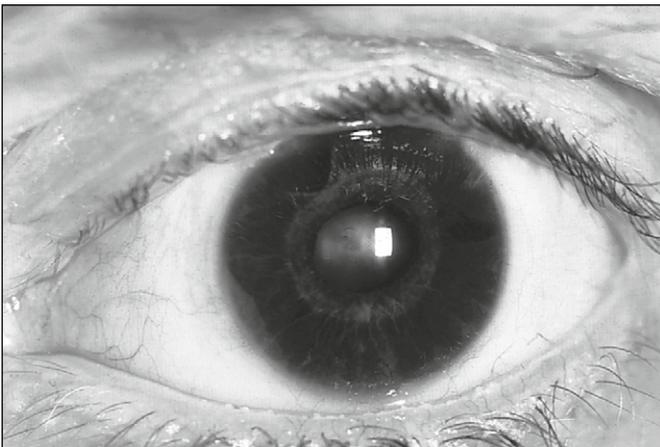
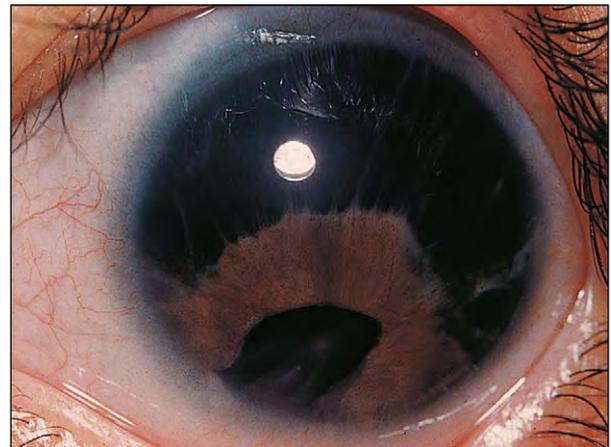


Fig. 19-33 Anterior stroma is hypoplastic and appears much like Axenfeld's syndrome; however, here there is no posterior embryotoxon. Full-thickness congenital defect occurs in iris at the 3 o'clock meridian.

pupillary abnormalities, such as distortion of the pupil, polyco-
ria, and corectopia.⁵ Occasionally the iris demonstrates hypoplastic
findings similar to the iridocorneal endothelial syndrome, but these
conditions are rarely confused. Many differences in their clinical
constellations – corneal specular microscopy, inheritance patterns,
laterality, etc. – distinguish the iridocorneal endothelial syndrome
from the Axenfeld-Rieger's syndromes.^{100,262,263} Progressive iris
thinning is most common following surgical intervention with
peripheral anterior synechiae formation and can be seen in eyes
with either Rieger's or Axenfeld's anomaly. The iris seems to be
pulled toward the peripheral anterior synechiae, possibly because
of contraction of endothelial cells that migrate across the periph-
eral anterior synechiae onto the exposed iris stroma (Fig. 19-35).
Microcornea or macrocornea may also be evident. These ocular
abnormalities are usually bilateral, and autosomal dominant trans-
mission is the common inheritance pattern.



(A)



(B)

Fig. 19-34 (A) Patient had a large portion of iris absent in the upper temporal quadrant with wedge-shaped adhesion between the remaining iris and cornea. (B) The same patient with typical malformed and missing teeth as seen in Rieger's syndrome.



(A)



(B)

Fig. 19-35 Iris adhesion to posterior embryotoxon in Axenfeld's anomaly (A) results in pupillary distortion (B).



Fig. 19-36 Central corneal opacity in Peter's anomaly.

Other ocular abnormalities have been associated less frequently and include strabismus, cataract, retinal detachment, macular degeneration, hypoplasia of the optic nerve, and chorioretinal colobomata.

When the ocular abnormalities are associated with dental, facial, or other systemic abnormalities, the term *Rieger's syndrome* is applied. Dental and facial anomalies (see Fig. 19-34B) are most common and include hypodontia, microdontia, and occasional anodontia; malar hypoplasia; hypertelorism; redundant periumbilical skin, and hypospadias. Other systemic anomalies include short stature, heart defects, neurologic problems, empty sella syndrome, deafness, and mental deficiency.

Because there may be overlap of the phenotypic presentations of Rieger's and Axenfeld's syndromes in the same family,²⁶⁴ they are sometimes treated as a single but protean syndrome called the *Axenfeld-Rieger's syndrome*.^{17,260,265} Linkage studies reveal a heterogeneous genetic picture; for example, the Rieger's anomaly does not always map consistently to the 4q chromosome, as does Rieger's syndrome.²⁶⁶ This suggests either the two phenotypic Rieger's phenomena are genetically distinct despite their clinical similarities, or that multiple genetic defects can cause both Rieger's anomaly and Rieger's syndrome.⁹ The cytogenetics and molecular genetics of these disorders are complex and evolving.^{265,267}

Glaucoma in the Axenfeld-Rieger's syndromes occurs in approximately 50% of affected individuals. The glaucoma may occur in infancy due to trabeculodysgenesis, but is usually delayed into the first or second decade of life. In infants, a goniotomy or trabeculotomy is the indicated surgical procedure. In older children, medical therapy should be tried before any surgical procedures. If surgery is necessary, the surgeon can choose a trabeculectomy with antimetabolite,¹⁸⁹ combined trabeculectomy-with-trabeculotomy,²⁶⁸ or glaucoma tube procedure.²⁶⁹

PETER'S ANOMALY

Peter's anomaly (Fig. 19-36) manifests as bilateral central corneal opacification with adhesions of the central iris to the posterior surface of the cornea. Frequently, these iris attachments arise from the collarette and attach to the cornea, where there is an absence of Descemet's membrane and thinning of the posterior corneal stroma.²⁷⁰ In extreme cases, the lens can adhere to the corneal endothelium, with a cataract present. One classification distinguishes Peter's eyes with normal lenses (type I) from a type with abnormal lenses (type II).²⁷¹ This condition has also been called *anterior chamber cleavage syndrome*.²

Approximately half of the patients with Peter's anomaly have ocular defects, and 60% have systemic defects.²⁷² The ocular findings in Peter's anomaly include microphthalmos, myopia, aniridia, and cataract.²⁷³ It has been genetically linked to the same mutation at the PAX6 locus as the aniridia gene in one study, although overlap of phenotypic expression is not prominent.⁹ Retinal detachment occurs spontaneously in up to 10% of patients.²⁷⁴

Systemic findings include developmental delay, congenital heart disease, congenital ear anomalies and hearing loss, genitourinary defects, cleft palate, and spinal defects.²⁷⁴ The 'Peter's-plus syndrome' includes Peter's anomaly, short stature, small hands, mental retardation, abnormal ears, and cleft lip and palate; it is inherited as an autosomal recessive and is the same as Kivlin syndrome.²⁷⁵

Glaucoma occurs in up to 50% of Peter's anomaly eyes and may be present even when the anterior chamber angle appears grossly normal, although trabeculodysgenesis may be present. The glaucoma may be first seen in infancy or later in life. When glaucoma exists in infants, goniotomy, trabeculotomy, and trabeculectomy have been used, with the preferred procedure individualized to each patient. Medical therapy is important in older children and

should be attempted before any surgical procedure. If surgery is necessary, a trabeculotomy or trabeculectomy is indicated.

Frequently the glaucoma is difficult to control in these patients and may require insertion of a synthetic drainage device or ciliodestructive procedures. Rarely is the vision in the glaucomatous eye better than 20/400, and as many as 50% of glaucomatous eyes are blind within the first decade of life.^{276,277}

Penetrating keratoplasty and cataract extraction may be required to provide a clear visual axis, and the surgical obstacles to success are formidable.²⁷⁸ More advanced forms of this disorder may demonstrate varying degrees of corneal thinning. Severe cases show actual full-thickness holes through the cornea, with flat anterior chambers and adherence of the lens to the posterior cornea. The visual prognosis of glaucoma with extensive corneal disease is grim, although exceptions have been reported.²⁷⁹

LOWE SYNDROME (OCULOCEREBRORENAL SYNDROME)

The oculocerebrorenal syndrome of Lowe is an X-linked disorder of the OCRL1 gene, with clinical manifestations that include congenital cataracts, mental retardation, and progressive renal tubular dysfunction.^{280–282} The inheritance pattern is sex-linked recessive: 100% of males have cataracts, and 50% of affected males have glaucoma.⁴³ Linkage analysis allows detection of carriers as well as prenatal diagnosis.^{283,284}

Female carriers of the defect exhibit characteristic (though not pathognomonic) irregular, radially arrayed anterior cortical lens opacities, sometimes with posterior capsular changes as well. The glaucomatous angle can have the appearance of isolated trabeculodysgenesis but rarely responds to goniotomy; filtering or tube surgery may be required. Possibly the early surgical removal of cataract introduces the complexities of aphakic open-angle glaucoma into the clinical picture.²⁸⁵

This syndrome must be distinguished from the Zellweger (hepatocerebrorenal) syndrome, a lethal peroxisomal biogenesis disorder that causes infantile hypotonia, seizures, and death within the first year. Ophthalmic manifestations include corneal opacification, cataract, glaucoma, pigmentary retinopathy, and optic atrophy.²⁸⁶

MICROCORNEA SYNDROMES

Microcornea is both an autosomal dominant defect,⁹⁶ as well as a non-specific finding seen in a variety of disorders (rubella syndrome, persistent hyperplastic primary vitreous, Rieger's anomaly, nanophthalmos, and microphthalmia). It can also be seen with miscellaneous systemic diseases, such as fetal alcohol syndrome, myotonic dystrophy, and achondroplasia,²⁸⁷ and a syndrome of absent frontal sinuses.²⁸⁸

The term generally refers to patients with microphthalmia in which the eye is hyperopic and has a corneal horizontal diameter less than 10mm, but microcornea can occur in a normal size globe, often with peripheral sclerocornea. Shallow anterior chambers and narrow angles may contribute to acute angle-closure glaucoma; treatment is directed toward the angle-closure glaucoma. Microcornea is an important predictive risk factor for determining which children operated on for congenital cataracts will go on to develop pediatric aphakic open-angle glaucoma.^{289,290} This risk exists for either anterior or pars plana removal of the lens (without IOLs).^{291,292}



Fig. 19-37 Rubella retinopathy with anomalous pigmentation.

RUBELLA

Congenital rubella syndrome has a wide variety of severe ophthalmic and systemic complications. A worldwide rubella epidemic from 1963 to 1965 affected thousands of infants, many of whom continue to be seen as adults. Ocular disease was the most commonly noted disorder (78%), followed by sensorineural hearing deficits (66%), psychomotor retardation (62%), cardiac abnormalities (58%), and mental retardation (42%). Multiorgan disease was typical (88%).²⁹³

Glaucoma, cataract, microcornea, keratitis, uveitis, and a pigmented retinopathy (Fig. 19-37) are the most common ocular manifestations of congenital rubella infection.²⁹⁴ There is no correlation with gestational age of infection and a specific ophthalmologic defect.²⁹³

Rubella keratitis, often of relatively short duration, causes deep corneal clouding in either a diffuse or disciform pattern. This must not be confused with corneal edema resulting from glaucoma. The glaucoma may present in infancy and have the appearance of isolated trabeculodysgenesis. This form is best managed by goniotomy.

Glaucoma can also arise from iridocyclitis. These patients respond poorly to goniotomy and should be treated with aqueous suppressants, anti-inflammatory therapy, and cycloplegics during the acute phase, which frequently subsides over several weeks. Later onset glaucoma is commonly seen in rubella eyes with microcornea and cataract extraction under the age of 1 year.²⁸⁹

CHROMOSOME ABNORMALITIES

Increasing numbers of chromosomal defects (Fig. 19-38) are associated with congenital glaucoma in its isolated or syndrome forms,^{9a,69} including trisomy 21²⁹⁵; trisomy 13–15; trisomy 17–18^{296,297}; Turner's syndrome; trisomy 3q; chromosome 6 and its associations with both iridocorneodysgenesis and oculodentodigital anomalies^{252,298,299}; and trisomy 2q.³⁰⁰ Multiple ocular and systemic defects may be evident, with a large variation in their presentations. The necessity for surgical or medical management must be individualized to each patient because some of these patients have a limited life expectancy. If isolated trabeculodysgenesis is evident on examination, a goniotomy would be the initial procedure.

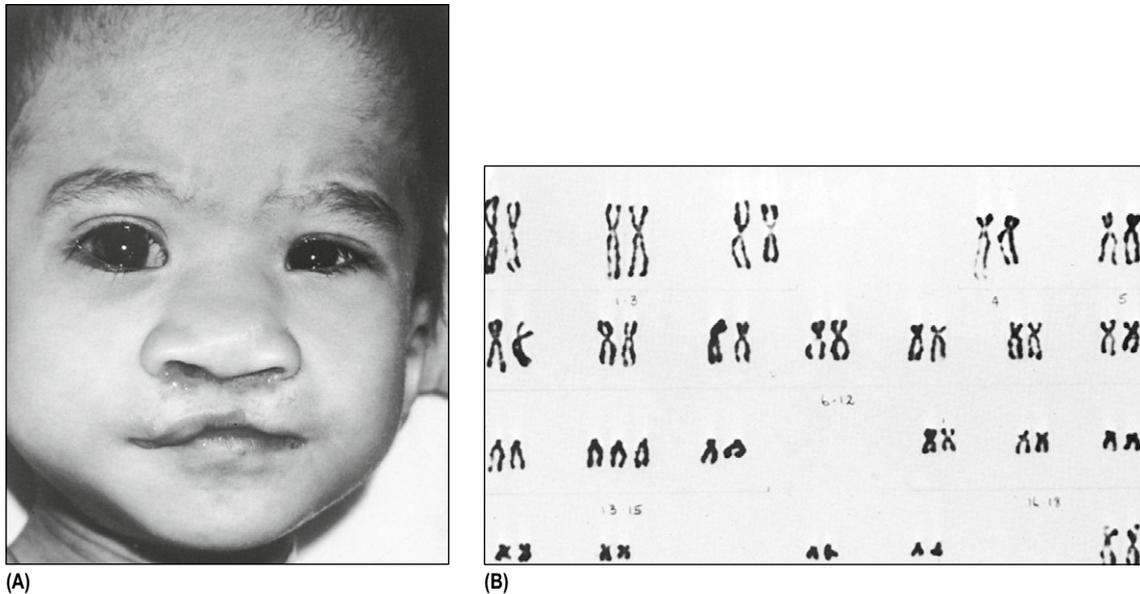


Fig. 19-38 (A) Child with unilateral glaucoma, cleft palate and lip, renal abnormalities, and mental retardation caused by a trisomy 13-15 (D) pattern. **(B)** An example of trisomy pattern.

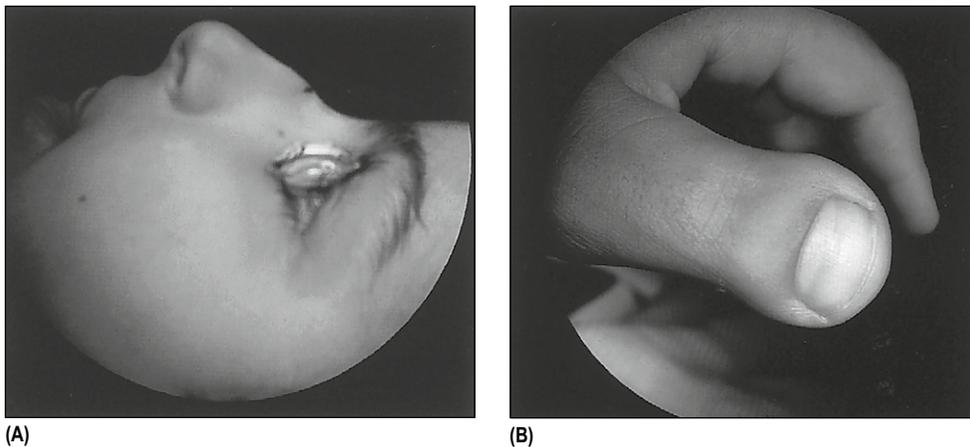


Fig. 19-39 (A) Note the prominent nose typical of Rubenstein-Taybi syndrome. This patient has a Koepple lens in position for examination. **(B)** Broad thumb is also typical of Rubenstein-Taybi syndrome.

BROAD THUMB SYNDROME (RUBENSTEIN-TAYBI SYNDROME)

Broad thumbs and great toes are the most evident abnormalities in broad thumb syndrome (Rubenstein-Taybi syndrome). They may occur in association with mental and motor retardation, lid colobomata, cataract, and a prominent beaked nose (the 'Barbara Streisand syndrome') (Fig. 19-39), as well as congenital glaucoma.³⁰¹ A recent survey of 24 patients found many instances of congenital cataract, nasolacrimal obstruction, and a high frequency of progressive retinal dysfunction by electroretinography testing in over three-quarters of patients.³⁰²

Congenital glaucoma or juvenile-onset glaucoma (after age 3) is common. It is important, however, to discriminate features often seen in this syndrome from those of non-glaucomatous etiologies: corneal lesions, megalocornea, colobomatous or cystic optic nerve, excavation of papilla, and large cup-to-disc ratios.³⁰³ Goniotomy can be successful in controlling the glaucoma.

SECONDARY GLAUCOMA IN INFANTS

PERSISTENT FETAL VASCULATURE (PERSISTENT HYPERPLASTIC PRIMARY VITREOUS)

A recent reassessment of the role and persistence of portions of the embryonic intraocular vasculature has led to a unifying concept of persistent fetal vasculature (Fig. 19-40).³⁰⁴ This term relates the syndrome complex known as *persistent hyperplastic primary vitreous* (PHPV), and relates various other anterior and posterior segment anomalies, such as pupillary membranes, Peter's anomaly, iridohyaloid vessels, and Mittendorf dot, to a common histopathologic sequence of maldevelopment.

At birth, the persistent fetal vasculature typically presents unilaterally in a microphthalmic eye. It results from failure of atrophy of the primary vitreous and its vascular structures. A retrolental fibrovascular membrane can attach to the posterior aspect of the lens,

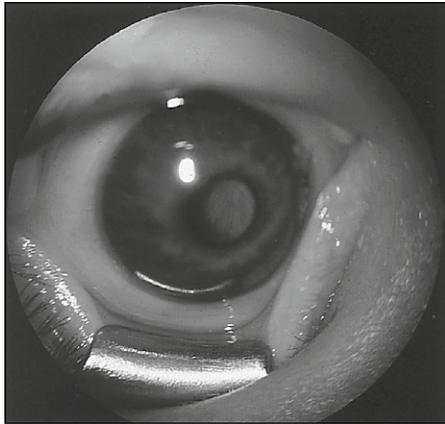


Fig. 19-40 Persistent fetal vasculature is seen with shallow anterior chamber, small eye, and leukokoria. Other causes of leukokoria should be excluded by appropriate diagnostic measures.

as well as to the elongated ciliary processes, thus drawing the processes into the pupillary space. The membrane may appear as a whitish mass in the pupil. Thus persistent hyperplastic primary vitreous should be considered in the differential diagnosis of leukokoria, for which sophisticated radiologic imaging may be appropriate.³⁰⁵

This condition usually manifests its glaucoma in an angle-closure configuration.³⁰⁶ Progressive opacification and swelling of the lens may occur, which can produce angle-closure glaucoma, as can contraction of the retrolental membrane, which pushes the lens forward. Hemorrhages into the eye may also result in glaucoma. Removal of the lens and membrane may prevent closure of the angle and is indicated if the angle is narrowing. But rendering the eye aphakic can lead to post-cataract glaucoma – an outcome possibly obviated by the use of an IOL.³⁰⁷ Such a glaucoma may require a tube surgery, such as the Baerveldt implant.³⁰⁸

The visual results of extensive intraocular surgery are sufficiently encouraging to warrant attention, especially in the absence of posterior pole defects.^{309,310} Peripheral iridectomy can delay the need for lens extraction, but the angle must be observed carefully for progressive closure.

RETINOPATHY OF PREMATURITY (RETROLENTAL FIBROPLASIAS)

Retinopathy of prematurity is a typically bilateral and fairly symmetric disease most often associated with a history of prematurity and oxygen therapy. The disease can be present asymmetrically.

Retinal blood vessels reach the ora serrata nasally at 8 months' gestation but do not fully vascularize the temporal retina until shortly after birth. The retinal vessels only appear susceptible to oxygen damage before their complete vascularization, thus explaining the propensity for retrolental fibroplasia to occur temporally.

The initial effect of oxygen on the retinal blood vessels is that of vasoconstriction. When the infant is placed in normal room air, vascular endothelial proliferation may occur adjacent to vessels that were constricted and closed during oxygen therapy. Regression is common in the earlier stages of the process, but with more advanced disease, neovascularization may grow through the internal limiting membrane onto the retinal surface and into the vitreous. If these advanced stages are reached, vitreous hemorrhage and fibrosis, retinal tears, and retinal detachment may occur; the long-term benefits are disappointing.³¹¹

The development of these retrolental fibrotic membranes can cause a forward displacement of the lens and iris, and this displacement can lead to angle-closure glaucoma, usually with some degree of pupillary block.^{312,313} Lens removal with removal of the retrolental membranes may be indicated in selected cases. Although the visual prognosis is guarded in such instances, proper glaucoma control is beneficial.³¹⁴ Surveillance and possible laser iridotomy may be needed, even into adult life.³¹⁵

LENS-RELATED GLAUCOMAS

Aphakic pediatric glaucoma

The most common childhood glaucoma related to the lens that the clinician is likely to encounter is in eyes rendered *aphakic* for congenital cataracts. In a large retrospective survey of all pediatric glaucomas in a tertiary-referral setting, aphakic glaucoma was responsible for 20% of cases, second only to primary congenital glaucoma.³¹⁶ Retrospective studies vary widely in their estimation of the risk for an aphakic infant developing glaucoma, with an approximate frequency of 10–25% commonly cited,^{317,318} A useful distinction has been made between actual glaucoma in such children versus ocular hypertension – the latter being much more common – as determined by studies several years after surgery, when the children could cooperate with a full ophthalmologic examination.^{319,320}

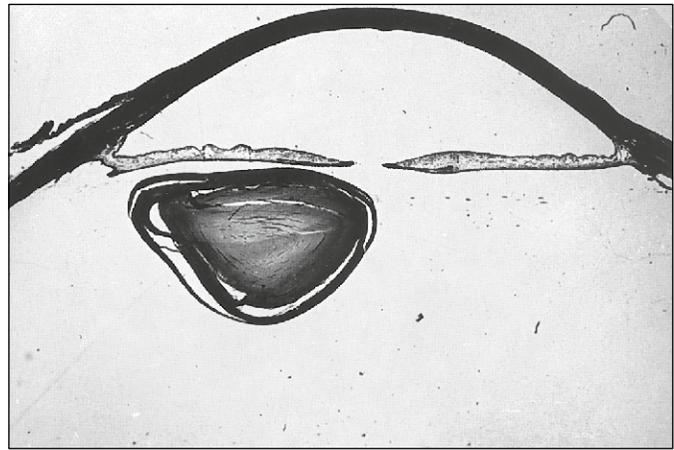
Among the important risk factors which increase the likelihood of developing aphakic glaucoma – in the absence of concurrent complex conditions such as cataract with persistent fetal vasculature – are small corneas (<10 mm),^{317,320} family history of aphakia,^{320a} and early age of cataract removal. One study found a significant risk if lensectomy was performed in the first week of life³¹⁸; a large retrospective study suggested that age 9 months was a 'threshold' for surgery, after which glaucoma was less likely to arise. In two large studies, glaucoma onset between 15–30 months following cataract surgery.^{320,320b,321a} Future studies which will elucidate the balancing of risks between early surgery to forestall amblyopia but deferred surgery to forestall postsurgical glaucoma will be enormously beneficial.

What is likely to be clarified in the next few years is tantalizing evidence that posterior IOL implantation in cases of congenital cataract surgery may offer a protective effect against later onset glaucoma.^{196,322} These studies reported on primary IOL implantation, but the optimal timing has yet to be determined. A recent report on the efficacy of a secondary posterior IOL in the ciliary sulcus of such aphakic children raises more questions as to when, if any, the pseudophakic protective benefit can be conferred.³²³ The exquisite observations by Walton on the progressive anterior iris repositioning against the trabecular meshwork (low synechiae) following pediatric lensectomy³²⁴ suggest a possible mechanism for the IOL 'benefit.' We can imagine that perhaps the infant's naturalistic pseudophakic acuity recruits consistent accommodative activity, with zonular/ciliary motility thus reducing static iris apposition against the angle, and facilitating the active pumping mechanism of the trabecular tissue.³²⁵

The management of aphakic pediatric glaucoma is challenging, with success rates for trabeculectomy with antimetabolite under 50% in several studies.^{326,327} Trans-scleral diode laser cyclodestruction, though effective in aphakic eyes,¹⁵⁷ is also associated with severe complications, such as choroidal and retinal detachments.^{162,328} Glaucoma tube surgery can also be undertaken.¹⁴⁷



(A)



(B)

Fig. 19-41 Marfan syndrome and glaucoma. **(A)** Arachnodactyly. **(B)** Low-power photomicrograph of an eye from a patient with Marfan syndrome demonstrating subluxed lens.

(B from Reeh MJ. *Trans Am Acad Ophthalmol Otolaryngol* 58:212, 1954.)

Subluxation and pupillary block

Marfan syndrome

There are three major diagnostic criteria for Marfan syndrome (also known as MFS1; Fig. 19-41) – ectopia lentis, aortic dilation-aneurysm, and skeletal anomalies – with a variety of auxiliary signs. Diagnosis may be clinically difficult because of variable manifestations and overlap with similar connective tissue disorders. Multiple mutations in the FBN1 gene for fibrillin, a component of elastin, have been linked with Marfan syndrome,^{329,330} with considerable genetic heterogeneity.³³¹ For example, one-third of patients with Marfan syndrome never demonstrate lens subluxation.³³²

The hereditary pattern of the disease is usually autosomal dominant, with sporadic cases comprising approximately 15%. Ocular abnormalities include ectopia lentis, microspherakia, myopia, megalocornea, hypoplasia of the iris stroma and dilator muscle, retinal detachment, and glaucoma.³³²⁻³³⁵

Secondary angle-closure glaucomas, from lens-related complications or postsurgical problems, are the most common kind of glaucoma seen in Marfan syndrome.³³⁵ One form results from pupillary block secondary to malposition of the lens. The lens usually is subluxed upward and held by zonules that are attenuated and stretched. The lens, however, can become dislocated in any direction into the pupil or anterior chamber, resulting in pupillary-block glaucoma. Such a secondary glaucoma is managed initially by dilation of the pupil. A peripheral iridectomy or a lens extraction usually is required.

Open-angle glaucoma can also develop, often appearing well into adulthood, and is frequently associated with abnormalities of the anterior chamber angle.^{335,336} Pectinate iris processes, often dense in appearance, can bridge the angle recess and insert anterior to the scleral spur. When the glaucoma occurs in later childhood, medical therapy should be attempted for initial control of the IOP. If medical therapy is not successful, a trabeculotomy or trabeculectomy is indicated.

Homocystinuria

Homocystinuria is a rare autosomal recessive disease, occurring in approximately 1 of 50 000 births, and can be detected in infancy by amino acid assays of urine. Heterozygote carriers can now be detected.³³⁷ Homocystinuria is an inborn error of metabolism

caused by a deficiency of cystathionine β -synthase. Responsive and non-responsive homocystinuria can be differentiated by the clinical response to high doses of pyridoxine.³³⁸ The most common symptoms of homocystinuria include lens dislocation (95%), mental retardation (88%), dental abnormalities (40%), and arachnodactyly (13%).³³⁹ Among pyridoxine-responsive homocystinuric patients, there may be a high number of early deaths due to vascular (thromboembolic) events.³⁴⁰

Ocular abnormalities include retinal detachment and ectopia lentis.^{341,342} The lens is usually subluxed inferiorly but may move anteriorly, resulting in pupillary-block glaucoma. This is not evident at birth, but usually appears by age 5.³⁴³ The slit-lamp appearance of the dislocated lens can often be used to clinically distinguish between Marfan syndrome and homocystinuria; there are elongated but intact zonules seen in the former and a fringe of ragged zonular remnants in the latter.^{342,344} Early dietary and vitamin supplementation can profoundly delay the onset of ectopia lentis in homocystinuria, although it may occur later in life.³⁴⁵

Treatment of the glaucoma includes dilation of the pupil and peripheral iridectomy to break the pupillary block. Lens extraction is required if the lens has dislocated into the anterior chamber. The risk of thromboembolic phenomena in these patients must be considered if general anesthesia is to be used.

Spherophakia and pupillary block

Weill-Marchesani and GEMSS syndromes

Weill-Marchesani syndrome includes short stature, brachydactyly, microspherophakia, glaucoma, and ectopia lentis. It is an autosomal recessive trait, occurring in 1 in 100 000 individuals.^{342,346} Ocular abnormalities are present only in homozygotes.³⁴⁷ The lenses are frequently small (microspherophakia), with loose zonules; they are more likely to dislocate than in cases of Marfan syndrome and do so in a downward direction.⁹⁵ A high degree of myopia with a shallow chamber should alert the physician to this diagnosis, especially in young persons (Fig. 19-42). Angle-closure glaucoma can occur in the absence of lens dislocation³⁴⁸; an argon laser peripheral iridoplasty can be used prophylactically.³⁴⁹ In the presence of angle-closure and cataractous visual loss, complex lensectomy, IOL insertion, and glaucoma shunt surgery have been described as a viable approach.³⁵⁰

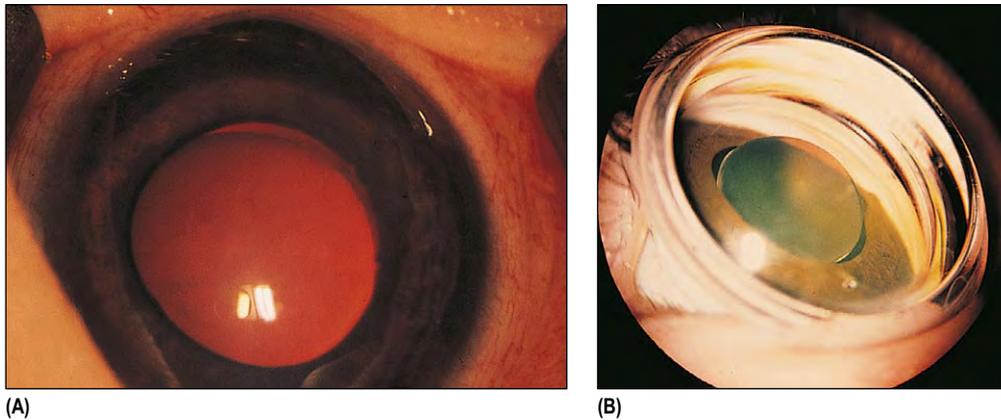


Fig. 19-42 (A) Microspherophakia with a very shallow anterior chamber. **(B)** Spherophakic lens spontaneously dislocated into anterior chamber.

A nearly identical syndrome (GEMSS syndrome) has been identified but with an autosomal dominant transmission.³⁵¹ GEMSS is an acronym for glaucoma + ectopia lentis + microspherophakia + stiff joints + short stature.

TUMORS

Ocular tumors are not common in children, but when present, they can cause a secondary glaucoma. A variety of mechanisms may be involved: obstruction or invasion of the trabecular meshwork area by tumor cells (e.g., leukemia) or inflammatory and pigmented debris (e.g., iris rhabdomyosarcoma)³⁵²; a forward displacement of the lens–iris diaphragm caused by the increased volume of the posterior segment with resultant angle closure (e.g., choroidal metastases or medulloepithelioma),³⁵³ and rubeosis iridis with neovascular glaucoma (e.g., retinoblastoma).

Retinoblastoma

Retinoblastoma is the most common intraocular tumor of infancy and childhood and usually presents with leukokoria and strabismus. Tumor cells may seed the anterior chamber, masquerading as an anterior uveitis with a pseudohypopyon. The tumor may also invade the iris and trabecular meshwork area. Rubeosis iridis is present in a number of cases.

In a large retrospective study of secondary glaucoma associated with intraocular tumors, 303 eyes with retinoblastoma were evaluated: 17% of these eyes had elevated IOPs, which were secondary to iris neovascularization in 70% of cases and to an angle closure without neovascularization in 27%.³⁵⁴ The commonest mechanism for the latter non-rubeotic glaucoma is extensive serous retinal detachment, with ciliary rotation of the lens–iris diaphragm inducing a secondary angle closure.

Juvenile xanthogranuloma

Juvenile xanthogranuloma (Fig. 19-43) is a benign, self-healing disorder characterized by solitary or multiple yellow-red papules on the skin and, occasionally, in other organs. It is predominantly a disease of infancy or early childhood, although adults may also be affected. Histologically, juvenile xanthogranuloma represents an accumulation of histiocytes lacking Birbeck granules (non-Langerhans cells), which can be differentiated from Langerhans cells by specific staining techniques. Affected persons have normal lipid metabolism. The patient's general health is not impaired, and in the absence of associated conditions, the prognosis is excellent.³⁵⁵

Ocular involvement is seen as a vascular, yellowish-white, solitary or diffuse mass of the iris. Tumor involvement of the trabecular

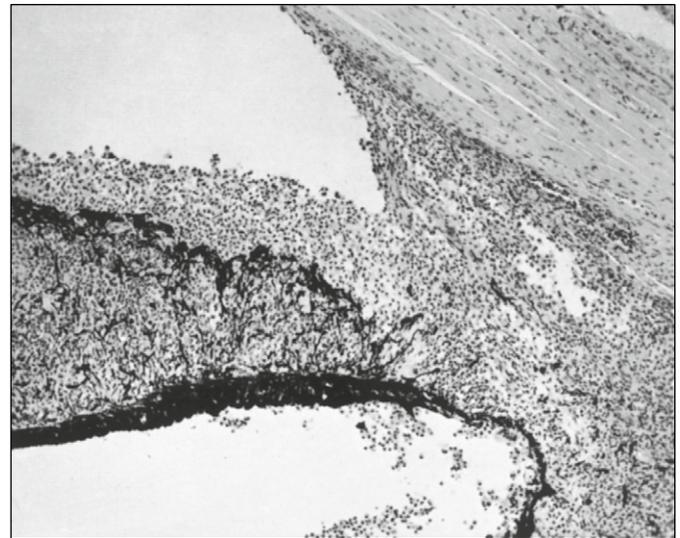


Fig. 19-43 Xanthogranuloma of the iris with obstruction of the trabecular meshwork. (From the Armed Forces Institute of Pathology collection, Washington, DC.)

meshwork area and ciliary body may also occur. Involvement of the eyes is nevertheless quite rare, reportedly seen in 0.4% of cases with cutaneous involvement. Major risk factors include a new diagnosis in a child under 2 years of age with multiple skin lesions.³⁵⁶

The most common cause of glaucoma is a spontaneous hemorrhage into the anterior chamber; bilateral cases have been reported.³⁵⁷ Because the ocular lesions may disappear spontaneously, the glaucoma initially should be controlled medically if possible. The intraocular tumors often regress with subconjunctival steroid injections, especially if treated early.³⁵⁸ A trial of topical and systemic corticosteroids is indicated when there is no evidence of spontaneous regression during follow-up.

INFLAMMATION

Inflammatory glaucoma can develop in infants and children much the same as in adults. A confounding issue that always requires discrimination is the relative role of the (often chronic) inflammation versus the eye's response to steroid therapy in contributing to the elevated IOP.³⁵⁹

Juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis is a particularly serious form of anterior uveitis that occurs in children. A chronic iridocyclitis results, usually affecting young girls (aged 0–4 years) who have pauciarthral joint involvement. Unlike most forms of acute iridocyclitis, there rarely is associated discomfort, redness, or photophobia. Because many of these patients do not have ocular symptoms, it is important that they be followed closely by an ophthalmologist to detect and treat any inflammatory disease and sequelae – specifically glaucoma, cataracts, and band keratopathy.

There are several ophthalmic prognostic factors that have been elucidated, the most important of which is whether there is uveitis at the time of presentation of the arthritis. With uveitis, one-quarter will likely lose vision to <20/200; one-half develop cataracts; one-quarter develop band keratopathy; and one-quarter develop glaucoma.^{360,361} If no uveitis appears in the first 5 to 7 years after the onset of juvenile rheumatoid arthritis, ocular involvement is unlikely.^{361,362}

Medical treatment of this glaucoma is similar to that for the uveitic glaucomas in adults: steroids, mydriatic cycloplegics, and topical and systemic antiglaucomatous medications.³⁶³ The glaucoma is frequently from secondary synechial angle closure. When surgery is required, a *trabeculodialysis* procedure has been used, producing reasonably successful results in this difficult disease.^{364,365} Trabeculodialysis is a rare instance where a goniotomy-like incision is effective in a non-infantile eye. In this procedure, after a parallel incision is made across the trabecular meshwork with a gonio-knife, small perpendicular flap edges are made at the two ends of the incision plane, and a long flap is peeled with the knife-point along its length towards the iris root. Scleral indentation, described for a similar procedure called goniosynechialysis in the management of chronic angle-closure glaucoma, may also enhance visualization for trabeculodialysis.³⁶⁶ Surgical alternatives include trabeculectomy with antimetabolites or glaucoma implant–shunt surgery.

As with adults, children suffering from infectious entities that afflict the anterior segment, such as herpes or opportunistic infections in immune-compromised patients,¹⁰⁷ require appropriate diagnosis, management of the underlying condition, and attention to any ocular manifestations.

STEROID GLAUCOMA IN CHILDREN

As discussed in Chapter 18, intensive exposure to topical or oral corticosteroids can often induce ocular hypertension, or even frank glaucoma in susceptible individuals, presumably on a genetic basis.^{367,368} This phenomenon has been well documented in children as well: in 4-week studies of b.i.d. or q.i.d. use of dexamethasone or fluorometholone topical drops in children under 10 years old, elevated peak and elevated net IOPs were seen after 10 days, correlating with the intensity of the regimen.^{369,370}

With the alarming worldwide increase of childhood-onset bronchial asthma, the widespread use of nasal and inhalation

corticosteroids on IOP is potentially of concern. Although only rare anecdotal cases have been reported^{371,372}, ophthalmic monitoring for children on long-term steroids is advisable. Interestingly, under the age of 40, the association between inhaled steroids and cataract formation is negligible.³⁷³

Another potential concern for steroid-related elevated IOPs in children is following the use of intravitreal triamcinolone for intractable uveitis or complications of diabetic retinopathy. In several series of adult patients treated for a variety of retinal diseases, elevated IOP responses greater than 10 mmHg were seen in between 28–60% of eyes after a single injection, manifesting between 1–12 weeks.^{374–376} Presumably the mechanism was that of steroid-induced trabecular metabolic dysfunction, since actual debris (from the injection) was rarely seen in the angle.³⁷⁷ Pressures, though usually responsive to topical medications, surgically responded either to removal of the intravitreal drug with pars plana vitrectomy³⁷⁸ or standard trabeculectomy.³⁷⁹ Given the comparable response of pediatric eyes to topical steroids as seen in adult eyes, monitoring for this complication of a new therapeutic modality is also warranted.

NEOVASCULAR GLAUCOMA

Neovascular glaucoma is the end-stage manifestation for many diseases in which the common pathway is vascular ischemia.^{380,381} Childhood glaucomas associated with this difficult form of angle closure include retinoblastoma, Eales disease, Coats disease,³⁸² X-linked familial exudative retinopathy (Norries disease),^{383–385} and so forth.

TRAUMA

Both blunt and penetrating trauma may occur in children and produce glaucoma from a variety of causes. Any two of the four cardinal signs of anterior segment injury may herald post-concussion glaucoma: angle recession more than 180°; traumatic cataracts; iris injuries; or lens displacement.³⁸⁶ Management is the same as that for trauma-induced glaucoma in the adult, but children require life-long surveillance for late-onset angle-recession glaucoma.

Birth injuries, particularly those caused by forceps damage, can present a difficult problem in the differential diagnosis of congenital glaucoma. Trauma to the periorbital skin area can be helpful in making this diagnosis, particularly when the glaucoma is unilateral. Forceps injury typically will cause breaks in Descemet's membrane, with corneal edema. The breaks tend to be multiple and vertically oriented but may occur in any direction. The corneal edema usually disappears over several weeks as the corneal endothelium heals. Ocular trauma associated with delivery can produce a transient or permanent glaucoma depending on the degree and area of damage.

Medical management of the IOP elevation is advised when birth injury is the suspected cause. Both the IOP and the corneal damage from trauma may improve over several weeks or months.

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CHAPTER
20

Genetics of glaucoma

INTRODUCTION

That primary open-angle glaucoma (POAG) and, especially, glaucoma occurring in childhood or associated with other developmental anomalies had familial characteristics has been known since the mid nineteenth century. Von Graefe described multiple families in which glaucoma had appeared in several generations.¹ Family members of patients with POAG are more likely to have the disease than family members of those without glaucoma in the general population.² A positive family history of glaucoma (especially a first-degree relative) is indeed a risk factor for POAG.³ Concordance of glaucoma is higher between monozygotic twins than dizygotic twins as would be expected if the disease was at least partially inherited.⁴

Elevated intraocular pressure (IOP), reduced facility of outflow, increased pressure response to corticosteroids and cup-to-disc ratio all have hereditary tendencies.⁵⁻¹⁰ The Beaver Dam Eye Study demonstrated that elevated IOP has both polygenetic and environmental influences.¹¹ That same study showed an even greater heritability of optic nerve parameters associated with POAG such as vertical cup-to-disc ratio than even IOP.¹² Similar findings were reported by the Salisbury Eye Study with the heritability of IOP estimated at 0.29 and that of cup-to-disc ratio at 0.56.¹³ A recent analysis of the Blue Mountains Eye Study data from Australia showed that genetically influenced IOP variance accounted for about 18% of the glaucoma in that large population study.¹⁴ The studies of both Becker and Armaly found that the development of elevated IOP following 6 weeks of topical corticosteroid treatment did roughly fit an autosomal recessive type of inheritance pattern. However, the pattern of inheritance of the actual disease did not seem to fit any of the classical Mendelian forms of inheritance such as autosomal recessive or sex-linked recessive.⁷⁻¹⁰

In a different condition, small eyes tend to run in families and angle-closure glaucoma is associated with small eyes. Certain developmental anomalies of the eye that are associated with glaucoma have been known for many decades to be familial in nature. Clearly, genetics plays an important role in many different forms of glaucoma. We still have a long way to go to sort out the effects of genetics versus environment but the serious study of these factors has begun. Science has given us tools that will continually accelerate this knowledge base.

The recent completion of the human genome project has offered a fascinating and hopeful glimpse into the future of medicine. Conceivably, in the not-too-distant future, we will have reclassified the glaucomas into more genetically appropriate conditions, we will be able to identify conditions like congenital glaucoma *in utero* as

well as identify those patients at high risk for open- and closed-angle glaucoma while still in childhood or young adulthood so appropriate monitoring can be accomplished. Identifying the genes associated with various kinds of glaucoma also raises the possibility that we may be able to attach reparative genes to non-pathologic viruses or other vectors and actually prevent these diseases from occurring at all. An example of this kind of possibility has been reported with retinoblastoma; in a family where the father had bilateral retinoblastoma, as did the first born child (as well as pinealoma), the development of retinoblastoma in subsequent children was prevented by a technique called pre-implantation genetic diagnosis in which a single fertilized egg lacking the retinoblastoma gene was chosen for implantation in the uterus from several *in-vitro* inseminated oocytes. The resulting child did not have retinoblastoma (or any other tumor) with 6 months follow-up.¹⁵ Pharmacogenetics may also allow us to tailor our therapy of those diseases that slip through the genetic screens as well of those that are not genetically repairable to enable each patient to have the most effective and efficient therapy (Box 20-1).

As far as glaucoma is concerned, none of the promises have yet been realized; we have only just begun to travel down this road. What we have learned so far seems on the surface to be dull and includes an ever increasing list of glaucoma conditions associated with specific gene defects. Despite having found more than a dozen genes associated with one or another form of glaucoma, collectively these discoveries can explain less than 10% of the total cases of glaucoma. This chapter will try to outline what we have achieved so far. Because of improvements in methodology, the knowledge is coming at a faster and faster pace. While the subject matter may be only facts right now, what lies around the corner is exciting. Already, the ability to develop animal models of glaucoma using specific genetic defects (knockout rodents, etc.) has improved our understanding of some

Box 20-1 Potential benefits for glaucoma patients of genetic studies

Better understanding of the pathogenesis of the glaucomas.
Newer and better classification based on cellular/molecular mechanisms.
Potential for genetic repair of mutations pre-implantation, *in utero* or early in life before glaucoma damage occurs.
Identification of potential or actual victims *in utero* or early in life so appropriate repair, monitoring and/or therapy can be initiated before visual loss.
Development of therapy targeted specifically at the molecular or cellular defect.
Using pharmacogenetics to develop and target individual therapy having the most efficacy and efficiency as well as least side effects.

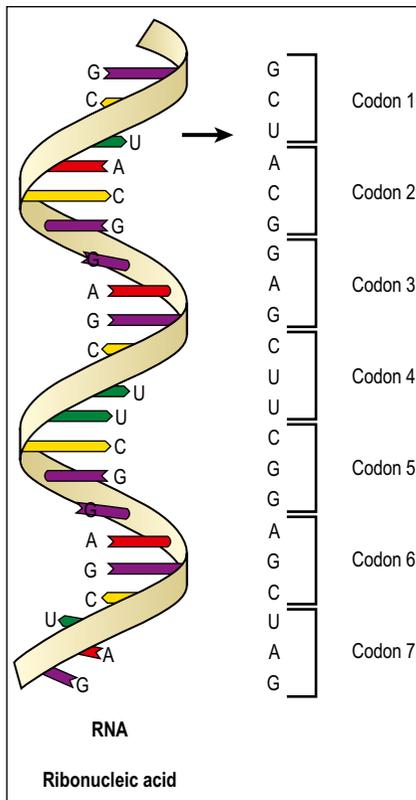


Fig. 20-1 Codon.
(From the National Human Genome Research Institute.)

pathogenetic mechanisms in glaucoma. The chances are good that soon many of the promises noted above may be realized.

BASIC GENETICS

All of the human traits fit into 23 pairs of chromosomes. Each individual has 22 autosomal pairs and one sex pair which contains either two X chromosomes (female) or one X and one Y chromosome (male). Each of the 23 human chromosomes are made up of thousands of genes which in turn are arrayed along one molecule of DNA. Each chromosome pair contains one DNA molecule from each parent. The DNA is made up of nucleotides each of which is formed by varying sequences of four nucleic acid bases; a codon is a series of three nucleic acid base pairs. It is the sequence of the base pairs and codons (Fig. 20-1) that determine the nature of the amino acid and protein synthesis directed by the DNA nucleotide, and it is the protein which determines a trait. There are over 30 000 genes each of which has an average of 3000 base pairs. The chromosomes have anywhere from 20 to 200 million base pairs.

DNA is the template from which RNA is made and RNA governs protein synthesis inside the cell. Groups of DNA bases that are transcribed into messenger (m) RNA which results in protein synthesis are called exons and the DNA strands that form inactive mRNA in between the exons are called introns. When the mRNA gets into the cytoplasm or other parts of the cell where the protein synthesis related to that RNA takes place, the introns are stripped away and only the active mRNA is left to drive protein formation. The RNA builds proteins by adding amino acid sequences. The process is complicated and incompletely understood. However, if an amino acid sequence even of thousands is altered by as little as

Table 20-1 Derivation of gene locus name

Name of disease (e.g., glaucoma)	Variant of disease (e.g., primary open angle)	Order of discovery (e.g., first identified in open-angle glaucoma)
GLC	1	A
Gene locus name depends on an acronym for the disease process (e.g., glaucoma), the particular variant of the disease (e.g., primary open angle), and the order of discovery of the mutation associated with the variant.		

one amino acid, the abnormal protein produced may be inconsequential or, more likely, devastating to life or function.

Abnormalities of chromosomes come in several varieties. Some are gross enough to be visible with the microscope, such as extra copies of a chromosome, a missing part, a broken chromosome, or abnormal rejoining (translocation). For example, Down syndrome is caused by an extra copy of chromosome 21, so instead of two copies, there are three. This can be diagnosed by karyotype analysis. Most changes in DNA are at the molecular level and cannot be seen by just looking at the chromosome. These changes are called mutations and, as noted above, can involve just one amino acid base pair exchange which can produce profoundly life-altering changes or even fatality. Examples of conditions produced by mutations in a single amino acid sequence in a single gene include sickle cell anemia, cystic fibrosis, Marfan syndrome and Tay-Sachs disease.

GENETIC NOMENCLATURE

The Human Genome Organization (HUGO) designates the name (locus) of the gene. The first three letters indicate the broad category of disease state. For example, GLC indicates primary (rather than secondary) glaucoma. The 1 (2 or 3) following the first three letters further defines the type of glaucoma; for example, 1 is open angle, 2 is closed angle and 3 is congenital. Finally, in chronological order, each newly mapped gene is given a sequential letter; for example, a is for the first, b for the second gene identified, and so on (Table 20-1).¹⁶ The name of the gene does not tell you anything about which chromosome or on what part of the chromosome the gene is located; the location of the gene is indicated by the term 'map locus.' The identified glaucoma genes are indicated in Table 20-2 along with a brief phenotype description, the locus, the age at onset, and the name of the gene as it relates to the protein it produces, if known. It is usually the abnormal protein produced by the mutated gene that is responsible for the structural or functional deficit in a genetic disorder.

PRIMARY OPEN-ANGLE, NORMAL-TENSION, AND JUVENILE-ONSET OPEN-ANGLE GLAUCOMA

As noted above, POAG has long been known to have hereditary tendencies. This is seen most poignantly in the fact that people of black African ancestry tend to get glaucoma four times more frequently

Table 20-2 Glaucoma genes

Locus	Location or reference	Gene or protein name	Phenotype	Age of onset	Inheritance	Per cent of phenotype with gene
GLC1A	1q23-q25	TIGR/myocilin	JOAG/POAG	Juvenile/adult	Dominant	3
GLC1B	2cen-q13	–	POAG	Adult	Dominant	Very low
GLC1C	3q21-24	–	POAG	Adult	Dominant	Very low
GLC1D	8q23	–	POAG	Adult	Dominant	Very low
GLC1E	10p15-14	Optineurin	POAG/NTG	Adult	Dominant	<5
GLC1F	7q35	–	POAG	Adult	Dominant	Very low
OPA1	3q28	OPA1	NTD	Adult	?	≈30%
GLC3A	2p21	CYP1B1	Congenital	Infant	Recessive	Majority
GLC3B	1p36	–	Congenital	Infant	Recessive	
NNOS	11	–	Angle closure/ nanophthalmos	Young-older adult	Dominant	Majority
RIEG1	4q25	PITX2	Rieger syndrome	Infant-childhood	Dominant	
RIEG2	13q14	FOXC1	Rieger syndrome	Infant-childhood	Dominant	
IRID1	6p25	FKHL7	Iridogoniodysgenesis	Infant-child	Dominant	
	7q35	–	Pigment dispersion	Young adult		
NPS	9q34	LMX1B	Nail-patella syndrome	Young adult	Dominant	
PAX6			Aniridia	Congenital		
LOXL1	15q21	Lysyl oxidase	Exfoliation syndrome and glaucoma	Late adult	?	5-10%

JOAG, juvenile-onset open-angle glaucoma; NTD, neural tube defect; POAG, primary open-angle glaucoma.

and at an earlier age; the result of this, plus environmental factors such as less access to medical care and, perhaps, less aggressive treatment, is that people of black African ancestry suffer blindness at 13 times the rate of Caucasians.¹⁷⁻²⁰ Clearly, both genetic and environmental influences are at work here. Yet, in the late 1980s, heritability of open-angle glaucoma was estimated at 13% with 87% attributed to non-genetic causes, based on Finnish twin studies.²¹ Genetic studies are particularly difficult in a disease like POAG because it is diagnosed so late in life and is relatively prevalent. Even in those families with a clearly identifiable gene mutation associated with glaucoma, penetrance is incomplete, the age of onset varies among family members, and the severity of the glaucoma is different. This suggests that multiple genetic factors as well as some, as yet undefined, environmental factors play a role in this disease.²² Perhaps, one or more genes influence aqueous dynamics and another set of genes (or a gene) determines susceptibility to optic nerve damage.²³

TIGR/MYOCILIN

The study of genetics in open-angle glaucoma received a needed boost when the first gene (GLC1A) related to this condition was mapped in a large family with juvenile-onset open-angle glaucoma in 1993.²⁴ The ice was broken, and over the next dozen years, six more loci of genes associated with open-angle or normal-pressure glaucoma were mapped. Point mutations in this gene can cause POAG.²⁵ Polansky and co-workers identified the abnormal protein produced by mutations in this gene and subsequently were able to determine the exact molecular sequence of this gene, including its promoter, introns, and exons, which he called TIGR (trabecular meshwork-inducible glucocorticoid response).^{26,27} An independent investigation also identified this protein and its concomitant sequence

and called it myocilin.²⁸ The Human Genome Organization then designated MYOC as the official gene symbol for the TIGR/myocilin gene.

Myocilin is a protein with over 500 amino acids. There are two major domains of the molecule, one like myosin and the other olfactomedin – a main component of mucous layers.²⁹ Olfactomedin is an old protein and can be found across the animal kingdom. In the human eye, the mRNA of myocilin is found not only in the trabecular meshwork but also in the retina, the choroid, ciliary body, aqueous humor, and iris.³⁰ Myocilin is also found in bones, skeletal muscle, mammary gland, thyroid, and trachea, although in smaller amounts than in the anterior segment of the eye. No systemic disease states have been associated with myocilin mutations or deficiencies.

Several groups were then able to identify mutations in the MYOC gene as being associated with families with juvenile- and adult-onset POAG.³¹⁻³³ It has been estimated that mutations in the MYOC gene account for about 3-5% of the cases of adult-onset open-angle glaucoma as well as a significant portion of familial juvenile-onset glaucoma.³⁴⁻³⁹ Some evidence exists to support the possibility that different mutations in the same gene may produce different aggressiveness of the disease.⁴⁰

That myocilin plays an important role in trabecular meshwork function seems clear. Just how that role interacts with glaucoma and causes dysfunction is not clear. Polansky and his group thought that the myocilin gene governed the response of the trabecular meshwork cells to corticosteroid administration.⁴⁰ Since a very large percentage of patients with glaucoma will respond to 6 weeks of topical steroid administration with a significant IOP rise, it seems logical to assume that a gene and its protein product that governs this function might have some relationship to the pathogenesis of glaucoma.⁹ Recombinant myocilin when injected into the anterior chamber decreases the outflow facility, whereas other similar proteins do not.⁴¹

If myocilin is overexpressed, trabecular meshwork cells lose adhesive and contractile properties.⁴²

Similar effects can be seen if myocilin is present in the extracellular environment.⁴³ Myocilin has been found to bind to fibronectin in the extracellular matrix of human trabecular meshwork cells.⁴⁴

Liu and Vollrath's work supports the idea that mutated myocilin causes accumulation of deleterious products in the endoplasmic reticulum of the trabecular cell and that these changes make the cell more susceptible to apoptosis.⁴⁵ Carriers of myocilin mutations, particularly the Thr377Met mutation, will have reduced outflow facility by tonography, so proper myocilin activity is necessary for normal trabecular drainage.⁴⁶ On the other hand, the trabecular meshwork malfunction in glaucoma does not seem to be due to the amount of myocilin since its absence or excess may not influence actual trabecular meshwork function.^{47–49} However, some evidence points to an increase in the function or change in quality of myocilin as opposed to amount.⁵⁰ Myocilin is found in abundance in the trabecular meshwork of eyes with late-onset open-angle glaucoma and with exfoliative glaucoma along with alpha B-crystallin, a stress protein.⁵¹ Myocilin also seems to be upregulated as a result of mechanical stretching of the trabecular meshwork.⁵² Tamm has postulated that mutated myocilin may assume an abnormal shape that either accumulates in the cell causing premature cell death or may physically block the trabecular meshwork, reducing aqueous outflow; direct evidence for this hypothesis has not been produced.²⁹ Myocilin has been found in the myelinated portions of the optic nerve in humans and, in monkeys, is expressed by astrocytes.⁵³ The significance of this finding is not clear.

Several mutations of MYOC have been mapped; each has its own amino acid change and location on the chromosome. The most common is the Gln368Stop mutation. At least two dozen other mutations have been identified in addition to the polymorphisms in the Mt1 promoter region described below. These include Gly434Ser, Asn450Asp, Val251Ala, Ile345Met, Ser393Asn, Phe369Leu, Gln368STOP, Val426Phe, Cys433Arg, and Tyr437His.^{54–57} Despite the different loci, the phenotypes of these mutations are rather similar and are characterized by families with early-onset, generally aggressive POAG with the exception of the Gln368STOP mutation. Using case-control methodology, Graul et al could not find any difference in age of onset or clinical course between those having the Gln368STOP mutation and those not having a MYOC mutation.⁵⁸

It is possible that the promoter region of MYOC may be abnormal in some patients. Polansky and co-workers have shown in a retrospective study that patients with advancing glaucoma are more likely to have polymorphisms in the promoter region (Mt1) of MYOC than patients whose glaucoma is stable.⁵⁹ Others have failed to find this association.⁶⁰ Whether this is due to differences in populations or techniques is not known at this time. A study by Mackey and co-workers in Tasmanian families with early-onset open-angle glaucoma showed that the specific Thr377Met mutation of the MYOC gene, although less common than Gln368STOP mutation, was associated with a younger age of onset, higher IOPs and higher likelihood of having had glaucoma drainage surgery.⁶¹

The best inference from the often conflicting findings about the MYOC gene and its role in glaucoma is that abnormalities in this gene somehow negatively affect the function of the trabecular meshwork and lead to glaucoma in a significant number of patients with early-onset open angle-glaucoma and in a minority of patients with adult-onset open-angle glaucoma. It is therefore likely that MYOC mutations do play a significant role, at least in a subset of glaucoma patients, but need other enabling genetic and/or

environmental factors to cause glaucoma. Further work will undoubtedly help explain the sometimes conflicting observations related to the myocilin gene.

The initial discovery of the MYOC mutations held the promise that relatives of glaucoma patients could be genetically screened early in life. The hope was that those at greatest risk would be identified so that closer monitoring and timely intervention would prevent vision loss. Towards that end, a commercial screening kit became available that screened for MYOC mutations, polymorphisms in the mt.1 promoter and, later, optineurin mutations. As the early promise that the major gene(s) for glaucoma had been identified began to fade, studies appeared that suggested that routine screening for these mutations could not be supported because of the low yield. For example, in the United Kingdom, a study of over 500 glaucoma patients found a mutation in MYOC in only 1.4% and the authors concluded that routine screening for MYOC mutations was not warranted.⁶² Similarly, in southern India, MYOC mutations were found in only 2% of patients with POAG.⁶³ However, Americans of African ancestry have both a higher incidence of glaucoma than those of European ancestry and harbor MYOC mutations more frequently.⁶⁴ There are other studies that show a lower incidence of MYOC mutations in black populations. MYOC mutations may account for as much as 5% of the POAG in France and Switzerland, up to 8% of familial glaucoma in Italy, and only 1% in Sweden.^{65–68} Despite evidence that POAG in a black population is inherited via a major co-dominant gene, no mutations in the MYOC gene were found in the Barbados Family Study of Open-Angle Glaucoma despite the high prevalence of glaucoma in this population.⁶⁹ A recent study from India implicates MYOC gene mutations in primary congenital glaucoma.⁷⁰

OPTINEURIN

Great excitement accompanied the announcement of the identification of the GLC1E locus on chromosome 10 and its association with a large family with both normal-pressure and high-pressure glaucoma.⁷¹ Sarfarazi and colleagues had already localized this gene to chromosome 10p14.⁷² The gene was named optineurin (optic neuropathy-inducing protein), a name which was accepted by the HUGO committee and abbreviated to OPTN.⁷³ Because optineurin is expressed in the retina and because it is associated with cellular apoptosis, it was thought that mutations in this gene could possibly explain why the optic nerves of patients with normal-pressure glaucoma are more susceptible to optic nerve deterioration. However, many of the patients in the large affected family had high-pressure glaucoma and there are conflicting reports of the importance of this gene to aqueous dynamics.

Polymorphisms in the OPTN gene were linked with both POAG in a large series of Japanese patients and with polymorphisms in the tumor necrosis factor gene.⁷⁴ The polymorphisms in this series were associated with specific changes in the amino acid sequences and also seemed to be associated with polymorphisms in tumor necrosis factor- α . Perhaps, these latter sequence variations help modulate severity. Another group of investigators found that mutations in the OPTN gene accounted for approximately 15% of both the POAG and normal-tension glaucoma in a small group of Japanese patients.^{75,76} However, yet another study in Japan failed to find any optineurin polymorphisms in over 300 patients with POAG and normal-tension glaucoma.⁷⁷ Although the Blue Mountains Eye Study in Australia found a higher prevalence of mutations of the OPTN gene in patients with high-tension glaucoma

compared to non-glaucoma subjects, the association failed to reach statistical significance.⁷⁸ None of their low-tension glaucoma patients had OPTN mutations. The same group found OPTN mutations in subjects without clinical evidence of glaucoma; these mutations were present in only 0.09% of the older, non-glaucomatous population.⁷⁹ Another study in the US failed to show any mutations in adult-onset open-angle glaucoma.⁸⁰ In a Chinese study, mutations in OPTN were found in patients with POAG but they were different mutations than those found in the Caucasian populations with normal-tension glaucoma.⁸¹ In a study of two English families with normal-tension glaucoma, the E50K mutation was associated with earlier onset, had more advanced disc cupping and had a higher likelihood of requiring surgery than patients with normal-tension glaucoma who did not carry the mutation.⁸² In conclusion, OPTN mutations are important for a small subset of POAG patients but, because the incidence is so low, it is not practical to conduct screening in general populations.

Clearly, racial differences (and perhaps environmental as well) exist as to what extent certain mutations account for different forms of glaucoma. In a Canadian study, mutations in OPTN were not associated with low-tension glaucoma but with juvenile-onset open-angle glaucoma.⁸³ An American study found a high prevalence of optineurin variations in families with normal-tension glaucoma but estimated that the gene was responsible for only 0.1% of open-angle glaucoma in the USA.⁸⁴ No mutations in OPTN were found in the Barbados Family Study of Open-Angle Glaucoma⁶⁹ or in a Swedish group of POAG.⁸⁵

Vittitow and Borrás suggested that optineurin served a protective function in the trabecular meshwork because OPTN is upregulated in tissue culture after 2–7 days of sustained elevated IOP as well as after prolonged dexamethasone treatment and by exposure to tumor necrosis factor- α .⁸⁶ It would then stand to reason that absence of OPTN or abnormal OPTN would allow for more tissue damage under stress situations than in a normal eye.

OTHER GENES IN OPEN-ANGLE GLAUCOMA

Families with open-angle glaucoma can have other mutations. For example, POAG in both an American and a Greek family maps to the GLC1C locus on chromosome 3.⁸⁷ A study of 86 families with open-angle glaucoma implicated GLC1I as one of the most common mutations (17%) and was localized to chromosome 15 (15q11-13).⁸⁸ The authors feel that one of the most important phenotypic markers is age at diagnosis and that early age at diagnosis can separate those with mutation-induced glaucoma from those with more multifactorial disease. If these data are borne out by other studies, the GLC1I gene would be the most common mutation identified so far for familial glaucoma. A multicenter group has identified a specific mutation in the WDR36 (GLC1G) locus mapped to chromosome 5 (5q22) as being a causative gene in about 6–7% of families with adult-onset glaucoma.⁸⁹ Another large POAG family that maps to this locus did not have mutations in the WDR36 gene.⁹⁰ The differences in genetic makeup of some families does indicate that the genetics of glaucoma are complex and no one genetic abnormality found thus far explains all similar phenotypes.

The OPA1 gene, which is responsible for dominant optic atrophy, has also been associated with normal-tension glaucoma in a Caucasian but not Korean population.⁹¹ Refining the screening technique for mutations, Powell and colleagues found a specific and hitherto unreported abnormality in the OPA1 gene in 28% of normal-tension glaucoma patients versus only 13% of controls.⁹²

On the other hand, Aung and co-workers were unable to find any differences in phenotype between normal-tension glaucoma patients with and without the OPA1 mutation.⁹³ A similar study in several Caucasian- and African-based populations was unable to find any association between polymorphisms in the OPA1 gene and POAG.⁹⁴

Genome-wide scans can be done in populations and do not depend on families with a known mode of Mendelian inheritance such as autosomal dominant. Such a scan was done on 180 pairs of siblings and linkages to chromosomes 2 (previously known), 14, 17 and 19 were found.⁹⁵ A similar genome-wide scan in the Beaver Dam Eye Study identified two previously unidentified genetic loci for open-angle glaucoma on chromosome 6 and one on 13.¹¹ The exact meaning of these findings remains to be elucidated at this time, but, obviously, multiple genes (as well as some environmental factors) seem to contribute to increased susceptibility to open-angle glaucoma.

Using a candidate gene approach, several potential POAG susceptibility genes have been identified. The renin-angiotensin system is present in the ciliary body and may play some role in the regulation of aqueous humor production. Polymorphisms in the angiotensin II receptor gene were found in Japanese POAG patients and some normal-tension glaucoma patients; those with the polymorphisms in the AGTR2 gene were more likely to have glaucoma and were likely to have worse visual fields than those without the polymorphism.⁹⁶ On the other hand, polymorphisms in the gene for angiotensin converting enzyme were not associated with glaucoma in an English population.⁹⁷ TAP1 and TAP2 genes play a role in the immunologic system; polymorphisms in these genes may be a risk factor for glaucoma.⁹⁸ Excess synthesis of fibronectin has been found in tissue cultures of trabecular meshwork cells from patients with POAG.⁹⁹ This opens a pathway of study to see if the excess fibronectin may play a role in reducing outflow facility in the glaucoma eye.

Sometimes, a promising pathway based on a sound hypothesis leads to a blind alley (as in any kind of medical research.) An example of this was the hypothesis that a mutation in apolipoprotein E, which can be found in several neurodegenerative disorders, might play a role in glaucoma which can also be considered a neurodegenerative disorder. The interest in this hypothesis was sparked by a report from Tasmania of an increased prevalence of normal-tension glaucoma in carriers of the epsilon4 apolipoprotein allele.¹⁰⁰ However, subsequent studies elsewhere failed to confirm this and polymorphisms in apolipoprotein E could not be found in patients with either open-angle or normal-tension glaucoma.^{101,102} Another example is with pigmentary glaucoma. Recently, a DBA/2J mouse was found with iris atrophy and pigmentary dispersion. The mutation responsible for this appeared to be in the TYRP1 gene. Unfortunately, no mutations in the TYRP1 gene were found in humans with pigmentary glaucoma.¹⁰³ On the other hand, at least in four families with pigmentary dispersion syndrome and pigmentary glaucoma, a mutation in a gene mapped to chromosome 7 (7q35-q36) has been found.¹⁰⁴

EXFOLIATION SYNDROME AND GLAUCOMA

The glaucoma world was stunned in late 2007 with the announcement that a genome-wide search had uncovered several single nucleotide polymorphisms in the 15q.24.1 region that were highly associated with exfoliative syndrome and exfoliative glaucoma in two Nordic populations – one in Iceland and one in Sweden.¹⁰⁵ Two of

these single polymorphisms in the lysyl oxidase-like 1 (LOXL1) gene explain 99% of the association. While these polymorphisms are seen in about 25% of the normal population, having one of these confers a 100-times risk of developing exfoliative syndrome or glaucoma. Normal LOXL1 proteins are necessary for elastin function;^{106,107} not surprisingly, exfoliative syndrome seems to be a condition of defective elastin formation and/or function.¹⁰⁵ The association of these polymorphisms has now been confirmed in the USA, Japan, Australia, India, and southern Europe.^{108–114} These genetic changes do not seem to be associated with primary open-angle or angle-closure glaucoma in either Caucasian or African populations.^{115–117} Furthermore, eyes with exfoliative syndrome or glaucoma are not associated with any of the other polymorphisms or mutations that have been associated with other forms of glaucoma.¹¹⁸ Single nucleotide polymorphisms in the LOXL1 gene have now been associated with dissecting aneurysm so, clearly, a normal gene is necessary for proper elastic tissue function.¹¹⁹

The finding of these abnormalities is very exciting and promises both a better understanding of the pathophysiology of this disorder and, ultimately, a treatment directed at the pathology. At this stage, we do not know why only a relatively small percentage of people with the polymorphisms actually get the disease. It may be that many of those without the disease but with the ‘right’ genetic makeup will eventually show signs of the condition. It may also be that an enabler gene is needed to trigger the clinical condition or the lack of an inhibitor gene. It could also be that some environmental stress is required in addition to the single nucleotide polymorphism for the condition to manifest. A knock-out mouse with absence of a normal LOXL1 gene has already been developed and may begin to provide some answers.¹²⁰ The answers to these questions will point the way toward better therapy and, hopefully, prevention of vision loss from this vexatious disease.

GLAUCOMA ASSOCIATED WITH DEVELOPMENTAL DISORDERS

The greatest improvement of our knowledge comes from the identification of specific genetic disorders associated with the developmental glaucomas. We have learned from this group of conditions that there is not a one-to-one correlation between a specific gene mutation and the phenotypic manifestation. The same mutation of one gene may lead to different anatomic changes in different patients or families and mutations of several quite different genes may produce phenotypically similar conditions. While all the genes associated with developmental anomalies of the outflow system of the eye seem to be associated with encoding for transcription factors, the animal models developed using the single gene mutations found in human glaucoma indicate that the development of the eye is complex and multifactorial.²⁹

PRIMARY CONGENITAL GLAUCOMA

Primary congenital glaucoma (PCG) (primary infantile glaucoma) develops *in utero*, early natal period, infancy, or early childhood. Its inheritance is either sporadic (most cases) or, on occasion, can be autosomal recessive. It is more common in the Middle East and in Gypsies than in other societies and may be related to the higher prevalence of consanguinity in these cultures. As noted above, HUGO has designated GLC3 as the label for the gene(s)

responsible for PCG. The first two loci identified (GLC3A and GLC3B) were mapped to chromosome 2 (2p21) and chromosome 1 (1p36.2–p36.1) respectively.^{121,122} Primary congenital glaucoma from the GLC3A families has been associated with various mutations in the CYP1B1 gene in multiple different ethnically diverse cultures.¹²³ This gene codes for a cytochrome enzyme.^{124,125} A Japanese study of 66 patients with PCG showed that roughly one-third had a sequence mutation in the CYP1B1 gene and that those who had the mutation were more likely to have an earlier onset and to be female.¹²⁶

Mutation in CYP1B1 has also been reported in Peter’s anomaly.¹²⁷ A recent study on both Peter’s anomaly and PCG in 10 Saudi Arabian families showed that many of the affected children had the same mutation in the CYP1B1 locus and that, even within a single family, those with the same mutation might have either Peter’s anomaly or PCG.¹²⁸ These findings certainly suggest strongly that not only do these two diseases share the same genetic mutation but also that the phenotypic differences might be just a matter of severity rather than indicating any qualitative difference. The modifiers that determine whether a child with the CYP1B1 mutation gets PCG or Peter’s anomaly remain to be identified. That there may be more than one phenotype of Peter’s anomaly is suggested by the findings below where Peter’s anomaly has been reported as a severe variant of the Axenfeld-Rieger syndromes. Mutations in the CYP1B1 gene have also been associated with childhood glaucoma and even adult-onset glaucoma.^{125,129}

Mouse models have begun to improve our understanding of the complexity surrounding gene mutations and their effects. For example, a mouse model has been developed with a *cyp1b1* mutation. In this model, defects in anterior chamber angle development can be seen including trabecular meshwork abnormalities and a small or absent Schlemm’s canal.¹³⁰ Cross breeding pigmented with albino mice showed that tyrosinase (present in pigmented but not in albino mice) seemed to exert a protective effect, preventing the more severe anomalies seen in the albino mice with the *cyp1b1* mutations. Interestingly, congenital glaucoma has been reported in association with albinism.^{131,132}

AXENFELD-RIEGER ANOMALY

Failure of the embryonic mesenchyme to differentiate into corneal endothelium, iris, angle structures, and crystalline lens leads to a spectrum of abnormalities collectively called Axenfeld-Rieger anomaly. The findings can be as innocuous as an anteriorly displaced and prominent Schwalbe’s line (posterior embryotoxin) with some peripheral iris processes to this anomalous Schwalbe’s line. More advanced cases may have iris adhesions from the mid periphery to the endothelium. The most advanced cases may have lens fused to the cornea with an absent endothelium (Peter’s anomaly). Many are associated with skeletal and dental abnormalities. Fifty per cent of those with Axenfeld-Rieger cases develop glaucoma in time probably related to the anterior segment dysgenesis (see Ch. 19). Tamm and co-workers have noted increased extracellular material in the trabecular meshwork and feel that this change may be part of the pathology leading to the glaucoma.²⁹ Axenfeld-Rieger anomaly has been associated with one of several possible mutations in the FOXC1 gene as well as in the PITX2 gene.^{131–137} In a study of several families, a single mutation (Phe112Ser) in the FOXC1 gene was responsible for a wide variance in the expression of the Axenfeld-Rieger anomalies and glaucoma. The same group reported the first case of Peter’s anomaly associated with a mutation in the FOXC1 gene.¹³⁸

On the other hand, several different mutations in the FOXC1 gene can produce the same clinical phenotype of Axenfeld-Rieger syndrome.¹³⁹ Mice with PITX2 and FOXC1 mutations have become available so better understanding of the developmental steps that lead to these conditions should be just ahead.¹⁴⁰ While mouse models may be helpful in improving our understanding, it is usually difficult to project findings from these models directly to humans; anatomy and chemistry are too different.

ANIRIDIA

Aniridia is another condition associated with infantile, childhood, or young adult-onset glaucoma. Several studies from around the world point towards mutation in the PAX6 gene as the causative agent for this disease.¹⁴¹ PAX6 is a gene that regulates eye development in many species. One family with a single PAX6 mutation demonstrated wide variability in the degree of aniridia ranging from total to partial with variable expression of cataract, keratitis, foveal hypoplasia, and optic disc anomalies.¹⁴² As with other genes, mutations can produce variable penetrance suggesting that other independent influences play an important role. About 50% of these patients develop glaucoma usually during childhood or young adulthood. Abnormal trabecular meshwork and absence of Schlemm's canal have been reported.¹⁴³ A mutant mouse with a PAX6 mutation has been engineered. These mice show many of the characteristics of aniridia including hypoplastic iris, absent Schlemm's canal, abnormal trabecular meshwork, and corneal opacities.¹⁴⁴

NAIL PATELLA SYNDROME

Nail patella syndrome is an autosomal dominant condition characterized by dysplastic fingernails, absent, hypoplastic or dislocated patellae, kidney abnormalities, gastrointestinal symptoms, neurological and vasomotor instability. Glaucoma resembling the primary open-angle type occurs in about 10% (increasing with age) and elevated IOP in

about 8%.¹⁴⁵ This condition has been associated with mutations in the transcription factor LMX1B at the 9q34 locus.¹⁴⁶

RENAL TUBULAR ACIDOSIS

A rare form of infantile or childhood glaucoma is that associated with renal tubular acidosis. The syndrome is also associated with cataracts. This syndrome has been mapped to a specific genetic locus NBCe1.¹⁴⁷ Some patients have been further characterized by a missense mutation that adversely affects Na⁺/HCO₃ metabolism in the kidney tubules, ciliary body, and lens.¹⁴⁸

SUMMARY

Genetic studies have shown that many familial types of glaucoma and some types not identified as familial may have a causative single mutated gene. This has been found especially true for the developmental glaucomas such as primary congenital glaucoma, Axenfeld-Rieger syndrome, aniridia, nail patella syndrome, and renal tubular acidosis. Juvenile-onset open-angle glaucoma and normal-tension glaucoma that have a strong familial character have also had mutations associated with them. However, the patients with glaucoma that have had genetic linkages only reach about 10% or so of the total number. While genetic studies may be helpful in identifying at-risk individuals in a single family with a strong tendency toward open-angle, juvenile open-angle, or low-tension glaucoma, routine genetic screening cannot yet be recommended.^{149,150} The ability to genetically engineer mice and other small mammals has given hope that we will be able to develop a better understanding of the tissue and molecular mechanisms by which glaucoma occurs and, perhaps, develop specific treatments that target these molecular mechanisms or processes that can interfere with the pathologic mechanisms.

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CHAPTER
21

Introduction to patient management

Despite the fact that there are many different types of glaucoma with different manifestations, diagnostic approaches, and treatment modalities, this chapter summarizes some of the generalizable concepts of glaucoma management. While there are probably as many approaches to glaucoma as there are different patients and different caregivers, the concepts presented here are the result of years of experience and are applicable to the extent that generalizations can be; however, they must be modified to the requirements of each patient and physician.

SYMPTOMS AND HISTORICAL INFORMATION RELATED TO THE GLAUCOMAS

Many factors in the patient's history bear on the diagnosis and treatment of glaucoma. Most patients with glaucoma, especially primary open-angle glaucoma (POAG), chronic angle-closure glaucoma, and other chronic forms of glaucoma, are asymptomatic until late in the course of the disease. However, certain patients may have symptoms such as pain, redness, halo vision, blurred vision, and a change in the appearance of the eye. Pain associated with glaucoma is related to the height of the intraocular pressure (IOP) and the rapidity with which it rises to that level. Conditions that cause rapid and sustained rises of IOP to high levels, such as acute angle-closure glaucoma, are often accompanied by pain. Conditions such as POAG that cause less dramatic changes in IOP are usually not associated with pain. Occasionally young patients with open-angle glaucoma (e.g., pigmentary glaucoma) may experience discomfort when IOP rises rapidly even to moderate levels. Other mechanisms for pain in glaucoma include inflammation, bullous keratopathy, and drug-induced side effects (e.g., miotic-induced ciliary and orbicularis muscle spasm). In angle-closure glaucoma or glaucoma associated with acute iritis, conjunctival injection may take the form of a ciliary flush. Other causes of red eyes in glaucoma patients include prostaglandin-like agents, other drug reactions, allergic conjunctivitis, endophthalmitis, neovascular glaucoma, hyphema, subconjunctival hemorrhage, bullous keratopathy, and increased episcleral venous pressure.

When IOP rises rapidly, the corneal endothelium may not be able to adequately pump fluid from the cornea – resulting in edema of the epithelium and, sometimes, the stroma. This condition may produce a visual sensation of colored halos around incandescent lights. Episodic blurring of vision is often noted when rapid elevations of IOP cause corneal edema. It is important to remember that many patients refer to uncolored semicircular or

radiating images as halos. This distortion in vision may be caused by opacities in the media, uncorrected refractive errors, and alterations in the tear film. In these latter conditions, the ophthalmologist can often elicit 'halo' vision in the office while the IOP is normal and the cornea is clear.

Glaucoma can alter vision in a number of other ways. Occasionally a patient may note a diminished visual field during some activity that requires monocular vision (e.g., aiming a rifle, looking through a camera). Patients with asymmetric vision loss may not be aware of their defect until they close the better eye. Loss of Snellen visual acuity usually occurs late in the course of glaucoma unless some other problem occurs, such as central retinal vein occlusion. However, loss of color perception, motion perception, contrast sensitivity, temporal contrast sensitivity, vernier acuity, and other visual functions may occur much earlier in the disease than previously thought; patients may be aware of these subtle changes and complain about them even when visual acuity and standard visual fields are normal.

A few patients may complain of a change in the appearance of the eye which may come from exophthalmos, haziness of the cornea, or an alteration in pupil size, shape, or position.

A careful medical history may provide important information related to glaucoma. The medical history should include the following points:

1. Ocular history should include queries about amblyopia, trauma, inflammation, surgery, cataract, retinal detachment, and inflammation. If not questioned directly, patients may not remember a 'trivial' eye injury that may have occurred many years ago.

2. General medical history should focus on obtaining information about vascular diseases (e.g., hypertension, diabetes, cardiac problems, hypotensive episodes) that might affect ocular perfusion, or other conditions that could mimic or aggravate glaucomatous visual field loss (e.g., demyelinating diseases, central nervous system tumors, or aneurysms). A history of migraine or other vasospastic disorders is important to elicit, particularly for 'normal-pressure' glaucoma. The clinician must know about the patient's general health before prescribing medication or considering surgery. For example, topical β -blocker agents can exacerbate asthma or congestive heart failure.

3. The patient's medication history and allergies should also be documented. Many drugs (e.g., corticosteroids or anticholinergic agents) can alter IOP and affect the course of glaucoma. Conversely, many ocular medications can induce or aggravate systemic medical problems. Frequent exchange of information between the ophthalmologist and the family physician is important. A history of sulfa allergy may make the use of carbonic anhydrase inhibitor therapy unwise unless no other alternative is available.

4. The presence of a family history of ocular diseases – especially glaucoma, but also including cataract, strabismus, amblyopia, and retinal problems – should be determined. Many glaucoma conditions are familial, and information about family members may aid diagnosis and treatment.

Furthermore, now that certain kinds of glaucoma have been related to specific gene abnormalities, elicitation of the family history and even pedigree may be very important for the patient and his or her siblings and offspring. Often, the patient may be aware of some familial eye problem but not be able to specifically identify it. Even in families with severe, blinding, genetic glaucoma, as much as one-quarter of the relatives may be unaware of the condition.¹

The ocular examination should include measurement of best visual acuity; an evaluation of the adnexa for exophthalmos, signs of trauma, or inflammation, and assessment of motility for signs of restriction or paresis. The pupil should be evaluated for size, shape, and reactivity. The slit lamp should be used for assessment of the cornea for epithelial, stromal, and endothelial abnormalities, and for anterior synechiae. The slit lamp should also be used to assess the iris for atrophy, growths, or blood vessels; the anterior chamber for depth and clarity, and the lens and vitreous for clarity. The IOP should be measured before dilation or gonioscopy. The examination should also include a careful evaluation of the retina and its vessels, the macula, and the optic nerve. The status of the optic nerve should be documented periodically, preferably by an objective method such as photography or another imaging technique. Careful descriptions or drawings are acceptable if photography or digital imaging is not available. The nerve fiber layer should be evaluated both for generalized thinning and for localized defects. Gonioscopy is indicated whenever the diagnosis of any kind of glaucoma is suspected. A visual field examination should also be undertaken either for baseline or for follow-up. Corneal thickness (pachymetry) should be ascertained in all open-angle glaucoma suspects and probably, at least once, in all glaucoma patients since thin corneas are a risk factor for progression to glaucoma from ocular hypertension and may help in determining target pressure ranges.²

DIAGNOSIS

Several risk factors are known to contribute to the development of glaucoma, its progression or lack thereof, and its extent. The known factors include heredity, ethnicity, the size of the eye (small for angle closure, large for open angle), the presence or absence of systemic vascular disease, vasospastic disorders including migraine, and the size and shape of the optic cup (see Table 21-1). Although elevated IOP is a major risk factor, it is not the only one and is not, in and of itself, enough to account for all of the damage unless it is very elevated. As noted above, a thin cornea is a significant risk factor for development of open-angle glaucoma among ocular hypertensive eyes.²

People of black African descent have a much higher risk of developing open angle glaucoma and of becoming blind as a result of it.³⁻⁵ People of Hispanic descent also have a somewhat higher risk of open-angle glaucoma.⁶ Individuals descended from certain south-east Asian peoples, such as Chinese and Vietnamese, have a higher rate of angle-closure glaucoma than Caucasians; included in this group are some indigenous Americans.^{7,8}

If glaucoma is thought of as a disease that damages the structural and/or functional integrity of the eye and can often be slowed or arrested by lowering IOP, then decisions are simplified. Those patients who have structural or functional damage either caused by pressure or affected by pressure should be treated. In most instances, the damage is fairly obvious, in the form of visual field loss, classic disc cupping, nerve fiber layer defects, corneal edema, arterial pulsations, or sometimes pain. Usually IOP is above the statistically normal range, so glaucoma is easy to diagnose. Once the disease is diagnosed, the decision to treat is simplified.

In other situations, things are not quite so simple. There may be questionable damage with normal pressure, or there may be elevated pressure without damage. These patients are glaucoma suspects and can be divided into four categories, depending on the level of IOP, the evidence of damage, and the presence of other risk factors.⁹

IDENTIFYING GLAUCOMA SUSPECTS

The purpose of identifying someone as a glaucoma suspect is to be able to monitor that individual for the earliest sign of damage and, by intervening at that point, to prevent any visually significant damage from occurring in that person's lifetime. This approach has the advantage of withholding treatment from those who may never need it. Thanks to the Ocular Hypertension Treatment Study (and later the European Glaucoma Prevention Study) we can now identify ocular hypertension patients who are at greatest risk of developing glaucoma and, perhaps, in these highest risk patients, begin treatment even before serious damage has occurred to the optic nerve.^{2,10} Actual risk calculators have been worked out and validated to determine the relative risk of developing glaucoma from ocular hypertension.^{11,12}

Although some patients have progressive glaucomatous damage with no recorded IOPs above 21 mmHg, other patients have IOPs frequently above 21 mmHg without exhibiting glaucomatous damage. The 21-mmHg mark remains useful for classifying glaucoma suspects for two reasons. First, 21 mmHg represents 2 standard deviations above the mean IOP of 16 mmHg in white populations. Pressure above this would occur in only 2.5% of normal cases if IOPs were indeed distributed normally in the population. Actually, the distribution of IOP is skewed to the right, so that 4–5% of 'normal' patients may have pressures higher than 21 mmHg. Although this is a small percentage of the normal patients, the actual number of patients with elevated IOP who never develop damage far exceeds the number of those who do develop damage. Therefore the chance of requiring treatment when only elevated IOP is present (<30 mmHg), with no other risk factors, is probably less than 10%.¹³ Second, elevated pressure can cause glaucomatous damage. This is certainly true in experimental animals. The higher the pressure, the more rapidly the damage progresses. If the damage has not progressed too far, it can be arrested in many cases by adequate lowering of the IOP. Thus elevated IOP is an important risk factor and must be taken seriously.

Anatomic signs may also make someone suspicious for glaucoma. Signs include the presence of narrow angles, an enlarged but not definitely pathologic optic cup, and thinning of or defects in the nerve fiber layer. Functional signs such as early but not definite visual field changes could also place someone in the suspect category. Color vision deficits may also herald the onset of glaucomatous damage. Finally, hereditary or genetic information – such as a

Box 21-1 Glaucoma suspect type I**Normal intraocular pressure, no damage**

Strong family history of glaucoma
 Retinal vascular occlusion
 Exfoliative syndrome
 Angle recession
 Pigmentary dispersion syndrome
 Narrow angles
 Uveitis
 History of halos

Management: monitor periodically and inform patient of need for follow-up.

Box 21-2 Glaucoma suspect type II**Normal intraocular pressure, possible damage**

Thin corneas
 Suspicious optic disc
 Suspicious nerve fiber layer defects
 Suspicious visual field
 Reduced psychophysical function

Management: confirm the finding by repeat testing if needed, as with suspicious visual fields. Demonstrate a normal variant, another cause of damage, or an elevated IOP expressed at other times. If the patient demonstrates increased IOP, then treat for glaucoma. Otherwise, treat any other existing disease or conduct annual or semi-annual examinations depending on risk factors.

Box 21-3 Glaucoma suspect type III**High intraocular pressure, no damage****Management:**

1. Pressure >35 mmHg (some authorities choose >30 mmHg): risk of damage is great. Treat.
2. Pressure 25–30 mmHg: treat if (1) other eye has damage; (2) patient is elderly or has siblings or parents with glaucoma; (3) patient has other risk factors; (4) patient has complicating ocular or vascular disease, or (5) there is poor patient follow-up or poor compliance or (6) thin corneas. If treatment is poorly tolerated, treatment may be stopped and the patient observed at least every 4 months for progression of the disease.
3. Pressure 21–24 mmHg: treat if other eye has damage. Otherwise, observe. Some authorities would treat if the risk factor(s) above exist.
4. Pressure \geq 25 mmHg and very narrow angles: consider laser iridotomy.

strong family history of glaucoma or possession of a gene associated with glaucoma, as well as other high-risk factors such as race or high myopia, even in the absence of elevated IOP or increased cupping – warrants closer observation than the general population. Table 21-1 lists the risk factors for primary open-angle glaucoma.

Damage to the optic nerve is central to the diagnosis of glaucoma. Damage to the functional or structural integrity of the eye that is

Box 21-4 Glaucoma suspect type IV**High intraocular pressure, possible damage**

Peripheral anterior synechiae and narrow angles
 Notch or local rim narrowing of optic nerve
 Early arcuate scotoma or paracentral scotoma

Management: Generally, treat such eyes, especially if the other eye has damage, the patient has a strong family history, or the patient has a complicating ocular disease.

Box 21-5 Possible glaucomatous damage**Visual field**

Generalized depression
 Baring of blind spot
 Nasal step < 10°
 Relative scotoma < 5°
 Statistical field loss index $P = 0.05$ –0.10

Visual function

Reduced color vision
 Reduced temporal contrast sensitivity
 Abnormal pattern electroretinogram

Optic nerve head

Cup-to-disc ratio > 0.5
 Asymmetry of disc cups > 0.2 cup-to-disc ratio
 Disc hemorrhage
 Disc pit
 Rim area < 1.10 mm²
 Vertically oval cup
 Diffuse or localized nerve fiber layer defect
 Chamber angle
 Peripheral anterior synechiae

typical of glaucoma may be absent, questionably present, or present. If it is present, the patient either has or has had glaucoma or some disease that mimics it. If it is absent or questionably present, the patient may have glaucoma. Usually, the dilemma arises when trying to recognize early optic nerve or visual function damage typical of POAG.

If a patient is a glaucoma suspect, the ophthalmologist must decide whether to treat or to observe the patient. That decision usually is based on both the physician's judgment of the amount of risk to the patient if left untreated and the patient's anxiety about the condition (or about medications). Boxes 21-1 through 21-4 list some examples of various types of glaucoma suspects and their management. Signs indicative of disc or field damage are listed in Box 21-5. The purpose of observing the glaucoma suspect is to recognize any evidence of early damage. If damage progresses, then the presence of glaucoma (or other optic neuropathy) has been proven, and treatment must commence or be escalated.

DETERMINING ADEQUACY OF TREATMENT

If the patient is treated, how does the ophthalmologist determine whether adequate treatment has been provided? In the future it may be possible to make the optic nerve more resistant to either pressure-related damage or non-pressure-related damage, or to

treat directly the causes of non-pressure-related damage. Presently, our therapeutic tools only lower the patient's IOP. The real object, though, is to prevent or slow further structural or functional damage. Hence the first test of successful therapy is whether IOP has been lowered, but the ultimate test is whether progressive structural or functional damage has been prevented. Another issue of great importance is the patient's quality of life. If the natural course of the disease has been for the cupping to progress but not to interfere with the patient's important activities, then this must be weighed against any treatment plan that may seriously impair the patient's quality of life – whether through functional interference or financial drain.

Intraocular pressure and its measurement are discussed in Chapter 4. One must remember, however, that it is difficult to know the patient's true pressure range. In reality, IOP is measured infrequently – almost never at night or on Sunday, rarely after vigorous exercise or emotional upset, and never when the patient is sleeping. Thus the sample size of IOPs is quite small. For example, if pressure is measured for a period of 5 seconds once every 3 months, the sample is for only 5 seconds out of 7776000 seconds, giving a sample frequency of 0.0000643%. To make matters worse, the physician introduces bias into the sample by telling patients that they are going to be tested for the effect of the treatment prescribed by measuring their IOP when they return. Most patients want good test results, so naturally they use the medication on the day they are tested – even though they may not use it regularly at other times.^{14,15}

Theoretically, the effect a given treatment has on IOP when only one eye is treated can be determined with reasonable certainty (see Ch. 22). The other eye acts as a control, although a modest 'cross-over' effect may be seen. While monocular treatment trial sounds like it should be an effective way of determining the effectiveness of treatment, it does not always work that way.¹⁶

Some medications may reach a peak effect in 2 hours after a single drop while others may take up to a month to reach full effect. The effects on IOP of the α -adrenergic agonists, prostaglandins, topical carbonic anhydrase inhibitors, and cholinergic agents can usually be assessed within a few hours of using a drop although the prostaglandin analogs may take as much as a month or more to reach peak effect. β -Blockers can produce a large immediate effect that diminishes over 4–6 weeks or, conversely, may require as much as a month for their full effect to develop. Adrenaline (epinephrine) derivatives, for example, may take as long as a month to show full effect, but their use is declining. Laser trabeculoplasty typically necessitates 4–5 weeks to reach maximum effect. Surgically lowering pressure rarely produces stabilized effects before 1 month, so it may take a month or more to determine the treatment's effect on pressure. With medications, the physician can only assume that the pressure measured reflects what the medication can do to the IOP. It should never be assumed that the medications are being used regularly by the glaucoma patient.

A reasonable first goal in a younger patient with little damage is to lower the pressure at least 20% from the baseline IOP. Baseline pressure should be derived from at least two, and preferably more, measurements taken hours or days apart. Pressures can vary from hour to hour and day to day. The authors have seen patients with POAG undergoing baseline examinations before drug trials demonstrate a pressure variation of as much as 10 mmHg within 1 hour. Thus pressure can fluctuate markedly just as with measurement of any biologic function. If feasible, a trial in one eye is useful. If after the appropriate period there is little effect on IOP in the treated eye as compared with the untreated eye, then either the treatment

is not sufficient or the patient is not using it. Either way, the treatment is not successful.

It is not enough to lower IOP into the statistically normal range. Many patients continue to progress despite IOPs under 21 or 22 mmHg. The physician should set a target pressure for each patient. The target pressure is a 'best guess' level of IOP, below which further damage is unlikely to occur. The estimate is based on the initial level of IOP, degree of existing damage, age, and presence of other risk factors (see Ch. 22). Clinical experience and some statistical data support the concept that the more severe the existing optic nerve damage, the lower the IOP must be to prevent further deterioration.^{17–20} Thus a patient with early damage may tolerate a pressure around 20 mmHg, whereas a patient with advanced cupping and field loss may deteriorate unless the pressure is consistently below 16 mmHg. Moreover, 20 mmHg is considered 'good' control for a patient with early damage and initial pressures of 30 mmHg, but it is considered 'poor' control for a patient with a cup-to-disc ratio of 0.9 and advanced visual field loss and whose pressures have never exceeded 23 mmHg. The Advanced Glaucoma Intervention Study indicated that progression is not likely to occur if IOPs are always kept under 18 mmHg and the average hovers around 12 or 13 mmHg.²¹ The more risk factors and the greater the damage at the time of diagnosis, the lower the target pressure should be set. As time goes on, the target pressure should be reassessed and lowered if progression of damage occurs.

TREATMENT FOLLOW-UP

The initial efficacy of therapy is determined by its effect on IOP, but long-term efficacy must be determined by analysis of damage. Therefore it is essential to have good baseline studies of the factors to be followed, which most often are the visual field and the optic nerve head (Table 21-1). Careful and rigorous documentation of the initial status of these factors is essential to ensure accurate decisions regarding future therapy. Analysis of both is discussed in detail in subsequent chapters.

Once a therapy has been determined effective, how should the treatment be followed? Determining follow-up procedures depends on two factors – amount of damage and adequacy of pressure control. Guidelines for pressure control for long-term management of chronic open-angle glaucoma are presented in Table 21-2. These guidelines may not be applicable in all situations, and the physician must individualize each case. One must also remember that the IOP measured in the office is a minute sample size of the patient's

Table 21-1 Levels of damage

	Disc	Visual field
Mild	0.0–0.5 with uniform pink rim	None, mild depression, or slight defect
Moderate	0.6–0.7 with some local narrowing of rim	General depression, arcuate defect, or paracentral scotoma
Advanced	0.8–0.9 with rim narrowing or notching	Large arcuate, double arcuate, hemifield loss, or fixation threatened

Table 21-2 Guidelines for level of intraocular pressure (mmHg) control related to damage level*

Control	Level of damage		
	Mild	Moderate	Advanced
Good	<21	<18	<16
Uncertain	21-24	19-22	16-18
Uncontrolled	>25	>21	>18

*These guidelines are only estimates. The target pressures should be individualized. The more advanced the glaucoma, the older the patient, the greater the number of risk factors, and the greater the vascular component, the lower the target pressure should be. The more advanced the damage and the poorer the control, the more frequent the re-evaluations must be. The fewer the number of risk factors and the less advanced the glaucoma, the more tolerant the optic nerve is likely to be of slightly elevated pressures. The better the control, the earlier the disease, and the fewer the number of risk factors, the less frequently the patient can be evaluated.

pressure; the ultimate decisions affecting therapy rest on changes in the visual field or the optic nerve head.

DOCUMENTATION OF PROGRESS

Like any psychophysical test, visual fields fluctuate. Computerized perimetry quantifies this fluctuation, thereby offering advantages over manual techniques. Recognition of change in the visual field, however, is confounded by this fluctuation. To minimize confusion introduced by this fluctuation, a newly diagnosed glaucoma patient may require two or three field examinations in the first year of diagnosis to establish a firm baseline for future comparison. This concept is discussed in Chapter 9.

Photographs or other forms of imaging of the optic nerve are also invaluable in evaluating progression of the disease and should be taken at the initial examination and subsequently whenever change is suspected. Careful examination of the disc should be performed at least every 6 months and more frequently if the pressure is uncontrolled. Repeat photographs or imaging should occur every 1–3 years even if there does not appear to be any clinical change. Usually photographs or imaging techniques detect subtle changes before the clinician can do so. The frequency of IOP measurements should be related to the adequacy of control of the disease. If the disease has been stable for several years and the pressure constant, then follow-up examinations can be performed safely 1–3 times a year. If the pressure is high or the disease is newly diagnosed and the physician is unsure of the response to medications, visits may be scheduled weekly or monthly until the physician is certain that rapid worsening of damage will not occur. If the pressure is very high then more frequent visits may be necessary.

Pressure measurements are at best a guideline for the effectiveness of therapy. It is necessary to measure the visual field and/or fundus to know if the disease is truly controlled. In advanced disease with fixation threatened, it is reasonable to perform visual field examinations every 6 months or so, perhaps using a high-resolution test pattern such as a 10–2, to detect the earliest sign of progression and start more aggressive therapy. Indeed, examinations less often

Table 21-3 Recommended frequency of visual field evaluation

Target intraocular pressure achieved?	Progression of damage	Duration of control (months)	Follow-up visual field interval (months)
Yes	No	<6	4-12
Yes	No	>6	6-24
Yes	Yes	N/A	2-6
No	No	N/A	2-6
No	Yes	N/A	1-6

Modified from American Academy of Ophthalmology: Primary open-angle glaucoma, preferred practice pattern. San Francisco, American Academy of Ophthalmology, 1996.
N/A, Not applicable.

than this make it difficult, if not impossible, to distinguish normal fluctuation of the test from pathologic change. In a patient with less severe damage whose IOP is well controlled, field examination once a year or so is sufficient. In glaucoma suspects, or in glaucoma patients with no visual field loss and well-controlled pressures, field examinations may be performed annually. One suggested schedule for the frequency of visual field follow-up is proposed by the American Academy of Ophthalmology's Preferred Practice Pattern for primary open-angle glaucoma (Table 21-3).

Optic nerve photography as well as newer tests such as laser-assisted imaging and computer analysis of the nerve fiber layer or optic nerve head also may be helpful in recognizing progression of the disease. The clinician can still provide sensitive and accurate determination of progression using a carefully performed clinical field examination supplemented with a clinical and photographic evaluation of the nerve head.

PATIENT EDUCATION

Because glaucoma is a chronic, lifelong condition with few debilitating symptoms, patient cooperation with follow-up and treatment is crucial to the success of management. Patients must be educated about their disease initially, then frequently during follow-up. Poor compliance with treatment is correlated with poor understanding of glaucoma and its long-term dangers.¹⁵ Even with good patient education, compliance may be inadequate in as high as one-third of patients.¹⁵ Many brochures (examples include those from the Glaucoma Research Foundation, the American Academy of Ophthalmology, Prevent Blindness America and several commercial publishers) are now available that help the physician to describe glaucoma, treatment alternatives, and the advantages and disadvantages of such alternatives. Some of these organizations provide an '800' number where questions about glaucoma or its treatment can be answered. Patients can also find information on the Internet, but the reliability of that information cannot always be confirmed. The physician should supplement any outside information with open discussion. Glaucoma support groups, where patients share their experiences, exist in some places and may be helpful.

Questions should be welcome. Many patients need constant encouragement and re-education over the years. Patients should also

be included in the therapeutic decision process because sometimes the major negative effect of glaucoma (especially early in the disease) may be from the treatment rather than the condition. Therapeutic goals and potential side effects and complications of each alternative of treatment should be discussed. Patient preferences should be sought.

Patients should be taught how to use eyedrops and about punctal occlusion and eyelid closure to minimize systemic side effects. The treating physician should encourage each patient to discuss possible side effects and effects on quality of life. Patients may not associate systemic side effects with eyedrop therapy or may be reluctant to mention such delicate issues as impotence or decreased libido with a busy eye doctor. An atmosphere of openness and partnership should be established from the beginning.

Patients with primary types of glaucoma also need to be reminded and re-reminded of the fact that their blood relatives, especially siblings, parents, and children are at increased risk of developing the disease and need to be screened at appropriate intervals to catch the onset at the earliest feasible point since progression is related to the degree of damage at onset.

EFFECTIVE JUDGMENT

Society is demanding more of physicians than ever before. In these days of cost containment and spiraling utilization of newer and

better medical techniques, it is the physician's responsibility to provide excellent and efficient care for each patient. The pressures of outside influences, such as managed care organizations, should not prevent the most effective care – cost and efficiency are important, but not the only considerations. By reducing the use of medical resources for those patients whose disease is well controlled and slowly (if at all) progressive, more resources can be directed toward patients whose conditions are uncontrolled or who face an imminent threat to their vision. It is a challenging but rewarding effort to tailor care to fit the patient's needs.

The treating doctor also needs to be an advocate for the patient in several different arenas. Often, social circumstances prevent optimal care of glaucoma. A sick spouse at home, solitary living, multiple system diseases, and economic constraints are examples of situations that often impede glaucoma care. The physician should make him or herself aware of these and do his/her best to find accommodations for the patient such as social services and help with medication expenses, travel to and from medical offices, and physical disabilities. Written instructions regarding medicines are often very helpful especially if the patient has to juggle multiple medications for different diseases. The physician should be aware of bureaucratic and healthcare management hindrances to patient care and intervene with phone calls or letters as needed. Finally, physicians might consider the larger picture and become involved on the national or even international scene to help improve health care for all.

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CHAPTER
22Medical treatment of glaucoma:
general principles

The ultimate goal of glaucoma treatment is to preserve enough vision during the patient's lifetime to meet their functional needs; ideally, treatment should also delay, stop,¹ and sometimes reverse² the damage to the optic nerve and ganglion cell layer caused by the glaucomatous process. The only way currently proven to slow or stop damage from progressing is to reduce intraocular pressure (IOP) below the level that will cause continued damage to the optic nerve. Although a medication that would directly protect the optic nerve or reverse the damage from glaucoma would be most welcome, no such medication has yet been proven to be effective. Medications that have some promise in this regard are discussed in a later chapter.

Although the concept that lowering IOP truly helps prevent or reduce glaucomatous damage has been called into question,³ the overwhelming majority of studies produce evidence that lowering IOP is indeed beneficial.^{4,5} As has been noted in Chapters 17 and 21, animal studies and secondary glaucomas clearly point to IOP as an important risk factor, if not a causal factor. Other studies strongly suggest that the lower the IOP, the less likely optic nerve damage is to develop or progress.⁶⁻⁸ Some of these same data indicate that past efforts to lower IOP into the 'normal' range of 21 mmHg or lower may have been inadequate and that 'control' really means an IOP of less than 15 or 16 mmHg, especially in advanced glaucoma. One recent long-term study showed that lowering IOP in normal-pressure glaucoma by at least 30% protects at least some patients from progression.⁹ The issue has been put to rest by the publication of four long-term, controlled trials that conclusively show that lowering IOP will slow or delay the appearance or progression of glaucomatous damage; these include the Ocular Hypertension Treatment Study (OHTS),¹⁰ the Advanced Glaucoma Intervention Study (AGIS),¹¹ the Collaborative Normal-Tension Glaucoma Study (CNTGS),⁹ and the Early Manifest Glaucoma Trial (EMGT).¹² Many of these studies have helped to identify risk factors that auger progression within fully manifest glaucoma and from ocular hypertension to manifest glaucoma. These risk factors are outlined in Boxes 22-1 and 22-2. Fluctuation of IOP has also been identified as an important risk factor for progression.^{13,14}

Box 22-1 Risk factors for progression from ocular hypertension to manifest glaucoma

Corneal thickness under 535 microns
Elevated IOP
Increasing age
Enlarged vertical cup-to-disc ratio
Increased pattern standard deviation on static threshold perimetry

Box 22-2 Risk factors for progression of manifest glaucoma**Established**

Elevated IOP
Over 18 mmHg any of the time
Increased fluctuation of IOP
Increasing age
Exfoliation of the lens capsule
Advanced cupping
Advanced visual field loss

Putative

Sleep apnea
Thin corneas
Nocturnal systemic hypotension

In approaching the treatment of someone who has glaucoma or who is at such high risk for its development that treatment is in order, many issues have to be considered. Among these are the level of IOP at which damage has occurred (or is likely to occur), the age of the patient, the degree of cupping and visual field loss, the presence of secondary features such as signs of exfoliative disease or pigmentary dispersion, systemic conditions or medications that might interact with glaucoma progression or treatment, social issues such as presence or absence of support systems, and economic issues. Most physicians today try to tailor therapy to the individual patient and his or her situation. Many find it useful to estimate and then aim for a 'target pressure.'

TARGET PRESSURE

The concept of target pressure arose from the observation that progression in advanced glaucoma, and occasionally even in early glaucoma, often occurs at what are thought to be 'physiologic' pressures. An IOP of 21 mmHg or lower – the previously sought goal – may not be low enough for many glaucomatous eyes. This observation was supported by the findings of the AGIS study which showed that the risk of progression was greatly reduced if all IOPs were under 18 mmHg.¹¹ The goal should be to lower the IOP to a level that is 'safe' for that particular eye. Because our current knowledge does not indicate with any certainty what a safe IOP level may be for any given patient, the target pressure is estimated for each patient based on initial IOP, degree of existing damage, how hard the patient has

to work to achieve the goal, the realities of adherence expectations for that individual, and what potential side effects, complications, and cost that particular regimen might entail. The target pressure is then continually reassessed and reset based on the clinical course.

The less the initial pretreatment IOP, the more advanced the optic nerve damage, and the older the patient, the lower the target pressure should be set. The presence of a vasculopathy such as diabetes or arteriosclerotic cardiovascular disease should also lower the target pressure. A young person with glaucoma secondary to trauma with a pretreatment IOP of 32 mmHg and a 0.5 cup-to-disc ratio with early visual field loss may do quite well with an initial target IOP in the low 20s. An elderly patient with a pretreatment IOP of 22 mmHg, a cup-to-disc ratio of 0.9, and advanced visual field loss may require a target pressure of 15 mmHg or lower.

The currently available approaches to lower IOP include medical therapy, laser trabeculoplasty, filtering surgery, and cyclodestructive procedures – each of these has its own risk:benefit ratios. Whichever method is chosen, it should ideally be predictable, safe, and easy for the patient to use. Unfortunately, there is no ideal treatment for glaucoma. Because the risk:benefit ratio for medical therapy seems to be lowest, both historical and current practice has been to attempt medical treatment before resorting to other alternatives. However, this approach has been called into question in recent years.¹⁵

MEDICAL THERAPY

ADVANTAGES

Medical therapy has been the mainstay of initial glaucoma treatment for over a century. The vast majority of patients respond to a simple regimen with a desirable reduction in IOP. Side effects are usually few and tolerable. When they do occur, side effects are often easily reversible by stopping the medication. Only rarely are vision- or life-threatening side effects seen. Medical therapy is less costly over the short term, and because many glaucoma patients are elderly, the cost of medical treatment may never exceed that of surgery. Finally, most patients expect a trial of medical therapy first and are likely to be somewhat suspicious of a too rapid suggestion for surgery.

DISADVANTAGES

Over the last decade, the disadvantages of medical therapy have been increasingly highlighted. Several prospective studies have pointed to medical therapy as less effective in lowering IOP and perhaps in preventing further visual field loss than either laser trabeculoplasty or filtering surgery.^{16–18} However, some of the differences between the medically and surgically treated groups in these studies may be the result of not setting the target IOP low enough in the medically treated group (the surgically treated groups had pressures ‘automatically’ set at low levels). The Glaucoma Laser Trial showed that after 2 years, only 30% of patients initially treated with medications were still being controlled with a single topical β -blocker.¹⁹ The Collaborative Glaucoma Initial Therapy Trial at the end of 5 years showed no difference in the progression of visual field loss with either medication as initial therapy in glaucoma or trabeculectomy.²⁰ While quality of life issues were similar in both groups, the medication group had more local eye symptoms and those in the surgery group were more likely to develop cataract and reduced visual acuity early. However,

by 5–8 years, cataract incidence and severity was again even in the two treatment groups.

Medically treated eyes may not have as good a success rate from subsequent filtering surgery compared with eyes treated with surgery from the outset.²¹ This may be due to an increased number of inflammatory cells and a decreased number of goblet cells in the conjunctiva of medically treated eyes compared with eyes treated initially with surgery.^{22,23} Medical treatment has the potential for significant and serious side effects, not all of which may be obvious to the patient or physician. During an 8-year period (1978–1985) in the United States, 32 deaths (of about 2 million glaucoma patients) were attributed to complications arising from the use of topical timolol maleate.²⁴ Carbonic anhydrase inhibitors also can produce rare fatal reactions.²⁵

Less dramatic side effects of topical medications include allergic reactions, toxic corneal changes, induced refractive errors, cataract formation, asthma, tachycardia, bradycardia, orthostatic hypotension, gastrointestinal symptoms, decreased libido, impotence, mood changes, possible memory loss, and alopecia. Systemic carbonic anhydrase inhibitors are notorious for significant side effects such as lethargy, depression, diarrhea, and loss of appetite. All of these may have subtle or profound effects on the patient’s quality of life.

In addition, many older patients are also taking a number of other medications, which may add to the potential for cross-reaction and confusing side effects. Patients and their primary care physicians often do not associate systemic side effects with topical eye medications, and the ophthalmologist may fail to ask about systemic symptoms; in these cases, the cause of a systemic problem induced by antiglaucoma medications may go undetected.

A further complication of antiglaucoma medications is their high cost. Retail prices for any one type of topical eyedrop may run as high as \$80 for a month’s supply. If the patient is using multiple glaucoma medications, the cost of antiglaucoma therapy could well be over \$120 per month.²⁶ For someone whose only source of income is a modest pension or social security, this may mean choosing between eating and taking needed medication. Because glaucoma is a chronic, lifetime condition, the cost of medications over the long term may be astronomical, both personally and from a public health/medical economics point of view. This is a major factor in nations with limited resources and can be a significant factor even in the most wealthy countries.

Finally, the issue of compliance must be addressed. It is probably unrealistic to think that a typical elderly patient who is taking medications for hypertension, diabetes, arthritis, and hiatal hernia is going to be able to accurately stick to a regimen that includes two or three topical medications and a carbonic anhydrase inhibitor. Kass and co-workers have shown that compliance is surprisingly poor, even with just one medication used four times a day.²⁷ Similar studies more recently have shown surprisingly low persistence rates even with once a day medication (prostaglandin or similar), although once daily dosing seems significantly better from a persistence point of view than medications requiring more frequent dosing during the day.^{28,29}

SURGICAL THERAPY

ADVANTAGES

As noted previously, surgical treatment (either laser trabeculoplasty or a filtering operation) is more likely than is medical treatment to

keep IOP ‘under control’ and at a lower level for a longer period of time.^{6,8,15–17,19,30} Visual function may be better preserved with surgery than with medical therapy but visual acuity is more immediately affected negatively.^{8,30} Quality of life in the long run may be affected less negatively with surgery because fewer or no medications are likely to be necessary after a short postoperative period. Surgery is also less dependent in the long run on compliance than is medical therapy. Finally, the cost of surgery, assuming no complications, may actually be less than the cost of medication if the positive effects of the surgery last at least 8 years.

DISADVANTAGES

Surgery is irreversible. The Rubicon is crossed, and the eye cannot be returned to its original status. Patients whose surgical intervention is successful are often quite happy to no longer require medications, but those who have a major complication are usually much more unhappy than patients who never had surgery. Significant vision- and life-threatening complications can occur from surgery. Such complications include respiratory arrest and cardiovascular failure from retrobulbar anesthesia, perforation of the globe, suprachoroidal hemorrhage, maculopathy from hypotony, corneal decompensation, cataract formation, and postoperative

endophthalmitis. Visual distortions may occur due to induced astigmatism, cataract, or large iridectomy. Prolonged postoperative discomfort may occur from a large bleb, dellen, or surgically-induced ptosis. A large bleb or iridectomy may be a cosmetic problem for some patients. Each episode of conjunctivitis, normally a minor annoyance, becomes a major medical emergency for a patient with a filtering bleb. Cosmetic contact lens use in the presence of a filtering bleb is usually inadvisable. Yet, in the Collaborative Initial Glaucoma Treatment Study (CIGTS) study, serious complications from initial trabeculectomy were uncommon.³⁰

In the Glaucoma Laser Trial, at least 40% of those treated initially with laser surgery needed supplemental medical therapy by 2 years after the laser treatment.¹⁹ The beneficial effect of laser treatment seems to be time limited and is frequently gone by 3–5 years after surgery. Finally, none of the prospective studies on initial laser or surgical treatment of glaucoma had follow-up beyond 5 years at the time of this writing. This is a short period compared with the lifetime nature of glaucoma to measure the true effect or actual longevity of the surgical approach. The advantages and disadvantages of medical and surgical treatment are presented in Tables 22-1 and 22-2.

Table 22-1 Advantages of medical and surgical therapy	
Medical therapy	Surgical therapy
Most patients are easily controlled	Intraocular pressure likely to be lower than with medical treatment
Serious side effects are rare	Visual function may be better preserved
Side effects are usually tolerable	Quality of life may be better than with medical treatment
Side effects are usually reversible	Less dependent on patient compliance
Costs are reasonable over short haul	Costs less over long haul

Table 22-2 Disadvantages of medical and surgical therapy	
Medical therapy	Surgical therapy
Less effective in lowering intraocular pressure than surgery	Irreversible damage to eye or vision possible
Medical treatment tends to escalate with time	Death or serious illness possible
May interfere with success of filtering surgery	Complications can occur late (e.g., endophthalmitis, hypotony, leak)
Potential for serious side effects	Effects may not last for life
Eye medications are not always identified as cause of side effects	Contact lens use limited
Potential for cross-reaction with systemic medications	Medical therapy may be needed anyway
Nuisance factor and side effects may interfere with quality of life	Patient disabled during initial operative and postoperative period
Long-term costs may be high	Initial costs high
Compliance often poor	Long-term follow-up lacking
	Surgery may have to be repeated

BASIC PHARMACOLOGY

Most drugs used for glaucoma therapy are administered topically to the eye. Before discussing these drugs individually, some of the general pharmacologic principles of topical ocular treatment should be considered.

To be effective, a drug must penetrate the eye and achieve an adequate concentration at its site of action. The eye is protected by a number of mechanisms (e.g., blinking, tear flow, active transport, blood–aqueous and blood–retinal barriers), however, that limit exposure to endogenous and exogenous noxious agents. These same protective mechanisms make it difficult to reach and maintain an effective intraocular drug concentration. This problem is compounded by the structure of the eye itself, which isolates ocular tissues from the ocular and systemic blood circulation and from the ocular surface. One of the major problems in ocular therapeutics is achieving the desired effect of topical medication despite these protective mechanisms and structural obstacles (i.e., achieving an adequate concentration of drug at the site of action without creating potentially dangerous concentrations elsewhere).³¹

The usefulness of a drug is determined by its efficacy, potency, duration of action, and therapeutic index. *Efficacy* is the maximum therapeutic effect obtainable. *Potency* is defined as the dose producing 50% of the maximum drug effect, usually expressed as E50 or an I50. *Duration of action* is the length of time a drug dose exerts a biologic action. *Therapeutic index* is the ratio of the dose of a drug producing a toxic effect divided by the dose producing the desired effect.

$$\text{Therapeutic index} = \frac{\text{Dose of a drug producing a toxic effect}}{\text{Dose of a drug producing the desired effect}}$$

The physician seeks drugs with a high therapeutic index (e.g., 10 or higher if possible). However, an acceptable therapeutic index depends on the nature of the drug and the nature of the disease being treated. Physicians use different standards when choosing

Box 22-3 Factors affecting bioavailability of topical ocular medication

- I. Tear factors
 - A. Rate of tearing
 - B. Punctal occlusion
 - C. Nasolacrimal drainage
 - D. Orbicularis function (eyelid squeezing)
 - E. Dilution with a second drug
- II. Corneal factors
- III. Drug and formulation factors
 - A. Concentration and volume instilled
 - B. Solubility characteristics
 - C. Dissociation constant
 - D. Molecular weight
 - E. pH
 - F. Tonicity
 - G. Electrolyte composition
 - H. Wetting agents/preservatives
 - I. Viscosity
 - J. Buffers
 - K. Vehicle or delivery system
- IV. Drug elimination
 - A. Tear flow
 - B. Diffusion into the vascular system
 - C. Diffusion from the cornea to the tear layer
 - D. Bulk flow of aqueous humor
 - E. Metabolism
 - F. Active transport
 - G. Binding to melanin
 - H. Binding to protein
- V. Miscellaneous
 - A. Genetic variation in ocular structure and function
 - B. General metabolic factors
 1. Blood flow
 2. Hormonal regulation
 3. Neural regulation
 4. Availability of nutrients
 5. Age
 - C. Drug-related factors
 1. Local and systemic side effects
 2. Drug-drug interaction
 3. Tolerance
 4. Compliance
- VI. Disease factors
 - A. Inflammation
 - B. Intactness of epithelium
 - C. State of blood–aqueous barrier and blood–retinal barrier
 - D. Aqueous humor and tear protein concentrations

Modified from Bergamini MVW. In: Drance SM, Neufeld AH, editors: *Glaucoma: applied pharmacology in medical treatment*. New York, Grune Stratton, 1984.

chemotherapy for cancer than they do when choosing eyedrops for minor ocular irritation.³²

Bioavailability refers to the rate and extent of absorption across a surface or tissue. The bioavailability of topical medication is considered in the following pages under the headings of tear film, corneal barriers, drug formulation, and drug elimination (Box 22-3). It is important to emphasize that the most important factors limiting the bioavailability of many common topical ocular medications are compliance and efficiency of instillation.³³ Discussion of these issues follows.

BIOAVAILABILITY OF TOPICAL OCULAR MEDICATION

The penetration of topically applied medication into the eye is proportional to the concentration of the drug that comes in contact with the cornea over time. For many drugs this relationship holds true over a wide range of concentrations (e.g., 10^{-6} to 10^{-1} M for pilocarpine).^{34,35} The drug concentration in contact with the cornea is diluted by tears and washed out into the lacrimal drainage system. The half-life of various drugs in the tear layer is estimated to be 2–20 minutes. Alteration of the molecule or vehicle in a way that increases the half-life, such as increasing the viscosity, will increase the efficacy and duration.

The normal volume of the conjunctival cul-de-sac is 7 μ l. After instillation of an eyedrop, the volume temporarily increases to 30 μ l.³⁶ Most commercial eyedrops have a volume of 30–75 μ l.³⁷ Thus even a single drop exceeds the capacity of the cul-de-sac, so that the excess drains onto the skin and into the lacrimal system. Some investigators have postulated that the relative bioavailability of many topical medications could be increased by decreasing the volume of the eyedrops to 5–20 μ l.^{38–40}

TEAR FILM

Under normal circumstances the turnover rate of the tear film is 15% per minute⁴¹; this depends on the rate of tearing rather than the capacity of the lacrimal drainage system. The instillation of eyedrops stimulates tearing and increases the turnover rate to 30% per minute. Eyedrop instillation also causes contraction of the orbicularis muscle (e.g., blinking, squeezing), which propels tears toward the lacrimal drainage system. It is possible to reduce the flow of tears and medication into the lacrimal system and prolong drug–cornea contact time by placing pressure over the canaliculi and closing the eyelids gently after administering eyedrops.^{42,43}

Drugs that pass into the nasolacrimal system can be absorbed rapidly by the heavily vascularized mucosa of the nasopharynx and oropharynx. Drugs absorbed in this manner do not pass through the gastrointestinal tract and the liver and are not metabolized by these tissues (i.e., there is no first-pass effect).⁴³ Thus drugs absorbed from the nasolacrimal passages can act as if they have been given by intravenous injection rather than oral administration. For this reason the instillation of multiple eyedrops over a short interval is more likely to produce increased systemic absorption and side effects than increased therapeutic benefit.

If saline solution is instilled in rabbits within 30 seconds of pilocarpine administration, the effect of pilocarpine on pupil diameter is reduced by 45% (Fig. 22-1). If saline solution is administered within 2 minutes, pilocarpine's effect is diminished by 17%. If saline solution is added after 5 minutes, there is little loss of response to pilocarpine.⁴⁴ Patients should be warned about this washout effect.

CORNEAL BARRIERS

Most topically administered drugs enter the eye by passing through the cornea. (The movement of drugs across the conjunctiva and sclera accounts for less than 2% of the intraocular concentration.)⁴⁵ This process usually occurs by passive diffusion and follows first-order kinetics (i.e., the absorption depends on the drug concentration gradient, the solubility characteristics of the substance, and

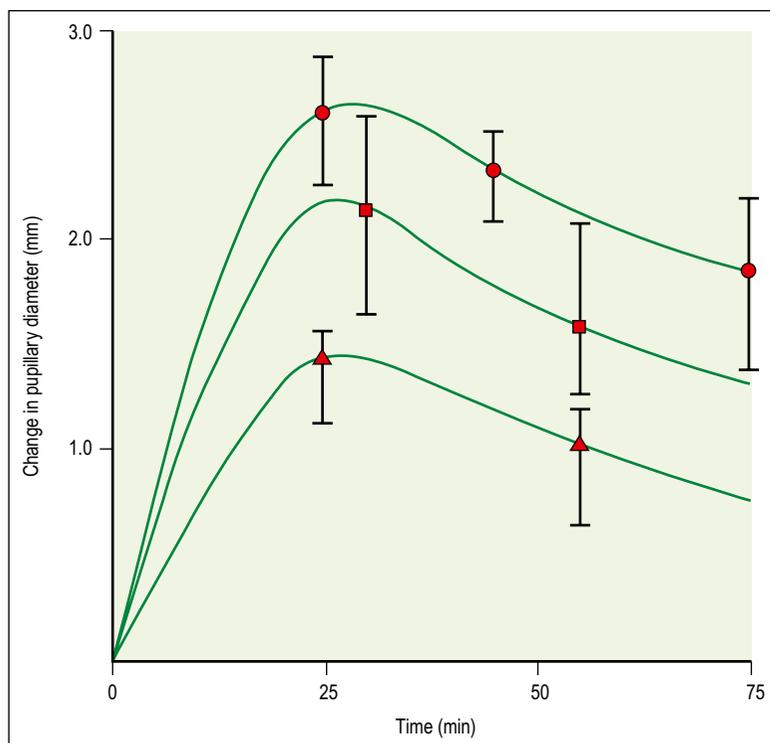


Fig. 22-1 Change in pupillary diameter after instillation of 25 μl of 2.5×10^{-2} M pilocarpine in rabbits (●), when 25 μl of saline solution is instilled 2 minutes later (■), and 30 seconds later (▲). (Modified from Chrai SS, and others: *J Pharm Sci* 63:333, 1974. Reproduced with permission of the copyright owner, the American Pharmaceutical Association.)

the dissociation constant for ionizable substances). Thus the rate of entry is initially high but declines rapidly.

To understand drug absorption, it is useful to think of the cornea as a lipid–water–lipid sandwich. The lipid content of the epithelium and endothelium is approximately 100 times greater than that of the stroma, and thus these former layers are more permeable to lipophilic than to hydrophilic substances.^{46–48} The corneal epithelium is the major barrier to drug penetration except for the most lipid-soluble substances. When the epithelium is disrupted (e.g., by irritation, ulcer, or abrasion), drug penetration is often increased. The corneal stroma is more permeable to hydrophilic than to lipophilic substances. Because of the dual nature of the corneal barriers, drugs possessing both lipid and water solubility penetrate the cornea more readily.

Many topical ophthalmic medications are weak acids or bases. The non-ionized drug molecule traverses the epithelium and then dissociates. The ionized form of the drug passes through the stroma more readily and then associates for passage through the endothelium.

Many topically administered medications accumulate in the cornea, which then becomes a temporary drug reservoir. When the medication concentration in the tears falls to low levels, there is a net movement of drug from the cornea to the tear layer. After absorption, many medications distribute rapidly and reach similar concentrations in the aqueous, iris, and ciliary body. Drug concentrations are usually lower in the lens and vitreous.^{49,50} Although there is controversy, most studies indicate that medications do not pass against aqueous flow from the anterior chamber through the pupil into the posterior chamber.^{51–54} Under some circumstances, however, certain agents such as topically applied epinephrine may get into the vitreous.⁵⁵ Drugs may reach the ciliary body by following the uveoscleral flow of aqueous humor.⁵⁶

DRUG FORMULATION

A number of properties of a drug and its formulation (e.g., molecular weight, pH, tonicity, electrolyte composition, wetting effect, stability, viscosity) influence ocular penetration. Most topical ocular drugs have a low molecular weight (i.e., less than 500 Da), which favors corneal passage.⁵⁷ As mentioned previously, many topical medications are weak acids or bases. These drugs are often more stable at non-physiologic pH levels (e.g., pilocarpine is more stable at pH 6.5 than at pH 7.4).^{58,59} Eyedrop solutions are adjusted to this pH but are not buffered so that the tear layer can return rapidly to physiologic pH levels. This ensures drug stability and prevents excessive irritation, which leads to tearing on instillation, diluting and washing away the drug.

Ocular penetration increases with increasing concentration of the drug in the eyedrop. However, if the drug concentration in the eyedrop is too great, the resulting increase in osmolality pulls fluid across the conjunctiva, diluting the medication in the tear film.⁶⁰ The ocular penetration of many topical medications is aided more by prolonging drug–cornea contact time than by increasing the concentration of the eyedrop.^{61–63} A number of systems have been used to prolong drug–cornea contact time and to enhance pulsed entry of medication into the eye. These include presoaked contact lenses,^{42,43} the addition of soluble polymers to eyedrop solutions,^{64–66} soluble gels,^{67,68} aqueous suspensions,⁶⁹ ointments,⁷⁰ solid hydrophilic inserts,⁷¹ binding to polymers,⁷² and binding to liposomes.^{73,74} A viscous vehicle can increase ocular drug penetration by 50–100%.^{75,76} The increased viscosity produces more rapid drug saturation and slower washout of medication by the tears.

Water-soluble polymers are commonly used to increase drug–cornea contact time. Currently used polymers have been assessed

with respect to corneal retention time or delivery of a marker compound and are listed in order of decreasing effectiveness: hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, and polyvinyl alcohol.⁷⁷⁻⁷⁹ However, the effect of water-soluble polymers on drug penetration appears to be greater in rabbit eyes than in human eyes because rabbits have a lower blink rate and a slower tear turnover.⁸⁰

Aqueous suspensions contain a drug dispersed as fine particles. The vehicle, often combined with a dispersion agent, is a saturated solution of the sparingly soluble drug. Tissue absorption occurs from the solution. As tearing dilutes the medication, the suspended drug particles go into the solution. The particles are retained longer in the cul-de-sac than are standard solutions and thus provide greater drug bioavailability.⁸¹ Ointments increase drug bioavailability by increasing drug–cornea contact time, decreasing dilution by tears, and slowing nasolacrimal drainage.⁸²⁻⁸⁴ Ointments are not used frequently, however, because they are difficult to instill and interfere with vision.

It is also possible to prolong drug–cornea contact time with systems that produce a controlled (i.e., steady) release of medication. Eyedrops produce a pulsed or biphasic pattern of drug delivery consisting of a transient overdose followed by a prolonged underdose. The initial overdose can be associated with systemic side effects. Controlled release requires a system that delivers medication with zero-order kinetics (i.e., drug delivery is independent of the amount of drug remaining). Therefore the rate of medication delivered remains constant until the supply is exhausted. Controlled-release systems have several potential advantages, including achieving a therapeutic effect with less medication, reducing side effects, and placing less reliance on patient compliance. The Ocusert system, the best example of this approach in ophthalmic therapy, uses a membrane that allows continuous diffusion of pilocarpine from a central reservoir.⁸⁵

Preservatives added to eyedrop solutions often increase drug penetration. For example, the therapeutic effect of carbachol is enhanced greatly by the presence of benzalkonium chloride, which acts both as a preservative and a wetting agent.^{86,87} However, evidence exists that the effect of preservatives may be mediated by structural changes in the cornea and conjunctiva that are not necessarily favorable.^{21-23,66}

DRUG ELIMINATION

The bioavailability of a drug at its active site within the eye depends on many processes besides the rate of transcorneal penetration. These include drug metabolism, active transport out of the eye, binding to melanin and protein, diffusion into the vascular system, and bulk flow with aqueous humor.⁸⁸ Most of the drug loss occurs soon after instillation in the cul-de-sac because of overflow onto the face and drainage into the nasolacrimal system.^{89,90} Once in the anterior chamber, the drug is eliminated with the bulk flow of aqueous humor via both the trabecular and uveoscleral outflow pathways.⁹¹ Some portion of the drug also diffuses into the vascular system of the anterior uvea, conjunctiva, and episclera. The diffusional loss to the vascular system is greater in inflamed eyes with dilated, more permeable vessels. As mentioned previously, the corneal epithelium serves as a drug reservoir for many medications. Drug from the cornea is also lost to the limbal blood vessels and the tear film.^{92,93}

The eye contains a variety of enzyme systems capable of metabolizing drugs.^{94,95} Some drugs (e.g., pilocarpine and dipivefrin)

are even metabolized during corneal passage.⁹⁶ This metabolic capability is used by the prodrug dipivefrin, which is converted to its active agent, epinephrine, by esterase enzymes located in the cornea and aqueous humor.⁹⁷⁻⁹⁹ In addition to metabolism, active transport systems in the ciliary body and retina remove drugs from the eye (e.g., penicillin, indomethacin).¹⁰⁰⁻¹⁰² These transport systems are similar to those found in the renal tubule and liver.¹⁰³

Many drugs (e.g., pilocarpine, timolol) bind to melanin pigment in the anterior uveal tract.¹⁰⁴⁻¹⁰⁶ This binding has a complex effect on drug bioavailability. On one hand, the melanin binding competes with the active site for the drug. Conversely, the melanin binding also creates a type of drug reservoir in the eye. The net effect of the binding process is to require higher concentrations of some drugs in pigmented eyes to produce the same therapeutic effect.¹⁰⁷⁻¹⁰⁹ It has been suggested that the difference in bioavailability of some drugs in pigmented eyes is not totally explained by melanin binding. The difference in bioavailability of some drugs also involves greater metabolism in pigmented eyes (e.g., the metabolic conversion of pilocarpine to pilocarpic acid is greater in pigmented rabbits).¹¹⁰ Drugs also bind to protein in the tears, cornea, and aqueous humor, thereby reducing bioavailability.¹¹¹ Protein binding increases when the eye is inflamed and the blood–aqueous and blood–retinal barriers are compromised.

COMPLIANCE

No discussion of general pharmacologic principles would be complete without examining the issue of compliance or adherence which is the newer preferred term. *Adherence* refers to the patient's behavior in following the prescribed regimen, including medications, follow-up visits, and lifestyle changes.

Most forms of open-angle glaucoma are chronic, slowly progressive, and asymptomatic; in fact, the only symptoms may arise from the therapy. Thus open-angle glaucoma is a fertile situation for patient defaulting.¹¹²⁻¹¹⁴ The physician should be very aware of the possibility that failure of medical treatment to meet the therapeutic goals may be caused, at least in part, by defaulting rather than by lack of efficacy of the drug regimen. Studies using eyedrop medication monitors have confirmed the longstanding suspicion that some glaucoma patients do not take their medication(s) as prescribed.¹¹⁵⁻¹¹⁹ In one study, 6% of patients administered less than one-quarter of prescribed pilocarpine doses, 15% less than one half of prescribed doses, and 35% less than three-quarters of prescribed doses.¹¹⁷ The corresponding figures for timolol are somewhat better but still indicate considerable room for improvement (i.e., 8% administered less than half of the prescribed doses, and 27% administered less than three-quarters of prescribed doses).¹¹⁸ Furthermore, patients sometimes compress doses during the day and skip entire days (i.e., take drug holidays); 24% of patients have at least 1 day per month in which they take no doses of pilocarpine, and 47% have at least 1 day per month in which they take no doses of timolol. It is likely that defaulting also occurs with epinephrine or dipivefrin treatment and is even more common with the systemic carbonic anhydrase inhibitors.^{120,121} Poor compliance may account for as much as 10% of the vision loss seen in glaucoma.¹²²

Patients usually remember to take their medication on the day they return to the office or clinic.¹¹⁷ This leads to IOP readings that may be misleading and not truly reflective of the patient's status over the past several weeks or months. This observation may explain some of the cases of progressive glaucomatous damage despite what appears to be good IOP control. Patients will often

not admit to poor compliance even if directly asked.¹²³ Patients who admit they forget to take their medications generally are telling the truth; those who swear they never miss a dose may or may not be telling the truth. No matter how well they think they know their patients, physicians are unable to identify those who are defaulting from antiglaucoma treatment.^{124,125}

Somewhat surprisingly, compliance (or lack thereof) is not associated with age, marital status, socioeconomic level, race, occupation, education level, or intelligence level.^{119,124,125} However, increased frequency of missed appointments, lack of understanding of the disease, dissatisfaction with physician or clinic, increased waiting times to see the physician, disinterest in one's health, and unstable family condition are associated with increased rates of poor compliance. Interestingly, even an excellent understanding of glaucoma and its potential for blindness does not guarantee good compliance; in one study, only two-thirds of the glaucoma patients who seemed to have an adequate understanding of their condition were compliant.¹²⁶ Conversely, of those in the same study who did not understand their condition, only one-third were compliant.

From 3% to 7% of patients do not even fill the prescriptions given to them by the physician.¹²⁷ Many do not understand the chronic nature of glaucoma therapy and may take the drops only for some fixed period such as a month or until the first bottle runs out. The continued use of a prescribed medication is referred to as *persistence*. As it is with most asymptomatic, chronic diseases, the persistence with glaucoma medications is surprisingly poor with, at best, only about 50% still refilling their prescriptions at 1 year.¹²⁸ Two recent surveys of large medication insurance plans show that persistence is best (although not terrific) for the prostaglandin group of agents and significantly poorer with the rest of the antiglaucoma agents.^{128,129}

Another problem relates to the fact that patients do not always know a satisfactory technique for administering eyedrops.¹³⁰ This is particularly true of ointments. The doctor often assumes (incorrectly) that the patient will somehow, perhaps intuitively, know how to administer drops or ointments to themselves. Patients with poor vision may not be able to distinguish the different eyedrop containers without color-coded caps or other markings. Elderly patients or those with difficulty using their hands may not be physically able to administer drops to themselves or may have great difficulty with some bottle designs. The small bottles associated with prostaglandin analogs may be particularly difficult for those with arthritic fingers. Patients may assume that if one drop is good, then two or even more may be better. Patients with busy or erratic lifestyles may not be able to keep to a regular dosing schedule.

GENERAL SUGGESTIONS FOR MEDICAL TREATMENT OF GLAUCOMA

How is the physician to achieve a safe and effective medical regimen for glaucoma based on the preceding discussion of the pharmacology of topical ocular drugs? It is impossible to develop guidelines that cover the medical treatment of all varieties of glaucoma in all stages of severity. The list summarized in **Box 22-4** gives general suggestions for the long-term treatment of some of the more common forms of chronic glaucoma, especially POAG or angle-closure glaucoma after iridotomy.¹³¹

Box 22-4 General suggestions for medical treatment of glaucoma

1. Establish a target pressure.
2. Adjust the treatment program to the patient and his/her lifestyle.
3. Initiate or change therapy through a therapeutic trial in one eye.
4. When therapy is ineffective, substitute rather than add drugs.
5. Continually monitor the assumptions related to the target pressure and change as indicated.
6. Ask about and monitor potential ocular and systemic side effects.
7. Simplify and reduce treatment when possible.
8. Teach patients the proper technique for instilling eyedrops.
9. Provide written directions.
10. Communicate with the patient's family physician.
11. Ask about problems with the medical regimen.
12. Consider defaulting as an explanation for the failure of medical treatment.
13. Educate patient about his/her illness and its treatment.
14. Stop treatment periodically to determine continuing effectiveness.
15. Measure IOP at different times of the day and at different intervals after the last administration of medication.
16. Recommend that the patient comparison shop for medication.

ESTABLISH A TARGET PRESSURE

The first step is to establish a target pressure, which is determined by the initial IOP level when the diagnosis was made, the degree of optic nerve damage, and the general health of the patient. The lower the initial IOP, the older the patient, the more advanced the optic nerve damage, and the presence of cardiovascular disease or diabetes, the lower the target pressure must be set.

Two examples may help to put this guideline in perspective. A 42-year-old man with an initial IOP of 32 mmHg, a 0.6 disc diameter cup, a small arcuate scotoma, and no other health problems may be able to tolerate pressures in the low 20s for many years. On the other hand, this individual has many years to live with his disease. Conversely, an 85-year-old woman with diabetes mellitus, an initial IOP of 23 mmHg, an 0.8 disc diameter cup, and an altitudinal visual field defect will probably require an IOP of 17 mmHg or lower to prevent further optic nerve damage. A 94-year-old man with moderate glaucoma, only modest visual field loss and multiple systemic diseases may die before his glaucoma robs him of functional vision; he may not require such aggressive therapy.

ADJUST THE TREATMENT PROGRAM TO THE PATIENT AND HIS OR HER LIFESTYLE

The systemic status of the patient is a very important consideration in determining the potential benefits and problems with medical therapy. Some systemic conditions that may be affected to a significant degree by topical or systemic antiglaucoma medications include obstructive pulmonary disease, asthma, heart failure, arrhythmia, diabetes mellitus, metabolic acidosis, metabolic alkalosis, renal lithiasis, renal disease, hepatic disease, dysautonomia, mood disorders, gastrointestinal disorders, and genitourinary disorders. A careful medical history and review of systems should be obtained from every patient for whom glaucoma treatment is contemplated. The patient should be informed of the common systemic side effects and told to call the doctor if any unusual or persistent symptoms appear.

The lifestyle, occupation, avocations, personality, and social situation of the patient should also be taken into account when initiating or changing therapy. It is unlikely that a hard-driving executive will take his or her medication four times daily. Similarly, a 40-year-old truck driver prescribed miotics may be unable to work because of fluctuating myopic refractive shift. It is counterproductive to prescribe a treatment program that the patient cannot or will not follow. This only invites dissatisfaction with the physician and defaulting from the regimen.

The busier the lifestyle, the less structured the environment, and the fewer resources the patient has, the simpler the regimen should be. Try to use the patient's most ingrained habits or activities as a tool to help him or her stick to the regimen. For example, twice-daily medication may be linked with breakfast and dinner or tooth brushing. Visual impairment may be initiated or exacerbated by the use of miotics when a patient has a lens opacity as well as glaucoma. Patients who use soft contact lenses should be warned about and monitored for the possible concentration of preservatives in the contact lens and the potential toxicity that such

concentrated preservatives may pose for the ocular surface. Similarly, those patients on multiple topical medications may fall victim to preservative toxicity.

For most patients, topical medical therapy is a good place to start. Initial laser treatment should be considered for those who are unlikely to take or tolerate medical therapy; examples include patients with Alzheimer's disease and those with advanced cardiovascular disease. Those who are unlikely to return for follow-up or are unlikely to respond to laser trabeculoplasty (e.g., failed in the fellow eye) should be considered for initial surgical intervention (Box 22-5).

INITIATE OR CHANGE THERAPY THROUGH A THERAPEUTIC TRIAL IN ONE EYE

Because IOP fluctuates from day to day and even from hour to hour, it is difficult to assess effectiveness of therapy without a therapeutic trial in one eye. For example, a patient whose IOP is 30 mmHg in each eye is prescribed 1% pilocarpine four times daily to both eyes (Fig. 22-2). If the patient returns in 2 weeks with an IOP of 22 mmHg in both eyes, the ophthalmologist does not know whether the reduction in IOP is related to treatment or represents a spontaneous fluctuation. However, this concept has been called into question recently due to the fact that not all patients respond to a medication the same way in both eyes and to the fact that there may be cross-over effects to the untreated eye from the treated one.¹³² Still, the idea of a unilateral trial does have some merit and should be considered when it is not clear if the patient is responding to treatment.

In a therapeutic trial in one eye, the physician prescribes timolol twice daily or one of the other agents at appropriate dosage levels to the right (or left) eye. When the patient returns 4 weeks later with an IOP of 22 mmHg in both eyes, the ophthalmologist knows that the drug is ineffective. Conversely, if the IOP is 22 mmHg in the right eye and 30 mmHg in the left eye on repeat examination, the effect of the drug is clear. Some drugs (e.g., timolol and other β -blocking agents) reduce IOP in both eyes after unilateral

Box 22-5 Initial approach to treatment of open-angle glaucoma

Medical therapy first

Most patients

Laser surgery first

Unlikely to tolerate medical therapy
Doesn't understand need for medical therapy
Unlikely to comply (e.g., Alzheimer's, mental retardation)
Multiple systemic medical treatments

Incisional surgery first

Same as for laser surgery but unlikely to respond to trabeculoplasty
Unable to perform laser trabeculoplasty
Unlikely or unable to follow up

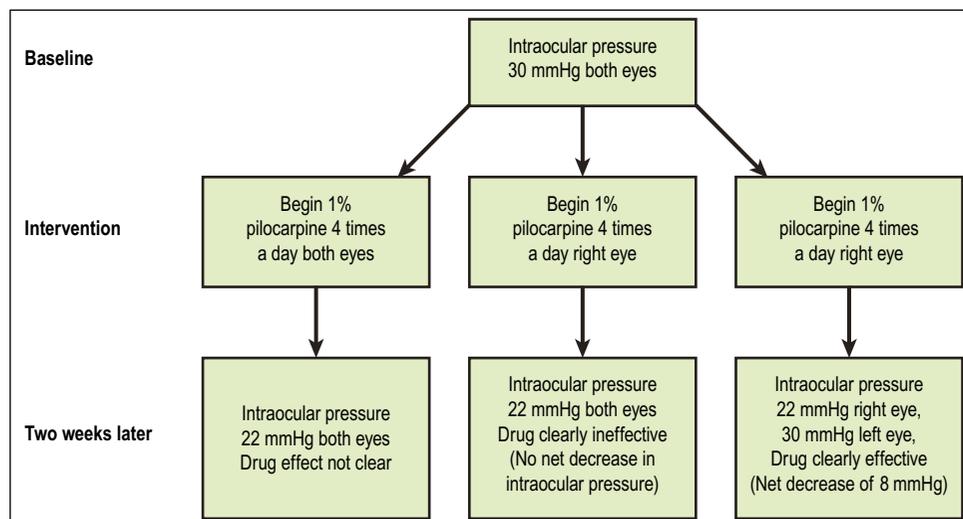


Fig. 22-2 Theoretical therapeutic trial in one eye.

administration. This may be a confounding factor in one-eye therapeutic trials. However, the contralateral effect is smaller than is the ipsilateral effect. Standard miotics can be evaluated in a few days to a week. Adrenaline (epinephrine), dipivefrin, α -adrenergic agonists, carbonic anhydrase inhibitors, and β -adrenergic antagonists should be evaluated after 2–4 weeks. Latanoprost and the other prostaglandins may take as long as 6 weeks to reach maximum effect.

The therapeutic trial in one eye is also useful when adding another medication (e.g., adding brimonidine or dorzolamide to a regimen of latanoprost) (Fig. 22-3). If a therapeutic trial is carried out for a few to several weeks, the ophthalmologist can determine whether the IOP reduction justifies the expense, bother, and potential side effects of the added drug.

The one-eye therapeutic trial requires more time and more visits to the office or clinic. However, the amount of information gained about drug efficacy and side effects justifies any additional time or expense on the part of the patient and physician. Therapeutic trials are not applicable in emergency situations or when glaucoma is unilateral or markedly asymmetric.

WHEN THERAPY IS INEFFECTIVE, SUBSTITUTE RATHER THAN ADD DRUGS

When IOP is considered too high, there is a tendency to add drugs to the regimen rather than to find a simple, effective regimen. If IOP rises after a patient has been controlled on a medication for some time, the drug should be stopped in one eye to determine whether it is still effective (Fig. 22-4). If the drug is ineffective or only partially effective, it should be discontinued and a more potent agent either in its class or in a different class substituted. If a drug is effective but the ophthalmologist believes that a lower IOP is necessary

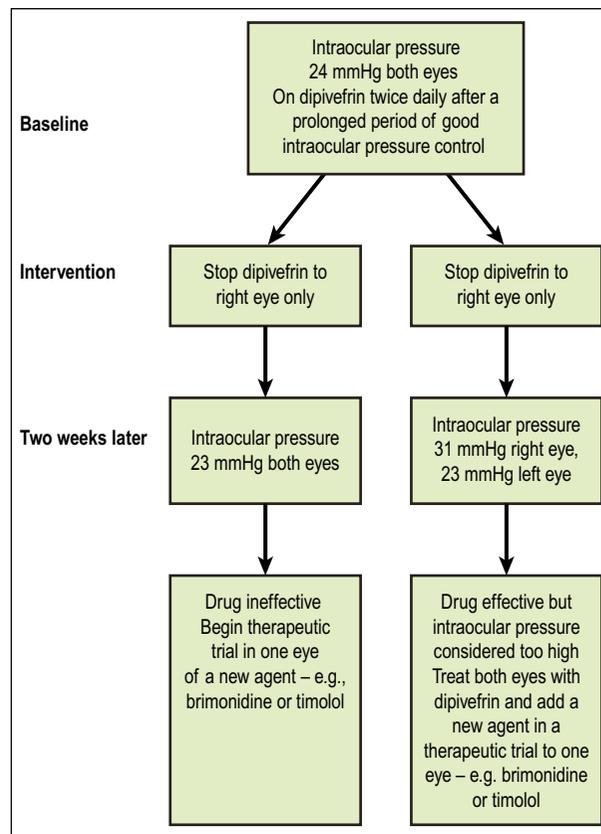


Fig. 22-4 Determining continued effectiveness of a drug through a theoretical therapeutic trial in one eye.

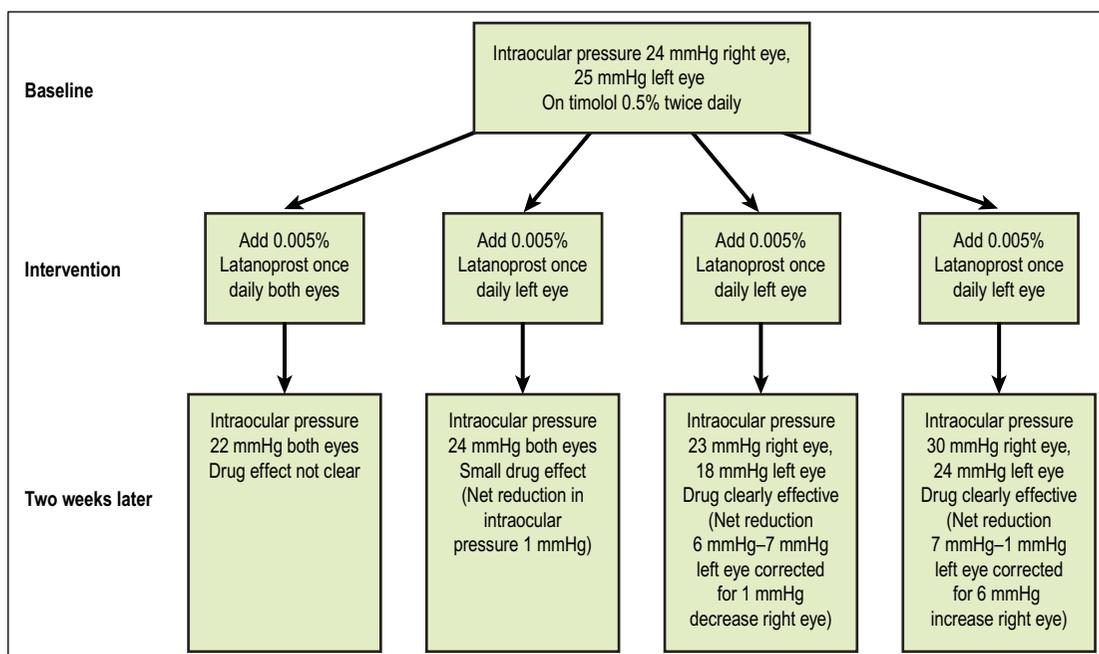


Fig. 22-3 Adding drugs in a theoretical therapeutic trial in one eye.

to prevent further damage, either a more potent drug may be substituted or a new drug can be added to the old regimen using a therapeutic trial in one eye. As a general rule, a 20–25% reduction in IOP is considered a sufficient response to justify continued treatment. However, there are situations in which a smaller reduction would be considered helpful. For example, a reduction in IOP from 19 to 17 mmHg (10.5% decrease) might warrant continued treatment in the presence of advanced optic nerve damage and visual field loss.

CONTINUALLY MONITOR THE TARGET PRESSURE

Determining the effectiveness of treatment requires constant monitoring of IOP, optic nerve appearance, and visual function. Deterioration in any of these parameters is a sign to consider more aggressive therapy (i.e., to set the target pressure at a lower level).

ASK ABOUT AND MONITOR OCULAR AND SYSTEMIC SIDE EFFECTS

Potential side effects should also be evaluated and placed in perspective by the physician–patient team. Patients will usually be forthcoming about ocular side effects. Often, however, patients do not relate systemic side effects to eyedrops. Therefore, the treating physician must be proactive and ask specifically about systemic side effects such as breathing difficulties, irregular heartbeat, gastrointestinal disturbances, fatigue, impotence, and mood or behavior changes.

SIMPLIFY AND REDUCE TREATMENT WHEN POSSIBLE

Patients should be treated with the lowest concentration(s), the smallest number of medicines, and the fewest number of administrations per day that have the desired therapeutic effect.¹³³ It is important to remember that the dose–response curve for an individual patient may differ from that derived from normal volunteers or a tested population of glaucoma patients. Some individuals are sensitive to a drug, whereas others do not respond at all. In some patients, 0.5% epinephrine, 1% pilocarpine, or 0.25% timolol produces the maximum IOP reduction. Higher concentrations may not be more effective and may only increase the possibility of side effects. Treatment is usually instituted using a low concentration of a drug. If this is effective but does not produce an acceptable IOP level, the drug should be administered to both eyes and the concentration increased in a therapeutic trial in one eye (Fig. 22-5). Some antiglaucoma agents (e.g., β -blocking agents or strong miotics) are capable of controlling IOP when instilled once daily. This must be proven by measuring IOP 20–26 hours after the last medication administration.

TEACH PATIENTS THE PROPER TECHNIQUE FOR INSTILLING EYEDROPS

Many patients use poor technique when administering eyedrops. Poor techniques include instilling excess drops, contaminating the dropper or bottle tip, and neglecting eyelid closure and punctal occlusion.^{130,134,135} Improper eyedrop administration may increase the expenditure for medication, decrease the therapeutic response (e.g., excess drops stimulate tearing and blinking and decrease drug penetration into the eye), and enhance side effects (especially those caused by systemic absorption of the drug).

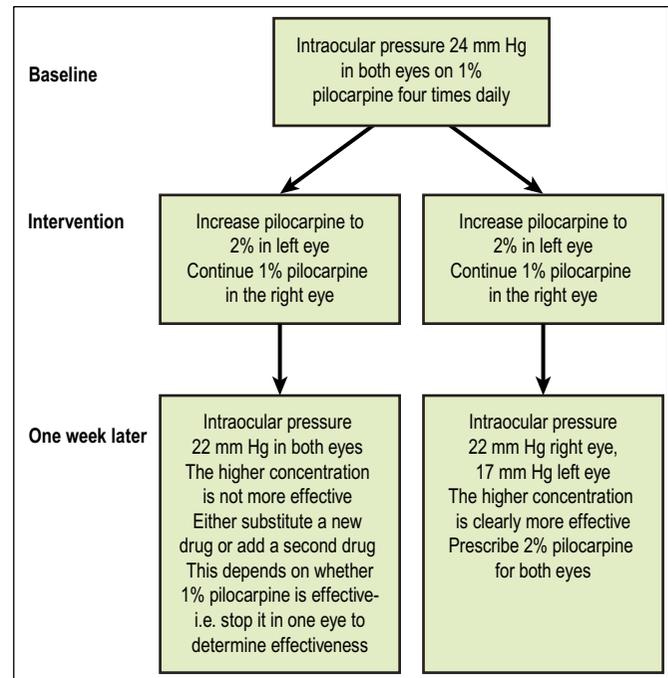


Fig. 22-5 Increasing drug concentration through a theoretical therapeutic trial in one eye.

In one study, patients were observed while they administered their eyedrop medication.¹³⁵ Under observation, 48% of the patients instilled two or more drops per eye per treatment, 24% instilled three or more drops, and 14% instilled five or more drops. Almost half of the individuals contaminated the dropper or bottle tip on the lashes, lids, or conjunctiva. Not a single patient in the group used punctal occlusion or simple eyelid closure after eyedrop administration. More than 20% of the individuals reported that they were partially or totally dependent on others to instill their eyedrops.¹³⁴ Thus in certain cases, spouses, children, or neighbors may need instruction about proper technique. After initial instruction, patients should be observed periodically to provide feedback and encouragement. If a patient complains that he or she cannot feel a medication reaching the cul-de-sac, the drug should be refrigerated to increase the sensation caused by the eyedrop.¹³² Patients frequently instill different eyedrop medications within a few seconds of one another.¹³⁴ Consecutive medications should be separated by at least 5 minutes to prevent washout and decreased effectiveness.³⁸ Many people are unable to learn punctal occlusion; sitting quietly for 5 minutes with the eyelids closed gently is almost as effective in reducing systemic absorption of eyedrops.⁴³

Fraunfelder¹³⁶ has suggested a specific technique to increase ocular contact time and to decrease systemic drug absorption:

1. Grasp the lower lid gently below the lashes and pull it forward slightly, creating a pocket.
2. Place one drop of the medication into the pocket without touching the ocular or periocular tissues with the eyedropper or bottle tip.
3. Hold the lid forward for a few seconds until the drop settles in the lower cul-de-sac.
4. Look down and bring the lower lid up until it touches the eye.
5. Close both eyes (simple eyelid closure).
6. Place gentle pressure over the puncta for 2 minutes (punctal occlusion).

PROVIDE WRITTEN INSTRUCTIONS

The physician, nurse, or patient should record the drug name(s), drug description(s) if indicated (e.g., green top, yellow label), and frequency and time(s) of administration(s). Many patients become confused about how often and when medication should be taken.^{137,138} Four times daily may be interpreted to mean 8 am, 10 am, 12 noon, and 2 pm, leaving 18 hours between the last dose of the day and the first dose the next morning. This problem is often compounded by the fact that patients with glaucoma are often elderly and are taking vitamins and multiple medications for systemic problems such as hypertension, heart disease, diabetes, anxiety, and hormone replacement.

Booklets like *Understanding and Living with Glaucoma* provided by the Glaucoma Research Foundation (251 Post Street, Suite 600, San Francisco, CA 94108, 1-800-826-6693) are extremely helpful in teaching the patient in simple language about glaucoma, its consequences, its treatment, and specifically how to use drops. Their toll-free number provides advice and counsel about the condition from long-term patients and helps to direct patients to resources that may be helpful. Similarly, several pharmaceutical companies provide devices that may make using drops easier for those with physical problems such as arthritis or balance problems. Some even provide electronic alarms and/or monitoring devices.

COMMUNICATE WITH THE PATIENT'S FAMILY PHYSICIAN

Increased communication may provide important information to the ophthalmologist and to the general physician and may prevent drug-induced side effects. Many general physicians need to be reminded that topically administered antiglaucoma medications (e.g., strong miotics, epinephrine, β -adrenergic antagonists) are capable of producing serious and even fatal systemic reactions. Many patients have been hospitalized for tests and treatment while continuing to receive the eyedrops responsible for the problem. The general physician can provide important information about the patient's general health (e.g., a patient with severe respiratory acidosis should not be treated with a carbonic anhydrase inhibitor, or one with chronic obstructive pulmonary disease a β -blocker). Many patients do not have a clear picture of their current and past health status and do not know the names or purposes of their medications.

ASK ABOUT PROBLEMS WITH THE MEDICAL REGIMEN

Patients should be questioned directly about expense, inconvenience, and possible medication-induced side effects. Patients may not connect systemic symptoms to an eyedrop (e.g., they may not realize that palpitations are caused by topical epinephrine).

CONSIDER DEFAULTING AS AN EXPLANATION FOR THE FAILURE OF MEDICAL TREATMENT

As noted previously, poor compliance is a frequent cause of medical failure. This problem can be associated with poor understanding of the disease, long waiting time to see the doctor, high cost of the medication, and a complex regimen.

EDUCATE PATIENTS ABOUT THEIR ILLNESS AND ITS TREATMENT

An informed patient is more likely to accept treatment and return for follow-up examinations. It is especially important to warn patients about common drug-induced side effects. Patients warned in advance are more likely to deal successfully with a difficult situation. Those who are not warned in advance are more likely to be frightened and to lose faith in the physician.

STOP TREATMENT PERIODICALLY TO DETERMINE CONTINUING EFFECTIVENESS

It is useful to stop a medication for a short time in one eye to confirm continued therapeutic benefit. If a drug is no longer effective, it should be discontinued and replaced if necessary. However, some agents may have a prolonged washout period. β -Blocking agents, for example, usually take 2 weeks but may take as much as a month to completely wash out of the eye.^{139,140} This may be too long to go without treatment for some patients with advanced disease.

MEASURE INTRAOCULAR PRESSURE AT DIFFERENT TIMES OF THE DAY AND AT DIFFERENT INTERVALS AFTER THE LAST ADMINISTRATION OF MEDICATION

The variability of IOP may be as important a factor in the progression of glaucoma as the absolute IOP level. Patients and physicians often fall into a pattern of scheduling appointments at the same time of day (e.g., early in the morning or after work). The patient may compound this situation by instilling his or her medication immediately before the appointment with the doctor so as to have a 'good showing.'

RECOMMEND COMPARISON SHOPPING FOR MEDICATIONS

Physicians often forget the high cost of chronic medical treatment, especially for older patients on fixed incomes. Prices at different pharmacies in the same neighborhood may vary by a factor of 2.^{141,142} Patients should be encouraged to buy medications at the pharmacy that offers the best price provided that the pharmacy also offers the services required by the individual (e.g., home delivery, comprehensive medication record). In recent years, Web-based pharmacies have become increasingly popular because of highly competitive prices. Of course, appropriate care is necessary to avoid being scammed. Generic drugs are often less expensive than drugs sold under a brand name. However, some glaucoma medications are not available as generic products (e.g., dorzolamide).^{138,141} Generic products are sometimes less comfortable to use than are the brand-name products. With the increasing influence of managed care in recent years, generic products may be substituted when a brand-name product was specifically prescribed or a more expensive, recently released brand-name drug may not be available at all.

One approach to treatment of most chronic glaucoma patients follows. The pharmacology of individual agents will be discussed in the following chapters. Start with agents that are likely to be effective and unlikely to produce significant side effects. Most physicians would start with a prostaglandin. The prostaglandin analogs are all now approved in the United States as first-line therapy and are the most commonly prescribed due to their efficacy, once-daily dosing

and relatively higher persistence rates than other agents. Many still use β -blocking agents because of their modest cost compared to prostaglandins (of course, the presence of respiratory or cardiovascular conditions might represent contraindications to their use). Betaxolol, a selective β -blocker, is somewhat safer than are non-selective β -blockers in patients with a history of asthma, other bronchospastic pulmonary conditions, or cardiovascular diseases negatively impacted by β -blocker treatment.

If the IOP fails to respond to the initial agent, *discontinue* it and start another agent – either a stronger one in that class or one belonging to a different class. If the IOP responds insufficiently to reach the target pressure, a second agent of a different type may be added. Medical escalation should proceed from the least toxic agents to the more potentially toxic ones. Brimonidine, an α agonist, is also an effective second agent that avoids the iris color and eyelash changes associated with prostaglandins. Another likely choice as a second agent would be a topical carbonic anhydrase inhibitor such as dorzolamide or brinzolamide, which has few topical or systemic side effects. Dipivefrin, an adrenergic agonist, is infrequently used today although it may have some additive benefit.

Pilocarpine drops or gel may be tried when laser trabeculoplasty or more invasive surgery are not options. The visual side effects may not be tolerated in younger patients or in those with central cataracts. They are best reserved for aphakic or pseudophakic patients. Apraclonidine may also produce a good adjunctive response to initial β -blocker therapy but has the disadvantages of a high tachyphylaxis rate and a high rate of allergic reaction. Systemic carbonic anhydrase inhibitors should be reserved for patients whose IOP is uncontrolled with topical medication or for those who are

intolerant to topical therapy and for whom laser or incisional surgery has failed or is not feasible. Despite the significant side effects that make these agents intolerable to many patients, the majority do get a satisfactory response and can tolerate them well.

Laser trabeculoplasty is probably worthwhile to consider any time after one or two topical agents fail to keep IOP in the target range. If target IOP is not reached with tolerated medical therapy, if cupping or visual field loss is progressing, if poor compliance is suspected, if medical therapy seems a significant burden for the patient, or if the patient's quality of life seems adversely affected, laser or filtering surgery should be considered.

If filtering surgery fails or carries a high risk of failure, a filtering operation with antifibrosis agents should be considered. Those with secondary glaucoma, previous eye surgery producing significant conjunctival scarring, or two or more failed filtering procedures may benefit from a tube shunt or ciliary body destructive procedure.

SUMMARY

Careful history taking by the physician, intensive education, and a cooperative approach are necessary to successfully manage glaucoma medically. The risk:benefit ratio of the treatment regimen must be considered at all times, along with the patient's wishes and individual needs. Fortunately, the vast majority of patients with glaucoma will be able to enjoy satisfactory visual function throughout their lives and also maintain a reasonable quality of life if the physician and patient work as a team.

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CHAPTER
23

Prostaglandins

The prostaglandins burst on the clinical scene in the 1990s and have become one of the mainstays of glaucoma treatment around the world. As a class, they are very potent intraocular pressure (IOP) lowering agents with a unique mechanism of action (Fig. 23-1). Prostaglandins are hormones that are produced, released, and effective locally; such agents are called autocooids. The prostaglandins are members of a family of substances called eicosanoids, which also include, among others, prostacyclin, thromboxane, and leukotrienes. Prostaglandin was first identified in seminal fluid in the 1930s. In 1955, Ambache¹ identified a substance in iris tissue that he called *irin* and that seemed to mediate the ocular response to irritation. This extract induced miosis when injected into the anterior chamber² and probably contained prostaglandins, as well as other substances.³ This was the first non-reproductive system source for this family of local hormones that are now known to be present throughout the body.

MECHANISM OF ACTION

Prostaglandins were first thought to mediate inflammation in both the eye and other tissues.⁴ High doses injected into the anterior chamber of rabbits produced signs of inflammation such as hyperemia, breakdown of the blood–aqueous barrier, and increased IOP.⁴ It soon became clear that the prostaglandins were synthesized by trabecular endothelial cells⁵ and by ciliary muscle cells⁶ from membrane phospholipids and arachidonic acid and released by several different ocular tissues during inflammation. Ocular tissues produce not only the prostaglandins E and F but also other eicosanoids.⁷

Many of the initial observations regarding the inflammation-mimicking effect of prostaglandins may have been due to the experimental techniques themselves (e.g., intraocular cannulation), the use of the very sensitive rabbit eye as the experimental model, and the rather high doses of injected prostaglandins used. Other mediators such as neuropeptides, interleukins, and platelet-activating factor appear to play a more significant role in the actual inflammatory process. Current thought relegates prostaglandins to ‘a minor, mostly regulatory, role’ in ocular inflammation in primates.³ In fact, prostaglandins may have some anti-inflammatory action because they may downregulate some aspects of the inflammatory response.⁷ Furthermore, because at least some prostaglandins improve uveoscleral outflow, these agents, when released during inflammation, may provide an alternate pathway for clearing the anterior chamber and uvea of inflammatory products.⁸

Because of the experimental observation that topical prostaglandins produced first an increase, but later a profound decrease, in IOP, and because of the clinical observation that intraocular

inflammation was often accompanied by low IOPs,⁹ work began to determine if one or more of the prostaglandins might be of value in glaucoma. Initial studies in rabbits showed that low doses of topical prostaglandins could reduce IOP in rabbits for as much as 20 hours.¹⁰ Using a relatively high topical dose of prostaglandin F₂ (PGF₂), Camras and Bito produced a reduction in IOP in monkey eyes lasting for up to 3 days.¹¹ This reduction seemed to be due to an increase in outflow facility without significant effect on aqueous formation, trabecular outflow facility, or episcleral venous pressure.^{12–14} In low doses, PGF₂ and other analogs were found to produce a very potent hypotensive response – capable of lowering IOP in monkey eyes to 5 mmHg without the initial hypertensive phase and without effects on refraction or pupil size.¹⁵

Considerable species differences exist in the magnitude of response to prostaglandins and, perhaps, even the mechanism of the pressure lowering and the role of prostaglandins in inducing inflammatory signs.^{3,16} Some prostaglandins even raise IOP in some species.³ Like the situation with adrenergic agents, several different prostaglandin receptor types exist. For example, five different human prostaglandin receptor types have been positively identified; DP, EP, FP, IP, and TP. Additionally, several subtypes of EP are now known.¹⁷ The same ocular tissues in different species may have different receptors, and the receptors may mediate different functions. Prostaglandins A, D, E, and F have been studied for their pressure-lowering effect. It appears that, in primates, the agents that affect the EP₃ and FP receptor types (i.e., those responsive to prostaglandins E and F) seem to be the most effective in lowering IOP.¹⁷ In addition, primates are much less likely than rabbits and cats to show a breakdown of the blood–aqueous barrier in response to prostaglandin application.¹⁹ EP and FP receptors have been found in the ciliary body and in the trabecular meshwork of primates.^{17,20} All of the currently available clinical agents have shown agonist activity at a cloned human FP receptor.²¹

Further studies show that the increase in outflow facility produced by prostaglandins, at least in primates, is due to increasing the flow through the uveoscleral pathway.^{22–24} The increased uveoscleral outflow was confirmed with the use of tracer substances in primate eyes.²⁵ Studies in humans are confirmatory.²⁶

Prostaglandins appear to alter not only the function of the uveoscleral pathway(s) but also the structure. Lütjen-Drecoll and co-workers^{27,28} have shown that prostaglandins produce extracellular matrix remodeling, widening of intermuscular spaces along the longitudinal ciliary muscle bundles, and dissolution of collagen types I and III. Another study using cultured human trabecular cells showed extensive remodeling of the extracellular matrix around these cells; specifically, there was reduction in both the density and the branching of type IV collagen and laminin, as well as a reduction in the density of type III collagen.²⁹ Other studies have shown an increase

likely the anatomic counterpart to the functional improvement in uveoscleral outflow associated with the clinical use of the prostaglandins. While improvement in uveoscleral outflow may be the most obvious mechanism by which these agents work, studies at the cellular level suggest that some other intracellular metabolic changes may also contribute to the overall effect.^{34,35}

All prostaglandin and prostaglandin-like agents seem to be changed as they traverse the cornea.³⁶ For some like latanoprost, it is the acid ester that is created during the transit across the cornea that becomes the active ingredient. For others, it is not clear whether it is the molecule itself or a metabolic product that does the job. Evidence does point to the fact that these agents can definitely get across the sclera directly and perhaps even facilitate this pathway.³⁷

There are two other agents whose potency and clinical activity seem to suggest similar prostaglandin activity. Travoprost seems to work directly on the FP receptors just as latanoprost does. However, controversy exists as to the exact mechanism of action of bimatoprost. While clinically it seems to work in the same way, evidence suggests that there may be some differences in the way it acts.³⁸ Bimatoprost by itself seems to have little effect on prostaglandin receptors. The manufacturer of bimatoprost has significant evidence that it is derived, at least in part, from and mimics the action of a seemingly parallel group of autocoids called prostamides. These hypotensive lipids are derived from the endocannabinoid family. Bimatoprost also seems to inhibit enzymes that metabolize prostaglandins.³⁹ Further evidence to support the theory that bimatoprost may not act exactly the same as latanoprost stems from the fact that, whereas latanoprost and travoprost seem to work mainly by increasing outflow via the uveoscleral outflow pathway, bimatoprost also seems to increase outflow through the pressure-sensitive (i.e., trabecular) pathway.⁴⁰ On the other hand, research from a rival company's laboratories suggested that all of the currently available agents are direct prostaglandin FP agonists in tissue cultures of human trabecular meshwork cells.⁴¹ Furthermore, investigators affiliated with yet another rival company found enough free acid of bimatoprost in the anterior chamber of patients undergoing cataract surgery to explain its IOP-lowering effects.⁴² Finally, an independent study showed that cornea, sclera and other ocular tissues do hydrolyze bimatoprost to its free acid which is a potent FP2a receptor agonist and that enough hydrolysis occurs to explain its action.⁴³ Because of the lack of clarity as to the mechanism of action of bimatoprost and perhaps unoprostone, the terms 'prostanoids' and 'hypotensive lipids' have been used to designate the entire group. Whether these terms are more accurate than the simpler 'prostaglandins' remains to be determined. Clearly, the solution of this controversy awaits some definitive studies to determine if bimatoprost is: 1) a compound that acts on a different set of receptors (e.g. prostamides) than the other prostaglandin-like agents; 2) a prodrug which is metabolized by the cornea into its free acid which is a potent FP receptor and, therefore, acts like the other agents, or 3) some combination of these. For the time being, this text will assume that they all have some common pathway since this does fit the clinical observations. The term 'prostanoid' will be used to designate the group of agents that have prostaglandin agonist-like activity.

Isopropyl unoprostone, a weaker chemical cousin with some unique properties, seems to also work by increasing cellular metalloproteinases and improving uveoscleral outflow via the extracellular, intercalary body muscular bundles.⁴⁴ Similar anatomical findings occur after chronic treatment with any of these agents.³⁰ Unoprostone has been placed in the class of agents called docosanoids.

DRUGS IN CLINICAL USE

Although the pressure-lowering effects of the prostaglandins have been known for almost two decades, it took almost that long to find analogs that were both effective and tolerable as far as side effects are concerned. The first prostaglandin analog to be tried in humans was prostaglandin F₂-tromethamine salt (PGF₂-TS). Although this agent lowered IOP, significant conjunctival hyperemia, stinging, foreign body sensation, and headache occurred in over one-third of patients.^{45,46}

The first usable prostaglandin was developed in Japan. Isopropyl unoprostone (Rescula) is a prodrug that is derived from a pulmonary metabolite of PGF₂, lowers IOP in a dose-dependent fashion with twice daily dosing, and is well tolerated.^{47,48}

Major progress was made with the development of a 17-phenyl-substituted PGF₂-isopropylester (PHXA34), which is considerably more potent than the PGF₂ without the phenyl substitution.^{49,50} A single dose of this agent lowered IOP by up to 5 mmHg in normal patients, and by about 40% in ocular hypertensive patients, for over 24 hours with very few side effects.^{51,52} Furthermore, the pressure lowering was maintained for at least a week with acceptable side effect levels.⁵³ PHXA34 is an epimeric mixture. The 15-R epimer is ten times more potent than the 15-S epimer and two times more potent than the mixture.⁴⁹ PHXA41 (latanoprost) has the same chemical structure as PHXA34 but is a solution of only the R epimer. One would expect it to be more potent, and it is!

LATANOPROST (XALATAN, PHXA41)

Latanoprost (Xalatan™ Pfizer, New Jersey) is a very potent IOP-lowering medication and has become one of the most useful antiglaucoma agents. In initial trials, latanoprost 0.005% reduced IOP by 25–35% with a single daily dose.^{54–57} The 0.005% dose seems to be the most efficient with the best balance of efficacy versus side effects.⁵⁸ Furthermore, unlike most drugs, more is not better; once-daily dosage appears to be superior to twice daily.^{59–61} At least during the first few months of use, an evening dose seems to be slightly superior in lowering morning IOP than a morning dose.⁶²

Several multicenter, controlled, randomized clinical trials in Scandinavia, the United States, the United Kingdom, and Japan showed topical latanoprost 0.005% once daily to compare favorably with timolol maleate 0.5% twice daily.^{63–67} In the Scandinavian study, latanoprost once daily was equal to timolol twice daily in general pressure-lowering activity if the dose of latanoprost was given in the morning. If the dose was given in the evening, then latanoprost was more effective in lowering the IOP than timolol. In the other studies, latanoprost produced a sustained decrease of 25–30% in IOP and was slightly more potent in reducing IOP than timolol, especially after 4 months of treatment. Latanoprost produced a higher incidence of conjunctival hyperemia than timolol, but the hyperemia was mild in all cases. No patients developed miosis or signs of intraocular inflammation. Latanoprost had no effect on heart rate or blood pressure, whereas timolol did slow the pulse an average of 2–3 beats per minute. After 1 year, latanoprost maintained good IOP control in patients switched from timolol with return of heart rate to pre-timolol baseline.⁶⁸ Latanoprost is superior in pressure lowering to once-daily timolol gel throughout the day from 8 am to 12 midnight.⁶⁹ Latanoprost has also been shown to be superior in diurnal IOP control to brimonidine.⁷⁰ In a study comparing latanoprost

with timolol, betaxalol and brimonidine, latanoprost had the best IOP-lowering effect, the least systemic side effects, and very few significant local side effects.⁷¹ Latanoprost has been shown to have no adverse effect on the respiratory system, even in patients with significant, steroid-dependent asthma.⁷²

In addition, the latanoprost-induced pressure drop and increase in uveoscleral outflow persist over 24 hours, unlike the timolol-induced decrease in aqueous formation, which is lost at night.^{73,74} Latanoprost effectively flattens the diurnal curve and is effective throughout the night in contrast to timolol which is not.⁷⁵ Like all other known ocular medications reducing IOP, latanoprost has no effect on the increase in IOP occurring when assuming the supine position.⁷⁶ When the phase III trials from the United States, Scandinavia, and the United Kingdom were combined and the patients followed for 1 year, not only was the effectiveness of latanoprost maintained with little evidence of drift, but the pressure control was not affected by race, eye color, sex, or age.⁷⁷ Even over a 2-year period, there is no evidence of tachyphylaxis.⁷⁸ Recent evidence suggests that all antiglaucoma medications may be inhibited in their action by thicker corneas.⁷⁹ True non-responders to latanoprost are unusual, occurring about 4–10% of the time;⁸⁰ however, the number of non-responders among Japanese patients with normal-tension glaucoma is as high as 20%.⁸¹

Latanoprost is rapidly converted by the cornea into its acid which appears to be the active ingredient.⁸² Therefore, latanoprost should be considered a prodrug. It reaches a maximum concentration in the aqueous humor 1–2 hours after topical application with a half-life of 2–3 hours. It reaches maximum concentration in the bloodstream in 5 minutes with a half-life of 17 minutes.⁸² Even in chronic users, the plasma levels are often undetectable.⁸² The acid is oxidized outside the eye; it is mostly excreted via the urine with a small amount eliminated in feces.⁸²

Several studies have shown that latanoprost has no effect on the blood–aqueous barrier as measured by flare meters and by fluorescein leakage into the anterior chamber after systemic administration.²⁶ Even after long-term use, no effect on the blood–aqueous barrier could be found.⁸³ In fact, timolol seemed to produce a higher concentration of protein in the anterior chamber than latanoprost.^{84,85} However, one study was able to show an adverse effect on the blood–aqueous barrier. Latanoprost seemed to be unaffected by concurrent oral administration of non-steroidal anti-inflammatory agents in one study;⁸⁶ however, further studies have suggested that concurrent administration of either an oral or topical non-steroidal anti-inflammatory agent may produce a slight but definite reduction or increase in the effectiveness of latanoprost.^{87–89} Either the effect on latanoprost of this class of drugs is agent specific or there are as yet unknown factors affecting the relationship. No effect of latanoprost (or timolol) on bloodflow velocity was noted using color Doppler imaging of the retrobulbar blood vessels.⁹⁰ Conversely, in normal patients, latanoprost did increase the pulsatile blood flow whereas timolol had no effect.⁹¹ The same clinic reported in another study that glaucoma patients show an increase in pulsatile blood flow and also retinal microcirculation with latanoprost.⁸⁶ In yet another study of normal-pressure glaucoma patients, once-daily latanoprost 0.005% was shown to significantly lower the IOP and increase the ocular perfusion pressure, whereas timolol did not significantly change the ocular perfusion.⁹² In this report, once-daily latanoprost 0.005% appears to be the most potent ocular hypotensive agent for patients with normal-pressure glaucoma among the β -blockers, α agonists and carbonic anhydrase inhibitors. The drug is also effective in pigmentary glaucoma

despite its propensity to increase pigment granules in the iris (see below).⁹³ Furthermore, it is effective in steroid-induced glaucoma.⁹⁴ While latanoprost may be very effective in some pediatric patients, it seems to be effective in fewer pediatric patients than in adults, although the nature of some pediatric glaucomas may be more the problem than the age of the patients.⁹⁵

Because latanoprost (and the other PGF₂ analogs) works by significantly increasing the outflow of aqueous through the uveoscleral pathways, its effects on IOP should be additive to any agent that decreases aqueous formation. PGF₂-isopropylester is additive to β -blocker therapy, causing a further decrease in IOP of 17% compared with timolol alone.^{96,97} In a subsequent study of patients whose conditions were uncontrolled with timolol, the addition of PGF₂-isopropylester reduced IOP an additional 6–9 mmHg below the level produced by timolol alone.⁹⁸ Similar results were obtained in studies with latanoprost producing a 13–17% reduction in IOP compared with timolol alone.⁹⁹ In patients whose IOP was not controlled under 25 mmHg with timolol, adding latanoprost reduced the IOP by 28–37% over 3 months.¹⁰⁰ However, not all patients respond to latanoprost; as many as 25% will demonstrate little or no reduction of IOP. A similar lack of response in some patients is seen with most other antiglaucoma agents. A fixed combination of latanoprost and timolol has been tested and found to be marginally better than latanoprost alone and significantly more effective in lowering IOP than timolol alone.¹⁰¹

Latanoprost is also additive with carbonic anhydrase inhibitors. In a double-masked study, adding topical latanoprost to the regimen of patients already taking 250 mg of oral acetazolamide twice daily produced a 21% drop in IOP.^{102,103} Latanoprost is also additive to topical carbonic anhydrase inhibitors.^{104,105} Latanoprost is also additive with topical adrenergic agonists. Two studies, one in England and one in Sweden, showed that latanoprost added to dipivefrin therapy reduced IOP about 28–32% and, conversely, that adding dipivefrin to latanoprost therapy produced a further reduction in IOP of 15–35%.¹⁰² Studies on the additivity of latanoprost with the α -adrenergic agonists have not been reported; however, the authors' experience strongly suggests that they are additive to each other.

Adding a prostaglandin analog to topical cholinergic therapy may be more problematic, at least theoretically. Cholinergic agents reduce IOP by direct stimulation of the ciliary muscle whose contraction opens the trabecular meshwork and improves trabecular outflow.¹⁰⁶ At the same time, cholinergic stimulation reduces uveoscleral outflow, possibly by reducing the spaces between the muscle fibers. Therefore pilocarpine or other cholinergic agonists could inhibit the action of prostaglandins on the uveoscleral outflow system. Several studies suggest that this is not a problem clinically. In the first, a single-dose study, one drop of latanoprost added to a 3-day regimen of pilocarpine produced a further mean reduction of IOP of 3.3 mmHg.¹⁰⁷ In another study, latanoprost was more potent as an ocular hypotensive agent than pilocarpine 2%.¹⁰⁸ In this same study, adding latanoprost to pilocarpine treatment produced a further reduction in IOP of 2.7 mmHg, whereas adding pilocarpine to latanoprost produced only an average additional pressure reduction of 1.5 mmHg. In a study of normal volunteers, adding latanoprost to the potent cholinergic agonist physostigmine produced additional lowering of pressure in normal volunteers.¹⁰⁹ Toris and co-workers found that pilocarpine did not inhibit the uveoscleral outflow improvement associated with latanoprost.¹¹⁰ However, in monkey eyes, the combination of miotics and at least one prostaglandin did reduce the effect on the uveoscleral outflow.¹¹¹

A generic latanoprost is available in India and should be in the US by 2011. A study of the generic agent available in India indicated that it did not exhibit equivalent pressure-lowering activity as the branded latanoprost (Xalatan®).¹¹² Whether or not this observation will be generalizable to other generic agents has yet to be demonstrated.

In summary, topical latanoprost was the first of the potent prostaglandin ocular hypotensive agents. It has been shown to be better than any of the other classes of drugs in terms of monotherapy, with additivity to most, if not all, of the other types of ocular hypotensive agents.

BIMATOPROST

Bimatoprost (Lumigan™ Allergan Inc., Irvine, CA) is a relatively new prostaglandin F2α analog where the carboxylic acid is replaced by a neutral ethylamide; the agent has little direct effect on prostaglandin F2α receptors.¹¹³ Numerous studies have shown its effectiveness in lowering IOP and its superiority in maintaining 24-hour control compared to timolol and dorzolamide.^{114–116} Like its chemical cousin, bimatoprost as monotherapy seems to be superior in flattening the diurnal curve to timolol alone and to timolol combined with dorzolamide.¹¹⁷

Most published studies to date have shown that when compared to latanoprost, bimatoprost seems to offer slightly improved pressure control or works in a greater percentage of patients.^{118–120} In addition, bimatoprost seems to have a slight edge in IOP control over travoprost.¹²¹ Furthermore, bimatoprost seems to have a slight advantage in those of African heritage although both travoprost and bimatoprost are effective in lowering IOP in that group.¹²² In a head-to-head randomized comparison of all three major prostanoid agents used for 6 months, Noecker and co-workers found a statistically significant but clinically small advantage for bimatoprost over both latanoprost and travoprost.¹²³ A meta-analysis of four controlled comparative studies revealed that bimatoprost seemed to improve pressure control by about 1–1.5 mmHg over latanoprost.¹²⁴

In contrast, another head-to-head comparison for 3 months failed to confirm any significant difference in IOP control between the three agents.¹²⁵ A study by one of the authors of this book in patients uncontrolled on latanoprost showed about one-third were brought back under control when bimatoprost was substituted for latanoprost.¹²⁶ Several studies support the fact that bimatoprost may be the most cost-effective agent since it has the greatest chance of reaching target pressure without needing adjunctive agents.¹²⁷

The preponderance of studies do seem to support a slight IOP advantage of bimatoprost over latanoprost. Most likely, in the average patient, this is not a clinically significant difference. However, in many, it might make enough of a difference to warrant a trial of bimatoprost if latanoprost is not as effective as desired. All of the above studies do agree that there is a higher incidence of hyperemia with bimatoprost and travoprost than latanoprost; it also appears that a somewhat larger percentage of patients have troublesome local side effects with bimatoprost compared to latanoprost.

In summary, bimatoprost, whatever its exact mechanism of action, seems to be, by a slight margin, the most potent of these agents but with a concomitant increase in local side effects.

TRAVOPROST

Travoprost (Travatan™, Alcon Laboratories, Ft Worth, TX) is the isopropyl ester of a potent prostaglandin F2α agonist. It is hydrolyzed

into the active agonist by the cornea and sclera and thus, like its cousins, is a prodrug.¹²⁸ Travaprost is a highly selective FP receptor agonist.¹²⁹ Like latanoprost, it is a very effective agent when used once daily for lowering IOP in most species including human; unlike latanoprost, it is more effective when used twice daily compared to once daily but, of course, side effects, especially conjunctival hyperemia, increase proportionately when that happens.¹³⁰ Like latanoprost, travoprost works by improving outflow facility; it is not clear how much of this is via trabecular and how much is via uveoscleral outflow.¹³¹ It seems to make little difference if the once-daily dosage is applied in the morning or evening although there is a slightly greater effectiveness when the dose is given at night, both in controlling the daytime IOP and limiting the fluctuation of IOP.¹³²

The obligatory studies comparing travoprost to timolol showed that both the 0.0015% and 0.004% solutions were superior in pressure-lowering activity by about 2 mmHg over 9 months versus timolol.¹³³ In this study of over 500 patients, travoprost did produce more hyperemia, itching, eye pain, and iris color change than timolol, but by and large the complications were tolerable. Similar results were obtained from a second prospective, randomized, masked study in the US.¹³⁴ In both studies, timolol slowed the pulse and reduced the blood pressure whereas travoprost had no effect on either. There were no other statistically significant differences between the two agents.

Compared to latanoprost, travoprost shows similar IOP levels over a 24-hour period but may have a greater duration of action – over 40 hours from a single dose.^{134,135} If a dose is missed, the effect on IOP is attenuated during the day but seems to be sustained during the nocturnal period when the pressure may be the highest.¹³⁶ As with bimatoprost, some patients uncontrolled with latanoprost may get improved control when switched to travoprost.¹³⁷ In a prospective randomized controlled study, Netland and co-workers found travoprost to be at least equal to (and perhaps slightly superior to) latanoprost and superior to timolol.¹³⁸ In a retrospective analysis of these data, they concluded that travoprost was superior to both latanoprost and timolol in black patients. The same authors did a retrospective meta-analysis of two large studies and came to the same conclusion.¹³⁹ A prospective, controlled and masked study in black patients took this concept one step further; it found that travoprost not only was superior to both timolol and latanoprost in reducing IOP, but it was less likely to result in visual field progression in these patients.¹⁴⁰ This difference in response between black and white patients has been seen with other autonomic-related topical agents. A similar analysis of bimatoprost data concluded that bimatoprost was equally effective in black and white patients and slightly more potent in that group than travoprost.¹⁴¹

As of this writing, travoprost is the only prostaglandin-like agent that is available with a different preservative than benzalkonium chloride (BAK) (Travatan Z™). The BAK-free travoprost may be particularly useful in those patients who are showing evidence of BAK toxicity and in those on multiple medications with ocular surface disease whose condition may be exacerbated by large doses of BAK. Like the other prostaglandin and prostaglandin-like agents, travoprost works well with timolol and other topical antiglaucoma medications.¹⁴² In summary, travoprost is an effective and relatively safe prostanoid.

ISOPROPYL UNOPROSTONE (UF-021, RESCULA™)

As noted previously, isopropyl unoprostone (Rescula™, Ciba Vision Care/Novartis, Duluth, GA) is a prodrug derived from a pulmonary metabolite of PGF₂. It reduces IOP in normal volunteers without

significant side effects for at least a 2-week period.^{47,48,143} In a large trial of patients with elevated IOP, twice-daily unoprostone given over a 12-week period reduced IOP by about 5 mmHg from baseline at 4 hours post dosing; this was equivalent to the effect produced by timolol twice daily.¹⁴⁴ Although there was no effect on blood pressure in the unoprostone-treated group, 4% of patients developed mild conjunctival hyperemia. The timolol group showed significant episodes of decreased blood pressure. In a 1-year study by the same multicenter group, patients with glaucoma or ocular hypertension were randomly assigned to either 0.06% or 0.12% of unoprostone twice daily.¹⁴⁵ Both groups showed a rather high 32–46% dropout rate – many for inadequate IOP control. Of those still in the study at 1 year, those in the 0.06% group had an average IOP drop from baseline of 3.4 mmHg, and those in the 0.12% group had an average IOP drop of 4.5 mmHg. All of these studies measured IOP 2–6 hours after dosing and did not measure the crucial ‘trough’ pressure before the next dose was due. In a randomized, masked study, unoprostone isopropyl 0.15% used twice daily reduced IOP in open-angle glaucoma patients but not quite as much as either timolol or betaxolol.¹⁴⁶ Several studies have shown unoprostone to be weaker than latanoprost.¹⁴⁷ Furthermore, adding unoprostone to latanoprost does not augment the effect of latanoprost while, as might be expected with a more potent agent, adding latanoprost to unoprostone produces the maximum effect expected from latanoprost alone.¹⁴⁸

Side effects included a dose-dependent conjunctival hyperemia, corneal epithelial defect, and headache. Increased iris pigmentation occurs but at lower frequency than latanoprost. Some side effects may have been related to the preservative rather than unoprostone. The higher dose was also associated with two cases each of dry mouth and paresthesia. On the basis of these studies, isopropyl unoprostone was approved for use as an antiglaucoma agent in Japan and was, in fact, the first prostanoid approved for clinical use in the world.

Like the other prostanoids, unoprostone appears to work by improving the outflow facility through the uveoscleral outflow system.^{149,150} Unoprostone also prevented IOP spikes following laser trabeculoplasty in rabbits.¹⁵¹

In normal volunteers, a single drop of unoprostone in one eye had no effect on IOP, blood pressure, heart rate, or pulsatile ocular blood flow.¹⁵² On the other hand, timolol reduced IOP in both eyes (more in the treated eye) but also reduced pulsatile ocular blood flow, blood pressure, and heart rate. In patients with glaucoma, unoprostone 0.15% twice daily also seems to increase pulsatile blood flow although not as much as latanoprost 0.005% once daily.¹⁵³ What pulsatile blood flow as measured by today’s technology means and what its implications are for the care of glaucoma have not been elucidated.

FIXED COMBINATION AGENTS

All three major prostaglandin analogues have been combined in a single bottle with timolol. In all three cases, the combination does as well or even slightly better than when the two drugs are administered separately but concomitantly.^{101,154,155} As of this writing, only the travatan/timolol combination (DuoTrav[®], Alcon, Ft Worth, TX) has been approved by the US Food and Drug Administration (FDA) because it is the only one that met the FDA criterion of at least 1.5 mmHg improvement over the base prostaglandin analogue alone. The travoprost/timolol combination may have a slightly longer duration of action than the latanoprost/timolol fixed combination.¹⁵⁶ The bimatoprost/timolol fixed combination seems, in one study anyway, to have slightly better IOP-lowering effect

than the fixed latanoprost/timolol combination.¹⁵⁷ Evening dosing with the fixed combinations seems to be slightly better than morning dosing.¹⁵⁸ The fixed combinations do combine the side effect potential of both agents so care must be taken to remember that β -blockers are contraindicated in patients with asthma, among other conditions, and to watch for the dizziness, low blood pressure, slow pulse, and other systemic side effects of these agents.

SIDE EFFECTS

Generally speaking, the prostanoids as a group are very well tolerated with side effects being relatively mild and local; serious side effects are infrequent and systemic ones rare. The most common side effects in the three multicenter, international, comparative studies after 6 months of latanoprost treatment were conjunctival hyperemia, foreign body sensation, eye irritation, and superficial punctate keratopathy, all of which were more common with latanoprost than with timolol (Table 23-1).¹⁵⁹ Other irritative and subjective symptoms such as burning, stinging, itching, eye pain, and tearing were similar for the two medications. The side effects for travoprost, bimatoprost, and unoprostone are roughly the same with bimatoprost having the most frequent conjunctival hyperemia, travoprost in the middle, and unoprostone the least. The incidence of conjunctival hyperemia ranges from 5% for latanoprost and unoprostone to 50% for travoprost and bimatoprost.^{160,161} However, the hyperemia is often transient lasting only 1–2 weeks after which it usually settles down to a tolerable level. The hyperemia is superficial and histopathologic study fails to show any pathological changes compared to untreated controls.¹⁶² Only 6–9% of patients withdrew from any of these studies because of side effects, defaulting, or ineffectiveness. The withdrawal rates were similar for both timolol and latanoprost. The withdrawal rate from studies is definitely higher for bimatoprost although, as noted above, target pressures are more frequently reached with bimatoprost than with the other agents.^{67,68,116,125,134,138,146–148}

All of the prostaglandin-like agents can cause histopathologic changes in conjunctival cells.¹⁶³ since conjunctival cytologic changes may be seen with all of the topical antiglaucoma agents, this may be due to preservative rather than the active IOP-lowering chemical itself. One study showed that none of the three major agents was particularly toxic to epithelial cells until the preservative was added.¹⁶⁴ All three prostanoid agents may cause decreased corneal sensitivity, tear break up time, and Schirmer tear quantities;¹⁶⁵ thus, patients with pre-existing tear deficiencies or neurotrophic problems may experience exacerbation with prolonged prostanoid treatment. Attention should be paid to this possibility and tear replacement therapy begun as indicated.

Superficial punctate staining of the cornea does occur with all of these agents. In a short term, cross-over study, Stewart and co-workers failed to find any difference in rates or severity of corneal staining in healthy subjects after topical use of any of the three major prostanoids.¹⁶⁶ While serious corneal structural changes seem to be rare, one case of corneal toxicity and one case of corneal neovascularization in an eye with previous trauma have been reported.^{167,168} Latanoprost use has been associated with an exacerbation of corneal changes in patients with a history of allergic conjunctivitis;¹⁶⁹ the commercial preparation of latanoprost has a high concentration of the preservative BAK which, when administered at night, may play a role in the corneal changes seen. Similarly, the preservative rather than the active ingredient has been implicated in disruption of the epithelial corneal barrier in cultured cells and whatever other corneal and conjunctival changes have been observed.^{170,171} In fact, the

Table 23-1 Side effects occurring at least once during 6 months of latanoprost therapy in three phase III trials*

Signs and Symptoms	Scandinavia		United Kingdom		United States	
	Latanoprost (n = 183) %	Timolol (n = 84) %	Latanoprost (n = 149) %	Timolol (n = 145) %	Latanoprost (n = 128) %	Timolol (n = 140) %
Superficial punctate keratopathy	7	2	13	4	13	18
Conjunctival hyperemia	3	0	15	6	5	3
Foreign body sensation	5	5	22	8	4	11
Blurred vision	3	7	11	13	10	6
Eye pain	1	0	9	7	2	4
Eye irritation†	22	25	40	32	24	45
Iris color change						
Definite	3	0	1	0	1	0
Suspect	4	0	9	0	2	0

Modified from Alm A, Camras CB, Watson PG: Phase III latanoprost studies in Scandinavia, the United Kingdom, and the United States. *Surv Ophthalmol* 41(suppl 2):S107, 1997.

*Includes adverse events as well as ocular symptoms.

†Includes burning, stinging, itching, and tearing.

effects on the epithelium of the cornea of the prostanoids seem to be less than that produced by the β -blocker agents.¹⁷²

Travoprost preserved with an alternative to BAK (Travatan Z[®], Alcon Laboratories, Ft Worth, TX) does seem to protect cells *in vitro* from some of the toxic effects of BAK.^{173,174} In rabbits, the BAK-free travoprost had significantly fewer effects on the corneal epithelium than BAK-preserved drops.¹⁷⁵ In the one clinical study reported to date, travoprost with and without BAK were similar in their efficacy and side effects in otherwise normal glaucoma patients; there was a 50% higher rate of hyperemia in the BAK-treated group but the differences were not statistically significant, although the numbers may have been too few to empower the study to detect a statistically significant difference.¹⁷⁶ Nevertheless, based on the evidence to date, it would seem prudent to consider using the BAK-free version in patients with pre-existing ocular surface disease or those on multiple agent therapy where total BAK dosage could cause or exacerbate ocular surface problems.

Activation of latent herpes simplex virus seems occasionally to be associated with prostanoid use. Both keratitis in the form of dendrites, pseudodendrites, and keratouveitis have been reported.^{177,178} In rabbits with latent herpetic infection, latanoprost did not increase the rate of viral shedding.¹⁷⁹ On the other hand, latanoprost, but not unoprostone, exacerbates experimental herpes simplex keratitis in rabbits.^{180,181} While this complication is unusual enough not to show up in the large studies, the association with the prostanoids appears to be real since, for example, herpes simplex keratitis has not been reported with timolol.

Periocular hyperpigmentation of the skin has been noted with all of these agents with chronic use in patients of all racial backgrounds, but may be especially common in those of African ancestry.¹⁸² The authors have noted similar changes especially in the skin of the lower eyelid in patients who are more darkly pigmented such as those of Hispanic and Asian background (Fig. 23-2). The onset of the hyperpigmentation is gradual and disappears with discontinuation of the drug.¹⁸³ Increase in periocular skin pigmentation may be slightly more common with bimatoprost than latanoprost but occurs with both agents.¹⁸⁴ Contact as well as herpes virus dermatitis of the eyelid have been reported.^{183,185,186}



Fig. 23-2 Note increased pigmentation of the skin of the right lower lid (arrow) in patient using bimatoprost in right eye only for 1 year.

Among the unique side effects of the prostanoids is the darkening and increase in length of the eyelashes (Fig. 23-3).^{187,188} The number of lashes also increases.¹⁸⁹ The rate of growth seems to be about 1 mm in 10 weeks.¹⁹⁰ The lashes may grow long enough to rub against spectacles especially with bimatoprost. Apparently, the prostanoids are able to induce resting follicles to enter the growth phase and prolong it.¹⁸⁹ These agents are also able to stimulate hair growth in the scalp of balding macaques and induce lash growth in those afflicted with alopecia.¹⁸⁹ They have been seen to replace eyelashes in a patient with alopecia.¹⁹¹ Actual trichiasis may occur as well.¹⁹² While most of the published reports of hypertrichosis and darkening have been with latanoprost, travoprost and bimatoprost seem equally or even more capable of causing this. At least one study and the experience of the authors of this text strongly suggest that the hypertrichosis is reversible when the prostanoid is discontinued.¹⁹³

In addition to stimulating the growth of eyelashes, these agents also seem to be able to stimulate the growth of the fine and coarse hairs of the eyelid skin (Fig. 23-4).¹⁸⁹ These vellus hairs of the

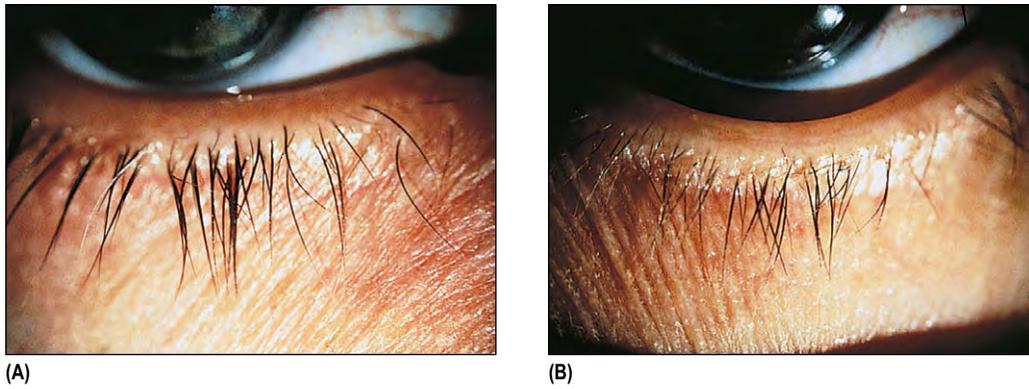


Fig. 23-3 (A) Right lower eyelid from patient who has been using latanoprost in the right eye only for 17 weeks. Note increased number and thickness of eyelashes compared with left eye. **(B)** Left lower eyelid from the same patient who has been using latanoprost in the right eye only. (From Johnstone MA: Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. *Am J Ophthalmol* 124:544, 1997. Courtesy of Dr Johnstone and the American Journal of Ophthalmology.)

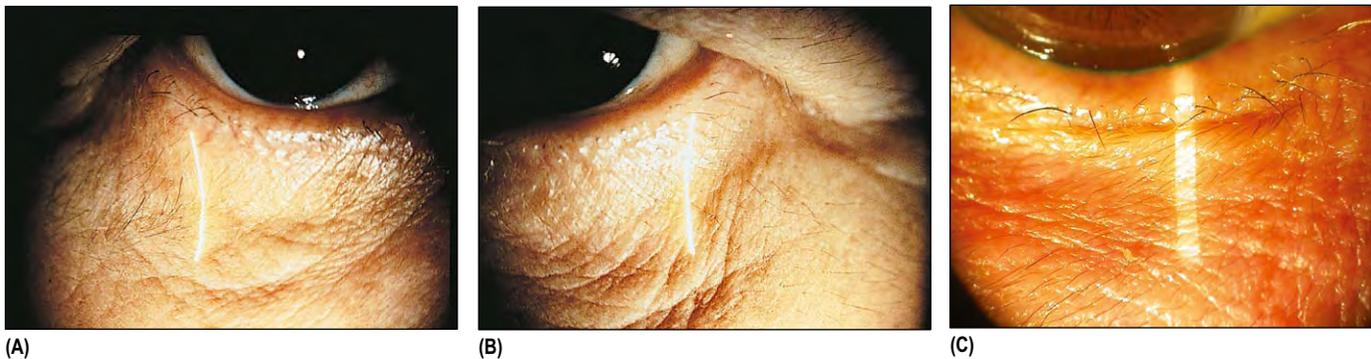


Fig. 23-4 (A) Right lower eyelid from patient who has been using latanoprost in right eye for 2 months. Note fine hairs on lateral portion of lower lid. **(B)** Left lower eyelid from patient who has been using latanoprost in right eye for 2 months. **(C)** Lower eyelid of another patient with increased vellus hairs after using travoprost for 16 months. (From Johnstone MA: Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. *Am J Ophthalmol* 124:544, 1997. Courtesy of Dr Johnstone and the American Journal of Ophthalmology.)

lower eyelid and malar region not only increase in number but become darker (paradoxically more notable in the more pigmented ethnic groups) and may become a cosmetic concern especially if the prostanoid is used unilaterally.¹⁹⁴ Conversely, poliosis has also been reported as a complication of prostanoid use.¹⁹⁵

Another side effect of the prostanoids that is rare but appears to be real is anterior uveitis. Uveitis in patients without a prior history and exacerbation of existing anterior uveitis have both been reported as unusual complications of prostanoid treatment.^{196–200} The incidence of anterior uveitis during latanoprost treatment was 5–6% in one retrospective study, with several cases being bilateral.²⁰¹ In the average patient, no change in the blood–aqueous barrier is seen after even 12 months of therapy with latanoprost so that the uveitis must be an idiosyncratic reaction.²⁰² However, in pseudophakic and aphakic patients, the prostaglandins can disrupt the blood–aqueous barrier.²⁰³

Related to the issue of uveitis is the association of cystoid macular edema (CME) with the use of topical prostanoid agents.²⁰⁴ Reports began appearing within two years of the release of these agents.^{205–207} The incidence has been estimated at 1–2% of aphakic or pseudophakic eyes.²⁰⁴ In one series, all of the eyes were either

aphakic or pseudophakic with open posterior capsules, or had other evidence of disrupted blood–retinal barrier such as previous complicated cataract surgery or previous cystoid macular edema.²⁰⁸ In this series, all improved when the prostaglandin was discontinued. In a retrospective series of 173 pseudophakic and 13 aphakic glaucoma patients, only 2% were found to have angiographic evidence of CME and all of these had open posterior capsules and had had vitrectomy.²⁰⁹ The incidence of CME in high-risk eyes was found to be about 5% in yet another series.²¹⁰ In another series, where the use of latanoprost with and without steroid or a non-steroidal anti-inflammatory agent (diclofenac) was compared in a random, masked fashion to the use without latanoprost but with the other agents in patients with recent cataract surgery, latanoprost use without concomitant diclofenac was associated with a higher incidence of CME.²¹¹ The non-steroidal anti-inflammatory agent was clearly protective when given concomitantly but maintained the pressure-lowering effect of latanoprost. One paper gives several reasons why latanoprost should not be a causative agent but concludes that careful monitoring should take place in those at risk.²¹² Similar findings have been noted for the other prostanoid agents.²¹³

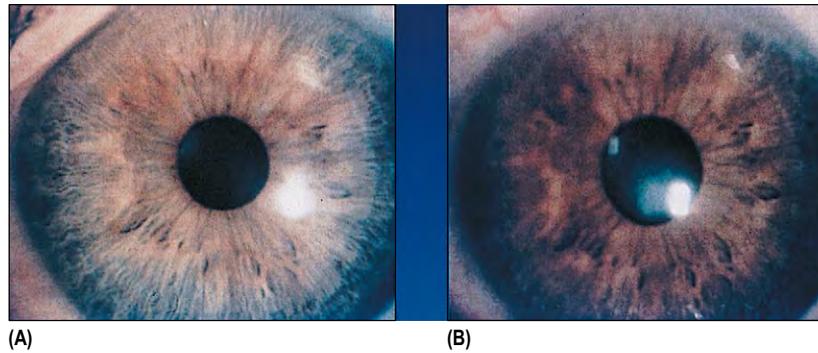


Fig. 23-5 Change in color of iris with latanoprost treatment. Left: green-brown iris before latanoprost treatment. Right: same eye after 6 months of latanoprost treatment. (From Watson PG, Stjernschantz J, Latanoprost Study Group: A six-month, randomized, double-masked study comparing latanoprost with timolol in open angle glaucoma and ocular hypertension, *Ophthalmology* 103:126, 1996.)

That these agents exacerbate pre-existing conditions is suggested by a study that used ocular coherence tomography to monitor retinal thickness in glaucoma patients with normal functioning blood-retinal barriers; the investigators found no effect of latanoprost treatment.²¹⁴ However, in a study of otherwise uncomplicated patients undergoing cataract extraction, use of latanoprost in the early postoperative period was associated with about a 3% incidence of visually significant CME, whereas none of the patients who had discontinued their latanoprost preoperatively developed CME.²¹⁵ So, a pre- or perioperative complication is not a prerequisite for prostanoid-induced CME.

Bimatoprost has been reported to be associated with CME even in patients who did not develop this complication while using latanoprost.²¹⁶ Another case report details the development of CME after switching from latanoprost to BAK-free travoprost.²¹⁷ The authors of this text also have found an occasional pseudophakic patient who developed CME after switching from latanoprost to bimatoprost.

Miyake and Ibaraki suggest that it may be the preservative rather than the prostaglandin that is the etiologic agent.²¹⁸ However, this complication has not been noted with timolol, brimonidine or dorzolamide which utilize similar preservatives. Based on the above, the authors recommend that any of the prostanoid agents be discontinued at the time of cataract surgery in glaucoma patients, and resumed, if possible, only after a 2- or 3-month postoperative period has passed. If prostanoids must be used to control glaucoma in the postoperative period, the patients should be monitored carefully for the possible development of CME and possibly treated with concomitant topical non-steroidal anti-inflammatory therapy. Fortunately, the CME associated with prostanoid use is usually reversible with cessation of the prostanoid and addition of topical non-steroidals and topical steroids (judiciously of course). Prostanoids should be used with caution and careful monitoring in patients with a history of previous CME, vitrectomy or disruption of the blood-retinal barrier.

Among the other potentially serious ocular side effects of the prostanoids are choroidal effusions.^{219,220}

Among the most intriguing side effects of the prostaglandins is the apparently permanent darkening of iris color in certain susceptible individuals. In subhuman primates, all of the topical prostaglandin analogs are capable of changing the iris color after several months of treatment.^{65,221} In the combined phase III trials of latanoprost, 1–3% of eyes had definite darkening of the iris color, and 2–9% had suspect iris color changes.¹⁵⁹ When these patients were followed out to

1 year, 11–23% showed changes. When three of the phase III trials were combined, overall, 12% of patients showed a definite or possible change in iris color.⁷⁷ In a 2-year study in the United Kingdom, only about 10% showed a definite iris color change.²²² Using a sensitive photographic method, Schwartz and co-workers noted that 11 of 22 patients using latanoprost for 36 months showed visible color change whereas only 8 of 22 patients using latanoprost for 36 months developed increase in the photographic color density of their iris.²²³ This may be the highest incidence of color change reported to date.

In some patients treated in only one eye, the change in pigmentation became apparent after only a few months of treatment (Fig. 23-5). However, in most cases the color change was not noted by the patient, relatives, or ophthalmologist. The longer the treatment, the greater is the likelihood that color change will become manifest. The eyes at greatest risk seem to be those eyes with a peripupillary brown ‘collar’ surrounded by a gray-green, yellow-brown, green-brown, blue-brown, or speckled light-brown periphery. Up to 50% of those eyes with green-brown eye color, and up to 100% of those with yellow-brown eye color, will show some change by 1 year (Fig. 23-6).²²⁴ The vast majority of patients with uniformly colored irides – whether gray, blue, or brown – show no changes.³ Furthermore, iris color changes are not seen in those of African descent. Similar changes have been observed in a few white patients treated with isopropyl unoprostone; however, many of the studies of this agent have been confined to Japanese patients, whose irides tend to be very dark to begin with and where color change may be difficult to detect.³ In a comparative study of latanoprost and unoprostone in Japanese patients, the incidence of increased iris pigmentation as measured by masked photographs was much higher than might be expected – 60% and 30% respectively after 6 months of treatment.²²⁵ In an analysis of two multicenter, prospective randomized US trials, McCarey and co-workers found the incidence of iris color change after 2 years of unoprostone treatment to be quite low (<1%).²²⁶ Clearly, the iris pigmentation effects are dependent on iris color and perhaps racial characteristics as yet undefined. The color changes associated with latanoprost cease progressing after cessation of treatment; they appear to be permanent, without evidence of decrease in pigmentation up to 2 years after treatment has ended.^{224,227}

Studies in primates suggest that an intact sympathetic innervation is not necessary for the increased pigmentation induced by prostaglandins to occur.²²¹ The suggestion has been made that the prostaglandins can replace the trophic effect of sympathetic innervation on

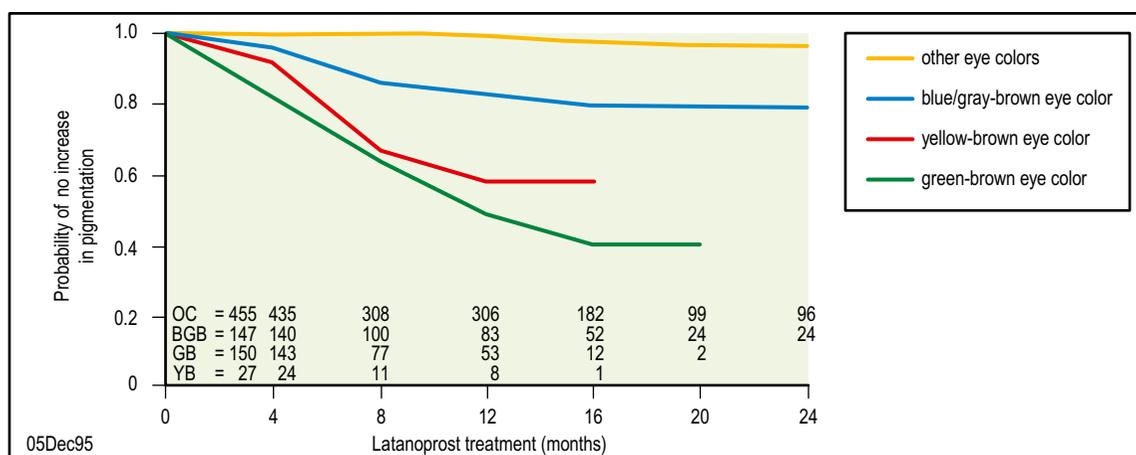


Fig. 23-6 Iridial pigmentation (Kaplan-Meier analysis).

(From Wistrand PJ, Stjernschantz J, Olsson K: The incidence and time-course of latanoprost-induced iridial pigmentation as a function of eye color, *Surv Ophthalmol* 38(supp 2):S129, 1997.)

iridial melanocytes that is required to reach the genetic maximum level of pigmentation in an individual.²²¹ This observation has been confirmed in rabbits with both unoprostone and latanoprost.^{228,229} Prostaglandins apparently stimulate the formation of extra melanin granules in the individual iris stromal melanocytes. There is no increase in the number of melanocytes and no effect at all on the iris epithelial melanocytes or melanin. The increased melanin granules remain in the melanocytes without any evidence of shedding into the anterior chamber or trabecular meshwork.^{224,230} The mechanism (at least in monkeys) may be related to an increase in tyrosinase transcription associated with latanoprost administration (at least); this increased transcription may be the cause of the increased melanogenesis.²³¹ Evidence in tissue culture suggests that fibroblasts may play some role in the process.²³²

A large-scale, multicenter histopathologic study of iridectomy specimens from patients with and without a history of latanoprost treatment found an increase in iris freckles and fibroblasts in those with a history of latanoprost treatment compared to those without.²³³ The mean number of melanocytes was statistically similar between the two groups. No evidence of malignant or premalignant changes were noted. Pfeiffer and co-workers randomly assigned a small number of patients awaiting trabeculectomy to 3 months of treatment with latanoprost or other antiglaucoma agents. They found no differences in cellularity at the end of the 3-month period between the two treatment groups.²³⁴ The same investigators performed a similar study only randomly assigning one eye to latanoprost for 6 months prior to trabeculectomy and immediate trabeculectomy in the fellow eye. At the end of 6 months, no histopathologic differences were found between the two sets of eyes. Yet another histopathologic study compared iridectomy specimens from one eye which had been treated with latanoprost and had iris darkening with the iridectomy from the fellow eye unexposed to latanoprost treatment.²³⁵ This study failed to show any difference in numbers of melanocytes or numbers of melanin granules in the melanocytes between the latanoprost-treated and untreated eyes. The only difference was that the latanoprost-treated irides had larger melanin granules. The same group looked at concomitant trabecular pigmentation and found that, although trabecular pigmentation increases with age and with duration of primary open-angle glaucoma, no increase of trabecular pigmentation was

associated with latanoprost use even in eyes that had demonstrable darkening of the iris.²³⁶

Despite increased melanin in the melanocytes of the iris, there is no evidence that the condition leads to increased pigment shedding; the anterior chamber angle (especially the trabecular meshwork color) appears to remain stable over at least a 3-year follow-up.²³⁷ Because the iris melanocyte melanin granules are approximately one-tenth the size of those in the epithelial melanocytes, they are easy to identify if they are shed. No effect of topical prostaglandin treatment has been detected on nevi, iris freckles, uveal melanocytes, melanocytes of the conjunctiva, or melanocytes of the skin of the eyelid.²³⁸ Because little is known about the effect of this increased iris melanocyte melanin over a period of decades, it seems prudent to monitor young patients as carefully as is practical when considering topical prostaglandin therapy, especially with those whose irides are at risk for color change or when single eye use is being considered.

Aside from headache, no systemic side effects of latanoprost, travoprost, bimatoprost, or unoprostone were reported in any of the phase III trials. However, a few patients report joint or muscle pains, dry mouth, backache, bitter taste, and allergic skin reactions. The prostaglandins are well tolerated by patients with asthma, although wheezing, and in rare cases asthma, has been reported in the post-market surveillance.²³⁹ Urge incontinence has been seen and confirmed with re-challenge.²⁴⁰ The reported side effects are summarized in Table 23-2.

SUGGESTIONS FOR USE

The prostanoids as a group are very effective ocular hypotensive agents. They lower IOP in most patients with primary and secondary open-angle glaucoma. They are particularly effective compared to other classes of medications in reducing IOP in patients with normal-pressure glaucoma. The effectiveness of these agents is not affected by episcleral venous pressure, so they can be used in the glaucomas that are associated with elevated episcleral venous pressure such as dysthyroid ophthalmopathy and Sturge-Weber syndrome. They are also useful in the residual glaucoma following iridotomy in angle-closure glaucoma.

The prostanoids have become the primary medical treatment for both open-angle glaucoma and angle closure (after iridotomy if

cost reasons; the switch was well tolerated by 85% of the patients and there was a slightly lower IOP with bimatoprost compared to latanoprost.²⁵⁹ In a prospective study, greater than 95% of patients tolerated a switch from latanoprost to travoprost without significant side effects or change in efficacy.²⁶⁰ Two studies have shown some advantage of using bimatoprost in patients not controlled on latanoprost.^{119,126} A recent retrospective study of a large health plan database showed that patients are more likely to need adjunctive medication with latanoprost than with either bimatoprost or travoprost.²⁶¹ Other evidence suggests a greater cost-effectiveness in reaching target pressure with bimatoprost compared to latanoprost.^{262,263} The Ocular Hypertension Treatment Study was unable to show any difference in effectiveness of the prostaglandin analogs based on race.²⁶⁴ In separate studies, both travoprost and bimatoprost have been shown to be slightly superior to latanoprost in exfoliative glaucoma patients.²⁶⁵

In all studies, the incidence of hyperemia is higher with both travoprost and bimatoprost than latanoprost. Therefore, on average, there may be little to choose between the agents. However, based on the above, when all other things are equal (e.g., cost, accessibility, acceptability of side effects), latanoprost is a good agent to try first as monotherapy in newly diagnosed glaucoma, but if it does not adequately lower the IOP, then bimatoprost or travoprost should be tried before resorting to multiple agent therapy. Travoprost may be the best agent if adherence to the treatment regimen is in question since it seems to be more forgiving to occasional forgotten doses.

Some evidence suggests that concomitant use of non-steroidal anti-inflammatory agents, either topical or oral, may reduce the pressure-lowering effect of latanoprost.²⁶⁶

Because of their propensity to exacerbate (or possibly cause) uveitis, prostanoids should be used with extreme caution in those patients with active uveitis or a recent history thereof. Patients with a remote history of uveitis should be monitored closely in the first few months of treatment. In addition, latanoprost should be used with great caution in those with active or recent cystoid macular edema or high risk factors for it (e.g., aphakia, recent cataract surgery, vitrectomy or discission, retinitis pigmentosa, active diabetic retinopathy). If any of these agents are used, both the patient and the doctor should monitor vision closely, and the fundus should be carefully perused periodically for signs of macular edema. Ocular coherence tomography is a useful adjunct in this monitoring. At the first sign of vision decrease that could be ascribed to cystoid macular edema or anatomic evidence of macular edema, the prostanoid should be discontinued.

The three major agents, latanoprost, travoprost, and bimatoprost, are best used as a once-daily dose given in the evening. Latanoprost seems to be more effective when given in the evening than when given in the morning over the first 6 months of treatment.⁶³ After 6 months of evening dosing, 69% of the patients had IOPs less than 17 mmHg, whereas only 34% of those with morning dosing had IOPs under 17 mmHg. Subsequent data suggest that after 3 months of treatment, morning and evening dosing produces the same results. Presumably (but not proven), the same could be said for bimatoprost; however, travoprost seems to perform slightly better when administered at night (see above). If the medication is to be used over a long period of time and compliance is a problem, consideration should be given to morning dosing. For all of these agents (except unoprostone), twice-daily dosing is probably less effective than once daily, possibly because of the development of receptor tolerance.⁵⁶ If the evening dosing is chosen, within 1 or 2 months after initiating therapy, IOP should be checked late in the day to see if the effect holds over the full 24 hours. If it does not,

consideration should be given to switching to travoprost which seems to have a somewhat longer duration of action.²⁶⁷ Similarly, if morning dosing is chosen, IOP should be checked early in the morning before instilling the drop.

Patients should be counseled that the bottle in which latanoprost is sold is made of a soft plastic unlike that of other eyedrop preparations with which he or she may be familiar. The bottle is designed to deliver one drop by simple gravity when held upside down or by gently tapping on the bottom; squeezing the bottle will produce a rivulet of medication on the cheek – an expensive waste. If a patient has arthritis or otherwise has difficulty maneuvering the bottle properly, Pfizer has available a trigger-operated dispenser that some of these patients find quite useful in delivering just one drop (XalEase™). Other companies have similar aids for drop delivery. Different manufacturers' bottles may require slight modification of instillation for most efficient use.²⁶⁸

The latanoprost (Xalatan™) bottle should be refrigerated if it will be open for longer than 6 weeks. This is usually not a problem unless the solution is used unilaterally or the patient maintains more than one open bottle at a time. Latanoprost is subject to deterioration when exposed to heat over 100°F for longer than 8 days (Xalatan package insert, Pfizer, NY). The other prostanoids seem to be somewhat more stable at temperatures likely to be found in most natural settings. All agents may deteriorate at an accelerated pace when exposed to direct sunlight.

Isopropyl unoprostone (Rescula™) is significantly less potent than latanoprost. It must be used twice daily. It may be somewhat better tolerated, with fewer and milder side effects, but this has not been tested in a side-by-side comparison. Because of its relatively low potency, unoprostone is not used much in the United States although it may be useful if pressure reduction goals are modest. The indications and cautions for the other agents apply to unoprostone as well.

The fixed combinations of a prostanoid and timolol do not seem to offer much additional pressure lowering over the prostanoids themselves except in an occasional patient. In fact, one study showed bimatoprost to be at least as good as the fixed combination of latanoprost and timolol.²⁶⁹ When adjunctive therapy is needed, better clinical results seem to be had using either a carbonic anhydrase inhibitor or brimonidine concomitantly with the prostaglandins rather than a β -blocker.²⁷⁰ Not all studies agree that timolol adds relatively little to the pressure-lowering effect of the prostaglandins;²⁷¹ therefore, after bimatoprost has been tried and is still not controlling the IOP, one of the prostaglandin/timolol combinations may be tried, especially if the patient would benefit from the convenience and adherence-enhancing effect of a single drop.

Hyperemia is a frequent side effect but often lessens after a few weeks. Patients should be notified about this so that they do not become alarmed. If the patient is warned, the hyperemia rarely is a cause for discontinuation of the medication. Iris color should be monitored by patient and doctor. Baseline photographic documentation may be helpful to detect early changes. Patients with gray-brown, blue-brown, hazel, or green-brown irides should be warned about iris color change and its permanence. If cosmesis is a concern to the patient, consideration should be given to alternative medications if possible. Similarly, patients should be warned that their eyelashes may grow longer and darker and may proliferate. Most patients will not mind this at all, but, again, if it may be a problem, consideration should be given to an alternative. Occasionally, patients may have to trim their lashes in order to prevent rubbing on the inside of spectacles. Because an increase of eyelid hair and

pigmentation of the eyelid skin are also potential side effects, they should be included in the warnings.

Because systemic side effects may be subtle and not usually associated with topical eyedrop medications, the patient should be asked specifically about myalgia, joint pain, headache, and bitter taste. Rarely are the systemic symptoms enough to warrant discontinuation. If systemic side effects become significant, eyelid closure and punctal occlusion should be tried before discontinuing.

The prostanoids have not been tested extensively in children or infants, although the studies that exist show moderate efficacy and

no unusual or unexpected side effects in this group.⁹⁵ There is little reason to withhold use if vision is threatened. Data regarding use in pregnancy are absent. Given the fact that prostaglandins are used to initiate labor, these agents should probably be avoided during the last phases of pregnancy, if possible.²⁷²

The appearance of the prostaglandin-like agents in the 1990s was as much a revolution in the medical treatment of glaucoma as the β -blocker agents were in the 1970s. We are indebted to Lazlo Bito (and his co-workers) for his foresight, persistence, and hard work in bringing them from the laboratory to the clinic.

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CHAPTER
24

The adrenergic system and adrenergic agonists

Adrenergic agonists have been used as ocular hypotensive agents since 1900 when Darier¹ treated glaucoma patients with subconjunctival injections of epinephrine. Two decades later, Hamburger² applied epinephrine topically to reduce intraocular pressure (IOP). Then epinephrine drugs fell into disrepute for years because the agents were unstable in solution and were capable of precipitating or aggravating angle-closure glaucoma. With the development of gonioscopy, which allowed more correct classification of the glaucomas, and with the availability of antioxidants to stabilize solutions, the epinephrine agents again assumed a major role in the treatment of glaucoma until the advent of the β -blocking agents.

Despite the fact that epinephrine has been used as a treatment for glaucoma since the beginning of the twentieth century, we still lack a complete understanding of the mechanism(s) by which, at least some, adrenergic agents reduce IOP (see section on mechanism(s) of action, pp. 377–8, for a more detailed discussion).

A brief review of the anatomy and physiology of the sympathetic nervous system may be helpful in understanding what is known about the action of adrenergic agents. The first-order sympathetic fibers arise in the hypothalamus and descend to the intermediolateral horn of the lower cervical and upper thoracic spinal cord. The second-order neurons pass through the white rami communicantes into the sympathetic chain and synapse in the superior cervical ganglion. The third-order neurons travel to the eye with the branches of the carotid artery, where they innervate a variety of tissues, including smooth muscle of the uveal vessels and iris dilator, as well as the ciliary processes.

Three main endogenous transmitters – norepinephrine, epinephrine, and dopamine – mediate the effects of the adrenergic system. Most adrenergic agents act directly or indirectly as either agonists or antagonists at neuroeffector junctions by binding to receptors located on the cell. Through the pioneering work of Ahlquist³ and Lands and co-workers,⁴ we now know that there are a variety of adrenergic receptors that are classified by their location and relative affinity for different agonists and antagonists. Currently five major types are recognized: α_1 , α_2 , β_1 , β_2 , and β_3 . Subtypes of both α_1 and α_2 have been identified throughout the body and in the eyes of both rabbits and humans.^{5,6} In the eye, stimulation of α_1 -receptors causes mydriasis, vasoconstriction, elevation of IOP, and eyelid retraction, whereas stimulation of α_2 -receptors causes decreased aqueous humor formation and, probably, increased outflow of aqueous. Obviously, inhibition of a particular receptor type will cause the opposite effect. Many agents have effects on more than one receptor type, causing a complicated and occasionally paradoxical response. Adrenergic agents in clinical use or of interest clinically include combined α and β agonists (e.g., epinephrine), α_2 agonists (e.g., brimonidine), α_1 and α_2 agonists (e.g., apraclonidine),

β agonists (e.g., isoproterenol), α antagonists (e.g., bunazosin), and β antagonists (e.g., timolol). A summary of the adrenergic receptors is given in Table 24-1.

Norepinephrine is the neurotransmitter at most sympathetic neuroeffector junctions. Norepinephrine is stored in synaptic vesicles in the cytoplasm of axon terminals, is released in response to nerve impulses, and diffuses across the junction to the effector organ. Norepinephrine is removed from active sites by a variety of mechanisms. Generally, norepinephrine is removed by active reuptake into axon terminals, where it either is metabolized or re-enters storage granules. Other pathways for norepinephrine removal include uptake into non-neuronal tissue, diffusion away from the active site, and metabolism by the enzymes monoamine oxidase and catechol *O*-methyltransferase.

Epinephrine is a circulating neurohumoral factor synthesized and released by the adrenal medulla. It is carried to local effector sites by the circulation. Epinephrine is mostly metabolized by the enzymes monoamine oxidase and catechol *O*-methyltransferase; a small portion of the circulating epinephrine is removed by active uptake into tissue.

When an agonist binds to a β -adrenergic receptor, the target cell goes from its normal state to an activated state. Coupling proteins are then released that activate the enzyme adenylyl cyclase, causing one of several known ‘second’ messengers to be synthesized and released into the cell. These second messengers – including Ca^{++} , cyclic adenosine monophosphate (cAMP), inositol triphosphate, and cyclic guanosine monophosphate – regulate protein phosphorylation, which, in turn, can cause changes in the cell metabolism, sensitivity, membrane permeability, or ion transport.^{7,8}

The mechanism by which α -receptors alter cellular metabolism is not as clear. It is postulated that the α_2 -adrenergic receptor is coupled in an inhibitory fashion to adenylyl cyclase.⁹ Activation of α_1 -adrenergic receptors stimulates turnover of membrane phosphoinositol and mobilizes intracellular calcium.^{10,11}

A number of substances called antagonists bind competitively to adrenergic receptors without triggering receptor action. These compounds inhibit neurotransmitters or agonists from stimulating adrenergic function. However, some antagonist agents also possess some capacity to stimulate adrenergic receptor sites; these agents are said to have intrinsic sympathomimetic activity (see Ch. 25).

When adrenergic receptors are stimulated by an agonist for some time, subsensitivity may develop; this phenomenon might be related to internalization of the cell surface receptors (i.e., down-regulation of receptors). Conversely, when receptors are exposed to an antagonist or receive defective neurotransmission over time, supersensitivity develops.¹² Denervation supersensitivity develops rapidly and is related to the loss of the neural tissue that ordinarily

Table 24-1 Systemic adrenergic receptors

Receptor	Location	Function	Agonist	Specific antagonist	Response to agonist
α_1	Postsynaptic, blood vessel, smooth muscle	Vasoconstriction	Methoxamine, Phenylephrine, Clonidine, Apraclonidine	Prazosin, Phenoxybenzamine, Bunazosin	$E \geq NE > I$
α_2	Presynaptic/ postsynaptic	Inhibit neurotransmitter release (e.g., norepinephrine)	Clonidine, Brimonidine, Apraclonidine	Yohimbine	$E \geq NE > I$
β_1	Cardiac muscle	Cardiac excitability and contraction	CGP 7760B	Atenolol, Practolol, Metoprolol, Betaxolol	$I > E = NE$
β_2	Blood vessel, smooth muscle, bronchi, gastrointestinal tract	Vasodilation, relax bronchial and gastrointestinal smooth muscle	Salbutamol	Butoxamine	$I \geq E > NE$

E, Epinephrine; NE, norepinephrine; I, isoproterenol.

removes agonists from the receptor sites. Non-denervation supersensitivity develops more slowly and consists of an increased response to ordinary concentrations of agonists at the receptors. In some cases, this may be related to an increased number of cell surface receptors (i.e., upregulation of receptors).

MECHANISM(S) OF ACTION

EPINEPHRINE

For many years it was generally thought that epinephrine lowered IOP by means of an early β -adrenergic-mediated effect decreasing aqueous humor production^{13,14} and a late α -adrenergic-mediated effect increasing outflow facility.^{15,16} However, recent studies have cast doubt on this theory. Unfortunately, some of the recent studies have yielded conflicting results rather than a new consensus concerning the mechanism by which epinephrine reduces IOP. Other important considerations in attempting to interpret the literature on this subject include species differences, an undue emphasis on short-term rather than long-term studies, and the difficulty in explaining the response of aged, human eyes with glaucoma by extrapolating results from experiments performed in young, healthy animal eyes.

The most widely accepted hypothesis regarding the ocular hypotensive effect of epinephrine is that it increases both conventional and unconventional outflow from the eye. Some investigators ascribe the effect of epinephrine on trabecular outflow to α -adrenergic receptors,^{17,18} to β -adrenergic receptors.^{19,20} The latter theory is supported by experiments in primates, which find that analogs of cAMP increase outflow facility²¹ and that the improved outflow of aqueous produced by epinephrine is blocked by pretreatment with timolol.²² On the other hand, approximately half of the increased outflow facility induced by epinephrine can be inhibited by indomethacin.²³ Whether this means that the prostaglandin system is involved in the epinephrine effect is not clear. A recent study confirms that prostaglandins may play some role in the effectiveness of epinephrine at least in rabbits.²⁴ Evidence in

rabbits also suggests that topical epinephrine causes adenosine release into the anterior chamber which may play an important role in its ocular hypotensive effect.²⁵

The influence of epinephrine on aqueous humor outflow is not abolished by detaching the ciliary muscle, suggesting a direct effect on the outflow channels.²⁶ Alvarado and co-workers showed that epinephrine in tissue culture opens the extracellular spaces of human Schlemm's canal endothelium and trabecular meshwork cells in tissue culture through a β -adrenergic-mediated mechanism.²⁷ Some authorities believe that the effect on uveoscleral outflow is greater than the effect on conventional outflow.¹⁷ This theory is supported by experiments in lower primates.²⁸ Some tonographic studies in humans suggest that the full effect of epinephrine on aqueous outflow may not develop for several months.¹⁵

Studies using fluorophotometry indicate that short-term epinephrine treatment produces a small increase rather than a decrease in aqueous humor formation.^{17,23} An increase in aqueous flow is also seen after administration of other β -adrenergic agonists such as salbutamol and metaproterenol;²⁹ this effect is blocked by the β -adrenergic antagonist timolol³⁰ but not the α -adrenergic antagonist thymoxamine.³¹ There is a small α -adrenergic effect, decreasing aqueous humor production, but this is only recognized after inhibition of β -adrenergic stimulation.²⁹ Thus the effect of epinephrine on IOP is a summation of several processes. The major therapeutic effect seems to be an increase in the outflow of aqueous via both conventional and unconventional pathways. Stimulation of cAMP is associated with at least some of this effect. Epinephrine seems to have little long-term effect on aqueous humor formation.³²

It is important to stress that the mechanism just outlined is controversial and disputed by many investigators. Some studies show that epinephrine treatment actually decreases aqueous humor formation.¹³ The findings of these studies are based on tonography, which does not measure aqueous production directly. However, a few studies using fluorophotometry also find an epinephrine-induced decrease in aqueous flow.²⁹ This apparent contradiction cannot be explained at present.

Pretreatment of rabbits with small doses of dexamethasone seems to facilitate the effect of even small doses of epinephrine. What

the mechanism of this effect might be, whether this effect holds for humans, and whether it can be used clinically remain conjectural.³³

A number of other theories have been proposed to explain the reduction in IOP after epinephrine treatment, including those that follow:

1. Decreased episcleral venous pressure. Epinephrine produces vasoconstriction and decreased episcleral venous pressure, but these effects are generally short-lived and do not explain the long duration of ocular hypotension.³⁴ Furthermore, drugs such as phenylephrine that produce vasoconstriction have little effect on IOP, whereas adrenergic drugs such as isoproterenol that do not produce vasoconstriction reduce IOP.
2. Alteration of pressure relationships in the intrascleral vascular plexus.³⁵
3. Destruction of adrenergic nerve terminals.^{36,37}
4. Reduction in the effective number of β -adrenergic receptors.³⁸
5. Induction of adrenergic supersensitivity.³⁹ It is possible that numbers 3, 4, and 5 are related.
6. Increase in prostaglandin synthesis.⁴⁰
7. Activation of lysosomal hyaluronidase, leading to an alteration in the components of the trabecular meshwork.⁴¹
8. Movement of fluid into the ciliary channel. Because the optic vesicle invaginates during embryologic development, the polarity of the non-pigmented epithelial cells of the ciliary body is reversed (i.e., fluid moves from the apex of the non-pigmented epithelial cells across the basal-lateral membranes into the posterior chamber). It is postulated that β -adrenergic stimulation increases fluid movement into the space between the pigmented and non-pigmented epithelial layers. This accumulation decreases net fluid flow into the posterior chamber.⁴²

None of these alternative theories has sufficient proof at present to warrant acceptance.

DIPIVEFRIN

Dipivefrin is a prodrug, which means that it must undergo biotransformation before exhibiting its pharmacologic effect. Dipivefrin itself has limited sympathomimetic activity until it is converted to epinephrine by esterase enzymes in the cornea and other tissues.⁴³ Dipivefrin, a synthetic analog of epinephrine, is created by adding two pivalic acid side chains to the parent molecule (Fig. 24.1).⁴⁴ This increases the lipid solubility of the compound by 600 times and the ocular penetration by 17 times when compared with epinephrine.⁴⁵ Thus administering dipivefrin in a low concentration produces a substantial intraocular concentration of epinephrine.

The assumption that dipivefrin functions strictly by conversion to epinephrine is questioned by at least one investigator.⁴⁶ It is known that dipivefrin is converted to a number of metabolites other than epinephrine, including 3-monopivalic acid, 4-monopivalic acid, and dipivalyl mandelic acid. The activity of these metabolites is unknown. Dipivefrin in its unmetabolized form also binds to β -adrenergic receptors in one animal model.³⁸ The significance of this observation is unclear at the present time.

NOREPINEPHRINE

Because norepinephrine is the normal postganglionic mediator of the adrenergic nervous system, the drug might be expected to have

a profound effect on aqueous humor dynamics. Intracameral norepinephrine produces a significant decrease in IOP by increasing the trabecular outflow facility; this is the case even when the ciliary muscle is disinserted, suggesting a direct effect on the trabecular meshwork.⁴⁷ Norepinephrine administered topically as a 2–4% solution does decrease IOP, perhaps through an α -adrenergic-mediated effect on outflow facility.^{48,49} However, the IOP-lowering effect of topical norepinephrine in humans is too modest for clinical effectiveness, perhaps because of limited ocular penetration or substantial neuronal reuptake.⁵⁰

When administered to rabbits, norepinephrine causes a biphasic alteration in IOP.⁵¹ The effect in animals is potentiated by bilateral cervical ganglionectomy⁵² and a variety of drugs, including monoamine oxidase inhibitors,⁵³ tetracaine, cocaine,⁵⁰ and corticosteroids.⁵⁴ In most cases, the apparent potentiation is caused by decreased neuronal uptake and by increased ocular penetration of norepinephrine as a result of altered corneal permeability.

α_1 -ADRENERGIC AGONISTS

Phenylephrine

Phenylephrine hydrochloride is a potent synthetic sympathomimetic agent that differs from epinephrine in that it lacks a hydroxyl group on the 4 position of the benzene ring (see Fig. 24-1). The drug acts predominantly on α_1 -adrenergic receptors and is used topically in concentrations of 0.125–10% to induce vasoconstriction or mydriasis or to break posterior synechiae. Following instillation of topical phenylephrine, mydriasis reaches a maximum in 60–90 minutes with recovery by 6 hours. Phenylephrine can produce mydriasis even in patients treated with strong miotics. The drug is often used in combination with, or as a diluent for, echothiophate to prevent the development of cysts of the iris pigment epithelium.⁵⁵ Phenylephrine produces a slight fall in IOP but is of little use in the chronic therapy of glaucoma. Occasionally topical phenylephrine administration produces an increase in IOP from the release of iris pigment particles.⁵⁶ This phenomenon may be more common in patients with the pigment dispersion syndrome or pigmentary glaucoma. Phenylephrine also has the capability of triggering an attack of acute angle closure in susceptible eyes.

α_2 -ADRENERGIC AGONISTS

The α_2 -adrenergic agonists reduce IOP largely by decreasing aqueous formation.^{57,58} Topical α_2 agonists have been studied and used for their ability to lower IOP for over a quarter of a century.^{59,60}

Clonidine

The first such α_2 -adrenergic agonist, clonidine, an imidazole derivative, is used as an antihypertensive agent. The drug acts principally as a central and peripheral α_2 agonist, thereby inhibiting norepinephrine release and suppressing sympathetic outflow to the cardiovascular system. The drug also acts as an α_1 agonist and α_1 and α_2 antagonist in some situations.

Applied topically to normal and glaucomatous eyes in concentrations of 0.125% and 0.05%, clonidine lowers IOP for 6–8 hours.⁶¹ The 0.15% concentration of clonidine is slightly less effective in reducing IOP than 2% pilocarpine.^{61,62} There is controversy concerning the mechanism by which clonidine lowers IOP; most investigators believe clonidine acts through central and peripheral adrenergic mechanisms to reduce aqueous humor formation by

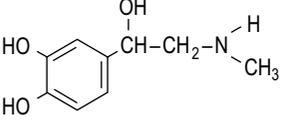
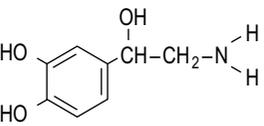
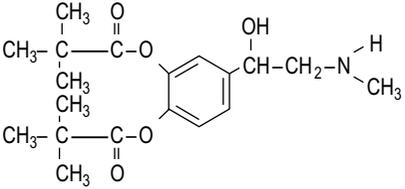
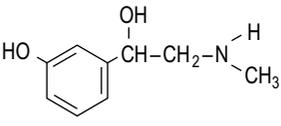
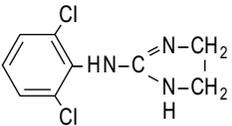
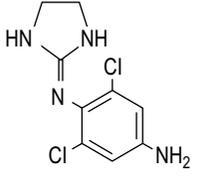
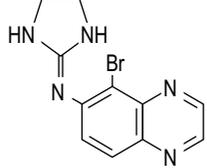
Adrenergic agonist	Formula	Dose
Epinephrine		0.25%-2% q 12-24 hr
Norepinephrine		2%-4% q 12-24 hr
Dipivefrin (Propine)		0.1% q 12 hr
Phenylephrine (Neosynephrine, Mydrin)		0.125%-10% q 10 min-12 hr
Clonidine (Catapres)		0.125% q 8 hr
Apraclonidine (Iopidine)		0.5%-1.0% q 8-12 hr
Brimonidine (Alphagan)		0.2%-0.5% q 8-12 hr

Fig. 24-1 Clinical adrenergic agonists.

means of vasoconstriction in the uveal tract.^{57,63,64} A few investigators note a small increase in outflow facility, but most detect little or no change.^{57,62} Clonidine also produces a transient reduction of episcleral venous pressure.⁵⁷ The drug apparently requires an intact central nervous system to lower IOP. Clonidine is known

to bind to α -receptors in rabbit ciliary body-iris preparations.³⁸ When the α_2 -receptors in the rabbit ciliary body are stimulated, they appear to couple with adenylate cyclase in the cell membrane to inhibit the synthesis of cAMP and thus inhibit aqueous production.⁶⁵ Therefore both α_2 -adrenergic stimulation and β -adrenergic

blockade will decrease aqueous humor formation. The effects are synergistic as documented by several clinical studies.^{66–68}

Apraclonidine

A derivative of clonidine, apraclonidine was found to act similarly to clonidine without the systemic side effects.^{69,70} The basic clonidine molecule is altered by having an amino group in the paraposition of the benzene ring. This alteration reduces the ability of the drug to penetrate the blood–brain barrier and thus reduces the risk of systemic hypotension.^{71,72} The agent was originally called par-amino-clonidine but was subsequently renamed apraclonidine. Its mechanism of action for lowering IOP is presumably the same as that of clonidine. Apraclonidine, like clonidine, may reduce episcleral venous pressure and, unlike clonidine, may increase trabecular outflow.^{73,74} Both clonidine and apraclonidine have some α_1 - and α_2 -adrenergic agonist activity.⁶³ Therefore some of the effect of the agents may be due to anterior segment vasoconstriction, which causes decreased blood flow to the ciliary body and consequent decreased aqueous formation.⁷⁵

Brimonidine

More recently, another α_2 -adrenergic agonist, brimonidine, has been identified as a potent ocular hypotensive agent.⁷⁶ Brimonidine is much more selective than clonidine and apraclonidine for α_2 -receptors. Like its pharmacologic cousins, it decreases IOP by reducing aqueous formation; in addition, it acts by increasing uveoscleral outflow.^{77,78} Furthermore, brimonidine seems to have the additional property of neuroprotection, at least in some animal models and in some small human studies.^{79–82} Because of its effectiveness and relatively low side effect profile compared to other adrenergic agonists, brimonidine has become the most commonly used antiglaucoma medication of this group of agents. Brimonidine's effectiveness may be reduced by concomitant administration of non-steroidal anti-inflammatory agents; this has implications both for its mechanism of action as well as in clinical use.⁸³

Brimonidine was first marketed in a 0.2% solution. However, more recently it has been produced in a 0.15% and even 0.1% solution. These latter solutions seem to be equally effective as the 0.2% solution with possibly reduced systemic and topical side effects. In addition, the use of preservatives other than benzalkonium chloride (e.g., polyquaternarium, Purite™) seems to reduce some of the topical side effects of brimonidine.⁸⁴ Brimonidine has been combined with timolol in a fixed combination with comparable results to the separate, concomitant medications.⁸⁵ Brimonidine can produce cardiovascular instability in infants and is therefore contraindicated in the first 5 years of life. Sleepiness and lethargy are relatively common side effects in children and thus these agents should be avoided in those under 15 years of age if possible.⁸⁶ Topical brimonidine (as well as some β -blocking agents and prostaglandin derivatives) alters the expression of matrix metalloproteinases and their inhibitors in corneal cells and thus may contribute to ocular surface disease.⁸⁷ Whether this is an effect of the agent directly or is caused by or affected by the preservative remains to be demonstrated.

β -ADRENERGIC AGONISTS

Isoproterenol

Isoproterenol is a non-selective β -adrenergic agonist having essentially equal activity at β_1 - and β_2 -receptors. Applied topically in concentrations of 1–5%, isoproterenol lowers IOP with little effect on pupillary diameter or accommodation.⁸⁸ The usefulness of the drug is limited by systemic side effects such as tachycardia, dysrhythmias,

and palpitations.⁸⁸ The *D*-isomer of isoproterenol lowers IOP in rabbits without producing cardiovascular changes but is inactive in primate and human eyes.⁸⁹

Salbutamol

Salbutamol (albuterol) is a selective β_2 -adrenergic agonist. Topical application of a 4% solution lowers aqueous humor production and IOP for up to 48 hours.⁹⁰ Clinical usefulness of the drug is limited by rapid tachyphylaxis and symptoms of conjunctival hyperemia and pain.

Others

Other selective β_2 -adrenergic agonists such as terbutaline, soterenol, and reproterol lower IOP in laboratory animals and man.^{90–92}

DOPAMINERGIC AGONISTS

Dopaminergic agents stimulate dopamine receptors (either type 1 or type 2 or both). In addition, most of these agents also stimulate α -adrenergic receptors (both α_1 and α_2). Stimulation of some dopamine receptors and α -adrenergic receptors shares the inhibition of cAMP release.⁹³ Dopamine lowers IOP by reducing aqueous humor formation.⁹⁴ Agonists having selective dopamine₂ receptor activity such as lergotril and pergolide appear to be better ocular hypotensive agents than dopamine itself.⁵² However, some of the same dopamine agonists can raise IOP in eyes with glaucoma.⁹⁵ Furthermore, some dopamine antagonists can lower IOP perhaps by inhibiting dopamine₁ receptors.⁹⁶ Likely, several subtypes of dopamine receptors with different actions exist; which ones are active in the eye, what they do, and how they interact with the α - and β -adrenergic receptors remain to be elucidated.

The dopamine receptor agonist bromocriptine lowers IOP in human eyes when administered orally or topically.^{97,98} This effect is blocked by intravenous metoclopramide, a dopamine₂ antagonist, suggesting that this agonist is truly acting through dopamine receptors.⁹⁷ A selective dopamine₁ agonist, fenoldapam, has actually been shown to raise IOP in humans possibly by activation of adenylyl cyclase.⁹⁹ None of the dopaminergic agents have found their way into active clinical use.

ADRENERGIC POTENTIATORS

MONOAMINE OXIDASE AND CATECHOL O-METHYLTRANSFERASE INHIBITORS

There have been a number of attempts to potentiate the effects of endogenous epinephrine and norepinephrine or exogenously administered catecholamines with drugs that inhibit either monoamine oxidase or catechol O-methyltransferase. The monoamine oxidase inhibitors clorgyline, deprenyl,^{100,101} and pargyline lower IOP in rabbit eyes when administered topically. There is one report that topical clorgyline lowers IOP in glaucomatous human eyes.¹⁰² A catechol O-methyltransferase inhibitor has been shown to potentiate the effects of topical epinephrine on the pupil and IOP (i.e., the dose–response curve is shifted to the left so that the same response can be obtained with a lower dose of epinephrine in the presence of the inhibitor).¹⁰³ Up to now these drugs have been of limited clinical use for the treatment of glaucoma.

6-HYDROXYDOPAMINE

6-Hydroxydopamine has been used to enhance the IOP response to topical epinephrine treatment.^{104,105} The drug is taken up into peripheral nerves and causes a temporary degeneration of axon terminals. This produces a transient chemical sympathectomy and a supersensitivity to both α - and β -adrenergic agonists. 6-Hydroxydopamine is administered to the eye by iontophoresis or more commonly by subconjunctival injection. The 6-hydroxydopamine injection causes release of endogenous norepinephrine, which increases outflow facility and decreases IOP for a few days to 2 weeks.^{106,107} The purpose of the 6-hydroxydopamine injection, however, is not the transient ocular hypotensive response but rather the development of supersensitivity to α - and β -adrenergic agonists. The supersensitivity phase lasts a few weeks to 6 months and can be re-established by repeating the injection.¹⁰⁸ It appears that 6-hydroxydopamine shifts the dose-response curve for epinephrine to the left (i.e., the same maximal response to epinephrine is obtained with a smaller dose of the drug) but probably does not increase the maximum effect. Similar hypersensitivity can be produced in rabbit eyes with the drug α -methyl-para-tyrosine, an inhibitor of norepinephrine synthesis.¹⁰⁰

Although early investigators believed that the combination of 6-hydroxydopamine and topical epinephrine was capable of aiding a high percentage of uncontrolled glaucoma patients, later investigators found this was not to be true.¹⁰⁹ The drug is rarely used today, but even during the time of maximal popularity, it was reserved for those patients whose conditions were uncontrolled with more conventional therapy. Injections of 6-hydroxydopamine can produce conjunctival hyperemia, subconjunctival hemorrhage, transient mydriasis, chemosis, lid edema, and ptosis, which persist for a few days to a few weeks. Systemic side effects were rare.

PROTRIPTYLINE

Protriptyline, a tricyclic antidepressant drug, blocks neuronal reuptake of norepinephrine. There is one report that protriptyline prolongs the ocular hypotensive response to norepinephrine.¹¹⁰ Other investigators failed to confirm this finding.

GUANETHIDINE (ISMELIN)

Guanethidine is a sympatholytic drug that acts by displacing norepinephrine from postganglionic sympathetic nerve endings. The drug depletes tissue stores of norepinephrine, decreases reuptake of norepinephrine by the nerve terminals, and lowers sympathetic tone.¹¹¹ Topical application of 5–10% guanethidine releases norepinephrine from nerve endings, leading to mydriasis, increased outflow facility, and decreased IOP. However, guanethidine alone is of little benefit in the long-term treatment of glaucoma. The drug is administered to produce a chemical sympathectomy and a supersensitivity to topical epinephrine.¹¹² Combinations of guanethidine (1–5%) and epinephrine (0.05–1%) are capable of lowering IOP in a wide variety of glaucoma conditions.^{113,114} Some investigators believe the combination of guanethidine and epinephrine is more effective than either agent alone, whereas other investigators believe the combination merely displaces the dose-response curve to the left. Topical guanethidine can produce discomfort, soreness, conjunctival hyperemia, superficial punctate keratitis, lid edema, and ptosis. Side effects are common. Although it was popular for a while in Europe, the drug never gained much headway as part of

the antiglaucoma regimen in the United States, either alone or in combination.

NONADRENERGIC ACTIVATORS OF ADENYLATE CYCLASE

A number of agents that bypass the β -adrenergic receptor and stimulate the adenylate cyclase system by nonadrenergic mechanisms also lower IOP. For example, cholera toxin administered intravitreally or by close arterial injection reduces IOP in animals.¹¹⁵ Similarly, organic fluorides¹¹⁶ and a number of gonadotropic hormones – including luteinizing hormone, thyroid-stimulating hormone, and follicle-stimulating hormone – act as ocular hypotensive agents. The best studied drug in this class is the plant derivative forskolin (non-proprietary name colforsin). Forskolin administered topically or intravitreally lowers IOP in rabbit and monkey eyes.^{117,118} Its proposed mechanism of action is to decrease aqueous formation by increasing cAMP formation; exactly how this would work has not been satisfactorily explained. This appears to be its mechanism of action in rabbits,¹¹⁹ however, forskolin seems to have little effect on the formation of aqueous humor in man.¹²⁰ In early experiments in human eyes, topical 1% forskolin reduced IOP for at least 5 hours.¹¹⁸ Forskolin also potentiates the effect of epinephrine in reducing both aqueous formation and IOP, possibly by increasing the permeability of the blood-aqueous barrier.¹¹⁹ However, multiple dosing in glaucomatous monkey eyes showed development of tachyphylaxis within 24 hours.¹²¹ This, plus a poor corneal penetration rate, have limited its use as an antiglaucoma drug.¹²² Because some forskolin analogs also reduce IOP, perhaps one or more will be found that penetrates the cornea better and produces little or no tachyphylaxis.¹²³

Clearly, the adrenergic system is complex; the mechanisms involved are elusive, and no single theory is fully able to explain why combined α - and β -adrenergic agonists such as epinephrine and dipivefrin, β -adrenergic agonists such as isoproterenol, α_2 agonists such as apraclonidine and brimonidine, α_1 antagonists such as bunazosin, and β antagonists such as timolol all are effective at lowering IOP – even in combination. Perhaps many of these mechanisms are active, and which one(s) predominate may be determined by dose, timing, and individual sensitivity, as well as other unidentified physiologic and pharmacologic factors.

DRUGS IN CLINICAL USE

The agents currently in clinical use, likely to be so in the near future, or of interest to this discussion include the combined α and β agonists (non-selective), the β agonists, the α_2 agonists, the α_1 antagonists, and the β antagonists (Table 24-2). However, of all these agents, brimonidine is the one that has the most use. See Chapter 25 for a discussion of the α - and β -blocking agents.

COMBINED α AND β AGONISTS (NON-SELECTIVE)

Epinephrine (Eppy, Epinal, Epifrin, and generics)

Epinephrine stimulates both α - and β -adrenergic receptors. It is manufactured for topical ophthalmic use in three different

Table 24-2 Adrenergic agents

Drug type	Effect on intraocular pressure	Mechanism	Site and action
Agonists			
α_1 (e.g., phenylephrine)	Mixed		Vasoconstriction
α_2 (e.g., clonidine, brimonidine, apraclonidine)	Decreases	Decreases aqueous formation, increases trabecular outflow (apraclonidine), increases uveoscleral outflow (brimonidine)	Inhibits ciliary epithelial adenylyl cyclase
β_2 (e.g., isoproterenol)	Decreases	Increases trabecular outflow, decreases aqueous formation (?)	Trabecular cell β receptor; ciliary body epithelium β receptor
Dopamine ₁	Increases	Unknown	Stimulates adenylyl cyclase
Dopamine ₂	Decreases	Decreases aqueous formation	Inhibits ciliary epithelial adenylyl cyclase
Antagonists			
α_1	Decreases	Decreases aqueous formation (?), increases uveoscleral outflow (?)	Unknown
α_2	Decreases	Unknown	Unknown
β_1 and β_2	Decreases	Decreases aqueous formation	Ciliary epithelium β receptor; inhibits ciliary body adenylyl cyclase
β_2 (e.g., betaxolol)	Decreases	Decreases aqueous formation	Ciliary epithelium β receptor; inhibits ciliary body adenylyl cyclase
Dopamine	Decreases	Unknown	Unknown

salt forms – hydrochloride, bitartrate, and borate (see Fig. 24.1). Commercial preparations are usually described as the concentration of epinephrine salt rather than the concentration of available free epinephrine. This is important in the case of epinephrine bitartrate because a 2% solution contains approximately 1.1% epinephrine. When administered in equivalent doses, the hydrochloride, borate, and bitartrate salts appear to be equally effective in reducing IOP.¹²⁴

Hydrochloride solutions are stable and have been available in 0.5%, 1%, and 2% concentrations. However, hydrochloride solutions are rather irritating because they have a pH of approximately 3.5. Borate solutions have been available in 0.5% and 1% concentrations and are less irritating because they have a pH of 7.4.¹²⁵ Bitartrate solutions are stable but are also irritating because of low pH.

The commercial epinephrine preparations contain preservatives and antioxidants. The latter are particularly important because oxidized epinephrine solutions are less effective and more irritating. Patients should be warned to discard epinephrine preparations that are discolored or muddy in appearance. Because of their relative chemical instability and relatively high rate of side effects, epinephrine compounds have been largely replaced by the prodrug dipivefrin and by the α_2 agonist brimonidine.

The effect of epinephrine on IOP is proportional to the concentration of the drug, reaching a maximum in most patients with the 1% or 2% solution.^{126,127}

After topical administration of epinephrine, IOP begins to fall in 1 hour, reaches a minimum in 2–6 hours, and returns to baseline in 12–24 hours.¹²⁶ The effect of epinephrine on IOP appears to be additive with that of the miotics and the carbonic anhydrase inhibitors. However, combined treatment of epinephrine and non-selective topical β -adrenergic antagonists is often disappointing. It appears that only a minority of patients obtain a clinically useful additional long-term reduction of IOP when epinephrine is added to a topical β -adrenergic antagonist or vice versa.¹²⁸ (See Ch. 25 for a detailed discussion.)

Dipivefrin (Propine and generics)

Dipivefrin, 0.1%, is roughly equivalent in its ocular hypotensive effect to 1–2% epinephrine.^{129–131} Dipivefrin is supplied as a 0.1% solution that is administered every 12–24 hours. Following topical administration, IOP begins to fall in 30–60 minutes, reaches a minimum in 1–4 hours, and returns to baseline in 12–24 hours. Because dipivefrin produces its ocular hypotensive effect by biotransformation to epinephrine, there is no reason to administer epinephrine and dipivefrin concurrently. Dipivefrin has the same additive effect to β -antagonist medications that epinephrine does. On average, one can expect an additional reduction in IOP of about 2 mmHg when adding dipivefrin to timolol.¹³² However, individual responses vary greatly, and a trial may be worthwhile.

Dipivefrin produces less external irritation, burning, and systemic side effects than does epinephrine (see the section on side effects, p. 383). Although the advent of dipivefrin caused the epinephrine salts to fall into disuse, the introduction of the α_2 agonists has reduced the usefulness of dipivefrin because of their improved additivity to β -blocking agents.

Suggestions for use

In the recent past, epinephrine and dipivefrin were used widely for the treatment of open-angle glaucoma. In addition, the drugs were helpful in patients with secondary glaucoma and in patients with angle-closure glaucoma following an iridectomy. Because administration of dipivefrin produces lower blood levels of epinephrine, it is the non-selective adrenergic agent of first choice; this is especially true in those patients in whom systemic conditions might be exacerbated by increased levels of circulating epinephrine. Dipivefrin has largely replaced epinephrine, and in the discussion that follows, they are treated as the same unless otherwise noted.

Patients and family physicians should be warned that topical epinephrine/dipivefrin treatment can induce systemic side effects. Patients should be instructed to instill only one drop of medication

in each eye and to use punctal occlusion and simple eyelid closure to reduce systemic absorption. If epinephrine treatment is used, it should be initiated with a low concentration of the drug and increased as needed. The common practice of initiating therapy in all patients with 1% or 2% epinephrine should be discouraged because many patients receive maximum benefit from lower concentrations of the drug and because most of the side effects are dose related.^{126,133} Old, discolored solutions should be discarded because they are less effective and more irritating. Aphakic and, perhaps, pseudophakic patients should be warned of potential visual loss from macular edema and should test their vision weekly at home.

It is helpful to initiate epinephrine treatment with a unilateral trial because only 70% of glaucoma patients respond with a significant fall in IOP. Epinephrine has a slight contralateral effect on IOP, but this is unlikely to confuse the results of a one-eye trial.

It is well known that topical epinephrine/dipivefrin may produce mydriasis, potentially precipitating or aggravating angle-closure glaucoma. Mydriasis is more marked with concomitant β -adrenergic antagonists and may occur despite concomitant miotic treatment. Thus all patients require careful gonioscopy before and soon after initiating epinephrine treatment. Pupillary dilation may improve vision in some patients receiving miotic treatment, especially those with opacities of the media. Other patients may complain of decreased vision, perhaps from the loss of the pinhole effect or as a direct effect on the retina.

Side effects

More than 50% of patients started on long-term epinephrine treatment become intolerant to the drug.¹³⁴ This figure is considerably less with dipivefrin.¹³⁵ Most of the intolerance reactions are external in nature, including hyperemia, irritation, tearing, and blepharoconjunctivitis (Box 24-1). A minority of the intolerance reactions are systemic in nature, including palpitations, hypertension, and premature ventricular contractions. These are even less frequent with dipivefrin. It is important to emphasize that one drop of a 2% epinephrine solution contains 0.1 mg of the drug; this amount, if completely absorbed, is within the range of the usual systemic dose used for the treatment of an acute asthma attack (i.e., 0.1–0.5 mg).

Epinephrine treatment is contraindicated in a number of conditions, including severe hypertension, cardiac disease, and thyrotoxicosis.¹³⁹ Patients treated with drugs that block uptake of epinephrine and norepinephrine (e.g., reserpine) or that inhibit monoamine oxidase (e.g., phenylzine, tranylcypromine) or catechol O-methyltransferase are at greater risk of developing systemic side effects with epinephrine treatment. The safety of topical epinephrine treatment in children and pregnant women has not been fully tested.

Patients with primary open-angle glaucoma (POAG) may be more susceptible to the effects of epinephrine in the eye and in the body in general,¹⁴⁰ which may make them more likely to develop systemic side effects. In one study, 69% of the patients with POAG treated with epinephrine developed premature ventricular contractions as noted on tonography, as opposed to 19% of patients with secondary glaucoma.¹⁴¹ This kind of study has not been repeated with dipivefrin.

Epinephrine causes an initial vasoconstriction followed by a rebound vasodilation. Many patients receiving epinephrine eye-drops complain of conjunctival hyperemia either because of the cosmetic appearance or because of the implication of alcohol consumption. Some individuals, believing that topical epinephrine relieves the hyperemia, begin a pattern of overuse. This same scenario has been seen with the apraclonidine. Tearing and burning

Box 24-1 Epinephrine/dipivefrin side effects

Lid and conjunctiva

- Hyperemia
- Burning/stinging
- Tearing
- Blepharoconjunctivitis
- Skin blanching
- Adrenochrome deposits
- Madarosis¹³⁶
- Ocular pemphigoid^{137,138}

Lacrimal system

- Lacrimal stones

Cornea

- Epithelial edema
- Endothelial toxicity
- Epithelial erosion from tarsal adrenochrome deposits
- Adrenochrome deposits
- Soft contact lens staining

Iris and uveal tract

- Mydriasis and angle closure
- Visual distortion/blurred vision
- Photophobia
- Iridocyclitis

Retina

- Cystoid macular edema

Systemic

- Headache/browache
- Tachycardia/dysrhythmia
- Premature ventricular contractions
- Palpitations
- Anxiety/nervousness/pallor/faintness
- Tremor
- Increased blood pressure
- Cerebrovascular accident
- Myocardial infarction
- Death

on drug instillation are also common symptoms. Switching to dipivefrin or an epinephrine borate preparation can often relieve these symptoms.

Instilled epinephrine undergoes oxidation and polymerization to form adrenochrome, a pigment of the melanin family. Adrenochrome deposits are often found in the lower conjunctival cul-de-sac,^{142,143} where they may be mistaken for foreign bodies (Fig. 24-2). These deposits generally produce no symptoms because they are encapsulated by squamous epithelium. On the other hand, adrenochrome deposits in the upper tarsal conjunctiva have a branching or stag-horn appearance and can cause corneal epithelial abrasions.^{142,144} Adrenochrome material can also be deposited in the corneal epithelium, especially in the presence of increased IOP and bullous keratopathy.^{145–147} A diffuse plaque of adrenochrome covering the cornea can resemble a malignant melanoma.¹⁴⁶ Adrenochrome deposits in the conjunctiva may last for years even after discontinuation of the drug.

Adrenochrome material is frequently deposited in the lacrimal sac¹⁴⁸ and nasolacrimal ducts;¹⁴⁹ this can be responsible for nasolacrimal system obstruction and epiphora, especially after long-term use.



Fig. 24-2 Adrenochrome deposits in conjunctiva from epinephrine.



Fig. 24-3 Follicular conjunctival reaction typical of adrenergic agonists.

Actual adrenochrome calculi may be found or felt in the lacrimal drainage system. Stopping the epinephrine product may help, but resolution may take years or may require removal or dacryocystorhinostomy. Adrenochrome deposits occur more commonly when patients use old, discolored epinephrine solutions and when they have been applying the medication for prolonged periods of time.

Epinephrine drugs can produce a hypersensitivity blepharoconjunctivitis, including lid erythema, lichenification, and conjunctival chemosis, vascular engorgement, and follicular hypertrophy^{150,151} (Fig. 24-3). Occasionally this is accompanied by mild iridocyclitis and subepithelial infiltration of the cornea.¹⁵² Some patients who develop hypersensitivity blepharoconjunctivitis with epinephrine treatment can tolerate dipivefrin indefinitely.¹⁵³ Some have cross-reactivity.¹⁵⁴ Other patients can continue epinephrine treatment if a weak topical corticosteroid such as 1% medrysone is administered concurrently. Medrysone is unlikely to elevate IOP, even with long-term administration.¹⁵⁵

Epinephrine solutions stain soft contact lenses.¹⁵⁶ The stain can be removed by soaking the lenses for 5 hours in 3% hydrogen peroxide.¹⁵⁷ Dipivefrin is much less likely than epinephrine to produce a stain in soft contact lenses,¹⁵⁸ but patients should still be cautioned to remove the lenses before instilling the drops.

Topical epinephrine treatment produces macular edema in 10–20% of aphakic eyes.^{159,160} Dipivefrin can also cause cystoid macular edema, but perhaps less commonly.¹⁶¹ The mechanism for this condition is unknown; speculation has centered around ultraviolet radiation and, more recently, the possible release into the eye of prostaglandin analogs by the epinephrine and their interaction on the retinal vasculature.¹⁶² The combination of an adrenergic agonist and prostaglandin has been shown to disrupt the blood-retinal barrier in experimental animals.¹⁶³

The macular edema occurs after months to years of treatment. It is manifested by a gradual decline in visual acuity that may reach the level of 20/200. The condition appears to be reversible if the drug is discontinued, although resolution may require several months. If epinephrine treatment is not stopped, structural damage of the retina can produce permanent loss of central vision. The retinal findings and the appearance on fluorescein angiography resemble the petaloid pattern of aphakic cystoid macular edema.

Occasionally the area of edema is surrounded by fine retinal hemorrhages. The relatively high incidence of epinephrine-induced macular edema suggests that epinephrine drugs are not the first choice for aphakic eyes or pseudophakic eyes with open posterior capsules. However, epinephrine can be used if needed in such eyes provided that the patients test their vision weekly at home and the clinician is particularly careful to note any loss of vision. Even a small decrease in vision in an aphakic or pseudophakic eye receiving epinephrine or dipivefrin treatment requires a careful examination to determine if cystoid macular edema is present; if so, epinephrine treatment should be discontinued. Unfortunately, this condition is often not recognized because of the gradual nature of its clinical onset; the reduction in vision may be ascribed to other causes. It is unclear whether epinephrine-induced macular edema occurs as commonly after extracapsular cataract extraction as after intracapsular cataract extraction because the decline in the use of intracapsular surgery has paralleled a decline in the use of epinephrine. An intact posterior capsule may be a mechanical barrier to posterior movement of small molecules such as epinephrine.¹⁶⁴

A few patients receiving epinephrine may develop corneal haze or even frank edema despite good IOP control, causing complaints of halos and blurred vision. The symptoms and corneal findings abate after discontinuing the drug. In rabbits, epinephrine administered intramuscularly or by iontophoresis activates latent herpes simplex virus.^{165,166} There is no evidence that topical epinephrine treatment influences herpetic disease in humans.

There is some concern that epinephrine-induced vasoconstriction may compromise optic nerve perfusion. Some postulate that this effect is worse with unilateral treatment because the fellow untreated eye does not have a lowered IOP to offset any decrease in perfusion. Further studies of the effects of topical and systemic medication on optic nerve blood flow are required to resolve this issue.

There are a number of approaches to reduce or control the side effects related to epinephrine treatment. Systemic side effects can be reduced by using low concentrations of the drug, instilling only one drop in each eye, using punctal occlusion, and having the patient sit quietly with the eyelids closed for 2 minutes. Using a different salt or using a concomitant weak topical corticosteroid that does not cross the cornea, such as medrysone, can reduce a number of local side effects. Another approach to reducing side effects is to prescribe dipivefrin. Dipivefrin is stable in solution and produces a lower incidence of external irritation than standard epinephrine preparations. As noted previously, administering concomitant topical

medrysone twice daily can allow continued use of epinephrine products in the face of mild to moderate blepharoconjunctivitis.

Because dipivefrin produces a similar intraocular concentration of epinephrine, it is just as likely to produce macular edema in aphakic eyes or angle closure in eyes with narrow angles. However, because of the lower concentration of drug administered and the localized ability to convert it to epinephrine, dipivefrin produces fewer systemic side effects than epinephrine. Therefore dipivefrin is the drug of choice in this group of agents for any patient with substantial cardiovascular disease, poorly controlled hypertension, or any other condition in which systemic administration of adrenaline might be inadvisable.

α_2 AGONISTS

The α_2 agonists are relatively new antiglaucoma agents. Their mechanisms of action include decreasing aqueous formation, increasing trabecular outflow (apraclonidine), and increasing uveoscleral outflow (brimonidine). Apraclonidine is the agent that has been in clinical use in the United States the longest and has been more widely studied as an acute pressure-lowering agent and as a prophylactic agent. However, brimonidine, although newer, has become the more widely used agent and has had the more long-term clinical trials in open-angle and other forms of chronic glaucoma. Where appropriate (as in prevention of pressure spikes after laser surgery), they will be treated together.

Clonidine

Topical clonidine is generally well tolerated except for minor drowsiness and dryness of the mouth. Clonidine has little effect on pupillary diameter, accommodation, or visual acuity. The major problem with clonidine is the high incidence of cardiovascular side effects. In one study, 10 of 20 patients treated with topical clonidine three times daily for a week experienced a decrease in systolic blood pressure of at least 30 mmHg at one or more measurements.⁶² Six subjects had a fall in diastolic pressure of at least 20 mmHg.

Experiments in animals using intravenous clonidine indicate that the drug induces vasoconstriction of the anterior and posterior uveal tract⁶³ and decreased ophthalmic artery pressure.⁵⁷ The vasoconstriction and fall in blood pressure could reduce blood flow to an already compromised optic nerve, exacerbating the visual loss from glaucoma even while lowering the IOP. One study suggests that 15 μ l minidrops of 0.25% and 0.5% clonidine lower IOP without lowering blood pressure.¹⁶⁷ However, a 15 μ l delivery system has not been made commercially available. Clonidine is not available for ocular administration in the United States and is used only infrequently in Europe.

Prophylaxis in anterior segment laser surgery

The topical α_2 agonists were first used clinically in the United States to prevent the pressure rise that often accompanies laser treatment to the anterior segment of the eye, including trabeculoplasty, iridotomy, and posterior capsulotomy. An acute, significant increase in IOP after any kind of anterior segment laser treatment can have serious ramifications for eyes that already have some glaucomatous damage but may also be of significance even for eyes without pre-existing glaucomatous changes. In an eye with pre-existing damage, an acute pressure elevation may produce additional damage to the nerve and even compromise vision.^{168–172} Therefore monitoring or, better yet, preventing the IOP increase

after anterior segment laser surgery has significant benefit, especially in eyes with glaucoma.

Argon laser trabeculoplasty

An acute post-laser pressure rise of 10 mmHg or more was noted to occur after trabeculoplasty in about 30–50% of eyes.^{168,173} The pressure rise usually occurs within the first 7 hours. Initially, pilocarpine was the only medication that seemed to be able to blunt the pressure rise, with steroids, non-steroidal agents, acetazolamide, and timolol showing little or no effect.^{173–175} Two different prospective, masked, controlled studies showed that topical 1% apraclonidine used 1 hour before and immediately after trabeculoplasty effectively reduced both the number of patients that had an IOP rise and the magnitude of that rise compared with placebo.^{176,177} Combining the results of the two studies, prophylactic apraclonidine drops allowed a pressure rise of any magnitude after laser trabeculoplasty in 15% of eyes and allowed an IOP rise greater than 9 mmHg in only 2.5% of eyes compared with 39% and 18% of eyes, respectively, when placebo was used. This result is better than with any other antiglaucoma medication preceding apraclonidine.¹⁷⁸ Common practice is to give one drop of 0.5% apraclonidine 30 minutes before the treatment and one drop immediately after the treatment. In those patients with relatively little optic nerve damage, one drop 30 minutes before the treatment or one immediately after is probably enough. One study suggested that chronic use of apraclonidine (not frequent today) may interfere with its effectiveness in preventing IOP rise after trabeculoplasty.¹⁷⁹

These results have been duplicated with two multicenter, double-masked, placebo-controlled studies using brimonidine 0.5%.^{180,181} One drop of 0.5% brimonidine either before or immediately after laser treatment appears to be as effective as, and less likely to produce side effects, than one drop both before and after.¹⁸² Most of the early studies on preventing pressure rise following laser trabeculoplasty with prophylactic brimonidine were performed using the 0.5% concentration, which is not commercially available in the United States. Several more recent studies have shown IOP spike protection with the commercially available 0.2% solution of brimonidine to be equivalent with that provided by 1% apraclonidine.^{183–185} No study has been published that compared chronic use of brimonidine to non-use in this regard, but in the authors' experience, chronic use does not seem to interfere with brimonidine's effectiveness in preventing IOP rise after trabeculoplasty.

Laser iridotomy

A pressure rise similar to that seen with trabeculoplasty has been reported following laser iridotomy. An acute IOP elevation over 10 mmHg is seen in about one-third of eyes after either argon or neodymium:yttrium-aluminum-garnet (Nd:YAG) iridotomy. No relationship has been found with total energy used or iris color. The cause may be related to the release of pigment, blood, and other cellular debris that is caught in the trabecular meshwork. As with trabeculoplasty, the pressure rise can be blunted both in amount and in the per cent of patients who suffer this complication by the topical application of apraclonidine.¹⁸⁶ Pressure rises after laser iridotomy have become rare with prophylactic use of apraclonidine.¹⁸⁷ Brimonidine is similarly protective.^{188,189}

Usually a drop is given 1 hour before the procedure, and one immediately after. In patients with relatively little optic nerve damage, one drop either before or after usually suffices. Apraclonidine might have an inherent advantage over brimonidine in this particular application because its α_1 activity does decrease iris blood

flow and may staunch or prevent bleeding, especially in iridotomies produced by the Nd:YAG laser.¹⁹⁰

Nd:YAG laser posterior capsulotomy

A pressure rise similar in magnitude and timing to that seen after laser iridotomy may be noted after Nd:YAG laser posterior capsulotomy. The mechanism is not known but may be related to inflammation and/or release of some debris that clogs the trabecular meshwork. Topical apraclonidine used prophylactically has been shown to be quite effective at reducing the incidence and severity of the pressure spike.¹⁹¹ Although no data have yet been published to support the use of brimonidine for this application, the authors' experience has shown it to be equally effective as apraclonidine in preventing pressure spikes after most types of anterior segment laser surgery.

Management of acute pressure rises

Apraclonidine has been found to be effective in combating acute pressure rises from sources other than laser surgery. Examples include the pressure elevation found in acute angle-closure glaucoma¹⁹² and that found after panretinal photocoagulation or vitreoretinal surgery.¹⁹³ Apraclonidine has also been found effective in preventing acute pressure rises caused by cycloplegia¹⁹⁴ and cataract surgery.^{195–197} Recently, however, the effectiveness of many antiglaucoma medications, including apraclonidine, for preventing a postoperative pressure rise after cataract surgery has been called into question.¹⁹⁸ The authors have also found apraclonidine useful in treatment of acute pressure rises associated with secondary glaucomas such as neovascular, uveitic, and traumatic. Brimonidine presumably has similar clinical uses based on its use in laser therapy, but its actual effectiveness in these conditions has not, as yet, been documented.

Management of open-angle and other chronic glaucomas

Both apraclonidine and brimonidine have been used to treat open-angle glaucoma. They are effective in lowering IOP in normal, ocular hypertensive, and glaucomatous eyes as monotherapy or as adjunctive therapy.^{199–201} In the United States, apraclonidine is approved by the Food and Drug Administration only for 'short-term' use in glaucoma. 'Short-term' has not been defined more exactly. However, studies with apraclonidine have shown a high rate of tachyphylaxis at 1 month (up to 50%) and also a high rate of allergic reactions (15–36%).²⁰² Brimonidine has a similar effectiveness, without the tachyphylaxis and with a lower rate of allergy.^{203,204} Brimonidine has an ocular hypotensive effect similar to timolol maleate, both acutely and over a 1-year period.²⁰² Brimonidine has also shown itself to be an excellent adjunctive agent in chronic glaucoma, with good additivity to prostaglandins, β -blockers, carbonic anhydrase inhibitors, and miotics.²⁰⁵

The literature is somewhat mixed when comparing the efficacy of brimonidine to that of the carbonic anhydrase inhibitors (CAIs) as adjunctive therapy with the prostaglandin family. For practical purposes, it is usually well tolerated and adds >20% additional lowering of IOP to prostaglandin monotherapy. Sometimes, it may even be superior to the CAIs as an adjunctive agent.^{206–210}

Where there is a contraindication to, or concern about, the use of prostaglandins or β -blocking agents, brimonidine is a reasonable alternative as monotherapy in chronic glaucoma.²¹¹ When used as monotherapy, IOP should be monitored toward late afternoon. If pressure is elevated, then three-times-a-day dosage is indicated; however, most of the time, twice-daily dosage is adequate especially when used as adjunctive therapy.^{212–216} Recently brimonidine in Purite™ (Alphagan-P₃ Allergan) vehicle has been introduced. This

Box 24-2 Side effects of α_2 agonists

Systemic

- Dry mouth
- Fatigue
- Drowsiness
- Headache
- Hypotension
- Bradycardia in neonates
- Hypothermia in neonates

Ocular

- Allergy
- Blurred vision
- Burning/stinging
- Follicular conjunctival response
- Hyperemia
- Itching
- Photophobia

formulation contains 25% less concentrated brimonidine than the original (and now generic equivalent) and has a 'gentler' preservative. It is equally effective as the original 0.2% solution with less topical and systemic side effects.^{217–219} Even more recently, the 0.1% solution has been introduced with apparently similar efficacy but reduced side effects.

Combination therapy

Recently, brimonidine and timolol as a combined medication has been introduced (Combigan®, Allergan). The combination seems to be as effective as the separate agents and promises improved adherence with a single drop.^{220–222} The combined drug seems to have fewer side effects than when brimonidine is given separately; the reasons for this are not known. Furthermore, the efficacy of the fixed brimonidine/timolol combination seems equally effective as the fixed dorzolamide/timolol combination, although it may be a little better tolerated.^{223,224} The place of this combination in chronic glaucoma treatment has not yet been clarified by studies for widespread or long-term use.

Side effects

The side effects of the α_2 agonists are summarized in Box 24-2. Originally, the primary systemic concern with α_2 agonists was systemic hypotension, either primary or orthostatic. As noted previously, clonidine reduces blood pressure by as much as 30 mmHg in up to 48% of subjects.⁶² Some of this may be centrally mediated; however, the newer agents, apraclonidine and brimonidine, do not cross the blood-brain barrier and would be expected to have less cardiovascular effects.²²⁵ In fact, apraclonidine and brimonidine have much less of an effect on blood pressure; although a statistically significant effect can be measured, it is rarely of clinical significance.²²⁶ Unlike timolol and the other non-selective β -blocking agents, brimonidine and apraclonidine have little effect on heart rate either while resting or during exercise. The α_2 agonists have no effect on pulmonary function.²²⁷ Furthermore, brimonidine has no effect on ocular and retinal blood flow as best as can be determined by current methodology.^{228,229} The α_2 agonists have a high rate of adverse reactions. In one study, about one-third of hospitalized patients were reported to have significant side effects.²³⁰

No teratogenic, reproductive, fertility, or other organ effects were noted in rats.²²⁵ A significant side effect noted with these agents is

dry mouth, which may be experienced by up to 30% of patients (compared with 17% of those on timolol therapy) but is rarely serious enough to require discontinuing the drug. Fatigue and drowsiness are seen with brimonidine and are dose dependent and occasionally severe enough to require cessation of therapy.²³¹ The brimonidine 0.15% in Purite™ vehicle seems to have less of either of these side effects than the 0.2% solution.^{217,218}

The use of brimonidine has been associated with bradycardia, hypotension, apnea, and central nervous system depression in neonates and very young children; therefore it is contraindicated in infants.^{232–235} Somnolence, extreme fatigue, and fainting have been reported in children of school age, although they are not common; one study raises the question of whether unreported subclinical somnolence may interfere with school work.^{236,237} In one large study, significant side effects occurred in over 80% of children taking brimonidine, with over 75% reporting somnolence or fatigue;²³⁸ the drug seemed to be better tolerated if the child was over 6 years of age and over 20 kg in weight. No large studies have been done with the newer lower dose versions. In any case, even in older children prior to puberty, brimonidine should be used with great caution and with careful pediatric supervision. The lowest effective concentration should be employed. Presumably, the brimonidine gets across the incompletely developed blood–brain barrier in these children causing profound central nervous system effects that are uncommonly seen and, if so, not severe in adults.

Ocular allergy is relatively common with these agents, as it is with all adrenergic agonists. Because conjunctival follicular response may be correlated with the oxidative potential of the agent and the reactivity of oxidative metabolites, the more stable agents like dipivefrin and brimonidine have a lower rate of local reaction. There also may be a correlation with locale as those areas with high rates of allergic conjunctivitis from environmental factors such as pollens also seem to have a higher rate of allergic reactions to brimonidine. There seems to be little cross-reactivity between apraclonidine allergy and brimonidine, as most patients (68–90%) with apraclonidine allergy can tolerate brimonidine.^{239–241} However, patients with allergies to any other topical ocular medication may be at greater risk for brimonidine allergy.²⁴² Whether this represents an allergy to the common benzalkonium chloride preservative or an individual propensity to topical allergy has not been determined – possibly both.

Stinging and burning on application are also seen, but to a lesser degree than with betaxolol and timolol.¹⁹⁶ Foreign body sensation occurs in about 3%. Blurred vision with brimonidine is less than with timolol. Rebound hyperemia is common with clonidine and apraclonidine and may be a cosmetic problem. Patients using brimonidine may display hyperemia, but it is less common

than with the other agents and is rarely cause for discontinuing the medication. Overall, brimonidine, and especially brimonidine in a Purite™ vehicle, seems to have the least propensity for ocular side effects in this group of drugs.¹³⁶

Suggestions for use

At the present time, it appears that either 0.5% apraclonidine or 0.2% brimonidine given within 30 minutes before, and/or immediately after, anterior segment laser treatment is effective in preventing the IOP spike most of the time. Either agent may be used with likely similar effects, although if the patient has been using apraclonidine chronically, then brimonidine should be chosen. The α_1 effects of apraclonidine may be beneficial to prevent or reduce bleeding in the particular instance of Nd:YAG laser iridotomy. Side effects from this regimen with either agent are rare.

Apraclonidine 0.5% is also useful to help reduce IOP in acute glaucomas such as angle closure, inflammatory, postsurgical, and traumatic. The drug is administered every 8 hours when used alone or may be used every 12 hours when used in combination with other antiglaucoma medications.

For chronic glaucoma, brimonidine is the α_2 -agent of first choice. It is effective as monotherapy in those patients in whom use of a prostaglandin or β -blocker is contraindicated or inadvisable; it is also useful in those intolerant of, or unresponsive to, β -blockers or other antiglaucoma medications. As monotherapy or adjunctive therapy, brimonidine 0.2% is effective in a twice-daily dosage. When used as monotherapy, dosage three times daily may be slightly more effective than twice daily. Brimonidine has been a very important addition to the glaucoma armamentarium.

SUMMARY

Topical adrenergic agonist agents have a long history of effectiveness in the treatment of glaucoma. The non-selective α/β agonists epinephrine and dipivefrin have a relatively high rate of local side effects, with epinephrine causing significant systemic effects in some patients. In the recent past, the more selective α_2 agonist agents apraclonidine and brimonidine have had increasing use for prophylaxis against pressure spikes in laser surgery. Most recently, the highly selective α_2 agonist brimonidine has found an important place in the management of chronic glaucoma in adults because of its lower rate of local side effects, sustained IOP lowering, and better additivity to other antiglaucoma medications. The lower concentration of brimonidine Purite™ with its reduced side effect profile may make it the preferable agent.

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CHAPTER
25

Adrenergic antagonists

In 1967 Phillips and co-workers reported that an intravenous injection of propranolol, a β -adrenergic antagonist, lowered intraocular pressure (IOP) in humans.¹ Within a short time, other investigators found that oral^{2,3} and topical^{4,5} propranolol also reduced IOP. A number of other β -adrenergic antagonists, including atenolol,^{6–8} pindolol,⁹ and bupranolol,¹⁰ were also found to be effective ocular hypotensive agents. With the development of topical timolol maleate, this class of drugs was firmly established as an effective treatment for glaucoma.^{11–13} Additional topical agents such as levobunolol, metipranolol, carteolol, and timolol hemihydrate have subsequently been added to the armamentarium.

Until the advent of latanoprost in the mid 1990s, the topical β -adrenergic antagonists were the most frequently used ocular hypotensive agents in most countries. Timolol and its pharmacologic cousins replaced both miotics and epinephrine analogues. The β -adrenergic antagonists were prescribed commonly because they are both effective in most types of glaucoma and relatively free of the annoying ocular side effects (e.g., miosis, myopic shift in refraction, conjunctival hyperemia) produced by other classes of drugs. As will be noted, however, these agents may have profound although sometimes subtle systemic side effects; it is this latter problem that has seen them take second place to the prostanooids. Nevertheless, the development of topical β -adrenergic blocking agents represents one of the major developments in glaucoma therapy. By 2002–2003, after a 30-year reign as the most popular type of antiglaucoma therapy, β -blocking agents were overtaken by prostaglandin-related agents.¹⁴

In addition to the β -adrenergic antagonists, a few other adrenergic antagonists do have effects on IOP and will be discussed at the end of this chapter.

MECHANISM OF ACTION

There is general agreement that β -adrenergic antagonists reduce IOP by decreasing aqueous humor formation. Fluorophotometric studies in humans indicate that a single administration of timolol or betaxolol reduces aqueous humor formation by 32–47%.^{15–18} With only a few exceptions, most investigators find little or no change in outflow facility after administration of timolol,^{19,20} propranolol,²¹ bupranolol, or pindolol.⁹ Additional confirmation for this proposed mechanism of action comes from experiments in rabbits, cats, and monkeys in which timolol and other β -adrenergic antagonists administered topically, intravenously, or intracamerally reduce IOP and aqueous humor formation without changing outflow facility.^{22–25}

Furthermore, timolol produces no morphologic change in the outflow channels of human eyes.²⁶ While some have proposed that reduced aqueous formation could lead to secondary adverse changes in the trabecular meshwork, no evidence exists to support this concept in humans.²⁷ Recently, some evidence to support this concept was demonstrated in monkeys, especially when reduced aqueous formation induced by topical β -blockade was supplemented by agents that diverted flow away from the trabecular meshwork.²⁸

Timolol reduces IOP even in subjects with Horner's syndrome²⁹; thus an intact nervous system is not necessary for topical β -adrenergic antagonists to lower IOP in humans. However, a few investigators believe that β -adrenergic blocking agents decrease aqueous humor formation by antagonizing a resting β -adrenergic tone in the ciliary processes. Such a tone would have to be supplied by either the sympathetic nervous system or circulating catecholamines.³⁰ There is little evidence to support the concept of a resting neural tone to the ciliary processes. Reiss and co-workers³¹ noted that aqueous humor production is reduced greatly during sleep and that little additional reduction occurs with the administration of timolol either just before or during sleeping hours. This suggests that circulating catecholamines stimulate the ciliary processes to produce aqueous humor. During sleep, the level of circulating catecholamines falls and aqueous humor production diminishes. Timolol could act by antagonizing the catecholamine-induced stimulation of aqueous humor production during waking hours. Thus it would have little effect during sleep when catecholamine levels are low.

Most evidence supports the theory that the effect of the β -adrenergic antagonists on IOP is mediated by the adrenergic system:

1. A large number of β -adrenergic antagonists reduce IOP.
2. β -Adrenergic receptors are found in the ciliary processes, which are thought to be the site of aqueous humor production.^{32–34}
3. β -Adrenergic antagonists are capable of inhibiting the actions of the β -adrenergic agonists isoproterenol and albuterol (salbutamol) on aqueous humor dynamics.^{24,35,36}
4. The effect of the β -adrenergic antagonists on IOP is not dependent on intrinsic sympathomimetic activity or membrane stabilizing properties.
5. β -Adrenergic antagonists have little or no effect on a number of ciliary epithelial enzymes and synthetic pathways related to aqueous humor production, including Na^+ , K^+ -ATPase, magnesium ATPase, carbonic anhydrase, and prostaglandin biosynthesis.²³ However, some of the action of the β -blockers is independent of

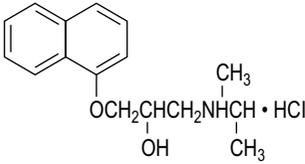
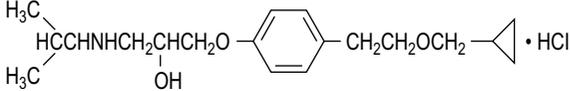
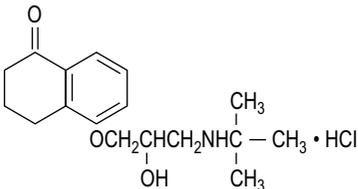
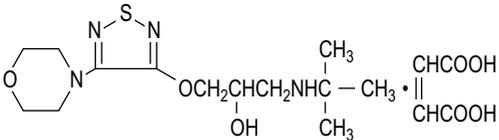
β -Adrenergic antagonists		
Name	Formula	Dose for the treatment of glaucoma
Propranolol hydrochloride (Inderal)		
Betaxolol hydrochloride (Betoptic)		0.5% every 12 hours
Levobunolol hydrochloride (Betagan)		0.5% every 12 to 24 hours
Timolol maleate (Timoptic)		0.25% to 0.5% every 12 to 24 hours

Fig. 25-1 Structure of β -adrenergic antagonists

cyclic AMP, the usual intracellular mediator of adrenergic agonists, and may relate to Cl^-/HCO exchange.³⁷

Topical administration of timolol and the other β -adrenergic antagonists to one eye reduces IOP in the contralateral eye.³⁸⁻⁴⁰ The fact that IOP in the contralateral eye is reduced less than in the ipsilateral eye suggests a local effect in the eye rather than an effect mediated by the central nervous system or by a reduction of blood pressure. Substantial levels of timolol are found in the contralateral eye after unilateral topical administration in rabbits,⁴¹ and small but clinically significant levels are found in humans.⁴²

DRUGS IN CLINICAL USE

Five different topical β -blocking agents are available for clinical use in the United States: timolol, levobunolol, betaxolol, metipranolol, and carteolol. Generic 'equivalents' are available for timolol, levobunolol, and carteolol. Timolol is available as the maleate salt and the hemihydrate salt; it is also available in various gel formulations that are suggested to prolong its time in contact with the cornea or enhance its transit into the anterior segment (potassium sorbate). The non-selective agents (all but betaxolol) appear clinically more alike than different, although there are some differences that may

be important in selected patients (Fig. 25-1). The major features of these agents are summarized in Table 25-1.

TIMOLOL MALEATE

Timolol maleate (TimopticTM, Merck, West Point, Penn and generics) is a nonselective β_1 - and β_2 -adrenergic antagonist that lacks substantial intrinsic sympathomimetic activity and membrane-stabilizing properties (see Table 25-1). The drug is about five times more potent than is propranolol. Timolol reduces IOP in normal and glaucomatous eyes without changing visual acuity, accommodation, or pupil size.^{11,38,39} On average, timolol lowers IOP by about 5 mmHg over a 6-12 month period.⁴³ While timolol (and the other β -blockers) do a reasonable job of flattening the diurnal curve, the β -blockers are less effective during the night-time hours, possibly because the secretion of aqueous is lowest during the night.⁴⁴ The only effect of timolol on the pupil is a clinically insignificant decrease in the amplitude of redilation as detected by pupillography.⁴⁵ Timolol binds to melanin and is not metabolized by ocular tissues.^{23,46} Timolol is excreted in the urine in the form of unknown metabolites. The ocular hypotensive effect of timolol is greater in human eyes than in animal eyes; in animals, the effect can often only be demonstrated in experimental ocular hypertensive conditions such as water loading. This is a good example of the importance of species differences in the ocular response to adrenergic drugs.

Table 25-1 Pharmacologic properties of clinical β -adrenergic antagonists

Property	Betaxolol hydrochloride	Carteolol hydrochloride	l-Bunolol hydrochloride	Metipranolol	Timolol maleate
Potency (propranolol = 1)	1.0	10	15	2.0	5.0
Selectivity	++	0	0	0	0
ISA	0	++	0	0	0
Anesthetic effect	0	0	0	0	0
Decrease heart rate	\pm	+	++	++	++
Bronchospasm	\pm	+	++	++	++
Lipid change	?	Slight	?	?	+
Effect on blood flow	\pm	\pm	?	?	\pm
Ocular discomfort	+++ (solution) ++ (suspension)	\pm	++	+	++

Data from Juzych MS, Zimmerman TJ, Robin AL: Update on adrenergic agents in glaucoma therapy. *Ophthalmol Clin North Am* 10:309, 1997.
ISA, Intrinsic sympathomimetic activity.

Timolol is supplied in 0.25% and 0.5% concentrations, each of which is administered every 12–24 hours. The 0.25% concentration is the top of the dose–response curve for most individuals with lightly pigmented irides, whereas the 0.5% concentration is more effective for most patients with dark irides.^{39,40,47} In some patients with light irides, the 0.5% concentration produces a longer duration of effect rather than a greater reduction in IOP.⁴⁸ Timolol was thought to be equally effective in black and white patients when administered in the appropriate concentration.⁴⁷ However, more recent studies suggest that the β -blockers may be less effective in those of African descent than in those of European descent.^{49,50}

Timolol penetrates the eye rapidly; following topical administration, IOP begins to fall in 30–60 minutes, reaches a low in 2 hours, and returns to baseline in 24–48 hours.^{11,39} Some residual effect of timolol on IOP may be detected for as long as 2–3 weeks, and β -blockade can be detected up to 1 month after discontinuation of the drug.⁵¹ Many patients are controlled on once-daily administration of timolol^{52,53}; however, this requires confirmation by measuring IOP 24–26 hours after the last administration of the drug.

Timolol maleate in a gel solution (Timoptic XE, Merck Inc., West Point, PA; timolol in gel-forming solution (GFS), Falcon Pharmaceuticals Ltd., Fort Worth, TX) for once-daily use has been found to prolong the contact time of timolol with the ocular surface and, therefore, theoretically, more gets into the anterior chamber, prolonging the action.⁵⁴ The gel formulations have been found to be nearly equivalent to timolol maleate given twice daily.⁵⁵ The two most popular gel formulations in the US appear to be equivalent in effectiveness and side effects.⁵⁶ The gel formulation, because of its once-a-day dosing, theoretically reduces the systemic side effects compared with the twice-daily aqueous preparation.⁵⁷ Although the gel has been compared in clinical studies to twice-daily aqueous administration, no study has compared the gel to once-daily timolol maleate solution. Studies with levobunolol and timolol hemihydrate suggest that the pressure-lowering effect of these agents administered once daily compares favorably with once-daily administration of timolol maleate gel.^{58,59} A non-preserved timolol gel formulation has recently become available in single-dose units with equivalent effect to multidose preserved doses.⁶⁰

A new formulation of timolol in potassium sorbate (timolol LA, Istalol®, Senju Pharmaceuticals, Osaka, Japan) has recently been shown in a double-masked, randomized, prospective study in the US to have equivalent IOP-lowering effect as timolol maleate 0.5% given twice daily, with a similar safety profile. It differed only in a higher rate of stinging on administration than the solution.⁶¹ The drug has been approved by the US Food and Drug Administration. Theoretically, the potassium sorbate makes the timolol more bioavailable to the tissues inside the eye through increased anterior chamber concentration, perhaps by increasing lipophilicity.⁶² The solution also has a lower dose of benzalkonium chloride than the standard solutions of timolol maleate.

Approximately 90% of patients respond to the initial administration of timolol. Often the response to the first few doses is a reduction in IOP of 40% or more. However, this effect diminishes over several days to a few weeks.⁶³ This decline in efficacy has been termed the ‘short-term escape’ by Boger and co-workers⁶³ and may relate to an increase in the number of β -adrenergic receptors in the ciliary processes under the condition of prolonged β -adrenergic blockade.⁶⁴ Unfortunately, the response to timolol at 1 month is not predicted by the response to a single administration given in the office.⁶⁵ After this initial adjustment process, most patients maintain a reduction in IOP for months to years. However, 10–20% of patients demonstrate some loss of drug effect over subsequent months.^{66,67} Fluorophotometric studies indicate that aqueous humor production is reduced 47% after 1 week of timolol treatment but only 25% after 1 year of treatment.⁶⁸ This process has been termed the ‘long-term drift’ by Steinert and co-workers⁶⁷ and may be explained by a time-dependent decrease in cellular sensitivity to adrenergic antagonists.

Timolol has become the ‘gold’ standard against which all newer glaucoma hypotensive agents are compared. It is less potent than the major prostaglandin analogs and equivalent to unoprostone, brimonidine, and the topical carbonic anhydrase inhibitors.^{69–73} Over the short term, timolol is more effective in reducing IOP than is pilocarpine^{74–76} or epinephrine.⁷⁷

The ocular hypotensive effect of timolol is additive to that of the miotics,^{63–68,74–79} and the carbonic anhydrase inhibitors (CAIs).^{63,80–82} It should be emphasized that timolol and the CAIs are only

somewhat additive in their effects on IOP.^{81,82} In one study, timolol alone reduced aqueous humor formation by 33%, acetazolamide alone reduced aqueous formation by 27%, and the combination reduced aqueous humor formation by 44%⁸³ (i.e., the combination was more effective than either agent alone but less effective than the sum of the two drugs). On the other hand, timolol adds well to the topical carbonic anhydrase inhibitors with a decrease in aqueous humor formation and IOP with the two drugs greater than either alone.⁸⁴ While timolol's effect on reducing aqueous formation is somewhat greater than brimonidine's (note brimonidine also improves uveoscleral outflow so only some of its effect is from reduction of aqueous flow), there is additivity of brimonidine's effect to timolol both in reducing aqueous formation and IOP.^{85,86} Timolol even is additive to bunazosin, an α -adrenergic antagonist.⁸⁷

The question arises as to whether topical timolol reduces IOP in patients treated with systemically administered β -adrenergic antagonists. The IOP response depends on the dose of the systemic agent. Topical timolol reduces IOP in patients treated with lower doses of the oral β -adrenergic antagonists (e.g., propranolol, 10–80 mg/day).⁸⁸ However, there is little additional reduction in IOP when topical timolol is administered to patients treated with larger doses of the systemic drugs (e.g., propranolol, 160 mg/day, or oral timolol, 20 mg/day).⁸⁹ A recent study confirmed the reduced efficacy of timolol in patients taking systemic β -blocking agents for hypertension, possibly because the systemic β -blocker has already blocked most of the β receptors and the topical agent can only block a few more.⁹⁰ If the use of topical β -blockers are being considered in this situation, a one-eye trial would be indicated to assess the effect of adding the topical agent, although the effectiveness in one-eye trials has been called into question especially with the use of β -blocking agents as they have contralateral effects.⁹¹

Timolol (and probably all the other β -adrenergic antagonists) can be affected by other drugs. For example, cimetidine, a histamine H_2 antagonist causes an increase in β -blockade when used concomitantly with topical timolol.⁹² Quinidine retards the metabolism of β -blockers and thus enhances their action.⁹³

TIMOLOL HEMIHYDRATE

Timolol hemihydrate (Betimol®, Ciba Vision, Duluth, GA) is a recently introduced new salt of timolol. Its clinical effectiveness and side effects are similar to those of timolol maleate.⁹⁴ The major advantage of this formulation seems to lie in its cost, which may be less than Timoptic but usually more than generic timolol maleate. Timolol hemihydrate is available in 0.25% and 0.5% solutions for use once or twice daily.⁵⁹

BETAXOLOL

Betaxolol (Betoptic, Alcon Laboratories, Fort Worth, TX) is a relatively selective β_1 -adrenergic antagonist that lacks intrinsic sympathomimetic activity and membrane-stabilizing properties (see Table 25-1). It is puzzling why a β_1 -adrenergic antagonist should lower IOP because the β receptors in the ciliary epithelium are thought to be β_2 in type.^{32,34} The most likely explanation is that betaxolol reaches the ciliary epithelium in sufficient concentration to inhibit β_2 receptors. Other possible explanations include the presence of β_1 receptors in the ciliary body or a non-adrenergic effect of betaxolol on IOP.⁹⁵ Betaxolol is supplied either in a 0.5% solution or a 0.25% microsuspension for administration every 12 hours. The drug reduces IOP⁹⁵⁻⁹⁷ by decreasing

aqueous humor formation.¹⁶ Betaxolol is effective at reducing IOP and flattening the diurnal curve.⁹⁸ Although a few studies indicate that betaxolol and timolol are equipotent,^{99,100} most physicians believe timolol is more effective at lowering IOP.¹⁰¹ The latter impression is supported by experiments indicating that selective β -adrenergic antagonists are less effective than are non-selective antagonists in reducing IOP in animal models of ocular hypertension.¹⁰² Clinical studies have also supported the slight superiority of timolol to betaxolol.⁶⁹ Betaxolol has similar IOP-lowering efficacy to dorzolamide.¹⁰³

Some clinical and animal studies suggest that tachyphylaxis is common with selective β -adrenergic antagonists;⁷ this has not been a major problem with long-term betaxolol treatment, although it does occur to some extent. Betaxolol appears to be additive in its ocular hypotensive effect with the prostanoids, brimonidine, miotics, and the CAIs.¹⁰⁴ Because of its relative β_1 specificity, betaxolol may not block the effect of epinephrine on aqueous outflow. A few studies suggest that betaxolol and epinephrine are more additive in their ocular hypotensive effects than are timolol or levobunolol and epinephrine.^{105,106}

Evidence is beginning to accumulate that betaxolol may be more 'neuroprotective' than its more non-selective cousins despite a weaker effect on IOP lowering. Betaxolol seems to reduce the progression of visual field defects compared with timolol^{107,108} and may even increase retinal sensitivity.¹⁰⁹ Betaxolol relaxes the smooth muscle in the walls of retinal microarterioles.¹¹⁰ Using Doppler color imaging of retinal vessels, which is an indirect measure of blood flow, topical betaxolol seems to increase retinal blood flow.¹¹¹ This appears to be particularly true in patients with normal-pressure glaucoma.¹¹² The clinical significance of these observations remains unknown, but the implication is that some property of betaxolol other than its pressure-lowering effect may improve blood flow and/or nerve function.

Betaxolol is less likely than is timolol to induce β_2 -adrenergic-mediated bronchial constriction and therefore is a better choice for patients with reactive airway disease.¹¹³ It must be emphasized that the β -adrenergic specificity of betaxolol is relative, and the drug can induce or exacerbate pulmonary problems in susceptible patients. Some investigators postulate that betaxolol is less likely than is timolol to produce cardiovascular and central nervous system side effects, perhaps because of decreased systemic effectiveness or more rapid metabolism.¹¹⁴ This impression requires further study. Betaxolol is less likely than is timolol to interfere with exercise tolerance.¹¹⁵ Betaxolol in solution form produces more burning and stinging on instillation than does timolol,¹¹⁶ whereas the microsuspension form has an ocular discomfort profile more like timolol.¹¹⁷

Levobetaxolol is the L-isomer of betaxolol which is a mixture of the isomers. Levobetaxolol (Betaxon™, Alcon Laboratories, Ft Worth, TX) is a more potent β_1 antagonist than betaxolol or the R-isomer.¹¹⁸ Whether this will make a better clinical agent than betaxolol remains to be demonstrated.

LEVOBUNOLOL

Levobunolol (Betagan, Allergan, Irvine, Calif) is a non-selective β_1 - and β_2 -adrenergic antagonist that lacks intrinsic sympathomimetic activity and local anesthetic properties.^{119,120} The drug is used systemically to treat hypertension, ventricular arrhythmias, and angina. Levobunolol is supplied as either a 0.25% or a 0.5% solution, which is administered every 12–24 hours. The drug appears to be similar to timolol with regard to both efficacy and safety.¹²¹⁻¹²⁴

It has been suggested that levobunolol is more likely than timolol to control IOP with once-daily administration.¹²⁵ However, the two drugs seem to have similar durations of action.¹²⁶ Levobunolol produces blepharoconjunctivitis more frequently than does timolol.^{127,128} The metabolites of levobunolol also appear to have ocular hypotensive effects.

CARTEOLOL

Carteolol (Ocupress, Otsuka America Pharmaceutical, Inc., Seattle; generics) is a non-selective, β -adrenergic antagonist. It is chemically related to timolol, metipranolol, levobunolol, and betaxolol with a potency 10 times that of propranolol; it has partial intrinsic agonist properties toward both β_1 and β_2 adrenoreceptors but no local anesthetic activity.¹²⁹ Carteolol is available as a 1% or 2% solution for use every 12 hours; the drug has a significant effect on IOP by 1 hour after administration and reaches its peak effect at about 4 hours after administration.¹³⁰ Carteolol 1% appears to produce a pressure-lowering effect similar to that of timolol 0.5% when administered every 12 hours.^{131,132} Carteolol seemed to produce fewer local side effects than does timolol.¹²⁶

Because of its intrinsic sympathomimetic activity, carteolol might be expected to produce fewer cardiovascular side effects, such as bradycardia and systemic hypotension, and perhaps fewer pulmonary effects. Carteolol produced less bradycardia, lowering of blood pressure, dizziness, and headache and had less of an effect on pulmonary function studies than did topical timolol.^{126,133} However, the differences are small and may be of only modest clinical significance. All of these side effects tend to occur more frequently with any of the non-selective β -blocking agents in a general population and with longer-term use compared to the carefully selected patients in formal studies.

Recently, a solution of carteolol 1% in alginate solution has been described; because the alginate prolongs the contact time, once-daily dosing seems reasonable. In a 2-month, masked clinical study, carteolol 1% in alginate given once daily in the morning was equivalent to carteolol 1% solution given twice daily.¹³⁴ Plasma levels of carteolol are lower after prolonged use of the long-acting gel formulation used once daily than in the patients using the standard solution twice daily.¹³⁵

METIPRANOLOL

Metipranolol (Optipranolol®, Bausch & Lomb, Tampa, FL) is a non-selective β_1 - and β_2 -adrenergic antagonist with a receptor selectivity similar to that of timolol and levobunolol. After several successful trials in Europe,¹³⁶ a double-masked, randomized study in the United States showed that metipranolol effectively reduces IOP by suppressing aqueous outflow in ocular hypertensive eyes.¹³⁷ The agent is similar in most respects to timolol in terms of effectiveness and side effects. It is available in the United States as a 0.3% solution for use twice daily.

Concern about metipranolol developed when several case reports of granulomatous uveitis appeared in association with its use.^{138,139} Although uveitis had been reported with the use of other topical β -blockers, the cases involving metipranolol seemed more virulent and occurred with greater frequency. Most of the reported cases seemed to come from Great Britain, where the agent differed from the American variety not only in concentration but also in preservative, pH, and method of sterilization. A subsequent retrospective study in the United States failed to find any evidence

of uveitis associated with the 0.3% solution of metipranolol.¹⁴⁰ However, one case report of a patient developing non-granulomatous anterior uveitis that reappeared after re-challenge with metipranolol appeared in the literature.¹⁴¹ Subsequent reports have not appeared, suggesting that this is a rare phenomenon in the US.

Metipranolol seems to have a reduced effect on exercise-induced tachycardia compared with timolol in healthy volunteers.¹⁴² Based on this study, it may be inferred that metipranolol could have fewer systemic cardiovascular side effects, although this has not been proven in a direct comparison. Metipranolol has achieved some success in the United States because it is less expensive than most of the other brand name β -blocking agents.¹⁴³

OTHER β -ADRENERGIC ANTAGONISTS

PROPRANOLOL

Propranolol (Inderal, Wyeth-Ayerst Laboratory, Philadelphia) is a non-selective β -adrenergic antagonist that is used widely for the treatment of a diverse group of medical conditions including arrhythmia, angina, hypertension, and migraine. Propranolol lowers IOP when administered topically,^{144,145} orally,^{146,147} or intravenously.¹⁴⁸ The drug has been shown to reduce aqueous humor formation in both monkey and human eyes.^{149,150} Most physicians have abandoned propranolol as a treatment for glaucoma because its membrane-stabilizing properties produce corneal anesthesia. Patients who are treated with oral propranolol for a medical condition such as hypertension generally experience a decrease in IOP, particularly when the dose exceeds 10 mg/day.^{151,152}

ATENOLOL

Atenolol (Tenormin, Zeneca Pharmaceuticals, Wilmington, DE) is a relatively selective β -adrenergic antagonist that lacks intrinsic sympathomimetic activity and membrane-stabilizing properties. The drug reduces IOP in normal and glaucomatous eyes when administered topically in a 1–4% concentration^{153–156} or orally in a dose of 50 mg/day.¹⁵⁷ There are a few reports of tachyphylaxis with atenolol treatment.¹⁴⁹ While oral atenolol is commonly used to treat systemic hypertension, neither topical nor oral atenolol is in clinical use for glaucoma treatment at this time.

PINDOLOL

Pindolol is a relatively selective β_1 -adrenergic antagonist that has some intrinsic sympathomimetic activity but lacks local anesthetic properties. Pindolol reduces IOP when administered orally¹⁵⁸ or topically in a 0.25–0.5% concentration.^{152,159}

NADOLOL

Nadolol is a non-selective β -adrenergic antagonist that lacks intrinsic sympathomimetic activity and membrane-stabilizing properties. Nadolol is two to four times more potent than propranolol. The drug reduces IOP when administered topically in a concentration of 0.3–2%¹⁶⁰ or orally in a dose of 20–40 mg.¹⁶¹ A prodrug of nadolol, diacetylnadolol, penetrates the eye more rapidly than does the parent compound and is only a little less effective than 0.5% timolol in reducing IOP.¹⁶² Like atenolol, nadolol has not yet become available for ophthalmic use in the United States.

METAPROLOL

Metoprolol is a relatively selective β_1 -adrenergic antagonist that has weak membrane-stabilizing properties but lacks intrinsic sympathomimetic activity. Metoprolol reduces IOP when administered orally in a dose of 50 mg three times daily.¹⁶³ Administered topically in a 3% concentration, metoprolol reduces IOP as effectively as does 2% pilocarpine.¹⁶⁴ Unfortunately, the drug commonly causes local irritation and superficial punctate keratitis.

LABETOLOL

Labetolol is a mixed α - and β -adrenergic antagonist. When administered topically in concentrations of 0.1–1%, the drug reduces IOP without changing outflow facility.¹⁶⁵

SUGGESTIONS FOR USE

The β -adrenergic antagonists are useful in nearly all forms of glaucoma – even in cases in which outflow facility cannot be improved.^{167,166} The β -adrenergic antagonists are usually better tolerated than are either the epinephrine agents or the standard miotics. The lack of any appreciable effect on pupil size or accommodation makes these drugs particularly helpful in young patients, in highly myopic patients, and in older patients with media opacities. While they have been surpassed in terms of usage by the prostaglandin analogs, the topical β -blockers are still very useful in the management of glaucoma. Contraindications to β -blocker use include bradycardia, second- or third-degree atrioventricular block, and active bronchoconstrictive disease (at least for non-selective β antagonists). Controversy exists about the use of β -blockers in congestive heart failure; careful and extensive consultation with the patient's other physicians is warranted in anyone with significant cardiovascular or pulmonary disease. Caution should be observed in patients with a history of asthma, in patients with keratoconjunctivitis sicca, and in smokers.

Because the differences between the non-specific agents are minimal, cost and availability can dictate which specific agent is selected. However, when a history of asthma (but no recent active obstructive airway disease) is present, consideration should be given to betaxolol. However, even betaxolol should be used with careful monitoring of pulmonary status in these patients; if active bronchospastic airway disease is present, betaxolol may exacerbate the condition. A history of hypercholesterolemia, hyperlipidemia, or a strong family history of coronary artery disease might favor the use of carteolol over other agents in this class. A trial of once-daily dosing at the lowest available concentration of an agent (preferably in one eye) would be a good way to start. Only then, if indicated, should the frequency and concentration be increased. β -Blocker agents, like other antiglaucoma medications, may not work as well in patients with thick corneas; therefore, before prescribing them, pachymetry should be performed.¹⁶⁸

Because the β -adrenergic antagonists can produce systemic β -blockade and attendant side effects (see next section), patients should be instructed to sit quietly with their eyes closed and their puncta occluded for at least 2 minutes after eyedrop administration. Telling the patient to perform this for the duration of one popular song or a radio headline news broadcast helps to give them a time frame to which they can relate with their eyes closed. Such

techniques have been shown to reduce blood levels of timolol by 60%.¹⁶⁹ Patients should also be instructed to administer the β -adrenergic antagonists according to the prescribed timetable and to limit instillation to one drop in each affected eye.

Compliance with timolol treatment is generally better than with pilocarpine treatment.¹⁷⁰ However, a substantial minority of patients administers timolol in suboptimal fashion. In one study, 8% of the patients administered less than 50% of the prescribed timolol doses and 27% administered less than 75%. More than 45% of the individuals reported at least 1 day per month with no administrations of timolol.¹⁶² One study suggests that, while the prostaglandin analogs are more likely to be utilized over the long haul than β -blockers, β -blockers had a lower overall cost.¹⁷¹ As noted previously, the β -blocking agents can be used with virtually any other antiglaucoma medication, regardless of mechanism, with the expectation that some additional pressure-lowering effect will be obtained. The one exception is the non-specific adrenergic agents such as epinephrine and dipivefrin, for which the additive effect to the non-selective β -blockers is minimal.

β Antagonists have been used successfully with CAIs, miotics, α_2 agonists, and prostaglandin analogues.¹⁷² As noted earlier, additivity with epinephrine and dipivefrin is limited except when betaxolol is the β -blocking agent.

OPEN-ANGLE GLAUCOMA

The β -adrenergic antagonists have their greatest use in the treatment of open-angle glaucoma; they have become the treatment of first choice in this condition unless systemic conditions preclude their use.

ANGLE-CLOSURE GLAUCOMA

In some patients, a β -adrenergic antagonist may lower IOP sufficiently to allow subsequent topical pilocarpine administration to produce miosis and stop an attack of acute angle-closure glaucoma. In other patients, the β -adrenergic antagonist must be used along with an α_2 agonist, CAI, or hyperosmotic drug. It should be emphasized that the medical treatment of acute angle-closure glaucoma is not a substitute for surgical therapy. The physician should not be lulled into a false sense of security when IOP drops to normal after an attack of acute angle-closure glaucoma. Iridectomy remains the treatment of choice for angle-closure glaucoma caused by pupillary block.

The topical β -adrenergic antagonists are also useful in treating late IOP elevations (chronic and residual angle-closure glaucoma) after laser or standard surgical iridectomy.¹⁷³

SECONDARY GLAUCOMA

The β -adrenergic antagonists are effective in reducing IOP in most of the secondary glaucomas. Because these agents do not produce either mydriasis or miosis, they are helpful in conditions in which movement of the pupil is of concern (i.e., hyphema with associated IOP elevation or early postoperative IOP rise after cataract surgery).^{174,175} The topical β -adrenergic antagonists can be used to treat inflamed eyes with secondary elevations of IOP. Although some authorities believe timolol breaks the blood-aqueous barrier,^{176,177} the bulk of the evidence suggests that there is no increased vascular permeability as determined by fluorescein angiography of the iris¹⁷⁸ or aqueous humor protein measurements.¹⁷⁹

Timolol is ineffective in reducing the immediate IOP elevation that occurs after penetrating keratoplasty¹⁸⁰ but is effective in the intermediate and late postoperative course.

GLAUCOMA IN CHILDREN

The β -adrenergic antagonists produce a substantial IOP reduction in approximately two-thirds of children with glaucoma.^{181,182} The response to treatment seems to be better in older children and in those without detectable congenital anomalies of the anterior segment of the eye. Unfortunately, complications are seen more often in children, perhaps because they have higher blood levels of the drug.¹⁸³ Common complications in children include asthma, bradycardia, dizziness, drowsiness, and hyperactivity.¹⁷⁸ Neonates and small infants must be monitored carefully for the development of apnea.^{184,185} When children are treated with β -adrenergic antagonists, lower concentrations should be used and punctal occlusion should be applied. It is likely that betaxolol is a safer choice for children with glaucoma, but no studies have been done to confirm this.

Whether the topical β -adrenergic antagonists can be administered safely to pregnant women is unclear. Systemic propranolol has been given to large numbers of pregnant women without teratogenic effect even though the drug does slow fetal heart rate.¹⁸⁶ Given the lack of specific information regarding the effect of these agents on pregnancy and the fetus, however, topical β -adrenergic antagonists must be prescribed with caution for pregnant women and women of childbearing age.

Timolol is actively secreted into mothers' milk; that is, the drug concentration is higher in milk than in plasma.¹⁸⁷ Although the total dose reaching the infant is relatively small, little is known about the long-term effects of even small amounts of β -blockade in neonates and infants; therefore, caution is indicated.

BLOOD FLOW AND NEUROPROTECTION

Neuroprotection has been defined in many different ways. Certainly, lowering IOP is neuroprotective. However, in general ophthalmologic use, neuroprotection refers to a property of a drug independent of its pressure-lowering capability. Neuroprotection may mean interfering chemically with the intracellular pathway of ganglion cell damage, enhancing cell survival characteristics, or possibly improving blood flow if it indeed is defective either chronically or intermittently in one or more types of glaucoma. Many studies have confirmed that some defect in ophthalmic, retinal, and/or optic nerve blood flow exists in glaucoma.¹⁸⁸ Whether these defects are causative of or contribute to the pathophysiology of damage in glaucoma, secondary to the death of ganglion cells by some other mechanism, or are incidental findings remains conjectural. A large literature exists on neuroprotection and blood flow as they may be affected by β -adrenergic antagonists.

Controversy exists as to the effect of β -blocker agents on retinal and optic nerve blood flow. Some investigators believe that topical timolol treatment may have an adverse effect on optic nerve circulation and visual function.¹⁸⁹ Some studies have suggested that β -blocking agents, especially the non-selective ones without intrinsic sympathomimetic activity, may decrease optic nerve blood flow by inducing vasospasm; this activity may have the long-term effect of competing with the IOP-lowering effect of these agents and ultimately lead to progression of optic nerve damage.¹⁹⁰ Although there is no general clinical impression that patients treated with timolol have a worse prognosis than patients treated

with other antiglaucoma medications, this matter requires careful study. At least one study has shown that betaxolol, despite having weaker IOP-lowering efficacy than timolol, is more likely to preserve visual function.¹⁹¹ This observation has not been confirmed in all studies.¹⁹²

Unfortunately, the methodology to date is relatively crude and can only give an indirect measure of capillary blood flow to the optic nerve, peripapillary choroid, and retina. One method is to use pulsatile blood flow measurements. These are gross measurements of total ocular blood flow and do not measure non-pulsatile blood flow at all. Another method measures the velocity of blood flow in capillaries by the laser Doppler method. This indirect method is akin to measuring the speed of cars on a busy freeway and inferring from their average speed the total volume of traffic. The methodology has become more sophisticated with time but the clinical and pathophysiologic meaning has not become any clearer. Some studies have pointed out that patients differ in their responses and that not all patients have similar responses in their blood flow to the same agent.¹⁹³ In addition, for example, patients with non-progressive glaucoma seem to have no real demonstrable vascular dysfunction and timolol has no effect on this essentially normal picture.¹⁹⁴ Moreover, studies differ in whether they use a single dose or long-term application. Some compare the active agent to placebo and others to alternative β -blocking agents. Depending on the study chosen, one can find no effect, a small positive effect, or a negative effect of non-selective β -blockers on retinal circulation.^{195,196}

Several studies suggest that the selective β -blocking agent betaxolol may have a beneficial effect on optic nerve blood flow.^{190,197} One study showed a smaller decrease in ocular pulsatile blood flow with long-term betaxolol treatment compared with long-term timolol treatment.¹⁹⁸ Other studies have shown an improvement in pulsatile blood flow with non-selective agents¹⁹⁹ and with non-selective agents having intrinsic sympathomimetic activity.²⁰⁰ One study has shown concurrent improvement in blood flow and slightly improved contrast sensitivity with betaxolol treatment versus timolol treatment in primary open-angle glaucoma patients.²⁰¹ Two studies have shown a beneficial effect of betaxolol compared with timolol on visual fields; these data would seem to correlate with those derived from the blood flow studies.^{202,203} However, a well-done, double-masked study failed to show any difference in the corrected loss variance between betaxolol- and timolol-treated eyes after 2 years.²⁰⁴ In another randomized study comparing timolol, betaxolol, and pilocarpine, the betaxolol-treated patients did marginally better than timolol on short-wavelength automated perimetry after 2 years despite better IOP reduction with timolol.¹⁹¹ Other studies have shown only a small, probably clinically insignificant, difference between timolol- and betaxolol-treated eyes.²⁰⁵ Furthermore, studies both *in vitro* and in experimental animals have shown some direct neuroprotective effects of betaxolol.^{206–209} Similar properties were found with metipranolol.²¹⁰ Nipradilol, a β -adrenergic blocking agent with nitric oxide donor properties in use in Japan, has been shown to have neuroprotective and regenerative properties on retinal ganglion cells in tissue culture.^{211,212}

What these many findings really mean for the management of glaucoma remains to be determined. While the β -adrenoreceptor antagonists may have theoretical neuroprotective properties, no agent or group of agents have been shown to have a decided advantage clinically, in terms of improving or protecting optic nerve function other than as relates to the agent's IOP-lowering capacity.²¹³ Clearly, further study is needed.

SIDE EFFECTS

When timolol (the first practical topical β -blocking agent) was introduced, it was thought to have very few side effects.³⁹ As often occurs with a new agent, significant ocular and systemic side effects began to be reported as the drug came into more widespread use. In addition, as patients used the medication for longer periods of time, subtle but important side effects became manifest. With miotics, epinephrine, and CAIs, the side effects are fairly obvious even from the beginning of use. Conversely, the effects of β -adrenergic antagonists tend to be cumulative over time; and many of these effects may be confused with conditions frequently associated with the aging process, such as forgetfulness, confusion, fatigue, moodiness.

Because the β antagonists tend to 'feel OK' when applied, the patient often does not associate this benign feeling with systemic problems. The ophthalmologist must be diligent in teasing out true side effects from the normal aging process. This sometimes includes asking specifically about some of the side effects to get patients, their families, and sometimes their primary care physicians to realize that a topical agent can indeed cause systemic problems. For example, impotence is an infrequent but significant side effect of β -blockade. Few ophthalmologists ask their patients about this directly, and patients usually do not associate a genitourinary symptom with an eyedrop.

OCULAR

The topical β -adrenergic antagonists cause a relatively low incidence of ocular side effects, especially when compared with other antiglaucoma preparations (Box 25-1). Although most of the studies have been done with timolol, the side effects of the other topical β -blocking agents are the same as timolol except when specifically indicated. Although the topical β antagonists do not generally cause severe discomfort on administration, stinging, burning, or itching does occur in 5–10% of patients. This rate increases to 40% for betaxolol solution.¹⁶³ Even with betaxolol, however, the discomfort is fleeting and rarely a cause for discontinuing the medication. Carteolol seems to cause less discomfort on administration than does timolol.¹²⁶ The incidence of significant ocular side effects for timolol is about 0.15%.²¹⁴ These include periocular dermatitis, allergic conjunctivitis, and punctate keratitis.

Ocular allergy to topical timolol is quite uncommon. In one large, long-term study, the incidence was about 1%.²¹⁵ Other ocular reactions to β antagonists include punctate keratitis, photophobia, ptosis, and blepharoconjunctivitis.¹⁶³ This latter reaction may be allergic in nature and seems to be less common with carteolol. Should it occur, switching to a different class of medication would probably be most effective in reversing it. Some patients report decreased vision soon after initiating β -blocker treatment. In most cases, this symptom is related to the loss of miosis and depth of field when miotic treatment is discontinued. However, in other cases, the symptom appears to be related to the β -blocker treatment through some unknown mechanism.^{216,217}

Topical timolol treatment can reduce baseline and reflex tearing (Schirmer I and II tests) and tear breakup time^{218,219} and can initiate or exacerbate keratoconjunctivitis sicca.²²⁰ This can be a problem particularly in contact lens wearers and can be aggravated by the development of corneal anesthesia, which has been reported in a few patients.^{221,222} The combination of gas-permeable contact lenses and topical timolol administration alters the corneal epithelium and

Box 25-1 Side effects from topical β -adrenergic antagonists

Ocular

External

- Burning/pain/discomfort
- Hyperemia of conjunctiva
- Superficial punctate keratitis
- Corneal anesthesia
- Allergic blepharoconjunctivitis
- Dry eye
- Corneal erosion in contact lens wearers
- Ptosis

Visual disturbances

- Dilated pupil with epinephrine treatment
- Hypotony

Systemic

Nervous system

- Depression
- Difficulty concentrating
- Anxiety
- Confusion/disorientation
- Hallucinations
- Dysarthria
- Fatigue/weakness/drowsiness
- Forgetfulness?
- Exacerbates myasthenia gravis
- Tinnitus
- Abnormal taste sensation
- Diplopia
- Emotional lability
- Dissociative behavior
- Tranquilization
- Lightheadedness
- Cerebrovascular accident
- Psychosis

Cardiovascular

- Bradycardia
- Raynaud's phenomenon
- Arrhythmia
- Heart failure
- Hypotension
- Hypertension
- Syncope
- Myocardial infarction
- Death

Pulmonary

- Dyspnea
- Airway obstruction/asthma
- Status asthmaticus
- Pulmonary failure
- Apnea, especially in children/sleep apnea

Dermatologic

- Maculopapular rash
- Alopecia
- Nail pigmentary changes
- Urticaria

Gastrointestinal

- Nausea
- Vomiting
- Diarrhea
- Abdominal cramping

Miscellaneous

- Impotence
- Altered response to hypoglycemia
- Decreased exercise tolerance

endothelium in rabbits.²²³ Benzalkonium chloride is absorbed by some types of soft contact lenses, and patients who use these lenses should administer their drops with the lenses out of the eye. One study reported that topical timolol treatment reduces tear lysosome concentration,¹⁸² but this was not confirmed in a second investigation.²²⁴ Levobunolol seems to have equivalent effect on the cornea and tear film as timolol.²²⁵ Both timolol hemihydrate and carteolol may have less effect on the corneal epithelium and tear film than timolol maleate.^{226,227} Clinically, the other β -adrenergic antagonists seem to have similar effects on the cornea as timolol maleate.

Timolol does not retard corneal re-epithelialization in rabbits,²²⁸ nor is it toxic to cultured bovine corneal endothelial cells.²²⁹ Long-term use is unlikely to affect the corneal endothelium in humans with normal corneas to start with.^{230–232} The effect of these agents on abnormal endothelial cells has not been documented but general experience has suggested that they are not particularly toxic even in those with advanced endothelial dysfunction.

Studies suggest that long-term use of topical β -blocking agents (specifically timolol maleate) may be associated with an increase in the number of fibroblasts and inflammatory cells in the conjunctiva.^{190,233} These changes may contribute to keratoconjunctivitis sicca and, perhaps more ominously, interfere with the subsequent success rate of filtering surgery.^{234,235} Furthermore, the changes can be reversed by discontinuing the β -blocker some weeks before surgery and pretreating the eye with topical corticosteroids.²³⁶ Not all investigators have confirmed the histopathologic changes associated with topical β -adrenergic antagonist therapy.²³⁷ Both timolol and betaxolol accumulate in Tenon's capsule where a reservoir effect may occur allowing gradual release of these agents long after they have been discontinued.²³⁸ Presumably, similar changes are seen with the other members of this class of drugs.

Benzalkonium chloride (BAK) has been implicated as a causative agent in the conjunctival inflammation and keratopathy associated with topical β -blocker use.^{239–242} Benzalkonium chloride seems to induce apoptosis in conjunctival cells in patients using topical antiglaucoma agents as measured by impression cytology.²⁴³ However, not all of the β -blockers' conjunctival effects are due to preservative; also evidence suggests that some of these changes are not reversible.²⁴⁴ All of the β -adrenergic antagonists contain benzalkonium chloride as the preservative except for Timoptic XE (the gel form), which has an analogue of benzalkonium. The concentrations differ, however, and patients who are sensitive to BAK may get some local relief by switching to an agent with a lower concentration such as Timoptic XE, Istalol, carteolol, metipranolol, and levobunolol. Finally, Merck has made on and off a non-preserved Timoptic, in addition, compounding pharmacists such as Leiter's in San Jose, CA, will also make a non-preserved timolol solution by prescription.

Furthermore, BAK has been shown to increase apoptosis in cultured trabecular meshwork cells suggesting that this may be one mechanism that may explain the increased rate of trabecular cell loss in patients with glaucoma.²⁴⁵ In addition, both timolol and BAK have been implicated as causative agents in post-cataract surgery cystoid macular edema, with BAK playing an exacerbating role.^{246,247} Presumably, both BAK and timolol lead to disruption of the blood-aqueous barrier in newly operated eyes thus causing additional prostaglandins and other inflammatory cytokines to reach the retina. On another note, levobunolol may contain sodium metabisulfite, an antioxidizing agent commonly used in foods for preservation; patients allergic to this preservative may experience severe local reactions on administration.

The combination of timolol and epinephrine produces greater mydriasis than does epinephrine alone, especially in eyes with light-colored irides.²²⁴ Combined treatment with these two drugs can precipitate angle-closure glaucoma in susceptible individuals and should be used with great caution in patients with anatomically narrow angles.

SYSTEMIC

The topical β -adrenergic antagonists are capable of producing systemic side effects through β -adrenergic blockade. Although topical timolol treatment generally yields serum drug concentrations of less than 5 ng/ml in adults, this level is apparently sufficient to produce systemic β -adrenergic blockade in susceptible individuals.^{177,248}

The effect may be cumulative and requires some time to manifest. Systemic drug levels can be reduced by using the lowest possible concentration of the drug and the fewest administrations necessary to control IOP. Drug concentrations in plasma can also be lowered by instructing patients to limit instillation to one drop of medication per eye and to use eyelid closure and punctal occlusion after administration.¹⁶¹ β -Blockers reaching the oral and nasal mucosa are absorbed rapidly and distributed to the body without first-pass metabolism in the liver; that is, the drug acts as if it has been given by a slow intravenous injection. Topical β -adrenergic antagonists should be used with great caution in patients with asthma or other reactive airway disease (including a history of asthma in childhood), heart failure, sinus bradycardia, hypotension, greater than first-degree heart block, hypokalemia, and brittle diabetes mellitus. Possible drug interactions with topical β -adrenergic antagonists include digitalis and calcium-channel blockers (bradycardia),²⁴⁹ reserpine (excessive β -blockade), sympathomimetics and the xanthene drugs (inhibit therapeutic effect of the drugs), and other systemic β -adrenergic antagonists (additive systemic β -adrenergic blockade). Concomitant use of quinidine can inhibit the metabolism of topical timolol, producing profound systemic β -blockade; it has been suggested that this effect may be genetically determined.²⁵⁰

Symptoms related to the central nervous system are common in patients receiving topical β -adrenergic antagonists and include mood changes, emotional lability, fatigue, trouble concentrating, confusion, and depression (see [Box 25-1](#)).²⁵¹ These symptoms usually appear after a few days to several months of treatment, although they may be transient in nature. The symptoms may be subtle, develop slowly, and be interpreted by the patient and family as a 'normal' part of aging. Many patients may be unaware of the problem until the drug is discontinued.^{221,222} Patients should be questioned specifically about these symptoms. However, large-scale evidence that topical β -blocker therapy leads to previously unrecognized clinical depression is lacking and, in one study, topical β -blockers were not associated with an increased risk of treatment for depression.²⁵² There is some evidence that the more selective β -blocker betaxolol may be less likely to produce these symptoms, and patients may show improvement when switched from a non-selective agent to a selective one.²⁵³

Topical β -adrenergic antagonists reduce forced expiratory volume and forced vital capacity in patients with asthma or other reactive airway disease, including cystic fibrosis and bronchitis.²⁵⁴ Severe asthma leading to hospitalization or even death has occurred. Topical β -blockers can induce bronchospasm in patients who have only a history of asthma and no active current disease. Susceptible patients are more likely to develop pulmonary problems when

they have an upper respiratory infection or allergy. The topical β -adrenergic antagonists can initiate, exacerbate, or prolong bronchitis, cystic fibrosis, and other respiratory problems. Even in asymptomatic older patients without a history of bronchospastic disease, a measurable reduction in respiratory function is present as a result of topical β -blocker therapy although this may not be clinically significant; in fact, asymptomatic respiratory depression and reduced expiratory facility may be seen in otherwise normal patients in as little as 3 months after initiation of topical timolol therapy.^{255–257} While most of the effects on the respiratory system disappear when the drug is discontinued, what is worrisome is that some of these effects may persist for months or even years after the topical β -blocker has been stopped.²⁵⁸

Betaxolol is less likely to induce bronchial constriction. However, the β_1 -adrenergic selectivity of betaxolol is only relative, and the drug is capable of inducing pulmonary side effects in susceptible patients. The non-selective β -blocking agents are contraindicated in patients with active bronchorestrictive airway disease and in those with a recent past history of asthma or similar respiratory problems. In those cases, if β -blocker therapy is indicated, a selective agent (betaxolol) should be used with careful respiratory monitoring, particularly over the long haul.²⁵⁹

Topical timolol treatment can decrease resting and maximal heart rate, oxygen consumption at maximal exercise, cardiac sympathetic tone, and ventricular inotropy.²⁶⁰ In fact, topical timolol's cardiovascular effects, plasma concentrations, half-life, and bioavailability mimic intravenously injected timolol.²⁶¹ The cardiovascular effects of timolol are directly proportional to its plasma concentration.²⁶² It has been suggested that betaxolol is less likely than is timolol to affect cardiac function, perhaps because of decreased systemic effectiveness, generally weaker activity, or a more rapid metabolism. β -Adrenergic antagonists can exacerbate congestive heart failure and should be used with caution in patients with this condition, although cardiologic opinion seems to be switching to utilization of β -blockers again in congestive heart failure.^{263,264} Severe atrioventricular heart block and bradycardia have been noted. Although severe cardiovascular events are rare, these agents should be used with caution in elderly patients with underlying cardiovascular disease.²⁶⁵ Certainly, consultation with the primary care physician and cardiologist would be indicated if topical therapy were to be initiated or continued in any patient with heart disease. In patients with low blood pressure, especially those with nocturnal hypotension, caution should be observed in the use of topical non-selective β -blockers; in these patients, if β -blockers are necessary, perhaps once-daily dosing in the morning might be safer.²⁶⁶

Timolol can also slow the fetal heart rate and even induce fetal arrhythmias; therefore, this agent and any of the other non-selective β -blockers should be used with extreme caution or not at all in pregnant women.²⁶⁷

Long-term use of topical timolol maleate has been shown to increase plasma triglycerides by an average of 12% and decrease high density lipoprotein (good) cholesterol levels by 9%.²⁶⁸ The authors²⁶⁸ estimated that over a period of years this could result in an increase of coronary heart disease by 21%; it is wise to remember, however, that this is an estimate and not a measurement. However, the Blue Mountains Eye Study from Australia did find a correlation between topical timolol use and cardiovascular mortality.²⁶⁹ There are no data to prove that the risk of heart disease is actually increased by use of topical β -blocking agents.

Because of its intrinsic sympathomimetic activity, carteolol does not appear to affect plasma lipid levels as much as does

timolol.²⁷⁰ Thus carteolol may have a slightly better therapeutic index than does timolol in these patients with hyperlipidemia or hypercholesterolemia.

Although some studies have failed to show an effect of topical β -blockers on exercise tolerance,²⁷¹ reduced exercise tolerance has been seen with topical β -blocker use in otherwise healthy individuals.²⁷² Because some of the effects of β -blocking agents are cumulative, the longer someone has been taking the agent the more likely systemic effects will be seen. Some of the differences in studies on exercise tolerance may relate to different lengths of time the patients were using the drug. Competitive athletes and those involved in heavy exercise should be warned that their peak capability may be reduced with the use of topical β -blockers.

Topical β -adrenergic antagonists should be administered with caution to diabetic patients who are prone to episodes of hypoglycemia. Systemic β -adrenergic blockade may mask the common symptoms of hypoglycemia and substitute unusual symptoms. Diabetic patients treated with topical β -adrenergic antagonists may experience an increased frequency of hypoglycemia²⁷³ and a relative resistance to glucose treatment.²⁷⁴ A recent study suggests that certain polymorphisms of the gene CYP2D6 may be associated with increased susceptibility to the systemic side effects of β -blocking agents due to 'slow' metabolism of the drugs and raises the possibility that, in the future, we will be able to adjust our therapy from the individual genotype of the patient.²⁷⁵ One study has shown not only an improvement in glaucoma control, but in quality of life, when switching from β -adrenergic antagonists to prostaglandin analogs.²⁷⁶

OTHER ADRENERGIC ANTAGONISTS

α -ADRENERGIC ANTAGONISTS

Thymoxamine

Thymoxamine hydrochloride is a selective α_1 -adrenergic antagonist. Unfortunately, the drug is not available in the United States. When administered topically, thymoxamine produces miosis by inhibiting the dilator muscle of the iris and allowing the sphincter muscle to act unopposed. In the normal eye, thymoxamine has little effect on IOP,²⁷⁷ outflow facility,²⁷⁸ or aqueous humor production.²⁷⁹ In patients with acute angle-closure glaucoma, however, the drug may terminate an attack by producing miosis,²⁸⁰ often without the addition of parasympathomimetic or hyperosmotic agents. The drug is also useful in differentiating chronic angle-closure glaucoma from open-angle glaucoma with coincident narrow angles. When thymoxamine is administered to an eye with chronic angle-closure glaucoma in which the angle is not totally closed by synechiae, IOP falls and the angle appears more open on gonioscopy. In contrast, when thymoxamine is administered to an eye with open-angle glaucoma and coincident narrow angles, the angle appears more open on gonioscopy but IOP is unchanged.²⁶⁰

It has been suggested that thymoxamine may be a treatment for pigmentary glaucoma. The drug can produce miosis and enough pupillary block to lift the peripheral iris from the zonules, thereby reducing pigment dispersion. Because it does not induce a fluctuating myopic shift in refraction, thymoxamine should be better tolerated than pilocarpine or the other standard miotics, especially in young patients.²⁸¹ No clinical studies of the use of thymoxamine have been reported to date; however, some success has been reported in preliminary studies with dapiprazole (another α -adrenergic

antagonist). Thymoxamine can also be used to reverse phenylephrine mydriasis,²⁸² alleviate mydriasis after penetrating keratoplasty,²⁶⁰ reposition an iris-supported intraocular lens, and treat lid retraction in conditions such as thyroid eye disease.²⁸³ The drug can cause stinging, conjunctival hyperemia, ptosis, and epistaxis.²⁷²

Dapiprazole

Dapiprazole (Rev-Eyes™, Storz Ophthalmics, a division of Bausch & Lomb, Rochester, NY) is an α -adrenergic antagonist clinically used for the reversal of pharmacologically-induced mydriasis.^{284,285} It has little direct effect on IOP in open-angle glaucoma. Dapiprazole has been used in patients with pigmentary glaucoma as a way of lifting the peripheral iris off the zonules without inducing accommodative spasm. Long-term dapiprazole seems to lead to improved outflow facility²⁸⁶ and reduced exercise-induced IOP elevation.²⁸⁷ The clinical significance of these observations has not yet been determined, but clearly further studies are indicated. At the time of publication, Bausch & Lomb has ceased manufacture and marketing of this agent.

Bunazosin

Bunazosin is a topical α_1 -selective adrenergic antagonist. In a 0.3% solution, it lowers IOP in normal volunteers and in glaucoma patients.^{288,289} Its mechanism of action appears to be to increase uveoscleral outflow, because there is no effect on aqueous inflow, outflow facility, episcleral venous pressure, or blood-aqueous barrier, perhaps by causing relaxation of the ciliary muscle rather than upregulation of matrix metalloproteinases as the prostanoids do.^{290,291} As might be expected, conjunctival hyperemia, miosis, and ptosis are side effects. In one study, miosis persisted for 24 hours after a single dose. It is additive to both prostanoids and β -blockers.⁸⁷ Bunazosin has not reached mainstream treatment status yet but may do so in the future.

Prazosin

Prazosin is a selective α_1 -adrenergic antagonist. The drug reduces aqueous humor formation and IOP in animal eyes when administered topically in concentrations of 0.001–0.1%.^{292,293} Its effect on aqueous humor production may be mediated in part by a decrease in blood pressure.

Others

Other α -adrenergic antagonists, including dibenzylchloethamine, phentolamine, phenoxybenzamine, and corynanthine, lower IOP in rabbit eyes when administered topically or systemically.^{284,294–295} Some of these drugs may reduce IOP through non-adrenergic mechanisms.

COMBINED α_1 - AND β -ADRENERGIC ANTAGONISTS

Several combined α_1 - and β -adrenergic antagonists have been developed. Some such as carvedilol are used clinically as anti-hypertensive agents and in congestive heart failure. Two, amosulalol and napradilol, have been tried as topical antiglaucoma agents. Amosulalol 0.1% reduces IOP and increases optic nerve head blood flow in rabbits.^{297,298} The mechanism of action appears to be both a decrease in aqueous production and an increase in uveoscleral outflow. Presumably the former comes from the β -blocking aspect and the latter from the α_1 -blocking aspect. Napradilol 0.25% topically also reduces IOP via similar mechanisms.²⁹⁹ Nipradilol also acts as a neuroprotectant *in vitro* for retinal ganglion cells through a nitric oxide mechanism. These agents have an antiangina effect purportedly through a similar mechanism.

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CHAPTER
26

Carbonic anhydrase inhibitors

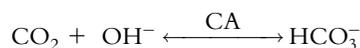
Carbonic anhydrase inhibitors (CAIs) continue to be the only systemic agents used for the long-term treatment of glaucoma, if only occasionally. A topical version introduced more than 40 years after the introduction of the systemic agent moved the oral agents quite far down on the list of practical options for the chronic treatment of glaucoma. These drugs are all derivatives of sulfonamides and were introduced into clinical practice as diuretics. Even with chronic use, their diuretic action is only effective for 1–2 weeks. CAIs reduce intraocular pressure (IOP) by decreasing aqueous humor formation. As such they are useful in essentially all forms of glaucoma, even when the anterior chamber angle is sealed or the outflow facility is very low.

Acetazolamide was introduced into clinical practice as an antiglaucoma drug in 1954 and remains the prototype for this class of drugs.¹ Other members of this group include the oral agents, methazolamide, ethoxzolamide, and dichlorphenamide, as well as the topical agents, dorzolamide and brinzolamide.

Carbonic anhydrase inhibitors have also been important tools for the study of aqueous humor dynamics. Their ability to alter aqueous humor formation has been useful in understanding the chemical composition, the turnover of substances, and the rate of aqueous humor formation.

MECHANISM OF ACTION

The enzyme carbonic anhydrase (CA) catalyzes the following reaction:



This enzyme is found in many tissues in the body, including the renal cortex, gastric mucosa, red blood cells (RBCs), lung, pancreas, and central nervous system (CNS). It is also found in many tissues in the eye, including the corneal endothelium, non-pigmented iris epithelium, pigmented and non-pigmented epithelium of the ciliary processes, Müller cells, and retinal pigment epithelium.² Carbonic anhydrase exists in multiple forms. Although type I and II CAs are both present in the corneal endothelium and lens, the type II isoenzyme (type C in another classification system) appears to be the only one of the two forms present in any quantity in human ciliary epithelium.^{3,4} Recent animal studies have placed both types III and IV CA in the non-pigmented ciliary epithelium of both rabbits and humans and have implicated it as having a role in aqueous production.^{5–8}

The notion that CAIs reduce aqueous humor formation is amply supported by a number of experimental and clinical studies

involving tonography,^{1,9} fluorophotometry,¹⁰ fluorescein appearance time in the anterior chamber,¹¹ photogrammetry,¹² changes in the steady-state concentration of endogenous ions (e.g., ascorbate, phosphate) in the anterior and posterior chambers,¹³ turnover of systemically administered substances (e.g., ascorbate, *p*-aminohippuric acid, urea, iodide, iodopyracet) in the anterior and posterior chambers,^{14–16} and dilution techniques measuring the loss of substances infused into the anterior or posterior chambers (e.g., inulin or isotopically labeled protein).^{17,18} Although all of these techniques have underlying assumptions and shortcomings, there is general agreement that CAIs in full doses reduce aqueous humor formation by about 40%. This means that at least 60% of aqueous humor formation is independent of the enzyme CA. This limits not only the efficacy of the inhibitors but also their potential ocular side effects. More than 99% of the enzyme activity must be inhibited before aqueous production is reduced.^{19,20}

There has been considerable debate about the mechanism by which CAIs decrease aqueous humor formation. This debate reflects our imperfect understanding of aqueous humor formation and the contradictory results of studies performed in different animal species. Among the issues under discussion are whether CAIs play a direct or indirect role in reducing aqueous humor formation and whether the effect is primarily ocular or systemic. With the advent of a successful topical CAI that does not change systemic parameters, that aspect of the debate is largely settled.

DIRECT EFFECT ON AQUEOUS HUMOR FORMATION

The bulk of evidence strongly suggests that CAIs reduce aqueous humor formation by a direct effect on ciliary epithelial CA:

1 Carbonic anhydrase is found in the non-pigmented epithelium of the ciliary processes.^{2–4} This metabolically active tissue is thought to be responsible for the secretion of aqueous humor.

2 Acetazolamide inhibits aqueous humor secretion by isolated rabbit ciliary processes.²¹

3 Intravenous injection of acetazolamide, 125 mg, does not lower IOP in patients with a congenital deficiency of CA II.²²

4 Small doses of CAIs can reduce IOP while producing minimal or no systemic acidosis or electrolyte imbalance.^{20,23}

5 The CAIs are capable of reducing IOP in nephrectomized rabbits.^{24,25} Friedman and co-workers found that intravenous injection of acetazolamide, 5 mg/kg, to nephrectomized rabbits lowered IOP without an effect on arterial pH, partial arterial pressure of carbon dioxide bicarbonate, or base excess.²⁵ Furthermore, acetazolamide lowers IOP in elasmobranchs that lack renal CA.

6 Topical application of CAIs lowers IOP without inducing changes in systemic acid–base or electrolyte balance.^{26–28} Furthermore, topical CAI administration to one eye with good reduction in IOP fails to significantly lower IOP in the fellow eye.^{29,30} While early studies failed to detect an effect of topical CAIs on IOP,^{19,24,31,32} this probably represented a lack of penetration of the drugs to active sites in the ciliary epithelium.

7 Intracavitary injection of acetazolamide in animals reduces IOP on the ipsilateral but not the contralateral side.³³

8 Carbonic anhydrase inhibitor administration reduces bicarbonate movement into the posterior chamber of rabbit, dog, and monkey eyes.³⁴ It is known that the rabbit eye has a posterior chamber bicarbonate concentration in excess of plasma as reflected by measurement of both cold concentration^{35,36} and $C^{14}CO_2$.³⁷ Furthermore, the entry of bicarbonate into the rabbit posterior chamber is slowed by acetazolamide.³⁷ The concentration of any ion, including bicarbonate, in the posterior chamber is affected by many factors (e.g., secretion, absorption, exchange). Acetazolamide does reduce the movement of bicarbonate from the plasma to the posterior chamber by 30–50%.³⁸ It is likely that the CAIs also reduce chloride ion transport into the posterior chamber.^{39,40}

INDIRECT EFFECT ON AQUEOUS HUMOR FORMATION

A few investigators have proposed that CA plays an indirect role in aqueous humor formation. It has been suggested that in various species the non-pigmented ciliary epithelium secretes either an acidic or a basic aqueous humor and then requires CA to generate hydrogen or bicarbonate ions for an intracellular buffering system. Such a system would help maintain intracellular pH for the enzymes involved in ion transport.^{21,41} Carbonic anhydrase inhibitors would interfere with this buffering system and indirectly reduce aqueous humor formation. Although this proposed mechanism has generated considerable discussion, there is no direct proof to support the hypothesis.

Some authorities propose that CAIs influence aqueous humor formation by altering systemic acid–base or electrolyte balance. Systemic administration of CAIs produces diuresis and metabolic acidosis. However, the diuresis and the concomitant loss of sodium, potassium, and bicarbonate in the urine are transient in nature and cannot explain the long-term lowering of IOP that is produced by CAIs.^{24,38} Other diuretic agents that are more potent and more persistent in their effects do not lower IOP.^{42,43} Furthermore, pre-treatment of animals with ammonium chloride prevents acetazolamide-induced diuresis yet does not block drug-induced IOP reduction.²⁵ Finally, in glaucomatous dogs, systemic administration of methazolamide does not increase the IOP-lowering effect of topical dorzolamide.⁴⁴

Systemic acidosis from either disease (e.g., diabetic coma) or the administration of pharmacologic agents (e.g., ascorbic acid or calcium chloride)⁴⁵ is associated with decreased IOP.^{45–47} Some investigators believe that CAI-induced IOP lowering correlates with changes in blood pH.⁴⁵ Other authorities dispute this conclusion and believe that the time course and magnitude of the ocular hypotensive response do not correlate well with changes in blood pH^{48,49}; for example, IOP declines in rabbits before acetazolamide causes any measurable effect on the kidney or blood pH.²⁴

A variety of other mechanisms has been proposed to explain the IOP reduction seen after CAI administration. Macri and Cevario⁵⁰

Carbonic Anhydrase Inhibitors	Formula	Dose
Acetazolamide (Diamox)		62.5-500 mg q 6-12 hr
Methazolamide (Neptazane)		25-100 mg q 12 hr
Dichlorophenamide (Daranide)		25-200 mg q 6-8 hr
Ethoxzolamide (Cardrase)		62.5-250 mg q 4-8 hr

Fig. 26-1 Carbonic anhydrase inhibitors.

postulated that acetazolamide lowers IOP by producing vasoconstriction in the anterior uveal tract. However, using a labeled microsphere technique in rabbits, Bill found no effect of acetazolamide on the blood flow to a number of ocular tissues, including the anterior uveal tract.⁵¹ Lütjen-Drecoll and co-workers noted that CAIs block the development of capillary fenestrations in a variety of tissues.⁵² They postulated that this phenomenon might be involved in the therapeutic effect of these drugs. Macri reported decreased episcleral venous pressure after CAI administration.⁵³ Thomas and Riley postulated that CAIs act through an adrenergic mechanism because the effects of the drugs in animals are altered by adrenalectomy and adrenergic blocking agents.⁵⁴

As stated previously, we lack a complete understanding of the mechanism of action of CAIs. The best evidence suggests that they lower IOP by reducing bicarbonate (and possibly chloride ion) movement and aqueous humor formation via a direct effect on ciliary epithelial CA. All of the CAIs share a common structure of the organic anion SO_2NH^- (Fig. 26-1). This suggests that CAIs may compete with the OH^- ion at the active site on the enzyme.^{36,55} The ocular hypotensive response is probably augmented by the induced systemic acidosis, which would explain the small increase in effect of systemic over topical agents in humans.⁵⁶

DRUGS IN CLINICAL USE

TOPICAL CARBONIC ANHYDRASE INHIBITORS

Because of the high incidence of systemic side effects with oral CAIs, investigators have long searched for active topical CAIs. Early reports indicated that topical CAIs were ineffective and speculated that circulating RBCs formed a sink that took up any drug reaching

the ciliary body.^{24,31,32,41,57} However, more recent investigations indicate that topical CAIs are quite effective in lowering IOP when administered in high concentration,^{26,58} with a soft contact lens,⁵⁹ as an analogue,^{60–62} or in an appropriate delivery system.^{63,64} As noted previously, topical CAIs are capable of lowering IOP while producing no effect on systemic electrolyte or acid–base balance. With the demonstration that a topical CAI could work, it was only a matter of time until a clinically useful agent would be developed.

Several sulfonamide-derived topical agents were examined. The original agent (ethoxzolamide gel) showed promise, but both the drug and its vehicle were noted to cause bulbar irritation in a very high percentage of patients.⁶⁵ MK-927 and its more potent S-enantiomer MK-417 were given trials and found to have satisfactory but not impressive effectiveness.^{61,66,67} Finally, dorzolamide (formerly known as L-671, 152, then MK-507) was found to have the right balance of effectiveness and minimal local side effects.^{68–70} Several years after the introduction of dorzolamide, brinzolamide, another topical CAI, was found to have similar clinical efficacy.⁷¹ These agents seem to have an equivalent effect on aqueous humor inhibition and differ only in small ways as far as side effects are concerned.⁷²

Dorzolamide

Dorzolamide (Trusopt, Merck, West Point, Penn) differs from the oral agents in that it has both a free sulfonamide group and a second amine group, which adds the right amount of lipid and aqueous solubility for good corneal penetration.⁷¹ Dorzolamide is effective in inhibiting isoenzymes II and IV, with a somewhat weaker effect on isoenzyme I.⁷¹ There is little crossover effect on the other eye, confirming its local rather than systemic action. The drug is excreted by the kidneys largely unmetabolized, but a small amount is metabolized by the liver to the *des*-ethyl form.^{73,74}

The *des*-ethyl form has a significant inhibitory effect on isoenzyme I.⁷⁵ Both dorzolamide and its metabolite are largely bound to RBC cholinesterase and are not present to any extent as free molecules in plasma. Systemic effects are minimal, but RBC CA is depressed to 21% of normal levels.⁷⁰ After 8 days of topical therapy, virtually all of the RBC CA is inhibited.⁷⁵ After 18 months of use, only about 1/200th of the concentration needed to induce significant systemic side effects is found in plasma.⁷⁵ The depression of CA in the RBCs may be seen for months after the drug has been discontinued. Despite this profound depression of RBC CA, no systemic symptoms or problems have been attributed to it.

Dose–response studies of 0.7%, 1.4%, and 2.0% have shown that the 2% solution is the most effective, producing peak and trough IOP reductions of 21% and 13%, respectively, with twice-daily usage and slightly better trough reduction with dosing three times daily.⁶⁹ The lower doses do have some effect, although they are not commercially available in the United States.⁷⁶ Topical dorzolamide reaches a peak effect on IOP at about 3 hours after dosing compared with 2 hours with oral acetazolamide.⁷³ At its peak, dorzolamide lowers IOP as well as does timolol maleate, but the effect does not last as long.⁷⁷ In monkeys, dorzolamide 2% will produce a 38% reduction in aqueous inflow.⁶² In a 1-year study, topical dorzolamide 2% appeared to be as effective and as well tolerated as topical betaxolol 0.5%.⁷⁸ Long-term studies have shown tolerability similar to or better than other topical agents such as timolol and pilocarpine.⁷⁹ Dorzolamide is available commercially as a 2% solution to be used every 8 hours as monotherapy and every 12 hours as adjunctive therapy.

In pediatric practice, dorzolamide, although not quite as effective as oral therapy, clinically worked in most of the children tested,

produced much less side effects, and was better tolerated than acetazolamide.⁸⁰ In adults with glaucoma, dorzolamide was nearly equivalent to systemic acetazolamide in lowering IOP but was much better tolerated with an improved quality of life compared to the oral agent.⁸¹

While probably not as effective as the prostaglandin analogs over the 24-hour period, dorzolamide appears comparable in pressure-lowering activity to both timolol and brimonidine when used three times daily in monotherapy.⁸² Long term, dorzolamide seems to maintain its effectiveness without tachyphylaxis and is reasonably well tolerated.⁸³ Topical dorzolamide is generally well tolerated and reasonably effective in children even under 6 years of age.^{84,85}

Surprisingly, dorzolamide is additive to other aqueous suppressants such as timolol, both clinically and in measurements of aqueous formation,^{86–89} and to drugs acting on the outflow system such as pilocarpine and prostaglandins.^{79,90} In fact, dorzolamide showed slightly better additivity in a retrospective study of 73 glaucoma patients to latanoprost than β -blockers or brimonidine.⁹¹ This slight superiority to brimonidine as an adjunctive medication was confirmed in a prospective study.⁹² In another prospective study, dorzolamide and carteolol were equally additive to latanoprost.⁹³

Dorzolamide has been used successfully in a fixed combination with timolol (Cosopt, Merck, West Point, Penn).⁹⁴ The combination certainly is more convenient than using either alone and seems to improve compliance compared to using both agents separately.^{95–97} While probably not quite as effective as bimatoprost given once daily, the fixed timolol/dorzolamide combination does seem to be as effective as latanoprost.^{98–100} One retrospective study of a large database suggests that the timolol/dorzolamide combination shows better efficacy and persistency than a fixed brimonidine/timolol combination.¹⁰¹

Brinzolamide

Another topical CAI, brinzolamide (Azopt, Alcon Laboratories, Fort Worth, TX), has become available.⁷¹ Brinzolamide was a known CAI that was irritating when used topically in solution because of its low pH and had a disappointing effect due to poor corneal penetration. Placing the compound in a suspension rather than in the traditional solution was found to improve its ability to get across the cornea, reduce the surface irritation, increase its pressure-reducing activity, and prolong the duration of action.¹⁰² In fact, topical brinzolamide 1% given three times daily to patients with glaucoma or ocular hypertension was shown in several masked studies to be at least as effective as dorzolamide 2% administered three times daily, with less discomfort on administration.^{103–105} In addition, twice-daily dosing with brinzolamide was equal in pressure-lowering efficacy to thrice-daily dorzolamide and twice-daily timolol maleate.⁷⁹ These findings were duplicated in another randomized, masked study.¹⁰⁶ In all of the studies comparing dorzolamide and brinzolamide to date, dorzolamide has a higher rate of stinging and pain on administration with brinzolamide having a higher rate of transient blurred vision from the suspension. Brinzolamide and latanoprost have been shown to be more effective when used concomitantly in keeping IOP controlled throughout the 24 hours in normal-tension glaucoma patients than either agent alone.¹⁰⁷

Like dorzolamide, brinzolamide lowers IOP an additional 13–16% when added to twice-daily timolol maleate therapy.^{108,109} Brinzolamide is additive in pressure-lowering activity when given with latanoprost.¹¹⁰ For all intents and purposes, brinzolamide 1% seems to be the therapeutic equivalent of dorzolamide.¹¹¹ Some

studies suggest that brinzolamide may be clinically more comfortable for patients than dorzolamide.^{111,112}

SYSTEMIC CARBONIC ANHYDRASE INHIBITORS

All of the commonly used oral CAIs produce similar IOP reductions and similar types of side effects when administered in equipotent doses. The various oral agents differ in potency and to some extent in efficacy; that is, they all produce a similar IOP reduction but at different doses. All of the compounds have a similar range of activity *in vitro* except for ethoxzolamide, which is five to ten times more active. The difference in potency of the various drugs *in vivo* reflects differences in lipid solubility and protein binding that affect body distribution (Table 26-1).

Acetazolamide

Acetazolamide (Diamox, Storz Ophthalmics, St Louis; Ak-Zol, Akorn, Inc., Abita Springs, LA) was the first CAI to receive widespread use in ophthalmology, and it remains the agent with which we have the greatest experience. It is supplied in 125 and 250 mg tablets and as a 500 mg sustained-release (SR) preparation. The 250 mg tablet administered four times daily produces an IOP reduction similar to that seen with the 500 mg SR preparation administered twice daily. The SR preparation is more convenient, not significantly more expensive per day, and better tolerated than are the tablets.^{113,114} In fact, the SR capsules are the fastest acting, most effective, and best tolerated at full dosage of the oral CAIs.¹¹⁵ It is rarely useful to prescribe acetazolamide in doses greater than 1000 mg/day.

After oral tablet administration, IOP begins to drop in 1–2 hours, reaches a minimum in 2–4 hours, and returns to baseline in 4–12 hours. After oral administration of a 500 mg SR preparation, IOP begins to drop in 2–4 hours, reaches a minimum in 8 hours, and returns to baseline in 12–24 hours. However, one study suggested that the SR preparation may be faster acting than previously thought.¹¹⁵

Oral acetazolamide can be administered to infants in a dose of 5–10 mg/kg every 6 hours. To prepare the medication, the pharmacist must crush the tablets and suspend the powder in flavored syrup.

Acetazolamide is also available in 500 mg emergency ampules. The drug is dissolved in 5–10 ml of distilled water and then intravenously or intramuscularly administered in a dose of 250–500 mg. After intravenous injection, IOP begins to fall within minutes, reaches a minimum in 15–30 minutes, and returns to baseline in 4–6 hours. Parenteral injection is indicated in conditions associated

with nausea and vomiting (e.g., acute angle-closure glaucoma) or when maximum IOP lowering is immediately imperative.

Acetazolamide penetrates the eye poorly because of high plasma binding and ready ionization. The serum half-life of the drug is approximately 4 hours. Acetazolamide is not metabolized and is actively secreted by the renal tubules and then passively resorbed by non-ionic diffusion.^{26,116} Older patients have a lower clearance of unbound acetazolamide, but this is mostly offset by a lower percentage of binding.¹¹⁷

The IOP reduction produced by acetazolamide generally parallels the plasma level of the drug. The maximum IOP reduction is generally obtained with plasma acetazolamide concentrations of 4–20 µg/ml.^{20,118,119} Initially, acetazolamide causes a loss of sodium, potassium, and bicarbonate in the urine. The mild metabolic acidosis that develops with acetazolamide therapy is a consequence of the initial bicarbonate loss. However, the electrolyte balance soon reaches a new steady state despite continued treatment. Bicarbonate resorption independent of carbonic anhydrase prevents further loss of this ion and progressive acidosis.¹¹⁸

Methazolamide

Methazolamide (Neptazane, Storz Ophthalmics, St Louis; Glauctabs, Akorn, Inc., Abita Springs, LA; MZM, Ciba Vision Ophthalmics, Duluth, GA) is supplied in 25 and 50 mg tablets. It is best to initiate methazolamide therapy with a low dose of the drug (e.g., 25 mg twice daily) and to increase this dose as required to control IOP. Low doses of methazolamide often reduce IOP while producing minimal acidosis and electrolyte disturbance as well as a low incidence of side effects.^{20,23} Higher doses of the drug produce greater IOP reductions but also greater acidosis and a higher incidence of side effects.^{23,119} The most common treatment regimen for methazolamide is 50–100 mg twice daily. Methazolamide, 50 mg twice daily, is slightly less effective than is acetazolamide, 250 mg four times daily or 500 mg SR preparations twice daily.^{23,119} After administration of a 50 mg tablet, IOP begins to drop in 1–2 hours, reaches a minimum in 4–6 hours, and returns to baseline in 12–24 hours. Because methazolamide has a serum half-life of 14 hours, it is unnecessary to administer the drug more frequently than twice daily.²⁰

Methazolamide is not actively secreted by the kidneys. Approximately 25% of the drug appears unchanged in the urine. The metabolic fate of the remainder is unknown, although some appears to be converted by glutathione.¹²⁰ The metabolism of methazolamide makes it a safer choice than acetazolamide for patients with advanced renal disease (e.g., a diabetic patient with neovascular glaucoma). Methazolamide has some advantages over acetazolamide. First, methazolamide diffuses into the eye more

Table 26-1 The chemical and pharmacologic properties of the systemic carbonic anhydrase inhibitors in clinical use

Name	$K_1 \times 10^{-9}$	pK _a	Unionized in plasma pH 7.4 (%)	Unbound in plasma (%)	Half-life in humans (hours)
Acetazolamide	6	7.4	50	5	4
Methazolamide	8	7.2	39	45	15
Ethoxzolamide	1	8.1	83	4	6
Dichlorphenamide	18	8.3	89	–	2

Modified from Friedland BR, Maren TH: Carbonic anhydrase: pharmacology of inhibitors and treatment of glaucoma. In: Sears ML, editor: Pharmacology of the eye: handbook of experimental ophthalmology, vol 69. Berlin, Springer-Verlag, 1984.

easily than does acetazolamide. This probably reflects in part the fact that methazolamide is less bound to plasma protein. Second, methazolamide is not actively taken up by the renal tubules as is the case with acetazolamide. Third, its duration of action makes it more convenient to use (twice daily) than acetazolamide tablets (four times daily). Some authorities postulate that methazolamide is less likely than is acetazolamide to produce urolithiasis because it produces less suppression of urinary citrate and less urine alkalinization.¹¹⁹ However, methazolamide therapy has been reported to cause urinary tract stones.^{121,122} Whether methazolamide actually has a lower incidence of urinary calculi than does acetazolamide has not been established, but most authorities prefer methazolamide to acetazolamide in patients with a history of renal lithiasis. Methazolamide diffuses more easily into the eye and CNS.^{114,123} Thus it is more likely than acetazolamide to produce such CNS-related symptoms as fatigue, depression, and drowsiness.

Ethoxzolamide

Ethoxzolamide is the most potent of the clinically used CAIs *in vitro*. However, its *in-vivo* activity is reduced by high plasma protein binding. Ethoxzolamide is supplied in a 125 mg tablet and prescribed in doses of 62.5–250 mg every 4–8 hours. The most commonly prescribed dose is 125 mg every 6 hours. After administration of a 125 mg tablet, IOP begins to fall in 2 hours, reaches a minimum in 5 hours, and returns to baseline in 12 hours.

Ethoxzolamide is a weak organic acid that is secreted slightly by the renal tubules. Forty per cent of the drug appears unchanged in the urine. The metabolic fate of the remainder is not entirely known, but some is converted by glutathione. Ethoxzolamide was the first CAI to be successfully used topically. This agent has essentially disappeared from current use in the United States.

Dichlorphenamide

Dichlorphenamide (Daramide, Merck, West Point, Penn) is supplied in a 50 mg tablet and prescribed in doses of 25–200 mg every 6–8 hours. After oral administration of a 50 mg tablet, IOP begins to fall in 30 minutes, reaches a minimum in 2–4 hours, and returns to baseline in 6–12 hours.

Despite the fact that the dichlorphenamide molecule contains two sulfonamide groups, it is no more effective than the other CAIs. Dichlorphenamide produces less metabolic acidosis because it has inherent chloruretic activity.¹²⁴ However, the continued loss of chloride sometimes produces sustained diuresis and potassium depletion. Dichlorphenamide produced more symptoms and side effects than did the other CAIs in one trial.¹²⁵ It is little used at this time.

SIDE EFFECTS

TOPICAL CARBONIC ANHYDRASE INHIBITORS

The side effects of the topical CAIs are largely ocular in nature (Box 26-1). Stinging on administration is the most common especially with dorzolamide.¹²⁶ Some patients experience actual ocular pain.¹²⁷ As noted above, brinzolamide often produces a transient blurring of vision. Presumably because of their sulfonamide derivation, the topical agents are associated with a relatively high rate of allergic reactions (about 10%), as are the oral agents. Contact dermatitis may be seen on the eyelids.^{128,129}

Superficial punctate keratopathy is seen in about 10% of cases. Transient myopia has been reported. All of the major topical

Box 26-1 Side effects of topical carbonic anhydrase inhibitors

Ocular

- Stinging
- Allergy
- Dryness
- Superficial punctate keratopathy
- Induced myopia

Systemic

- Metallic taste
- Urticaria
- Neutropenia
- Headache
- Gastrointestinal distress
- Dizziness
- Paresthesias
- ?Aplastic anemia
- ?Stevens-Johnson syndrome

antiglaucoma medications can be associated after long-term use with squamous metaplasia of the conjunctiva and the topical CAIs are no exception.¹³⁰ What this finding portends clinically is not known, although rare patients may react to long-term topical medication use with a syndrome that looks like ocular cicatricial pemphigoid.

As can happen with any sulfa-derived medication, choroidal detachments with induced myopia and hypotony have been reported.^{131–133} A prospective study on 34 glaucoma patients of the effect of dorzolamide on axial length and refraction failed to show any change in refraction after 2 weeks of use.¹³⁴

The corneal endothelium is rich in CA; this fact caused concern that CA inhibition by topical agents might interfere with endothelial function. Using ultrasonic pachymetry, Wilkerson and co-workers⁷⁰ showed that topical dorzolamide administered over 4 weeks increases the corneal thickness very slightly compared with placebo; however, it is unlikely that this small change is clinically significant, as confirmed by Kaminski and co-workers.¹³⁵ Furthermore, Serle and co-workers failed to show any change in corneal thickness after 6 weeks of application.¹³⁶ In a multicenter study, Lass and co-workers were unable to demonstrate any differences in corneal thickness or specular microscopy after 1 year of topical therapy with either dorzolamide, timolol, or betaxolol.¹³⁷ In a controlled study spanning over 6 years, Baratz and co-workers were unable to show any changes in specular or confocal microscopy of the cornea with chronic glaucoma therapy versus no treatment.¹³⁸ Finally, one study induced acute corneal edema through contact lens overwear in 19 patients with glaucoma or ocular hypertension without finding any effect of dorzolamide on recovery time.¹³⁹ These were otherwise healthy corneas and the results might not be generalizable to those with borderline or worse endothelial function.¹³⁹ On the other hand, several small series have shown an increase in corneal thickness after chronic dorzolamide therapy.¹⁴⁰

Despite the lack of evidence that dorzolamide or brinzolamide affect corneal thickness or microscopic structure in normal corneas, case reports have surfaced of corneal decompensation in patients treated with dorzolamide.^{141,142} Whether this is an effect of the carbonic anhydrase inhibition or whether these corneas had Fuch's dystrophy or were predisposed to aphakic or pseudophakic bullous keratopathy is not clear at this time. Clearly, this is an uncommon or even rare complication, but until further information is received,

caution is indicated regarding the use of topical CAIs in those patients with borderline corneal endothelial function. Other agents should be tried first. However, CAIs are probably less toxic to the endothelium than intraocular surgery so they could be tried with careful monitoring.

Although serious systemic side effects are not common, some do occur. A metallic taste in the mouth, especially associated with carbonated beverages, is relatively common (25%). Obviously, systemic side effects can be reduced by having the patient use simple eyelid closure and punctal occlusion immediately after administering the drops. Some of the more serious side effects associated with the oral agents (e.g., aplastic anemia and Stevens-Johnson syndrome) have not been reported with topical agents; however, anecdotal reports of neutropenia suggest that it may only be a matter of time before the rare case is actually seen.^{143,144} Gastrointestinal distress may occur particularly in the first few days of use. Urticaria and dizziness have also been reported in rare instances as has bullous pemphigoid.¹⁴⁵ Although RBC CA is depressed with topical dorzolamide, no symptoms appear to be associated with this finding. Nephrolithiasis has been reported in one patient.¹⁴⁶ Erythema multiforme has been associated with topical dorzolamide use.¹⁴⁷ Other side effects, especially those associated with systemic agents, may be seen as the topical agents are used in more patients for longer periods.¹⁴⁸

ORAL CARBONIC ANHYDRASE INHIBITORS

It is estimated that 50% of glaucoma patients cannot tolerate long-term treatment with oral CAIs because of the associated side effects (Box 26-2). The etiology of many of the side effects is unclear but may be related to acidosis or carbon dioxide retention. It is important to emphasize that the incidence and severity of side effects can be reduced greatly by using the medication in the lowest dose and frequency necessary for IOP control. Patients should be warned of potential side effects and told that many side effects will diminish in severity after a few days to a few weeks of treatment. Patients prepared in this manner are more trusting of the physician and are more ready to accept problems when they occur. Older patients are generally less tolerant of oral CAIs.¹⁵⁷

One important study found that patient tolerance to the various CAIs in fixed doses is as follows (in order of decreasing tolerance): acetazolamide, 500 mg SR preparation twice daily; methazolamide, 50 mg every 6 hours; ethoxzolamide, 125 mg every 6 hours; acetazolamide, 250 mg every 6 hours, and dichlorphenamide, 50 mg every 6 hours.¹²⁵ Although no study has placed methazolamide, 25 mg every 12 hours, in this tolerance ranking, in the authors' experience it is often effective and the best tolerated of the oral CAIs. A patient who is intolerant of one CAI may be more tolerant of another. Generally, however, the side effects are more closely linked to the dose than to the specific drug.

CONTRAINDICATIONS

The relative contraindications to CAI treatment include Addison's disease and adrenal insufficiency, cirrhosis of the liver,¹⁵⁸ chronic respiratory acidosis,¹⁵⁹ renal failure, hyperchloremic acidosis, depressed serum sodium or potassium levels, diabetic ketoacidosis, and repeated episodes of urolithiasis. When treated with CAIs, patients with cirrhosis of the liver may retain ammonia and develop hepatic coma.¹⁵¹ Combined treatment with a CAI and aspirin may cause severe acidosis and salicylate intoxication.¹⁶⁰ Salicylate may

Box 26-2 Side effects associated with oral carbonic anhydrase inhibitor therapy

Myopic shift*

Paresthesias of fingers, toes, circumoral region*

Decreased dexterity

Electrolyte disturbances

Metabolic acidosis*

Potassium depletion associated with concomitant use of diuretics or corticosteroid

Chloride depletion associated with use of dichlorphenamide

Uric acid retention¹¹⁵

Gastrointestinal

Abdominal cramping/discomfort*

Metallic taste to carbonated beverages*

Nausea

Diarrhea*

Anorexia

Weight loss*

Constipation

Genitourinary

Nocturia

Urolithiasis*

Impotence¹⁴⁹

Frequency with polydipsia* (especially in the first week of treatment)

Hypersensitivity nephropathy*¹⁵⁰

Central nervous system

Malaise*

Excitement

Elevated cerebrospinal fluid pressure¹⁵¹

Fatigue*

Confusion

Depression*

Drowsiness*

Headache

Decreased libido

Vertigo

Irritability*

Insomnia

Tremor

Blood dyscrasias

Thrombocytopenia*

Agranulocytosis*

Hyperchromic anemia

Aplastic anemia*

Neutropenia

Interference with anticholinesterase treatment of myasthenia gravis¹⁵²

Exacerbation of effect of diphenylhydantoin on bone demineralization¹⁵³

Dyspnea*

Leg cramps

Hearing loss

Birth defects

Hypersensitivity hepatitis¹⁵⁴

Dermatologic

Rash

Exfoliative dermatitis* (Stevens-Johnson syndrome)

Pruritis*

Hair loss¹⁵⁵

Flushing

Hirsutism¹⁵⁶

*Effects are either common or of major clinical concern.

also inhibit protein acetazolamide binding and plasma clearance of unbound drug.¹⁶¹ Patients with severe chronic obstructive pulmonary disease who are treated with CAIs may develop carbon dioxide retention and respiratory acidosis.¹⁵²

The only ocular side effect caused by the oral CAIs is a transient myopic refractive shift that develops within hours and lasts for hours to a few days. There is controversy about the mechanism of this side effect. Some investigators believe that the refractive shift is caused by an increased refractive power of the lens, whereas others believe that the lens moves forward because of ciliary body swelling and rotation.¹⁶² Subsequent doses of the medication may cause no further difficulty.¹⁶³

Almost all patients initiating oral CAI treatment develop paresthesias of the fingers, toes, and perioral region. This symptom usually subsides after a few weeks of treatment. It is rarely incapacitating, although an occasional patient may complain of decreased dexterity.

Many patients taking CAIs complain of one or more of a group of symptoms, including malaise, fatigue, weight loss, anorexia, depression, and decreased libido. Some investigators believe this symptom complex is related to systemic acidosis,¹⁶⁴ but others question this relationship.¹⁶⁵ Epstein and Grant¹⁶⁴ recommend measuring serum carbon dioxide and chloride levels in symptomatic patients receiving CAIs. If the blood tests indicate systemic acidosis, they suggest treatment with sodium acetate in doses of 90 mEq/day; this treatment improves the symptom complex in more than 50% of their symptomatic patients.¹⁶⁶ It should be noted, however, that the treatment does not seem to reduce the systemic acidosis to a corresponding degree. Furthermore, previous attempts to treat symptomatic patients with potassium chloride, sodium chloride, sodium citrate, and sodium bicarbonate have yielded mixed results.^{164,167,168} Further studies are needed to determine the efficacy of this approach, although the advent of topical agents may make this type of approach unnecessary in the vast majority of patients.

Acidosis and sickling of red blood cells

There is one situation in which the acidosis induced, especially by acetazolamide, may be dangerous. Sickling of RBCs in susceptible patients is exacerbated by acidosis. Care should be taken in patients with sickle cell disease of any kind when using oral CAIs. This is particularly true in acute glaucomas associated with trauma, in which the acidosis produced by oral or parenteral CAIs may cause increased sickling of RBCs. This increased sickling can further clog the trabecular meshwork, delay the resolution of hyphema, and even compromise the circulation of the optic nerve. Systemic CAIs should be avoided or used with great caution in this circumstance.¹⁶⁹

Other severe symptoms

Epstein and Grant¹⁶⁴ and Arrigg and co-workers¹⁶⁶ suggest additional tests in patients who develop severe symptoms from CAIs. They recommend checking serum creatinine levels to determine whether reduced renal function calls for a reduced dose of the drug. They also suggest measuring serum potassium levels, particularly in patients receiving potassium-losing diuretics. Potassium loss occurs during the early phase of CAI treatment but usually ceases over time. However, patients who are receiving both CAIs and drugs such as chlorothiazide diuretics or corticosteroids may develop severe potassium deficiency. It should be emphasized that the vast majority of patients receiving CAIs are not potassium depleted and do not benefit from routine potassium supplementation.¹⁷⁰ Epstein and Grant¹⁶⁴ and Arrigg and co-workers¹⁶⁶

also recommend measuring the serum drug level in symptomatic patients. Some patients maintain very high serum drug levels despite standard clinical doses of medication. Reducing the dose may decrease the side effects in these patients without diminishing the therapeutic effect of the drug.

Gastric burning and irritation are common in patients receiving CAIs. This occurs despite a reduction in hydrochloric acid production by the stomach. These side effects appear to be caused by local irritation of the gastric mucosa, and as such they may be reduced by antacids or by taking the drug with meals. Like other sulfonamide derivatives, CAIs are associated with hematologic reactions, including aplastic anemia, leukopenia, pancytopenia, agranulocytosis, and (rarely) thrombocytopenia.^{171–173} As of 1989, there were 139 reports of patients developing blood dyscrasias while taking CAIs; more than one-third of these patients died as a result of the bone marrow depression.¹⁷² Fraunfelder and co-workers^{173,174} suggest that all patients receiving CAIs have complete blood counts every 6 months. This approach assumes that the blood dyscrasias are dose related rather than idiosyncratic and that stopping the drug sooner improves the prognosis. These assumptions are unproven, however, and the efficacy of routine blood tests is unknown.

Because most episodes of bone marrow depression occur within 6 months of initiating CAI therapy,¹⁷³ some clinicians have suggested that blood counts be performed every 2 months for the first several months of treatment.¹⁷⁵ Once again, however, the value of this approach is unproven. The vast majority of clinicians do not currently order routine blood tests,¹⁷⁶ but it is reasonable to ask patients about symptoms that could be related to bone marrow depression such as bruising, excessive bleeding, and susceptibility to infection. It is also wise to alert patients to the possibility of bone marrow suppression and the early symptoms thereof in the hopes of catching the condition before it becomes irreversible. However, there is no evidence that any precautions are valuable in this idiosyncratic situation.

Urolithiasis is an important side effect of oral CAI treatment.^{177–179} It is postulated that CAIs decrease the urinary concentration of citrate and magnesium, thereby favoring the precipitation of calcium salts.^{177,180} The CAIs also produce a temporary urine alkalization, which favors urolithiasis.¹⁸¹ A retrospective case study notes that CAI therapy is associated with an 11- to 15-fold increase in urolithiasis compared with the same patients before treatment or a control group receiving no treatment (Fig. 26-2).¹⁸² Most calculi occur within the first 12 months of treatment. Patients with a

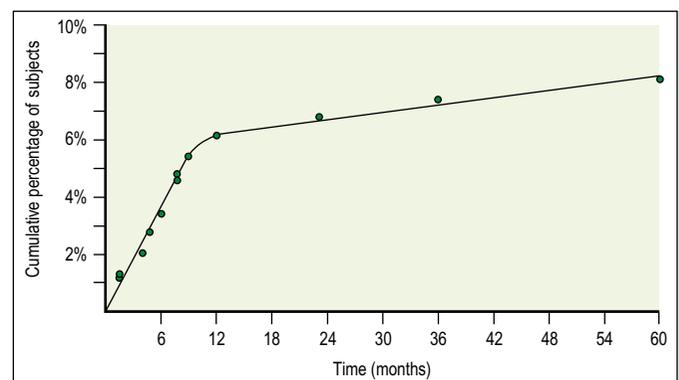


Fig. 26-2 Cumulative percentage of individuals developing one or more episodes of urolithiasis while being treated with acetazolamide. (From Kass MA, et al: *Ophthalmology* 88:261, 1981. Published courtesy of *Ophthalmology*.)

history of a single episode of a calculus before treatment appear to be at no greater risk of stone formation with CAI therapy. However, patients who develop a stone while on CAI treatment have a 50% incidence of additional stones if that treatment is continued.¹⁸² It is unknown whether diet, other drugs, or vitamin D interact with the CAIs to influence the production of calculi. There is one report that concomitant oral potassium citrate or sodium citrate treatment reduces the incidence of calculi in patients receiving CAIs.¹⁸³ This report has not yet been confirmed.

Like other sulfonamides, the oral CAIs can be associated with severe allergic reactions. A generalized maculopapular rash is relatively common with the oral agents. Exfoliative dermatitis (Stevens-Johnson syndrome) has also been reported with both acetazolamide and methazolamide.¹⁸⁴ This is a very rare but potentially fatal problem for which there is no prophylaxis. Patients should be warned to report the first signs of skin rash or mucous membrane difficulties.

One case report links CAIs with sacrococcygeal teratoma.¹⁸⁵ The CAIs have also been reported to cause teratogenic effects on forelimb development in rat, hamsters, and mice.^{186–188} For these reasons, great caution should be exercised in prescribing CAIs for pregnant women, especially in the first trimester. Acetazolamide also appears in human milk. However, the dose to the child appears to be very low.¹⁸⁹

On the positive side, long-term (more than 4 years) use of oral CAI in postmenopausal women is associated with less bone demineralization than in control subjects.¹⁹⁰

Retinal-choroidal blood flow and neuroprotection

Many studies and much speculation have suggested that glaucomatous damage may be, at least in part, caused by reduced blood flow to either the optic nerve or nerve fiber layer. Systemic CAIs were noted, relatively early, to dilate vessels, and that observation is now a routine part of assessing vascular perfusion reserve in the brain.^{191–193} The mechanism may be, in part, a cascade related to CO₂ retention with nitric oxide and Ca⁺⁺ channel blockade also playing a role.^{194–196} Speculation began to build that the carbonic anhydrase inhibitors might be instrumental in increasing blood flow to the retina and optic nerve and have value in reducing ischemic injury from acute glaucoma, diabetic retinopathy, and other vascular disorders.¹⁹⁷ An increase in choroidal pulsatile blood flow was noted with oral acetazolamide raising the hopes that improved optic nerve circulation could be a beneficial side effect of its use.¹⁹⁸

Shortly after dorzolamide was released, studies began regarding its effect on ocular blood flow. Both topical brinzolamide and dorzolamide do get back to the retina in sufficient concentration to potentially dilate retinal vessels.¹⁹⁹ One of the first studies noted increased ocular pulse pressure following its use.²⁰⁰ Another noted dilation of major retinal vessels, although the significance of this for optic nerve blood flow is not clear.²⁰¹ However, not all studies agree; two studies failed to show any change after dorzolamide treatment in optic nerve capillary blood flow, presumably due to intact autoregulation or other retinal hemodynamic characteristics.^{202,203} A study by Harris and co-workers suggested that dorzolamide might increase retinal blood velocity without affecting retrobulbar parameters; this same study demonstrated an increase in contrast sensitivity after a month's treatment with topical dorzolamide compared to control.^{204,205} This observation was confirmed in two independent studies.^{206,207} However, other studies have provided conflicting results (often from the same author).^{208–212} One study of brinzolamide showed increased peripapillary blood flow

by Doppler flowmetry suggesting that brinzolamide has similar hemodynamic effects to dorzolamide.²¹³ The clinical significance (if any) of these observations is not yet clear.

Part of the problem may lie in the difficulty of assessing blood flow in the eye. Most of the current methods for assessment in human eyes are indirect, such as measurement of pulse pressure or blood velocity rather than actual flow. Another problem in interpreting data relates to the fact that some studies observe single-dose or short-term effects in what is basically a chronic disease. For the moment, the data do suggest a somewhat positive effect on ocular blood flow of the topical CAIs but the clinical significance of this observation is not clear. One study in glaucomatous rats suggests that dorzolamide may have neuroprotective properties but it is not clear in this study whether the neuroprotection resulted from lowering IOP or from some effect independent of IOP lowering.²¹⁴

SUGGESTIONS FOR USE

Carbonic anhydrase inhibitors cause a substantial reduction in aqueous humor production and IOP in 80–90% of patients.²¹⁵ Because of more frequent topical side effects and a relatively lower potency compared to prostaglandins, the topical CAIs are relegated to second-line or adjunctive status. Furthermore, adherence and persistence are likely to be inferior to that seen with the prostaglandins, probably related to the difference in the number of times per day of dosing.²¹⁶ The topical carbonic anhydrase inhibitors may be used as monotherapy especially in those intolerant to other agents or those with cosmetic issues related to the prostaglandin-like agents.

For chronic use, most physicians would use topical agents first and use oral agents only as a very last resort because long-term glaucoma control with a medical regimen that includes oral CAIs can be maintained in only about 50% of cases.¹¹⁵ Nevertheless, many patients do get a significant incremental lowering of IOP from the oral agents compared to the topical ones and can tolerate the medication for long periods of time. Because side effects are often dose dependent, one can start with 25 mg of methazolamide twice daily and increase that to 50 mg twice daily or even three times daily. Higher doses than 50 mg three times daily often produce side effects and acetazolamide sustained-release capsules 500 mg twice daily become more tolerable (and more likely to be taken at the twice-daily dosage.) The least tolerable of the regimens is acetazolamide tablets four times daily. In general, adding oral and topical CAIs concomitantly should have little additive effect.^{217,218} However, sometimes the additive effect can be substantial, especially in children or those with secondary glaucomas.²¹⁹ Whether this incremental effect is truly due to additive effects or the stronger oral agent alone is not clear at this time.

Most of the therapeutic failures of the oral agents are caused by intolerable side effects. A minority of the therapeutic failures are due to lack of efficacy of the medication.²²⁰ It is not surprising that IOP is not controlled with CAIs in some patients because the drugs are usually prescribed for individuals with advanced disease that is uncontrolled by the maximum tolerated topical therapy. In eyes with very poor outflow facilities, even a 40% reduction in aqueous humor formation may be inadequate to maintain IOP at acceptable levels. Oral CAI therapy, like other types of medical therapy, can also fail because of at least three other reasons – the expense of the medication, variable drug absorption and

metabolism, and poor compliance. The availability of therapeutically equivalent generic acetazolamide and methazolamide has greatly decreased the potential cost of these agents.²²¹

Another cause of therapeutic failure is variable drug absorption. The relationship between the dose of a CAI and the resulting serum level of the drug is quite variable. For example, in one study there was as much as a six-fold difference in the dose required to achieve a therapeutic serum drug level.¹⁶⁴ A third cause of therapeutic failure is patient defaulting. Alward and Wilensky¹⁶⁵ estimated compliance with acetazolamide on the basis of serum carbon dioxide levels. They found that 35% of outpatients were non-compliant (i.e., serum carbon dioxide = 25 mEq/l), and 22% were partially compliant (i.e., serum carbon dioxide between 20 and 24.9 mEq/l) with acetazolamide treatment.

In view of the possible systemic side effects, most ophthalmologists are cautious in prescribing oral CAIs for unilateral glaucoma. This is especially true if the involved eye has limited visual potential. Use of oral CAIs should be avoided or used with great caution in patients with a past history of allergy to sulfonamide or its derivatives and in those with renal or hepatic failure. All patients using oral CAIs chronically should be warned to watch for generalized rash, itching, depression, prolonged bleeding, and increased infection rate, as, if caught early, these are usually reversible but may not be if diagnosis is delayed.

ANGLE-CLOSURE GLAUCOMA

Acetazolamide is used frequently for the treatment of acute angle-closure glaucoma in conjunction with a topical miotic agent, a topical α and/or β -adrenergic antagonist, and a hyperosmotic agent. All of these drugs are used to stop the acute attack, permit the sphincter to again be reactive to miotics, prevent damage to the optic nerve, allow better examination after the corneal edema clears, and quiet the eye in preparation for surgery. If a patient with acute angle-closure glaucoma has nausea and vomiting, acetazolamide can be given intravenously or intramuscularly in doses of 250–500 mg (repeated in 4–6 hours). After iridectomy, topical CAIs may be required to control residual glaucoma.

OPEN-ANGLE GLAUCOMA

The CAIs have their greatest use in the long-term treatment of open-angle glaucoma. They are additive in their effect on IOP with the miotics, epinephrine, dipivefrin, and the topical β -adrenergic antagonists.^{79,86,222,223} The most detailed studies performed involve acetazolamide and timolol. These studies indicate that the drugs are partially and not fully additive; acetazolamide reduces outflow pressure by 46–49%, timolol reduces outflow pressure by 36–39%, and the two drugs together reduce outflow pressure by 61–62%.^{222,224} Some pharmacologists refer to this as *multiplicative additivity*; acetazolamide reduces outflow pressure by 45% and timolol reduces the remaining 55% by 35% (i.e., 19%), for a total reduction of outflow pressure of 64%.

For open-angle glaucoma, dorzolamide or brinzolamide can be used as additive therapy in typical cases after a β -blocker and/or a prostaglandin-type drug have been tried. Evidence exists in many studies to support the additive effects of dorzolamide to both β -blockers and prostaglandin-like agents.^{225,226} Dorzolamide or brinzolamide can be used as primary therapy if there are relative or absolute contraindications to β -blocker therapy, if the patient is uncomfortable with the possibility of iris color change from

latanoprost, and if brimonidine is not a viable option. When used as primary therapy, dosage should be started at three times daily. When used as adjunctive therapy, the dosage should be started at twice daily and increased to three times daily if there is a mid-day or late afternoon spike in IOP.

While most ophthalmologists would agree that laser trabeculoplasty is a more appropriate option than oral CAIs, in most cases a trial of oral CAIs may be appropriate if laser or incisional surgery is likely to fail, is contraindicated by the patient's physical or mental condition, or is unacceptable to the patient. Some increment in IOP control can be obtained with the oral agents compared with topical dorzolamide.⁵⁶ No evidence exists to justify using both topical and oral agents concurrently in adults although some additivity has been reported in the pediatric age group.²²⁷

If oral CAI therapy is indicated, it is best to initiate treatment in an adult with a low dose of the drug (e.g., the SR preparation of acetazolamide once daily or 25 mg of methazolamide twice daily) and to increase this to higher doses only if required by the clinical condition. It is often counterproductive to initiate therapy with the 250 mg tablets four times daily or the 500 mg SR preparation twice daily because acetazolamide in large doses often produces such severe side effects, especially at first, that patients may refuse to continue treatment. Lower doses of acetazolamide or methazolamide are often effective in controlling the IOP while producing fewer side effects than the full doses. It is easier to convince a patient to increase the dose of acetazolamide when the therapeutic effect is inadequate than to reduce the dose when the side effects are overwhelming.^{228,229}

SECONDARY GLAUCOMA

Topical CAIs seem to work quite well in secondary glaucomas for both short- and long-term use. The oral CAIs may be useful for treating self-limited secondary glaucomas such as that seen after trauma. The drugs should be used only as long as necessary. The oral CAIs can also be used (with caution) for the long-term treatment of secondary glaucoma following the suggestions outlined in the section on open-angle glaucoma.

INFANTILE AND JUVENILE GLAUCOMA

Acetazolamide is used preoperatively to lower IOP in infants and young children with glaucoma to clear the cornea, allow a better examination, and facilitate surgery. The drug is administered in doses of 5–10 mg/kg every 6 hours. Dorzolamide or brinzolamide may be used chronically for surgically unresponsive infantile glaucoma or for juvenile glaucoma. If oral agents are necessary in a long-term treatment regimen, both infants and children may develop acidosis with concomitant lethargy and reduced appetite.

OTHER USES

Based on the observation that it increases the adhesion between the retina and the retinal pigment epithelium,²³⁰ oral acetazolamide was used by Cox and co-workers to treat chronic macular edema.²³¹ The drug had limited but measurable success in some patients. The same effect could not be obtained with a thiazide diuretic. Response was most likely in patients with inherited outer retinal disease or uveitis and was unlikely in those with primary retinal vascular disorders. At 500 mg/day, visual acuity improved and there was reduced macular edema on fluorescein angiography.²³²

In one study, topical dorzolamide given twice daily showed some improvement in fluorescein angiographic appearance in 2 of 5 patients compared with placebo, but visual acuity was not improved in any of the patients.²³³ Conversely, oral acetazolamide showed improvement in visual acuity in 3 of 5 patients and improvement in fluorescein angiographic appearance in all 5 patients. This suggests that topical dorzolamide may have some positive effect, but oral acetazolamide is superior in this particular application.

Carbonic anhydrase inhibitors are also used in cases of benign intracranial hypertension (pseudotumor cerebri)²³⁴ and in preventing and treating mountain (high-altitude) sickness.²³⁵ Acetazolamide has also been used in central retinal artery occlusion in the hopes of dilating the retinal vasculature and allowing the embolus or thrombus to move downstream.²³⁶

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CHAPTER
27

Cholinergic drugs

The cholinergic drugs are the oldest effective medical treatment for glaucoma. More than 100 years ago, Laqueur¹ used physostigmine (eserine), an extract from the Calabar or ordeal bean, for the treatment of glaucoma, and Weber² described the effects of pilocarpine, an extract from the leaf of a South American plant, on the pupil. The cholinergic drugs mimic the effects of acetylcholine, which is a transmitter at postganglionic parasympathetic junctions, some postganglionic sympathetic endings (e.g., sweat glands), autonomic ganglia, somatic motor nerve endings (i.e., skeletal muscle), and some central nervous system synapses. Acetylcholine is synthesized by the enzyme choline acetyltransferase and produces its effects by binding to cholinergic receptors in various tissues. Cholinergic drugs are applied topically for the treatment of glaucoma because of their effect on parasympathetic receptors in the iris and ciliary body. However, topical miotics absorbed systemically can produce side effects by stimulating cholinergic receptors in other sites.

Drugs that mimic the effects of acetylcholine act at muscarinic and/or nicotinic receptors, the latter being subdivided into N_1 and N_2 types. This classification system is based on the relative potency of various agonists and antagonists at the different receptor sites. As a rule, muscarinic receptors are found in smooth muscle and glands, stimulated by muscarine and inhibited by atropine. N_1 nicotinic receptors are found in autonomic ganglia, stimulated by dimethylphenylpiperazine and inhibited by hexamethonium and D-tubocurarine. N_2 receptors are found in striated muscle, stimulated by paratrimethylammonium and inhibited by decamethonium or D-tubocurarine. Nicotine stimulates N_1 and N_2 receptors at low doses and inhibits them at high doses.

Acetylcholine is released from vesicles in nerve terminals and then hydrolyzed within a few milliseconds by acetylcholinesterase. The rapid destruction of acetylcholine permits the cholinergic receptors to repolarize and prepare for the next stimulation. Cholinergic drugs act either directly by stimulating cholinergic receptors or indirectly by inhibiting the enzyme cholinesterase, thereby potentiating and prolonging the effects of endogenous acetylcholine.

Strictly speaking, the words *cholinergic*, *parasympathomimetic*, and *miotic* are not synonymous; cholinergic refers to acetylcholine, parasympathomimetic refers to the parasympathetic nervous system, and miotic refers to a constricted pupil. However, we will follow common ophthalmic usage in this text and use the three words interchangeably to refer to this entire class of drugs.

MECHANISMS OF ACTION

ANGLE-CLOSURE GLAUCOMA

Cholinergic drugs are useful for the short-term management of angle-closure glaucoma associated with pupillary block. Miotic agents help prepare an eye for iridotomy and are not a substitute for it in pupillary block angle-closure glaucoma. Cholinergic drugs constrict the pupillary sphincter, tighten the iris, decrease the volume of iris tissue in the angle, and pull the peripheral iris away from the trabecular meshwork. These changes reduce intraocular pressure (IOP) by allowing aqueous humor to reach the outflow channels. If the IOP is quite elevated (i.e., above 45 or 50 mmHg), the pupillary sphincter may be ischemic and may not respond to cholinergic stimulation.³ In this situation, other drugs (i.e., a topical α -adrenergic antagonist, topical apraclonidine or brimonidine, possibly a topical or systemic carbonic anhydrase inhibitor, and, if necessary, a systemic hyperosmotic agent) are used to reduce IOP sufficiently so that a parasympathomimetic agent can produce miosis.

While tradition and over a century of experience have confirmed the utility of pilocarpine use in acute angle-closure attacks, recent evidence suggests that our understanding of how the drug accomplishes what it does and under what circumstances is incomplete. For example, Chinese with acute angle-closure attacks in one eye show less opening of the angle after topical pilocarpine in the fellow eye.⁴ Certainly, caution is warranted when considering the use of these agents chronically in narrow-angle eyes without iridotomy.

It is important to emphasize that miotic agents are capable of narrowing the angle in some eyes, especially in eyes with shallow anterior chambers or spherophakia. Constricting the pupil increases the area of contact between the iris and the lens and may augment pupillary block and iris bombé. Furthermore, contraction of the ciliary muscle loosens the zonules, allowing the lens to move forward and become more spheric in shape. Usually the net effect of direct-acting cholinergic drugs such as pilocarpine and carbachol is to open narrow angles. Occasionally, standard miotic agents in high concentrations or cholinesterase inhibitors such as demecarium and echothiophate can produce sufficient miosis, forward movement of the lens, and vascular congestion to precipitate or aggravate angle-closure glaucoma.^{5,6} Cholinesterase inhibitors are difficult to reverse and are rarely indicated in unoperated cases of angle-closure glaucoma with pupillary block. Following a laser or standard iridectomy, cholinesterase inhibitors may be useful in controlling residual glaucoma.

OPEN-ANGLE GLAUCOMA

In open-angle glaucoma, the cholinergic agents reduce IOP by increasing the facility of outflow. Parasympathomimetic drugs stimulate the ciliary muscle, putting traction on the scleral spur and the trabecular meshwork, which separates the trabecular sheets and prevents Schlemm's canal from collapsing. This mechanical change in the configuration of the meshwork increases fluid conductivity.⁷⁻⁹ The cholinergic drugs do not cure the basic outflow disorder of glaucoma (i.e., primary open-angle glaucoma is not caused by cholinergic insufficiency), but they do reduce the obstruction to outflow, thereby lowering IOP and preventing or reducing optic nerve damage. Several lines of evidence support this proposed mechanism of action of the cholinergic drugs:

1. A number of experimental conditions that pull on the scleral spur or contract the ciliary muscle reduce resistance to outflow, including voluntary accommodation,¹⁰ electrical stimulation of the oculomotor nerve,¹¹ posterior depression of the lens,¹¹ tension on the choroid,¹³ and traction on the iris root with a suture.¹⁴

2. Histologic studies indicate that cholinergic agents widen the intertrabecular spaces, distend the juxtacanalicular tissue, and increase the number of giant vacuoles in the endothelium of Schlemm's canal, implying an increased flow through the meshwork.^{15,16} Some of these changes are also seen in tissue culture.¹⁷

3. Topical, intracameral, and systemic cholinergic drugs reduce outflow resistance in animal eyes.¹⁸ Conversely, ganglionic blocking agents and cholinergic antagonists increase resistance to outflow.¹⁹⁻²¹

4. Intravenous injection of pilocarpine produces an almost instantaneous increase in outflow facility in monkey eyes.¹⁸ This implies that the effect is mediated by an arterially perfused structure (i.e., the ciliary muscle as opposed to Schlemm's canal).

5. Detaching the ciliary muscle from the scleral spur in monkey eyes almost abolishes the facility-increasing effect of miotic agents.²²⁻²⁴ This indicates that cholinergic drugs do not have a major direct action on the trabecular meshwork or Schlemm's canal, as had been proposed in the past. However, some improvement in outflow with the use of miotics persists even when the ciliary muscle has been disinserted, suggesting that other mechanisms may be at work as well; furthermore, although ciliary muscle function declines with age, the effect of cholinergic stimulation does not appear to be affected by age.²⁵ The residual effect on outflow facility may be mediated by cyclic AMP.²⁶

Cholinergic agents reduce unconventional or uveoscleral outflow.²⁷ Thus the net decrease in IOP produced by miotic drugs represents a predominance of the trabecular effect over the uveoscleral effect.

The effect of cholinergic agents on outflow facility does not depend on pupil size. Parasympathomimetic drugs increase outflow facility in the presence of a bound-down pupil, a sector iridectomy, or multiple sphincterotomies. Dilating the pupil with phenylephrine does not inhibit the effect of cholinergic agents on outflow facility. In monkeys, totally removing the iris has no effect on IOP, aqueous outflow, or the response of outflow resistance to pilocarpine.²³

A number of studies using tonography have detected an apparent pilocarpine-induced reduction in aqueous humor formation. It has been postulated that cholinergic agents alter aqueous humor

formation by constricting afferent arterioles in the ciliary body.²⁸ However, other studies, including direct measurements of aqueous formation by fluorophotometry, fail to confirm this.²⁹ Miotic agents are reported to produce a slight but clinically insignificant increase in episcleral venous pressure.²⁹

Continuous exposure to high levels of one cholinergic agonist produces subsensitivity to stimulation by another agonist in a number of animal models.^{30,31} The induced subsensitivity appears to be more profound after treatment with cholinesterase inhibitors or constant-release preparations of direct cholinergic agents.^{31,32} In part, this process may be caused by a decrease in the number of cholinergic receptors on the ciliary muscle cell membranes (i.e., 'downregulation of receptors').³³ However, there is also experimental evidence in animals suggesting a direct or indirect toxic effect of miotic agents on the trabecular meshwork and ciliary epithelium, muscle, and stroma.³⁴ The clinical significance of these findings is unclear at present. It is unknown whether these processes explain the loss of therapeutic responsiveness to cholinergic agents seen in some patients.

Cholinergic agents are additive to virtually all other classes of IOP-lowering agents including the prostaglandin-like ones.^{35,36} Fixed combinations such as timolol/pilocarpine have the advantage of convenience and therefore may enhance compliance. In addition, the fixed combinations reduce the amount of preservative to which the eye is exposed. However, the combinations have the disadvantage of non-optimal dosing. For example, timolol/pilocarpine combines a once or twice a day medication with a four times a day medication, raising the issue of either overdosing with one or underdosing with the other. Pilocarpine does seem to block some of the IOP-lowering effect of latanoprost when used in combination (at least in monkey eyes) but the net effect is synergistic with lowering that is greater than either agent alone.³⁷

Pilocarpine may be used to prevent IOP spikes after argon laser trabeculoplasty; it is at least as effective as apraclonidine although with more visual side effects.³⁸ Pilocarpine may be especially useful in this regard in patients who are already using apraclonidine or brimonidine.

DRUGS IN CLINICAL USE

All cholinergic agents increase the facility of outflow, constrict the pupil, and reduce IOP. The various drugs differ in their duration of action and their potential for producing side effects. At one time, the miotics were the most commonly prescribed type of antiglaucoma agent. However, with the advent of antiglaucoma agents whose side effects are less likely to interfere with visual function, the use of the miotics as antiglaucoma medications has declined. Because they are still potent IOP-lowering drugs, improve outflow facility rather than reduce aqueous formation, and work well in concert with the other agents, they should still have a place in the armamentarium as third-line drugs.³⁹

Miotics either stimulate cholinergic receptors directly or inhibit the enzyme cholinesterase, thereby potentiating the effects of endogenous acetylcholine (Table 27-1). Based on which of these two mechanisms of action they exhibit, cholinergic agents are divided into direct-acting and indirect-acting agents.

Table 27-1 Cholinergic drugs used to treat glaucoma

Drug	Major mechanism of action	Concentration (formulation)	Usual dosage in glaucoma	Duration of hypotensive effect
Pilocarpine	Direct	0.5–10% (solution)	4 times daily	4–8 hours
Carbachol	Strong direct; weak indirect	0.75–3%	3 or 4 times daily	6–12 hours
Methacholine (Mecholyl)	Direct	2–20% (solution)	Every 2–12 hours	1–12 hours
Aceclidine (Glaucostat)	Direct; weak indirect	0.5–4% (solution)	4 times daily	4–8 hours
Echothiophate iodide (Phospholine iodide, Echodide)	Strong indirect	0.03–0.25% (solution)	Every 12 to 24 hours	0.5–7 days
Demecarium bromide (Humorsol, Tosmilen)	Strong indirect	0.125–0.25% (solution)	Every 12 to 24 hours	0.5–7 days
Physostigmine (Eserine)	Weak indirect	0.25–1% (solution) 0.25–0.5% (ointment)	4 times daily at bedtime	4–6 hours
Neostigmine (Prostigmine)	Weak indirect	3–5% (solution)	4 times daily	4–6 hours
Isoflurophate (DFP, Floropryl)	Strong indirect	0.25% (ointment)	Every 12 hours, at bedtime	0.5–7 days

Miotic	Formula	Dose
Acetylcholine	$\text{CH}_3\text{C}(=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2 \cdot \text{Cl}^-$	
Carbachol (Carcholin, Doryl, Carbamyl chloride)	$\text{NH}_2\text{C}(=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2 \cdot \text{Cl}^-$	0.75% – 3% q. 4-8 hr
Pilocarpine (hydrochloride or nitrate)	$\text{C}_2\text{H}_5-\text{CH}(\text{O}-\text{C}(=\text{O})-\text{O}-\text{CH}_2)-\text{CH}-\text{CH}_2-\text{C}(\text{CH}=\text{N}-\text{CH}_3)=\text{CH}_2$	0.5% – 10% q. 4-6 hr

Fig. 27-1 Direct-acting cholinergic agents.

DIRECT-ACTING CHOLINERGIC AGENTS

Acetylcholine

Acetylcholine is the prototype direct-acting cholinergic drug. When injected into the anterior chamber, acetylcholine stimulates parasympathetic end organs in the iris and ciliary body. Acetylcholine is not used for the treatment of glaucoma because it penetrates the cornea poorly and is destroyed rapidly by cholinesterase.

Intracameral acetylcholine is used almost exclusively during ocular surgery to constrict the pupil. Intracameral acetylcholine causes rapid pupil contraction and reduces the risk of immediate postoperative IOP rise after extracapsular cataract extraction.⁴⁰ Intracameral carbachol produces a slower miosis but extends protection from IOP elevation to over 24 hours⁴¹ and is more effective at lowering IOP in the immediate postoperative period than placebo, pilocarpine gel, or acetylcholine.^{42,43}

Pilocarpine

Pilocarpine is still the most widely prescribed miotic agent. It is more potent at muscarinic than at nicotinic receptor sites.

Pilocarpine is manufactured as a water-soluble hydrochloride or nitrate in solutions ranging from 0.25–10% (Fig. 27-1). The aqueous solutions are stable at slightly acidic pH levels. Pilocarpine penetrates the cornea well and produces a low incidence of allergic reactions. Animal studies indicate that the cornea absorbs pilocarpine rapidly and then releases it slowly to the aqueous humor (i.e., the cornea serves as a drug reservoir).⁴⁴ The usual vehicles for pilocarpine are hydroxypropyl methylcellulose and polyvinyl alcohol. Benzalkonium chloride and sodium ethylenediamine tetraacetic acid (EDTA) are added to prevent microbial growth and to facilitate penetration.

Topical pilocarpine administration produces a reduction in IOP that begins in an hour and lasts for 4 to 8 hours.⁴⁵ Pilocarpine is prescribed for use four times daily (i.e., as close to every 6 hours as possible) to ensure good IOP control. Pilocarpine (as well as its other miotic cousins) works well with other antiglaucoma agents. Specifically, miotics have been shown to work well with β -blocking agents, carbonic anhydrase inhibitors, adrenergic agonists, and latanoprost. When used in conjunction with other antiglaucoma

medications, control can sometimes be obtained with administration three times (or even twice) daily. Several formulations containing both pilocarpine and a β -blocking agent have been reported to be synergistic and have the convenience of a twice-daily dosage with a single drop.^{46–51} These studies encompass most of the available topical β -blockers. One study even suggests that combination therapy may work better than the individual agents used alone.⁵²

Because pilocarpine binds to melanin in the iris and ciliary body, iris color may influence IOP response. Studies indicate that 2% pilocarpine often yields the maximum IOP reduction in blue-eyed patients.⁵³ Eyes with darkly pigmented irides may require 4% pilocarpine for maximum effect.^{45,54} Some darkly-pigmented patients (e.g., those of black African ancestry) may obtain additional therapeutic effect from 6% or even 8% solutions.^{54,55} When the top of the dose–response curve is reached, higher concentrations of pilocarpine often extend the duration of action without increasing the maximum effect. The increased duration of effect, however, must be weighed against the increased incidence of side effects produced by the stronger solutions. It is important to emphasize that the dose–response characteristics and duration of drug effect for a given patient can only be determined in a therapeutic trial.

Alternative drug delivery systems

Because of the inconvenient dosage schedule and variable visual side effects mandated by the relatively short duration of action of pilocarpine, a variety of delivery systems have been used to prolong drug retention in the cul-de-sac and enhance drug penetration through the cornea. These systems have been used in hopes of reducing the frequency of drug administrations, improving convenience and patient compliance, minimizing side effects, and increasing therapeutic effect. The simplest of these systems is a viscous vehicle capable of prolonging drug–corneal contact time.⁵⁶ Pilocarpine in 1.6% polyvinylpyrrolidone (Adorbocarpine) was reported to produce good IOP control with twice-daily administrations.⁵⁷ However, this was not confirmed by subsequent studies.^{58,59}

Soft contact lenses The hydrophilic soft contact lens is capable of taking up medication and serving as a drug reservoir (i.e., releasing medication over a period of time to the tear film).^{60,61} If a soft contact lens is soaked for 2 minutes in 0.5% pilocarpine and then placed on the eye for 60 minutes, IOP may be reduced for 24 hours.⁶⁰ Administration of 1% pilocarpine over a soft contact lens has a greater effect on IOP than instillation of 8% pilocarpine drops without the lens.⁶² Although this system is too cumbersome for general use, a few patients with difficult conditions have been treated successfully in this manner.

Membrane-controlled delivery (Ocuser) Pilocarpine can be sealed within a multilayered polymer envelope to form the Ocuser delivery system (Fig. 27-2).^{63–66} The system is manufactured in two forms that release the drug continuously into the tear film at either 20 μ g per hour or 40 μ g per hour. The lower rate gives an IOP reduction comparable to 1% pilocarpine eyedrops administered four times daily, whereas the higher rate gives a reduction comparable to 2–4% pilocarpine. A single Ocuser generally reduces IOP for 1 week. However, the ophthalmologist must determine the duration of the IOP reduction in each patient.⁶⁶ The advantages of the system include less miosis, a more constant and less pronounced myopic shift, and better diurnal pressure control as compared with eyedrops. The disadvantages of the system include increased cost, difficulty in insertion and removal, loss from the cul-de-sac, and foreign body sensation.



Fig. 27-2 Ocuser in place in lower cul-de-sac.

The Ocuser system releases more medication during the first several hours after insertion. Patients tolerate this best if the new Ocuser is inserted Saturday night before retiring, assuming a standard Monday to Friday work week. Occasionally an Ocuser bursts, causing intense miosis and myopic refractive shift.⁶⁵ Also, the Ocuser may fall out unnoticed by the patient, or it may twist and become ineffective. Given proper introduction, education, and encouragement, many patients are helped by Ocusers. These devices were particularly helpful in younger patients with glaucoma. To a lesser degree, they may be useful in older patients with lens opacities. Unfortunately, because of the relatively small market, they are no longer being manufactured as of the current date.

Pilocarpine gel (Pilopine HS gel) Pilocarpine is now formulated in a high-viscosity gel.⁶⁷ The gel prolongs contact time between the drug and the tear film, enhances drug penetration, and reduces the frequency of drug administration. A single dose of 4% pilocarpine gel applied at bed time is approximately equal in effect to 4% pilocarpine eyedrops applied four times daily.⁶⁸ Some patients prefer the gel because it is more convenient, whereas others prefer it because of lessened side effects. However, it is not clear whether the gel applied once daily can control IOP for 24 hours in all patients. Some studies suggest a diminishing effect of the gel after 18 hours.⁶⁷ In addition, in one study, 20% of the patients treated with pilocarpine gel for several months developed reversible anterior stromal haze of the cornea.⁶⁹

Pilocarpine polymer (Piloplex) Piloplex represents another attempt to obtain a prolonged drug effect from a single administration of pilocarpine. Piloplex is an aqueous emulsion consisting of a polymeric material to which pilocarpine base is chemically bound. The drug is released over a period of hours as the polymer is hydrolyzed. Piloplex appears to be effective in preliminary trials and may provide better control of IOP when administered twice daily than pilocarpine eyedrops do when administered four times daily.^{70–72} Despite the positive reports, Piloplex has failed to make any inroads in the United States.

Methacholine (Mechoyl)

Methacholine chloride is a synthetic derivative of acetylcholine. In the past, 10–20% methacholine was administered every 5–10 minutes to treat angle-closure glaucoma, and 2–10% methacholine was given alone or combined with neostigmine to treat open-angle glaucoma. The drug is rarely used anymore because it is unstable in

solution and is short acting, and it penetrates the cornea poorly. Its major use today is in the diagnosis of Adie's pupil.

Carbachol

Carbachol, a synthetic derivative of choline, acts primarily by stimulating muscarinic receptors. It also releases acetylcholine at certain neuroeffector junctions and ganglia.⁷³ Carbachol is manufactured in aqueous solutions of 0.75–3% and is administered 3–4 times daily (i.e., every 6–8 hours). It is more powerful than pilocarpine on a concentration basis (e.g., 1.5% carbachol has the same ocular effect as 2% pilocarpine) and has a more prolonged effect.⁷⁴ However, carbachol penetrates the cornea poorly and must be combined with a wetting agent or a preservative such as benzalkonium chloride to reach an effective intraocular concentration.⁷⁵ Like pilocarpine, carbachol is not destroyed by cholinesterase.

Carbachol is an excellent miotic agent that could be used more frequently for the treatment of glaucoma. It can be used to initiate cholinergic treatment or to substitute for pilocarpine and other miotics when the patient develops resistance or intolerance.⁷⁶ Carbachol has a greater tendency than pilocarpine to produce headache and accommodative spasm, especially during the first few days of treatment. It is also a more potent miotic that can cause more interference with vision than pilocarpine for those patients with lens opacities.

The use of carbachol has declined with the general decline in the use of miotics. Today, it finds its widest use intracamerally to reduce the risk of a postoperative IOP spike in glaucoma patients whose optic nerves might be further damaged.

Aceclidine (Glaucostat)

Aceclidine, a synthetic cholinergic drug, is used extensively in Europe for the treatment of glaucoma.^{77,78} Aceclidine stimulates muscarinic receptors directly and inhibits cholinesterase weakly. It is less effective than pilocarpine on a concentration basis (e.g., 4% aceclidine has the same ocular hypotensive effect as 2% pilocarpine). Aceclidine is thought to induce less ciliary muscle spasm and accommodation than pilocarpine.⁷⁹

INDIRECT (ANTICHOLINESTERASE) AGENTS

Anticholinesterase drugs inhibit the enzyme acetylcholinesterase, thereby potentiating the effects of endogenous acetylcholine. In general, these agents produce more side effects than the direct-acting cholinergic drugs, including hyperemia, irritation, vascular congestion, and spasm of the orbicularis, ciliary, and iris sphincter muscles.⁸⁰ Cholinesterase inhibitors are rarely administered to eyes with narrow angles before iridectomy; the drug-induced miosis, forward movement of the lens, and vascular congestion can precipitate or aggravate angle closure. In the past, anticholinesterase drugs were classified as reversible (e.g., physostigmine, neostigmine) or irreversible (e.g., isofluorophate, echothiophate) enzyme inhibitors. It is probably more accurate to classify these drugs as weak/short-acting or strong/long-acting inhibitors of cholinesterase.

Echothiophate iodide (phospholine iodide)

Echothiophate, a potent inhibitor of both true cholinesterase and pseudocholinesterase, is manufactured as a white crystalline solid that is mixed with a diluent at the time of dispensing. Because of limited stability, solutions of the drug should be refrigerated. Echothiophate is administered as an aqueous solution in concentrations of 0.03–0.25% every 12–48 hours (Fig. 27-3).

The 0.06% concentration produces the maximum IOP reduction in most patients and is roughly equivalent in peak effect to 4% pilocarpine.^{81,82} Echothiophate, however, has a much longer duration of action than pilocarpine⁸³ and controls IOP in some eyes that have not responded adequately to direct-acting cholinergic agents.⁸⁴ However, the benefits of echothiophate are offset by the systemic and ocular side effects, particularly cataract formation. Because of these side effects, echothiophate and the other strong inhibitors of cholinesterase are used mostly in adult aphakic and pseudophakic eyes and in eyes that have not responded adequately to standard medical and surgical treatment for glaucoma. Manufacture of echothiophate has been episodic in the last several years.

Demecarium bromide (Humorsol, Tosmilen)

Demecarium is a potent, stable, long-acting cholinesterase inhibitor with considerable specificity for acetylcholinesterase. It is usually administered in aqueous solutions of 0.12–0.25% every 12–48 hours. The resulting IOP reduction occurs 30 minutes after administration, reaches a maximum at 24 hours, and lasts for 1 to several days.⁸⁵ Demecarium is less effective than echothiophate on a concentration basis (e.g., 0.12% demecarium is equal in effect to 0.06% echothiophate). However, demecarium is effective in some patients who have not responded adequately to echothiophate. Its major advantage is that it does not require refrigeration as does echothiophate. However, it is no longer manufactured.

Isofluorophate (Floropryl, di-isopropyl fluorophosphate, Dyflos)

Isofluorophate, an extremely potent cholinesterase inhibitor, is more active against non-specific or pseudocholinesterase than against acetylcholinesterase. Isofluorophate is usually administered as an ointment (0.025%) every 12–72 hours.⁸⁶ The drug is also available as a 0.01–0.1% solution in anhydrous peanut oil. The oil frequently causes allergic reactions and must be refrigerated. Isofluorophate produces intense miosis, ciliary spasm, and headache and is hydrolyzed so rapidly that touching the lids with the eye-dropper during application may inactivate the drug. Isofluorophate has largely been replaced by the more stable anticholinesterase agents echothiophate and demecarium and is not used in the United States.

Physostigmine (eserine)

Physostigmine is a short-acting inhibitor of cholinesterase. It is administered in aqueous solution as a salicylate (0.25–1%) every 4–6 hours, or as an alkaloid in an oily vehicle (0.25–0.5%) once or twice daily. Topical administration of physostigmine produces an IOP reduction that begins in 10–30 minutes, reaches a maximum in 1–2 hours, and lasts for 4–6 hours. Physostigmine solutions are unstable and decompose with pH changes or on exposure to light. Patients should be cautioned that discolored solutions are irritating and less effective. Physostigmine can rarely be used for long periods of time because it produces irritation and follicular hypertrophy of the conjunctiva. It also can cause depigmentation of the eyelids in black patients.⁸⁷ This agent is rarely used for chronic glaucoma therapy.

Neostigmine (prostigmine)

Neostigmine is a short-acting anticholinesterase agent similar in effect to physostigmine. It is administered in 3–5% aqueous solutions every 4–6 hours. Neostigmine is more stable and more potent than physostigmine and causes less vascular congestion and

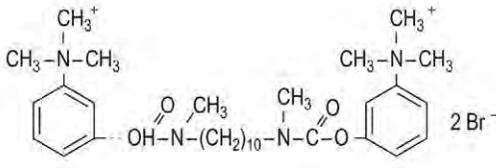
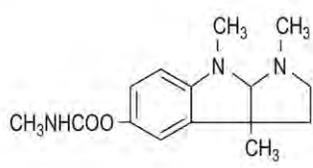
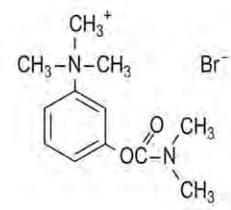
Miotic	Formula	Dose
Echothiophate (Phospholine) iodide	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{O} \\ \\ (\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{S}-\text{P}=\text{O} \cdot \text{I}^- \\ \\ \text{O} \\ \\ \text{C}_2\text{H}_5 \end{array} $	0.03% – 0.25% q 12–48 hr
Demecarium bromide (Humorsol, Tosmilen)		0.12% – 1.0% q 12–48 hr
Physostigmine (eserine)		0.25% – 1% q 4–6 hr
Neostigmine bromide (Prostigmine)		3% – 5% q 4–6 hr
Isoflurophate (Floropryl)	$ \begin{array}{c} \text{H} \\ \\ \text{CH}_3-\text{C}-\text{CH}_3 \\ \\ \text{O} \\ \\ \text{F}-\text{P}=\text{O} \\ \\ \text{O} \\ \\ \text{CH}_3-\text{C}-\text{CH}_3 \\ \\ \text{H} \end{array} $	0.01% – 0.1% q 12–72 hr

Fig. 27-3 Indirect-acting cholinergic agents (acetylcholinesterase inhibitors).

conjunctival follicular hypertrophy. However, neostigmine is ultimately less effective because of poor corneal penetration.

SIDE EFFECTS

OCULAR

Miotic drugs commonly produce ocular side effects, including conjunctival injection, ocular and periocular pain (headache), twitching of the eyelids, fluctuating myopic shift in refraction, and decreased vision in dim illumination. Almost all of the ocular side effects are more common and more severe with the anticholinesterase agents

(Box 27-1). Patients are more likely to accept the side effects if the physician provides encouragement, explains that the symptoms improve spontaneously over the first several days, and initiates treatment with a low concentration of the cholinergic drug. Pain and headache can be relieved by salicylates. Older patients, particularly those with lens opacities, often complain of decreased vision in dim illumination. They should be warned about the dangers of driving at night. Some of these patients may be helped by concomitant treatment with phenylephrine. Other alternatives include a prostaglandin-like agent, β -adrenergic antagonists, an α -adrenergic agonist, a topical carbonic anhydrase inhibitor, the Ocusert delivery system, and pilocarpine gel.

Younger patients often complain of a fluctuating myopic shift in refraction that may be 12–15D in magnitude. Younger patients

Box 27-1 Ocular side effects of topical cholinergic drugs*

Miosis, decreased vision in dim illumination
 Ciliary muscle spasm, fluctuating vision, headache
 Orbicularis muscle spasm, lid twitching, periocular pain
 Vascular dilation, conjunctival and iris hyperemia
 Increased vascular permeability, formation of posterior synechiae,
 postoperative inflammation
 Production or enhancement of angle-closure glaucoma
 Temporary increase in IOP
 Cataract formation
 Stinging, irritation
 Tearing
 Allergic blepharoconjunctivitis^{88†}
 Cyst of the iris pigment epithelium
 Retinal hole, retinal detachment, vitreous hemorrhage
 Lacrimal obstruction, ocular pseudophymoid⁸⁹
 Corneal epithelial staining, vascularization†
 Atypical band keratopathy caused by phenylmercuric nitrate preservative⁹⁰

*Almost all ocular side effects are more common and more severe with the anticholinesterase drugs.

†These side effects are an exception.

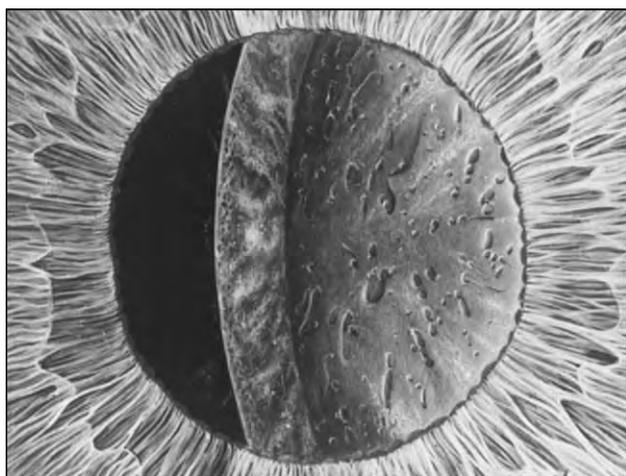


Fig. 27-4 Slit-lamp appearance of anterior subcapsular lens changes in patient treated with echothiophate.
 (From Shaffer RN, Hetherington J Jr: *Am J Ophthalmol* 62:613, 1966.
 Published with permission from the American Journal of Ophthalmology.)

often prefer pilocarpine gel or the Ocusert system to standard miotic eyedrops four times daily. Generally, other topical agents should be tried first.

Anticholinesterase drugs initiate and speed the development of cataracts, especially in patients over age 50.⁹¹⁻⁹⁴ The initial lens changes consist of small anterior subcapsular vacuoles arranged in a cluster, giving a characteristic mossy appearance (Fig. 27-4).^{91,95} Such changes are noted in approximately 10% of non-glaucomatous eyes and 30–50% of eyes treated with echothiophate or demecarium for 6 months.^{96,97} Visual acuity is not affected at this stage, and most cases do not progress if treatment is stopped. If anticholinesterase treatment is continued for 3 years, approximately 50% of patients over age 50 have a decrease in visual acuity of two lines or more because of cataract.⁹⁸ Progressive drug-related



Fig. 27-5 Pigment epithelial cyst of the pupil secondary to echothiophate use.

cataract involves all layers and zones of the lens. If cataract (or any other kind of intraocular) surgery becomes necessary, anticholinesterase drugs should be discontinued 3–4 weeks beforehand to reduce the risk of hyphema and marked postoperative inflammation. Posterior synechiae are frequent after long-term anticholinesterase therapy and usually have to be lysed with a blunt spatula.

The relation of direct-acting cholinergic drug therapy and cataract remains controversial. The studies of Levene⁹⁹ suggest that standard miotics do have a mild cataractogenic effect. Cholinergic agents alter lens permeability in animal eyes, leading to a shift in lens cations and an accumulation of water.^{96,97,100}

Considerable circumstantial evidence linking miotic therapy and retinal detachment has been accumulated.^{98,101,102} It is postulated that the drug-induced ciliary muscle contraction transmits tension to the peripheral retina, choroid, and vitreous. Patients with pre-existing vitreoretinal pathologic conditions seem more susceptible to this complication, as do aphakic and highly myopic patients. Careful examination of the peripheral retina is mandatory before prescribing miotic treatment.

Anticholinesterase therapy leads to proliferation of the pigment epithelium of the iris, forming cysts near the pupillary margin (Fig. 27-5).¹⁰³ The cysts may narrow the anterior chamber angle, increasing the risk of angle closure. Furthermore, the combination of a tiny pupil and a peripupillary epithelial cyst may significantly interfere with vision. Concomitant administration of topical phenylephrine may inhibit the proliferation or make it less apparent. The cysts decrease in size after the anticholinesterase drug is discontinued.

Cholinergic drugs produce hyperemia and congestion of the conjunctival and iris blood vessels and breakdown of the blood-aqueous barrier.^{14,104} There are reports of apparent drug-induced iritis in patients treated with anticholinesterase agents. Likewise, ocular pemphigoid associated with miotic use has been reported as well as with other topical antiglaucoma agents¹⁰⁵; whether this is a chance association, a true cause-and-effect relationship, or a special sensitivity of some patients to the chronic use of any topical medication (or its preservative) is unknown. Morphologic changes in the conjunctiva and Tenon's layer have been shown to occur with multiple different topical glaucoma medications.^{106,107} Some of these changes have been related to the preservative benzalkonium chloride.¹⁰⁸

SYSTEMIC

Cholinergic drugs can produce a variety of systemic side effects, including nausea, vomiting, diarrhea, abdominal cramping, salivation, sweating, bradycardia, hypotension, bronchospasm, muscle weakness, and central nervous system stimulation (Box 27-2). Anticholinesterase drugs can produce systemic reactions even when administered as directed, whereas the direct-acting miotics are more likely to produce these symptoms when instilled every few minutes during the treatment of acute angle-closure glaucoma.¹¹¹ Because of the risk of systemic side effects from rapid, multiple dose administration of pilocarpine drops, this form of treatment for acute angle-closure glaucoma should be avoided. It is better to treat first with other pressure-lowering agents to get the IOP into a range that will allow no more than four drops of pilocarpine 2% to produce the desired miosis.

Farm workers exposed to both anticholinesterase medication and organophosphorus insecticides and pesticides are at great risk of developing these reactions.¹¹² The side effects are caused by systemic distribution of the drug after absorption through the conjunctiva and the mucosa of the oropharynx and nasopharynx. Severe systemic reactions to anticholinesterase eyedrops are reported in patients following conjunctivodacryocystorhinostomies (Jones' procedures).¹¹³

The potential systemic side effects of these drugs must be understood not only by ophthalmologists but also by family physicians, internists, and general surgeons. Failure to recognize the systemic effects of anticholinesterase medication applied topically to the eye can result in unnecessary laboratory and X-ray studies, unwarranted medical treatment, and even dangerous exploratory surgery. Ophthalmologists should inquire about the presence of side effects and warn patients and patients' other physicians about the potential toxicity of these agents.

Systemic side effects may be reduced by punctal occlusion. A patient who develops a severe and potentially life-threatening systemic reaction to anticholinesterase medication should be treated with 2 mg of atropine, injected subcutaneously or intravenously, and 25 mg/kg of pralidoxime (Protopam), infused intravenously over 2 hours. Pralidoxime releases cholinesterase from the phosphoryl group of the cholinesterase inhibitor.^{114,115}

Systemic absorption of anticholinesterase medication inhibits plasma pseudocholinesterase. This enzyme is necessary for the metabolism of succinylcholine and the metabolism of local anesthetics with ester linkages (e.g., procaine and tetracaine).^{116,117} Thus patients receiving cholinesterase inhibitors are at risk of developing

protracted apnea after succinylcholine or toxic reactions to some local anesthetics. The anesthesiologist and the patient must be warned of these dangers.

SUGGESTIONS FOR USE

Miotics have become third-level drugs since the advent of α -adrenergic agonists, β -blockers, prostaglandin analogs, and topical carbonic anhydrase inhibitors – all of which have fewer visual side effects. When prescribing a miotic, it is wise to start with a low concentration of a direct cholinergic agent (e.g., 1% pilocarpine). The concentration should then be increased as needed, preferably using a therapeutic trial in one eye. Alternatively one should consider pilocarpine gel as the miotic of first choice because of the convenience of administration and the relative lack of daytime side effects; this is especially true in young patients or in those with lens opacities. All direct cholinergic drugs (except pilocarpine gel and Ocusert) are prescribed for use every 6–8 hours.

Administration of standard miotics on a twice-daily basis produces adequate IOP control in less than 60% of patients.⁴⁵ Higher concentrations of miotics often have a longer duration of effect than lower concentrations. The increased duration of action, however, is offset by increased symptoms and side effects. The duration of action of both pilocarpine and carbachol can be prolonged, the concentration lowered and the frequency of administration reduced by the simple act of nasolacrimal occlusion.¹¹⁸

Patients should be instructed about the purpose of the drug, the time schedule for administration, and the proper technique for instillation, including nasolacrimal occlusion. They should be warned about the common side effects, including headache, fluctuating vision, and dim vision at night. The headache and fluctuating vision often become less severe with time and frequently disappear after a few days.

EXAMINATION

Before initiating miotic treatment, a careful examination of the peripheral retina should be performed whenever possible. If substantial vitreoretinal abnormalities are found, it may be safer to choose a non-miotic ocular hypotensive agent. If no safer medical or surgical options are available, laser or cryotherapy to any retinal pathology that might presage a retinal detachment should be considered before commencing a cholinergic treatment.

Because miotic agents can produce paradoxical pupillary block by moving the lens-iris diaphragm forward, patients should be re-examined by gonioscopy after miotic therapy has commenced to determine whether the angle has narrowed.^{5,119} Drug-induced angle closure is more common with the anticholinesterase agents and is more likely in patients with anatomically narrow angles or spherophakia. Visual field studies should be performed after pupillary dilation; otherwise, miosis may reduce sensitivity and produce artifactual depression of the visual field. If this is not discovered for a period of time, progressive glaucomatous damage may be suspected. Alternatively (although perhaps not as academically correct), all visual fields can be performed with a miotic pupil as long as the pupil is the same size each time.

The pupil should be dilated at least twice a year to prevent formation of posterior synechiae, to allow visualization of the optic disc and peripheral retina, and to determine the true field of vision.

Box 27-2 Systemic side effects of topical cholinergic drugs

Bronchial spasm, asthma, pulmonary edema
 Nausea, vomiting, abdominal pain
 Weakness, fatigue, muscle spasm – may mimic myasthenia gravis^{109,110}
 Paresthesia
 Prolonged respiratory paralysis after general anesthesia including succinylcholine
 Toxic reactions to local anesthetics containing an ester linkage group
 Sweating, salivation, lacrimation
 Hypotension, bradycardia
 Nightmares, depression, delusions
 Exacerbation of myasthenia gravis and interference with its drug treatment

Note: all systemic side effects are more common and more severe with the anticholinesterase drugs.

Phenylephrine 2.5% can partially reverse the miosis produced by cholinergic drugs, even anticholinesterase agents, without reversing their beneficial effect on IOP and outflow facility.¹²⁰ Prolonged use of parasympathomimetic agents can produce an irreversible miosis, fibrosis of the pupillary sphincter, formation of posterior synechiae, and degeneration of the dilator muscle.

Cholinesterase inhibitors are generally prescribed only for aphakic or pseudophakic eyes or for eyes that have not responded adequately to standard medical and surgical treatment. Although they can achieve IOP reduction over and above that seen with direct miotics,¹²¹ patients should be warned about the numerous side effects of these agents. Likewise, patients should carry a card summarizing their medical therapy and should be re-examined within a few days of initiating treatment to evaluate their response. If intraocular surgery is contemplated, cholinesterase inhibitors should be discontinued 3–4 weeks before the operation. Continued use of these agents to the time of surgery may lead to hyphema and marked postoperative inflammation. Pilocarpine or carbachol can be substituted for the anticholinesterase agent during this interval.

There is no advantage in administering two miotic drugs in combination. Combinations do not produce a greater reduction of IOP than either agent alone in appropriate concentration, and they expose the patient to increased cost, bother, side effects, and the opportunity to develop tolerance to both agents.^{122,123} When

one miotic agent loses its effect, another cholinergic drug should be substituted and not added. Depending on the situation, this can be one direct cholinergic agent for another or a cholinesterase inhibitor for a direct cholinergic agent. Frequently a patient may regain his or her responsiveness to a drug after it is discontinued for a period of time. The ocular hypotensive effect of the miotics is additive to that of the prostaglandin analogs, carbonic anhydrase inhibitors, epinephrine, dipivefrin, α -adrenergic agonists, and β -adrenergic antagonists. However, timing of the dosing of pilocarpine with respect to latanoprost may affect the efficacy of pressure lowering.¹²⁴

CONTRAINDICATIONS

Miotic therapy is generally contraindicated in patients with active intraocular inflammation or known hypersensitivity to the drug. Relative contraindications, especially to anticholinesterase therapy, include chronic obstructive airway disease, peptic ulcer, Parkinson's disease, bradycardia, hypotension, myasthenia gravis, peripheral retinal degeneration, high myopia, and a history of retinal detachment.

Cholinergic treatment may be counterproductive when a patient has little or no conventional outflow (e.g., chronic angle-closure glaucoma with total peripheral anterior synechiae as well as neovascular glaucoma).

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CHAPTER
28

Hyperosmotic agents

Although the effect of hyperosmotic agents on intraocular pressure (IOP) has been known for almost a century,^{1–3} these agents became widely used in ophthalmology only in the past 40 years. Hyperosmotic agents are useful for the short-term management of acute glaucoma. These drugs can prevent the need for surgery in transient glaucoma conditions, such as occurs with traumatic hyphema. They also may be used for lowering IOP preoperatively. Hyperosmotic agents have reduced the risk of surgically decompressing eyes with markedly elevated IOPs. In addition, they are used in cases of acute cerebral edema and (topically) for corneal edema.

MECHANISMS OF ACTION

Hyperosmotic agents reduce IOP by increasing the osmolality of the plasma and drawing water from the eye into the circulation via the blood vessels of the retina and uveal tract.⁴ This transient effect lasts until osmotic equilibrium is re-established. Within a few hours, the hyperosmotic agent may penetrate the eye. If the agent has already cleared the plasma,⁵ reversal of the osmotic gradient occurs (i.e., plasma osmolality decreases to a level below that of the dehydrated tissues), with a rebound increase in IOP. For most agents in clinical use, effective IOP lowering is achieved when plasma osmolality is increased by 20–30 mOsm/l. Most of the fluid drawn from the eye comes from the vitreous; vitreous weight is reduced by 2.7–3.9% in experimental animals after administration of hyperosmotic agents in doses equivalent to those used clinically.⁶ Glaucomatous eyes appear to get a proportionately greater IOP-lowering effect from an osmotic challenge than do normal eyes.⁷

Hyperosmotic agents also appear to lower IOP by a second mechanism; they decrease aqueous humor production via a central nervous system (CNS) pathway involving osmoreceptors in the hypothalamus. The evidence for this second mechanism is summarized as follows:

1. After the administration of hyperosmotic agents, the decrease in IOP and the increase in plasma osmolality are not correlated closely in terms of magnitude of effect or time course.⁸
2. Small doses of hyperosmotic agents administered intravenously can reduce IOP without changing plasma osmolality.⁹
3. Intracarotid injections of hyperosmotic and hypo-osmotic solutions alter electric activity in regions of the hypothalamus that are known to affect fluid balance in the body.^{10,11}
4. Destruction of the supraoptic nuclei abolishes the IOP response to hypo-osmotic solutions.¹²
5. Injections of hyperosmotic and hypo-osmotic agents into the third ventricle alter IOP without affecting plasma osmolality.¹³

It has been postulated that the osmoreceptors in the hypothalamus alter aqueous humor production via efferent fibers in the optic nerve. This theory was stimulated by the observation that human eyes with optic nerve lesions develop less elevation of IOP after water loading.⁸ Furthermore, some investigators have noted that unilateral optic nerve transection in experimental animals diminishes the IOP response to hyperosmotic and hypo-osmotic agents administered intravenously or into the third ventricle.^{8,14,15} However, other researchers have failed to confirm the effect of optic nerve transection and have questioned the existence of osmoregulatory efferent fibers in the optic nerve.^{16,17}

Intra-arterial injections of hyperosmotic agents lead to breakdown of the blood–aqueous barrier and destruction of the non-pigmented ciliary epithelium.^{18,19} However, intravenous injections do not have the same effect.¹⁹ Thus it is unlikely that this mechanism plays a role in the clinical response to hyperosmotic agents.

Hyperosmotic agents pull water from the eye along an osmotic gradient and reduce aqueous humor formation via osmoreceptors in the hypothalamus. The specifics of this latter mechanism remain unknown.

DRUGS IN CLINICAL USE

A number of factors are important in determining the osmotic gradient induced between plasma and the ocular fluids. Because the change in plasma osmolality depends on the number of milliosmols of substance administered, agents of low molecular weight (e.g., urea) have a greater effect per gram administered than do compounds of high molecular weight (e.g., mannitol) at the same dose.^{20,21} Agents confined to the extracellular fluid space (e.g., mannitol) produce a greater effect on plasma osmolality than do agents distributed in total body water (e.g., urea). This latter factor has a larger effect than that associated with molecular weight. Some drugs rapidly enter the eye (e.g., alcohol), thereby producing less of an osmotic gradient than do those that penetrate slowly (e.g., glycerol). Agents administered intravenously bypass gastrointestinal absorption and produce a more rapid and a slightly greater rise in plasma osmolality.²²

Other factors that affect the osmotic gradient include the rate of elimination of the agent from the circulation, the production of hypo-osmotic diuresis (e.g., alcohol), the condition of the ocular vessels, and the state of the blood–aqueous and blood–retinal barriers (e.g., inflammation).^{23,24} It is peculiar that these many factors tend to balance each other sufficiently so that most hyperosmotic drugs in clinical use are effective in doses of 1–2 g/kg. Patients

should be cautioned not to drink water or other fluids after administration of the agent because doing so may reduce the osmotic gradient.²⁴

ORAL AGENTS

Orally administered hyperosmotic agents are slightly less effective and have a slower onset of action than do the intravenous agents.²⁴ Variable absorption from the gastrointestinal tract makes their effect less predictable. These differences are not great, however, and the oral agents are safer and less likely to produce volumetric overload in patients with borderline cardiac status. Oral agents are not well tolerated by patients with nausea and vomiting.

Glycerol

Glycerol (Glyrol, Osmoglyn), the most commonly prescribed hyperosmotic agent, is usually administered as a 50% solution in a dose of 1.5–3 ml/kg^{7,25} (Table 28-1). (Glycerol is also available as a 75% solution.) It begins to lower IOP in 10–30 minutes, reaches a maximum effect in 45–120 minutes, and has a duration of effect of 4–5 hours.^{7,25,26} Glycerol has an intense, sweet taste and is more palatable when given in an iced unsweetened fruit juice or cola base. If necessary, glycerol can be administered repeatedly because it penetrates the eye and other tissues poorly and is confined to the extracellular water.

The major disadvantage of glycerol is the relatively high frequency of associated nausea and vomiting. Glycerol is metabolized in the liver and produces 4.32 kcal/g of energy. The caloric value of glycerol and its metabolites as well as the osmotic dehydration it produces can lead to ketoacidosis and other problems in diabetic patients.^{27,28}

Isosorbide

Isosorbide (Ismotic, Hydronol) is a dihydric alcohol formed by the removal of two molecules of water from sorbitol. It is an effective oral hyperosmotic agent, administered as a 45% solution in doses of 1.5–4 ml/kg^{29–31} (see Table 28-1). Its time of onset and duration

of action are similar to those of glycerol.³² Isosorbide is absorbed rapidly from the gastrointestinal tract and is excreted unchanged in the urine. It must be given in somewhat larger doses than glycerol to produce a comparable effect on IOP. Isosorbide is more expensive than glycerol.

Isosorbide is less likely to produce nausea and vomiting but more likely to produce diarrhea than is glycerol.^{33,34} Because isosorbide is not metabolized and is excreted unchanged in the urine, it does not produce any calories and is thus a better choice for diabetic patients.³⁴ Unfortunately, because of relatively infrequent usage, isosorbide is no longer manufactured in the United States and obtaining it may be difficult or impossible. It is possible to confuse isosorbide with isosorbide dinitrate (Isordil), which is used to treat angina.³⁵

Ethyl alcohol

Ethyl alcohol may be an effective oral hyperosmotic agent when administered as straight spirits or diluted with appropriate mixers to a final dose of about 1.0–1.8 ml/kg of absolute alcohol (about 1–2 ml/kg of a 40–50% solution (80–100 proof)). Alcohol also induces hypotonic diuresis by inhibiting production of antidiuretic hormone. This prolongs and increases the osmotic gradient. Alcohol enters the eye rapidly, but vitreous penetration is sufficiently delayed to create an osmotic gradient. The effects of alcohol on the CNS as well as on the gastric mucosa limit its chronic use. It is important to know about alcohol's effect on IOP because a low IOP after a three-martini (or even a one-martini) lunch may not be representative of other afternoon pressures. Like glycerol, ethyl alcohol is metabolized, producing calories that may be a problem for diabetic patients. Its use in this context is limited to emergency situations in which other, more appropriate agents are not available.

INTRAVENOUS AGENTS

Intravenously administered hyperosmotic agents produce a more rapid onset of action and a slightly greater effect than do agents

Table 28-1 Hyperosmotic agents

Agents	Molecular weight	Distribution	Ocular penetration	Usual dose (gm/kg)	Excreted	Other
<i>Oral</i>						
Glycerol	92	Extracellular	Poor	1-1.5 (1.5–3 ml/kg 50% solution)	Urine and metabolized	May cause nausea and vomiting; source of calories
Isosorbide	146	Total body water	Good	1-2 (1.5–4 ml/kg 45% solution)	Urine	May cause diarrhea
Ethanol	46	Total body water	Good	0.8-1.5 (2–3 ml/kg 40–50% solution)	Metabolized	Hypotonic diuresis, source of calories, may cause nausea, vomiting, central nervous system and gastrointestinal effects
<i>Intravenous</i>						
Urea	60	Total body water	Good	1-2 (2–7 ml/kg 30% solution, 60 drops/min)	Urine	Unstable solution, skin slough
Mannitol	182	Extracellular	Poor	1-2 (2.5–7 ml/kg, 20% solution, 60 drops/min)	Urine	Increases blood urea nitrogen, not very soluble, large volume of solution, dehydration

administered orally.²⁴ The intravenous drugs are usually administered over a period of 45–60 minutes.

Mannitol

Mannitol (Osmitol) is an effective hyperosmotic drug that is currently the agent of choice for intravenous administration. The usual dose is 2.5–7.0 ml/kg of the 20% solution (see Table 28-1). The drug begins to lower IOP in 15–30 minutes, reaches a maximum effect in 30–60 minutes, and has a duration of action of approximately 6 hours.^{30,36–38} It is not necessary to administer the full dose of the drug; when IOP falls to the desired level, the infusion can be terminated. Mannitol is excreted unchanged in the urine (i.e., it is not metabolized). Because it penetrates the eye poorly, mannitol is especially useful as a hypotensive agent in the presence of ocular inflammation.²⁴ The 20% solution is stable and less irritating to blood vessels and subcutaneous tissue than is urea.³⁶

The major disadvantages of mannitol are the greater likelihood of cellular dehydration because of its confinement to extracellular water and the larger volume of fluid required because of its limited solubility.³⁹ Cellular dehydration in the CNS may produce symptoms of dementia and disorientation, especially in the elderly. Great caution should be observed in patients with renal failure because they may be unable to excrete the large quantity of fluid extracted from the cells. Similarly, the increased blood volume may place an intolerable load on patients with congestive heart failure. The 20% solution should be warmed to dissolve crystals, and a blood administration filter should be used in the intravenous line. An anaphylactic reaction to mannitol has been reported.⁴⁰

Urea

Urea (Urevert, Urephil) was the first intravenous agent used for the treatment of glaucoma. Administered intravenously as a 30% solution in a dose of 2.0–7.0 ml/kg (see Table 28-1), urea begins to lower IOP in 15–30 minutes, reaches a maximum effect in 60 minutes, and has a duration of action of 4–6 hours.^{41–44} Urea is slightly less effective than is mannitol because urea diffuses more freely through body water and penetrates the eye more readily. The latter is especially true in inflamed eyes.²³ The drug is prepared in a 10% invert sugar solution to prevent hemolysis. Urea is not metabolized and is excreted rapidly in urine.

As urea is cleared from the circulation, the plasma osmolality may fall below that of the vitreous, resulting in a rebound increase in IOP. Only fresh urea solutions should be administered because old solutions decompose to ammonia. However, fresh solutions must be warmed to compensate for the endothermic reaction of dissolving the drug. The physician should be aware that warming the solution to 50°C or higher produces ammonia. Extravasation of urea results in thrombophlebitis and skin necrosis.⁴³ Because of these side effects, urea is rarely used.

SIDE EFFECTS

Side effects from hyperosmotic agents are relatively common (Box 28-1). Although most of the associated side effects are relatively mild, some are serious and even potentially fatal. These drugs should be administered with caution in patients with cardiac, renal, and hepatic disease. Headache, nausea, vomiting, and diuresis are the most frequent side effects and are seen with all of the agents in clinical use.^{29,43} Intense diuresis after hyperosmotic therapy may lead to urinary retention and a need for catheterization, especially in older men

Box 28-1 Side effects of hyperosmotic agents

Gastrointestinal

- Nausea
- Vomiting
- Diarrhea
- Abdominal cramping

Cardiovascular

- Angina
- Congestive heart failure
- Pulmonary edema

Central nervous system

- Headache
- Backache
- Confusion
- Disorientation
- Chills
- Fever
- Subdural hematoma⁴⁵

Renal/genitourinary

- Diuresis
- Loss of potassium
- Urinary retention
- Anuria⁴⁶

Miscellaneous

- Arm pain
- Skin slough
- Thrombophlebitis
- Acidosis
- Diabetic ketoacidosis
- Hyperosmolar non-ketotic coma²⁷
- Urticaria
- Laryngeal edema
- Anaphylactic reaction
- Hyphema
- Suprachoroidal hemorrhage

with prostatic enlargement. Nausea, vomiting, and a desire to void may interfere with the calm conditions desired for surgery. For this reason, patients should void before coming to the operating room.

Hyperosmotic agents, especially those restricted to extracellular water, may precipitate pulmonary edema and congestive heart failure in elderly patients with borderline cardiac and renal status. In patients with borderline or poor renal function, acute renal failure may be precipitated by intravenous agents.^{45,47} Cellular dehydration, including cerebral dehydration with resulting disorientation, is also more common with agents limited to the extracellular space. Subdural hematoma is a life-threatening complication that occurs when shrinkage of the cerebral cortex stretches and ruptures aqueous veins between the sagittal sinus and the brain surface.⁴⁸ Many of the serious side effects are dose related, so patients should receive the minimum dose necessary to reduce IOP to the desired level.

SUGGESTIONS FOR CLINICAL USE

With the availability of many new topical agents, the need for hyperosmotics has declined significantly. However, they may be useful in some acute situations in which topical agents and systemic carbonic anhydrase inhibitors are unable to control IOP.

ANGLE-CLOSURE GLAUCOMA

Hyperosmotic agents are of great value in the management of acute angle-closure glaucoma.^{44,46} The combination of a topical β -adrenergic antagonist and an α agonist will lower the pressure enough to allow a topical miotic to work. Probably, prostaglandin agents are also useful in this context although their onset of action may be too long for an acute attack. If topical agents are unable to lower the pressure enough so that miotics can join the action, oral glycerol or isosorbide will terminate most attacks of angle-closure glaucoma. If the patient is vomiting, intravenous mannitol can be administered. In many cases, it is not necessary to administer the entire intravenous dose; administration can be stopped when the IOP falls and the pupil constricts. It is safer and easier to perform laser iridectomy after the acute attack has been terminated by medical treatment, especially if the cornea is hazy as a result of the attack.

SECONDARY GLAUCOMA

Hyperosmotic agents are useful in the secondary glaucomas as a preparation for surgery or as a means of controlling IOP and preventing optic nerve damage (if topical agents fail to do so) until the underlying disease process abates. Hyperosmotic agents are helpful in patients with sickle cell trait or disease who develop traumatic hyphema and uncontrolled IOP and who should not receive carbonic anhydrase inhibitors.⁴⁹ The acute glaucoma seen after blunt trauma often subsides spontaneously after several days but may be very difficult to control until that time. Hyperosmotic agents can be given one to four times daily in this situation, but the patient's electrolyte status should be monitored. Glycerol and isosorbide are useful in treating those few extremely high, transient IOP elevations seen after laser iridectomy and trabeculoplasty not controlled with topical agents. Surgery for traumatic hyphema associated with secondary glaucoma can often be avoided or delayed when hyperosmotic agents are given. In markedly inflamed eyes and in neovascular glaucoma, glycerol and intravenous mannitol are preferable because they penetrate the eye poorly. Oral isosorbide is the drug of choice in diabetic patients because it does not provide calories.

CILIARY BLOCK (MALIGNANT) GLAUCOMA

Hyperosmotic agents are an important part of the medical treatment for ciliary block (malignant) glaucoma. If necessary, they can be administered in conjunction with mydriatic agents (e.g., atropine and phenylephrine), a β -adrenergic antagonist, an α agonist and a carbonic anhydrase inhibitor. Hyperosmotic agents pull fluid from the vitreous and move the vitreous face posteriorly. This may help to re-establish the normal flow of aqueous from the posterior to the anterior chamber. It is estimated that 50% of ciliary block glaucoma cases can be treated successfully with this medical regimen.

TOPICAL HYPEROSMOTIC AGENTS

Topical hyperosmotic agents are very useful to clear corneal edema and allow better visualization of the anterior chamber and iris. This may be crucial to establish an accurate diagnosis and begin appropriate therapy when the attendant corneal edema prevents slit-lamp or gonioscopic viewing. One drop of glycerin (100%) will often clear the cornea enough to allow determination of iris neovascularization, narrow angles, or cellular debris in the anterior chamber and to allow gonioscopy. Topical glycerin may also clear the cornea enough to allow goniotomy in congenital glaucoma with a cloudy cornea. Because the glycerin is very uncomfortable, it is best to provide topical anesthetic first. If glycerin is not available, topical hypertonic (5%) saline (e.g., Muro 128) may work as may Karo or another table syrup with a high sugar content.

OTHER

Some have proposed using systemic hyperosmotic agents as part of an aggressive regimen in the face of an acute central retinal artery occlusion; the regimen includes lowering IOP with ocular massage, topical drops, systemic hyperosmotic agent, and anterior chamber paracentesis as well as sublingual isosorbide dinitrate, systemic methylprednisolone, and streptokinase.⁵⁰ Whether this aggressive regimen is any better than less aggressive treatment has not been proven.

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CHAPTER
29

General aspects of laser therapy

Michael S Berlin

Laser therapy has become the method of choice for treating many forms of glaucoma, especially when medical modalities prove inadequate or patient compliance with medical regimens is poor. In angle-closure glaucoma with pupillary block, for example, neodymium:yttrium-aluminum-garnet (Nd:YAG) or argon laser iridotomy has replaced surgical iridectomy, which is generally reserved for situations in which a laser approach is not possible. Laser trabeculoplasty has advanced the treatment of primary open-angle glaucoma by providing a safe and usually effective means of achieving intraocular pressure (IOP) reductions with fewer complications than invasive surgical procedures such as trabeculectomy. In cases of medically and surgically uncontrollable glaucoma, diode, argon laser cyclophotocoagulation, and Nd:YAG of the ciliary body have proven effective. Laser techniques are generally less invasive, carry fewer risks, and result in fewer complications than their surgical counterparts. Because laser procedures involve risks of their own, however, a thorough understanding of the principles of clinical laser therapy is essential.

GENERAL ASPECTS OF LASER THERAPY

Laser energy can be delivered in a variety of wavelengths and time durations, from extremely short-burst lasers to continuous-wave lasers. The effect of laser energy on target and surrounding tissue depends on the amount and duration of energy absorbed, which are dependent on tissue pigmentation, wavelength, amount of energy delivered, exposure time, and size of the laser spot.¹⁻⁸

TISSUE EFFECTS OF LASER**THERMAL EFFECTS (PHOTOCOAGULATION, PHOTOVAPORIZATION)**

In general, long exposures by lasers at relatively low energy densities produce a coagulative effect that shrinks collagen (Box 29-1 and Fig. 29-1). Higher energy densities can vaporize tissue.⁹ If this vaporization occurs rapidly, the steam expansion effect is explosive. Thus high energy for short exposures can cause tissue explosions. These effects are dependent on the tissue's chromophore components, which determine the relative absorption, transmission, reflection, and scattering of incident laser radiation. The frequency of the laser can then be matched to the absorption characteristics of the target tissues. Continuous-wave Nd:YAG laser energy, in contrast

to q-switched Nd:YAG laser energy, is absorbed primarily by pigmented tissues and penetrates deeply. It can thus be directed with minimal absorption through the unpigmented sclera. The energy generated by the erbium-YAG laser (2.94 μm), however, is absorbed by the water in high water content tissues with a short absorption depth. This type of laser can be employed to create sclerostomies but not be used for procedures such as cyclophotocoagulation or iridectomy, in which transmission through the sclera or cornea is necessary.

If the thermal effect is intense, carbonization of tissue may occur. Carbonization results when tissue fluid has been vaporized (photo-vaporization) and the remaining tissue is converted to carbon by heat converted from additional laser energy absorption in the presence of oxygen. Such a reaction may be seen as black shiny material in the treated portion of a dark brown iris during argon laser iridectomy. This material is extremely hard and may be impervious to subsequent laser applications.

PHOTODISRUPTION

Lasers may also disrupt tissue by photodisruption, which is the optical breakdown of molecules. This is typical of short-pulsed (i.e., q-switched Nd:YAG) lasers. Power density is so great that molecules are broken apart into their component ions, creating a rapidly expanding ion 'plasma.' This ionization and expanding plasma create subsequent shock-wave effects which cause an explosive disruption of tissue to create an excision. These mechanical effects are

Box 29-1 Laser procedures by laser type

- Iridectomy (both)
- Trabeculoplasty (argon)
- Trabeculopuncture (Nd:YAG)
- Gonioplasty (iridoplasty) (argon)
- Synechiolysis (both)
- Reopening filtering blebs (both)
- Cutting sutures (argon)
- Filtration surgery (Nd:YAG)
- Cyclophotocoagulation (Nd:YAG)
- Rupture cysts of iris or ciliary body (both)
- Goniophotocoagulation (argon)
- Pupilloplasty (argon)
- Sphincterotomy (both)
- Cyclodialysis (Nd:YAG)
- Closing cyclodialysis cleft (argon)

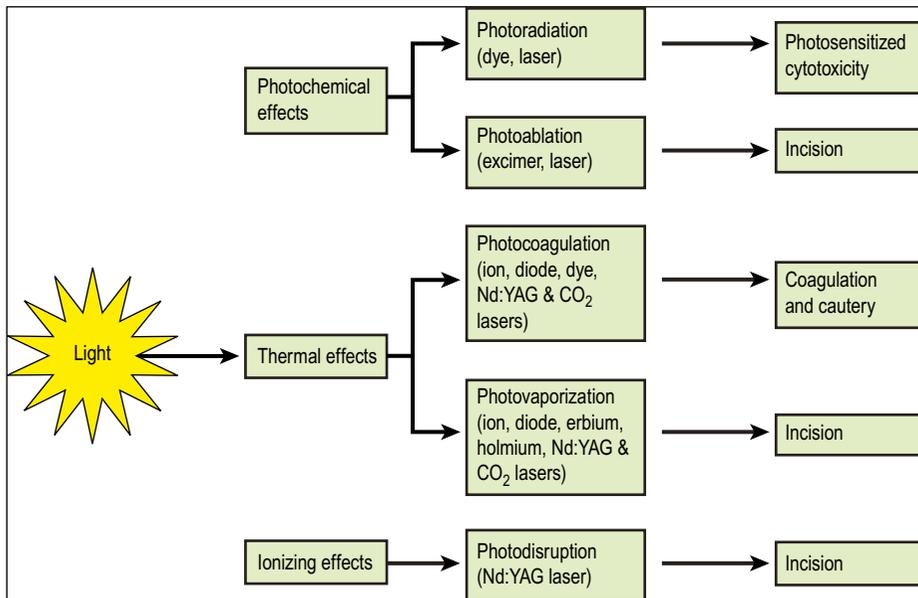


Fig. 29-1 Laser-tissue interactions may be divided into photochemical, thermal, or ionizing effects. Often, interactions include a mix of these (see text). (Modified from Mainster MA: Ophthalmic laser surgery: principles, technology, and technique. In: Klein EA, editor: Symposium on the laser in ophthalmology and glaucoma update, Transactions of the New Orleans Academy of Ophthalmology, St Louis, Mosby, 1985.)

useful in opening transparent tissue as they do not depend on tissue absorption of the energy.

PHOTOABLATION

Photoablation is typified by excimer lasers (*excited dimer*), which generate intense ultraviolet energy beams. At 193 μm , the ultraviolet argon fluoride excimer laser energy breaks molecular bonds, disintegrating tissue into molecular fragments that are ejected from target sites at high velocities. Adjacent tissues are usually not affected. This approach has been used in photorefractive keratectomy to sculpt the corneal surface with excisions of precise shape and depth with perfectly smooth and regular edges.^{7,10-13} In a similar way, at 308 nm, the xenon chloride excimer laser is used to precisely excise the meshwork tissue via a fiber-optic probe to remove obstructions to outflow without provoking inflammation in the adjacent tissues. The depth at which most of the energy is absorbed by the tissues at this wavelength is very short, preventing damage to internal structures within the eye. In a similar manner, the short tissue absorption depth of the infrared 2.94- μm erbium:YAG laser, although slightly more thermal than UV wavelengths, allows precise tissue removal with minimal adjacent tissue effects.

PHOTOCHEMICAL EFFECTS

Laser energy can cause chemical reactions in tissues. Photodynamic therapy involves the reaction of a photochemical sensitizer to a wavelength-appropriate laser energy (often red light, 625–635 nm) to create oxygen free radicals in order to create a targeted tissue response. Medical use currently includes destruction of tumors previously sensitized by hematoporphyrin derivatives and precise chorioretinal thermal damage for subretinal neovascularization.

In addition, just as sunlight can cause mutations in skin cells, ultraviolet lasers may have direct mutagenic capabilities and can crosslink proteins to DNA.

GENERAL PREPARATION OF THE PATIENT

Patients should have a clear understanding of the planned laser surgery procedure, including its purpose and rationale. Many patients are fearful of lasers. Fearful patients should be reminded that laser modalities are safer and less invasive than their surgical counterparts. Many laser procedures require slit-lamp delivery systems. The patient should be seated comfortably at the slit lamp so that movement and discomfort are minimized. The patient should also understand that there may be sounds, bright flashes, and possibly slight sensations with each laser pulse. The patient should be told that the surgeon will assist in stabilizing the eye. The patient should be instructed to warn the surgeon immediately if he or she feels uncomfortable. The combination of anxiety, pressure on the globe, and possible side effects of drugs being used can result in a syncope episode during laser therapy. The surgeon and the room should be prepared for this possibility so that the patient does not fall and sustain injury. Resuscitative equipment should be available.

A skilled laser surgeon can perform the planned procedure quickly with the fewest required laser applications. If prolonged sessions are necessary, consideration should be given to allowing the patient occasional breaks.

Lasers have brought increased safety and simplicity to glaucoma management. As technology improves, so will our abilities to use these new tools.

BASIC LASER SAFETY

The laser surgeon's eyes must be protected against reflected laser energy by using filters in the slit-lamp operating biomicroscope or protective goggles or safety glasses. Contact lenses used for laser surgical procedures generally have antireflective coatings to minimize the intensity of reflected laser light, but unshielded eyes in the operating room are still vulnerable to reflected light. Access

to the operating room should be restricted to persons directly involved in the laser procedure; the eyes of individuals assisting the surgeon must also be protected with appropriate goggles that are wavelength matched to the laser being used. The room containing the laser should have appropriate signage so that accidental entry is avoided, both for the safety of the intruder and so that the surgeon or patient is not startled.

Lasers often operate at high voltages; therefore, laser device enclosures must be secure and all lasers must be grounded electrically to avoid inadvertent exposure to these high voltages. Periodic checks should be made of the electrical connections to ensure continued reliability. For those lasers requiring cooling systems, these should have periodic examinations to be sure that flow continues at a safe level and filters are clean.

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CHAPTER
30Laser treatment for internal
flow block*Michael S Berlin***LASER PERIPHERAL IRIDOTOMY**

Laser iridotomy has, for the most part, replaced incisional surgical iridectomy. It is safer, achieves similar results, and is preferred by patients.¹⁻³ Laser iridotomy is indicated for all forms of angle-closure glaucoma involving pupillary block and as a prophylactic measure for patients with occludable angles. A success rate of almost 100% can be achieved by experienced laser surgeons. Late failure is rare, especially in eyes treated with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.^{4,5}

Using light energy transmitted through the cornea instead of a blade incision to create an iridotomy was first demonstrated by Meyer-Schwickerath⁶ in 1956 with a xenon light source. Argon and Q-switched Nd:YAG lasers have enabled the creation of iridotomies more safely than by incisional surgical methods because the eye need not be opened. The laser procedure requires only topical anesthesia.⁷⁻¹² In addition, the postoperative recovery period is shorter. This improvement in the risk:benefit ratio has changed the criteria for iridotomy. Surgical iridotomy is currently used only when laser iridotomy is not possible, such as when the cornea is opacified or the anterior chamber is very shallow.

INDICATIONS

A firm indication for laser iridotomy exists if the patient has pupillary block as evidenced by an anterior bowing of the peripheral iris with occludable angles accompanied by one or more conditions (Box 30-1). Certainly, laser iridotomy should be a strong consideration in any patient who has had symptoms of intermittent blurring of vision accompanied by rainbow-colored haloes around lights, occurring under circumstances that promote pupil dilation and whose examination shows bowing forward of the peripheral iris and very narrow or worse angles on gonioscopy.

Not all patients with narrow angles require iridotomy; most such patients never develop glaucoma. Relative indications for laser iridotomy exist because the procedure is not totally free of complications, and it is not always possible by gonioscopy alone to predict who will develop acute or chronic angle-closure glaucoma.

However, some asymptomatic patients in whom the angles are critically narrow are well served by laser iridotomy. In general, asymptomatic elderly patients who have access to adequate medical care can be counted on to report symptoms typical of angle closure and return for routine monitoring and can be observed safely. However, care must be taken to monitor these patients so that iridotomy can be instituted if progressive narrowing of the angle, formation of peripheral anterior synechiae, or elevated intraocular pressure (IOP) occurs.

Box 30-1 Indications for laser iridotomy**Firm indications**

- Acute angle-closure glaucoma
- Chronic angle-closure glaucoma with peripheral anterior synechiae
- Intermittent angle-closure glaucoma with classic symptoms of angle closure
- Aphakic or pseudophakic pupillary block
- Anatomically narrow angles and signs of previous attacks
- Narrow-angle eye with acute angle-closure glaucoma in the fellow eye
- Incomplete surgical iridectomy
- Luxated or subluxated crystalline lens
- Anterior chamber lens implant
- Nanophthalmos
- Pupillary block from silicone oil after vitrectomy¹³
- Mixed-mechanism forms of glaucoma when filtering surgery might not be necessary for adequate pressure control

Relative indications

- Critically narrow angles in asymptomatic patients
- Younger patients, especially those who live some distance from medical care or who travel frequently
- Narrow angles with positive provocative test
- Iris-trabecular contact demonstrated by compression gonioscopy

Laser iridotomy should be considered in asymptomatic patients whose angles are narrow such that a portion is closed, in patients whose life expectancy will allow their lens to increase in size with subsequent angle narrowing and for whom cataract extraction is not anticipated in the immediate future, and in patients who do not have constant ready access to medical care such as frequent travelers or those who live in remote areas. This procedure is generally preferred over miotic therapy in such patients because, in many cases, miotic treatment does not prevent angle closure. If the choice is not clear and the two eyes are similar gonioscopically, iridotomy can be performed in one eye and the other eye can be observed.

In acute angle-closure glaucoma caused by pupillary block, treatment is initiated with medication to decrease IOP and help restore corneal clarity. Laser iridotomy, which is the definitive treatment, can then be performed more successfully.

TYPES OF LASER

Types of laser commonly used for iridotomy include the photodisruptive Q-switched Nd:YAG laser, the photothermal argon lasers, or the solid state lasers.^{9,11,14-29} The Q-switched Nd:YAG laser is preferred by many surgeons because it perforates the iris easily. This is

particularly true in dark brown or light blue irides. It is more difficult to penetrate dark brown irides with photothermal argon or solid-state lasers because they have a tendency to char during treatment; light blue irides can be difficult because pale irides do not absorb argon or solid-state laser energy very well. Moreover, Nd:YAG iridotomies may be less likely to close over time.^{24,26,30-32}

Because the Nd:YAG laser (unlike photothermal argon or solid-state lasers) has no coagulative effect, bleeding occurs more frequently. Local hemorrhage is usually self-limited and rarely of consequence. Bleeding may be limited by pretreating the proposed iridotomy site with the coagulative energy from an argon laser or a 532-nm frequency-doubled solid-state Nd:YAG laser,³³ but this is rarely performed. However, it may be indicated in those who have a coagulative disorder or who are using anticoagulative medications. In patients with severe coagulative disorders, pretreatment with intravenous blood derivatives to replace a missing factor(s) may help limit intraocular bleeding. The vast majority of the time, if bleeding does occur at the surgical site, it can be stopped by pressing on the contact lens and temporarily raising the IOP (Fig. 30-1).

GENERAL PREPARATION

Miosis, which helps to tighten and thin the peripheral iris and pull it away from the cornea, can be accomplished with a drop of pilocarpine 1% or 2%. Topical anesthesia is achieved with proparacaine hydrochloride 0.5%.

An Abraham iridotomy lens (Fig. 30-2) greatly improves visualization, separates the lids, stabilizes the eye, minimizes epithelial burns because it acts as a heat sink, and increases the power density by concentrating the energy into a smaller spot size at the iris. The Wise lens modification³⁴ provides a higher power density at the tissue site but causes greater image distortion as a result of the higher magnification. A variety of other lenses that are especially corrected for argon or Nd:YAG wavelengths have been developed for this purpose. One relatively recent one is the Pollack lens (Ocular Instruments, Bellevue, WA) which we have found to be useful for iridotomies, trabeculoplasty, and also for iridoplasty (see below).

The iridotomy should be placed in the periphery of the iris. Such placement reduces the likelihood of lens injury and possible subsequent sealing of the iridotomy by posterior synechiae to the lens. Furthermore, peripheral placement also reduces the likelihood of later ghost images through the iridotomy. If a dense arcus senilis is present, the iridotomy site must be central to it. A site between the 11 and 1 o'clock meridians is preferable because it will be covered by the upper lid. Iridotomies within the palpebral fissure can cause visual disturbances due to polycoria. The 12 o'clock meridian should be avoided because (1) with argon or solid-state laser iridotomy, gas bubbles rise to this area and may obscure the laser site before treatment can be completed, and (2) with Nd:YAG laser iridotomy, a small trickle of hemorrhage may cascade down from the treatment site and obscure the patient's vision temporarily. Both of these problems will be avoided if the iridotomy is placed closer to the 11 or 1 o'clock positions. Wand (Personal Communication) has advocated placing the iridotomies in the temporal or nasal periphery and reports no visual problems or ghost images with this technique.

With careful examination, a relatively thin region in the iris can often be identified. This area may be located in the depths of a crypt or in an area evidenced by a rather lacy, translucent appearance of the superficial stroma. In blue irides, the dense white radial cords of the iris stroma should be avoided. Perforation of the iris is recognized by release of a pigment cloud billowing forward from

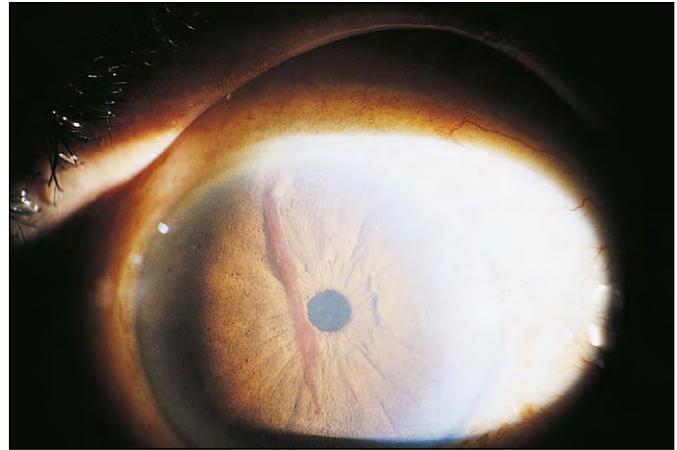


Fig. 30-1 Small cascade of hemorrhage from the site of Nd:YAG iridotomy. Bleeding is effectively stopped by gentle pressure on the globe via the Abraham contact lens (see Fig. 30-2)

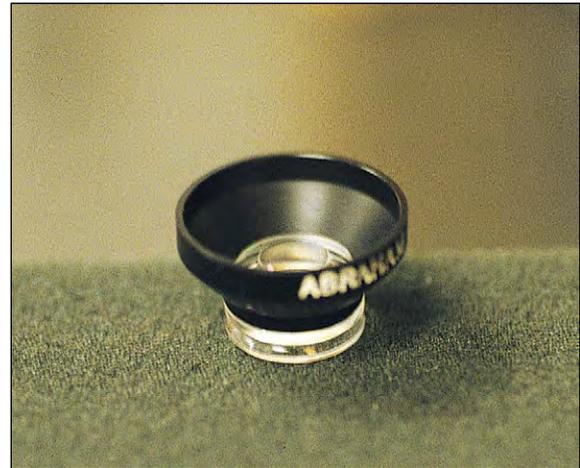


Fig. 30-2 Abraham iridotomy lens is a modified Goldmann fundus lens. A small 66D plano convex button is added to a flattened surface. This focussing effect increases the power density by a factor of 4.

the iridotomy site and the posterior movement of the iris deepening the anterior chamber. With Nd:YAG iridotomies a rapid gush of fluid is often indicated by small flecks of pigment racing through the opening. Transillumination through the iridotomy is a reasonably good sign of complete perforation in a brown iris but can be misleading in a light blue or grey iris. Clear evidence of perforation is direct observation of the anterior lens capsule through the iridotomy site. Another useful technique is to direct the aiming beam into the depths of the iridotomy. Be sure the main beam is inoperative. If the opening is through-and-through the iris, the aiming beam will disappear. The aiming beam is also helpful for coherent transillumination. A small but complete peripheral perforation is the ideal end point. It is important to have the patient gaze upward, both to clear a peripheral corneal arcus and to ensure that no laser light will be aimed toward the macula.

ND:YAG LASER IRIDOTOMY

Q-switched Nd:YAG lasers (1064nm) are very useful for iridotomy (Figs 30-3 and 30-4). Power settings depend on the power

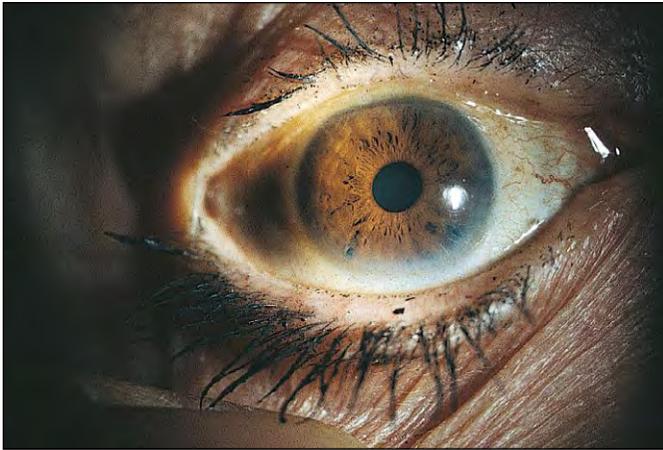


Fig. 30-3 Patent laser iridotomy.



Fig. 30-5 Argon laser iridotomy.



Fig. 30-4 Magnified view of Nd:YAG laser iridotomy showing the characteristic ragged edge.

density produced by the individual laser. It is important that the surgeon be familiar with the power characteristics of the laser being used and to pretest the laser for focus in an appropriate test chamber before treating the patient.

For lasers that provide multiple bursts, an initial trial at 2–3 shots/burst using approximately 1–3 mJ/burst will be effective in most irides. If a single burst is used, slightly higher power is usually necessary. High-power settings (2–5 mJ) are needed for some particularly thick, velvety brown irides, in Asian patients.

Careful focusing is critical. Because the shock wave travels toward the surgeon from the point of focus,³⁵ it is ideal to have the focal point within the iris stroma. This can be accomplished by focusing precisely on the surface of the iris and then offsetting the Nd:YAG beam so that it converges behind the aiming beam focal point, 0.1 mm in the iris stroma. Because the shock wave propagates toward the surgeon, this approach is hazardous to the cornea when the chamber is very shallow. Enlarging Nd:YAG iridotomy is hazardous because of the risk of lens injury. A tiny iridotomy (<0.1 mm) may be inadequate for preventing subsequent pupillary block³⁶ and is potentially more susceptible to later closure by pigment.³⁷ If the surgeon is unsure of the adequacy of the iridotomy created, it may be preferable to choose another site and use somewhat higher energy levels for a second attempt, rather than to try to enlarge the first opening, or to consider subsequent enlargement with an argon laser.

If the initial attempt at Nd:YAG iridotomy fails, repeat treatments can be directed to the same site using fewer shots per burst and/or less energy for additional treatments. Repeat attempts are most effective shortly after the initial attempt because pigment debris created by the first attempt may cloud the anterior chamber and reduce the amount of laser energy reaching the iris. After several failed attempts, anterior chamber clarity can be compromised, and further treatments are fruitless. In this situation, it is helpful to have the patient sit quietly for 10–15 minutes to allow the optical pathway to clear of pigment. Once anterior chamber clarity has improved, the treatment can be completed. In particularly resistant cases, the patient can be asked to return several days later. By this time, localized iris atrophy will have thinned the iridotomy site, and the treatment can almost always be completed.

ARGON OR SOLID-STATE LASER IRIDOTOMY

Argon and solid-state lasers (Fig. 30-5) produce coagulative effects with lower energies at longer exposures or explosive effects due to rapid vaporization when higher energies are used.

Photocoagulative lasers act differently with tissues that have different amounts of pigmentation. Because of these variables, iridotomy with photocoagulative lasers requires more adjustments in technique and a greater variety of techniques³⁸ than does Nd:YAG laser iridotomy. The fact that the Nd:YAG laser is easier and more effective explains its greater popularity over argon and solid-state lasers. Photocoagulative lasers remain good choices in many circumstances. The following discussion outlines a few useful argon and solid-state iridotomy techniques.^{7,9,10,24,39,40}

Iris color (pigment density) is the most influential factor in the outcome of photothermal laser iridotomy. The chromophore (energy absorber) for laser iridotomy is in the iris pigment epithelium posterior to the stroma. For this discussion of laser iridotomy, the iris color can be divided into three categories: light brown, dark brown, and blue. Light brown irides are the most easily perforated and are discussed first.

LIGHT BROWN IRIS

The surgeon can usually locate a thin area in the anterior stroma, often in the base of a crypt, and can actually see into the depths of the iris. The laser beam should be aimed away from the posterior pole

by having the patient gaze upwards, especially while enlarging the perforation. When the laser energy strikes the iris, a deep pit is produced. These signs indicate that the iris is relatively soft and absorbs the laser energy well so that iridotomy will be easily accomplished.

Initial power settings should be 600–1000 mW with a spot size of 50 μm and a shutter speed of 0.02–0.05 second. Repeated applications of the laser in the center of the pit produced by the first shot will result in a 200- to 300- μm crater in the iris stroma. When the pigment epithelium is penetrated, a cloud of pigment will come out of the pit. Shutter speed can then be reduced to 0.02 second to remove the pigment epithelium from the depths of the pit and create an opening that is at least 0.2 mm in diameter. This is best done by chipping away at the edges of the small initial opening in the pigment epithelium by aiming the laser beam so that two-thirds of the beam is on the pigment epithelium and one-third is in the opening. Again, the surgeon should avoid aiming the laser toward the posterior pole by asking the patient to look up.

This technique usually produces a complete iridotomy with 10–20 shots in a light brown iris.

Dark brown iris

The densely pigmented dark brown iris has a uniform surface with no apparent thin areas. Charring of the surface occurs frequently with exposure times of longer than 0.05 second. This char appears as black shiny material ('carbon') at the laser application site. Additional laser applications do not penetrate the char, and instead of forming a coherent single bubble, multiple tiny bubbles spray off the surface after each application. After such charring occurs, it is very difficult, if not impossible, to penetrate that area, and a new location must be chosen. Another option is to use the Nd:YAG laser to perforate the charred site.

To avoid charring, short exposure times of 0.02–0.05 second should be used with initial power settings of 400–1000 mW and a spot size of 50 μm . If a reasonable pit develops in the iris, these settings can be continued, striking the same spot and slowly advancing the focal point until perforation of the pigment epithelium is recognized by formation of the typical pigment cloud. The hole is then enlarged in the same manner as with light brown irides.

If a pit does not develop or is very small, power can be increased in 200-mW increments until an effective power is obtained. It is rarely necessary to go above 1000 mW. Exposure times should not be increased above 0.10 second because charring is very likely with longer exposures. Completion of an iridotomy can usually be accomplished with 20–50 applications.

Light blue iris

Blue or pale grey irides have insufficient stromal pigment to absorb laser energy. The energy can pass directly through the stroma, leaving it intact, and separate the pigment epithelium from the back of the iris. This can be recognized as a transillumination defect in the iris with intact overlying stroma. Subsequent shots simply pass through the iris stroma without creating a hole (Fig. 30-6).

Occasionally a small pigmented area, which will respond much like a light brown iris, may be found in an appropriate site for iridotomy. If there is no pigmented area, longer exposures will generate heat in the pigment epithelium; the heat is then transmitted into the stroma and destroys it. The surgeon's goal is to create a bubble at the laser site before the pigment epithelium is destroyed. Then, by firing additional shots through the apex of the bubble, the stroma is destroyed, exposing the underlying pigment epithelium.⁴¹

The initial setting should be a 200- μm spot, 200–400 mW, 0.1 second duration to anneal the pigment epithelium to the stroma.

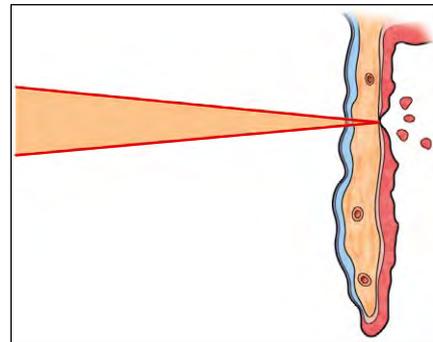


Fig. 30-6 Argon laser peripheral iridotomy in a light blue iris. The argon beam may pass directly through the light blue stroma and blast the pigment off the back of the iris. Subsequent laser applications will pass through the stroma without affecting it because there is no adjacent pigmented material to absorb the energy.

Then the spot size is reduced to 50 μm and the power increased to 600–1000 mW at 0.02–0.1 second to perforate. If the stroma is clearly being treated, as evidenced by its clumping and opacification, then these settings can be continued. If penetration has not occurred in 20–40 shots, then a new spot should be treated with an alternative technique.

One alternative technique requires higher energy (1200–1500 mW), with exposure times of 0.3–0.4 second and a 50- μm spot size. The shutter speed is set at 0.5 second. As the firing pedal is depressed, a bubble will form. When the bubble is about 0.5 mm in diameter, the pedal is released. Before the bubble can float away, a second laser application is fired directly through the apex of the bubble (Fig. 30-7). Occasionally a third such application is required. These initial high-energy shots will create a crater whose base is the pigment epithelium. It is then a simple matter to remove the pigment epithelium by using shorter exposures (0.05–0.1 second) at lower energies (400–600 mW), as described for brown irides.

Another alternative uses low-energy 'stretch' burns of 200 mW and a 200- μm spot size for 0.1–0.2 second on either side of (or surrounding) the site to be perforated. The concept behind this technique is to tighten the iris between the stretch burns, making iris perforation easier. Most iridectomies can be performed without this additional trauma.

COMPLICATIONS OF LASER IRIDOTOMY

Iritis

Some degree of iritis always follows laser iridotomy. Iritis can be minimized by topical corticosteroid eyedrops (e.g., prednisolone acetate 1% hourly until bed time on the day of laser treatment and four times daily for the following day or two), but most patients do quite well without treatment. Sometimes, following argon or diode laser iridotomy, posterior synechiae develop. Occasionally patients develop recurrent iritis after laser iridotomy. This represents aggravation of a pre-existing condition in most patients but rarely arises *de novo* after the laser therapy. Hypopyon is rare.

Pressure elevation

Preventive therapy to limit a potential rise in IOP is recommended. Intraocular pressure elevation commonly occurs 1–4 hours after laser iridotomy and is usually self-limited. Elevations greater than 10 mmHg are seen in roughly 17–27% of patients.^{42,43} Treatment

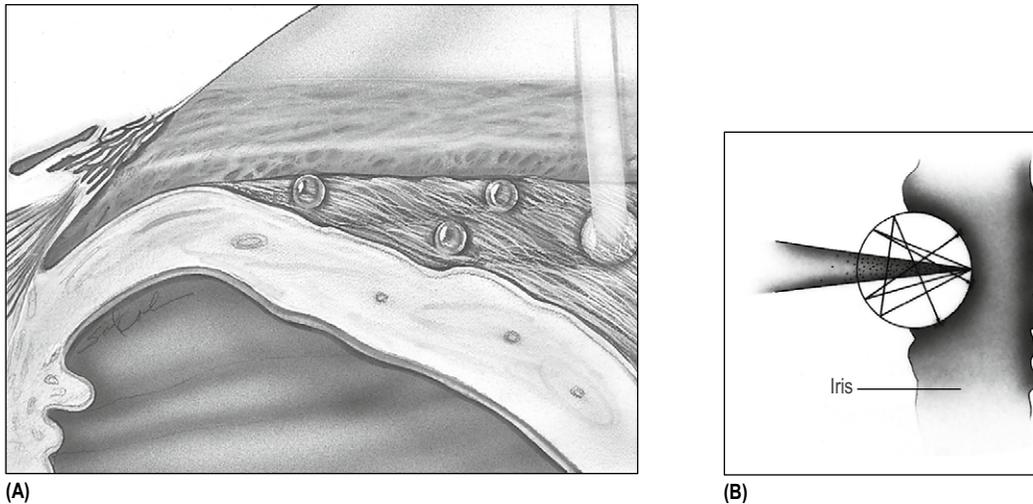


Fig. 30-7 (A) Bubbles are often created at the site of laser impact into the iris tissue and can be advantageous, transferring greater energy from each application into the iridotomy site. **(B)** A bubble captured in the iris stroma acts much like a concave mirror redirecting reflected energy back into the iris stroma. Where the iris pigment epithelium is in contact with the stroma, the laser energy escapes from the bubble and is absorbed by the tissue. The bubble enhances the effect of the laser energy, allowing development of a crater in the iris surface with fewer applications. However, if the bubble is in contact with the corneal endothelium, the laser energy will be absorbed by the endothelium and cause an endothelial burn.

options include the use of an α -adrenergic agonist (Iopidine 0.5–1%,⁴² Alphagan 0.2%), a β -blocker (Timoptic 0.5%, Betoptic 0.5%), carbonic anhydrase inhibitors (Trusopt 2%, Diamox, Neptazane), or an osmotic agent (Ismotic). Most recommend either topical apraclonidine or topical brimonidine, one drop before treatment, and some add one drop after.

Usually the IOP returns to pretreatment or lower levels within 24 hours. In combined-mechanism forms of glaucoma in which the outflow is abnormal before laser therapy, however, the IOP elevation can be severe and sustained. Such patients should be warned before undergoing laser surgery that filtering surgery may be required to control this pressure elevation. This complication is more likely if high IOP is associated preoperatively with a chamber angle that, although quite narrow, is open, so that aqueous has access to the trabecular meshwork. These findings indicate that although the incomplete angle closure may be contributing in part to the IOP elevation, the trabecular meshwork is not functioning adequately. The trauma of the laser iridotomy and the pigment released may further tax the meshwork, precipitating the need for filtering surgery.

Cataract

Cataract formation can occur after surgical iridotomy. Follow-up of patients who had argon laser iridotomies indicates that the laser treatment has no greater likelihood of causing cataract than does surgical iridectomy.^{26,44–48}

Argon laser iridotomy frequently causes localized injury to the lens beneath the iridotomy site. The injury can be seen as a whitening of this area of the lens. Fortunately, long-term follow-up has shown that these focal opacities do not progress. Nd:YAG iridotomy has caused lens capsule perforation in monkeys.⁴⁹ Obviously the Nd:YAG laser can rupture the capsule in humans as well, thus focus is critical. This complication is rare.

It is reasonable to assume that iridotomy (surgical or laser) is a traumatic experience to the eye. Mild postoperative iritis is common and may be responsible for the metabolic lens changes that accelerate cataract formation.

In some patients undergoing extracapsular cataract surgery, zonular weakness in the area of the argon laser iridotomy has been noted. It is conceivable that the laser peripheral iridotomy may have damaged these zonules.

HypHEMA

HypHEMA is a rare occurrence with argon laser iridotomy⁵⁰ but is common after Nd:YAG laser iridotomy. The bleeding is usually self-limited and of little consequence except that it may contribute to transient IOP elevation and reduced vision.⁵¹ Temporary IOP elevation created by pressing on the contact lens is usually adequate to control the bleeding site.

Corneal epithelial injury

Corneal epithelial injury occurs commonly with laser iridotomy. If high energy levels are used, if a chromophore such as fluorescein is on the corneal surface, or if the epithelium is slightly edematous, small white burns may appear. All evidence of any topical dye should be gone before attempting laser iridotomy with argon or diode lasers. When burns do occur, they disappear after a day or so without long-term effects. Use of a contact lens helps minimize corneal burns in most patients.

Endothelial damage

Endothelial damage also occurs with argon, solid-state, and Nd:YAG laser iridotomy (Fig. 30-8).^{52–54} If the iris is very near or touching the cornea, both types of laser can cause burns. If a bubble is pressed against the endothelium at the point of laser impact or if the laser is focused poorly, an endothelial burn will occur with photothermal laser energy.

Epithelial and endothelial burns reduce both corneal clarity and the amount of laser energy reaching the iris, making the procedure more difficult. If burns occur, power or exposure time should be reduced. If it is not possible to avoid the burn by changing the approach, a new site should be chosen. Extensive endothelial burns can lead to persistent corneal edema. Nd:YAG laser treatments close to the endothelium can also cause tiny glass-like cracks at Descemet's membrane.

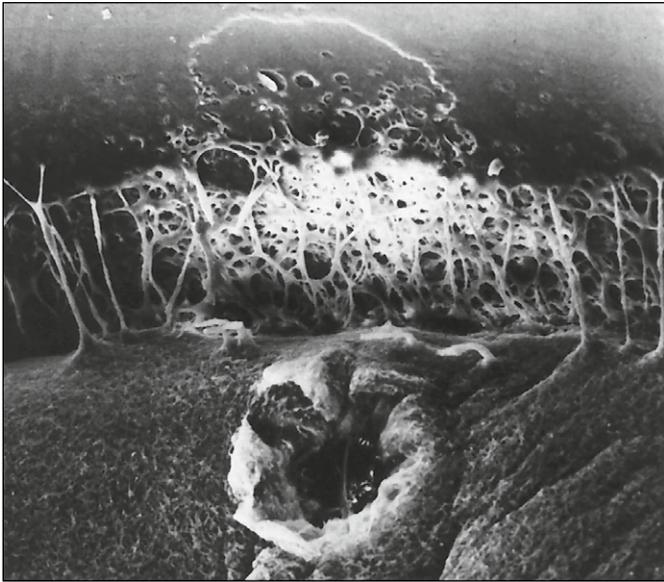


Fig. 30-8 This scanning electron micrograph of Nd:YAG laser iridotomy performed in a monkey eye demonstrates the dispersion of power that occurs at the site of laser impact. This is a full-thickness iridotomy through which a ciliary process can be seen (lower half of photo). Note the damage to the adjacent trabecular meshwork and the corneal endothelium caused by the shock-wave (upper half of photo). (Photo courtesy of Thomas M Richardson, MD, Harvard Medical School, Boston.)

Corneal stroma

A poorly focused Nd:YAG laser treatment or backward movement by the patient in the instant the treatment is delivered can result in the energy being delivered to the mid stroma. This results in a localized but rather spectacular effect called *corneal emphysema*, in which a series of small bubbles gives the affected cornea the appearance of a shattered windshield. This effect usually dissipates within an hour or so without clinically significant sequelae.

Increased trabecular pigmentation may occur as a result of iris pigment released by laser iridotomy. This pigment cleared with no microscopic sequelae in healthy monkey eyes,⁵⁵ but it could likely reduce outflow in an impaired trabecular meshwork.

Failure to perforate

Failure to perforate is rare. Occasionally patients will require a second treatment in 1–3 days. Waiting an hour often allows anterior chamber debris to clear adequately to complete the procedure. In patients with acute angle-closure glaucoma, it is important to obtain a patent iridotomy at the first attempt. An incomplete attempt will generate inflammation that can cause permanent peripheral anterior synechiae if the angle is not opened. If laser iridotomy cannot be accomplished, urgent surgical iridotomy is advisable unless the angle is opened medically. Medical therapy for angle-closure glaucoma usually clears the cornea adequately for successful laser iridotomy by Nd:YAG laser when argon laser iridotomy is not possible.

Late closure

It is estimated that a 15- μ m hole is adequate for aqueous flow through the eye,⁵⁶ but an iridotomy may become narrow as the pupil dilates.⁵⁵ Also, pigment clumps may be released into the posterior chamber, which can subsequently occlude small iridotomies.⁵⁷ Deposition and proliferation of pigment may narrow a patent

laser iridotomy during the first few weeks after treatment. To prevent subsequent closure, it is best to have an opening of at least 100 μ m. Although rare 2 months after the procedure, closure can even occur years later. If the opening does occlude, retreatment in the same place with either Nd:YAG or photothermal laser at relatively low doses easily re-opens the site. When removing pigment with argon or diode laser, it is important that gaze be directed such that any potential for the laser beam reaching the macula is prevented.

Retinal burn

Retinal burns, including burns of the fovea, have been reported with argon lasers.⁴⁶ Rarely are peripheral retinal burns of any consequence. They can be prevented by taking care not to fire the argon or solid-state laser directly through a patent iridotomy.

Aphakia and pseudophakia with pupillary block

Pupillary block is more common in pseudophakic eyes with anterior chamber lenses than in eyes with posterior chamber lenses. It can occur with any type of lens, however, especially in diabetic eyes and eyes without an iridotomy. Anterior chamber lenses often present with the iris bulging forward around the implant. A first iridotomy should be performed through a portion of the iris that is not touching the cornea. This breaks the block and allows the iris to fall back after a few minutes. Additional iridotomies should be placed in other quadrants of the iris because, especially with anterior chamber intraocular lenses, the posterior chamber may act as though it were divided into separate pockets of sequestered fluid. The vitreous body is often pressed against the back of the iris and can occlude an iridotomy. Because the vitreous seems to encourage closure of these iridotomies with pigment, iridotomies must be observed carefully for the first 6 months and subsequently three to four times a year.^{58–62} The Nd:YAG laser may be more effective in treating this problem because it creates less local iris inflammation and can disrupt the anterior hyaloid at the iridotomy site, if necessary.

LASER IRIDOPLASTY (GONIOPLASTY)

PLATEAU IRIS

Plateau iris (Fig. 30-9) may not be resolved by iridotomy alone. The peripheral iris may continue to crowd and obstruct the angle. Laser iridoplasty can be used to contract the peripheral iris, pulling it away from the angle. Argon or solid-state lasers are used with the lowest power setting that creates contraction of the iris. The surgeon should avoid explosive or vaporizing effects. Typical settings are a 100–200- μ m spot size and 100–30 mW at 0.1 second. Lighter irides will require slightly higher energy levels than darker. Ten to twenty spots evenly distributed over 360° of the iris are usually sufficient, but more or fewer may be placed as the condition warrants.^{63,64} In some cases, the effect is not permanent. Higher energy levels and longer exposures cause greater contraction of collagen but also cause more trauma and iritis. A safe approach is to use lower energy levels initially and, if the condition recurs after 1–6 months, repeat the treatment with higher power. Peaking of the pupil can be accomplished by a similar technique used in only one section of the iris. Laser iridoplasty may assist in breaking an acute attack of angle-closure glaucoma but is less satisfactory than is a completed iridotomy.

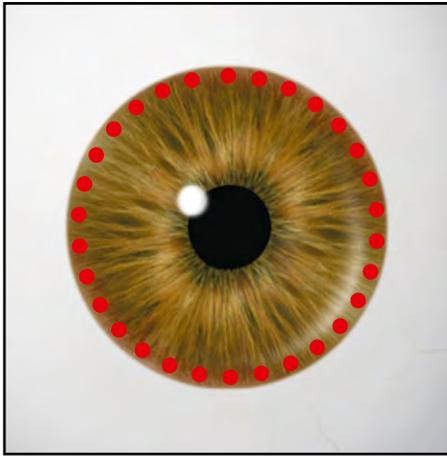


Fig. 30-9 Peripheral iridoplasty using contraction burns. Burns are placed around the circumference of the iris as peripherally as possible. When each burn is placed, the iris stroma contracts toward it from all directions. Contraction of stroma peripheral to the burn site eliminates its contact with the trabecular meshwork.

(From Ritch R, Liebmann JM: Laser iridotomy and peripheral iridoplasty. In: Ritch R, Shields MB, Krupin T, editors: The glaucomas, 2nd edn, St Louis, Mosby, 1996.)

NANOPHTHALMOS

Nanophthalmos may also require iridoplasty in addition to iridotomy. In this condition, the angle is narrowed partially because of the crowded anterior segment and possibly because of intermittent uveal effusion, which pushes the iris–lens diaphragm forward. Iridoplasty may retard this process and prevent progressive angle closure.^{65–68}

LASERS IN MALIGNANT GLAUCOMA

If ciliary processes are visible through an iridotomy, 2–4 ciliary processes can be shrunk with an argon or solid-state laser using 200–800 mW for 0.1 second with a 100–200- μ m spot size. This may restore the normal forward flow of aqueous, especially when

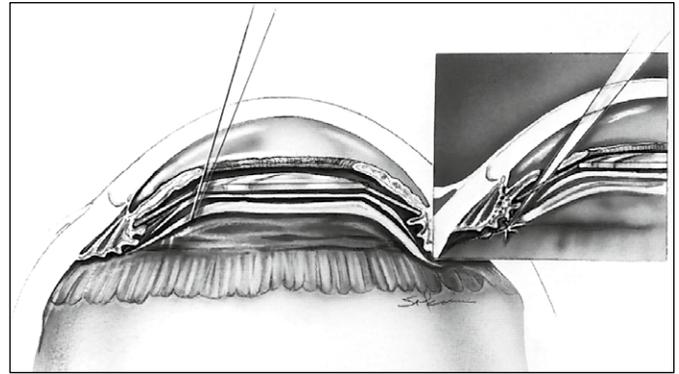


Fig. 30-10 The Nd:YAG laser may be used to disrupt the posterior capsule or the anterior hyaloid directly through the pupil or through a peripheral iridotomy in the case of ciliary block with pseudophakos.

accompanied by aggressive cycloplegic, mydriatic, and hyperosmotic therapy.^{69,70} The Nd:YAG laser can be used in a similar manner to disrupt ciliovitreal compression. The Nd:YAG beam is directed at the anterior hyaloid face between the ciliary processes using a single burst at power settings used for posterior capsulotomy. Care must be taken to avoid the periphery of the lens and the vascular ciliary processes.^{71,72}

In aphakic ciliary block glaucoma (cilio–irido–vitreal adhesion), the Nd:YAG laser can rupture the vitreous face and break the block. A patent iridotomy should be present to eliminate simple pupillary block as the cause of the flat chamber. Power settings for vitreous rupture can be as low as 0.5 mJ with a single burst. The hyaloid face can be ruptured through an iridotomy or through the pupil.^{73,74}

Pseudophakic ciliary block glaucoma can also be treated with a Nd:YAG laser by rupturing only the anterior hyaloid and leaving the posterior capsule intact.^{75,76} Rupture of the posterior capsule may be needed to break the block in some cases (Fig. 30-10). In aphakic and pseudophakic patients with ciliary block glaucoma, it is important to create a peripheral iridotomy if one does not exist. At times it may be difficult to break the attack by treating through the pupil. In these cases, a large iridotomy facilitates effective treatment.⁷⁷

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Laser treatment for outflow obstruction

Michael S Berlin

LASER TRABECULOPLASTY

HISTORY

Modifications of the trabecular meshwork to increase the outflow of aqueous humor have evolved since Krasnov¹ first reported the temporary lowering of intraocular pressure (IOP) after ‘trabeculopuncture’ with the Q-switched ruby laser. Wise and Witter,² extending the experimental work of Wickham and Worthen,³ popularized the argon laser technique that is used with modifications by most physicians today. Laser trabeculoplasty (LTP) increases aqueous humor outflow through the trabecular meshwork.² In addition to argon laser trabeculoplasty, LTP is now also performed with solid-state and diode lasers, though research has shown argon laser trabeculoplasty (ALT) to be more effective.⁴ Clinically, LTP now involves the use of either 488 and 514.5-nm argon, 532-nm solid-state, or 810-nm diode wavelengths; differences in wavelength result in varying absorption and scattering effects.⁵

The exact mechanism by which LTP lowers IOP is unclear.⁶ Mechanisms of action include mechanical and biomechanical theories. One proposed by Wise and Witter² is that focal burns of the trabecular meshwork created with an argon laser beam of 50- μ m spot size and 1000-mW power for 0.1 second cause local contraction of the meshwork tissues. A series of these burns placed 360° around the meshwork causes a circumferential shortening of the meshwork ring, pulling the inner layer of the meshwork toward the pupil and separating the trabecular sheets to increase the outflow of aqueous humor. Another is the mechanical distortion of the meshwork as a result of laser tissue modifications.

Biochemical or cellular responses of the meshwork to LTP include an increase in the replication rates of cells involved in maintaining trabecular meshwork outflow.⁷⁻⁹ Bylsma and co-workers found a 180% increase in trabecular cell division within 2 days of argon LTP.¹⁰ Parshley and co-workers^{11,12} investigated the extracellular matrix reaction to argon LTP and found, among other things, an increase in stromelysin expression. An increase in stromelysin activity should increase degradation of trabecular proteoglycans, in turn resulting in an increase in outflow facility.^{11,12} Perhaps further work in these areas will find that a combination of these and other mechanisms is responsible for the clinically significant reduction in IOP seen after LTP.

RESULTS

The efficacy of LTP in lowering IOP has been well documented in the literature.¹³⁻¹⁵ Long-term studies, however, have shown that the

efficacy of LTP decreases significantly over time, from 77% success rate at 1 year, to 49% at 5 years, and to 32% at 10 years (Table 31-1).¹⁶ Additionally, because of the significant scarring ALT causes to the trabecular meshwork, repeat treatments are not recommended and have not proven successful clinically.¹⁷ Laser trabeculoplasty causes thermal coagulative damage to the uveoscleral meshwork, disruption of the the trabecular beams, and heat damage to the surrounding structural collagen fibers. This thermal damage is in part responsible for the inflammatory response, scarring of the trabecular meshwork tissue, peripheral anterior synechiae and IOP spike sometimes observed in eyes which have undergone LTP.¹⁸ Laser trabeculoplasty has proven successful in lowering IOP both as primary therapy and when used in conjunction with medications. Most patients continue to require medications after LTP, although one-third to one-half may be able to reduce their pre-LTP level of treatment. This may be helpful in relieving a patient of intolerable side effects from drugs such as miotics or carbonic anhydrase inhibitors (CAIs).

Much attention and discussion has been devoted to determining the most effective role of LTP in the glaucoma treatment paradigm that includes medical therapy and surgical intervention. Research has shown that the cost of medical therapy can be prohibitive for many patients, especially those on small fixed incomes, without medication insurance, or without adequate resources to purchase medications. Compliance with a medical regimen, especially one that includes daily use of multiple topical drops, has proven difficult for many patients. Extensive research between 1980 and

Table 31-1 Success rate of laser trabeculoplasty on various diagnoses

	Success rate 1 year after laser trabeculoplasty (%)	Success rate 4 years after laser trabeculoplasty (%)
Primary open-angle glaucoma	56	35
Exfoliative glaucoma	56	34
Pigmentary glaucoma	54	25
Aphakic primary open-angle glaucoma	51	22

From unpublished data by H Dunbar Hoskins Jr, MD, John Hetherington, MD, and Christopher J Dickens, MD.

2004 has shown patient non-compliance rates of at least 25%, with most studies showing depressingly high non-compliance rates, and researchers have noted that patients are likely to discontinue long-term prescriptions as much as 76% of the time. The Glaucoma Laser Trial compared the efficacy of argon laser trabeculoplasty and timolol maleate 0.5% as initial therapy for primary open-angle glaucoma.¹³ The initial trial and subsequent follow-up study measured IOP reduction, visual field and optic nerve status in a total of 203 patients. Over an average of seven years of follow-up, eyes treated with ALT had 1.2mmHg greater reduction in IOP ($P < 0.001$), and 0.6dB greater improvement in visual field ($P < 0.001$). There was slightly more deterioration in the cup-to-disk ratio ($P = 0.005$) for eyes initially treated with topical medication. In a 2-year study comparing the efficacy of ALT and pilocarpine 2% in treating primary open-angle glaucoma, similar results were observed.¹⁹

Different studies have yielded various success rates for LTP. In one study (Fig. 31-1), initial IOP reductions of 7–10mmHg were not maintained through long-term follow-up. At 5 years after treatment, only 30–60% of patients maintained adequate IOP control.

Argon LTP is effective in most forms of open-angle glaucoma.^{20,21,22} It is rarely effective in cases of trauma or inflammation and often aggravates inflammation. It may be effective after failed filtering surgery. Laser trabeculoplasty is more effective in older patients with POAG; the effect diminishes in patients younger than 40 years of age.^{23–29} Dramatically lowered IOP, sometimes greater than 20mmHg, may occur in patients with pseudoexfoliation glaucoma, but the effect may be brief so these patients continue to require close monitoring.³⁰ Pigmentary glaucoma also responds unpredictably^{25,26,28,31–33} and may have lower long-term success rates than POAG.^{34,35}

RETREATMENT OF A PREVIOUSLY LASER-TREATED ANGLE

Repeat argon LTP is often not advised.^{36–38} If considered for patients who have previously received treatment to 360° of the angle, the patient should be warned that filtering surgery may be required soon after the retreatment if it is unsuccessful.³⁹

It is clear that LTP can postpone filtering surgery³⁸ in patients on maximum medical therapy who would benefit from and who achieve a 9–10-mmHg decrease in IOP. However, if a greater

decrease is needed because of advanced glaucomatous damage, filtering surgery should be considered first.³²

SELECTIVE LASER TRABECULOPLASTY

Concept

In contrast to argon, solid-state, and diode laser pulse durations for LTP of 0.1 seconds, recent advances in trabeculoplasty have utilized lasers with short pulse durations of 3–10ns. Selective laser trabeculoplasty (SLT), based on the principle of selective photothermolysis, relies on selective absorption of a short laser pulse to generate and spatially confine heat to pigmented targets within trabecular meshwork cells.^{40,41} Selective laser trabeculoplasty uses a Q-switched, frequency-doubled 532-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. Q-switching of the laser allows for a single, extremely brief, high-power light pulse to be delivered to the target tissue. The short duration of the pulse is critical in preventing collateral damage to the surrounding tissues.⁴² The energy level of available lasers varies between 0.2 and 1.7mJ.

An advantage of SLT over LTP performed with larger pulsed lasers is that there is much less thermal damage to the trabecular meshwork. Preserving the trabecular meshwork may become important in the near future as surgical techniques are developed to operate directly on Schlemm's canal or the juxtacanalicular trabecular meshwork, the region considered responsible for most of the outflow obstruction that causes open-angle glaucoma. Thermal LTP would preclude these patients from the new procedures, as their trabecular meshwork and Schlemm's canal would be damaged.

Mechanism

The exact mechanism behind SLT remains unclear. Histopathologic evaluation of the trabecular meshwork in eyes treated with both ALT and SLT showed coagulative damage to the trabecular meshwork after ALT but not SLT.⁴³ However, two main theories exist which attempt to explain the IOP-lowering effect. One mechanical theory states that SLT results in a stretching of the trabecular meshwork beams. Another states that the trabecular meshwork beams are separated and their mobility is increased following SLT. The biological theory states that SLT causes the release of chemical mediators and stimulates endothelial cell replication.⁴⁴ In fact, it is likely that a combination of both mechanical and biological mechanisms causes the IOP decrease seen after LTP.

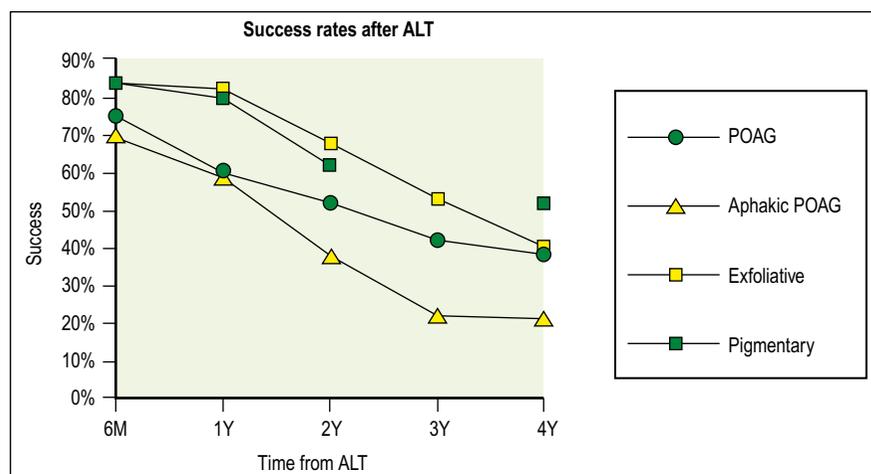


Fig. 31-1 Failure is defined as the need for further surgery or trabeculoplasty or IOP higher than 80% of the preoperative level. (From unpublished data by H Dunbar Hoskins Jr., MD, John Hetherington, MD, CJ Dickens, MD; Ritch R, and others: *Ophthalmology* 100:909, 1993; Schwartz AL, Wilson MC, Schwartz LW: *Ophthalmic Surg Lasers* 28:215, 1997; and Threlkeld AB, and others: *J Glaucoma* 5:311, 1996.)

Technique

Patient preparation

Preoperatively, the patient maintains their usual medication regimen. Additionally, the surgeon may choose to use pilocarpine 2% 30 minutes to 1 hour prior to the LTP procedure, which can help to further expose the trabecular meshwork and prevent IOP spikes. Topical α_2 agonists are the most effective preventive for postlaser IOP spikes. Topical fluorescein, often used in conjunction with Goldmann applanation tonometry, is a chromophore for most LTP wavelengths; therefore, preoperative IOP is measured with a tonometer not requiring fluorescein or a suitable time period is allowed to elapse between IOP measurement and laser treatment. The procedure is performed under topical anesthetic.

Procedure

General preparation for LTP should be the same as that for any laser treatment of the anterior segment (see Ch. 29). While the patient is seated at the laser–slit–lamp system, a coated three-mirror Goldmann gonioscopy lens or a specially constructed trabeculoplasty lens such as the Ritch or Karichoff lens is attached to the eye with methylcellulose gonioscopy solution (e.g. Goniosol[®]). For SLT, a Latina or other suitable SLT lens is used to view the angle. The surgeon examines the entire circumference of the angle to ensure proper orientation in the trabecular meshwork and good visibility of the angle structures. In order to identify markers, it can be helpful to locate a pigmented portion of the trabecular meshwork or the scleral spur (see Ch. 6). The helium–neon aiming beam is focused onto the pigmented trabecular meshwork.

Laser trabeculoplasty. The laser delivery system is first calibrated to ensure a focal spot of 50 μm . This 50 μm spot is used with 0.1 second exposure time.⁴⁵ The power is titrated to the visible effect. In an eye with moderate or average trabecular pigmentation, the initial power of 400–500 mW is increased in 100-mW increments (to a maximum of 1000 mW) until a slight blanching effect occurs or small bubbles form at the point of laser impact. Less energy is required for more heavily pigmented angles. Reducing the power below 500 mW in lightly pigmented eyes, however, seems to decrease the treatment's effectiveness.⁴⁶

Orientation may be difficult in patients with little or no pigment in the angle. The surgeon should clearly identify the region

between the anterior border of the ciliary body and Schwalbe's line. The middle of the trabecular meshwork lies near the midpoint of this region. If possible the scleral spur should be identified and visualized 360°. Pigmentation anterior to Schwalbe's line may resemble trabecular pigmentation and confuse the surgeon. Identifying and following the scleral spur helps to eliminate this confusion. The lens is held so that the laser beam is focused clearly as a sharp circular spot. Asking the patient to gaze toward the mirror (e.g., if the mirror is to the right during the examination the patient is asked to look to the right) may assist in viewing the angle, especially when the iris is convex. Poor or astigmatic focusing diffuses the laser energy and increases tissue damage unnecessarily.⁴⁷ Although treatment at the level of the ciliary body, scleral spur, posterior meshwork, and anterior meshwork have all been proposed, fewer complications and equal effectiveness result from treating at the junction of the trabecular pigment band and anterior meshwork (Fig. 31–2).

Laser applications are then positioned 3–4° apart so that approximately 20–25 spots are created per quadrant. Debate continues over how many quadrants should be treated. There is less postoperative inflammatory response and fewer pressure spikes when there are fewer spots.^{48,49} Most physicians advise initial treatment of 180°. If only 180° is treated, the patient is re-evaluated in 4–6 weeks. If the IOP drop is inadequate, the remaining 180° is treated.²⁶ If the IOP drop is adequate, the patient is observed until a lower IOP is necessary, at which time the second 180° is treated. A few patients will achieve a substantial drop in IOP with a second 180° treatment, even though treatment of the first 180° was disappointing. When considering eyes that have had the second 180° treated, there appears to be little difference between the long-term efficacy of initial treatment of 180° and 360° (Fig. 31–3).

The patient should be closely monitored on the day of surgery and on the first postoperative day for pressure spikes and iritis. The final effect of LTP may not be evident for 4–6 weeks.

Selective laser trabeculoplasty. The 400- μm spot size – compared to the 50- μm spot size of ALT (Fig. 31–4) – covers most of the angle structures and iris root. However, the short pulse duration enables selective absorption by the intracellular melanin target. The other, non-pigmented, tissues irradiated by the beam are not affected.

The energy level for SLT treatment is set initially at 0.8 mJ. A test pulse is delivered at the set energy. If the surgeon visualizes bubble

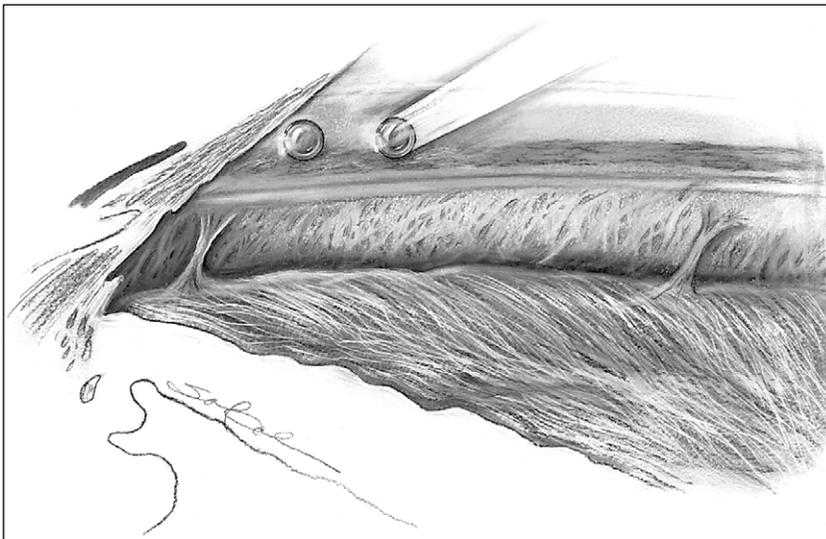


Fig. 31-2 The laser beam is directed toward the middle of the trabecular meshwork at the anterior edge of the pigmented trabecular band. Small bubble formation or blanching of the meshwork should be visible at the point of treatment.

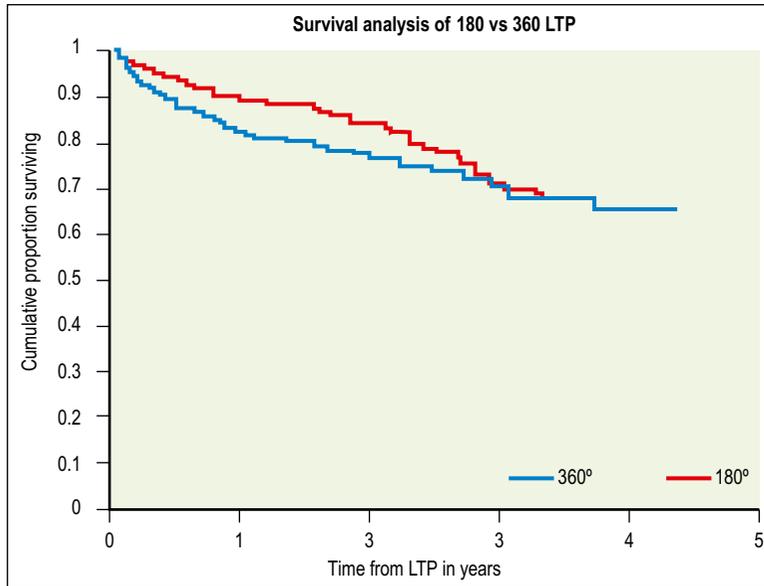


Fig. 31-3 In analyzing the cumulative success of argon laser trabeculoplasty by comparing the efficacy of the initial 360° of treatment versus initial 180° of treatment, there is little difference in the success rate over time. In this particular study, patients who had 180° of treatment were allowed to undergo subsequent 180° of treatment if pressure rose to pre-laser levels. Approximately 50% of the initially-treated 180° group underwent treatment subsequently. (From unpublished data by H Dunbar Hoskins Jr., MD, and John Hetherington Jr., MD.)

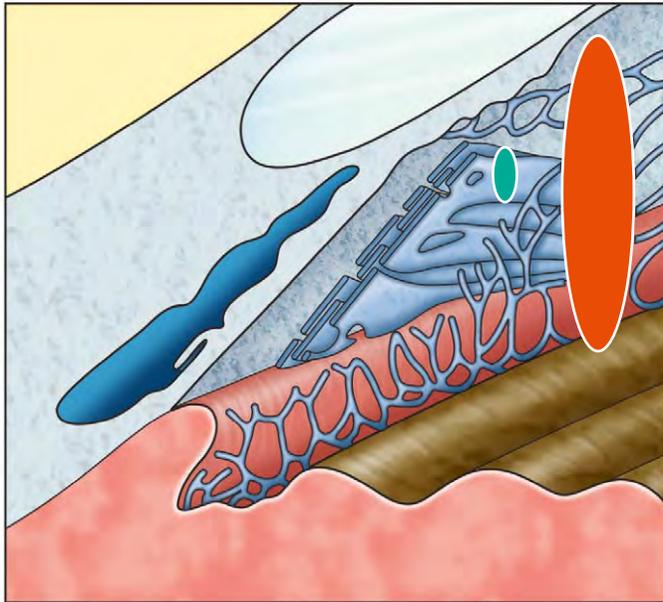


Fig. 31-4 Significantly larger spot size of SLT (400 μ m) compared to that created during ALT (50 μ m).

formation like that typically associated with ALT, pulse energy is decreased in 0.1-mJ intervals until minimal bubble formation is detected. Once the suitable pulse energy is determined, treatment proceeds in single-pulse mode. In eyes with varying degrees of trabecular meshwork pigmentation, more bubble formation may be observed intermittently throughout the procedure. If more bubble formation occurs, pulse energy is decreased appropriately.

Recommended procedure protocols for SLT are in flux and vary from treatment of 180° with 50 spots, to 360° with 100 spots, evenly spaced over the trabecular meshwork for patients with most open-angle glaucomas. The pressure-lowering effect is improved with 360° treatment.⁵¹ An exception is treating patients with pigmentary glaucoma. In pigmentary glaucoma, the trabecular

meshwork surface is covered with pigment, which absorbs the SLT energy, thermally affecting the underlying trabecular meshwork and becoming dispersed into the anterior chamber, both causing pressure spikes. Therefore it is recommended that SLT treatment for patients with pigmentary glaucoma be performed in multiple sessions, treating 90° of the angle at each, and using minimal energy with no bubble formation.

The extent to which the trabecular meshwork should be treated with SLT remains controversial. Though the standard treatment regimen for SLT uses 50 spots at 0.6–1.0 mJ over 180° of trabecular meshwork, Chen and colleagues found that SLT with 25 laser spots on 90° of trabecular meshwork has a similar pressure-lowering effect.⁵² More recently, Song and co-workers found failure rates of 68–75% in patients who underwent 180° SLT (with failure defined as IOP decrease of <3 mmHg or IOP decrease of <20%).⁵¹ Nagar,⁵³ comparing treatment with 90°, 180°, and 360° SLT on 28, 34, and 31 eyes respectively, found significantly greater reduction in IOP in eyes treated with 360° SLT; there was also a significantly greater incidence of adverse effects in this treatment group, including patient discomfort, anterior chamber activity, and pressure spikes.⁵³

POSTOPERATIVE TREATMENT

Postoperative treatment protocols are also in flux. If the biological theory of SLT is correct, mild postoperative cell response is welcome and postoperative steroids are not used. However, most surgeons prefer a modification of the following regimen.

Immediately after completion of the procedure, and after the treated eye has been thoroughly rinsed, 1 drop of prednisolone 1% is instilled. The patient instills 1 drop of prednisolone 1% every 2 hours or q.i.d. on the same day as the procedure. Prednisolone is reduced to q.i.d. 1 day post LTP. The patient may return for a slit-lamp examination and evaluation of IOP response to LTP the day after the procedure. The surgeon evaluates the eye for inflammation and IOP elevation. If IOP response is reasonable, and inflammation mild or non-existent, prednisolone remains at q.i.d. on the second and third day post LTP, and is reduced to b.i.d. the fourth and fifth day post LTP. After 5 days, prednisolone is discontinued. Others use

a mild steroid like fluoromethalone 0.1% (FML™) or loteprednol 0.5% (Lotemax™) q.i.d. for 1 week. The patient may be seen 1–2 hours after the treatment to monitor for IOP elevation, and if the eye is quiet and with reasonable IOP, the patient may be seen after several weeks. Many surgeons do not use any anti-inflammatory agents after SLT since the postoperative inflammation is rarely a problem and the authors have noted a less vigorous IOP reduction when anti-inflammatory agents are used.

The patient returns for an evaluation 1 month and 3 months after the procedure to evaluate and monitor IOP. The patient's preoperative medication regime continues unaltered postoperatively, including in the immediate postoperative period. Maximum effects from ALT may not be seen until 6 weeks whereas maximum response to SLT may take as much as 3 months. Repeat SLT should not be performed until at least 3 months after the initial SLT to be sure that enough time has been given for the response to take place. If the IOP decreases enough, the surgeon may decide to decrease the patient's medication use.

OUTCOMES

Kramer and Noecker first studied the effects of ALT and SLT on human eye-bank eyes.⁵⁴ Evaluation of the trabecular meshwork of eyes which had undergone ALT revealed crater formation in the uveal meshwork, coagulative damage with disruption of the collagen beams and fibrinous exudates, and lysis of endothelial cells. By comparison, the trabecular meshwork of eyes which had undergone SLT showed no evidence of coagulative damage or disruption of the corneoscleral or uveal trabecular beam structure. Selective laser trabeculoplasty therefore preserves the meshwork for future medical, laser, or surgical intervention, if necessary. Additionally, eyes which had previously undergone failed ALT demonstrated a significantly greater reduction in IOP when treated with SLT than those treated with repeat ALT.¹⁷

A preliminary clinical trial studying the safety and efficacy of SLT in treating primary open-angle glaucoma demonstrated a mean IOP decrease of 30% at 1 day, 27% at 8 weeks, and 29% at 49 weeks.⁵⁵ No serious adverse effects were reported. Melamed and co-workers performed the procedure in 45 eyes of 31 patients, and recorded a decrease in IOP from 25.5 ± 2.5 mmHg to 17.9 ± 2.8 mmHg, or 30%.⁵⁶ No serious adverse effects were related to SLT.⁵⁶ Several multicenter, prospective clinical trials have been conducted which further demonstrate the efficacy and safety of SLT. Pressure reductions ranged from 2.85 to 10.6 mmHg with follow-up periods of 6 weeks to 26 months.¹⁸ Subsequent studies have compared the safety and efficacy of ALT and SLT in treating various types of glaucoma.

In their comparison of the long-term success rates of SLT and ALT, Juzych and co-workers found that both techniques are similarly effective in lowering IOP over a 5-year follow-up period.⁵⁷ Likewise, in a clinical study of 40 patients, 20 of whom were treated with SLT (180°) and 20 with ALT (180°), Martinez-de-la-Casa and colleagues found that at 6 months following treatment, pressure reduction was similar in both groups.⁵⁸ In addition, the energy released during treatment and inflammation in the anterior chamber in the immediate postoperative period was significantly lower for the SLT procedure, as was pain reported by the patients during treatment.⁵⁸ Similarly, in a prospective trial with a follow-up period of 36 months, there was no significant difference between IOP reductions in patients who had undergone ALT and those who had undergone SLT.¹⁷

CONTRAINDICATIONS

Contraindications to ALT include inadequate visualization of the trabecular meshwork, hazy media, closure of the iridocorneal angle, corneal edema, uveitic glaucoma, juvenile glaucoma (usually), patient age of 35 years or less, and a need for IOP-lowering greater than 7–10 mmHg.

While inflammatory glaucoma is considered a contraindication for ALT, in a study of 130 eyes of 87 patients with allergic, uveitic, and post-transplantation diagnoses, IOP was reduced by 4 mmHg or more in 56% of eyes treated with SLT.⁵⁹

A heavily pigmented trabecular meshwork, especially combined with previous ALT, may be a contraindication to SLT. In a retrospective, non-comparative case series of 4 eyes which presented with IOP spikes after undergoing SLT, Harasymowycz and colleagues found that all eyes were characterized by heavy trabecular meshwork pigmentation, and 50% had previously undergone ALT.⁶⁰ The authors suggest that eyes with heavy pigmentation and a history of previous ALT should be considered at increased risk for IOP spikes post SLT.⁶⁰

AS INITIAL THERAPY

The Glaucoma Laser Trial demonstrated the efficacy of ALT as initial therapy for open-angle glaucoma.¹³ Selective laser trabeculoplasty may prove equally effective as initial therapy. To evaluate the potential of SLT as a replacement for medications, Francis and colleagues performed SLT inferiorly on 66 eyes of 66 patients with medically controlled open-angle or exfoliative glaucoma.⁶¹ At 12 months, 87% of patients achieved a significant reduction in medications (mean reduction at 12 months: 1.5), while maintaining a previously determined target IOP.⁶¹ Further study is needed to determine if clinically significant IOP control is possible using SLT as primary treatment.

PREDICTORS OF OUTCOME

While it has been suggested that pigmentation may contribute to determining the outcome of SLT, several studies have shown otherwise. Hodge and associates evaluated whether any characteristics of 72 patients, including age, race, sex, pigmentation, or other risk factors for glaucoma, were predictors of successful SLT at 1 year (successful SLT defined as a reduction in IOP = 20%).⁶² Only baseline IOP was a significant predictor of successful SLT.

APHAKIC AND PSEUDOPHAKIC OPEN-ANGLE GLAUCOMA

Laser trabeculoplasty is generally less effective in aphakic eyes,³⁰ but when it is successful the decrease in IOP in aphakic open-angle glaucoma is similar to that for chronic open-angle glaucoma (average, approximately 7 mmHg). Preliminary data indicate that LTP may be as effective in pseudophakic eyes with posterior chamber lenses as it is in phakic eyes. Cataract surgery after LTP seems not to have a deleterious effect on IOP control. Laser trabeculoplasty performed before cataract surgery may be more effective than that performed afterward.

COMPLICATIONS

Intraocular pressure elevation

Few complications are associated with LTP (Table 31-2).⁴⁸⁻⁵⁰ Up to 50% of patients, however, experience a transient IOP spike

Table 31-2 Possible complications of laser trabeculoplasty

Complication	Seen	Suspected	Serious	Not serious
Corneal abrasion	X			X
Endothelial damage	X			X
Dilated pupil	X			X
Hyphema	X			X
Iris burns	X			X
Iritis (transient)	X			X
Peripheral anterior synechiae	X		X	X
Iritis (persistent)	X		X	
Decreased vision	X		X	
Trabecular damage	X			?
Tension rise (persistent)	X		X	
Tension rise (transient)	X		X	
Progressive visual field loss	X		X	
Inadequate effect	X		X	
Syncope	X		X	
Cystoid macular edema		X	X	
Refractive change		X		X
Reduced success of filter		X	X	

Modified from Hoskins HD, and others: Ophthalmology 90:796, 1983.

similar to that seen after laser iridotomy (see Ch. 30) and respond to the same therapeutic approach. Pretreatment and/or post treatment with most of the antiglaucoma agents have all helped reduce the spike but topical α agonists (apraclonidine, brimonidine) seem to be the preferred agents because of their effectiveness and lack of side effects with short-term use.⁶³ Intraocular pressure spikes increase with the number of laser applications – which is one argument for treating only 180° of the angle initially. A pressure spike may be delayed for 2 hours but almost always appears within 3 hours. Patients have had loss of central acuity, which might have been related to a pressure spike, and although rare, central vein occlusion has reportedly occurred within 24 hours of LTP.

Sustained intraocular pressure increase

A sustained IOP increase occurs in 1.5–3% of patients undergoing LTP. This must be considered and discussed with patients before treating someone whose glaucoma is easily controlled with medications.

Hyphema

Hyphema occurs rarely, is self-limited, and is usually of little consequence. When bleeding does occur, it is seen at or adjacent to a burn site. Bleeding may be stopped by briefly increasing pressure on the globe with the gonioscopes. Some surgeons photocoagulate bleeding sites with 200 mW of power, a 200- μ m spot size, and 0.2 second of argon laser energy.

Peripheral anterior synechiae

Peripheral anterior synechiae occur more commonly with large burns that are positioned posterior in the trabecular meshwork. Thus anterior placement of spots with just enough energy to cause

a visible reaction is preferred. Peripheral anterior synechiae seem to reduce the ultimate effect of ALT and are undesirable. Peripheral anterior synechiae have not been reported with SLT.

Iritis

Although mild, iritis is common after argon LTP and can be treated by vigorous use of topical steroid drops as often as hourly on the day of treatment, reduced to four times daily for 2–3 days after treatment. Some patients may require prolonged steroid treatment and monitoring. Topical steroid treatment decreases postoperative inflammation but does not appear to affect the outcome of the procedure.⁶⁴ Laser trabeculoplasty in patients with pre-existing uveitis generally aggravates the uveitis, is unsuccessful in lowering IOP, and should be avoided unless there are compelling reasons to try it. However, since incisional surgery in glaucoma associated with uveitis has a relatively poor outcome, SLT may be tried.

Uveitis

Mild uveitis has been reported in approximately 80% of patients treated with SLT.¹⁸ However, such sequelae rarely persist for more than 24 hours. Researchers have reported postoperative IOP spikes in a very small proportion of patients, typically resolving with further SLT treatment (if only 180° was previously treated) or medication use.

EXCIMER LASER TRABECULOSTOMY

Concept

Historically, there have been many attempts to utilize various lasers to fistulize the anterior chamber into Schlemm's canal in order to bypass the outflow obstruction, since most of the outflow obstruction in open-angle glaucoma is localized to the juxtacanalicular trabecular meshwork and the inner wall of Schlemm's canal. Most of these attempts have failed. The lasers used caused damage to surrounding tissues from thermal and mechanical laser/tissue effects evoking healing and scarring responses.^{40,65–67} A more precise, less thermal laser was needed.

Ultraviolet excimer laser photoablation enables both precise tissue removal and no thermal damage to surrounding tissues, exemplified by the 193-nm wavelength used for corneal surface ablation. However, this wavelength is not readily transmissible via fiber-optics and could not be used intracamerally. The 308-nm wavelength excimer laser energy is fiber-optically transmissible and became the wavelength of choice for these types of *ab-interno* fistulizing procedures, both for sclerostomy, creating a bleb via an *ab-interno* approach, and for trabeculostomy, creating flow into Schlemm's canal.

In a study of the effects of 308-nm excimer laser energy applied *ab interno* to the sclera of rabbit eyes, long-term decreases in IOP were achieved. The 308-nm laser–tissue interaction enables significant advantages: the excimer laser is less likely to evoke a cicatricial response in the trabecular meshwork or sclera than visible or infrared lasers, which cause a thermal tissue reaction. In addition there is minimal exposure of adjacent tissue to radiation enabled by direct contact of the laser energy to the target tissue via a fiber-optic delivery system. This study formed the basis for the development of excimer laser trabeculostomy (ELT).

Technique

Excimer laser trabeculostomy, first used clinically in 1998, treats the pathology responsible for most open-angle glaucoma by decreasing the outflow obstruction at the juxtacanalicular trabecular meshwork and the inner wall of Schlemm's canal.⁶⁸ It is performed

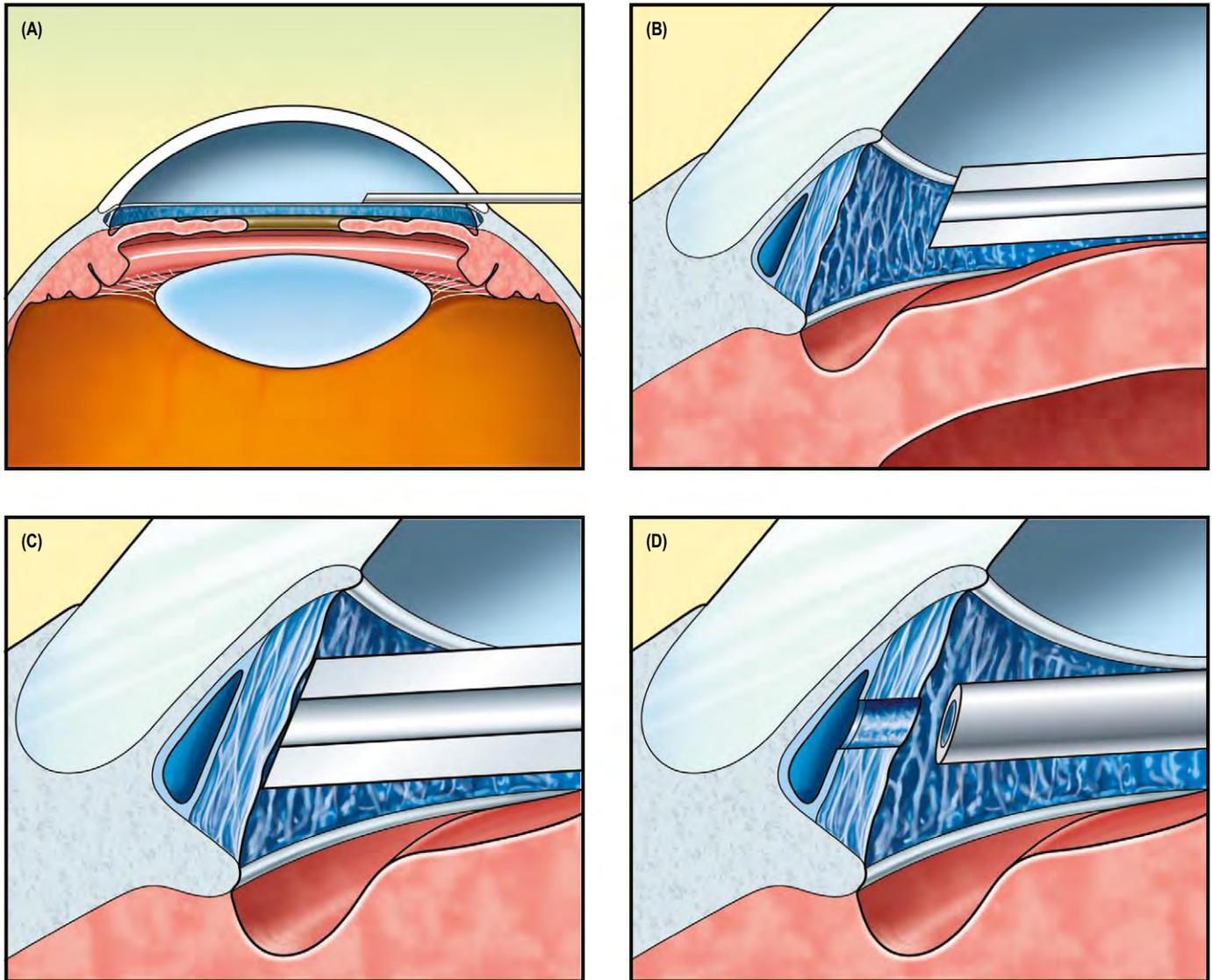


Fig. 31-5 During ELT surgery, following paracentesis, a fiber-optic probe is advanced across the anterior chamber and placed in contact with the trabecular meshwork. An ablation hole is created through the trabecular meshwork, the juxtacanalicular trabecular meshwork, and the inner wall of Schlemm's canal.

with a short-pulsed (80 ns)⁶⁹ 308-nm xenon-chloride (XeCl) excimer laser which delivers photoablative energy to precisely remove the tissue which obstructs fluid outflow with minimal thermal damage to adjacent tissue. Excimer laser trabeculostomy surgery is performed as an outpatient procedure, under topical anesthesia. Following a paracentesis and stabilization of the anterior chamber with viscoelastic, the surgeon introduces a fiberoptic probe, which is advanced across the anterior chamber and placed in contact with the trabecular meshwork (Fig. 31-5). Probe placement is controlled by direct observation using either a gonioscope or an endoscope. Four to ten openings are created into Schlemm's canal. A small amount of blood reflux is a common but inconsequential occurrence. The probe is then removed, the viscoelastic is removed, and the patient is monitored postoperatively.

By means of photoablation, ELT 'evaporates human tissue and denatures organic structures without producing undesirable marginal necrosis.'⁷⁰ Excimer laser trabeculostomy excises the trabecular meshwork, the juxtacanalicular trabecular meshwork, and the inner wall of

Schlemm's canal without damaging the outer wall of Schlemm's canal or the collector channels.⁷¹ It creates no filtering fistula or bleb.^{72,73}

Outcomes

Various studies evaluating ELT both as monotherapy and in combination with lensectomy demonstrate favorable outcomes (Table 31-3).

The clinical trials involving ELT are limited. The trials were neither randomized nor controlled. Technique varied depending on the surgeon, as did the number of openings created. Controlled, randomized, multicenter trials are currently underway to determine the extent of the IOP-lowering effect observed after ELT, how long the IOP reduction lasts, and to determine ideal treatment protocols.

OTHER LASER SCLEROSTOMY TECHNIQUES

Laser sclerostomy may offer better results than repeat trabeculectomy in eyes that have undergone prior filtering surgery.⁷⁴ Perforation of the sclera in the area of the chamber angle to create a filtering

Table 31-3 Compiled results of known ELT studies

Study	Treatment	No. of eyes	Type of glaucoma	Duration of follow-up	IOP decrease (%)	Medication use decrease (%)
Neuhann ⁶⁹	ELT	14	POAG	6 months	40	N/A
Welt*	ELT	104	POAG/OHT	12 months	40	N/A
Neuhann*	ELT	149	POAG	18 months	43	97
Funk†	ELT	69	POAG	24 months	32	74
	ELT + lensectomy	197	POAG	18 months	38	77

*Data presented at the ELT Users Meeting in Munich, Germany, 2003.
†Data presented at the American Society of Cataract and Refractive Surgery, 2004.

N/A, not available.

sclerostomy has been successfully performed with the Nd:YAG laser, the dye laser,⁷⁵ the 308-nm XeCl excimer laser,³⁵ the argon fluoride excimer laser,⁷⁶ the erbium:YAG laser,⁷⁷ diode lasers, the holmium:YAG laser,⁷⁸ the Nd:yttrium-lithium-fluoride (YLF) laser,⁷⁹ and the thulium-holmium-chromium (THC):YAG ('holmium') laser.⁸⁰⁻⁸² Delivery methods may be *ab externo* or *ab interno*. *Ab-externo* delivery involves the use of a stationary or advancing probe applied to the scleral surface under a conjunctival flap. *Ab-interno* delivery can be invasive or non-invasive through a gonioscope. Invasive *ab-interno* delivery incorporates a stationary or advancing probe introduced into the anterior chamber through a paracentesis incision.

Laser therapy for glaucoma puts treatment in the hands of the surgeon rather than the patient, minimizing the compliance

and cost issues associated with daily medication use and dose-dependent diurnal fluctuation in IOP. In light of the minimally invasive nature and therapeutic efficacy of SLT and ELT, these modalities may become more useful both as primary therapy and after only one or two medications have been tried. In the near future, patients may receive a trial with one or two medications and then be subjected to SLT or its successor. When SLT fails, ELT may become the next treatment. It is possible that as the efficacy and safety of laser therapies for the treatment of glaucoma improve, lasers may replace medications as first-line therapies. This may be especially true among the poor and in developing countries where the costs of medications may be prohibitive and access to monitoring of IOP may be limited.

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CHAPTER
32Miscellaneous laser procedures
including laser ciliary body
therapy

Michael S Berlin

CYCLOPHOTOCOAGULATION

If all other therapies fail or are contraindicated, it is possible to reduce aqueous production and lower intraocular pressure (IOP) by destroying elements of the ciliary body. Cyclophotocoagulation procedures destroy the ciliary epithelium, stroma, and vascular supply (Fig. 32-1). They have been found to be effective, but complications are significant. In *successful* cases, inflammation, postoperative IOP increases, iritis, pain, and perhaps some loss of visual acuity are common. Thus laser cyclophotocoagulation procedures have historically been considered a last resort, with indications similar to those for cyclocryodestruction. Laser therapies tend to have fewer complications than does cyclocryodestruction,¹ but most glaucoma specialists do not attempt cyclophotocoagulation until other attempts at IOP reduction have failed. Age, preoperative IOP, and gender do not appear to affect the success of these procedures.²

Destruction of the ciliary processes to reduce aqueous production can be accomplished by direct visualization with a variety of lasers, or trans-sclerally, with a 1064-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser in the thermal continuous wave (cw) mode³⁻⁵ or an 810-nm diode laser. Direct (transpupillary or intracamerally with endoscopic control) cyclophotocoagulation has the advantage of ensuring that laser light is targeted accurately on the ciliary epithelium, which may be missed in trans-scleral laser cyclophotocoagulation.⁶ Because most glaucoma patients do not possess the large pupils and clear media necessary for the

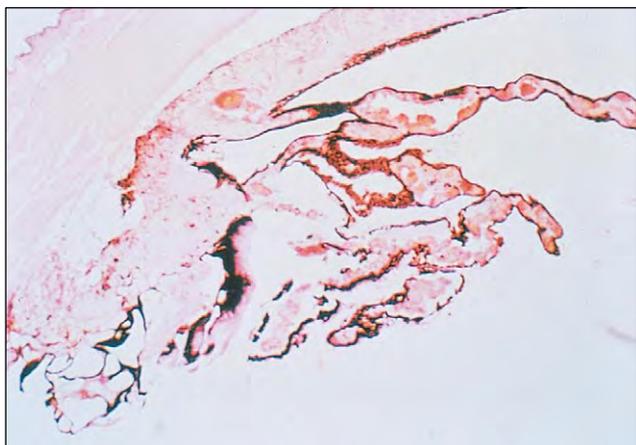


Fig. 32-1 Histopathology of a rabbit ciliary body treated with trans-scleral cyclophotocoagulation (TCP).

transpupillary approach, however, trans-scleral cyclophotocoagulation with the Nd:YAG or 810-nm diode laser is used more frequently. Recently, endocyclophotocoagulation (see below) has been increasingly popular.

In laser trans-scleral destruction of ciliary processes,^{3,7-9} 30–40 applications of energy are directed at the limbus at an angle that will strike the secretory portion of the ciliary processes. The laser energy may be delivered with a slit-lamp (non-contact) delivery system or with a fiber-optic probe placed directly on the conjunctiva (contact) (Fig. 32-2). Retrobulbar anesthesia is usually required for the patient's comfort during and after the procedure. The patient's eyelids may be separated manually or, more conveniently, with a speculum. A specialized contact lens may be useful to help control eye movement, compress the conjunctiva, and assist in placing laser applications with the non-contact variety.^{2,10,11} With non-contact treatment, the angle of laser incidence of the beam should roughly parallel the visual axis and strike the globe approximately 1–2mm posterior to the limbus.¹² Generally the 3 and 9 o'clock meridians are avoided to prevent damage to the long posterior ciliary arteries. Preoperative vasoconstriction with an α agonist (iopidine, alphagan P) may reduce energy absorption by conjunctival vessels and decrease the likelihood of subconjunctival hemorrhage.

Laser energy parameters are variable, because the energy output of various instruments is also variable. One technique⁸ uses energy levels of 0.5–2.75J for 32 applications distributed over 360° of the ciliary body.¹³ Treating 270° with 16–18 applications may decrease the incidence of complications and is recommended. Exposure

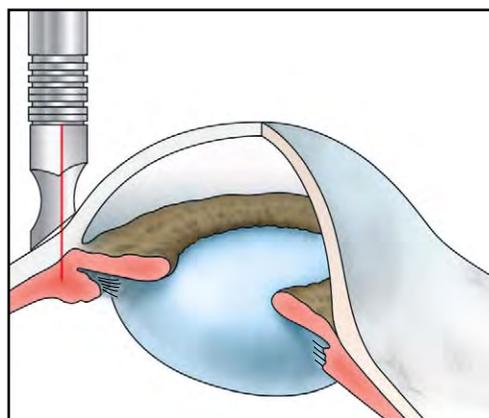


Fig. 32-2 The G-probe is positioned on the limbus to allow direct treatment of the ciliary body.

times range from 10 to 20 ms. Some surgeons use up to 8 J. Because of the varying amounts of energy delivered by each type of laser instrument, it is advisable to obtain recommendations from a surgeon experienced with the particular instrument being used.

Although repeat treatments often are needed, 60–70% of cases can be controlled, maintaining IOPs of 22 mmHg or lower. Complications include reduced visual acuity, uveitis, pain, hemorrhage, and phthisis bulbi. All of these complications, especially pain and inflammation, seem less severe than those experienced after cyclocryotherapy.

Contact trans-scleral cyclophotocoagulation (TCP) (Fig. 32-3) has been accomplished using the same laser energy levels but delivered with a fiber-optic probe lightly pressed onto the conjunctiva (Tables 32-1 and 32-2).^{14–17} Slightly lower energy levels than those

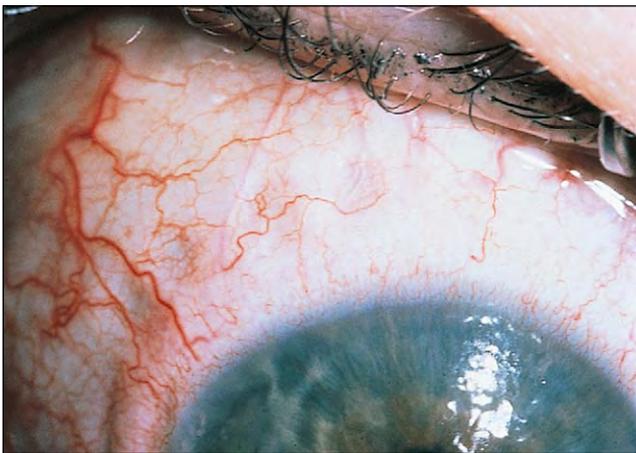


Fig. 32-3 Superior conjunctiva immediately after contact TCP. Small depressions in the conjunctiva disappear within minutes and the eye often appears essentially normal in 24 hours.

used for non-contact procedures are advisable because the contact pressure increases the transparency of the sclera. Retrobulbar anesthesia is necessary, as is a speculum to separate the eyelids. The probe should be placed 0.5–1.0 mm from the limbus and held as perpendicular to the sclera as possible. Probes made especially for cyclophotocoagulation such as the G-Probe™ of Gaasterland make placement easier and more uniform.¹⁸

All forms of trans-scleral laser cyclophotocoagulation may damage ciliary muscle as well as ciliary epithelium, adjacent iris, and retina. Extreme care must also be taken to avoid excessive destruction of the ciliary body, which could lead to hypotony and possibly phthisis. To target the ciliary epithelium more accurately, some physicians favor the use of an endoscopic probe and laser delivery fiber introduced via a limbal incision.¹⁹ This allows the surgeon to directly visualize and destroy the ciliary processes.²⁰ This is an invasive technique, however, that requires sterile technique but is gaining in popularity.

Endocyclophotocoagulation procedures are currently under clinical and laboratory investigation. Endocyclophotocoagulation may be most useful for aphakic and pseudophakic eyes or in combination with phacoemulsification procedures.^{21,22} Following endocyclophotocoagulation, some surgeons inject sub-Tenon's dexamethasone over the perilimbal area treated by the laser; others use topical steroids and atropine drops alone.

Since immediate postoperative pressure spikes are common with all types of cyclophotocoagulation, often an oral carbonic anhydrase inhibitor (acetazolamide 500 mg, methazolamide 50–100 mg) is administered immediately pre- or postoperatively. It is important to monitor patients closely in the short-term postoperative period.

The operated eye is usually patched postoperatively overnight or until the anesthetic wears off. Long-acting anesthetics such as bupivacaine help with immediate postoperative pain control. The patient should be sent home with an adequate supply of major analgesic medication as the eye may be quite painful after the anesthetic wears off. Topical regimens typically include prednisolone acetate 1% four times daily and atropine sulfate 1% twice daily. Medications are tapered gradually until inflammation has disappeared. Preoperative glaucoma medications may be continued as needed, except for miotics. Repeat cyclodestructive procedures are often necessary, although fewer spots should be treated to avoid hypotony and phthisis.

These procedures are alternatives to cyclocryotherapy. All cyclodestructive procedures may cause side effects of pain, phthisis, and reduced vision, although laser techniques may cause less pain and allow for more precise control of energy delivery.

Table 32-1 Trans-scleral contact cyclophotocoagulation techniques

	1064-nm Nd:YAG	810-nm Diode
Power	5–6 J ¹⁴	1.5–2.5 W, 1–2 sec ¹⁵
Lesions	30–40	16–18
Distance from limbus	0.5–1 mm	1.2 mm
Spot size	0.9 mm	100–400 μm

Table 32-2 Trans-scleral non-contact cyclophotocoagulation techniques

	1064-nm Nd:YAG	810-nm Diode
Power	4–8 J ¹⁶	1200–1500 mW, 1 sec ¹⁷
Lesions	30–40	30–40
Distance from limbus	1–2 mm	0.5–1.0 mm
Spot size	0.9 mm	100–400 μm
Depth of focus	3.6 mm beyond surface	3.6 mm beyond surface

OTHER LASER PROCEDURES

Lasers have also achieved widespread use in conjunction with surgical procedures such as trabeculectomy. Laser suture lysis, for example, can safely sever trabeculectomy flap sutures to increase filtration. Laser bleb reopening and remodeling may reduce the need for further invasive filtration surgery. Finally, lasers provide a safe and often effective approach to closing cyclodialysis clefts, removing peripheral anterior synechiae from the angle or cornea, and enlarging miotic pupils. Laser procedures are safer than surgical alternatives in all of these capacities.

SEVERING OF SUTURES

Subconjunctival trabeculectomy flap sutures can be lysed with the laser postoperatively if there is inadequate filtration. Dark nylon or prolene sutures can usually be severed with the argon laser using settings of 200–1000 mW for 0.02–0.15 second with a 50–100- μ m spot size.²³ This allows the surgeon to suture the wound more securely at the time of surgery.^{24,25} Tighter suturing maintains the integrity of the eye better and reduces the incidence of flat chambers and hypotony in the early postoperative period. The procedure is feasible from about 3–15 days after surgery or up to at least 2 months or more after mitomycin-C use.²⁶

Laser suture lysis (LSL) is accomplished by first anesthetizing the eye with an appropriate topical agent and then compressing the conjunctiva overlying the suture with the flat corner of a four-mirror gonioprism or specially designed laser suture lens such as that described by Hoskins.²³ Phenylephrine 2.5% or apraclonidine 0.5% (Iopidine[®]) is useful to blanch the superficial vessels of the conjunctiva. Gentle but constant pressure with the lens will displace fluid from the most edematous conjunctiva and provide a clear view of the underlying suture, which usually can be lysed with one or two laser applications. If possible, sutures should be lysed close to their tissue penetration site to prevent the loose ends from springing up and potentially disrupting the conjunctiva. Very edematous flaps may require 1–2 minutes of sustained gentle pressure over the suture before the suture is clearly visible (Figs 32-4 and 32-5). Dense hemorrhage in the tissues overlying the suture will absorb the energy, prevent treatment, and possibly cause conjunctival perforation. Similarly, fluorescein-stained conjunctiva limits argon laser energy transmission to the sutures and may cause conjunctival perforation. Therefore eyes with conjunctival hemorrhage obscuring the suture cannot be treated with this technique.

A thick, inflamed Tenon's capsule may also preclude successful LSL. This is unfortunate because these eyes commonly suffer from inadequate filtration. After the suture is cut, gentle pressure on the scleral edge of the incision will elevate the bleb and increase flow.

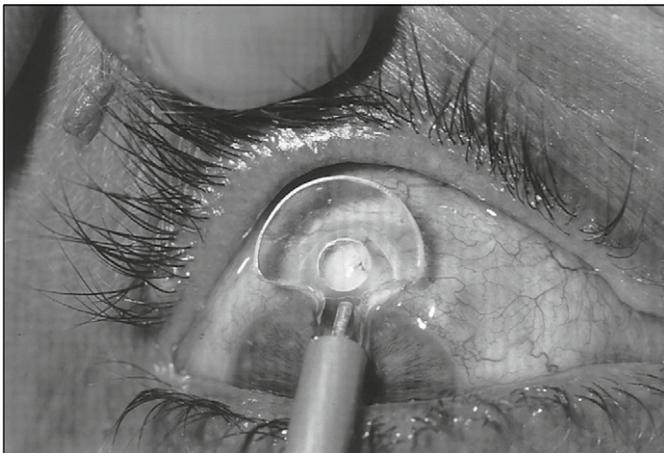


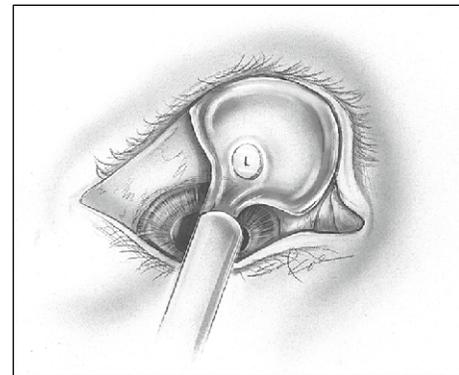
Fig. 32-4 Laser suture lens. The device has a small convex lens that compresses the edematous conjunctiva, permitting a clear view of the tiny nylon suture underneath the conjunctiva. This suture then can be cut easily with a 50- μ m spot laser beam using 400 mW of energy for 0.1 second. (Photo courtesy of John Hetherington Jr, MD, University of California, San Francisco.)

Topical steroids are often useful postoperatively to reduce external scarring. An important point to remember is that only one suture should be severed at a time because excessive filtration might occur,²³ leading to a flat anterior chamber. The eye should be examined carefully after the LSL session to ensure that the wound is intact. Additional sutures can be lysed 1 or 2 days later if filtration is still inadequate.

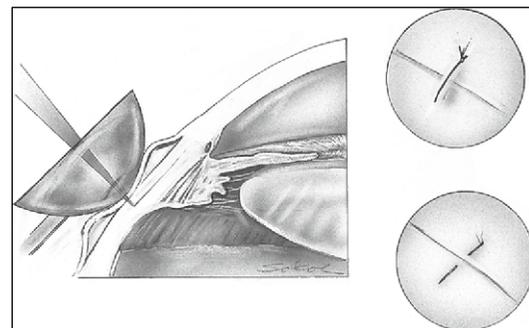
REOPENING FAILED FILTRATION SITES

Filtering sites can close because of fibrosis on the external side beneath the conjunctiva or because of membrane formation or iris incarceration on the internal side of the sclerostomy. In any case, if the bleb is to be salvaged, reopening should be attempted early, before the episclera has completely closed the external opening at the sclerostomy because of lack of aqueous flow.

A Goldmann three-mirror gonioscope or specially designed laser gonioscope is used to view the internal site. If pigmented tissue is obstructing the sclerostomy, the argon or Q-switched Nd:YAG laser can vaporize it.^{27–29} With the argon laser, settings of 300–1000 mW at 0.1–0.2 second with a 50–100- μ m spot are used. If the obstruction is a pillar of iris, the laser is directed toward one side of the anterior edge of the iridocorneal adhesion. If the attachment is

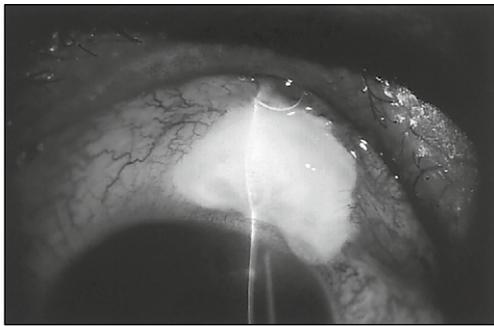


(A)

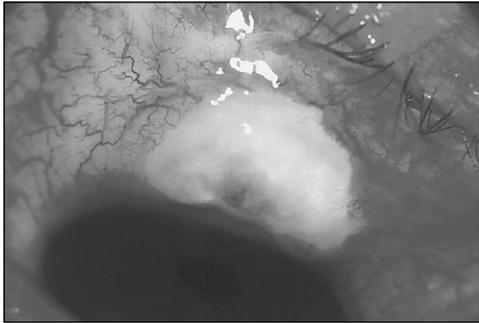


(B)

Fig. 32-5 (A) When lasering sutures, the flange of the Hoskins laser suture lens holds up the lid. The suture is located under the laser slit lamp. (B) The lens is pressed steadily against the conjunctiva, displacing edema until a clear image of the suture is seen (upper right). The suture usually is treated near the knot. The long end of the suture will then retract into the sclera (lower right).



(A)



(B)

Fig. 32-6 (A) Before Nd:YAG laser therapy. Despite what appeared to be a healthy bleb, the pressure was 30 mmHg in this eye. Note the dense white membrane existing beneath the bleb surface. (B) After Nd:YAG laser therapy. The Nd:YAG laser was focused deep into the bleb with four applications at 8 mJ. Note the dark area where the whitish membrane had been. Intraocular pressure fell immediately to 18 mmHg, and the bleb enlarged.

not too solid, the synechiae can be dissected away from the sclerostomy site with similar settings on the argon laser by freeing up one edge of the synechia with laser applications and gradually working across the line of iridocorneal adhesion with additional laser applications. Pigmented tissue within the site should also be vaporized. The Nd:YAG laser is also useful in opening an obstructed sclerostomy.^{5,30-33} Single bursts of 2–4 mJ are delivered via a Nd:YAG-coated gonioscope to disrupt any translucent membrane obstructing it. Lower power levels (i.e., 1–2 mJ) should be used initially to dissect any iris adhesions. Bleeding may obscure the view, requiring a delay between treatments, but this is rarely serious.

Laser treatment may produce an instantaneous lowering of IOP, or approximately 1 day may be required for the pressure to fall. Digital pressure applied three to four times daily may be helpful. An increase in the size of the bleb indicates that the sclerostomy has indeed been opened and that the pressure decline is not simply a result of inflammation.

Blockage occurring on the episcleral side of the bleb rarely can be opened. The Nd:YAG laser can be used through translucent tissue to rupture pigmented or non-pigmented membranes overlying sclerostomy sites.^{34,35} It is essential that the laser be focused at least 0.5 mm internal to the surface of the bleb or else the shock wave, which expands toward the surgeon from the point of focus, will rupture the overlying bleb (Fig. 32-6). This is especially true with thin blebs such as those seen after mitomycin-C use.

In all of these situations it is advisable to start with a lower power level, increasing it as indicated by the tissue reaction. Success with

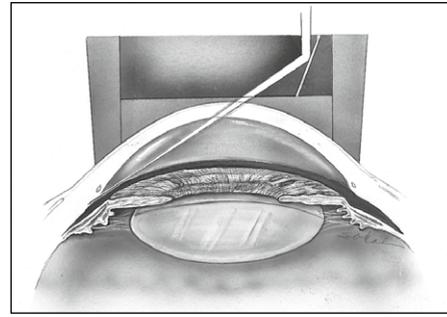


Fig. 32-7 Closure of a cyclodialysis cleft. The beam is aimed deep into the cleft to create an inflammatory response and generate closure. Postoperative mydriasis and cycloplegia may aid this process.

any of these procedures is limited, but their simplicity encourages an attempt.

CYCLODIALYSIS AND LASER

Cyclodialysis clefts have been both opened and closed with laser.³⁶ Most reports are limited to a relatively small number of cases because cyclodialysis is rarely seen.³⁷⁻³⁹ A variety of successful techniques have been employed.^{40,41} One patient undergoing a cyclodialysis in conjunction with trabeculectomy had the cyclodialysis reopened 2 months after filtering surgery. A hyaline membrane covering the cleft was divided with a Q-switched Nd:YAG laser using a single pulse of 3.8 mJ. Postoperative treatment included strong miotics and corticosteroids.⁴²

Argon laser photocoagulation using thermal burns of 0.1 second, 100- μ m spot size, and 500 mW can be used to close cyclodialysis clefts and reduce hypotony (Fig. 32-7). Three patients have reportedly had successful long-term effects.⁴³ In these patients, up to 100 burns were delivered to the area in and around the clefts posterior to the scleral spur.⁴³ Postoperative treatment should include topical steroids and cycloplegics.

Sudden rises of IOP often occur after closure of cyclodialysis clefts. These usually require aqueous suppression therapy.⁴³

LASER SYNECHIALYSIS

The argon laser can be used to pull early or lightly adherent peripheral anterior synechiae away from the angle or cornea. Settings similar to those used for iridoplasty (400–800 mW, 0.1–0.2 second, 50–100- μ m spot size) are used. If used early, this may be helpful to break and arrest formation of iridocorneal adhesions after penetrating keratoplasty or other forms of peripheral anterior synechiae. This procedure is most likely to work if it is performed very soon after the synechiae have formed. Chronic synechiae can be very resistant to argon iridoplasty. If it is obvious after the first few applications that the iris is firmly adherent, it is useless to persist because this will only cause additional iritis.⁴⁴

The Nd:YAG laser can lyse iris adhesion. This technique may be useful in early irido-corneal-endothelial (ICE) syndrome to disrupt synechiae, although bleeding may occur. This procedure is also used for reopening filtration blebs and sometimes for preventing further peripheral anterior synechiae after penetrating keratoplasty.⁴⁵ Nd:YAG lysis of posterior synechiae has been used

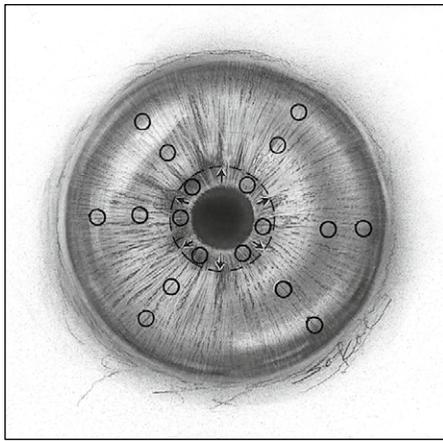


Fig. 32-8 One method of placing laser applications to create photomydriasis. Arrows indicate the anticipated enlargement of the pupil.

to successfully block recurrent pigmented membrane formation on the anterior surface of silicone intraocular lens implants.⁴⁶

GONIOPHOTOCOAGULATION

Direct coagulation of new vessels in the angle was reported by Simmons and co-workers to be useful in some cases of anterior segment neovascularization.⁴⁷ This procedure should not be used as an alternative to retinal ablation techniques because goniophotocoagulation treats only the result and not the stimulus of the neovascularization.

The goal of goniophotocoagulation is the immediate ablation of the vessels as they cross the scleral spur by direct application of 150–500 mW of argon laser energy in a 100- μ m spot size for

0.1–0.2 second. The vessels in the angle are treated in the first session, and subsequent sessions at 2–3-week intervals can be directed toward ablating more centrally located iris vessels. Bleeding is common, and gross hyphema may occur. If the rubeosis is subsiding or if panretinal photocoagulation or cryoablation has been performed, goniophotocoagulation may be avoided because the rubeosis will usually regress after panretinal photocoagulation.

Goniophotocoagulation is useful to obliterate fragile vessels in a surgical wound, such as those in cataract incisions or trabeculectomy or goniotomy wounds. Spontaneous bleeding of these vessels can be responsible for transient IOP elevation or obscurity of vision. Koeppe gonioscopy performed while the patient is supine, with or without jugular compression, is the best way to identify the vessels. Argon laser energy using a 100- μ m spot size for 0.1–0.2 second and 300–500 mW of energy will usually obliterate these vessels. Recurrence is common, and retreatment may be needed.

PHOTOMYDRIASIS (PUPILLOPLASTY)

In miotic pupils, the laser can be used to enlarge the pupillary area by contracting the collagen fibers of the iris and widening the pupil (Fig. 32-8). Applications should first be 200- μ m spots of 200–500 mW for 0.1–0.2 second. It is important to begin with very low energy levels and increase power until the desired effect is seen. Dark brown irides absorb much more energy than do light blue irides, so the treatment level must be titrated to the individual patient. The applications should be placed in a row peripheral to the pupillary border and peripheral to the sphincter to avoid inadvertent retinal exposure by transferring light. Another laser series at a 500- μ m spot size should then be placed just peripheral to the first row. Their effect, however, may not be permanent if miotics are resumed. Care must be taken to avoid burning or vaporizing tissue and to avoid retinal injury.

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CHAPTER
33

General surgical care

THE SURGICAL DECISION

The decision to operate on any eye is a serious one that glaucoma surgeons confront in two basic situations. The first is when the intraocular pressure (IOP) is very high and the patient has pain, corneal edema, and rapid deterioration of vision. In this situation, the patient can easily appreciate that vision is immediately threatened and can understand the need for surgery with its attendant risks, discomfort, and inconvenience. The surgeon also understands this, and the decision to operate is clear.

The other situation is one in which the patient may not be experiencing any discomfort or visual impairment. This situation is more typical in patients with chronic open-angle glaucoma or, even more problematic, normal-pressure glaucoma. In this situation, the indication for surgery is progressive or worrisome visual field loss or deterioration of the optic nerve, which the physician can recognize but the patient usually does not. The patient must agree to subject an eye with adequate or even normal vision to a procedure that may actually worsen vision and thus decrease the ability to read, drive, watch television, or recognize family and friends. The surgery poses the potential but very real risk, from the patient's point of view, of harming the vision rather than saving it.

It is important in this latter situation to remember that the goal of glaucoma therapy is to maintain good vision for the patient's lifetime. Thus to make the right recommendation to the patient, the surgeon must consider the life expectancy of the patient, the rate of disease progression, and the risks and benefits of other therapies. The surgeon must also weigh the surgical benefit (i.e., the likelihood that the surgery will be successful and prevent further visual loss) against the risks of surgical failure or complications.¹

It is also important to remember that visual loss from damage to the optic nerve is irreversible, whereas visual loss from the most common complications of glaucoma surgery (cataract or refractive change) can be corrected. Therefore the guiding principle in this situation must be to protect the optic nerve. For each patient, the physician must weigh the evidence of progressive nerve damage against the need for and likelihood of arresting that progression (Box 33-1).

PREOPERATIVE CARE

Nothing is more reassuring to a patient than to have complete confidence in his or her physician and the other members of the health-care team. Preparing a patient for surgery begins with a careful and

Box 33-1 Indications for filtering surgery

- Documented visual field and optic nerve damage, despite maximum tolerated medications and laser therapy, that threatens the patient's vision.
- Anticipated progressive damage (e.g., experience in the same or fellow eye that indicates the current course will lead to loss of vision) or intolerably high IOP. Medication failure because of ineffectiveness, intolerance, poor compliance, or complications.
- Intraocular pressure that is high enough to place the future health of the optic nerve at significant risk. This pressure will differ dramatically, depending on the condition of the nerve and the patient's prior history. For example, if the patient has extensive fixation threatening field loss, pressures in or near the 'normal' range may be too high for the nerve to tolerate. If the physician waits for further progression before operating, central vision may be lost.
- Dysfunctional ocular tissues (corneal edema or bullous keratopathy, pulsating central retinal artery).
- Combined with cataract procedure if there is borderline IOP control, advanced damage, or history of postoperative IOP rise in the fellow eye.

thorough history and physical examination by the ophthalmologist. The ophthalmologist must know the patient's medical history as well as his or her current physical status. Consultation with the primary care physician should be a routine part of the preoperative plan. It is important that the surgical decision be made in the context of the patient's whole life. Family, social, and work-related issues are important in the patient's decision to proceed with surgery as well as in the patient's ability to follow the prescribed postoperative treatment plan. When outpatient or 'come-and-go' surgery is performed, rehabilitation takes place away from the traditional healthcare setting. Postoperative care is crucial in glaucoma surgical management. Every effort should be made to ensure that the patient is being discharged to an appropriately supportive environment.

INSTRUCTIONS TO THE PATIENT

The physician should tell the patient what to expect with the surgical experience, including a careful explanation of the expected rehabilitation and recovery period. Successful filtration surgery is often followed by a period of relative hypotony and poor vision, which may last from several days to a few weeks after the procedure. Patients can become needlessly demoralized during this period if they have not been properly counseled to expect that

visual recovery will take time. A thorough explanation of potential complications is mandatory.

Physicians are now legally required to provide this information to obtain the patient's agreement to operate (informed consent). Patients must be warned that they may lose vision or even the eye. They may develop cataracts, infection, and hemorrhage. The risk of these complications for each patient should be estimated using the best available evidence and should be shared with the patient. It is best to give these data as ranges, simple ratios, or approximate percentages so that the patient can understand the risk. The surgery itself and the probability of success can be explained reassuringly so that the patient can develop realistic expectations. It is useful to emphasize the unfortunate fact that glaucoma surgery is rarely intended or expected to improve vision, but rather such surgery is performed in an effort to protect the remaining vision. Patients who expect the operation to restore lost vision can be profoundly disappointed with a result that the surgeon views as completely successful.

It is important to explain to the patient that the local anesthetic will be momentarily painful but that the surgery itself is essentially painless. A well-prepared patient is more calm, less apprehensive, and more cooperative; preoperative sedation is more effective, and the surgery will go more smoothly for both the patient and surgeon.

A history of previous illnesses and a review of symptoms particularly related to the cardiovascular system are in order. Significant findings should be further evaluated by the appropriate physical examination or laboratory tests. Laboratory studies, radiography, electrocardiography, and other diagnostic tests should be ordered when indicated by these findings. Electrolyte levels, including potassium, may be altered, especially in patients using oral carbonic anhydrase inhibitors and thiazide diuretics.

Before the orders are written, the surgeon should question the patient about possible allergy to medications. The patient should take to the hospital any medications he or she routinely uses at home, including systemic medications as well as ophthalmic eyedrops and tablets, and should continue to use these on the same schedule as at home.

OUTPATIENT VERSUS INPATIENT SURGERY

Outpatient surgery has been routine for cataract extraction for many years. Glaucoma surgery leaves a filtering wound that disrupts the integrity of the eye and, unlike cataract surgery, may leave the eye hypotonous and susceptible to injury from external pressure or Valsalva's maneuvers. Nevertheless, many patients have undergone successful and uncomplicated outpatient filtering surgery,² and many patients prefer not to stay in the hospital. In many places, particularly the United States, health plans do not authorize overnight stays for routine glaucoma surgery.

Surgical arrangements should be tailored to each patient's needs. There may be cardiac, pulmonary, or other systemic problems that require hospitalization either before or after surgery. Hospitalization may be indicated if there is a history of a complication in the other eye, if the patient is one eyed, or if there is risk of hemorrhage or other complication. Patients traveling from long distances may need to stay in a hotel or guest house for some portion of the preoperative or postoperative period. Although this is not as convenient as staying in the hospital, it is preferable to driving long distances for daily follow-up and is much less expensive than the hospital.

PREOPERATIVE MEDICATIONS

With the exception of the strong cholinesterase inhibitors, glaucoma medications should be continued until surgery. The cholinesterase inhibitors demecarium bromide (Humorsol) and echothiophate iodide (Phospholine) caused prolonged postoperative inflammation and possibly increase surgical bleeding.^{3,4} These medications are used rarely today. A weaker miotic (e.g., pilocarpine) should be substituted for these drops 2 or 3 weeks before surgery if time permits.

The cholinesterase inhibitors also lower blood cholinesterase and pseudocholinesterase for weeks. Therefore adjunctive anesthetic agents such as succinylcholine may cause prolonged apnea. The anesthesiologist should be told of all drugs that have been taken recently by the patient. Some surgeons try to discontinue the prostaglandin analogs several days to a week prior to surgery although most do not. Those who discontinue these agents prior to surgery feel that they may contribute to postoperative inflammation or even cystoid macular edema.

Most systemic medications should be continued unless they have the potential to cause bleeding. Aspirin is one such medication and should be discontinued for 10–14 days before surgery if possible. A surprising number of patients fail to list aspirin among the medicines they are taking unless asked specifically. The ophthalmologist should consult with the treating physician for patients who are using coumadin or other antithrombotic therapy such as ticlopidine and clopidogrel. Surgery can often be performed safely while the patient is using these agents; however, they do add risk especially for retro- or peribulbar hemorrhage as well as suprachoroidal hemorrhage, periocular intraoperative bleeding, and hyphema; therefore, it may be better whenever possible to delay surgery until their effects can be reduced or stopped.

Preoperative sedation eases the patient's passage through the operating room. If an anesthesiologist is not in attendance, meperidine (Demerol) and hydroxyzine hydrochloride (Vistaril), each given in a dose of 0.5–1 mg/kg body weight, make an excellent combination of analgesic and tranquilizer. A wide variety of other perianesthetic agents have been used as well, and each physician should be familiar with the appropriate agents and choose the most appropriate medication for the patient.

OPERATIVE CARE

THE OPERATING ROOM

The patient is the center of attention in the operating room. The patient should be transferred to the operating table with care and positioned comfortably. A pillow under the knees often eases back strain. Conversation should be quiet and purposeful. A relaxed atmosphere is good, but the patient may find joking and laughter inappropriate.

Patient monitoring is simple and necessary. Devices that monitor pulse with appropriate alarm capability are commonly used. More sophisticated monitors that measure blood pressure and oxygen saturation and provide electrocardiographic tracings give more precise indications of patient status. It may be wise to take a moment before the start of sedation or anesthesia to confirm the patient's name, diagnosis, and intended surgical site; such a 'time out' should prevent the rare but devastating complications of operating on the wrong eye or the wrong patient.

Cardiac arrest occurs in approximately 1 in 10 000 patients receiving general anesthesia,^{5,6} with a higher incidence in children and the elderly. Death from cardiac or respiratory arrest also occurs with regional anesthesia in about 5 per 100 000.⁷ The physician must therefore be familiar with resuscitation equipment, medications, and procedures. If an anesthesiologist is present, he or she will monitor the patient and lead any resuscitation effort; however, if an anesthesiologist is not present, the surgeon is responsible.

ANESTHESIA

The choice of anesthesia depends on the patient. Children require general anesthesia, whereas most adults do well with preoperative or intraoperative sedation and local block. Although regional anesthesia is preferred for the majority of adult ophthalmic patients, it is not without risk.⁷

Neuroleptanalgesic, ataractic, or dissociative anesthesia is provided by an anesthesiologist. The result is sedation with analgesia, hypomobility, antiemesis, vasomotor stability, and emotional detachment. These agents are usually provided intravenously using varying amounts and combinations of meperidine, medazolam, hydroxyzine hydrochloride, phencyclidine, alfentanil, fentanyl, or propofol, all of which can be supplemented as needed throughout the procedure. These agents make the injection of the retrobulbar or peribulbar block more palatable for the patient. Their positive effects of relaxation, sedation, and amnesia must be weighed against the potential for apnea, uncontrollable restlessness related to dissociation, and prolonged postoperative recovery which may include emesis and cognitive dysfunction.^{8,9}

Retrobulbar local block is accomplished with lidocaine (Xylocaine) 2–4% either alone or combined with bupivacaine hydrochloride (Marcaine) 0.5% or 0.75% combined with hyaluronidase. An injection of 1.5–3 ml usually is adequate for most types of glaucoma surgery when supplemented with topical proparacaine or tetracaine drops instilled three or four times into the eye. Some surgeons prefer to use larger volumes of less-concentrated anesthetic agents.

Retrobulbar block is one of the most frequently utilized methods in patients who do not receive general anesthesia, although many experienced surgeons use peribulbar, subtenon's, topical, or topical/intracameral anesthesia in selected cases.^{10–12} Surgeons opting for topical anesthesia should have extensive experience with topical anesthesia for cataract surgery, as well as significant personal comfort with performing glaucoma filtration procedures. Patient cooperation is a critical feature for successful topical anesthesia, thus patient selection and an operating team and facilities that will facilitate a smooth, rapid procedure are particularly important. When retrobulbar anesthesia is more appropriate, an anesthesiologist can administer a small amount of pentobarbital, propofol or other short-acting agent intravenously immediately before the retrobulbar injection so the patient will not feel it. It is not necessary for the patient to be awake and cooperative to accurately inject retrobulbar anesthesia. O'Brien, van Lint, or Nadbath lid block traditionally has been given with the same solution, but this is not strictly necessary. A 0.5-cc injection into the subcutaneous area of the lower lid as the syringe is withdrawn from a retrobulbar or peribulbar injection serves the purpose of preventing blepharospasm as well as the aforementioned extra injections.

EQUIPMENT

A good surgical microscope providing magnification up to 25× is needed for procedures that require precise localization of

Schlemm's canal (e.g., trabeculotomy). In most other situations, 16× or 10× magnification is adequate for glaucoma surgery. Zoom controls add convenience.

Light from the microscope can damage the retina.^{13–15} Even though many surgical glaucoma patients have miotic pupils, the surgeon should use the least amount of light that is adequate. The microscope should be angled preferably by about 15° so that light is not directed at the macula. A corneal cover, which is included in many surgical kits or can be fashioned during surgery from part of a cellulose sponge, can help protect the retina during stages of the operation in which visualization of the anterior chamber is not necessary. Appropriate optical filters on the light source can also reduce risk of retinal damage.^{16,17} Fine-quality instruments that are well maintained with sharp edges and delicate teeth reduce tissue trauma and surgeon frustration.

Cauterization is accomplished with a bipolar instrument, an erasure tip, or the unipolar tip, which should be adjusted to achieve hemostasis without charring. Although each system has advantages, we prefer the unipolar tip because of its precision and because it simplifies cauterization of the trabeculectomy site if bleeding occurs from the region of the ciliary body.

Swabs that leave debris (e.g., cotton-tipped applicators) should be avoided. Precut cellulose swabs are effective. A variety of good suture material is available, and selection is often related to surgeon preference. The surgeon should generally use the least amount of suture that has the least amount of inflammatory stimulus. Cutting needles are preferred for the sclera. Nylon sutures, commonly 10-0 or 9-0, can be cut with the laser in the postoperative period if necessary. Some surgeons advocate finely-tapered needles to create smaller needle tracts for limbus-based conjunctival closure, especially when antimetabolites are used (see Ch. 34).

POSTOPERATIVE CARE

ACTIVITY

The shift to outpatient ophthalmic surgery has resulted in earlier ambulation of patients. Earlier ambulation leads to more rapid systemic recovery, especially in elderly patients. As soon as the effects of sedation and anesthesia have subsided, ambulation can begin. Unless there has been excessive bleeding or the eye is extremely hypotonous, there is little reason to restrict the patient to bed rest.

Because of visual limitations, one-eyed adults or those with poor vision in the unoperated eye may be kept hospitalized until it is safe for them to return home. Conversely, children may feel more secure at home, and parents may feel quite comfortable caring for them there.

Patients should refrain from vigorous activity and movements that cause a Valsalva's effect (e.g., straining, lifting, and bending) for the first week after filtering surgery. Reading causes rapid jerky eye movements, whereas watching television requires less eye motion. However, no evidence exists that would implicate reading as a cause of postoperative complications of glaucoma surgery. Looking out of the window while riding in a car can induce rapid saccades as sign posts, telephone poles, and other similar objects are tracked and released almost subconsciously. If patients must travel a great distance by car in the immediate postoperative period they may have less eye movement if they look straight ahead or keep their eyes closed.

MEDICATIONS

With the exception of antithrombotic medication, systemic drugs should be continued after surgery. Because of the bleeding aspirin may induce, acetaminophen (Tylenol) or mild narcotics should be taken to relieve pain.

Pain after glaucoma surgery is unusual. If pain is severe, the ophthalmologist should consider complications such as anterior or posterior hemorrhage, infection, or elevated IOP. Severe postoperative pain is an emergency and should be evaluated immediately by a member of the surgical team. Anxiety is responsible for much of the postoperative unrest. If reassurance is not adequate, a gentle tranquilizer such as diazepam (Valium) is better than sedation when the patient is recuperating at home.

Glaucoma medications should be continued in the unoperated eye. Fluctuations in IOP in the unoperated eye are common and may range several millimeters up or down during the weeks after surgery. Fluctuations are also seen in the untreated eye after laser trabeculectomy and may be related to a central pressure-regulating mechanism. It may also be that the IOP is being measured more frequently and so physiologic or pathologic fluctuations are being seen.

Systemic aqueous suppressants such as carbonic anhydrase inhibitors (CAIs) reduce the flow of aqueous through the newly formed stoma in filtering surgery. The flow of aqueous inhibits scarring and helps form and maintain an adequate bleb. If possible, these

drugs should be discontinued for at least several weeks postoperatively. Our current practice is to replace systemic CAIs with a topical CAI in the unoperated eye. If this is insufficient to maintain IOP control, we begin to consider surgery in the unoperated eye rather than reinstating systemic CAIs. In the postoperative setting, we tend to reserve CAIs for patients who have had bilateral surgery and still failed to achieve adequate IOP control.

Management of the operated eye depends on the procedure performed. Generally, the eye is patched for the first 24 hours. Topical steroid drops, such as prednisolone 1% or dexamethasone 0.1%, will reduce inflammation and scarring. Dose frequency varies from once hourly to twice daily for the first week. Steroids are effective in reducing inflammation and should be used abundantly when necessary. Often the steroids are administered in combination with a broad-spectrum antibiotic. If so, the antibiotic usually can be discontinued after a week or so. Steroid drops often are continued for 2–3 weeks or until the eye is quiet. In some cases, we continue using very-low-dose steroid drops for many weeks postoperatively. We always taper steroid drops rather than discontinuing them abruptly.

Some surgeons advocate systemic steroid therapy for patients in whom previous filtering surgery has failed or in those who have pre-existing inflammation. In routine cases, systemic steroids offer little advantage over topical therapy, but do pose additional risk.¹⁸

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CHAPTER
34

Glaucoma outflow procedures

GENERAL CONSIDERATIONS

If there is no internal flow block and intraocular pressure (IOP) remains too high despite maximally tolerated medical therapy, surgery to relieve outflow block is needed. Such procedures are designed to increase the flow of aqueous out of the eye, thus reducing IOP.

Laser trabeculoplasty to relieve outflow block is described in detail in Chapter 31. Laser trabeculoplasty is generally attempted before incisional surgery unless the IOP is very high or the optic nerve is severely damaged. Incisional surgery is sometimes the only viable intervention: when subnormal IOPs may be required, as in progressive disease; or when conditions are not amenable to trabecular laser response, such as inflammatory, traumatic, or developmental glaucomas; when the angle is damaged or covered by synechiae; or the cornea is clouded. Several studies have supported using filtration surgery as the initial therapy in routine open-angle glaucoma, citing better medium- and long-term visual outcome as one of the major benefits.^{1,2} Although this remains an area of active debate,^{3–5} there is widespread agreement that the individual circumstances of the patient must be evaluated before the appropriate initial therapy can be chosen.

Incisional surgery to relieve outflow block may create external filtration (e.g., trabeculectomy or full-thickness filtering procedures) or internal filtration (e.g., cyclodialysis), or it may essentially disrupt the trabecular meshwork from the outflow pathway (e.g., trabeculotomy *ab externo* and goniotomy). Regardless of the procedure used, the goal is to reduce the IOP to a level that will prevent further damage to the optic nerve but not reduce it so much as to cause problems from hypotony. The lowest IOP that can be tolerated by the eye is generally above 5 mmHg, although this may depend on the patient's age: older patients (over 55 years old) can often retain 20/20 acuity with IOPs under 4 mmHg, whereas younger patients (with presumably more elastic and deformable sclera) may develop vision-altering hypotonous maculopathy at similar tensions.^{6–8} Low single-digit IOPs can predispose to cataracts, choroidal effusion, optic nerve swelling, or refractive instability. (Of course the central corneal thickness (CCT) correction for applanation readings needs to be considered: some 'low' IOPs are, when adjusted for CCT, actually above the 'hypotony' range.)

There is no evidence to support the notion that a specific protective effect is conferred on glaucoma patients whose pressure is simply reduced to 20 mmHg or lower, as though this were a magical number. Some long-term studies indicate that more severely damaged nerves may require pressures in the low teens if damage is to be stopped;^{9–11} with a significant advantage conferred by reducing IOP fluctuations.^{12,13} Although it is felt that external filtration of aqueous does in fact dampen IOP fluctuations,^{13b} the role of fluctuating pressures *per se* in contributing to progressive glaucomatous

loss remains controversial. Some authors assert that fluctuating IOPs contribute neither to the conversion of ocular hypertensives into glaucoma nor to destabilization of visual field function.^{13c,13d} Long-term results of the Advanced Glaucoma Intervention Study (AGIS), however, suggest that IOP fluctuation is a 'risk factor' for continued visual field and optic nerve deterioration.^{13e,13f}

There is ample prospective evidence to substantiate that lowering the IOP in glaucoma patients slows the rate of visual field loss, even in normal-tension glaucoma.^{14,15} Rather than choosing a specific target pressure, most multicenter studies prospectively select an end-point percentage for pressure reduction as the research target goal: e.g., a 30% reduction in the Normal-Tension Glaucoma Study,^{16,17} 25% reduction in the Early Manifest Glaucoma Trial,¹⁸ or 20% reduction in the Ocular Hypertensive Treatment Study.¹⁹

Full-thickness procedures generally provide lower pressures for a longer time than did guarded filtration procedures *viz* trabeculectomies before the era of antimetabolite usage.^{20–22} However, such full-thickness procedures also had a higher complication rate in most surgeons' hands. Efforts continue to achieve better pressure control with fewer complications using modifications of trabeculectomy technique, pharmacologic modifications of wound healing, and manipulations of flap closure using releasable sutures or laser suture lysis.

EXTERNAL FILTRATION SURGERY

The goal of external filtration is to create a new drainage pathway that allows aqueous to pass from the anterior chamber into the subconjunctival space. There the fluid either is absorbed into the conjunctival blood vessels or lymphatic equivalents or, if the bleb is thin walled, passes directly across the conjunctiva into the tear layer.^{23–26}

Filtering surgery requires an opening through the scleral wall at the limbus. The surgeon makes this opening much larger than the 15- μ m diameter hole that (theoretically) is adequate for total aqueous flow out of the eye,²⁷ because the healing process works to reduce the ultimate or effective size of the opening. Indeed, the healing process often obliterates the opening entirely. A larger initial opening, however, does not ensure success and may in fact lead to higher failure and complication rates. These rates increase because initial hypotony causes production of secondary aqueous, which apparently contains factors which accelerate wound healing,²⁸ and may eventually reduce the flow of aqueous humor through the sclerostomy. This causes the episcleral surface to scar down around the sclerostomy and close it.

Early postoperative hypotony is to be avoided when possible. The ideal procedure would lower IOP to 8–10 mmHg immediately and keep it there. Ideally the collagenolytic activity of pure aqueous

passing through the sclerostomy can modify the conjunctiva, converting it to an acellular matrix that is porous to aqueous percolation. If the aqueous contains protein and serum as a result of hypotony, healing is accelerated rather than retarded, and the outcome may be poor.

There are two basic types of external filtration procedures: guarded and full thickness.

GUARDED PROCEDURES

When the filtering sclerostomy is protected from excessive flow either by partially closing it with a scleral flap or by suturing techniques, it is described in terms such as *guarded*, *protected*, *subsceral*, or *partial-thickness filtration surgery*. The advantage of such techniques is that the initial egress of aqueous from the anterior chamber is retarded, which reduces the incidence of postoperative flat chambers.²⁹ Additionally, such maneuvers may reduce the incidence of hypotony and suprachoroidal hemorrhage.

Decreasing the incidence of postoperative hypotony and flat chamber appears to reduce inflammation, peripheral anterior syn-echiae, and cataract formation as well. Guarded filtration procedures may also reduce the long-term success rate of the surgery and prevent attainment of the very low pressures that seem desirable in advanced glaucoma or normal-tension glaucoma.²¹

Guarded procedures with or without antimetabolites are generally preferred except under unusual circumstances. There are a number of guarded filtering techniques, of which trabeculectomy and its variations are the most popular.

FULL-THICKNESS PROCEDURES

Procedures such as thermal sclerostomy, posterior or anterior lip sclerectomy, or Elliott's trephination have no guard over the external surface of the sclerostomy other than the conjunctiva and Tenon's capsule. These procedures are referred to as the Scheie procedure or *full-thickness filtration surgery*. Prior to the use of antimetabolites in guarded filtration surgery, such full-thickness procedures were deemed appropriate if either very low pressures were desired (e.g., in normal-tension glaucoma) or if guarded filtration surgery had failed.³⁰ They usually require a limbal-based conjunctival flap because of high aqueous outflow in the early postoperative period. Such procedures are associated with a high incidence of complications, including shallow (or flat) anterior chambers, premature cataract formation, and late infections.³¹

RESULTS OF EXTERNAL FILTRATION SURGERY

External filtration surgery achieves reasonable IOP lowering in 65–85% of adults, depending on the condition of the eye, the use of antimetabolites, postoperative healing, duration of follow-up, and the skill with which the surgery is performed. This success rate may be increased to over 90% if resumption of IOP-lowering medications is included.

It is difficult to compare surgical results because of variations in techniques and definitions of success. In a prospective, randomized study of the differences between thermal sclerostomy and trabeculectomy, Blondeau and Phelps reported IOPs less than 22 mmHg in 65% of thermal sclerostomies and 76% of trabeculectomies without anti-metabolites followed up for 5 years.²⁰ When medications were added, the success rates rose to 91% for the eyes treated with thermal sclerostomy and 94% for those treated with

trabeculectomy. Pressures tended to be somewhat lower in eyes undergoing thermal sclerostomy, but visually significant cataracts occurred three times more often and hypotony twice as often with thermal sclerostomy.²⁰ Thinner blebs were also more frequent with thermal sclerostomy. Even eyes with no detectable bleb at 5 years after either procedure (approximately one-third of the total), however, had average IOPs of 17 mmHg.²⁰

In a retrospective comparison of full-thickness filtration versus trabeculectomy, Lamping and co-workers found that the former offered much better long-term pressure control.²¹ They and others have noted an equal frequency of problems with hypotony with guarded and full-thickness procedures.^{21,22} The frequency of full-thickness procedures temporarily increased with the advent of holmium laser sclerostomy in the early 1990s, but convincing long-term success rates were elusive.³² The incidence of complications with full-thickness procedures has historically been high enough to dissuade the occasional glaucoma surgeon.

THE CONJUNCTIVAL FLAP

A conjunctival flap is required for all filtration procedures. Both limbus- and fornix-based conjunctival flaps are used for guarded filters, whereas a limbus-based flap is preferred by most surgeons for full-thickness filtration surgery.

LIMBUS-BASED FLAP

A limbus-based conjunctival flap allows tight wound closure, which may be important if early postoperative massage, suture cutting, or pharmacologic inhibition of wound healing is anticipated. On the other hand, there is a marked tendency over months to years for limbal-based blebs to 'migrate' towards the limbus over time: the long suture track of the superior conjunctiva can cicatricially contract and circumscribe the posterior flow of aqueous. This frequently results in elevated, thin-walled, 'mulberry-shaped' cystic blebs hugging the superior limbus, which can cause symptomatic irritation, or at worst, can be prone to leak or infection (Fig. 34-1A).³³

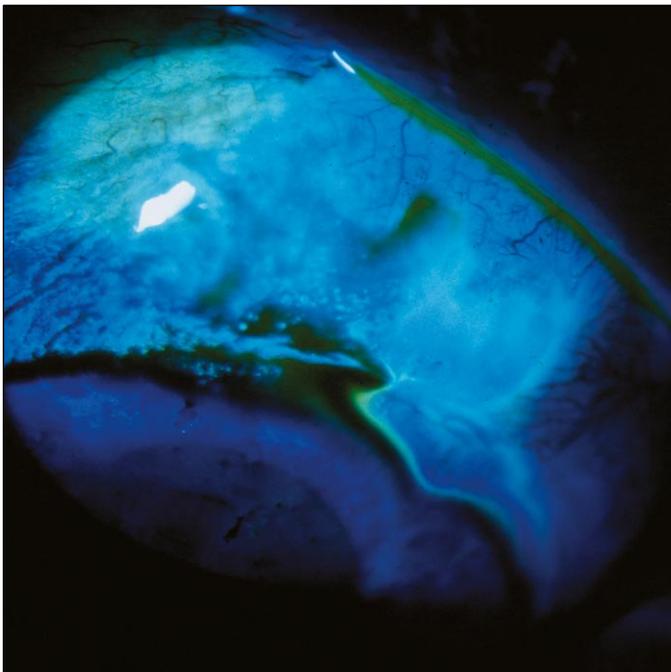
Technically the limbal-based filter is relatively easy to master, facilitating rapid surgery. The conjunctiva can first be elevated by injecting balanced salt solution (BSS) in the area of the flap to ease dissection. This injection should be made with a 30-gauge needle that penetrates the conjunctiva well away from the sclerostomy site. An incision is made at least 8 mm from the limbus and away from the insertion of the rectus muscles to avoid bleeding (Fig. 34-2). The incision should be carried through Tenon's capsule to the sclera. The capsule is then undermined or disinserted to elevate it from the sclera, and the incision is enlarged circumferentially to allow exposure of 4–5 mm of the limbal area. Blunt scissors should be viewed through the outer surface of the conjunctiva during this dissection to prevent button-holing. The incision can be elliptical to come in front of the rectus muscle insertion if necessary for adequate exposure.

Closure of the conjunctival incision varies markedly from surgeon to surgeon. Most prefer a water-tight closure achieved with a running suture that incorporates both Tenon's capsule and the conjunctiva. Some prefer a meticulous two-layered closure, which combines an interrupted closure of Tenon's capsule with a running closure of the conjunctiva.

Suture material also varies. Many surgeons prefer non-absorbable sutures such as 9-0 or 10-0 nylon. Others prefer 8-0 silk, which can



(A)



(B)



(C)

Fig. 34-1 (A) Cystic bleb. A 'mulberry' cystic bleb at the limbus, whose thin translucent walls are at risk for leaks and bacterial infiltration. (B) Seidel leak. Staining with a fluorescein strip reveals rivulets of aqueous streaming from microscopic limbal leak. (C) Blebitis. A cystic bleb at the limbus whose internal architecture is clouded by infectious infiltrate, with minimal anterior chamber reaction; if untreated, this frequently progresses to frank endophthalmitis.

be removed in 5–7 days; whereas 8-0, 9-0, or 10-0 Vicryl is preferred by some because it will be absorbed. Fine-tapered BV (blood vessel) vascular needles, such as those available on 10-0 Prolene, 9-0 or 10-0 Vicryl sutures, are preferred by some surgeons because they leave smaller needle tracts, which may prevent leaks, especially if wound-modulating agents are used. Non-absorbable nylon or Prolene sutures have been recommended for cases in which antimetabolites are used, because full healing may take several weeks and absorbable sutures can occasionally lose their strength before that time; however, long-term suture persistence may result in symptomatic ocular irritation.

FORNIX-BASED FLAP

The fornix-based conjunctival flap provides easier exposure of the surgical site and reduces handling of the conjunctival flap, but may require longer operative time. Unless they are closed carefully, such

flaps may leak in the postoperative period and fail to retain aqueous, so that the bleb flattens. Such leakage may be problematic under several common postoperative circumstances: if massage is needed to elevate the bleb; if an anti-wound-healing agent such as 5-fluorouracil (5-FU) or mitomycin-C is used; or if postoperative lasering of scleral flap sutures is performed.

A fornix-based flap is created by cutting the conjunctiva and Tenon's capsule together or separately (Fig. 34-3) flush with the limbus over a circumference of about 6–8 mm. Pre-incisional ballooning of the subconjunctival space with epinephrine containing xylocaine may be helpful, using a 30-gauge needle introduced at the 12 o'clock limbus. The conjunctival flap can then be undermined posteriorly with blunt dissection (Fig. 34-4), exposing the area for the scleral incision. A short radial relaxing incision can be made at one or both ends of the flap if exposure is restricted or if a particularly wide exposure is needed to insert a seton or valve.

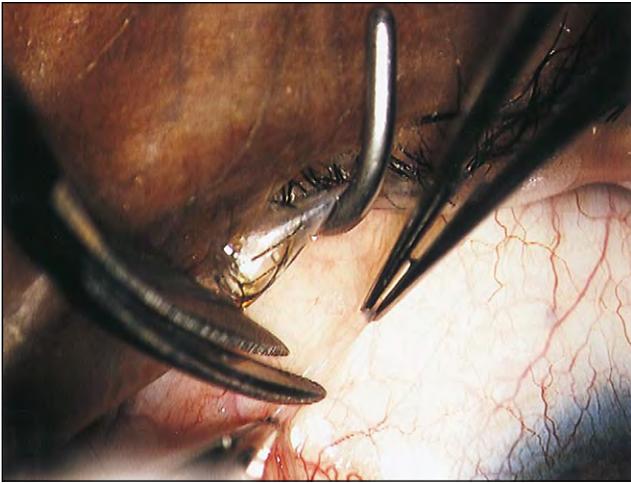


Fig. 34-2 Preparing for an initial superonasal quadrant incision for a limbal-based conjunctival flap. Conjunctiva and Tenon's capsule will be incised circumferentially after the initial opening is made.

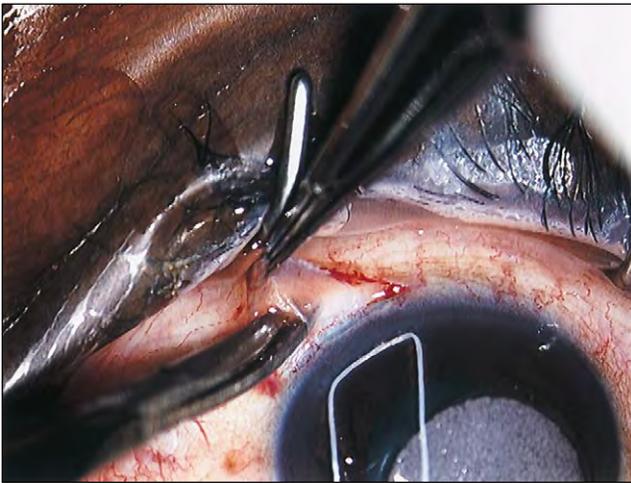


Fig. 34-3 Conjunctival flap. The conjunctiva has been incised over a circumference of 7 mm. Sharp dissection is now being used to incise Tenon's capsule separately.

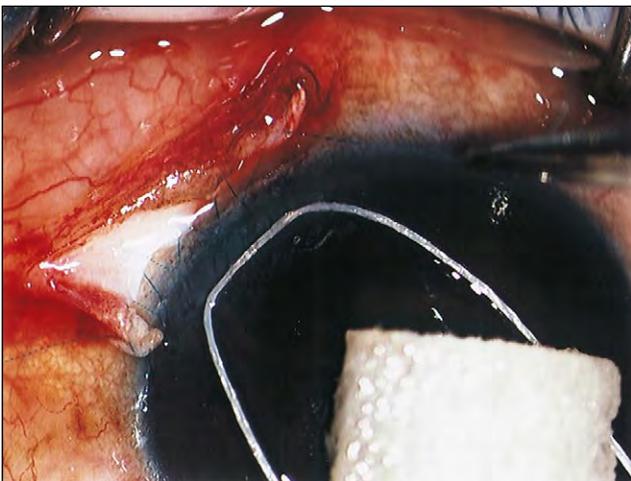


Fig. 34-5 Running 10-0 Prolene closure of Tenon's portion of a conjunctival flap.

Various techniques have been devised for a rapid but leak-proof closure of the fornix-flap. A careful running suture in two layers, first closing Tenon's and then its overlying conjunctiva at the limbus, though tedious, is reliably water tight. (Figs 34-5 and 34-6). A complex single-suture closure has been described by Wise as a running mattress closure (Fig. 34-7A,B).^{34,35} Slightly quicker to learn and perform is Khaw's use of lateral #9-0 or #10-0 nylon or Vicryl sutures to initially close the distal ends of the conjunctiva phimotically to the limbal tissue; and then bury the knots of three to five separate #10-0 Vicryl mattress sutures in shallow corneal 'scratch' incisions, parallel to the limbus, thus firmly attaching conjunctiva along the length of the superior cornea (Fig. 34-7C,D).^{36,36b,36c}

Comparisons between the fornix-flap and limbus-flap conjunctival closures, before the widespread adoption of antimetabolites, recognized no difference in success between them.³⁷⁻³⁹ Another study of difficult glaucoma cases, without the benefit of antimetabolites, showed a higher failure rate with fornix-based flaps compared with limbus-based flaps.⁴⁰ On the other hand, fornix-based flaps lessen the likelihood of developing elevated, thin-walled cystic blebs at the

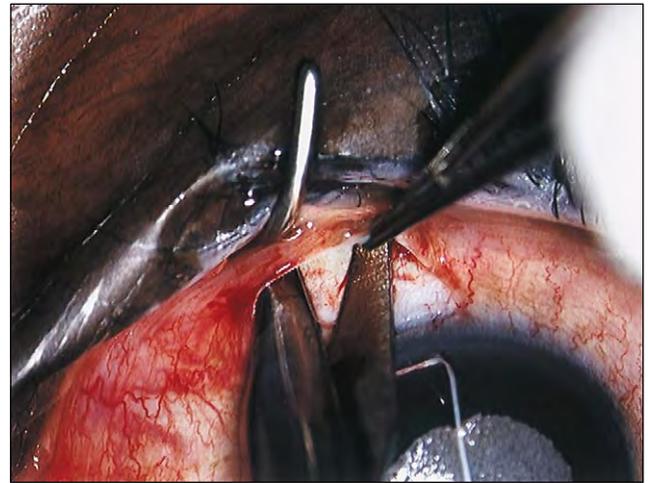


Fig. 34-4 Blunt dissection under a conjunctival flap.

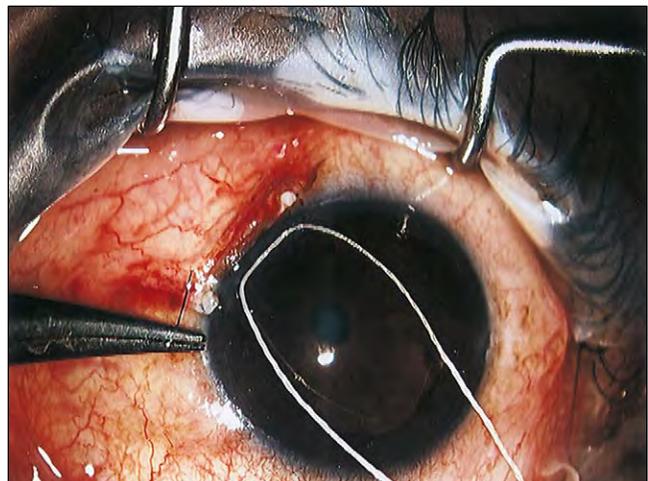
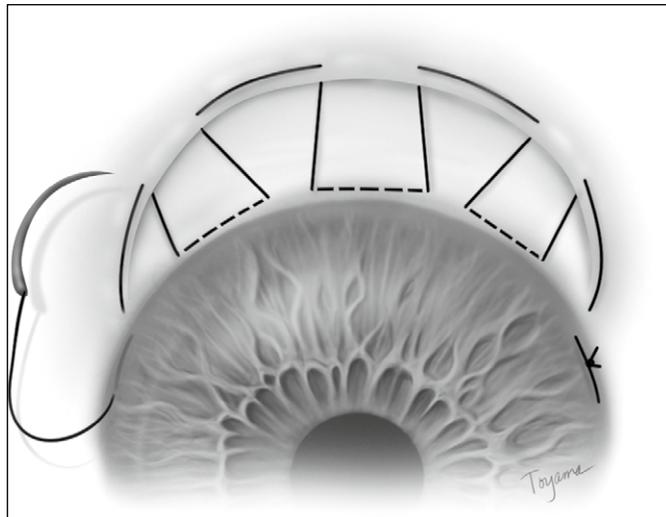
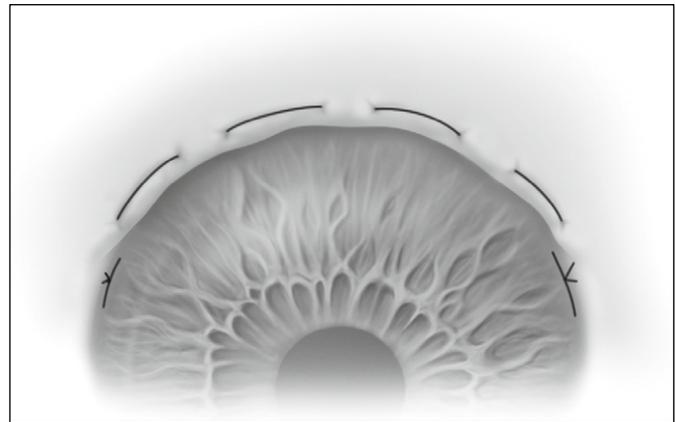


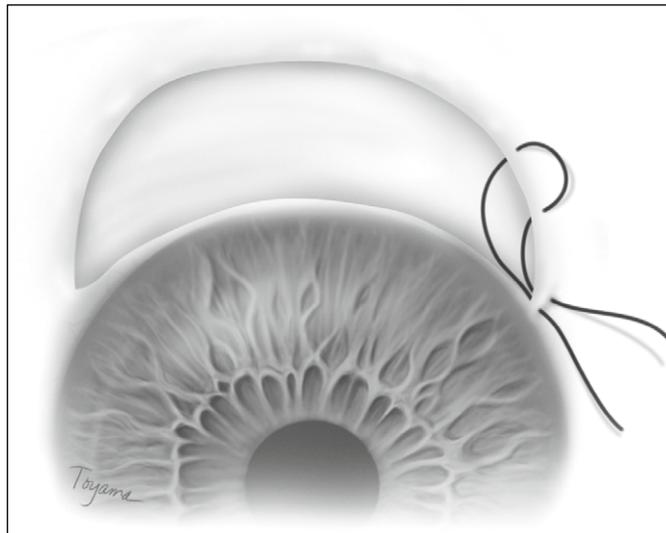
Fig. 34-6 Winged conjunctival closure (in this case after Tenon's closure).



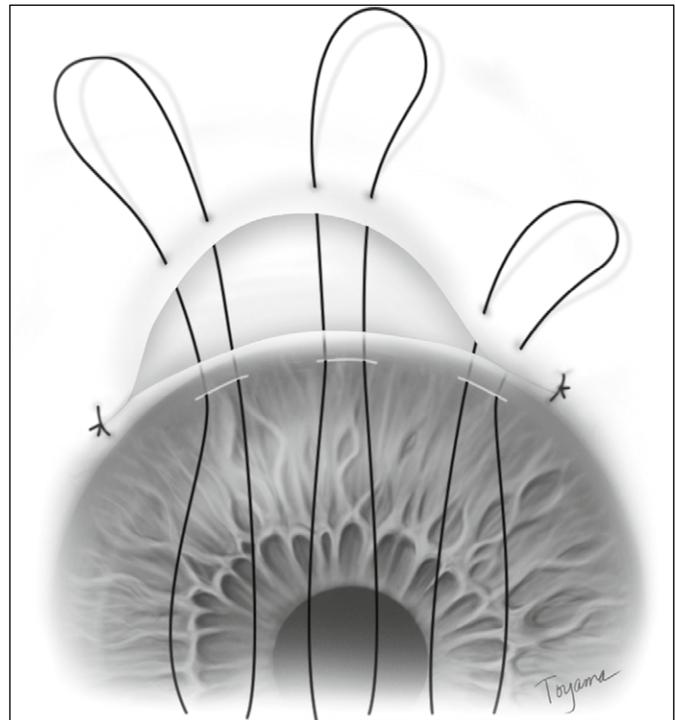
(A)



(B)



(C)



(D)

Fig. 34-7 (A) Wise closure: a #9-0 nylon suture is meticulously closed in an oblique trapezoidal running mattress pattern through limbus and conjunctiva. (B) Wise closure: serial tightening each pass of the suture (as in a running closure of a keratoplasty) firmly cinches the conjunctiva to the limbus. (C) Khaw closure: phimotic lateral closure with a #10-0 Vicryl suture anchors the entire length of conjunctiva firmly to the limbus. (D) Khaw closure: multiple separate #10-0 Vicryl mattress closures between peripheral cornea and conjunctiva preclude limbal leakage; knots are buried in shallow corneal scratch incisions, and eventually dissolve.

limbus (as commonly seen with limbus-based flaps), thus reducing the risk of serious complications such as leaks or endophthalmitis. The advantage of diffuse, low blebs with fornix-flap closure, when combined with mitomycin usage and releasable (or adjustable) flap sutures, makes it a technique of increasing and compelling popularity.⁴¹

EXCISION OF TENON'S CAPSULE

Some studies have suggested that excision of Tenon's capsule in young people, in African-Americans, or in people who require reoperations may enhance filtration success.⁴²⁻⁴⁵ Evidence for this is not conclusive, and the use of antimetabolites has made much of the issue moot.⁴⁶ If excision of Tenon's capsule is desired, the dissection can be

facilitated by injecting xylocaine or saline between the capsule and conjunctiva; care must be taken to avoid conjunctival buttonholes.

GUARDED FILTRATION PROCEDURE

TRABECULECTOMY

Trabeculectomy, with its many modifications, is the most commonly used guarded filtration procedure. Cairns introduced the modern-day trabeculectomy in the 1960s.⁴⁷ It was initially believed that aqueous escaped through the cut ends of Schlemm's canal, but it subsequently became obvious that the major effect of the surgery

occurred via filtration of aqueous into the subconjunctival space.⁴⁸ The reduced incidence of hypotony and flat anterior chambers made trabeculectomy attractive to glaucoma surgeons.

Indications

Trabeculectomy has become the standard glaucoma procedure, with excellent results for most forms of open-angle and chronic angle-closure glaucoma. Aphakic, inflammatory, traumatic, and other secondary forms of uncontrolled glaucoma also are treated by trabeculectomy; success rates are good when wound-healing retardants are used,^{49–51} although success rates tend to be lower than in uncomplicated cases. So long as mobile conjunctiva is available superiorly, despite a history of prior surgeries, the predictability of the trabeculectomy and its long-term efficacy at maximally lowering IOP make it the procedure of choice for the majority of uncontrolled glaucoma eyes.

As discussed more extensively in Chapter 37, trabeculectomy can be successfully combined with cataract extraction under a variety of circumstances. The most important advance allowing combined surgeries at one sitting has been the advent of the small-incision cataract/intraocular lens procedure. Thus modern techniques have broadened the indications^{52,53} for combining these procedures, and many surgeons report excellent results.^{54–57}

Standard technique

There is a wide variety of surgical preferences and techniques developed in the last half-century of the trabeculectomy's development, and we begin with a generalized approach, and conclude with the specifics of a successful fornix-flap technique from the Moorfield's Eye Hospital in London.

The initial trabeculectomy procedure is usually performed at a site superiorly and slightly nasal.⁵⁸ (This preserves the superotemporal area for repeat trabeculectomy or tube surgery if needed.) A corneal traction suture (e.g. 7-0 or 8-0 Vicryl) is preferable to a superior rectus suture, so as to minimize conjunctival perforation superiorly, an area of potential bleb formation. In aphakic or pseudophakic glaucoma, the surgical area selected should have minimal conjunctival scarring. This can be determined by attempting to move the anesthetized conjunctiva with an instrument or by injecting xylocaine with epinephrine under the conjunctiva at the time of surgery. If the conjunctiva is tightly adherent to the globe, another site should be selected, based on the response to subconjunctival fluid dissection. In the face of inoperable superior conjunctival scarring, an alternative procedure, such as an inferonasal glaucoma shunt, can be selected.

The episcleral surface planned for the scleral flap is lightly cauterized (Fig. 34-8) to reduce bleeding. Excessive cauterization should be avoided, however. Cauterization can be done with wetfield cautery or with a microdiathermy instrument. Microdiathermy offers the advantage of pinpoint cauterization, which is useful when cauterizing individual vessels during the early parts of the procedure, and later in the operation for persistent microhemorrhage from the iris, ciliary body or deep sclera after excising the trabeculectomy specimen.

The scleral flap is usually one-third to one-half the scleral thickness, rectangular or triangular in shape, and dissected anteriorly towards the limbus (Fig. 34-9). Antimetabolites may be administered before or after the scleral flap is developed, but usually before any opening is made into the anterior chamber (Fig. 34-10). It is important to place a paracentesis at the peripheral limbus using a super-sharp blade after preparing the scleral flap but before otherwise entering the globe (Fig. 34-11). The paracentesis site is used to fill the chamber in the course of the procedure (e.g., with intracameral miotic or saline), or to re-form a flat anterior chamber with saline or viscoelastic during the first postoperative weeks.

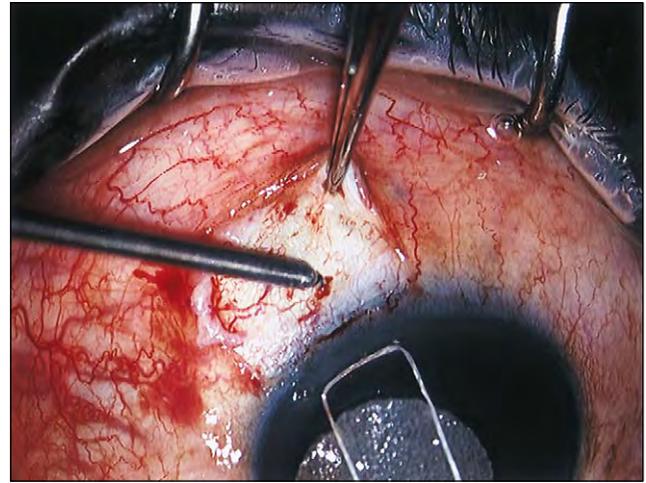


Fig. 34-8 Unipolar cautery to a scleral bleed in preparation for developing a scleral flap.

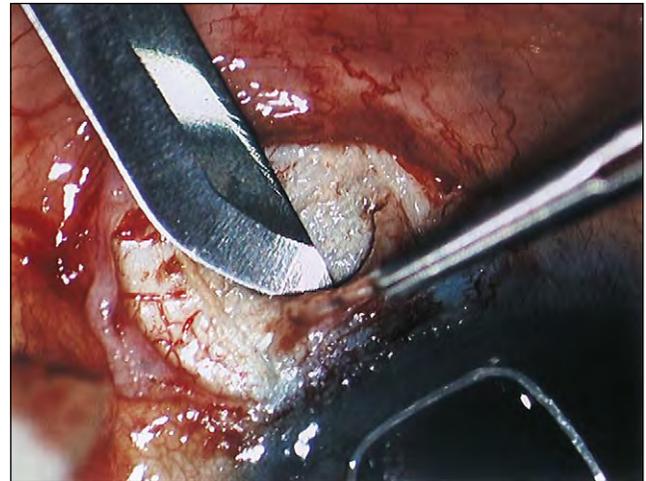


Fig. 34-9 Scleral flap.

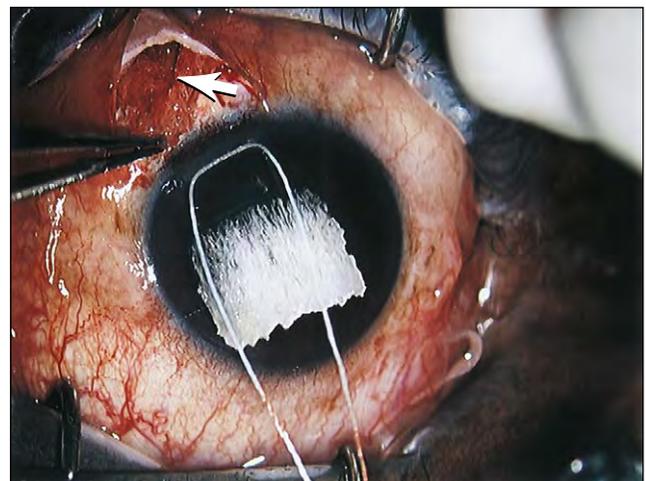


Fig. 34-10 Mitomycin-C-soaked sponge (arrow) being removed from the subconjunctival space after 3–5 minutes of scleral contact.

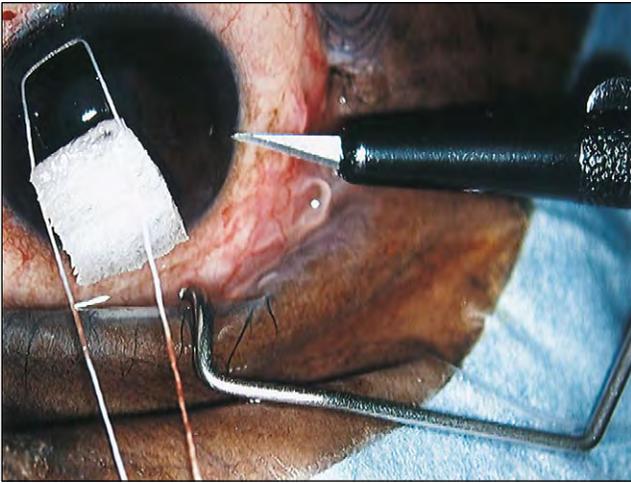


Fig. 34-11 Paracentesis with a super-sharp blade.

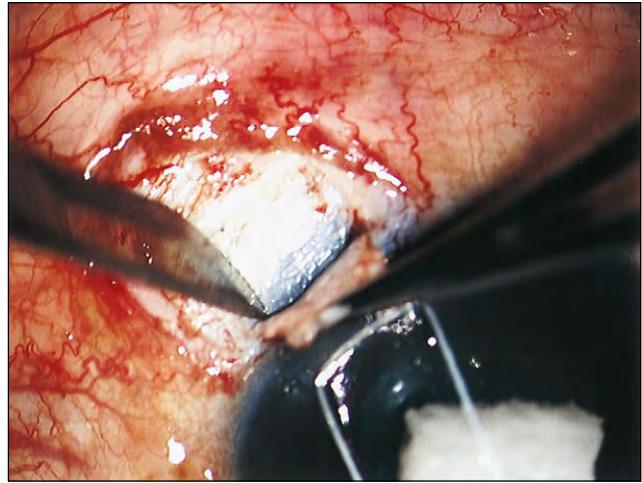


Fig. 34-13 The site of the trabeculectomy specimen is outlined.

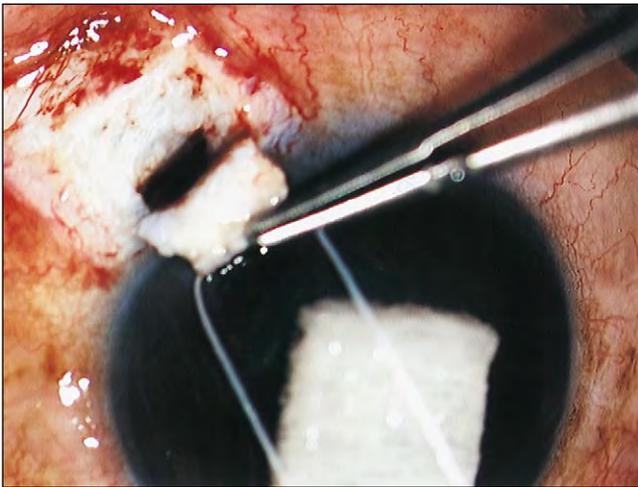


Fig. 34-12 A rectangular block of tissue has been excised.

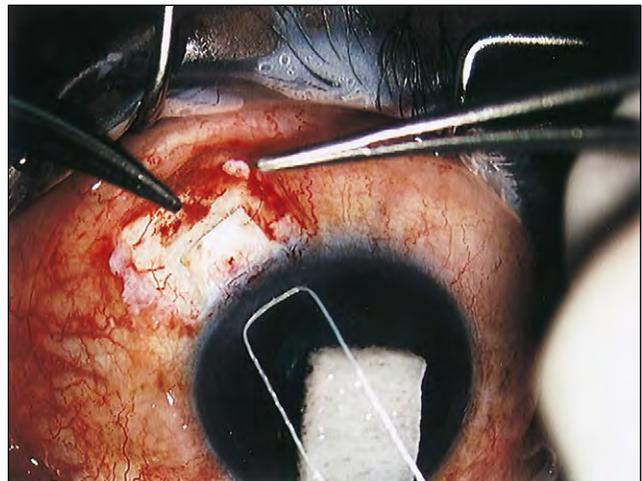


Fig. 34-14 A scleral flap is sutured at the corners.

After the scleral flap is extended past the limbus into the cornea and the paracentesis site has been made, the anterior chamber is entered under the flap (Fig. 34-12) and a block of tissue approximately 1.5–2.5 mm wide is removed with a Descemet's punch just anterior to the scleral spur. Removal of the trabeculectomy block too posterior to the scleral spur offers no advantage and increases the risk of hemorrhage.

The surgeon may excise the block with Vannas scissors, a trephine, a scleral punch, or thermal cautery (Fig. 34-13). The success rate of these approaches is similar. A peripheral iridectomy should be performed in all phakic eyes, with care taken to avoid the iris base and ciliary body to prevent hemorrhage. (In an effort to avoid encountering vitreous prolapse through the trabeculectomy site, some surgeons omit an iridectomy in aphakic or pseudophakic eyes if another iridectomy is already present, or if laser iridotomy is readily available in the postoperative setting.)⁵⁹

The scleral flap is reapproximated with 9-0 or 10-0 nylon sutures placed so that the anterior chamber is maintained after injection of saline, with a slow leak of fluid through the scleral wound indicating adequate filtration flow (Figs 34-14 and 34-15). In a simulation of the patient's natural blinking effect on filtration, flow adequacy



Fig. 34-15 A slow leak of fluid from beneath the flap may be detectable under the operating microscope.

at the site can be checked by gently ‘burping’ or depressing posterior to the scleral flap with a surgical instrument. Based on clinical experience, the surgeon tightens the flap, anticipating future adjustment with either releasable sutures or with laser suture lysis during the follow-up period.^{60–64b} Since the surgeon’s careful assessment of flow is critical before closing the eye, intracameral viscoelastic – which temporarily interferes with fluid flow – is rarely helpful during uncomplicated filtering surgery.

The conjunctival flap is closed as described above, depending on the use of the fornix-based or limbal-based approach. The conjunctival flap should be water tight, as assessed by intracameral filling and inspection of the bleb (Fig. 34-16). Especially if an antimetabolite has been used, intraoperative leaks should be scrupulously identified (with either high-magnification inspection or fluorescein drops) and then closed; a #10-0 nylon or a #10-0 Vicryl suture on a tapered BV vascular needle works well for this. Most filters show quiet tissue after healing has completed (Fig. 34-17).

Moorfields Safer Surgery System technique

The technique popularized as the ‘Moorfields Safer Surgery System’^{36,36b,36c,65} has been meticulously developed for consistent

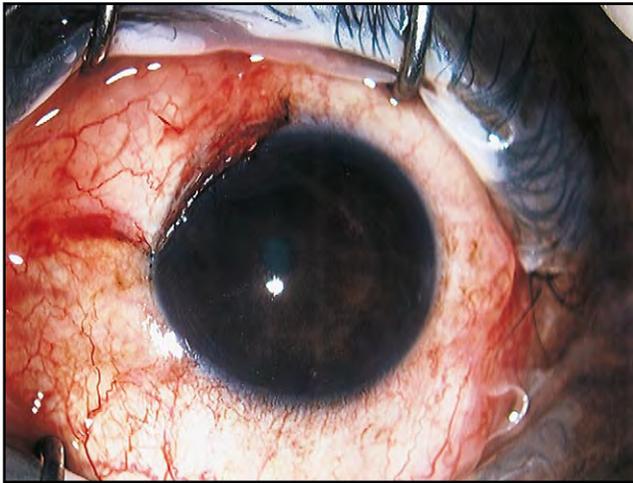


Fig. 34-16 Water-tight conjunctival closure. A diffuse bleb has begun to form immediately.

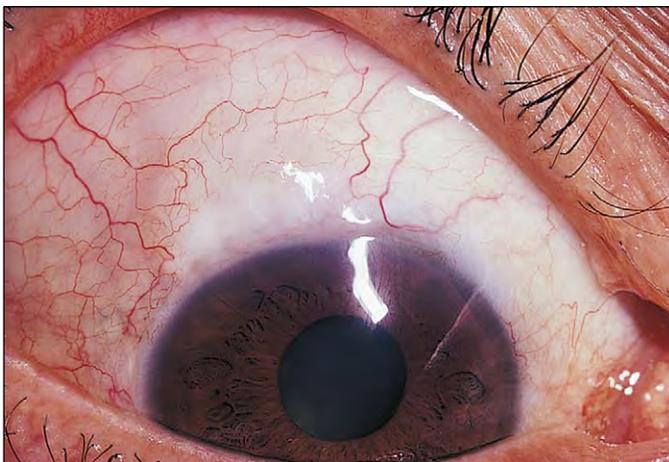


Fig. 34-17 Filtering bleb 1 year after trabeculectomy.

results in a wide range of complicated glaucomas. The hallmark features of this technique as originally described are a fornix-based conjunctival flap, an anterior chamber maintainer, a standardized punch technique, and a combination of adjustable and releasable sutures. It is also compatible with a single-site combined phacoemulsification/intraocular lens procedure, with minimal modification.

A fornix flap is prepared, with careful posterior dissection lateral to the superior rectus muscle, in preparation for a dispersed application of mitomycin-C-soaked sponges for a diffuse, posterior bleb (Fig. 34-18). Next a 4–6 mm wide half-thickness scleral tunnel is prepared 4 mm from and centered at the 12 o’clock limbus. Only partial (1–2 mm) lateral incisions of the tunnel flap are made, but not extended to the limbus itself; this inhibits any lateral aqueous accumulation at the limbus and instead encourages its posterior flow superiorly (Fig. 34-19A).

The recommended applicators for antimetabolite are bisected, 6-mm polyvinyl-alcohol round, corneal sponges (used in LASIK surgery), whose advantages include a predictable release of antimetabolite as well as resistance to shredding under the conjunctiva. (Alternative applicators can be cut free-hand as longitudinal strips of triangular-shaped cellulose sponges, which when cut thin enough will, with hydration by antimetabolite, become flat rectangular strips, easily insinuated and removed from the subconjunctival space (Fig. 34-19B,C,D). Either mitomycin-C (0.2 mg/cc) or 5-FU as 5 mg/0.1 cc is applied to the sponge strips. As many as six hemi-sponges are carefully insinuated posteriorly beneath the conjunctiva, adjacent to the superior rectus muscle and laterally (Fig. 34-20). While the sponges are in place, the conjunctival edges are carefully suspended away from the mitomycin. A small sponge (or strip fragment) is placed beneath the trabeculectomy flap in the bed of the scleral tunnel (Fig. 34-21). After 3 minutes the sponges are all removed, a sponge count is performed, and subconjunctival irrigation performed.

Next a Lewicke anterior chamber maintainer is placed through a microvitreal (MVR)-blade incision at the 6 o’clock peripheral cornea. Adjusting the bottle height for transcorneal flow of fluid allows precise control of chamber depth and IOP

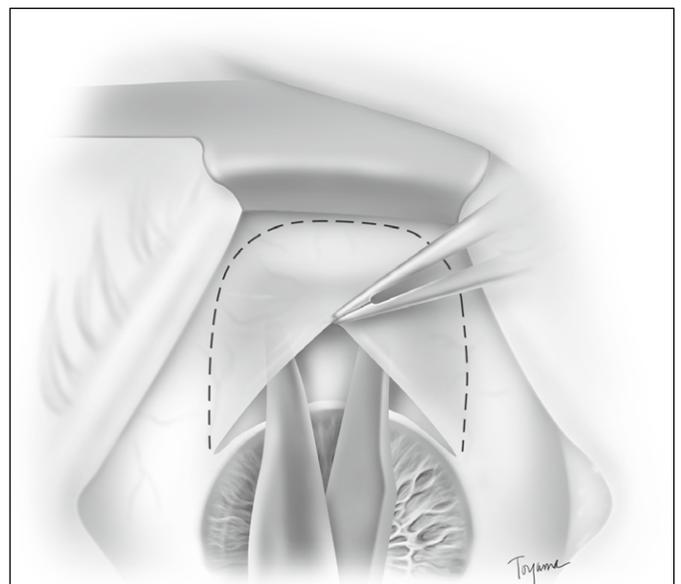
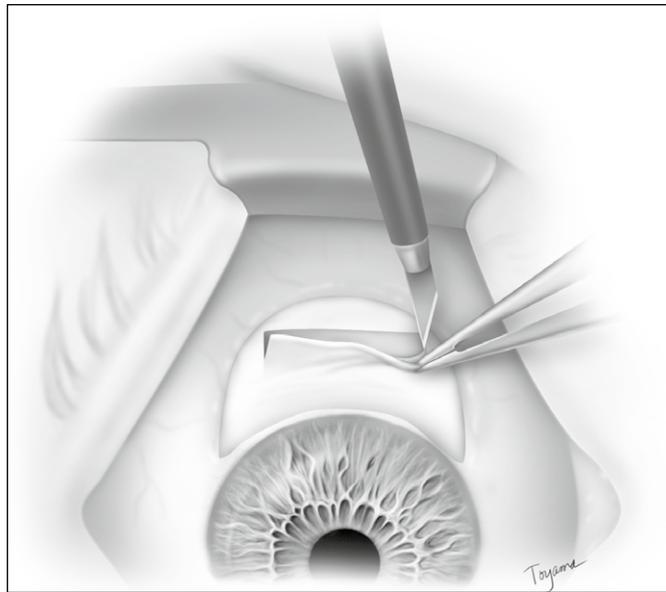
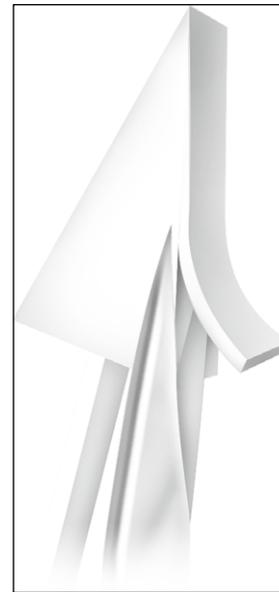


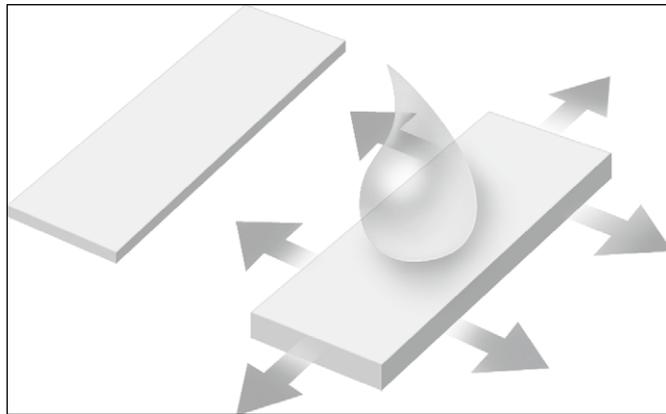
Fig. 34-18 Fornix flap allows posterior undermining of conjunctiva adjacent to superior rectus.



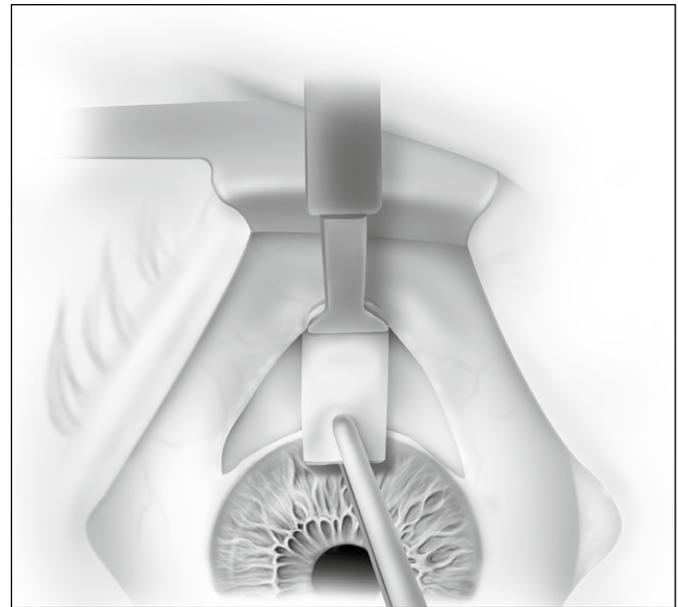
(A)



(B)



(C)



(D)

Fig. 34-19 (A) A 4–6 mm long scleral tunnel is prepared, with minimal radial incisions not extending to the limbus. (B) Applicators can be cut as thin, long strips (2×7 mm) from the edges of commonly available triangular cellulose sponges. (C) When hydrated with antimetabolite, the strips expand into flat rectangles. (D) The large flat strips can be subconjunctivally placed, covering large areas and amenable to a ‘sponge count’ upon removal.

(Fig. 34-22A,B). A relatively small trabeculectomy stoma (0.5–1 mm) is created with a scleral punch beneath the flap, and a peripheral iridectomy performed (Fig. 34-23). The flap is closed with two or more ‘adjustable’ sutures, using a 4-loop slip-knot closure (Figs 34-24 and 34-25). The conjunctival flap is then closed at the limbus using lateral phimotic stitches and corneal ‘scratch’ incisions to bury #10-0 Vicryl mattress sutures (see Fig. 34-7C,D). The merit of the ‘adjustable’ sutures is that postoperatively at the slit lamp, a blunt forceps (e.g., fine needle driver) can transconjunctivally wiggle and loosen them, effecting an incremental drop in IOP (Fig. 34-25).

The typical postoperative course following trabeculectomy surgery is characterized by little discomfort, several weeks of improving vision, and frequent office visits. Unless severe hypotony, a flat anterior chamber, or a hyphema is present, there is little reason to limit the patient’s activity beyond the routine restrictions common to outpatient eye surgery. Although hospitalization may be useful for the convenience or medical access of the patient, it is not warranted on the basis of the procedure’s healing course: trabeculectomy is considered an outpatient operation. Subconjunctival steroids and antibiotics are injected at the end of surgery, and topical steroids are usually instilled 4–8 times per day during the first

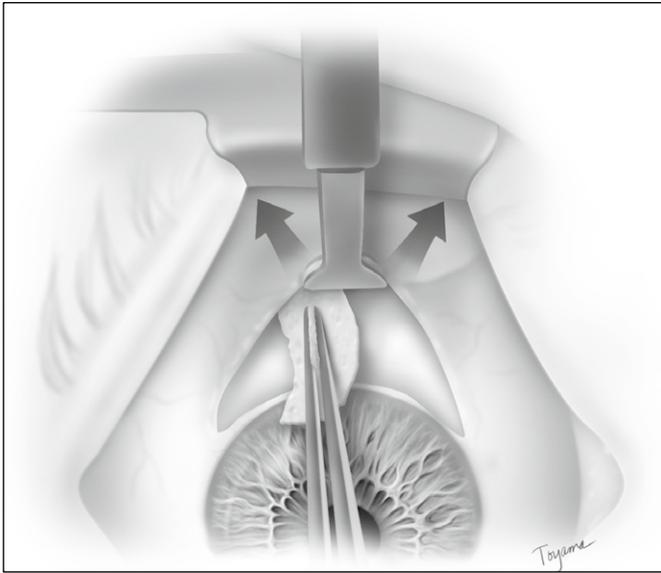


Fig. 34-20 Multiple (4–6) bisected LASIK sponges are saturated with mitomycin-C and placed posteriorly, adjacent and lateral to the superior rectus muscle. The conjunctival edge does not contact the sponges.

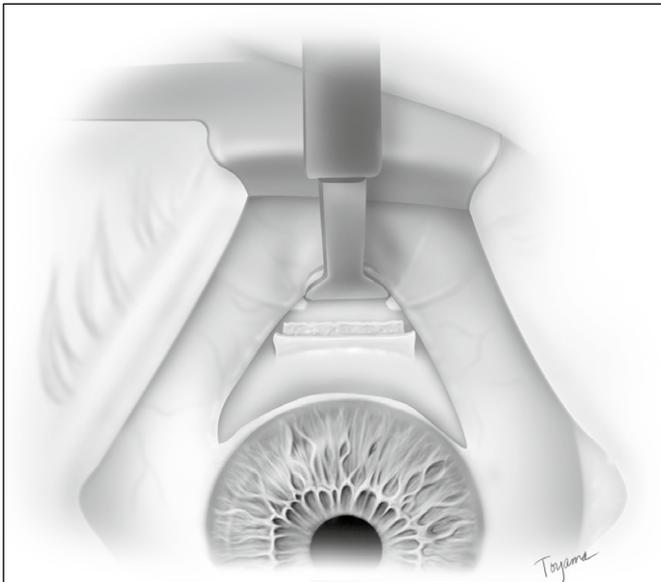
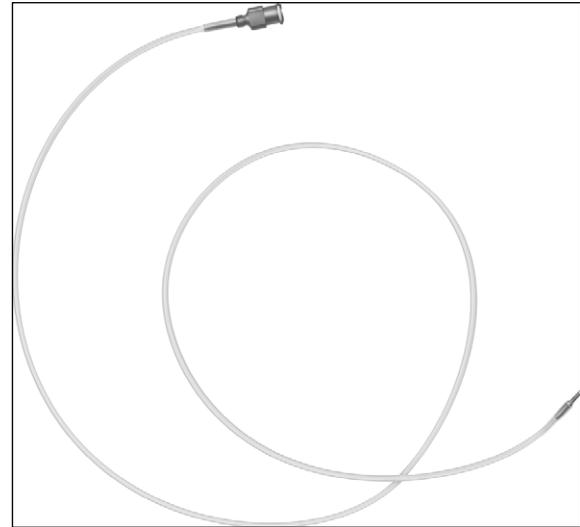


Fig. 34-21 A single hemi-sponge with mitomycin-C is placed under the scleral flap, again avoiding the conjunctival edge.

postoperative weeks. Cycloplegics are sometimes used to reduce photophobia and prevent synechiae. Some surgeons though, to minimize any non-essential potential conjunctival irritant which might adversely affect the bleb, use neither mydriatic nor antibiotic, applying only steroid drops after surgery.

With remodeling over the first few months, low posterior diffuse blebs are less prone to complications, such as leakage, than are thin-walled, multicystic blebs. Several schemes for clinically classifying blebs have been proposed, which if widely adopted could significantly help standardize the surgical literature in distinguishing outcomes and problems with specific bleb morphology.^{66–68} One



(A)



(B)

Fig. 34-22 (A) Lewicke anterior chamber maintainer (Visitec™) is connected to a 3-way stopcock and irrigating solution; its threaded metal end fits through an MVR-blade paracentesis. **(B)** Lewicke cannula obliquely situated in anterior chamber, allows for controlled intraoperative IOP.

system from Moorfields (Fig. 34-26A) has been developed for non-ophthalmic graders assessing clinical postoperative photographs. A slightly simpler system, called the Indiana Bleb Appearance Grading System, is easily applied at the slit lamp for clinical notations (Fig. 34-26B). The value of consistent descriptions of blebs is relevant not only to research protocols, but to direct clinical care as well; for example, the not uncommon issue as to whether or not a contact lens is 'safe to wear' following trabeculectomy. Clinically the decision is based on the bleb morphology: common wisdom is that it can be worn more safely with low, diffuse blebs than with elevated thin blebs;⁶⁹ but greater descriptive precision to correlate with the infection rates for specific types of blebs would be invaluable. And on the technological horizon, new advances with *in-vivo* confocal imaging of filtration blebs may yield even greater information as to structural and functional correlations.^{70,70b,70c}

Results

With the rapid evolution of surgical techniques and preferences over the past three decades, there are few rigorous long-term randomized

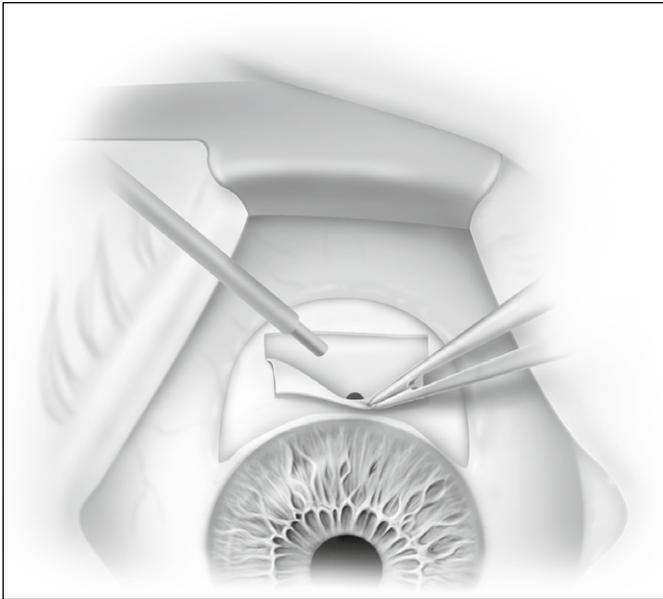
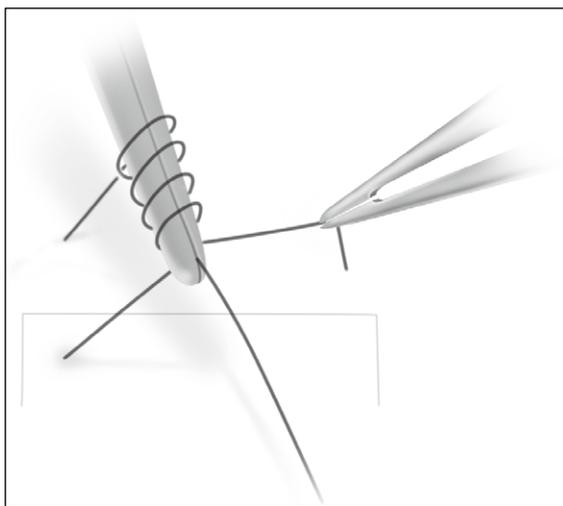


Fig. 34-23 A small sclerostomy is made, followed by iridectomy.



(A)



(B)

Fig. 34-24 (A) A 4-loop slip knot serves as an 'adjustable' suture for flap closure, tightened according to surgeon's assessment of flow. (B) The flap is closed with multiple 'adjustable' sutures, which can be wiggled loose at the slit lamp postoperatively.

controlled trials comparing surgical versus medical treatment for primary open-angle glaucoma.⁷¹ Lower IOPs are usually achieved surgically, with better preservation of visual fields; acuity, however, is sometimes adversely affected by surgery due to cataract formation.^{2,72}

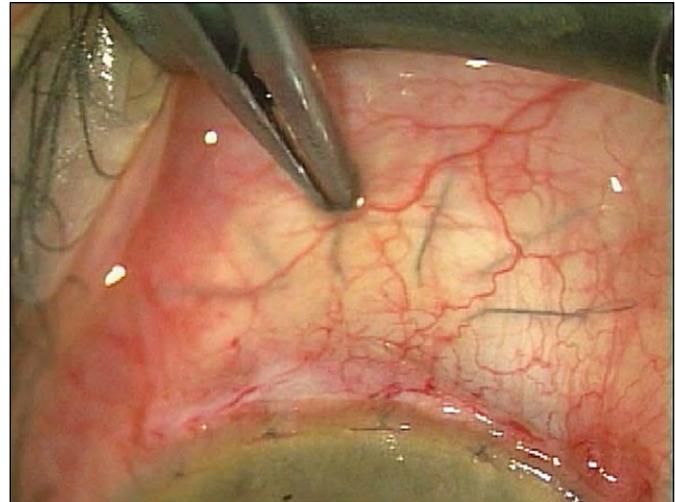
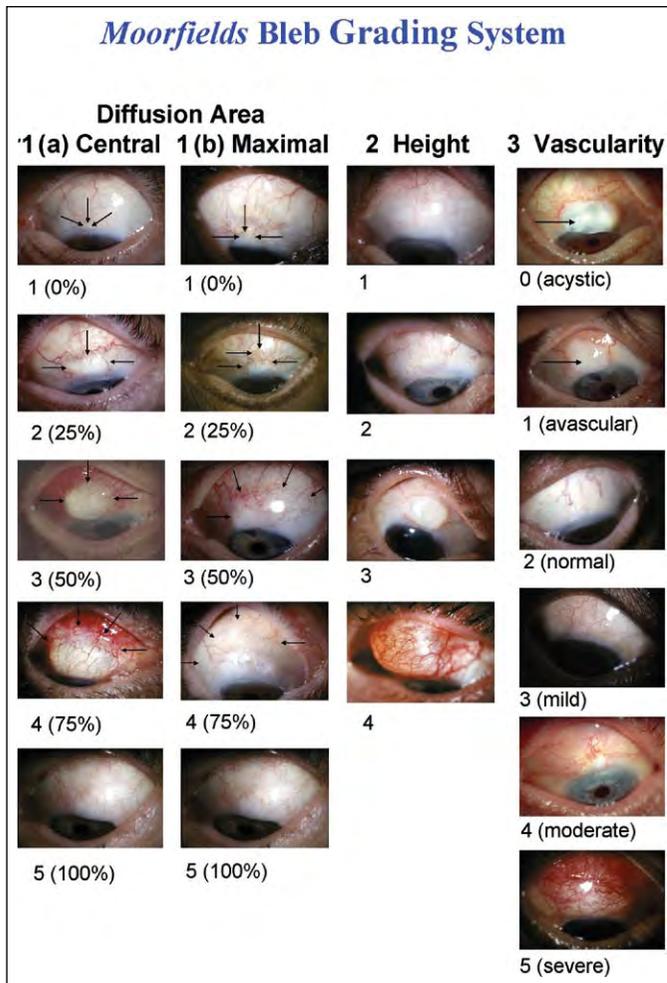


Fig. 34-25 Slit-lamp transconjunctival adjustment of suture with blunt forceps. (Courtesy of P Khaw.)

In the literature published before the wide use of antimetabolites with trabeculectomy, pressure levels of 21 mmHg or lower with or without medications were achieved in the first 2 years in about 80% of eyes with primary open-angle glaucoma;^{20,22,73-78} secondary glaucomas generally responded less well. Success in aphakic eyes was usually less than 50%;⁷⁹⁻⁸² young patients also had a lower success rate.^{45,83-85} After 4-5 years, however, success rates for achieving IOPs between 16 and 21 mmHg diminish towards 50%, regardless of race.^{86,87}

There is substantial cumulative evidence that use of an antimetabolite at the time of trabeculectomy surgery (either 5-FU or mitomycin-C) provides lower long-term IOP control than not using such agents.^{88-90,90b} However, the reported trials include different types of glaucoma at variable risk for surgical failure; a variety of drug concentrations, application times, and delivery methods; and different lengths of clinical follow-up. Trends suggest that in the first year following surgery, 5-FU and mitomycin results are comparable, with over 85% of eyes with 'controlled' IOPs;^{91,92} longer follow-up suggests a decay rate towards 65% at 5 years and towards 40% over 10 yrs.^{93,94} Despite long-term fall-off of surgical control, both the lower IOPs achieved and the dampening of IOP fluctuation are felt to significantly reduce the rate of visual field deterioration.^{12,13} Serious complications such as bleb leaks, hypotensive maculopathy, and endophthalmitis are seen with both drugs, and neither has rigorously demonstrated superiority in clinical efficacy or safety.^{88,88b}

Some eyes undergoing trabeculectomy may develop a modest IOP elevation during the first several weeks after surgery. This pressure rise is transient and may not alter the success of the procedure. In one series⁷³ evaluated before the advent of antimetabolites, releasable sutures or of laser suture lysis, up to 45% of eyes had pressures higher than 20 mmHg during the first month after surgery. At 1 year, however, less than 15% had pressures over 20 mmHg. It is important to realize that such a rise in IOP does not necessarily affect the ultimate outcome of the operation, and aqueous inhibitors should be avoided during the early post-operative period to maximize bleb dynamics. Although transient high post-operative IOP may be tolerated in some patients, it is not desirable. The ideal postoperative course begins with very low pressure (around 4-6 mmHg) and sees the pressure rise to



(A)

Fig. 34-26 (A) Moorfields Bleb Grading System. The bleb is assessed either photographically or at the slit-lamp, and characterized with respect to *height* and to *vascularity* in three zones: central bleb, peripheral bleb, and non-bleb. An elaborate photographic set of standards is available, as well as a standardized form for reporting (www.blebs.net). (1) Central bleb area: an estimation into five categories of percentages (0%, 25%, 50%, 75%, and 100%) is made of the relative size of the central demarcated area of the bleb relative to the visible conjunctival field superiorly. Often this is confined to the area over the scleral flap; in a uniform bleb, central and peripheral estimations are congruent. (2) Peripheral bleb area: the maximal extent of the bleb is assessed using a similar scale of five percentage estimations. This parameter assesses the maximal diffusion area of the bleb, as evidenced by slight bogginess or guttering at the edges. (3) Bleb height: in reference to the standardized photographs, the maximal central bleb height is scaled as flat, low, moderately elevated, or maximally elevated. (4) Vascularity: considered the most important prognostic parameter for bleb failure, this scale is applied to three areas: the central demarcated bleb, the bleb's peripheral extent of diffusion, and the surrounding non-bleb conjunctiva. Five grades of vascularity are used: avascular, normal, mild vascularity, moderate vascularity, and severe vascularity. Subconjunctival blood is also noted.

roughly 10 or 12mmHg in 6–8 weeks. Factors that contribute to surgical failure include intrinsic difficulties (e.g., eye with previous surgery or trauma, ocular-surface disease with conjunctival inflammation) and intraoperative factors (e.g., use of superior rectus suture, inexperience with trabeculectomy technique, etc.).⁹⁷

Surgical options and modifications

A number of intraoperative modifications of the original trabeculectomy procedure have been popularized. Although every surgeon has individual preferences, none of the variations below have demonstrable superiority over its alternatives.

Triangular versus rectangular flap

A triangular scleral flap is easier to dissect in a single plane towards the limbus than is a rectangular flap. Sometimes a single suture at the apex is sufficient for closure.

Early trabeculectomy technique specified a rectilinear 4-mm × 6-mm long scleral flap overlying a 3-mm wide × 1.5-mm deep sclerostomy. A 'short-flap' modification reduces these dimensions to a 3-mm long × 3-mm wide rectangular flap. This was developed to more nearly approximate full-thickness filtration while keeping the chamber retention aspects of the guarded filter. This technique has advantages when used in conjunction with postoperative laser- ing of flap sutures because of the ease in visualizing subconjunctival sutures so close to the limbus. The scleral flap extends less than 1 mm from the sclerostomy on all sides. Sutures at each distal corner are tied securely to retain the chamber. Additional flap sutures may be used as desired. Because the flap is small, it leaks more freely; this could be too much if excessive cautery near the edges is employed. If enhanced filtration is desired, the scleral flap sutures can be lasered or released postoperatively. Theoretically this technique combines the advantages of guarded and full-thickness filtration.

Note that both the triangular and rectangular scleral flaps are cut down to the limbus itself. In contrast, either a scleral tunnel approach or the Moorfields Safer Surgery technique specifically avoid bringing the flap edges so far anteriorly, to facilitate posterior aqueous flow away from the limbus.

Postoperative laser- ing, adjustment, or release of sutures

If the scleral flap has been secured with 9-0 or 10-0 nylon sutures, the sutures may be cut in the postoperative period with the argon green, argon blue-green, diode, or krypton red laser.⁹⁸ (The yttrium-aluminum-garnet (YAG) laser can also cut sutures but is capable of rupturing conjunctival and episcleral blood vessels, possibly leading to subconjunctival hemorrhage; hence it is rarely used.) *Laser suture lysis* is greatly facilitated by compressing the overlying conjunctiva to visualize the suture. This can be done without magnification with the edge of a four-mirror Zeiss gonioprism^{98b} or with the Hoskins laser suture lens (see Figs 32-4 and 32-5).⁹⁹ High-magnification suture-lysis contact lenses are commercially available (e.g., Mandelkorn lens [Fig. 34-27] or Blumenthal lens [Fig. 34-28A]), which, without coupling gel, both blanch the conjunctiva and intensify the power density of the laser beam (Fig. 34-28B). Such lenses are enormously helpful with argon, krypton, and diode slit-lamp delivery lasers.

Generally the sutures should usually be cut within the first three postoperative weeks to enhance filtration before irrevocable scarring occurs. The outside window may extend as far as 8 weeks if mitomycin-C is used intraoperatively¹⁰⁰⁻¹⁰² and there is little conjunctival inflammation in the interim. Because mitomycin-C and other antimetabolites delay tight wound healing for many weeks, a late wound leak or hyperfiltration with hypotony can follow suture lysis.¹⁰³⁻¹⁰⁷ Often, however, small, pinpoint bleb leaks from the laser beam will spontaneously heal within a few days, in the temporary reduction or absence of steroids, and use of antibiotic drops. Gentle digital pressure on the globe through the lid or directly on the posterior edge of the scleral flap will often open the wound and

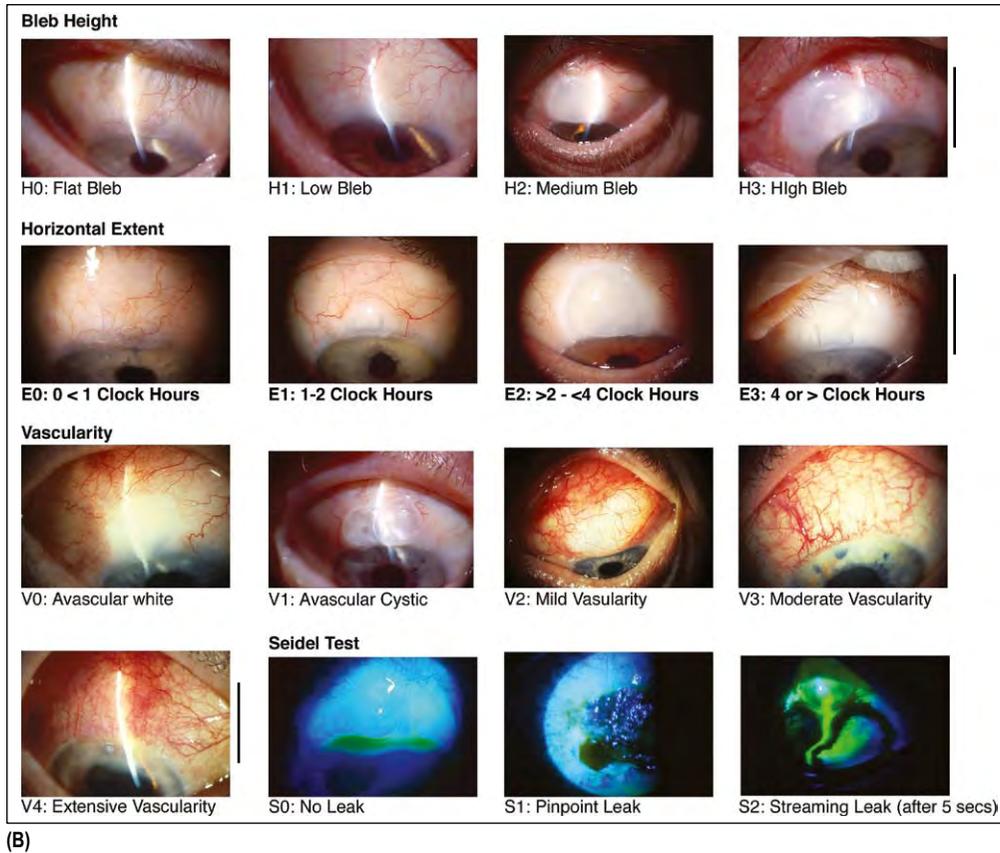


Fig. 34-26 (B) Indiana Bleb Grading System. Four parameters are assessed at the slit lamp, using a narrow beam, against a standardized photographic set of blebs. (1) Bleb height: this describes the maximal vertical *elevation* of the bleb: flat, low, medium, or high. (2) Horizontal extent: the maximal horizontal extent is described relative to limbal clock hours: <1 hr, 1-2 hr, >2-<4 hr, and >4 hr. (3) Vascularity: five simple categories are elaborated: white and avascular, cystic and avascular (with microcysts), mild vascularity, moderate vascularity, and extensive vascularity. (4) Seidel leakage: in the testing for a bleb leak with a fluorescein strip at the slit lamp, the bleb is categorized as showing no leak, multiple pinpoint leaks without streaming, or brisk streaming within 5 seconds.



Fig. 34-27 Mandelkorn contact lens for laser suture lysis. (Courtesy of Ocular Instruments.)

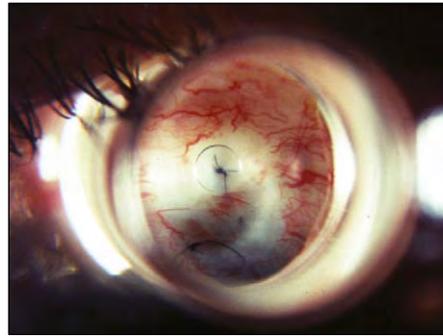
elevate the bleb if it fails to do so spontaneously after the suture is cut. Laser suture lysis is also useful to release sutures that are inducing astigmatism and/or to enhance filtration after combined cataract and trabeculectomy surgery.

If the suture can be seen clearly, it can be cut with a single application of argon laser energy delivered at 400mW for 0.1 second with a 50- μ m spot size. Unfortunately, it can be very difficult to visualize and cut sutures through an inflamed, thickened and failing bleb. Careful focus with the laser maximizes energy delivery and minimizes collateral tissue damage. Blood overlying the suture may prevent suture visualization or cause excessive absorption of the laser energy, potentially leading to a conjunctival hole. Though such a small breach may leak aqueous, a reduction in topical steroids and patience usually effect spontaneous healing within a few days.

Several alternative methods have been described. Though not widely available in an office setting, an endolaser probe to compress the conjunctiva overlying the suture has been used in cutting sutures under a conjunctival flap.¹⁰⁸ An ingenious adaptation of the standard scleral flap closure can allow visualization and laser lysis of these sutures with slit-lamp gonioscopy in the postoperative period, independent of the conjunctival appearance and dependent only on sufficient corneal clarity for gonioscopy.¹⁰⁹ This technique is adaptable to any variation of trabeculectomy technique; it is illustrated here using a standard #10-0 nylon for closing the scleral flap (Figs 34-29 through 34-34). So long as the anterior chamber remains deep and there is no internal obstruction of the trabeculectomy stoma (by iris, blood, debris, etc.), this technique reliably and elegantly bypasses difficulties of subconjunctival edema



(A)



(B)

Fig. 34-28 (A) Blumenthal contact lens for laser suture lysis. (B) Pressure on lens focally blanches and compresses conjunctiva, enhancing visualization for laser suture lysis. (Courtesy of Volk Instruments).

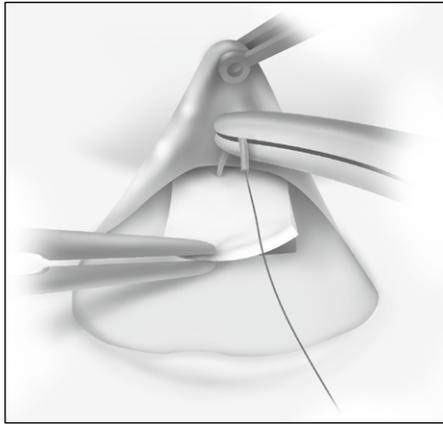


Fig. 34-29 A #10-0 nylon suture passed through flap base, seen from above.

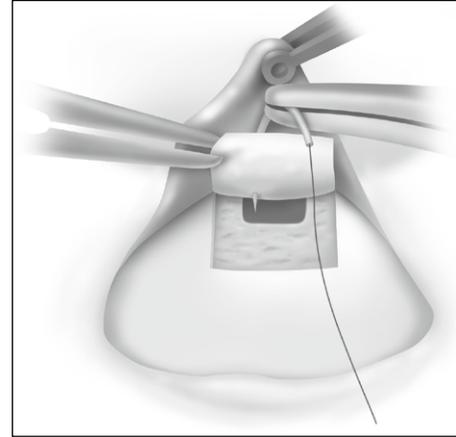


Fig. 34-30 A #10-0 nylon suture passed through flap base, seen overhanging sclerostomy.

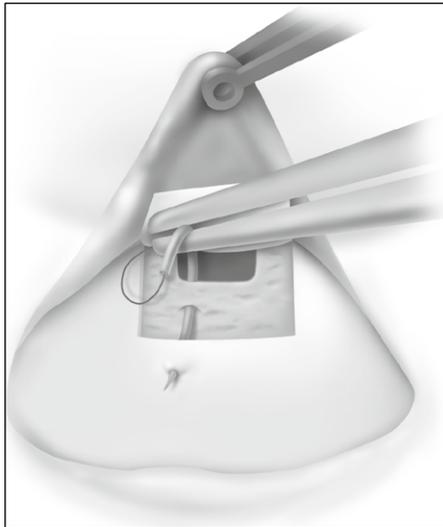


Fig. 34-31 Suture passed through posterior bed of flap.

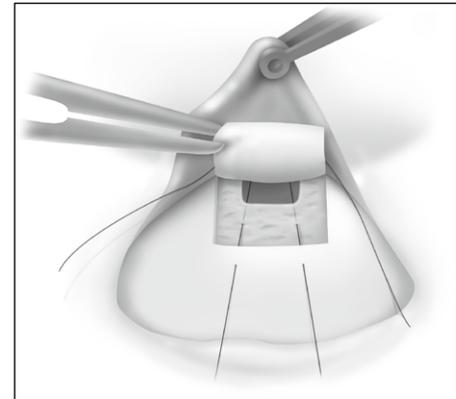


Fig. 34-32 Two sutures suspended over stoma before closing flap.

or hemorrhage which can obscure sutures which might require lysing.

Laser suture lysis may not be a viable clinical option if a suitable laser is simply neither available nor accessible in the postoperative period: hence many surgeons prefer using *releasable sutures* at the time of trabeculectomy.^{62,64b,110} This approach has proven to be a simple,

low-cost, and efficacious way to influence postsurgical filtration in the first several weeks postoperatively.¹¹¹⁻¹¹³ Several techniques have been described: they essentially begin with a #10-0 or #9-0 nylon suture through the perlimbal cornea, bringing it out through the hinged area of the scleral flap, and then closing the flap edge with a slip knot; several such stitches can be placed. Postoperatively at the slit lamp, the corneal end of the suture can be grasped with a forcep and removed; the mechanical disruption of the flap edge by this maneuver is felt efficacious in disrupting adherence between the flap and its scleral bed, thus facilitating aqueous egress. To avoid a loose

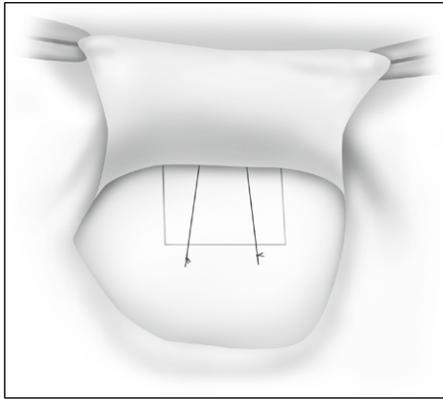


Fig. 34-33 Flap closed with standard knots.

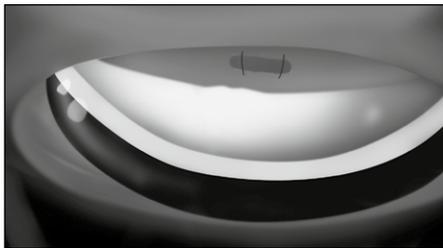


Fig. 34-34 Gonioscopic appearance of sutures for laser lysis.

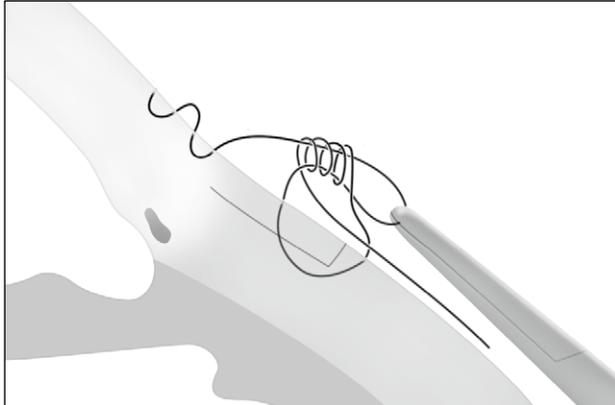


Fig. 34-35 Beginning in the limbal cornea, an intracorneal loop is made before proceeding through cornea and securing the scleral flap, with a 4-loop slip-knot closure. Postoperatively, by grasping the loop, the suture can be fully retracted, disrupting the flap closure; otherwise the loop is soon epithelized over.

suture end disrupting the corneal surface (“windshield-wiper keratopathy”¹¹⁴), a small loop can be crafted which effectively buries the suture intracorneally (Fig. 34-35). This maneuver avoids a free suture end, which is potentially irritating and contributory to endophthalmitis;¹¹⁵⁻¹¹⁷ the suture loop is soon epithelized over in the event that no release is required, and can be left indefinitely.

Adjustable sutures are an integral part of the Moorfields Safer Surgery System described above;^{36,36b,36c} two or more 4-loop slip knots are used to close the scleral flap, after the application of the

antimetabolite. At the slit lamp over the following weeks, transconjunctival disruption of these sutures with a non-perforating forceps allows incremental titration of the IOP. Experimental studies of the technique suggest mechanical advantages over either direct massage or releasable sutures.¹¹⁸

Wound-healing retardants

The use of antimetabolites such as 5-FU and mitomycin-C has had a dramatic effect on the outcome of filtering surgery. These agents are further discussed in Chapter 36.

FULL-THICKNESS FILTRATION PROCEDURES

Full-thickness procedures are rarely performed today. Their popularity had been somewhat cyclic during the last part of the twentieth century. During the late 1960s and early 1970s, full-thickness procedures were replaced in many cases by trabeculectomy, which manifested fewer postoperative complications and excellent IOP control. By the mid 1980s (before antimetabolites came in vogue) some surgeons were not happy with the level of pressure control offered by trabeculectomy, particularly in certain high-risk populations,^{29,119} and they supported the use of full-thickness procedures in selected cases. In the early 1990s, thermal sclerostomies using infrared holmium lasers gained popularity.^{120,121} Results however were not sufficiently reliable to warrant commercial availability of the devices. Currently the use of antimetabolites with trabeculectomy, and the availability both of glaucoma drainage devices and of cyclodestructive laser modalities, have obviated the need for full-thickness procedures in glaucoma surgery. Full-thickness procedures could be useful, however, in clinical settings where antimetabolites, micro-instruments or laser technologies are unavailable. Hence they are addressed below for completeness’ sake.

THERMAL SCLEROSTOMY (SCHEIE PROCEDURE)

The limbal-based conjunctival flap is preferred, anticipating unimpeded aqueous flow and the need to minimize anterior chamber shallowing and flattening. A paracentesis is made, to allow irrigation and elevation of the bleb after the conjunctiva is closed. In open-angle eyes, a slightly beveled *ab-externo* incision is made through the cornea at or just anterior to the external corneoscleral sulcus. In narrow-angle eyes, the incision must be placed farther forward at the conjunctival reflection, so as to avoid anterior synechial adhesions in the angle. All bleeding is carefully controlled by cautery. As the 3-mm incision is deepened, its edges are seared to produce shrinkage, with care taken that the shrinkage extends into the depths of the incision. The incision is deepened with alternating cautery and sharp dissection. A peripheral iridotomy is performed on the prolapsed iris. If aqueous flow is inadequate, wetfield cautery can be used to enlarge the sclerostomy site.

The success rate of thermal sclerostomy appears to be about the same as that of sclerectomy with a punch. There is sometimes uncertainty as to the amount of tissue thermally destroyed. In some eyes, the IOP is elevated for 1 or 2 days after the operation, and in these eyes, the inner aspects of the incision may not be patent. Some of these eyes develop filtration later. In other eyes, drainage is excessive, with prolonged collapse of the anterior chamber and formation of synechiae. A beveled temporal paracentesis site created at surgery allows the anterior chamber to be re-formed with viscoelastic at

the slit lamp, which can be most helpful when managing a patient with a wound leak or overfiltration and a flat chamber.

SCLERECTOMY

The scleral tissue to be excised is always the limbal tissue, but the *ab-externo* incision can be varied, depending on whether the sclerectomy is to be performed on the anterior or posterior lips of the incision.

Posterior lip sclerectomy

In posterior lip sclerectomy, the *ab-externo* incision is placed just behind the point of reflection (using a limbal-based flap) of the conjunctiva at the anterior limbus. It is beveled forward somewhat more so than for other procedures. The length of the incision must be at least 3–4 mm to permit the standard 1-mm scleral punch to slide easily under the back lip of the incision. Among the many instruments available for this purpose, the Kelley, Elliott, Walser, or Gass punches have seen broad acceptance. With these punches, the cutting blade can be inserted into the anterior chamber through a small incision. One or two 1-mm bites placed side by side are adequate. This opening must be inspected carefully. Not infrequently the outer sclera is excised, but the punch slips off before the internal limbal tissues are excised, and a full-thickness opening is not made. As in the trephine operation, the specimen removed provides opportunities for studying the pathology, histology, and electron microscopic appearance of freshly excised trabecular meshwork in glaucomatous eyes. After sclerectomy, the iris usually prolapses into the opening. If it does not, it should be grasped gently by forceps and a peripheral iridectomy performed. Closure of the limbus-flapped conjunctival incision is as previously described.

Anterior lip sclerectomy

In anterior lip sclerectomy, the *ab-externo* incision must be placed back at the corneoscleral sulcus to permit removal of the tissue between the incision and the conjunctival reflection; otherwise, the procedure is the same. Scissors also can be used to excise the 1-mm semicircle of tissue. Buttonholing of the conjunctival flap while cutting out the scleral fragment is the principal danger in anterior lip sclerectomy. Most surgeons prefer the posterior lip technique.

TREPHINATION

Corneoscleral trephination, using a 1–2-mm glaucoma trephine, is a difficult procedure for surgeons who perform it only occasionally. Disastrous errors can occur during surgery, such as misplacement of the trephine, button-holing of the flap, injury to the lens or ciliary body, and incomplete removal of the corneoscleral button. The large opening produced by trephination invites hypotony, flat anterior chamber, and incarceration of intraocular tissue, particularly in the crowded segment of narrow-angle eyes. Although similar complications can occur with other operations, they are less frequent and more easily avoided. In patients who require full-thickness procedures, punch sclerectomy is generally simpler and probably safer for surgeons who perform trephination infrequently.

IRIDENCELEISIS

Iridenceleisis is rarely, if ever, used today. Historically, it was anecdotally observed that inadvertently incarcerated iris in the wound after intracapsular cataract extraction or surgical iridectomy sometimes resulted in IOP lowering. The presumed mechanism was a ‘wicking’ of aqueous by the iris tissue. However, reports of chronic

iritis, infection, and sympathetic ophthalmia led to other techniques being explored. The procedure is described briefly here for historical completeness.

An *ab-externo* incision is placed at the corneoscleral sulcus and beveled forward slightly toward the anterior chamber. The entrance into the anterior chamber is approximately 2–3 mm in length. If only one pillar is to be incarcerated, the surgeon pulls the iris out until the pupillary margin is visible and then runs de Wecker iridectomy scissors under the iris to its base to perform a complete vertical iridotomy beside the forceps. The iris is then wedged firmly in the incision and released. To construct a double-pillar iris incarceration, the assistant should grasp the iris beside the surgeon’s forceps. The radial iridotomy is similarly completed between the two forceps, and the pillars are incarcerated in opposite edges of the incision.

GLAUCOMA DRAINAGE DEVICES

There is a long history of various devices to facilitate aqueous flow out of the anterior chamber to control IOP, but the nomenclature requires precision.^{122,123} *Setons* are solid stents or wicks,^{123–130} using the principle of surface-tension flow for fluid to exit the anterior chamber, while structurally intended to maintain a patent drainage fistula. Historically, horsehair, silk, metal sutures, tantalum mesh, tubes of gold, platinum, polyethylene, collagen and silicone, Gelfilm, cartilage, and acrylic plates have all been used in various ways, but either fibrosis around the stent or conjunctival scarring rendered them ineffective. Open-tubed devices have been synthesized to serve as *shunts*, secured translimbally to allow flow subconjunctivally (e.g., Molteno or Baerveldt implants). Unless modified by surgical technique, problems can arise with such shunts from either excessive flow or from later cicatricial effects, ascribed to early aqueous flow on bleb development. Subsequently, *valved* devices were elaborated to forestall postoperative hypotony, by constricting flow when the IOP is lower than a predetermined threshold (e.g., Krupin or Ahmed valves). It is most accurate to refer to this entire class of surgical tools as *glaucoma drainage devices*.

THE MOLTENO IMPLANT

In 1969, Molteno¹³¹ established the idea of connecting a tube from the anterior chamber to a posterior drainage field provided by an acrylic plate, a concept which has served as a prototype for a generation of glaucoma drainage devices.^{132–133} Over decades of clinical observation and surgical innovation, Molteno elaborated three critical principles for the success of glaucoma drainage devices, principles whose relevance remains fundamental in the design of newer implants.¹³⁵ First was the importance of locating a non-inflammatory, biocompatible device¹³⁶ away from the limbus: a round polypropylene plate was designed to be placed between the rectus muscles, 8–10 mm away from the cornea. This all-important posterior location in a quadrant overlying the equator sequesters the resulting bleb away from the interpalpebral fissure, where lid blinking and exposure to normal drying facilitate bleb leaks and implant erosion.

A second innovation was to design the plate size so as to maximize the potential space within the plate’s surrounding capsular cyst, or bleb, whose walls the sequestered aqueous would need to traverse

for active filtration. Similar to the concept of a large septic drainage field for a house, a large plate prevents episcleral–conjunctival adhesion in an area equal to that of the plate, thus forming a bleb which serves as a fluid reservoir. The cyst's capsular wall heals through stages of variable thickness, eventually allowing incremental aqueous transudation across the bleb.¹³⁷ Surgical techniques were designed to allow either immediate or delayed flow of aqueous onto the plate, with differential effects noted of 'early' or 'late' aqueous on wound healing.

Molteno's third principle recognized that an unmodified shunt's outflow was too great in the immediate postoperative period, resulting in prolonged initial hypotony, with its undesirable sequelae of cataract, choroidal effusions, synechiae, etc. He initially addressed this problem by using a two-stage procedure: first to secure the plate subconjunctivally in a quadrant, without inserting the tube into the anterior chamber and thus allowing the bleb to become encapsulated.¹³² Six weeks later, in a second procedure, the tube was removed from its sequestration beneath a rectus muscle and introduced into the anterior chamber to allow the aqueous to drain into the matured fibrovascular cyst surrounding the plate. This preformed bleb provided both a controlled reservoir and an absorption membrane for the aqueous.

To prevent excessive fibrosis of the bleb in the early postoperative months, Molteno prescribed a complex regimen of antifibrosis therapy – including systemic non-steroidal anti-inflammatory agents, oral colchicine (as a mitotic inhibitor), and topical drops of atropine, epinephrine, and steroids.^{137,138} Few surgeons, however, emulated this complicated topical and oral regimen. Alternatives to avoid a second surgery were soon elaborated, so that both the plate and the intracameral tube could be secured in one operation; the challenge was to prevent excess flow. Some use an intratubal chromic or #3-0 Prolene stent suture, secured subconjunctivally inferotemporally, for later removal at the slit lamp.¹³⁹ Others prefer to externally ligate the tube with either an absorbable Vicryl ligature or nylon suture which can later be cut with a laser.^{140,141} If a clear corneal graft is used to cover the tube (instead of the more commonly used scleral or dural patch), visualization may facilitate suture lysis.^{142,144}

The earliest Molteno implant designed was a single plate, which sometimes failed to provide an optimal IOP reduction, a limitation ascribed to its small plate area. Double-plated Molteno implants were developed, designated 'right' and 'left,' depending not on which eye the implant was to be used with, but rather whether the anterior chamber tube came off the right or left plate for optimal positioning in the anterior chamber. Molteno and others have reported long-term success rates for IOP control and vision retention with various devices in a variety of serious forms of glaucoma, with IOP reduction with or without medications in approximately 50% of eyes after several years' follow-up.^{131–134,143,146–151}

Although the correlation of plate size with IOP reduction is imperfect, up to a point larger surface areas are thought by some to provide greater IOP reduction,^{152,152b} while others are unconvinced that there is any consistent superiority between larger or different devices.^{153,153b,153c} Nevertheless, many surgeons use either a double-plate Molteno or 350-mm² Baerveldt implant; the Ahmed implant has undergone a similar evolution, with two plates now offered. If one smaller implant has been unsuccessful, inserting an additional drainage device, such as in the unoperated inferonasal quadrant¹⁶⁷ can sometimes be effective.^{154–156}

A recent issue of concern is the role and success of drainage devices in eyes with failing corneas, either requiring or already

having had a penetrating keratoplasty.¹⁵⁶ Although IOP control may be achieved with drainage devices, regardless of which drainage device is used, approximately half of pre-existing corneal grafts fail within 3 years.^{157–162} The reasons for graft failure remain undetermined. An intriguing immunologic explanation emphasizes the loss of the cornea's immune privilege with non-valved devices, allowing bi-directional flow and access between the anterior chamber and the episcleral surface, with its access to the vascular-borne immune system. Evidence of focal corneal edema adjacent to the intracameral end of drainage tubes has suggested mechanical trauma to the endothelial surface, especially with eye rubbing or forceful blinking, as can be seen with ultrasound biomicroscopy. There is no advantage to one sequence of surgeries over another, with graft failure reported with drainage devices placed either after or before the keratoplasty.^{158,163,164}

Assuming the mechanical factor to be determinative for graft failure, placement of a drainage device tube through the pars plana, to reside far from the cornea behind the iris plane, has shown promising results at reducing graft failure – although there are significant risks for retinal complications with the complete posterior vitrectomy that is required to thoroughly clear the anterior vitreous skirt overlying the pars plana.^{164–166} Pars plana placement requires both a specially designed device to forestall tube kinking (e.g., the 90° Hoffman elbow for the Baerveldt implant) and coordination of surgery with a skilled vitrectomist as co-surgeon working with the surgeon implanting the glaucoma device.

Techniques

Many of the comments here are applicable to the entire range of glaucoma drainage devices.^{166b} The surgeon needs first to determine the most appropriate intracameral location for the tube, taking into account iridectomies, lens implant positioning, corneal health, etc.; the plate is thus situated with this ultimate tube location in mind. One of the superior quadrants is the usual site for surgery, with the temporal quadrant preferred for single-plate devices (e.g., Molteno or Ahmed), so as to minimize mechanical involvement with the superior oblique muscle and postoperative strabismus. If the superior quadrants are unavailable, the inferonasal quadrant, approached with the surgeon sitting at the customary 12 o'clock position, is an excellent alternative location for surgery.¹⁶⁷

Drainage devices are best placed under a fornix-based conjunctival flap, to reduce the stress of the foreign-body plate on the overlying suture line of a limbus-based flap. Since a drainage device is frequently performed in eyes with prior cataract or trabeculectomy surgery, the scarred tissue may require a subconjunctival injection of xylocaine with epinephrine to assess the suitability of the tissue for dissection and later coverage over the implant. When the peritomy incision is made at the limbus, a radial relaxing incision is usually required for 6–8 mm above the horizontal rectus to allow access for positioning of the drainage plate over the equator of the globe, situated posteriorly enough (7–9 mm) to avoid an interpalpebral position of the plate.

Before inserting and securing the plate(s), some surgeons advocate the intense subconjunctival application of mitomycin-C for glaucoma drainage devices, using doses such as 0.5 mg/cc for 5–8 minutes in the target quadrant(s). Though some reports suggested efficacy,^{168,168b,169,170} the general consensus,^{171–177} including a comprehensive review of fifteen published trials involving over 1150 patients,^{153c} is that anti-metabolites confer no demonstrable advantage with drainage device surgery.

All plates have eyelets on the anterior edge for securing the implant to the sclera with a non-absorbable suture, such as the

#6-0 Mersilene suture used with retinal buckles. Fixation of the plate prevents both plate extrusion through the conjunctiva and plate displacement, thus keeping the latter either from retracting out of or extending too far into the anterior chamber. The plate should be positioned posterior to the insertion of the rectus muscles; 8–10 mm is measured with calipers from the limbus to the central plate edge. If a double-plate implant is used, a plate is positioned in each quadrant. The tube connecting the two plates sometimes can be passed under the superior rectus, but in practice this is often quite difficult to achieve, and the tube can lie over the muscle.

With all drainage devices, the tube connecting the plate to the anterior chamber is covered so as to minimize erosion through the overlying conjunctiva. Some surgeons construct a scleral tunnel to cover the tube; the disadvantage is that the suturing of the overlying flap may tilt the tube in the anterior chamber up towards the cornea. Usually the tube is covered with some sterile biodegradable tissue, such as donor sclera, pericardium, or dura, all of which seem to be equally efficacious.¹⁷⁸

After determining the desired position for the tube in the anterior chamber and the placement of a small dollup of intracameral viscoelastic in the target area of the angle, the tube is placed through a #23-gauge needle track initiated 3 mm from the limbus and aligned parallel to the iris plane; this allows positioning of the tube through the trabecular meshwork, to sit equidistant between the iris and the cornea. If the scleral tunnel is made with too large a bore needle, excessive leakage can lead to early hyperfiltration. If the scleral tunnel seems too small to smoothly insert the pliable silicone tube, two adjunctive maneuvers can be tried: applying viscoelastic within the tunnel, and/or placing a thin iris spatula through a paracentesis 180° across the anterior chamber and out through the tunnel, where it can be inserted into the tube to act as a guide stent for intracameral placement as the spatula is withdrawn.

The tube should be carefully measured so that after insertion it will extend 2–3 mm into the anterior chamber; excessive tube length can cause trauma to the cornea endothelium, and too short a tube may allow it to retract out of the anterior chamber postoperatively. (A technique for intracameral shortening of the tube has been described.)¹⁷⁹ In pseudophakic eyes, sometimes the tube can be manipulated through an iridectomy (if need be, fashioned intracamerally with a #23-gauge needle), allowing the tube to sit between the posterior chamber intraocular lens and the overlying iris; the tube should be cut long enough to be visualized at the pupillary margin. The advantage of this placement behind the iris plane is that it significantly reduces any possible physical contact of the tube against the cornea, thereby reducing the risk of late corneal failure.

As mentioned above, a one-stage surgery usually requires some temporary closure of the tube, either with an internal suture stent (e.g., a #3-0 Prolene suture for an unvalved Baerveldt shunt) or an external ligature. If some filtration is desired immediately postoperatively, two options are available. The first is to perform a concomitant trabeculectomy adjacent to the occluded-tube site, without antimetabolite – with the expectation that the trabeculectomy will fail within weeks, at which time the drainage device reservoir is available for function. Alternatively, a suture needle can be passed through and through in two or three locations of the unoccluded tube section below an external ligature or a retracted internal stent, just posterior to its scleral insertion.¹⁸⁰ These fenestrations, fancifully described as a ‘garden hose sprinkling system,’ allow a few weeks of aqueous leakage with little risk of hypotony, before the tube is sheathed by transparent granulation tissue.

Once the tissue over the flap has been secured and the surgeon is ready to attach the conjunctival fornix flap to the limbus with an #8-0 Vicryl, sometimes the conjunctiva over the device is stretched and seems unable to be placed at the limbus without tearing. In such circumstances, blunt posterior subconjunctival undermining with Westcott scissors may be required to undermine its attachments deep in the fornix, creating slack and permitting it to be brought forward for a water-tight closure.

If a two-stage procedure is used, as with Molteno or Baerveldt devices, the plate is secured as usual to the posterior episcleral site between the rectus muscles but the tube is bent and temporarily sutured onto the sclera after being tucked beneath a muscle insertion. In 5–6 weeks, after the drainage bleb has developed, the second surgery simply identifies the tube and positions it in the anterior chamber, as described above. No tube ligature is required in the two-stage procedure.

SCHOCKET PROCEDURE

Schocket and co-workers introduced a variation of the Molteno concept that involves shunting of aqueous via a tube to an encircling band.^{181,182} The appeal of this procedure was its relative low cost, using commonly available ophthalmic components: useful under conditions where dedicated glaucoma drainage devices are unavailable. Results with the Schocket implant are similar to those with the Molteno implant, but most authors report slightly higher complication or reoperation rates.^{183–187}

A 30-mm long silastic lacrimal tube with an internal diameter of 0.30 mm is sutured inside the groove of a #20 silicone band, leaving 15 mm of the tube extending from the band. The encircling band is circumferentially sutured to the sclera, 10–12 mm from the limbus beneath the four rectus muscles, with 5-0 Supramid sutures. A square 3–4 mm scleral flap hinged at the limbus is elevated, and a slightly beveled puncture wound is made into the anterior chamber. The end of the tube is beveled and inserted into the anterior chamber so that a 3-mm length is suspended between the iris and cornea with the bevel facing anteriorly. The scleral flap is closed with 10-0 nylon, and the conjunctival flap is sutured with 8-0 Vicryl. As with the Molteno implant, the silastic tube may be ligated at the end of the procedure to prevent immediate postoperative hypotony. Some surgeons use a 0.30- μ m diameter angiocatheter passed through the edge of the encircling band. When the needle is withdrawn, the angiocatheter can be used in place of the silicone tubing. Unfortunately, a common cause of failure is the unpredictable tube kinking or of fibrosis within the small-diameter tubing.

KRUPIN VALVE AND EX-PRESS IMPLANT

Molteno recognized the problem of initial overfiltration with his device and developed a two-stage procedure to overcome it. Subsequent experience with both Molteno and Baerveldt shunts has led to a variety of methods to perform a single operation yet forestall flow, with internal stents or external tube ligation. Krupin and co-workers^{188–190} approached this problem by developing a *valve* of silicone and Supramid that was unidirectional and required a pressure head of 11–14 mm to initiate flow. The initial design had a short outflow tube that ended 2–3 mm posterior to the limbus under a scleral flap. Failure, however, was frequent, due to failure of the bleb to be sustained at the tube’s end in the interpalpebral fissure. Subsequent modifications expanded the drainage area, and the outflow portion of the tube was extended to either reside in an

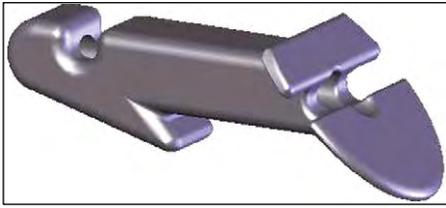


Fig. 34-36 Redesigned Ex-PRESS implant has blunt entry tip and recessed stoma to avoid closure by overlying scleral flap.

encircling scleral band, conceptually similar to the Schocket procedure,¹⁹¹ or in a later iteration, was attached to a disc similar to the Molteno plate. Like other glaucoma drainage devices, the Krupin valve enjoyed some success in eyes that had otherwise failed conventional therapy.^{192,193} The valve, however, did not always prevent hypotony, presumably because of leakage around the tube; nor did the larger plate surface prevent postoperative pressure spikes in all patients.¹⁹³⁻¹⁹⁵ As with other implantable devices, a variety of complications have been reported, including motility disturbances,^{196,197} suprachoroidal hemorrhage, and endophthalmitis.

A more contemporary device reminiscent of the earliest Krupin valve design is the Ex-PRESS shunt, consisting of a small stainless steel tube (equivalent to a 26-gauge needle) with a barbed end to anchor it in the trabecular tissue, through which it is placed on a stent and secured without suture. Originally designed to be placed subconjunctivally in a matter of minutes, common complications of excessive hypotony, tube dislocation, or erosion have largely led to the abandonment of this rapid surgical approach.^{198,199} Although the subconjunctival insertion in combination with phacoemulsification surgery showed reasonable short-term results,²⁰⁰ a newer model has been designed to function under a standard trabeculectomy scleral flap, a technique which appears promising (Figs 34-36 and 34-37).¹⁹⁹ The Express under scleral flap offers the theoretical advantages over a trabeculectomy of no tissue excision with less chance of bleeding, quieter eyes postoperatively and simpler operative technique. One study showed fewer complications of early hypotony and hyphema compared to trabeculectomy with equivalent pressure lowering at one year.^{198b} Nevertheless, the Ex-PRESS implant's long-term success or advantage over standard filtration surgeries has yet to be prospectively established.

AHMED VALVE

The Ahmed valve shares features with several other currently available devices, but gained in popularity because of its small size, ease of insertion, and intrinsic valve system designed to forestall early hypotony. The valve feature is a millipore filter which restricts flow below 7 mmHg – although leakage around the tube at its scleral insertion site can still result in excessive filtration.²⁰¹ Its single-plate design has the appeal of relatively rapid subconjunctival attachment in a single quadrant, thus avoiding multiquadrant surgery and strategies of ligation or stent placement to limit aqueous flow.

The surgical technique used to implant the single-plate Ahmed valve is similar to that used for a single-plate Molteno.^{201b} A fornix-flap conjunctival peritomy is made in either of the superior quadrants, extending approximately from the 12 o'clock meridian to the horizontal meridian. (Inferonasal placement can be performed in an identical fashion, with adjusted orientation of muscles and clock hours.) Often a 6-mm relaxing incision is made parallel to the edge of a horizontal muscle, maximizing exposure

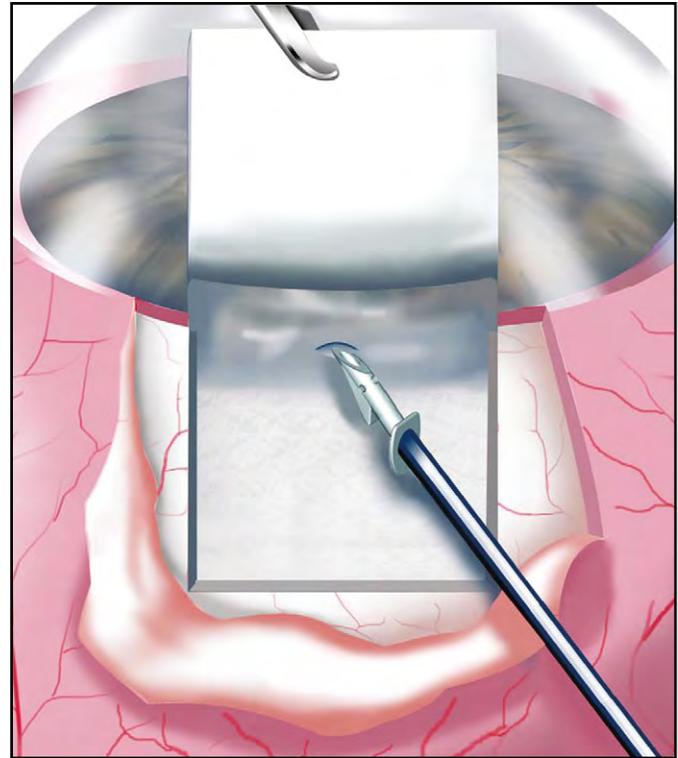


Fig. 34-37 Placement of Ex-PRESS implant on its delivery stent, into angle, under standard trabeculectomy flap. (Courtesy of E Dahan.)

of the quadrant for plate placement. The conjunctival–Tenon's flap is undermined with blunt dissection using Westcott scissors. If desired by the surgeon, pledgets soaked in mitomycin-C (5 μm/ml) are placed beneath the undermined conjunctiva for 5–8 minutes. After the pledgets are removed, the subconjunctival area is copiously irrigated.

The Ahmed valve is removed from its package and its tube primed by a retrograde flush of saline through a 30-gauge cannula, into the free end of the silicone tube, thus priming the valve system imbedded in the plate. This maneuver is unique among glaucoma drainage devices, and cannot be overlooked. The implant is positioned posteriorly in the exposed quadrant, with the anterior edge of the plate 8–9 mm posterior to the limbus. Two #6-0 Mersilene sutures are passed through the two eyelets on the anterior edge of the plate to secure the device to the sclera. A paracentesis is made and a dollop of viscoelastic is injected into the angle, pushing the iris root posteriorly, at the intended site for tube placement. A 23-gauge disposable needle is attached to the viscoelastic syringe and bent, bevel up, to an angle of about 120°. The needle is passed through the sclera 2–3 mm behind the limbus, aiming for the mid angle and parallel to the iris plane, trailing viscoelastic upon the needle's retraction to lubricate the tube's insertion. (In an inferonasal placement while the surgeon sits at the 12 o'clock position, the 23-gauge needle needs to be bent into an 'L-shape' or 'Z-shape' to access the anterior chamber parallel to the iris plane.) The length of silicone tube is assessed by laying the tube upon the cornea and trimming it bevel up, so that it will extend 2–3 mm into the anterior chamber. Using smooth forceps, the trimmed silicone tube is inserted through the 23-gauge opening into the anterior chamber, to lie equidistant between iris and cornea. (If the tube kinks and fails to enter the anterior chamber



Fig. 34-38 The standard single-piece Ahmed S-2 model (lower part of figure) is capable of connection to an additional plate (upper part of figure) with a tube, doubling filtration capacity.

through its tunnel, an iris spatula brought across the anterior chamber and out through the tunnel can be inserted within the tube as an internal stent guide for threading the tube forward.) In pseudophakic eyes, the tube can sometimes be insinuated to lie between the intraocular lens and the overlying iris. The tube is then covered with either donor sclera, pericardium, or dura mater. The conjunctiva is brought back to the limbus and sutured with #8-0 Vicryl for a water-tight closure. Double-plate Ahmed devices (Fig. 34-38) are inserted as above, with the additional steps of exposing an adjacent quadrant, connecting a tube between two plates, placing the tube over the superior rectus muscle, and securing the additional plate to the episcleral surface.

Clinical experience with the Ahmed valve has produced pressure-lowering results that are similar to those of other implant devices. It has been demonstrated to provide comparable midterm IOP lowering to what is seen with Baerveldt implants,²⁰²⁻²⁰⁴ Molteno devices,^{152,206} and even trabeculectomy with mitomycin-C.²⁰⁷ Postoperative complications associated with overfiltration appear to occur less frequently with the Ahmed implant than with other alternatives.²⁰⁸ Recent 5-year results with a single Ahmed plate in refractory glaucomas demonstrated a respectable 50% success rate.²⁰⁹ Nevertheless, the tendency for a larger drainage surface area to correlate, up to a certain size, with lower IOP over the long-term²¹⁰ has resulted in the propagation of the double-Ahmed plate system, whose surface area is comparable to the double-Molteno and 350-mm² Baerveldt implants, and whose insertion time is comparable.

BAERVELDT IMPLANT

The Baerveldt implant incorporates many of the design features of the Molteno device, but the Baerveldt plate is comprised of soft silicone material. The resultant flexibility and low profile allow easy insinuation of the implant posteriorly into a quadrant, with

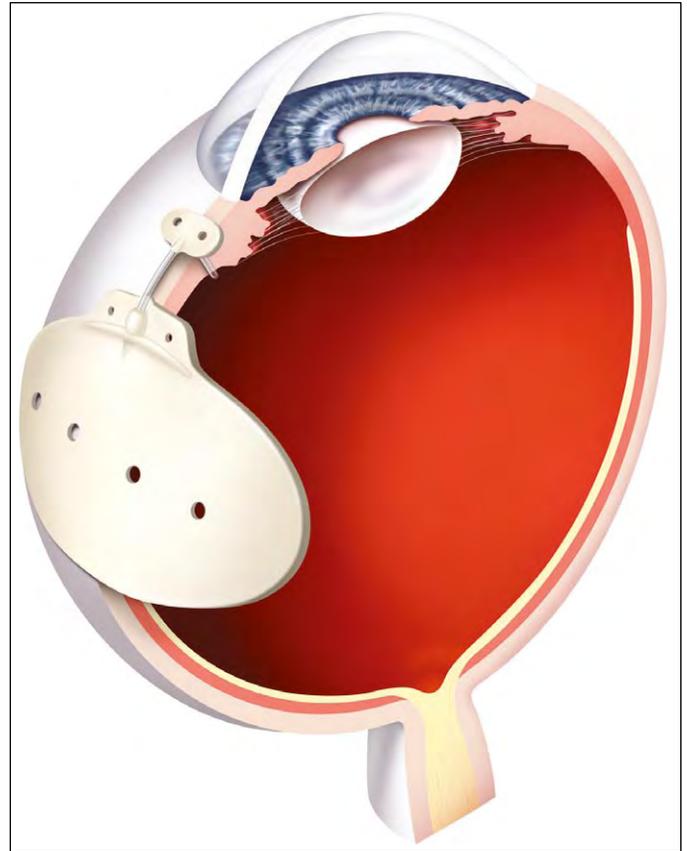


Fig. 34-39 Baerveldt pars plana implant, whose tube makes a 90° entry through the Hoffman elbow, and is secured over the vitreal base 4 mm from the limbus.

the wings of the plate slipping beneath the adjacent muscles. Adult glaucomas are usually managed with the 350-mm² implants; a larger 500-mm² Baerveldt was discontinued after it showed limited efficacy.^{210,211} The smaller 250-mm² device is available for small eyes, such as in children or eyes with retinal buckles, when the larger 350-mm² plate cannot fit; or in eyes with presumed limited aqueous production, such as in uveitic glaucoma (Fig. 34-40).

The implantation technique is similar to the Molteno implant, with both devices requiring special maneuvers to temporarily obstruct flow in the early period. This can be achieved either with an internal stent (e.g., a long #3-0 Prolene suture placed into the tube, and secured subconjunctivally in an inferior quadrant for later extraction at the slit lamp), or with external tubal ligation (e.g., #7-0 Vicryl suture for spontaneous release). The results of the two devices are similar.²¹¹⁻²¹⁵ The development of the Hoffman-elbowed pars plana Baerveldt device (Fig. 34-39) has been particularly useful in eyes undergoing vitrectomy (e.g., for diabetic hemorrhage and neovascular glaucoma) or in eyes with corneal grafts. (A pars plana design is also available for the Ahmed implant (Fig. 34-41).)

RESULTS AND COMPLICATIONS OF DRAINAGE DEVICES

By and large, glaucoma drainage devices are employed under two circumstances by most experienced surgeons: (1) as a 'back-up' procedure after prior ocular surgery (e.g., failed trabeculectomy, retinal detachment procedure, etc.) has left superior conjunctival adhesions,

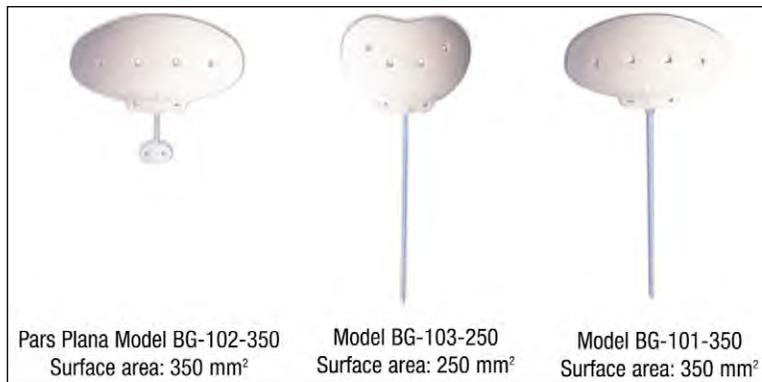


Fig. 34-40 Currently available Baerveldt implants: pars plana implant (350 mm²) (left), small (250 mm²) (center), and standard (350 mm²) (right).

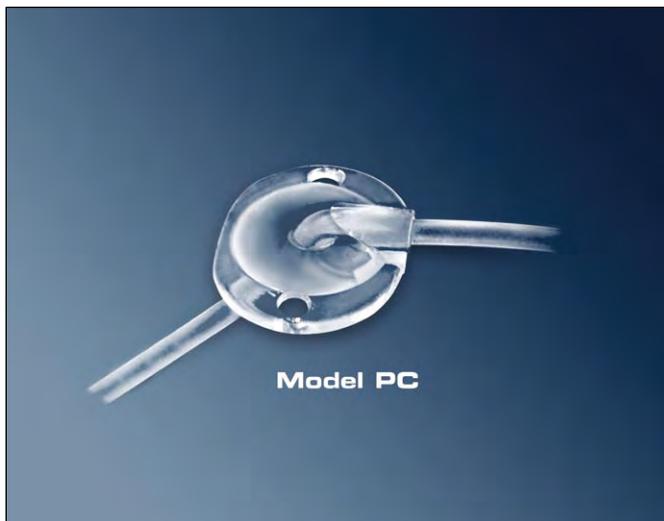


Fig. 34-41 The tube of the standard Ahmed S-2 can be connected to the 'PC' deflection plate for pars plana insertion, which avoids kinking.

precluding a successful repeat trabeculectomy; or, (2) as the initial procedure for secondary glaucomas (e.g., uveitic or neovascular glaucoma) where the surgical goal may simply be to achieve an IOP in the upper-normal range with reduced medications. Trabeculectomy with antimetabolites is usually preferred as the first surgical choice when, in the face of progressive or severe visual field and optic nerve damage, a target pressure range in the subnormal range of 10–14 mmHg is required for the long term. Glaucoma drainage devices greatly augment the surgeon's armamentarium to control the IOP – especially after failed trabeculectomies – but they rarely consistently deliver the very low IOPs needed to stabilize advancing primary open- or chronic angle-closure glaucoma.

The results of follow-up studies for glaucoma drainage devices are difficult to generalize from, often because complicated cases (e.g., neovascular glaucoma, aphakic glaucoma, or advanced developmental glaucoma, etc.) are being treated in a non-randomized manner.^{153c} Specific numbers defy comparison because diagnostic criteria, study entry criteria, procedures, and definitions of success vary tremendously. Nevertheless nearly all eyes in these studies have uncontrolled, elevated pressures and are threatened with visual loss; as with most complex and secondary glaucomas, the emphasis is on IOP control and vision retention rather than disc and visual field function. Glaucoma drainage devices of all varieties can usually palliate these diseases and preserve some vision in otherwise hopeless cases.^{131,181,215,216}

Generally speaking for this class of devices, approximately 60–80% of treated eyes maintain pressures below 22 mmHg at 1 year, when most failures manifest.^{149,202,204} For example, a long-term study of Molteno implants discriminated between 'complete success' (i.e., IOP < 22 mmHg without medications) and 'qualified success' (i.e., IOP < 22 mmHg with medications): at nearly 4 years' follow-up, two-thirds of eyes were 'qualified successes.'¹⁵⁰ A retrospective analysis at 2 years' follow-up of Baerveldt 350-mm² cases distinguished differential success rates with different types of glaucoma: approximately 80% of both primary open-angle glaucoma and neovascular eyes showed IOPs reduced by greater than half of their presenting IOP – in contrast to only 50% of the uveitic and the miscellaneous glaucomas showing comparable IOP reduction – though nearly all groups reduced their medications.¹⁵¹ In one study of the Ahmed implant, eyes which received single plates showed an 87% success at 1 year and a 75% success at 2 years in reducing IOP to less than 22 mmHg, with fewer medications.²¹⁸ As mentioned earlier, a recent study of single-plate Ahmed surgery in refractory glaucomas reported a 5-year 50% qualified success rate, defined as IOPs < 21 mmHg or minimal 15% reduction of baseline pressures, with medications.²⁰⁹ Another study found nearly identical results at 1 year for both Baerveldt 350-mm² and Ahmed implants, demonstrating two-thirds of eyes reduced IOP by 30% with or without medications – and with identical low rates of postoperative hypotony for both devices.²⁰³ Thus it appears there is remarkable equivalency of results among the various glaucoma drainage devices in use, without any demonstrable advantage or drawback to any implant of the surgeon's preference.

Some of the complications of glaucoma drainage implants have been mentioned above; specifically, strategies to avoid postoperative hypotony, and corneal decompensation. The sequelae of a prolonged shallow or flat anterior chamber, such as synechial adhesions, cataract acceleration, choroidal detachments, etc., are unwelcome but familiar complications of any intraocular glaucoma surgery.²¹⁹ 'Generic' complications, such as epithelial downgrowth, endophthalmitis, and retinal detachment, have all been documented with drainage devices.^{220–222}

Motility problems resulting in diplopia have been reported with nearly all glaucoma drainage devices, large and small. This has been ascribed either to mechanical involvement of the superior oblique muscle if the implant impinges on the superonasal quadrant, or to the elevated space-occupying bleb that can form over the plate, causing restriction and muscular limitation.^{223–224} Interestingly, with the four-holed fenestration of the Baerveldt silicon plate – allowing pillars of fibroblastic proliferation to grow from the episcleral surface through the plate and up to the inside of the bleb dome, thus

contracting the overall height of the bleb – this problem has been clinically less pronounced, and this design incorporated in newer models of other drainage devices.

An intriguing phenomenon of elevated IOP after drainage implants has been described as the ‘ocular hypertensive phase,’ occurring 1–3 months following surgery with a variety of devices. This is not to be confused with elevated pressure due to early postoperative complications, such as aqueous misdirection, tube retraction, or obstruction of the intracameral tube lumen by vitreous, blood, or iris.²¹⁸ Molteno, in justifying his two-stage surgical approach, had postulated that when aqueous encounters the conjunctival tissue surrounding a plate in the immediate postoperative period – as with a one-sitting insertion of an unobstructed glaucoma drainage device – capsular fibrosis is affected and a relative thickening to transudation occurs, manifesting in an inflamed bleb and sustained IOP elevation.¹³⁷ Such an ‘ocular hypertensive’ phase was described in over 80% of eyes with Ahmed plates (a one-sitting insertion with early aqueous contact with the bleb conjunctiva) as peaking at the first month and subsiding by 6 months.²²⁵ Some have advocated placing the plate above the Tenon’s tissue and yet subconjunctivally, to reduce this problem.¹⁵⁴

Sometimes this ‘remodeling ocular hypertension phase’ is difficult to distinguish from a secondary steroid-induced IOP elevation, described both after trabeculectomy and glaucoma drainage surgeries.²²⁶ Temporary reinstatement of a topical glaucoma regimen often allows the IOP to return to a lower level within a few months, and can be titrated over time.

Regrettably, only a few late complications are amenable to surgical correction: tube retraction can sometimes be reversed by using tube extenders,^{227,228} and a migrating plate can sometimes be addressed with repeat episcleral anchoring sutures. Late-occurring

problems with drainage devices and their blebs are frustrating to manage. Any exposure of the device has a poor prognosis for successful repair. Device exposure can manifest either as frank plate extrusion from conjunctival breakdown (e.g., in eyes with pediatric glaucoma²²⁹ or active uveitis^{230,231}) or as focal erosion of the tube through overlying covering material (e.g., donor sclera or pericardium) and its overlying conjunctiva. Repair can be attempted, but recurrence of tissue breakdown is common. Late bleb encapsulation, months after surgery, is particularly frustrating, and rarely responds either to bleb needling (with or without 5-FU injections) or to surgical bleb revision with antimetabolite. Frequently an additional glaucoma procedure, such as implanting another drainage device inferonasally, or initiating laser cyclodestruction, is necessary.

As this revision of our text is written, an important multi-center, multi-year comparative study of the “Tubes vs. Trabeculectomy Study” is in progress.^{232,233} It was designed to address the common clinical quandary of which surgical approach is best for a previously operated eye (either cataract surgery or failed trabeculectomy) with uncontrolled glaucoma: a Baerveldt 350-mm² glaucoma drainage device or a trabeculectomy with mitomycin-C? Preliminary one-year data suggests that pressure control <13 mmHg was comparable between the two groups of >105 eyes each, with slightly more medications in the tube group – but with a cumulative probability of failure of 13.5% with trabeculectomy vs. 3.9% with the shunt. Serious complications resulting in vision loss or re-operation were comparable between the two groups. Although there of course remain many outstanding questions regarding the role of glaucoma drainage devices vs. trabeculectomy – such as their comparative efficacy in virgin eyes, or how other devices such as the Ahmed might compare – such an ambitious and complex multi-year study will prove of great value to all clinicians.

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CHAPTER
35

Surgical management of cataract and glaucoma

The primary issue with regard to cataract surgery and glaucoma surgery in the same eye is how to position the cataract operation in the management scheme of the patient's condition. Is it better to choose one sequence and type of surgery before the other, or to combine the two procedures? Although this has been a matter of unresolved controversy, the choice of surgery has been dramatically influenced in the past two decades by three significant and independent advances. The first is the evolution of ever more refined small-incision phacoemulsification techniques and small-profile intraocular lens (IOL) implants – thus allowing for smaller wounds, less postoperative inflammation, and choices for surgical entry sites. The second advance is the demonstrated advantage of using antimetabolites to enhance filtration surgery. Third is the availability of novel glaucoma procedures – non-penetrating glaucoma surgeries¹ and endocyclophotocoagulation² – which have also been combined with small-incision cataract surgery. Together these auspicious developments have resulted in a panoply of surgical solutions far superior to what was available to our patients a generation ago.

Despite the wider spectrum of surgical options, however, the quality of clinical reports, in terms of their epidemiologic and methodological rigor, leave much to be desired.³ In the absence of firm, evidence-based data, personal clinical experience and preference dominate the decision-making process.

CATARACT SURGERY IN THE GLAUCOMATOUS EYE

Glaucoma and cataract often occur together, especially in the elderly, and each condition can influence management of the other. Progressive lens change can mimic progressive visual field loss, reduce visual acuity, and narrow the drainage angle. Glaucoma medications that cause miosis can aggravate visual impairment from cataract; and the now rarely-used anticholinesterase class of miotics can accelerate the development of cataracts. In addition, prior glaucoma surgery leads to a clinically significant acceleration of cataract morbidity in the years following trabeculectomy.⁴ Thus each of these diseases must be considered when treating the other.

The first consideration is which specific type of glaucoma is being treated; different diseases have different surgical outcomes and complications. Next is the decision regarding the sequence of procedures. Unless a minimal and unpredictable long-term IOP-lowering effect of 2–4 mm is deemed sufficient for glaucoma control, cataract extraction alone is usually insufficient to address the pressure-lowering (or medication-reduction) needs of the glaucomatous eye.⁵ Some advocate that either a cataract or filtration procedure

be done first and separately; others recommend combination surgery in one procedure. Here, too, results differ between phacoemulsification and extracapsular cataract extraction (ECCE) procedures, as well as whether and how antimetabolites are used. However, rigorous evaluation of the literature on techniques and timing for cataract and filtration surgery has failed to demonstrate convincing evidence of an unequivocally superior approach. Nevertheless, suggestive trends (such as use of mitomycin-C, separate incision sites, and phacoemulsification rather than ECCE) were discerned.⁶ Similarly, surgical alternatives such as trabeculectomy,^{2,7–9} and both older and newer forms of non-filtering trabecular surgery^{11–13} have been used to control IOP at the time of cataract surgery, but all such reports lack sufficient statistical rigor.

Other considerations are important in individualizing treatment for a given patient. Such issues include the efficacy of and compliance with the current medical regimen, the financial costs or possible side effects of the medical regimen, the chosen target pressure for the eye, the surgeon's skill and experience, the status of the optic nerve and visual field, and the visual requirements and quality of life that the patient desires to obtain. Every effort should be made in the preoperative evaluation to distinguish between the cataractous and glaucomatous components of a patient's visual status. This requires dilation for visual field studies, cataract inspection, and detailed ophthalmoscopy.

TYPES OF GLAUCOMA AND THEIR INFLUENCE ON CATARACT MANAGEMENT

In the absence of peripheral anterior synechiae, eyes with cataract, glaucoma, and progressively *narrow angles* may respond to approaches other than a combined procedure. Lens size increases with aging and can further narrow an already compromised angle. Laser iridotomy in such patients may facilitate IOP control by relieving any pupillary block component and allowing the angle to widen. Many such patients with primary angle-closure glaucoma (PACG) often show a significant improvement in their IOP control after cataract removal, implying that there is some phacomorphic component to their underlying disease, even in the presence of an iridotomy.^{14–16} Accordingly, if a non-Asian patient with PACG presents with relatively good IOP control on minimal medical therapy and evidence of greater than 50% available trabecular meshwork, it may be sufficient to proceed with cataract extraction and IOL implantation alone,¹⁷ reasonably anticipating a good chance that the glaucoma will remain controlled, if not improved.

An alternate approach combining phacoemulsification with goniosynechialysis has also been advocated, avoiding filtration surgery.¹⁸

Diabetic eyes with primary open-angle glaucoma risk worsening of their ocular health after cataract surgery, with or without lens implantation. In the days of intracapsular cataract extraction, the incidence of neovascular glaucoma was reported to be as high as 9% after intracapsular surgery, a rate nearly identical to that reported for neovascular glaucoma after ECCE surgery in the presence of either an inadvertent or deliberate capsulotomy (11%).¹⁹ These rates are in contrast to the much-reduced risk of a rubeotic glaucoma in the presence of an intact capsule. Often, violation of the capsule is unavoidable at the time of cataract/IOL surgery; later it may be unavoidable because of the need for a capsulotomy to maximize either vision or ophthalmologic visualization of the fundus.

Similar findings were reported in a large retrospective study of large-incision ECEE cases in which an important distinction was made as to whether proliferative diabetic retinopathy was present before cataract surgery. If present, there was a 40% rate of neovascular glaucoma and a greater than 20% rate of vitreous hemorrhage related to the cataract extraction.²⁰ Every effort should be made to address a preproliferative retina with panretinal photocoagulation before cataract extraction. In the presence of actual iris neovascularization or proliferative retinopathy, reports on the efficacy of intravitreal bevacizumab (Avastin™) for temporarily inducing neovascular regression in the anterior segment (and by implication its potential utility in the preoperative setting) are encouraging.^{21–24}

Although immediate postoperative problems with fibrin formation and hyphema are seen, the overall success rate for both visual improvement and IOP control is still good in the eyes of diabetic patients.²⁵ There is, however, a higher likelihood of developing pupillary block glaucoma in such eyes.²⁶ Although peripheral iridectomy is currently not routinely performed by most lens implant surgeons (especially with temporal corneal incisions), it is highly advisable that either surgical iridectomy, or access for a postoperative laser iridotomy, be considered in planning cataract surgery in patients with diabetic retinopathy.

Patients that present with *pseudoexfoliation* are certainly more prone to develop cataracts and have a much higher association of glaucoma (as well as subtle systemic anomalies²⁷) which must be detected before cataract extraction is undertaken.^{28,29} Many features of the eye with pseudoexfoliation make cataract surgery particularly challenging, including (1) a tendency toward incomplete mydriasis, with a subsequent small pupil that can complicate cataract extraction; (2) a tendency toward multiple surgical challenges – phacodonesis, lens subluxation, zonular laxity or dehiscence, and capsular rupture with lens dislocation and vitreous loss³⁰; (3) a cornea that may be more vulnerable to endothelial damage; (4) a tendency toward hyphema during surgery, and (5) a tendency for unreliable zonular integrity, such that even an in-the-bag lens implant can displace into the vitreous.³¹ Undiagnosed lens subluxation from weak zonules is often noted intra-operatively,³² but when this condition is anticipated, good results are nevertheless possible with careful phacoemulsification,³³ judicious use of viscoelastics, pupillary retractors, capsular tension rings and other advanced cataract techniques.³⁴

Eyes with *uveitic glaucoma* embrace a wide spectrum of diseases and perisurgical responses. Although cataract/IOL surgery can be performed without incident in eyes with Fuchs' heterochromic uveitis,³⁵ other reports have observed several specific features of this condition that bear directly on the management of cataractous eyes.³⁶ In more than 103 patients with this condition, some 25% had open-angle glaucoma.³⁷ However, many patients developed

persistent inflammation and peripheral anterior synechiae, rubeosis of the iris and angle, pupillary block, and recurrent hyphemas. When these patients underwent glaucoma surgery, more than half failed standard filtration operations (in the absence of antimetabolites). Similar problems may arise in eyes with other conditions of chronic uveitis and secondary glaucoma. The underlying inflammatory condition, rather than the glaucoma, is responsible for a host of potential postsurgical complications from combined surgery: filtration failure, accelerated posterior capsular fibrosis, cystoid macular edema (CME), fibrinous iritis, etc. Maximal perioperative control of inflammation is essential.³⁸

Occasionally a loose or subluxed lens resulting from *traumatic* rupture of some of the zonules can be appreciated. In such cases, the lens can shift forward, increasing pupillary block and narrowing the angle. This may be suspected if the chamber is shallow unilaterally, if there is a history of trauma, or if any iridodonesis is evident. In such cases, cycloplegia can deepen the chamber, widen the angle, and allow the surgeon to detect vitreous anterior to the lens if true subluxation exists. Laser iridotomy can be attempted to improve glaucoma control in these eyes, performed away from any area of vitreous prolapse. As with traumatic cataracts, such surgical situations may require complex maneuvers: lensectomy with vitrectomy; capsular tension rings and pupillary retractors; sulcus-IOL support, etc.³⁹

If the angle is open and the cornea healthy, anterior chamber IOL implantation is an option. An alternative is scleral fixation of a posterior chamber IOL behind the iris plane after vitrectomy or loss of the capsule.^{40–45} This challenging option should be reserved for surgeons skilled in this procedure. Many complications with this technique have been reported in patients undergoing penetrating keratoplasty, including CME, glaucoma exacerbation, and decentered IOLs.^{46,47} This higher-risk profile merits caution when surgery in the glaucomatous eye is being considered.

SELECTING THE APPROPRIATE SURGICAL APPROACH

For the vast majority of patients with glaucoma and visually significant cataract, there are three choices:

1. Undergo cataract extraction alone, and pay no surgical attention *per se* to the glaucomatous condition;
2. Undergo glaucoma filtering surgery first and allow full healing before undergoing a second operation for cataract removal;
3. Undergo a single combined cataract and IOL implantation operation at the time of the glaucoma filtering procedure.

Before cataract extraction, it is important to achieve the best possible IOP control, which is defined as a tolerable medical regimen that meets the target pressure, preserving the optic nerve and visual field from progressive worsening. Maximal presurgical therapy also includes the application of selective^{48,49} or argon laser trabeculoplasty,^{50,51} whose beneficial effects are not likely to change after cataract surgery.

Cataract surgery alone cannot be expected to provide clinically meaningful IOP control.^{4,52} Whether using phacoemulsification or ECCE with IOL, the long-term pressure reduction after cataract surgery is in the order of 2–4 mmHg,^{16,53–55} with the great majority of eyes requiring the same or an increased glaucoma medical regimen after 1 year.^{56,57} In a patient with minimal disc and field change and reasonably well-controlled IOP on a simple medical

regimen, these findings may suggest a course of cataract extraction alone. An attractive approach is to proceed with a temporal, clear-corneal phacoemulsification or small-incision ECCE procedure⁵⁸; these approaches for cataract-only surgery will not adversely impact later filtration surgery if needed, since the superior conjunctiva remains untouched. In summary, pre-cataract IOP control in glaucoma is unlikely to be lost after cataract-IOL surgery alone and may be, at least, temporarily improved.

Another option is that the glaucoma be surgically addressed first and cataract extraction subsequently undertaken.⁵⁹ In the presence of marginal cataractous changes or of a complicated glaucoma that has resisted IOP control by medications or prior surgery, establishing successful filtration may well be the first priority. The question is what effect later cataract surgery may have on an established, successful filter.

Most studies report a high likelihood for a subsequent cataract procedure to compromise a pre-existing filter, with a bleb failure rate as high as 30–40% after lens surgery.^{60–63} This phenomenon was reported even with a clear corneal cataract approach designed to avoid disrupting the conjunctiva.⁶³ This suggests that the inflammation caused by lens extraction is detrimental to long-term bleb survival – although the presence of a bleb is helpful in blunting the post-cataract IOP spike.⁶⁴ Whether the survival of a pre-existing bleb can be enhanced by intraoperative needling or perioperative applications of topical mitomycin-C or subconjunctival 5-fluorouracil (5-FU) has not been systematically studied. Reports of the effect of phacoemulsification-IOL procedures, even performed temporally, uniformly conclude that there is some adverse effect on pre-existing glaucoma control: an increase in postoperative IOP, an increased need for glaucoma medications, or alterations in bleb morphology.^{65–68} It is therefore realistic to anticipate loss of some IOP control from a pre-existing filtration surgery, to a greater or lesser extent, if the eye later undergoes cataract surgery by either ECCE or phacoemulsification, with or without antimetabolite supplementation of the original bleb.

The arguments for combining trabeculectomy with cataract extraction are persuasive on many grounds. In the absence of pre-existing retinal disease, there is every expectation that excellent visual acuity will be obtained in the overwhelming majority of patients.^{69,70} Although trabeculectomy in a combined cataract surgery may not be as effective in lowering the IOP when compared with trabeculectomy performed alone, the combined procedure nevertheless provides long-term lower IOPs than when cataract surgery is performed in a glaucomatous eye without filtration.^{4,52,71–76}

The decision for a combined surgery is not formulaic, and requires a blend of multiple considerations, both positive and negative. We commonly encounter variations of four basic situations, which often present in combinations unique to each eye. These scenarios are:

1. Cataractous loss of acuity in an eye with glaucomatous disc or visual field changes, unreliably maintaining IOPs below a designated 'target range' despite medical or laser management.

2. Cataractous loss of acuity in an eye requiring medications, where faulty compliance with, allergic sensitivity to, or unsustainable cost of medical therapy recommend a surgical solution to IOP management.

3. Cataractous loss of acuity in eye with far advanced visual field loss near fixation or with extensive disc damage, which despite adequate IOP control, nevertheless would be at risk

following cataract surgery alone: either at risk for precipitous deterioration by any potential IOP spike, or whose maximal utilization of topical medications precludes additional agents should IOPs rise postoperatively.

4. Uncontrolled glaucoma in an eye with borderline clinically cataractous changes, anticipating accelerated cataract progression following filtration surgery.⁴ Such situations might include either the patient's preference for a single operation rather than a two-staged surgery, or the patient's physical frailty (usually elderly with multiple medical problems) meriting a single surgical intervention.

As always with any surgery, benefits and risks need be weighed and disclosed: for example, a combined phaco/filter usually requires a longer interval for visual rehabilitation than cataract alone; a trabeculectomy alone usually provides lower IOPs than a combined procedure – yet subsequent cataract surgery often adversely affects prior filtration control.⁷⁸

A particularly compelling argument for a combined procedure is to protect the glaucomatous eye as much as possible from the likelihood of significant IOP elevations after cataract surgery when performed alone. There is ample evidence for cataract extraction causing significant pressure spikes in glaucoma. One series reported a 2.5 times greater incidence of elevated IOPs in the absence of trabeculectomy than when the combined procedure was performed⁵⁵; this protective advantage of the concomitant trabeculectomy has also been reported by others.⁷² Pressure spikes have been detected in nearly two-thirds of patients with pre-existing glaucoma undergoing cataract surgery, in contrast to 10% of normal eyes.⁵⁶

Nevertheless, the combination of trabeculectomy with cataract extraction does not guarantee the absence of a pressure rise. Krupin and co-workers⁷⁹ investigated the IOP course in glaucomatous patients who underwent ECCE with or without a concomitant trabeculectomy. They reported an alarming IOP rise on the first day after surgery among the ECCE-only eyes; an IOP rise of 10 mmHg or more occurred in 69% of patients, with three-quarters of those eyes measuring an absolute IOP over 25 mmHg. Of the patients undergoing ECCE + trabeculectomy, 14% showed an IOP rise of 10 mmHg or more. Of these, 21% showed an IOP over 25 mmHg. Such patients may continue to show IOP fluctuations for several months after ECCE surgery, and close surveillance is warranted.^{79,80} Similar IOP spikes have also been reported in up to 40% of eyes using phacoemulsification combined with trabeculectomy and mitomycin-C.⁸¹ It should be understood that a combined procedure can definitely reduce, but not predictably eliminate, the problem of intermittent IOP elevations.

SELECTING THE APPROPRIATE PROCEDURE: HISTORICAL CONSIDERATIONS

There are few more dramatic illustrations of evolutionary changes in glaucoma surgery in the past quarter-century than the literature on combined cataract and glaucoma surgery. This reflects the advent both of antimetabolite therapy in filtration surgery and of small cataract incisions, in which the same 3–4-mm wound is used for phacoemulsification, IOL insertion, and filtration. Because a spectrum of equipment and techniques may be available to the surgeon at different times, it is useful to understand the results of key technical variations in the development of combined procedures.

By the end of the 1980s, the efficacy of the combined *ECCE + IOL + trabeculectomy* procedure had been established.^{70,82–84} Visual results were encouraging, IOPs were brought down to the mid- to high-teens in the majority of cases, and fewer glaucoma medications were required. It was also noted that long-term IOP control was often seen in the absence of anatomic blebs.

When *ECCE + IOL + trabeculectomy* was compared with *phacoemulsification + IOL + trabeculectomy*, the latter procedure was usually found to be superior. Phacoemulsification + *IOL + trabeculectomy* reliably resulted in better visual acuity, lower IOPs with fewer medications, fewer postoperative complications (e.g., postoperative IOP spikes), and more robust-appearing blebs.^{85–89} These advantages were usually ascribed to the smaller wound incision of the phacoemulsification site, where the filtration procedure was also performed.

When antimetabolites were used as adjunct to the combined procedures, there again seemed to be an advantage to a smaller wound. Surprisingly, when *ECCE + IOL + trabeculectomy + 5-FU* injections postoperatively were undertaken, there was no greater reduction of IOP than when 5-FU was not administered.^{90,91} In contrast, when *phacoemulsification + IOL + trabeculectomy + 5-FU* was performed, lower IOPs were usually (but not always⁹²) seen compared with a combined phacoemulsification + *IOL + trabeculectomy* procedure without 5-FU.^{93,94} This enhanced effect was also seen when the trabeculectomy was performed superiorly and the cataract incision made through the temporal clear cornea.^{74,76,95}

The choice of antimetabolite is also important, with mitomycin-C apparently conferring sustained and lower IOP reduction compared with 5-FU. When results of *ECCE + IOL + trabeculectomy + mitomycin-C* were reported, the IOPs were brought into the low- to mid-teens – better than when 5-FU was used with this procedure.⁹⁶ However, the *ECCE + IOL + trabeculectomy + mitomycin-C* results were not as good as with the phacoemulsification method: only 60% of *ECCE*-treated patients had visual acuity better than 0.5, and 15% showed significant astigmatism of greater than 2D against the rule.

In summary: unlike the valuable role of 5-FU as an effective antimetabolite when used with trabeculectomy alone, there is abundant evidence that 5-FU's efficacy is virtually nil when used with trabeculectomy at the time of any kind of cataract surgery.^{5,6,78} This is significantly different from the utility of mitomycin-C with either trabeculectomy alone or with combined procedures.

Low IOPs and good visual acuity results have been consistently reported with the *phacoemulsification + IOL + trabeculectomy + mitomycin-C* procedure,^{97,98} although some have doubted the contribution of the mitomycin-C in all cases.^{81,99} Intraocular pressures tend to run in the low teens, medications are virtually eliminated, and blebs tend to be large and functional. In two placebo-controlled, double-masked studies, the combined procedure with mitomycin-C was unequivocally more successful than no antimetabolite at lowering IOPs and reducing postsurgical glaucoma medications.^{100,101}

As with all filtration surgery combined with mitomycin-C, the complications of hypotony and bleb leaks are not uncommon, and higher rates of endophthalmitis may be associated with the thin, cystic avascular blebs that form.^{102–105} Risk factors that favor use of mitomycin-C include African-American patients, higher pre-surgical IOPs (over 21 mmHg), more than two pre-operative antiglaucoma medications, and diabetes.^{106,107}

SURGICAL TECHNIQUES FOR COMBINED PROCEDURES

It thus seems that the most advantageous factors for successful combined cataract and glaucoma surgery are a small wound (as in phacoemulsification) and a potent antimetabolite (mitomycin-C). The technology for the variety of combined glaucoma and cataract techniques is not universally available, however. This section surveys the technical aspects of performing the combined procedure, both with a small incision for phacoemulsification and with a larger *ECCE* wound.

GENERAL PREOPERATIVE CONSIDERATIONS

It is important to inform the patient that a combined cataract and glaucoma operation may take longer to heal than a simple *IOL* implant procedure. In the event that the patient is taking a carbonic anhydrase inhibitor and filtration surgery is undertaken, it is common to eventually discontinue the systemic medication postoperatively to enhance filtration; but this may risk possible loss of IOP control in the fellow, unoperated eye. Accordingly, the patient may have to consider that the decision whether to undergo filtration surgery in one eye may soon lead to filtration surgery in the other eye as well.

It is useful to stop any miotic several days before surgery, both to reduce postoperative inflammation and to allow maximal dilation for cataract surgery. Preoperative dilation in the clinic by the surgeon should provide information as to the maximum pupillary dilation that can be expected in the operating room. Other topical glaucoma medications can be used until the day of surgery. α -agonists, such as apraclonidine or brimonidine, when applied immediately preoperatively, may cause conjunctival vasoconstriction and thus enhance hemostasis. In conjunction with the patient's primary care physician, it may be advisable to preoperatively discontinue systemic medications, such as anticoagulants (aspirin, coumadin, etc.) or α_1 -adrenergic receptor agonists (e.g., tamsulosin, used for benign prostatic hypertrophy, and responsible for floppy-iris syndrome during cataract surgery),^{108–110} although most reports find discontinuing either class of drug irrelevant.^{111,112}

SMALL-INCISION COMBINED SURGERY

Many technical variations are available for small-incision* combined surgery, few of which have been rigorously evaluated in a prospective, controlled fashion. Often the selection is based on the surgeon's technical skill and experience in performing phacoemulsification surgery and in managing filtration surgery with antimetabolites (Box 35-1). The technique that we use is illustrated in step-by-step detail in Figures 35-1 through 35-13.

Incision sites

There is no demonstrated superiority with regard to whether the combined procedure should be performed using one small incision site for the cataract removal, *IOL* placement, and trabeculectomy or if separate surgical sites should be made.^{6,112b} Some have advocated a straightforward trabeculectomy superiorly, usually with an antimetabolite, and performing the cataract surgery separately from

* In this discussion, 'small incision' refers to phacoemulsification surgery – and not the small-wound *ECCE* surgery often performed in Nepal and elsewhere.^{58,161,162} That particular technique, when performed temporally, is fully compatible with a combined, two-site filtration surgery performed superiorly.

Box 35-1 Surgical decisions in small-incision combined cataract–glaucoma surgery

- Single vs. separate incision sites
- Fornix vs. limbal conjunctival flap
- Type of scleral incision: phaco tunnel vs. trabeculectomy flap
- Mitomycin-C use: When to apply? Concentration? Duration?
- Management of small pupil: Stretch? Iris hooks? Pupil expander? Large iridectomy?
- Phacoemulsification technique: Divide-and-conquer? Stop-and-chop?
- IOL type: Foldable IOL through small wound? Silicone or acrylic?
- Anticipating complications (no capsular support): Sulcus suture fixation? Anterior chamber – IOL temporarily?
- Scleral tunnel or flap closure: Anticipate laser lysis? Pre-place releasable sutures? Adjustable sutures?
- Immediate postoperative therapy: Topical glaucoma medications? Intravenous or oral carbonic anhydrase inhibitors?

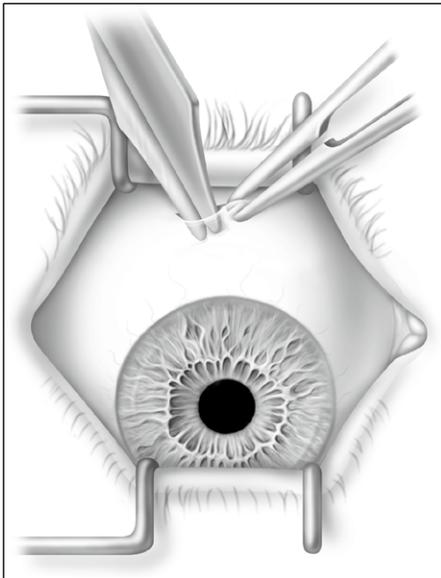


Fig. 35-1 Phacoemulsification + IOL + trabeculectomy + mitomycin-C. Preparation of a limbus-based conjunctival flap approximately 8 mm from the superior limbus, with dissection of conjunctiva and Tenon's tissue anteriorly to expose the superior 6 mm of the limbal tissue. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

a temporal, corneal approach.^{74,95,113–115} Others use the single incision for the entire procedure.^{97,98,100,101}

Fornix versus limbal conjunctival flap

Prospective assessments of the advantages of performing the combined procedure under a fornix-based or limbus-based conjunctival flap have shown few differences.^{89,116–120} As the standard approach to cataract surgery when performed alone, the fornix-based flap is a familiar technique; in contrast, the limbus-based flap may obstruct the view of the limbus during surgery, and assistance may be required to shift the conjunctiva back and forth. When antimetabolites are used, the fornix flap requires considerable attention to meticulous water-tight wound closure to minimize postoperative leaks. Conversely, the fornix flap has been associated with

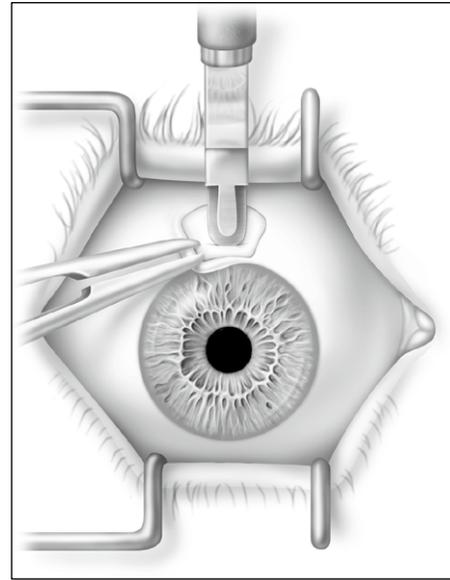


Fig. 35-2 Preparation of a standard phacoemulsification scleral tunnel, which is approximately 2 mm from the limbus surface posteriorly, 3.5 mm in width, and at a depth of one-half the scleral thickness. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

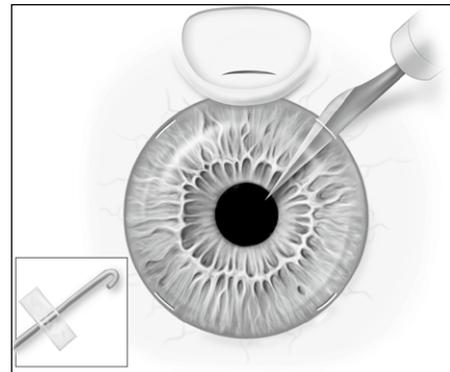


Fig. 35-3 If the pupil fails to dilate, four Prolene transcorneal iris retractors (inset) can be used. (The retractor shafts are available as either re-usable metal or disposable suture material, with rectangular sleeves of soft silicone.) Creation of four separate paracentesis 'stab wounds' with a 15° sharp blade anterior to the limbal vessels and with each insertion 90° apart allows placement of the retractors. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

blebs that appear non-cystic and less thin than those seen with the limbal flap.¹¹⁹

Scleral flap

Some surgeons fashion their small-incision phacoemulsification incisions beneath either the triangular or rectangular scleral flap used in routine trabeculectomy surgery. One of our two standard techniques is to fashion a non-frowned, scleral tunnel for the phacoemulsification

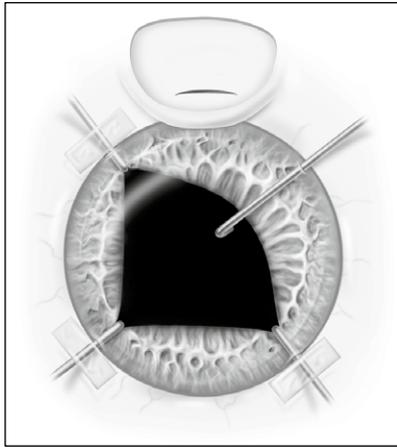


Fig. 35-4 Introduction of transcorneal iris retractors. Each hook is introduced to grasp the pupillary edge and pull it peripherally to the limbus. The large, square pupil is secured by sliding the clear plastic sleeves forward along the shaft of the retractor up to the limbus itself. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

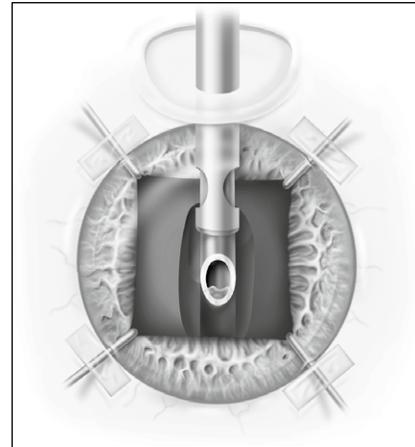


Fig. 35-5 With the enlargement of the pupil, a standard phacoemulsification can proceed, with capsulorrhexis and cataract removal. The superior iris is sometimes 'tented' between the two superior iris retractors; care is necessary to avoid trauma to the superior iris both when entering the eye and when intracamerally manipulating the phacoemulsification unit. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

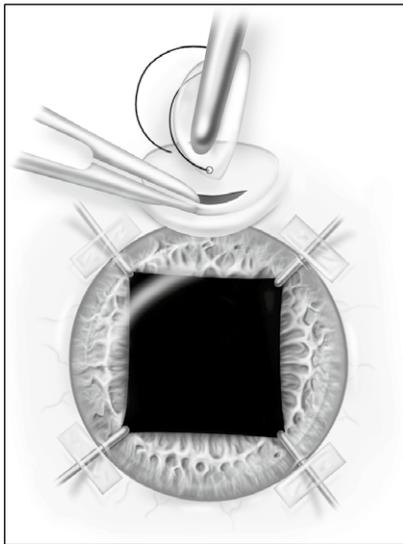


Fig. 35-6 After completion of the irrigation and aspiration of the lens, the foldable lens is placed through the scleral tunnel. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

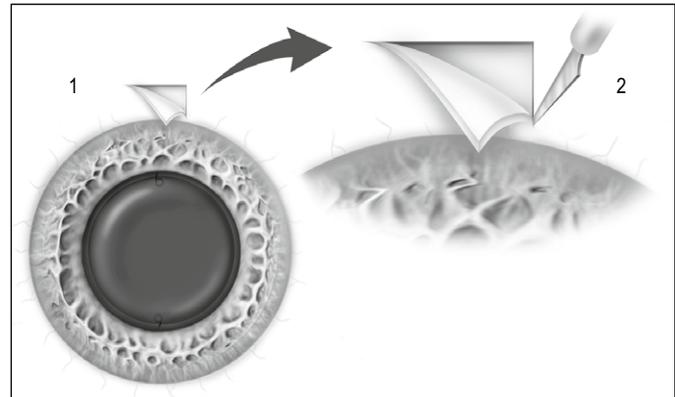


Fig. 35-7 After placement of the posterior chamber lens implant in the capsular bag, the surgeon converts the phacoscleral tunnel (1) into a non-standard trabeculectomy flap. This is simply fashioned by making a radial cut (2) from the corner of the scleral tunnel anteriorly to the limbus itself. (From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

under a limbal-based conjunctival flap, and later extend the 12 o'clock edge to the limbus, converting the cataract wound into a filtration site (see Figs. 35-1 through 35-13).^{97,121} Our other approach uses a fornix-based conjunctival flap: we construct the same scleral tunnel, but *without* cutting any radial incisions towards the limbus. Through this tunnel a trabeculectomy is made with a small scleral punch, so that the tunnel itself acts as a valve, reducing the occurrence of hypotony,^{122,123} as well as directs aqueous outflow posteriorly away from the limbus. The scleral tunnel construction advocated by Khaw at Moorfields,^{124,124b,124c} and illustrated in the previous chapter (Fig. 34-19), is compatible without any modification whatsoever for

phacoemulsification, which is performed prior to the use of the scleral punch.

Antimetabolite use

Although 5-FU is effective with trabeculectomy alone – either applied on a 5-FU saturated sponge (5mg/cc) to the surgical site,¹²⁵ or injected sub-conjunctivally post-operatively – this anti-metabolite confers virtually none of its bleb-sustaining effects when used during concomitant cataract surgery.^{5,6,78} In contrast, mitomycin-C has proven potent in combined surgeries. It was originally used in doses of 0.5mg/ml and applied for 5 minutes either over the trabeculectomy flap or in the scleral bed under the flap.¹²⁶ Others have found efficacy at lower doses and shorter durations (e.g., 0.25mg/ml applied for 2–3 minutes), with the parameters adjusted according to

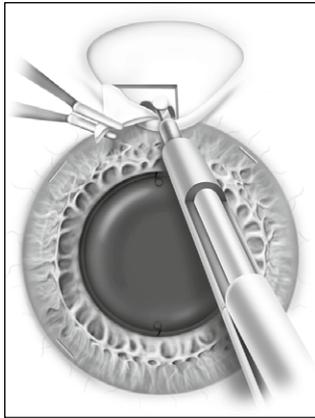


Fig. 35-8 At the phacoemulsification site at the limbus, a Descemet's punch is used to fashion the trabeculectomy stoma, which is approximately 2×2 mm in size.

(From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

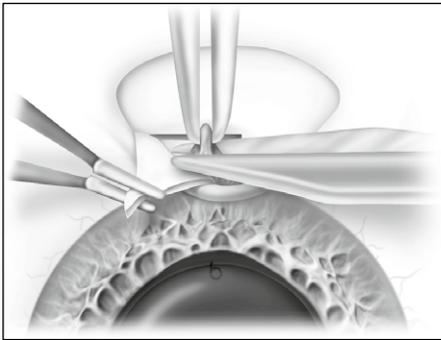


Fig. 35-9 A basal peripheral iridectomy is performed at the site of the trabeculectomy.

(From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

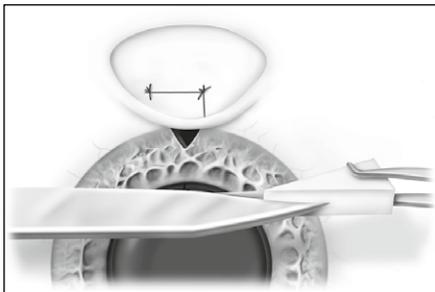


Fig. 35-10 After suturing the phacoemulsification wound with one 10-0 nylon suture at the corner and an optional suture along the length of the bed of the scleral tunnel, the surgeon prepares for the placement of the antimetabolite (either mitomycin-C or 5-FU). A sponge that is one-half the thickness of the triangular cellulose is cut parallel to the surface of the sponge (shown here), and this triangular element is again cut so that the triangular sides are approximately 4–5 mm in length. The sponge fragment is then saturated with the antimetabolite, using a few drops delivered via syringe and a small needle. Polyvinyl acetal (Meroce[®]) corneal shields can be cut in half and used as a non-shredding alternative to cellulose.

(From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

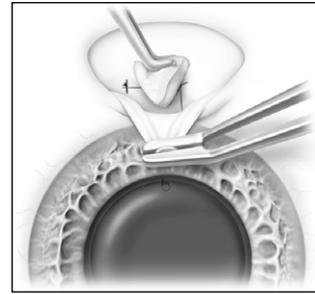


Fig. 35-11 The saturated cellulose sponge fragment is carefully placed over the trabeculectomy flap, with care taken to lift the Tenon's tissue and overlying conjunctiva on top of the saturated sponge but to avoid contact between the conjunctival wound edge and the sponge. Exposure of the antimetabolite to the wound depends on several factors but is approximately 1–5 minutes depending on the concentration and antimetabolite chosen.

(From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)



Fig. 35-12 After removal of the antimetabolite sponge from the area, followed by copious irrigation with saline solution, the limbus-based conjunctival flap is prepared for closure. Any excess Tenon's tissue is excised from the edge of the wound (shown here), but the excision need not be extensive.

(From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

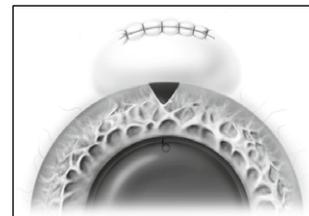


Fig. 35-13 With a meticulous running suture, preferably using a small-tapered needle (e.g., BV-100 on a 9-0 Vicryl suture), the wound is made water tight. This is verified by re-forming the anterior chamber, pressing adjacent to the bleb, and checking for bleb integrity.

(From Lieberman MF: Complications in glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1990.)

whether the risk of filtration failure is high (e.g., with previous surgery, uveitis).^{107,127–129} Although most surgeons prefer placement of the mitomycin-C over the surgical incision site before entering the anterior chamber, it can also be safely applied at the conclusion of the surgery before closing the conjunctival flap.^{97,100,121}

Managing the small pupil

A glaucomatous eye may fail to sufficiently dilate for optimal cataract removal for a variety of reasons: pupillary dysfunction (as in pseudoexfoliation); prior use of miotics; posterior synechiae to the anterior lens capsule following laser iridotomies, etc. Multiple approaches are available for the mechanical enlargement of the pupil.¹³⁰ Either a sector iridectomy (excising iris) or radial iridotomy (incising from the pupil to the iris insertion) can be performed, and optionally resutured at the end of surgery to restore a round pupil. Such techniques have optical benefits for the patient and may reduce the incidence of posterior chamber lens capture (Fig. 35-14).⁹⁷ Multiple, small, radial sphincterotomies under viscoelastic can be performed with scissors intraoperatively; in combination with mechanical stretching of the sphincter, this can result in a large enough pupillary diameter to proceed with surgery. Exaggerated mechanical stretching alone is often sufficient, using a two-handed technique with small iris hooks or notched instruments, opposed 180° apart and pulling the pupil to 8 mm or so along two to three axes.

Other surgical strategies include the introduction of devices designed to enlarge the pupil. For example, transcorneal iris retractors, made of either metal or Prolene suture material, can produce a square, 8-mm pupil that is ample for capsulotomy and management of the nucleus; these retractors can then be removed before or after lens implantation (see Figs 35-3 through 35-6).¹³¹ Devices such as the Graether pupil expanding system or the Beehler pupil dilator are also available.¹³² The Malyugin ring has been useful in this regard in our hands.^{132a}

Sufficiently enlarging the pupil is a critical step in the combined procedure. If the capsulorrhexis is not well visualized, capsular tears can result; this may in turn compromise the stability of the IOL or even allow for vitreous loss. If the pupil is too small during phacoemulsification, complications of capsular rupture and inadvertent iris emulsification may ensue.

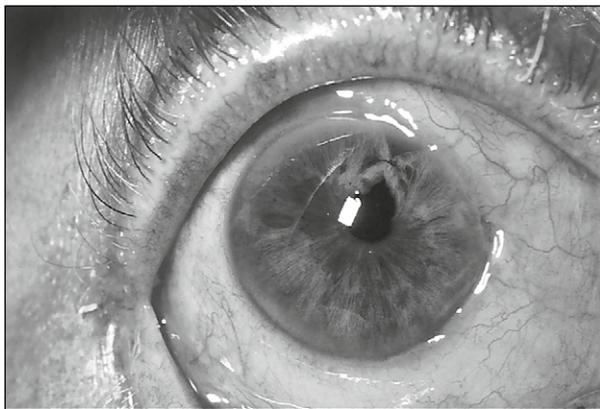


Fig. 35-14 This patient had combined cataract extraction with radial iridotomy and suturing of the pillars. There is an excellent bleb present. Over time, the iris pillars have torn slightly, leaving small gaps in the iris adjacent to the suture site.

Phacoemulsification techniques

A wide variety of techniques have been described to remove the nucleus in small segments (e.g., divide-and-conquer, stop-and-chop).^{132–134} Some techniques may be more suitable for the circumstances of a given eye; for example, eyes with angle-closure glaucoma may tend toward shallower anterior chambers, making in-the-bag phacoemulsification more appropriate than a technique that floats the nucleus up toward the pupillary plane.¹³⁵ What is crucial is that the surgeon performing the combined procedure be accomplished in standard phacoemulsification surgery before attempting it in conjunction with a trabeculectomy procedure in a glaucomatous eye.

Intraocular lens selection

Although some authors contend that smaller IOLs are superior to larger IOLs in the early postoperative period, there are virtually no differences in the final visual outcome or effect on glaucoma control between foldable IOLs (acrylic or silicone) and small-profile 5 × 6-mm all-polymethylmethacrylate lenses.^{88,136–144} In the event of zonular instability, a capsular tension ring can be introduced before completion of the phacoemulsification to stabilize the capsule.³⁴ If capsular rupture precludes an in-the-bag posterior chamber lens placement, suture fixation to the iris of a posterior acrylic IOL¹⁴⁵ or an anterior chamber IOL can be inserted, which may be well tolerated in eyes with open-angle glaucoma.¹⁴⁶

Trabeculectomy formation

There are several ways to excise the peripheral cornea and/or trabecular tissue beneath the scleral flap (e.g., free-hand scissor excision, Descemet 1-mm punch). A peripheral iridectomy is made to prevent iris occlusion of the trabeculectomy stoma, although some surgeons believe that deeper anterior chamber following cataract surgery makes occlusion unlikely; it is also unnecessary if a prior laser iridotomy is patent.

Flap closure

At the conclusion of the IOL implantation and the trabeculectomy incisions, the scleral flap should be tightened to permit sufficient easy aqueous outflow for pressure control, without shallowing the anterior chamber or precipitating hypotony. Although some surgeons deliberately construct their scleral flap so as to require one or no suture to close,^{147,148} most surgeons prefer stability of the eye – knowing that sutures can be easily relaxed postoperatively, but not easily replaced. With standard wound construction, a wide variety of releasable suture techniques have been described.^{100,149–153,153b} The Khaw technique allows postoperative transconjunctival adjustment of slip-knotted #10-0 nylon flap sutures at the slit lamp with a blunt forceps.¹²⁴ If either an argon or diode laser is accessible, the standard 9-0 or 10-0 black nylon sutures used to close the scleral flap can later be visualized for suture lysis.^{154,155} The use of mitomycin-C prolongs the postoperative window to several weeks, during which the sutures can be cut.^{156,157}

Postoperative medical management

Although the combined procedure is valuable in large part because it reduces the incidence and magnitude of IOP spikes after cataract surgery, IOP elevation may still occur. In one study that investigated strategies to reduce these elevations, the combined use of 500 mg of perioperative acetazolamide (Diamox™) and intraoperative acetylcholine (Miochol™) or carbachol (Miostat™) reduced pressure significantly more when both the oral and intraocular drugs were used than when either alone was used – yet 7% of the maximally

treated patients still experienced a mild pressure elevation.^{158,159} Perioperative β -blockers may be useful as well. Such precautions are especially indicated in eyes with advanced visual field loss encroaching on fixation. Any temporary decrease in aqueous formation in the first 24–48 hours will, in the presence of an anti-metabolite-treated bleb, be inconsequential in final bleb formation.

EXTRACAPSULAR CATARACT EXTRACTION COMBINED SURGERY

When phacoemulsification is not an option, as is often the case in the developing world, the combination of ECCE + IOL implantation + trabeculectomy can still be performed. Modified ECCE techniques that remove the nucleus through a small 6-mm wound, as described by Jaffe and co-workers¹³² or Blumenthal and co-workers,^{160,161} in combination with glaucoma filtration surgery and antimetabolite use apply identical principles as discussed above with phacoemulsification techniques, and with excellent results.¹⁶² Their relatively small incision, especially when performed temporally with a two-site strategy for trabeculectomy superiorly, confers the same advantage that combined phacoemulsification procedures have over 10–12-mm ECCE wounds. Temporal small-incision ECCE surgery is comparable to phacoemulsification in all respects,⁵⁸ and its precise steps easily learned using standard instruments.^{163,164}

For Western-trained surgeons used to the superior approach for ECCE surgery, the technique described by Gross¹⁶⁵ is easily adapted (Figs 35-15 through 35-23). Many of the decisions discussed above in relation to small-incision surgery must also be made with the ECCE combined procedure, but with slightly different concerns and details. It should be borne in mind, however, that 5-FU is ineffective when used intra-operatively in a combined ECCE/trabeculectomy approach. Mitomycin-C can be used, with the possibility of induced cylinder against-the-rule from relaxed healing of the superior wound.

Miotic pupil

Because a larger pupil is required for nuclear expression during an ECCE than during phacoemulsification, various strategies for

addressing the miotic pupil must be considered. In all of these approaches, filling the anterior chamber with viscoelastic will both protect the corneal endothelium and stabilize the iris during manipulation.

Stretching the pupil with a microspatula will break any posterior synechiae and will often enlarge the pupil to 5 mm or more (Fig. 35-24). Nuclear expression will be more difficult unless the pupil exceeds 5 mm because the nucleus can become trapped behind the rather rigid sphincter. The Simcoe irrigating vectus is useful in such cases. The iris is pulled toward the surgeon with

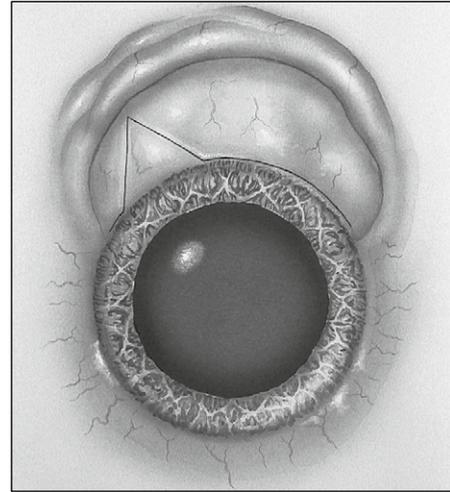


Fig. 35-16 Grooved trabeculectomy flap and circumferential cataract with limbal wound.

(From Gross R: Cataracts and glaucoma: technique of combined procedures. In: Higginbotham EJ, Lee DA, editors: Management of difficult glaucomas: a clinician's guide, Boston, Blackwell Scientific, 1994.)

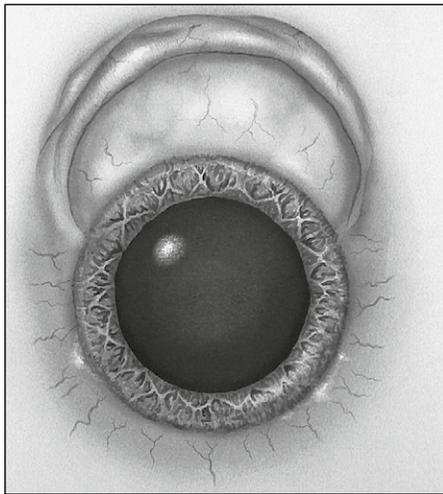


Fig. 35-15 Fornix-based conjunctival flap.

(From Gross R: Cataracts and glaucoma: technique of combined procedures. In: Higginbotham EJ, Lee DA, editors: Management of difficult glaucomas: a clinician's guide, Boston, Blackwell Scientific, 1994.)

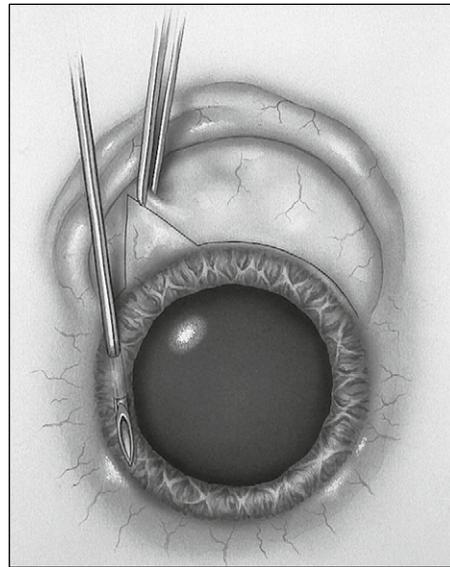


Fig. 35-17 Clear corneal paracentesis.

(From Gross R: Cataracts and glaucoma: technique of combined procedures. In: Higginbotham EJ, Lee DA, editors: Management of difficult glaucomas: a clinician's guide, Boston, Blackwell Scientific, 1994.)

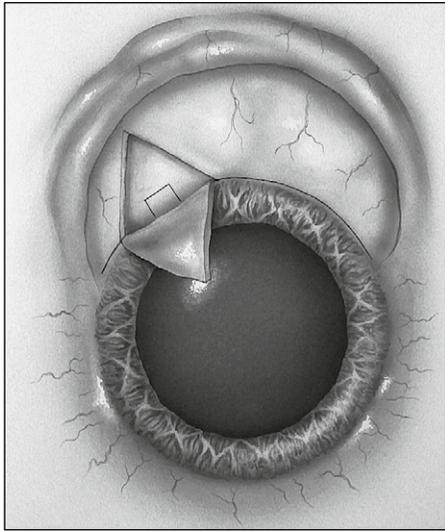


Fig. 35-18 Incised triangular trabeculotomy flap. Through this opening viscoelastic is injected and a capsulotomy is performed. (From Gross R: *Cataracts and glaucoma: technique of combined procedures*. In: Higginbotham EJ, Lee DA, editors: *Management of difficult glaucomas: a clinician's guide*, Boston, Blackwell Scientific, 1994.)

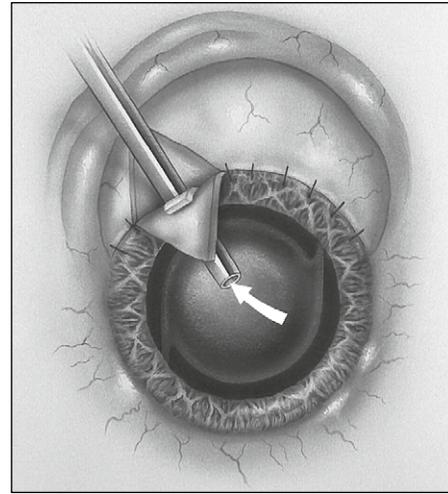


Fig. 35-20 The limbal wound is closed with 10-0 nylon and the viscoelastic removed through the ostium. (From Gross R: *Cataracts and glaucoma: technique of combined procedures*. In: Higginbotham EJ, Lee DA, editors: *Management of difficult glaucomas: a clinician's guide*, Boston, Blackwell Scientific, 1994.)

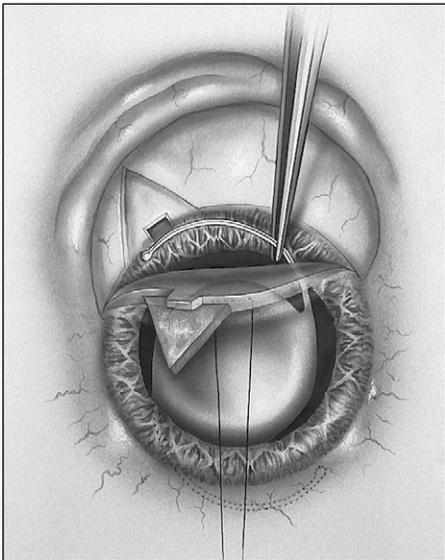


Fig. 35-19 Through the limbal wound the ECCE and intraocular lens implantation are performed. (From Gross R: *Cataracts and glaucoma: technique of combined procedures*. In: Higginbotham EJ, Lee DA, editors: *Management of difficult glaucomas: a clinician's guide*, Boston, Blackwell Scientific, 1994.)

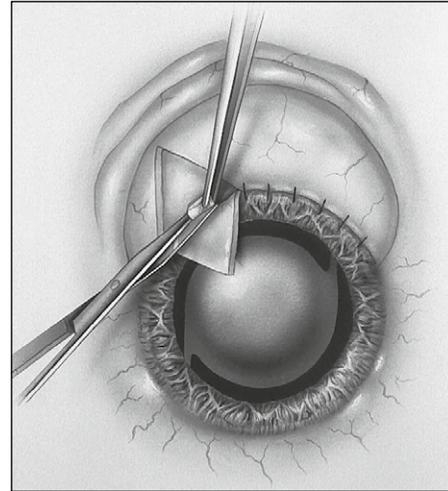


Fig. 35-21 The trabeculotomy block is excised. (From Gross R: *Cataracts and glaucoma: technique of combined procedures*. In: Higginbotham EJ, Lee DA, editors: *Management of difficult glaucomas: a clinician's guide*, Boston, Blackwell Scientific, 1994.)

smooth forceps to expose the edge of the nucleus. The vectus tip is placed behind the nucleus. The vectus is then rotated behind the nucleus in a plane that parallels the long axis of the nucleus. The serrated anterior surface of the vectus grabs the posterior surface of the nucleus, and with gentle forward lifting of the nucleus it slides out of the capsule toward the surgeon. When the nucleus is about halfway out of the eye, it may be held by the sides of the pupil.

The iris can be wiped with a cellulose sponge toward the edge of the nucleus while the surgeon continues to pull the vectus out of the eye in a line directed toward the middle of his or her chest. If the nucleus fails to follow the vectus, it should be speared with any sharp instrument and rotated through the pupil out of the eye. If the nucleus is very hard and large, this maneuver may result in some tearing of the sphincter.

If the pupil cannot be enlarged beyond 4 mm, it is unlikely that delivery of the nucleus can be accomplished without major tearing

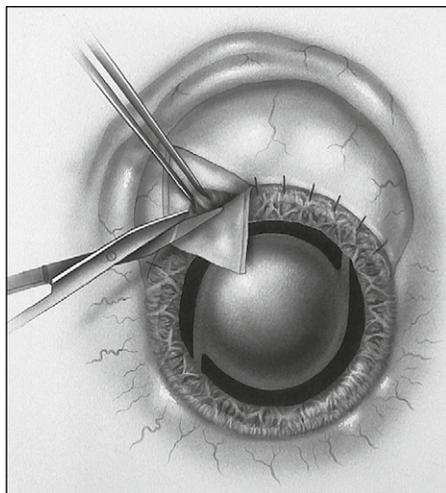


Fig. 35-22 A peripheral iridectomy is made.
(From Gross R: *Cataracts and glaucoma: technique of combined procedures*. In: Higginbotham EJ, Lee DA, editors: *Management of difficult glaucomas: a clinician's guide*, Boston, Blackwell Scientific, 1994.)

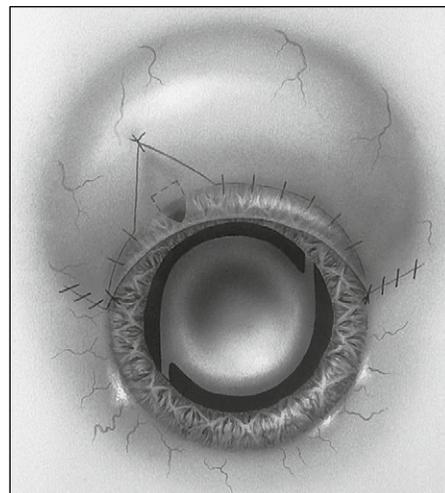


Fig. 35-23 The fornix conjunctival flap is closed to be water tight.
(From Gross R: *Cataracts and glaucoma: technique of combined procedures*. In: Higginbotham EJ, Lee DA, editors: *Management of difficult glaucomas: a clinician's guide*, Boston, Blackwell Scientific, 1994.)

of the sphincter. Use of excess pressure may rupture zonules or the posterior capsule. Three options exist to enlarge the pupil: sphincterotomies, radial iridotomy, and sector iridectomy. Each has its advocates, advantages, and disadvantages.

Sphincterotomies (Fig. 35-25) create multiple cuts through the iris sphincter muscle. Each cut may bleed and release serum into the eye. Nevertheless, this technique leaves a relatively round pupil that retains limited motility. Usually four sphincterotomies are placed at the vertical and horizontal positions of the pupil. Some surgeons prefer five smaller cuts, and a few use three larger ones. Rapazzo haptic scissors are particularly useful for this maneuver because they are angled and can be introduced through a small incision that usually does not require closure before performing the capsulotomy.

Radial iridotomy (Fig. 35-26) requires a 4–5-mm corneoscleral incision to introduce small, blunt-tipped scissors. It is usually performed by creating a peripheral iridectomy and then placing one blade of the scissors through the iridectomy and cutting radially through the iris and sphincter muscle. Care must be taken to avoid injuring the anterior capsule with the posterior blade of the scissors. The advantage of this technique is that the pillars of the iris can later be sutured together to create a round pupil (see Fig. 35-14). A non-degradable suture (e.g., 10-0 Prolene) should be placed and the knot rotated posteriorly behind the iris. Indeed, if the iris pillars are not sutured together, they may be floppy and migrate behind the lens optic postoperatively. Suturing the iris pillars creates a more cosmetic result than does a sector iridectomy in a patient with a blue iris. It is not clear, however, that suturing the iris pillars offers real functional advantage, because the upper lid covers the upper portion of the sector iridectomy in most individuals.

Sector iridectomy can be performed through a 3-mm corneoscleral incision by grasping the iris with toothed forceps and pulling it through the wound. A second pair of forceps can then be used to grasp the protruding iris closer to the sphincter

and pull the sphincter through the incision. The protruding iris, including the superior sphincter, is then excised. The initial grasp of the iris should be as far toward the sphincter as possible so that the iris root is not torn from the ciliary body. This provides a nice U-shaped sector iridectomy with abundant room for a capsulotomy and nucleus delivery. The pillars of the iris are not floppy, as in a radial iridotomy, and are unlikely to fall or be pulled behind the lens, especially if posteriorly angled haptics are used.

Incision construction

The corneoscleral incision is crucial in the ECCE combined procedure (Fig. 35-27). In general, the more posterior the incision, the less likelihood there is of inducing astigmatism, but there is a greater chance of bleeding from the wound. Because most eyes undergoing combined surgery have been treated with multiple medications for a number of years, the vessels are prominent and bleeding is more likely. Therefore superficial cautery should be used to eliminate anterior scleral vessels, and a two-plane incision in the midlimbal area is desirable. This represents a compromise between a posterior shelving incision that reduces astigmatism and an anterior incision that reduces bleeding.

If the nucleus is to be expressed, a chord diameter of the corneoscleral wound should be 10.5–11 mm. It is better to have the incision 1 mm too long than to cause complications by trying to squeeze a large nucleus through a corneoscleral incision that is too small.

Secure closure of the scleral flap with less resulting astigmatism can be accomplished if the angle between the keratectomy incision groove and the posteriorly directed scleral incisions of the scleral trabeculectomy flap exceeds 90° (see Fig. 35-27B). The sutures at the junction of the trabeculectomy flap with the corneoscleral incision should be snugly tied. Postoperative lasering of sutures holding the trabeculectomy flap can then be performed, with less resultant astigmatism.

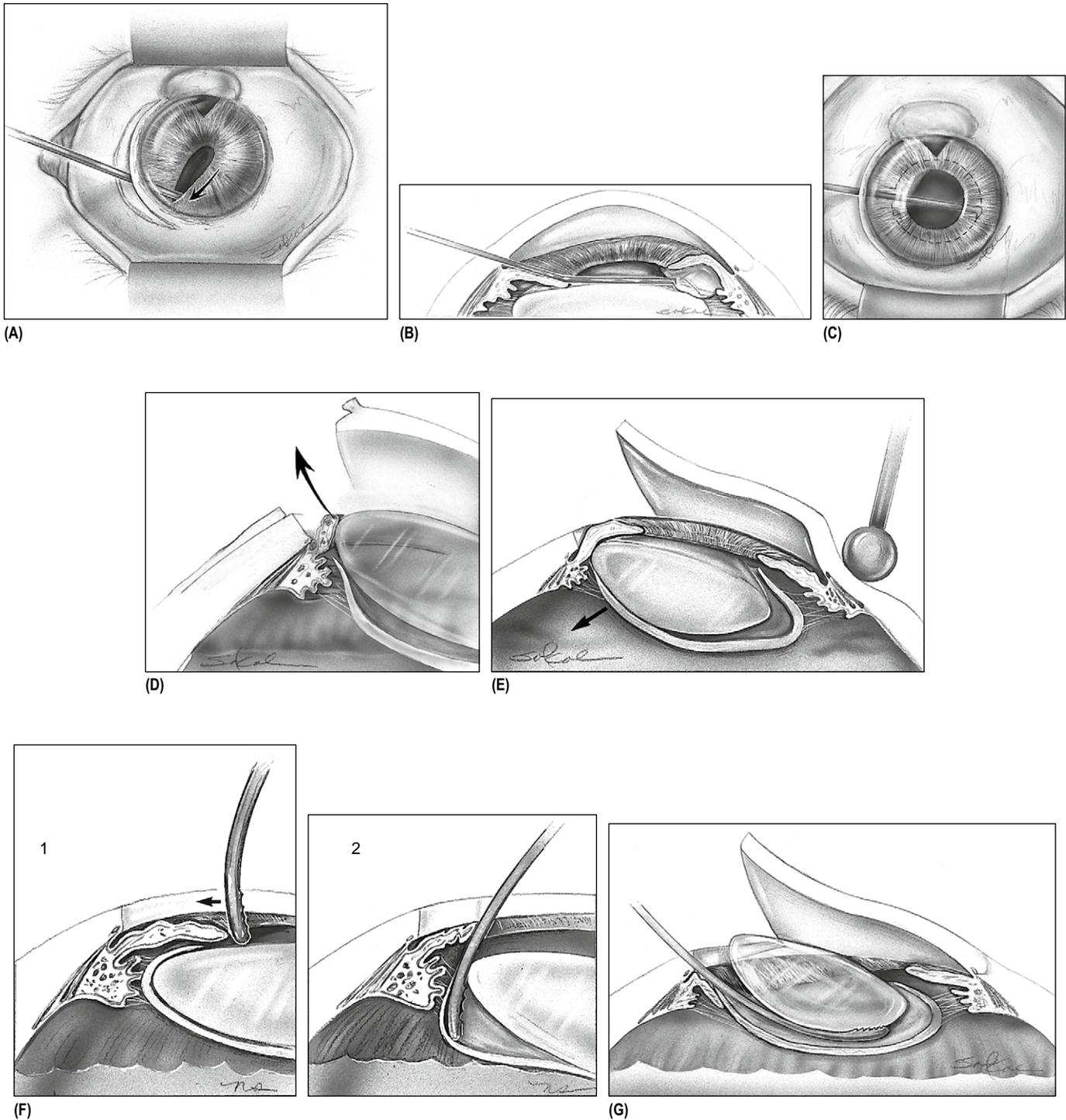


Fig. 35-24 Temporal ECCE in presence of superior pre-existing bleb. **(A)** After making an initial fornix-based flap, a stab incision is made. A microspatula is used to stretch the pupil and break any existing synechiae. **(B)** Viscoelastic material is injected under the iris to stretch the pupil and elevate the iris from the anterior capsule. **(C)** The capsulotomy is done behind the iris. It should be done slowly with minimal trauma to the posterior surface of the iris. **(D)** In an eye with a well-dilated pupil, the nucleus slides easily past the pupillary margin. **(E)** A miotic pupil tends to trap the nucleus behind the iris. Excessive pressure may force the nucleus posteriorly (arrow) and rupture the zonules. **(F)** A curved irrigating vectus, such as the one designed by Simcoe, retracts the iris (1) and slips behind the nucleus (2). **(G)** The vectus is then slid beneath the nucleus to facilitate its delivery.



Fig. 35-25 This patient had an upper nasal temporal extraction through a miotic pupil to preserve the filtering bleb. Five sphincterotomies were performed. Even so, small pupillary tears between the sphincterotomies can be seen. The laxity of the temporal iris allowed a small amount of pupillary capture to occur even though posteriorly angled haptics were used. This capture was not evident until 2 weeks after surgery.

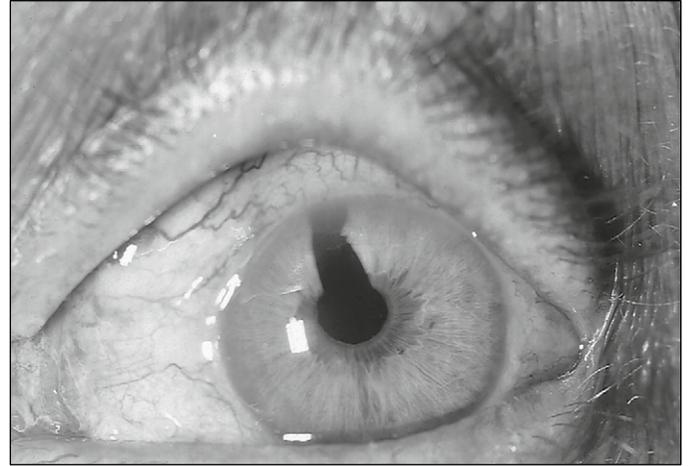
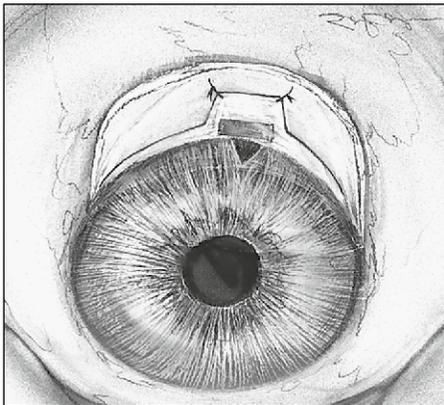
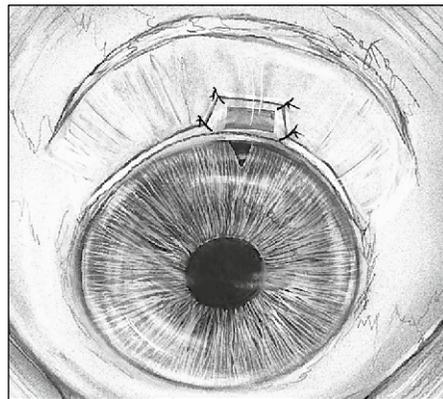


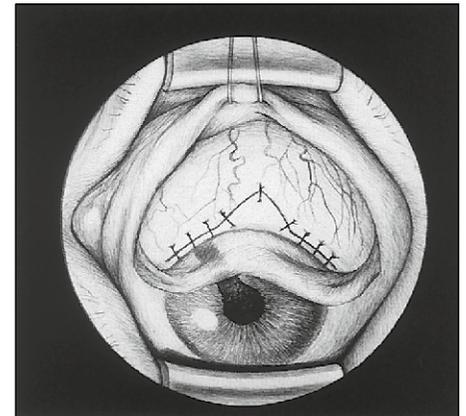
Fig. 35-26 This patient had radial iridotomy performed through peripheral iridectomy existing from previous trabeculectomy surgery. She had a revision of the existing trabeculectomy because of poor filtration at the time of cataract surgery and posterior chamber IOL implantation (see Fig. 35-28).



(A)



(B)



(C)

Fig. 35-27 Variations of combined ECCE-filtration procedures. **(A)** A fornix-based flap simplifies the surgeon's approach. The block of scleral and trabecular tissue should be removed after insertion of the IOL. If this block of tissue is excised before nuclear expression, it weakens the corneal ring and may result in zonular rupture. Combined procedures with fornix-based flaps leak in the postoperative period, and some surgeons believe that this reduces the likelihood of successful filtration. They are effective, however, for reducing pressure spikes in the immediate postoperative period. **(B)** The limbal-based flap provides excellent exposure but is technically more difficult because the flap is often in the surgeon's way. Because water-tight closure is possible, some surgeons believe that a bleb is more likely to develop. Angulation of the junction of the trabeculectomy flap and corneoscleral incision greater than 90° allows more secure closure of the corneoscleral wound. Tying the sutures snugly at this point reduces postoperative astigmatism. **(C)** Final closure with a triangular trabeculectomy flap.

CATARACT SURGERY WITH PRE-EXISTING FILTRATION BLEB

The great advantage of the small-incision cataract procedure is that it can be used adjacent to a pre-existing filtering bleb in the superior quadrants, or temporally through clear cornea. As discussed earlier, a certain loss of IOP control from impaired bleb function should be anticipated after cataract surgery. Sometimes the bleb can be 'reinvigorated' with 25-gauge needling at the time of the surgery, disrupting the episcleral adhesions that demarcate the bleb and

expanding the potential subconjunctival space for filtration. Also, at the conclusion of the cataract/IOL operation, the internal ostium of the trabeculectomy can be penetrated either (1) by a needle in the subconjunctival space, through (or under, if visualized) the scleral flap, and into the anterior chamber, or (2) by a transcorneal goniotomy knife or long needle across the chamber into the bleb itself. Subconjunctival 5-FU or intra-bleb mitomycin-C,¹⁶⁶ or a mitomycin-soaked (0.5 mg/cc) cellulose sponge laid atop the bleb for 5 minutes can be administered.¹⁶⁷

When an ECCE procedure is undertaken with a pre-existing bleb, the larger incision and its healing are more likely to

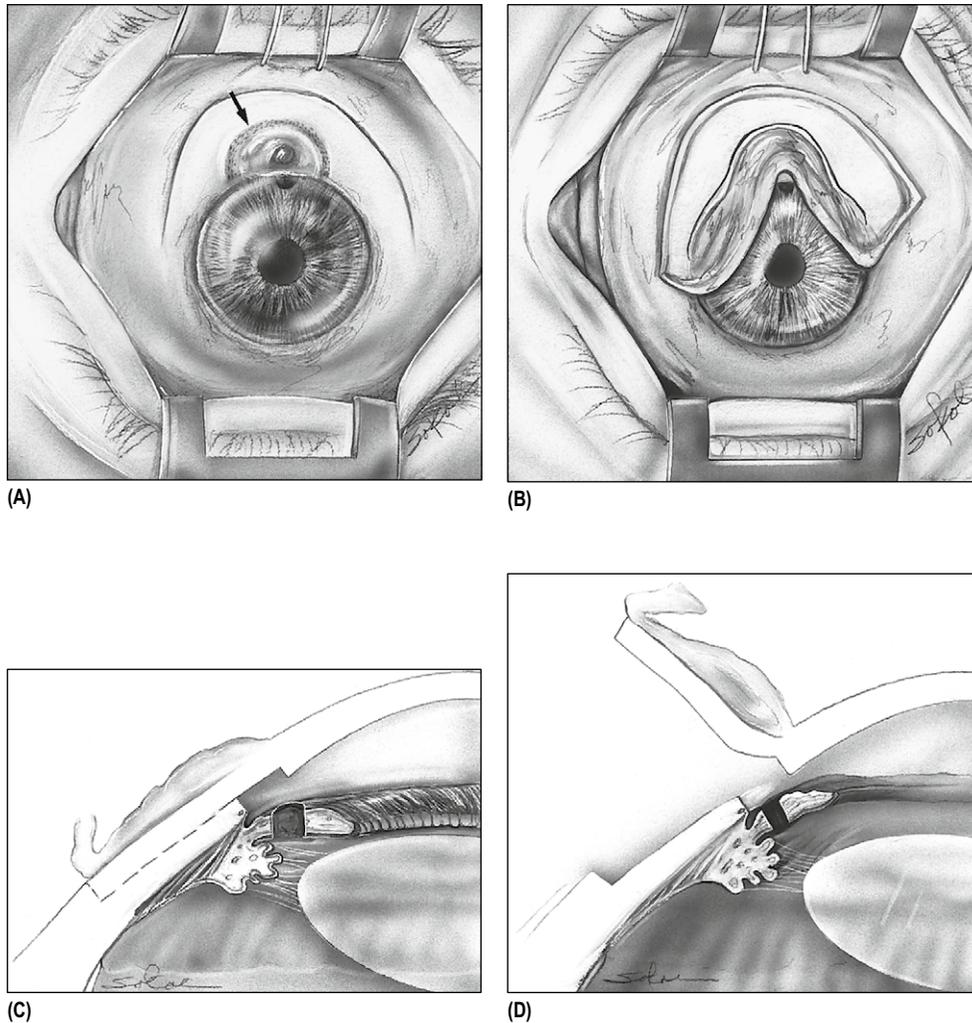


Fig. 35-28 (A) A bleb that is functioning inadequately may be enhanced at the time of ECCE surgery by a limbal-based conjunctival flap approach. The shaded area (arrow) represents the zone of adherent conjunctiva surrounding the bleb. (B) The flap is reflected forward until it reaches the point of adherence to the periphery of the bleb. On either side of the bleb, which is dissected down to the limbus, the scleral incision is made just posterior to the conjunctival adherence and long enough to allow expression of the nucleus. (C) The scleral flap will be undermined approximately one-half the scleral thickness, beneath the bleb, often following the plane of the original trabeculectomy flap (dotted line), until the chamber is entered. (D) This allows the elevation of the intact bleb in the *en bloc* method. The large ECCE incision is extended temporally and nasally in the usual manner.

adversely affect the bleb's survival. If the bleb is functioning well, it is best avoided by removing the cataract via a temporal or clear corneal incision. If the bleb is functioning poorly, filtration may be enhanced at the time of surgery by revising the filtration site (Fig. 35-28).

Although we now advocate mastery of the more recently described ECCE small-incision techniques performed temporally,^{163,164} the classic ECCE temporal extraction is illustrated in Figure 35-24. When viewed from the front, the corneoscleral junction is an ellipse with the long axis in the horizontal meridian. Thus a temporal incision is further from the center of the pupil, making expression of the nucleus more difficult if the pupil fails to dilate because the nucleus becomes trapped behind the iris. Excessive pressure will rupture the zonules. A sector iridectomy in this area is undesirable because it is not covered by the lid and will result in reflections off the edge of the lens. One option is to place a sector iridectomy far enough superiorly as to be covered by the

lid. This is possible if the original filtration site is in the upper nasal quadrant. Another possibility is to perform a radial iridectomy to allow delivery of the nucleus and then suture the pillars of the iris together with a 10-0 Prolene suture. A third option is to use an irrigating vectus to retract the iris and deliver the nucleus. Once the nucleus is expressed, the rest of the procedure can be performed as usual.

A superior corneal incision allows a superior iridectomy and may be more familiar to the surgeon. If the bleb is positioned posteriorly away from the limbus, a small fornix-based flap can be created, and the procedure varies little from a routine extraction. If the bleb has migrated into the cornea, the incision should be anterior to it and more vertical than beveled. A beveled incision will enter the anterior chamber too centrally and have a short chord length that causes difficulty in expressing the nucleus. More sutures are usually required to close a vertical incision as compared with a beveled incision.

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CHAPTER
36Complications and failure of
filtering surgery

Glaucoma filtering surgery is fraught with various complications for the simple reason that it is designed to interrupt the integrity of the globe. In all other intraocular procedures, ophthalmologists try to restore the ocular compartments to prevent hypotony or the extrusion of intraocular contents or fluids. The goal in glaucoma surgery, however, is just the opposite. The globe is left in a non-physiologic state, which can result in the many complications described in this chapter.

BUTTONHOLING THE CONJUNCTIVA

Tiny inadvertent perforations of the conjunctival flap are often overlooked until the procedure is completed. In guarded filters, such as trabeculectomy, small perforations (e.g., from a suture needle) usually heal spontaneously, even in the presence of antimetabolites, within 24–72 hours by simply withholding steroid drops; subconjunctival Healon-5 can be used to retard the flow of such leaks and facilitate healing.¹ Focal perforations 1–2 mm in size should be closed with a 10-0 nylon suture on a microvascular tapered needle (e.g., Ethicon BV100), using a mattress or purse-string closure. For large perforations, it may be necessary either to prepare a relaxing incision near the fornix that allows anterior sliding of fresh conjunctiva toward the limbus^{2,3} or to procure a piece of Tenon's capsule from a remote site and incorporate it into the closure (Fig. 36-1).⁴

If the buttonhole exists at the limbal junction during a fornix-based flap procedure, a peritomy can be performed and the conjunctiva advanced and sutured directly to the corneoscleral junction or into a corneal groove (Fig. 36-2). If the buttonhole is noted in friable conjunctival tissue before the creation of the sclerostomy, a new site may be selected for the procedure.

Because of the possibility of inadvertent buttonholes, some physicians defer applying antimetabolites until the conclusion of surgery, before the conjunctival closure. They assess conjunctival integrity at the conclusion of the operation and then apply cellulose sponges saturated with either 5-fluorouracil (5-FU) or mitomycin-C on top of the trabeculectomy flap before the final conjunctival closure.^{5–8} If a Seidel-positive leak is seen from the buttonhole in the postoperative period, subconjunctival injections of 5-FU can be deferred until the leak closes.

Postoperatively, it is useful to distinguish between *point leaks* (seen in 2% of eyes at 3 months following either 5-FU or mitomycin-C filtration surgery) and transconjunctival *aqueous ooze* (seen in 12% of eyes, especially in large avascular areas, and following digital massage).^{9,10} Often such defects can be carefully monitored and/or treated prophylactically with antibiotic drops, with the vast

majority spontaneously resolving (and often benignly recurring.) Recurrent leaks have a higher association with blebitis or endophthalmitis.¹¹ Patients, of course, need to be alerted to the symptoms of early infection, so as to seek immediate medical attention.

THE SHALLOW AND FLAT ANTERIOR CHAMBER

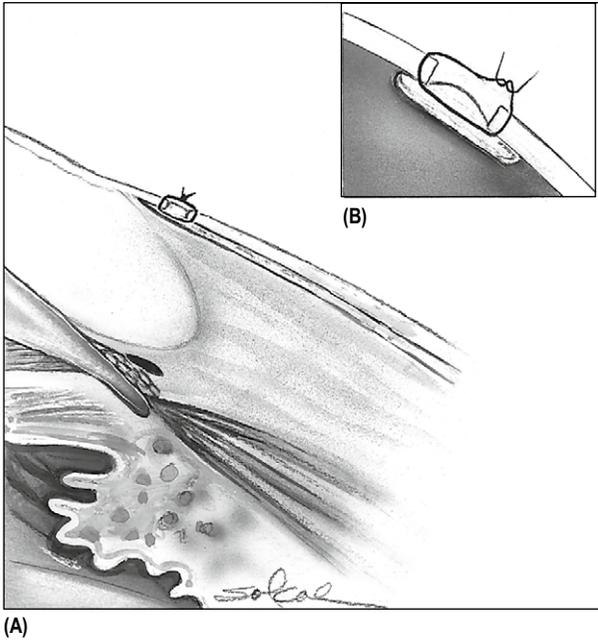
The appearance of the eye in the first days after filtering surgery depends on many variables, not all of which can be controlled. Although it is customary to conclude a filtration procedure after ascertaining that the chamber is formed and a bleb is present, it is not uncommon to find that the appearance has changed 24 hours later. The depth of the chamber and the extent of the bleb will depend on several factors, including whether a full-thickness or guarded procedure (trabeculectomy) was performed, the tightness of the scleral flap, the firmness of the eyepatch, the use of antimetabolites at the time of the surgery, and the use of intracameral viscoelastics.

The clinical classification of shallow chambers popularized by Spaeth^{12,13} is particularly useful in the postoperative management. In *grade 1* (Fig. 36-3), the anterior chamber is peripherally flat, with the peripheral iris and cornea touching but with preservation of the anterior chamber in front of the pupillary space. In the *grade 2* shallow chamber (Fig. 36-4), there is greater apposition between the mid iris and the cornea, but some space between the anterior surface of the lens (or vitreous) and the cornea in the pupillary region is retained. For daily reference, it is useful to estimate the actual depth of the small, central chamber in terms of how many 'corneal thicknesses' there are between the cornea and the pupillary plane. The *grade 3* anterior chamber (Fig. 36-5) is truly flat, with complete contact of the iris and the pupillary space with the posterior surface of the cornea (Fig. 36-6).

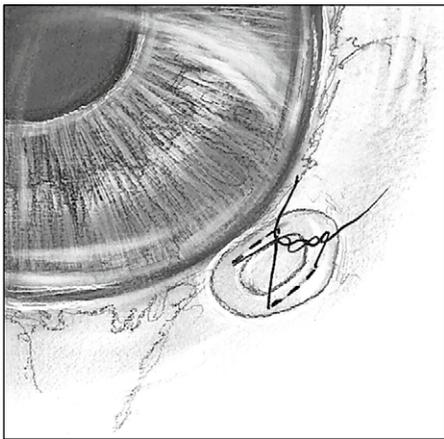
The most important determination after classifying the chamber depth is to determine whether the intraocular pressure (IOP) is either higher than expected or excessively low in conjunction with one of these three configurations of shallow chamber. By and large, grades 1 and 2 will almost always reverse spontaneously with time, responding to moderate intervention such as atropine cycloplegia. The grade 3 flat chamber is a 'medical urgency,' which requires frequent monitoring and possible surgical intervention (e.g., choroidal drainage) if not spontaneously resolved within a short period (3–7 days).

FLAT ANTERIOR CHAMBER WITH HYPOTONY

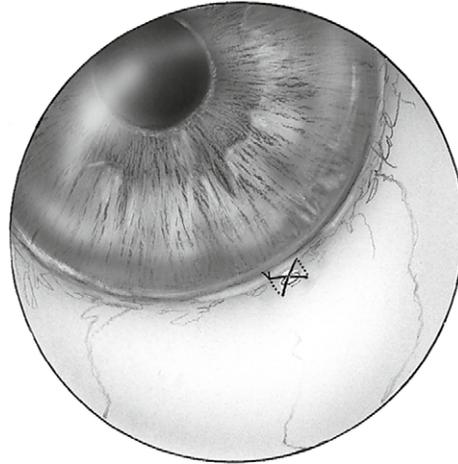
Hypotony with a flat anterior chamber after filtration surgery most commonly results from overfiltration or bleb leaks; it is very often



(A)

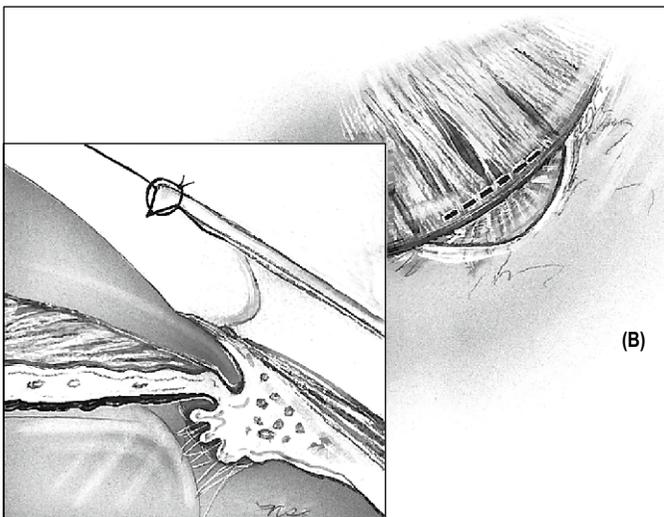


(C)

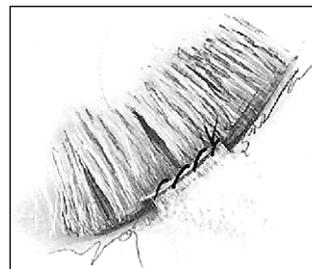


(D)

Fig. 36-1 (A, B) A small piece of Tenon's capsule is sutured into the buttonhole. **(C, D)** A mattress suture using 10-1 Prolene on a microvascular needle is useful for this. When the suture is drawn tight, the buttonhole will be sealed by Tenon's capsule with the epithelial surface approximated.



(A)



(C)

Fig. 36-2 (A) A tear in the conjunctiva at the limbus can be closed by making a small corneal groove. **(B, C)** Suturing the conjunctiva into the groove.

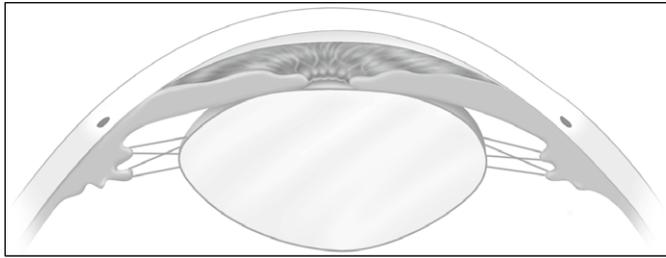


Fig. 36-3 Grade 1 shallow chamber. Although the peripheral iris and cornea are touching, the central anterior chamber surrounding the pupillary area remains formed.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

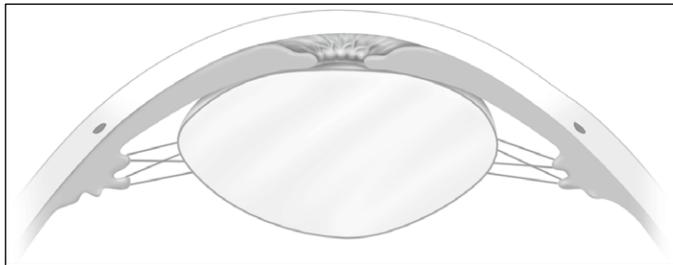


Fig. 36-4 Grade 2 shallow chamber. The anterior chamber is quite compromised, with iris-to-corneal apposition peripherally and centrally, although the area anterior to the pupil and lens remains formed. To clinically monitor this small chamber over time, its depth can be graded with that of a fraction of the overlying cornea (e.g., 'central chamber one-half corneal thickness').

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

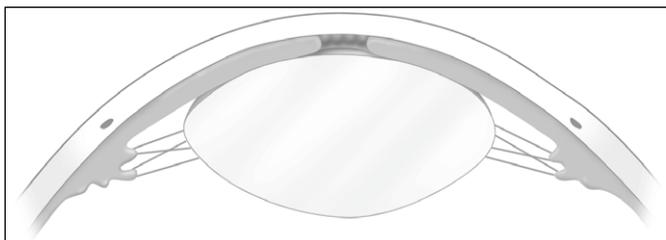


Fig. 36-5 Grade 3 shallow chamber. The anterior chamber is completely collapsed, with pupillary-corneal touch and sometimes even lens-corneal touch.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

seen in the first few days after full-thickness surgery. As many as one-third of trabeculectomies show an IOP (less than 8 mmHg) near the hypotonous range for as long as 2 weeks postoperatively.¹⁴ However, low IOP in the first postoperative weeks does not correlate with poor IOP control later.¹⁵

Immediate postoperative hypotony is often accompanied by choroidal effusions or detachment.^{16–20} Such effusions can appear as either a low, annular detachment – sometimes appreciated only because of the ease with which the ora serrata is visualized – or

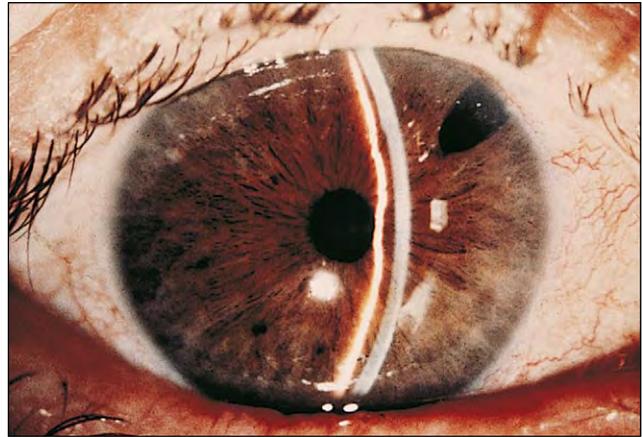


Fig. 36-6 Flat anterior chamber after filtration surgery.

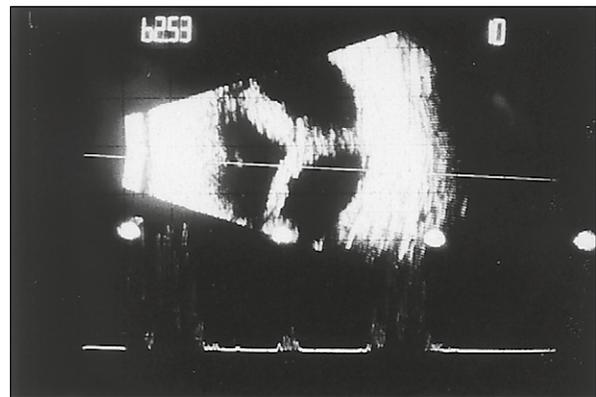


Fig. 36-7 Ultrasonogram of a patient with a large 'kissing choroida' with filtering surgery that is overfunctioning.

as large choroidal effusions that may compromise the visual axis when two detachments 'kiss' in the midvitreal cavity. In a national survey of complications of glaucoma surgery among 1240 cases performed throughout the United Kingdom, early complications included hypotony (24%), wound leak (18%), and choroidal detachment (14%). These arose independent of whether the surgeon was a subspecialist or performed glaucoma surgery frequently; they bespeak of common intraoperative or postsurgical events in glaucoma surgery.²¹ A not dissimilar pattern of events was reported in the United States.²²

The choroidal detachment becomes of greatest clinical concern when the anterior chamber progressively shallows over time – even progressing to a grade 3 flat chamber. If effusions are seen in the absence of a conjunctival wound leak, however, most surgeons defer any surgical intervention. Indications for surgery are usually reserved for the persistence of 'kissing choroidals,' in which the retinal surfaces are in contact astride large bullous choroidal detachments (Fig. 36-7), or a grade 3 flat chamber with actual or potential compromise of the corneal endothelium. Shy of these two events, however, the choroidal effusions will often resolve with time, and with the use of atropine cycloplegia and steroids to reduce inflammation.²³ One exceptional circumstance that often fails to respond to medications and requires early surgical intervention is an eye with chronic angle-closure glaucoma and an extremely shallow chamber after trabeculectomy; such circumstances predispose to aqueous misdirection (malignant glaucoma) syndrome.²⁴

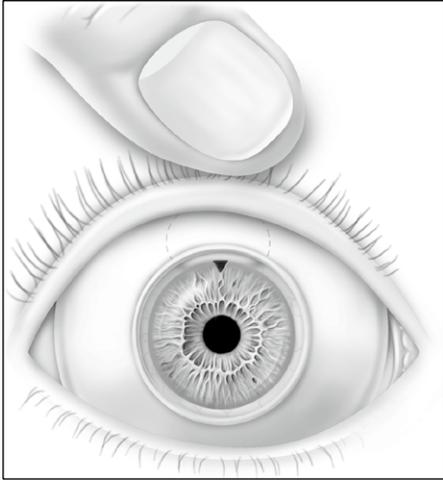


Fig. 36-8 Bleb compression. As an alternative to the Simmons shell technique, which involves tamponade of a bleb with excessive filtration, a modified symblepharon ring can be applied, leaving the cornea free for IOP measurements and for the patient's vision. The ring is available in either colored or clear plastic. The surgeon also has the option of using a large soft contact lens beneath the ring for corneal comfort.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

A large soft contact lens, a symblepharon ring (Fig. 36-8),²⁵ or the Simmons shell²⁶⁻²⁸ may impede aqueous flow through the sclerostomy, encourage any buttonhole to heal, and help form the chamber sooner. Such a sequence is more likely if no intraoperative antimetabolite was used. In the event of a small wound dehiscence, either topical cyanoacrylate or tissue glue covered with a bandage contact lens^{7,29} (see section on Thin-Walled Blebs, p. 522-4) or a compression suture can be attempted. The compression suture is rendered by 9-0 nylon that is attached at the corneal limbus, fashioned in an X-crossing at the leak site, and anchored in episcleral tissue posterior to the edge of the bleb. It can remain for several weeks before removal.

If the lens or IOL is pushed against the cornea, the endothelium may be rapidly damaged, causing corneal decompensation. There is an increased loss of endothelial cells when the eye passes from a grade 2 to grade 3 shallowing of the chamber.^{30,31} In cases of truly flat grade 3 anterior chambers, an attempt to re-form the chamber at the slit lamp should be made immediately through a paracentesis, either by air or viscoelastic injection or by intraocular gas.²⁴ If a paracentesis opening does not exist or cannot be found, injection with a disposable 30-gauge needle passed into the anterior chamber through the cornea (Fig. 36-9) can be used.³²

If the injected material passes out of the eye through the sclerostomy site, as is commonly seen with full-thickness or hyperfiltrating trabeculectomy procedures, it may be necessary to return to the operating room for drainage of the suprachoroidal fluid with or without surgical modification of the filtration site.^{16,33} For drainage, one or more sclerostomies inferiorly are made 4 mm behind the limbus and over the pars plana; the anterior chamber is re-formed with balanced salt solution (BSS) or viscoelastic, and attempts

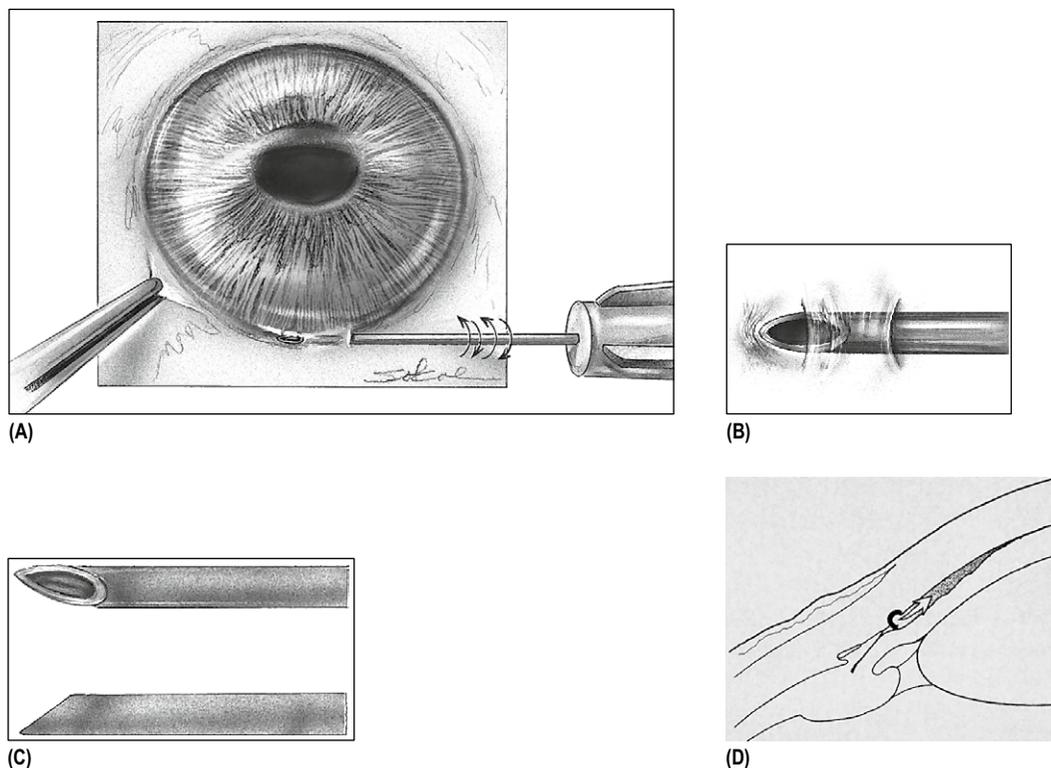


Fig. 36-9 (A) A disposable 30-gauge needle can be used to penetrate the cornea of even a hypotonous eye by gently rotating the tip back and forth. (B) The bevel should face the surgeon as the tip is passed through the cornea until the tip can just be seen to move the iris. (C) The tip is then rotated (1 to 2) so that (D) air can be injected into the anterior chamber through the beveled portion of the needle even though the full tip is not yet in the anterior chamber.

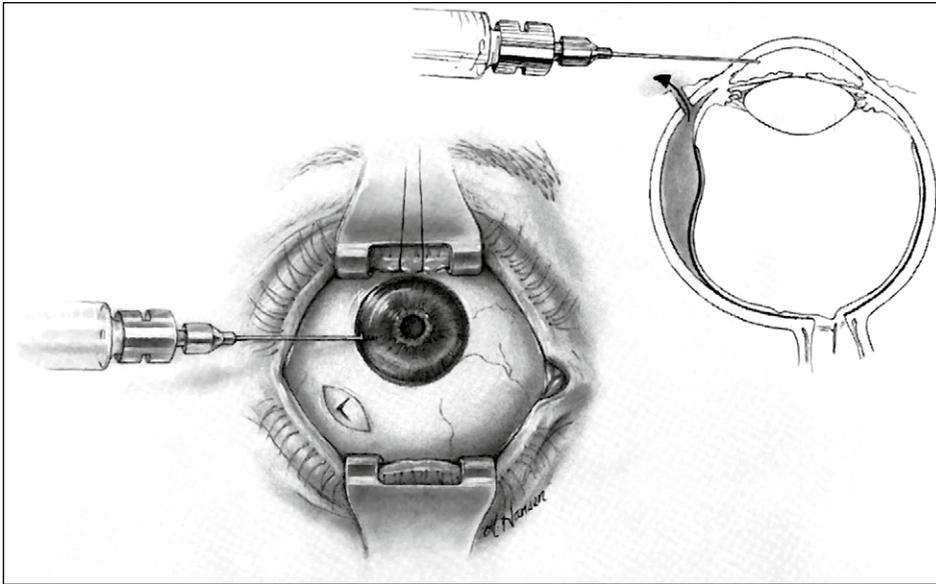


Fig. 36-10 Posterior sclerostomy and injection into the anterior chamber.

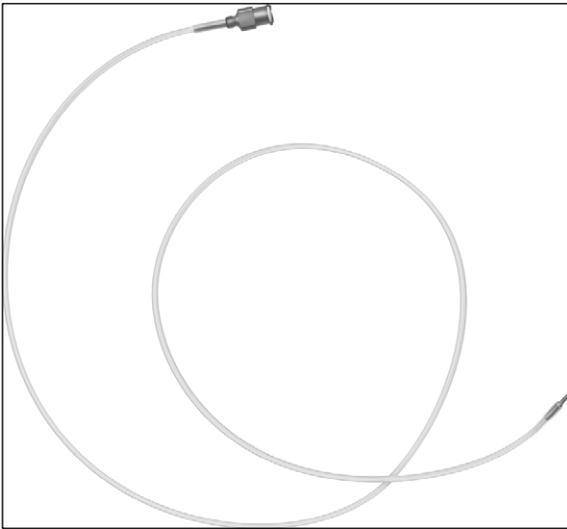


Fig. 36-11 Lewicke Anterior Chamber Maintainer (Visitec™) is connected to a 3-way stopcock and irrigating solution; its threaded metal end fits through a microvitreal retinal (MVR) blade paracentesis.



Fig. 36-12 Lewicke cannula obliquely situated in anterior chamber allows for controlled intraoperative IOP.

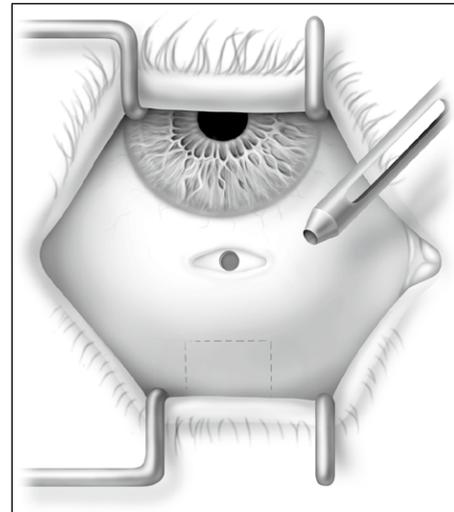


Fig. 36-13 Dellaporta technique for choroidal drainage – A. After a conjunctival incision is made 4 mm from the limbus at the 6 o'clock position over the pars plana (and anterior to the inferior rectus muscle), a 1-mm trephine is used to remove a divot of sclera, with great care taken to avoid penetrating the underlying uveal tissue. The divot of sclera can be removed after the drainage of fluid or be lightly sutured into place. (From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications. Philadelphia, Lippincott-Raven, 1995.)

are made to drain the suprachoroidal effusion while maintaining the chamber at as normal a depth as possible (Fig. 36-10). Intraoperative hypotony can be obviated by using an intracameral maintainer device (e.g., Lewicke anterior chamber; Figs 36-11 and 36-12). Another drainage approach involves 1-mm trephination through the sclera, anterior to the inferior rectus muscle, which remains open for several days to allow suprachoroidal fluid to drain subconjunctivally (Figs 36-13 and 36-14).³⁴

The benefits of choroidal drainage may take several months to fully manifest: in one retrospective series of 94 procedures, 60% of effusions resolved by 1 month, increasing to 90% by 4 months, accompanied by slight loss of IOP control but statistically improved

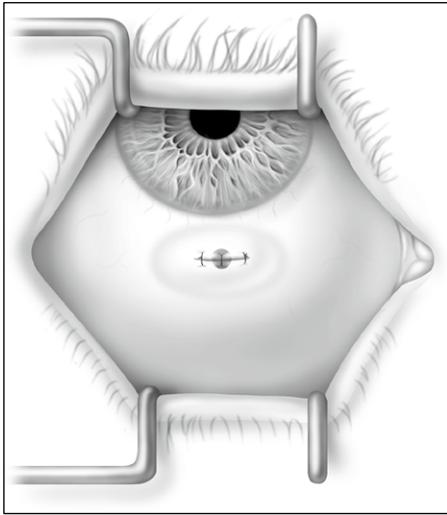


Fig. 36-14 Dellen technique – B. After a water-tight closure of the conjunctival wound (e.g., using 9-0 Vicryl suture), a dependent bleb forms from the persistent egress of fluid through the 1-mm trephine hole. Uveal prolapse is rarely seen, and the drainage of fluid, activated by the extraocular movements, can sometimes persist for several days, thus reducing the tendency for recurrent accumulation of suprachoroidal effusion. (From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

visual acuity. However, over three-quarters of phakic eyes developed cataracts within the first year, a complication worth explaining during informed consent.³⁵

FLAT ANTERIOR CHAMBER IN NORMOTENSIVE AND HYPERTENSIVE EYES

Normal or elevated IOPs with a flat anterior chamber indicate that excessive filtration is not the cause of the flat chamber. The flat anterior chamber in such eyes is caused by increased volume or pressure behind the lens–iris diaphragm. Four mechanisms need to be methodically considered: (1) pupillary block with an incomplete iridectomy; (2) expansion of the choroid or enlargement of the suprachoroidal space by blood or effusion; (3) an increase in vitreous volume caused by blood or effusion, or (4) the misdirection of aqueous. If an iridectomy is not present or conclusively patent, one should be created immediately either by laser or, if necessary, incisional surgery.

If a patent iridectomy exists, there are two common causes of flat chamber with normal or high IOP after glaucoma surgery: ciliary block (e.g., aqueous misdirection syndrome, malignant glaucoma) and suprachoroidal hemorrhage (SCH).

CILIARY BLOCK (MALIGNANT GLAUCOMA)

The term *ciliary block* or *malignant glaucoma* refers to a spectrum of atypical angle-closure glaucomas that share several essential features.³⁶ Other terms have been proposed for this condition, many of which purportedly point to the underlying pathophysiology. These terms include *aqueous misdirection*, *hyaloid block glaucoma* and *posterior*

aqueous entrapment. Historically this condition was commonly appreciated as a complication of a filtering procedure in eyes with pre-existing angle-closure glaucoma or shallow anterior chambers (See Ch. 16 – Secondary Angle-Closure Glaucoma.)

There is good agreement in the literature about several essential features of this condition, but other features are more controversial. Clinically, ciliary block glaucoma is suspected in the presence of a grade 2 or 3 shallow chamber, with the prominent shallowing of the peripheral and central anterior chambers simultaneously. The pressure is usually higher than expected: in the early postoperative period it may simply be between 15 and 20 mmHg despite the appearance of what would seem to be an otherwise adequate bleb; in other cases the pressure can be quite high indeed.

To diagnose ciliary block glaucoma, it is essential to eliminate the possibility of pupillary block; hence a patent iridotomy must be established before this diagnosis can be considered. Sometimes the diagnosis is made only in retrospect, after evaluating the eye's response to several interventions. For example, cycloplegics can be curative of malignant glaucoma and miotics can be exacerbative. If surgical intervention is necessary, disrupting the hyaloid face or collapsing the vitreous is usually curative.

Other aspects that are sometimes seen with ciliary block glaucoma include the rarity of spontaneous resolution – and hence its 'malignant' designation. It is usually bilateral in predisposition, and it is often worsened by conventional glaucoma surgery such as iridectomy or filtration procedures. The clinical presentation of ciliary block glaucoma is similar to that of other conditions, notably angle-closure glaucoma with ciliary choroidal detachment.³⁷ For example, some authors have observed the accumulation of fluid in the suprachoroidal space in some cases of ciliary block glaucoma,^{36,38} and this has been confirmed by ultrasonic biomicroscopy.³⁹ Other situations that may overlap with the appearance of ciliary block glaucoma include eyes that have undergone cataract extraction, with or without lens implantation, with sequestration of aqueous behind the iris plane. These conditions have been referred to as 'iridovitreal block'⁴⁰ and 'retrocapsular aqueous misdirection'.⁴¹

The pathophysiological sequence of ciliary block glaucoma is thought to be as follows.^{42,43} After some initiating event (e.g., shallowing of the chamber during trabeculectomy) there is cause for misdirection of the aqueous to circulate into or behind the vitreous body. This apparently leads to an alteration of the vitreous volume and its compaction, with a cycle of increasing vitreous swelling and reduced conductivity of aqueous anteriorly. (A recent model proposes that choroidal expansion, suspected as an initiating event in acute angle-closure glaucoma, may also be a contributory event for anterior vitreal movement in malignant glaucoma, and hence the clinical association of the two disorders.⁴⁴) The enlarging vitreous body is unable to exchange aqueous across the hyaloid face at the junction of the zonules, vitreous face, and ciliary processes. This progressive vitreal engorgement results in shallowing both axially and peripherally in the anterior chamber, with increasing apposition of the peripheral iris into the angle, setting up a further cycle of angle-closure glaucoma.

The management of ciliary block glaucoma is straightforward. It is important to eliminate the possibility of pupillary block glaucoma by verifying or creating a patent iridotomy. Miotic medications should be discontinued, and vigorous cycloplegia as well as the use of topical steroids should be instituted. Other agents to reduce aqueous production, such as topical α -agonists or β -blockers, carbonic anhydrase inhibitors, or osmotic agents, can be used to reduce the pressure. A waiting period of approximately 5 days has been advised

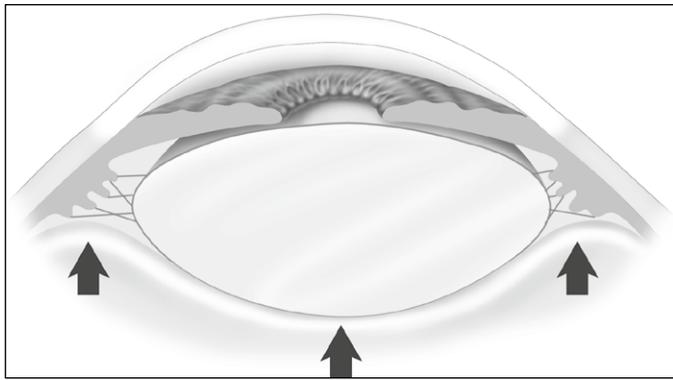


Fig. 36-15 Phakic malignant glaucoma. With the sequestration of aqueous within the vitreous body, there is compression of the anterior chamber both axially and peripherally (arrows), causing central shallowing of the chamber with forward movement of the lens and peripheral angle closure. (From Lieberman MF: *Complications of glaucoma surgery*. In: Charlton J, Weinstein G, editors: *Ophthalmic surgery complications*, Philadelphia, Lippincott-Raven, 1995.)

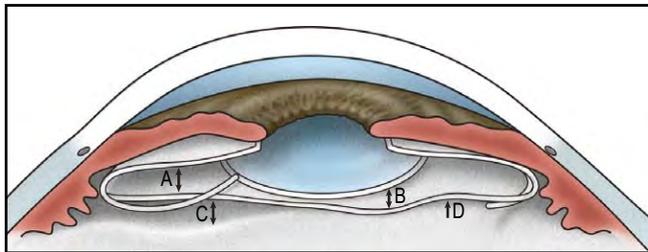


Fig. 36-16 Capsular malignant glaucoma. In the presence of a posterior capsule with a posterior chamber intraocular lens there are multiple sites in which aqueous can be sequestered, and these sites must be sequentially eliminated: (A) aqueous pockets between the iris and anterior capsule; (B) pockets within the capsular bag and lens implant; (C) pockets between the posterior capsule and hyaloid face, and (D) aqueous trapped within the vitreous cavity behind an intact hyaloid face. (From Lieberman MF: *Complications of glaucoma surgery*. In: Charlton J, Weinstein G, editors: *Ophthalmic surgery complications*, Philadelphia, Lippincott-Raven, 1995.)

with this intensive medical regimen to see if there is resolution, with as many as half of the cases resolving during this interval.⁴⁵

In the event that surgical intervention is necessary, either a needle aspiration of vitreous through the pars plana⁴⁶ or pars plana vitrectomy⁴⁷ will usually be curative in phakic eyes (Fig. 36-15). Eyes that have cataract extraction – with or without a lens implant – and a retained posterior capsule offer a less complicated intervention: direct incision of the hyaloid face using the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.^{48,49} In this presentation with a retained posterior capsule (Fig. 36-16), it is necessary to sequentially eliminate pupillary block, retrocapsular block, and hyaloid block by respectively laser through the iris, posterior capsule, and hyaloid face.³⁶ In the acapsular eye (e.g., aphakia) (Fig. 36-17), hyaloidectomy centrally and peripherally can be undertaken with the Nd:YAG laser or with incisional surgery.

Vigorous surveillance is still necessary in these eyes because recurrent cases of ciliary block glaucoma have been reported, especially after vitreous aspiration or vitrectomy, which may not have been sufficiently anterior in the phakic eye to interrupt the obstruction of the hyaloid face. In rare cases, it is necessary to

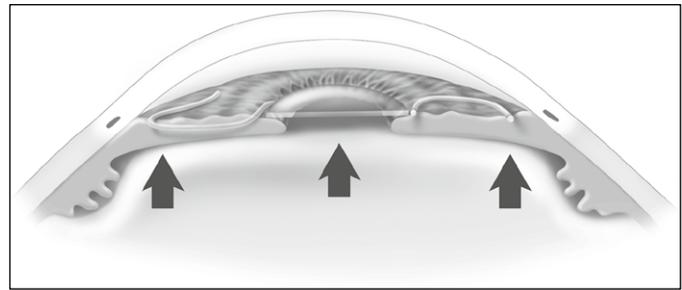


Fig. 36-17 Acapsular malignant glaucoma. In the absence of a posterior capsule – such as aphakia or, as seen here, an anterior chamber intraocular lens – the abnormal vitreous forces compress the anterior chamber axially and peripherally (arrows), but the abnormal hyaloid surface is accessible to laser or incisional surgery.

(From Lieberman MF: *Complications of glaucoma surgery*. In: Charlton J, Weinstein G, editors: *Ophthalmic surgery complications*, Philadelphia, Lippincott-Raven, 1995.)

sacrifice the lens to access the hyaloid itself. Chronic atropine drops may be needed, and great attention should be paid to the fellow eye, which is at a high risk for recapitulating the events of the first eye's ciliary block glaucoma attack.

SUPRACHOROIDAL HEMORRHAGE (SCH)

Fortunately, SCH after glaucoma surgery is rare.⁵⁰ It occurs more commonly in traumatized eyes, in aphakia, in vitrectomized eyes, and in large eyes with pathologic myopia or congenital glaucoma.^{51–58} Patients taking systemic anticoagulants and eyes with significant post-operative hypotony are also at higher risk.⁵⁹ In a large prospective study of antimetabolite usage,⁶⁰ there was a remarkably strong association between the appearance of SCH and the preoperative IOP level. Among the patients with IOPs under 30 mmHg, there was no incidence of SCH; the incidence of SCH was 6% in eyes with IOPs between 30 and 39 mmHg and 11% in eyes with IOPs of 40–49 mmHg; and in three patients with IOPs over 50 mmHg the incidence of SCH was nearly 20%. A different analysis using a case-control methodology also identified the risk factor of elevated IOP and specifically called attention to the greater risk for SCH in the presence of an axial length greater than 25.8 mm.⁶¹ Suprachoroidal hemorrhage can appear after virtually any glaucoma operations, with or without antimetabolites; there may be a higher frequency following glaucoma shunt procedures.⁵⁹

It is rare for a hemorrhage to occur during surgery in the phakic eye. More commonly, the patient experiences a sudden, severe pain accompanied by sudden loss of vision during the first 4 or 5 postoperative days. If the hemorrhage is severe, the pressure may be quite high and the patient may have nausea and vomiting.

If aqueous suppressants and hyperosmotic agents fail to lower the IOP, the hemorrhage may require drainage. Four to five days are usually necessary for a clot to lyse in the suprachoroidal space. Therefore, if drainage can be delayed for that period of time, drainage will be more easily accomplished through a posterior sclerostomy placed directly over the area of elevated choroid.

If pain and pressure cannot be controlled or the pressure elevation is very high, earlier drainage is required. In such cases, the clot will not have lysed, so a large scleral incision (possibly as large as 10–12 mm) may be required for the clot to slide out of the suprachoroidal space.⁶²

The sclerotomy incision should be placed near the center of the choroidal elevation as determined visually or by ultrasound. If the clot has not lysed, it may have the appearance of choroid. The surgeon should not try to pull the clot from the wound with an instrument but rather express it with gentle pressure while gradually enlarging the sclerostomy site as needed.

If the clot has lysed, a 2-mm sclerostomy is usually adequate to allow the escape of the xanthochromic fluid followed by the black 'sludge' of the clot. Balanced salt solution (BSS), air, or viscoelastic can be injected gently to re-form the anterior chamber via a paracentesis opening⁶³; or, as with re-formation of flat anterior chambers, an anterior chamber maintaining device is helpful to prevent intraoperative hypotony. Maintenance of high-normal IOP helps force more of this dissolved clot out through the sclerotomy opening. It is helpful to inject viscoelastic into the anterior chamber at the conclusion of the procedure to maximally maintain ocular integrity, and to allow the eye to run pressures in the 25–35-mmHg range a few days before intervening medically.

The goal of this surgical intervention is to allow the blood residue to escape from the suprachoroidal space while restoring the normal intraocular relationships. Every effort should be made to prevent choroidal injury, which might cause blood to get into the vitreous cavity where it promotes inflammation and scarring.

In aphakia, the choroid and often the retina are pushed so far forward that they present in the pupillary space. Immediate attention is warranted for such eyes. Air, fluid, and intraocular gas have been used to push the choroid and retina back after a posterior sclerostomy has allowed evacuation of the suprachoroidal blood.^{56,57,63–65}

If there is no extrusion of intraocular contents other than aqueous and liquified vitreous, if blood does not break through into the vitreous cavity, and if high IOP is not sustained, the prognosis for these eyes is reasonably good, with visual recovery in the majority of cases. Outcome is usually favorable in eyes with focal SCHs or if surgical drainage is undertaken within 14 days.⁵⁴ Prognosis is particularly poor if there is concomitant retinal detachment or a 360° SCH.⁶⁶

Postoperative SCH seems to occur most often in aphakic eyes with other pathology. The vitreous is often synergetic. In a hypotonous eye with little resistance to outflow through a glaucoma filtration site, liquified vitreous offers an insufficient tamponading effect to prevent expansion of the hemorrhage. Thus in such eyes, more secure closure of the guarding scleral flap may increase this resistance and reduce the likelihood of hypotony. After a few days, when inflammation from the surgery has subsided and the conjunctiva has healed enough to offer some resistance to the aqueous outflow, the scleral flap sutures can be lasered transconjunctivally to increase the scleral opening. Re-formation of the chamber with a viscoelastic substance also increases the resistance to expulsion of the intraocular contents and should be considered in high-risk eyes.

Intra-operative expulsive SCH is rarely seen in eyes undergoing glaucoma surgery. If it does occur, the limbal incision must be closed instantly and a posterior sclerotomy performed immediately over the presumed site of bleeding to allow the blood to escape from the suprachoroidal space without causing extrusion of intraocular contents or bleeding into the vitreous cavity. An anterior chamber maintainer can be inserted to maintain control of IOP. If the hemorrhage is small, it may not be located easily and therefore will be impossible to drain. In the phakic eye, it will absorb enough to allow the chamber to form, usually in 1–2 days (Fig. 36-18).



Fig. 36-18 Self-limited intraoperative subchoroidal hemorrhage below the inferior temporal arcade during trabeculectomy. This absorbed spontaneously.

(Photo courtesy of Douglas Day, MD, Atlanta.)

INTRAOPERATIVE FLAT ANTERIOR CHAMBER

Anterior chamber flattening during glaucoma surgery may occur from causes other than suprachoroidal hemorrhage (Table 36-1). In Sturge-Weber syndrome or other glaucomas with elevated venous pressure, lowering the IOP at surgery may cause immediate expansion of a choroidal hemangioma with both suprachoroidal and subretinal effusion.⁶⁷ This has been noted in approximately 20% of such cases and appears to be more common in the more severely involved side of bilateral cases.^{68,69} A posterior sclerotomy may allow suprachoroidal effusion to escape and may resolve the problem (as in nanophthalmos).⁶⁸

Sometimes, however, intrachoroidal expansion of the hemangioma occurs, and a posterior sclerotomy will reveal only the choroid, even when it is placed over the apparent mass. It is imperative that this choroid not be penetrated because it will result in massive hemorrhage and probable loss of the globe. Instead, the surgeon should close the trabeculectomy site and wait.

After a few days, as the IOP returns to preoperative levels, the anterior chamber will re-form and the choroidal mass will subside. This phenomenon probably results from arteriolar communications to the choroidal hemangioma. When IOP falls below the arteriolar pressure level of approximately 30 mmHg, there is not enough resistance to keep the hemangioma from expanding, creating a serious dilemma for both the surgeon and the patient (see the section on Sturge-Weber syndrome in Chapter 19.) In all such high-risk surgeries, the anterior chamber maintainer is invaluable.

Ciliary block glaucoma may occur during surgery when saline injected into the anterior chamber is inadvertently diverted into the vitreous cavity and the chamber becomes shallow while the eye becomes firm. One may close the trabeculectomy flap securely and try to re-form the chamber through a paracentesis opening. If this fails, 0.5–1.0 ml of liquified vitreous should be removed through a sclerostomy positioned 3 mm posterior to the limbus. If the chamber then cannot be re-formed with saline, viscoelastic substance or a large air bubble should be placed into the anterior chamber to maintain it. Atropine and topical steroids should be

Table 36-1 Causes and management of intraoperative flat anterior chamber

Condition	Causes	Management
Scleral contraction	Young eyes usually with relatively high IOP	Secure the wound as best possible; administer atropine
Choroidal expansion	Hemangioma (e.g., Sturge-Weber syndrome); effusion (nanophthalmos)	Recognize choroidal elevation; secure the wound; perform posterior sclerotomy that <i>does not</i> perforate choroid (for drainage of subchoroidal fluid); administer atropine
Suprachoroidal hemorrhage	Rare in phakic eyes unless it is buphthalmic	Recognize vitreous loss; secure the wound; perform posterior sclerotomy over choroidal elevation area to drain blood; administer atropine
Ciliary block (malignant glaucoma)	Absence of choroidal elevation; anterior chamber flattens and eye firms as balanced salt solution is injected into the anterior chamber	Secure the wound; confirm the absence of choroidal expansion or suprachoroidal hemorrhage; perform vitrectomy or aspiration 3 mm posterior to the limbus; inject air into the anterior chamber; administer atropine

Modified from Hoskins HD Jr, Migliazzo CV: Filtering surgery for glaucoma. Focal points 1986: clinical modules for ophthalmologists, vol 4, mod 9, San Francisco, American Academy of Ophthalmology, 1986.

used frequently in the early postoperative period. The eye should be observed carefully for recurrence of the ciliary block if the atropine is discontinued.

HYPHEMA

Hemorrhage may accompany any intraocular procedure, particularly in the first 3–5 postoperative days. Where compatible with general health, anticoagulants which are risk factors for intraocular bleeding during surgery should be discontinued. Consultation with the patient's provider of primary care, cardiologist, or other appropriate specialist is appropriate before discontinuing these agents. While some feel that the risks are low, studies have shown anticoagulant therapy to be a significant risk factor for intra- and postoperative bleeding^{70,71}; similarly, low-dose aspirin or ginkgo biloba preparations may need to be preoperatively discontinued, although the evidence for serious bleeding difficulties while using these agents is not convincing. Bleeding is usually from the iris, anterior ciliary body, or corneoscleral wound, producing a hyphema that commonly subsides without intervention. Activities must be restricted, and a protective eye shield should be worn during the critical follow-up period. Evacuation of the hyphema is rarely necessary, unless the IOP is persistently elevated or the corneal health threatened. If the hyphema remains for several days or increases, laser photocoagulation of localized hemorrhaging in the angle or stoma site may be possible through a clear portion of the anterior chamber. Rarely, the incision area must be re-entered to apply wetfield cautery to the bleeding site. Clot lysis, with prompt resolution of the hyphema, can be effected with intracameral or subconjunctival administration of tissue plasminogen activator^{72–75} or urokinase.⁷⁶

LARGE HYPHEMA

Very rarely, the surgeon will encounter a large, clotted hyphema postoperatively. This is usually associated with some other precipitating factor such as the use of salicylates or other clotting

inhibitors, trauma, inflammation, or rubeosis iridis. Its management must be tailored to the particular situation. High pressure can be relieved by periodically depressing the posterior lip of the sclerotomy or of the paracentesis incision if one exists.

Clot removal from the anterior chamber can be accomplished with a vitrectomy, but which significantly risks causing a cataract.⁷⁷ Careful aspiration with an irrigation/aspiration unit can, in conjunction with intracameral viscoelastic for visualization, be successful. In the absence of such phacoemulsification machinery, repeated drainage and irrigation of the anterior chamber via a 2-mm paracentesis incision can also be successful.⁷⁸ Here too the use of intracameral fibrinolytic agents (e.g., tissue plasminogen activator or urokinase) may be useful.

Late hyphema is rare; it is usually the result of a small capillary or vein in the filtration site that ruptures during a Valsalva maneuver. If the site of bleeding can be visualized gonioscopically, it can be cauterized with argon laser. Failing that, a single application of cryotherapy over the area of the bleeding site may stimulate scarring and closure of the vessel, though occasionally at the cost of scarring the filtration site.

INTRAOCULAR INFECTION

Fortunately, infection is a rare complication after glaucoma surgery. As with any intraocular procedure, infections can occur in the early postoperative period but may also be seen months to years later when a filtering bleb is present.^{79–82} After filtering surgery, all patients should be thoroughly informed about the symptoms and signs of infection, including pain, reduced vision, and purulent discharge; patients should be instructed to contact an ophthalmologist immediately if these symptoms occur. Intensive self-medication with sterile antibiotic eyedrops may be begun while awaiting ophthalmologic evaluation. If infection is even suspected, smears and cultures should be obtained from the lids, conjunctiva, and filtering bleb.

The presence of a thin-walled bleb in general and of antimetabolite use in particular are major risk factors for intraocular infection. Other risk factors include myopia, thin-walled blebs with

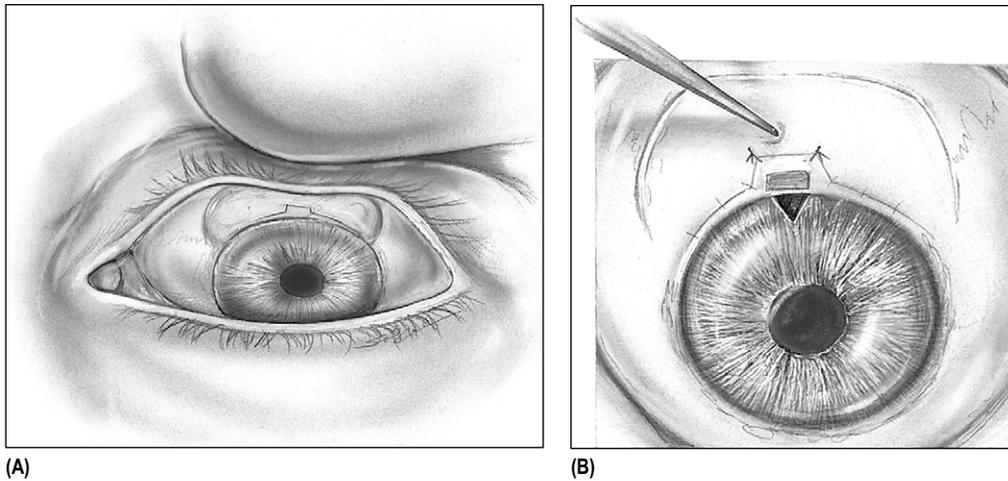


Fig. 36-19 Slit-lamp massage. **(A)** Digital pressure may be performed with a finger through the upper lid or with the tip of a relatively blunt instrument or cotton swab.

(B) Pressure should be applied to the sclera adjacent to the trabeculectomy flap. This technique may be used in standard guarded procedures, full-thickness procedures, or combined cataract and filtering procedures. In the early postoperative period, the bleb will elevate immediately upon successful opening of the wound.

leaks, the presence of releasable sutures, concurrent upper respiratory infection, and blebs located at the inferior limbus.⁸³⁻⁸⁷ Onset of infection can be anywhere from the first few days to up to 20 years later.⁸⁴ Other risk factors include unguarded filtration surgery, intermittent postoperative use of antibiotics, and diabetes mellitus.^{88,89}

Both of the most commonly used antimetabolites, mitomycin-C and 5-FU, have seemingly increased the frequency of postoperative endophthalmitis – to estimates as high as a 2.0% incidence.^{83,86,90-93} In one study, following a primary trabeculectomy with 5-FU or mitomycin-C, the 5-year probabilities for postoperative complications of bleb leak, blebitis, and endophthalmitis were 18%, 6%, and 7.5% respectively.⁹⁴ The morbidity of such infection can be appallingly high: nearly one-third of eyes following filtering surgery and treated for bacterial endophthalmitis with intensive medical treatment were at no light perception (NLP) at 1 year following infection.⁹⁵ Positive bacterial cultures carried a worse visual prognosis.

An important distinction has been made between bacterial infection confined to the bleb with limited anterior chamber reaction ('blebitis') and infection that penetrates into the vitreous cavity (classic endophthalmitis).^{96,97} Blebitis is more likely to respond promptly to intensive antibiotic treatment; it can be treated in an outpatient setting⁹⁸; and it has a more favorable visual outcome than does diffuse intraocular infection.^{97,99,100} Nevertheless, bouts of blebitis may be prodromal to frank endophthalmitis.¹⁰¹ *Staphylococcus* and *Streptococcus* species account for approximately half of the culture-positive organisms.

When hypopyon is present, fluid for culture should be obtained from the anterior chamber and vitreous. Antibiotics should be initiated while the specific causative organism is determined at the laboratory. Frank endophthalmitis usually requires aggressive vitrectomy with intracameral antibiotics (\pm steroids).¹⁰²

Prevention of such a devastating complication is problematic. Even the role of postoperative antibiotics in preventing endophthalmitis following routine cataract surgery has not yet been definitively established; nevertheless such usage remains common standard practice for nearly all intraocular surgeries.¹⁰³ The importance of patient awareness cannot be stressed enough: to detect new and unusual symptoms, to promptly seek medical attention, and to initiate antibiotic drops if a delay is encountered being seen by an ophthalmologist.

SYMPATHETIC OPHTHALMIA

Sympathetic ophthalmia may arise 2 weeks to many years after any form of intraocular surgery, but it is more common after procedures that involve intentional or unintentional incarceration of the iris or ciliary body (e.g., following vitrectomy or cataract surgery^{104,105} or after ciliary body destruction with either cryotherapy or transcleral laser.¹⁰⁶⁻¹¹¹ An incidence of 0.08% has been estimated after glaucoma operations.

Although rare, sympathetic ophthalmia is severe enough that ophthalmologists should be alerted to its symptoms and signs to make the diagnosis. Symptoms and signs include photophobia, blurred vision, and redness first in the traumatized eye and then in the fellow eye. Keratic precipitates, iris nodules, and anterior chamber flare and cell are part of the granulomatous uveitis. Dalen-Fuchs nodules form in the peripheral fundus and appear ophthalmoscopically as yellow-white spots. Fundus fluorescein angiography has characteristic patterns that establish the correct diagnosis. A thorough evaluation is advised to establish the correct diagnosis, which then requires aggressive immunosuppressive therapy,¹¹² atropine, and possibly enucleation of the exciting eye.

FILTRATION FAILURE

Failure of filtration surgery can occur any time during the first weeks after surgery or may be delayed for months or years. Early failure may result from surgical complications or technical error or simply from a vigorous healing process in the eye. The use of antimetabolites during and after filtration surgery has reduced the frequency of bleb failure from scarring, but at the cost of thinner blebs that are more prone to leak and be infected. Management of filtration failure depends on the cause and the interval since surgery.

DIGITAL PRESSURE

Digital pressure also known as *ocular massage*, is a useful technique that is used to try to salvage and retain failing filtering blebs. It is

based on the observation that forcing aqueous through a closing sclerostomy may (1) prevent closure of the sclerostomy; (2) elevate the conjunctiva and episcleral tissues away from the external opening of the sclerostomy and retard or prevent scarring, and (3) allow aqueous to flow into the filtering cicatrix to weaken its collagen structure, resulting in a more permeable bleb.

In the early postoperative period, the goal is to separate the edges of the healing scleral incision. When applied after 3 months following surgery, no effect was seen in a controlled study.¹¹³ Pressure at one side of that incision will indent it and break adhesions forming within it.¹¹⁴ This massage should be performed by the surgeon at the slit lamp. A simpler and equally effective technique is for the surgeon, at the slit lamp, to apply firm, momentary pressure through the upper lid adjacent to the bleb (Fig. 36-19). Putting pressure along the limbal or lateral edges of a trabeculectomy flap depresses the plane of the sclera while increasing the pressure in the eye. The combination of forces causes the scleral flap of the trabeculectomy to lift off of its bed so that aqueous escapes from the eye. In a thermal sclerostomy incision, point pressure with any small blunt instrument can be placed at the posterior wound edge, which will tend to rupture and reopen the slit-like sclerostomy. Based on experimental investigations, the IOP after mechanical wound distortion should be checked 40 minutes after manipulation to most accurately assess efficacy.¹¹⁵

If the sclerostomy incision is open but the bleb appears to be sealing down over it, *digital pressure* can be applied on a regular basis by the patient, through the closed eyelid, at any point on the globe away from the filtration site. One useful method is to instruct the patient to press through the upper lid on the lateral aspect of the globe until the eye just begins to ache and to hold the pressure for 10 seconds. After a 30-second pause, this can be repeated three or four times sequentially, four to six times daily. The surgeon should have the patient perform the technique in the office to measure its effect and instruct the patient appropriately. If the eye softens easily and rapidly, the patient should not be permitted to apply excessive digital pressure for fear of collapsing the globe. In diffuse blebs, the pressure reduction may last for several hours.¹¹⁶

The goal of digital pressure is to force primary aqueous into the bleb without causing hypotony. If the IOP is reduced much below 7–10 mmHg with digital pressure, secondary aqueous may be produced with its increased protein content, which could increase ocular inflammation and encourage bleb scarring. Fluctuating vision from optical distortion of the cornea with transient hypotony may also limit its effectiveness.

Gonioscopy should first be performed before pressure is used to force aqueous out of the eye, to ensure that the internal sclerostomy is not plugged by material such as iris, lens, or vitreous, which should not be forced out of the eye. Digital pressure should be used with caution in patients who have had penetrating keratoplasty or recent intraocular lens implantation. One case of corneal wound dehiscence occurred from digital pressure 10 years after penetrating keratoplasty.¹¹⁷

FAILURE DURING THE FIRST POSTOPERATIVE WEEK

Pressure elevation within the first postoperative week usually indicates a surgical complication or technical problem such as those listed in Box 36-1. If the chamber is flat with elevated IOP, the possibility of pupillary or ciliary block or a posterior segment-expanding mass must be investigated.

Box 36-1 Causes of early failure of filtering surgery

Iris, vitreous, clot, ciliary process, or lens-plugging sclerostomy
Retained viscoelastic substance
Imperforate Descemet's membrane
Scleral flap too tightly sutured
Ciliary or pupillary block

PLUGGED SCLEROSTOMY SITE

If the chamber is formed, gonioscopy is imperative to rule out obstruction of the internal filtering site by iris, clot, vitreous, or lens. Iris usually plugs the sclerostomy site after a flat chamber or if the peripheral iridectomy is too small. Iris should be removed as soon as it is recognized as an obstruction to filtration because iris tissue can seal the internal opening of either a trabeculectomy or a full-thickness sclerostomy. Pilocarpine 2% or 4% may pull the iris out of the wound. If this fails, argon laser applications through a contact lens across the anterior chamber have been successful.^{118–120} Typical settings are 50- μ m spot size and 1500 mW for 0.05-second exposure to chip the iris out of the sclerostomy. The beam is aimed at the point of adhesion between the iris and the wound, and the laser energy is used to cut the iris away from the wound. This may create a new iridotomy.

Nd:YAG laser can also be used to cut the iris away from the wound.^{121–124} Occasionally this can cause more bleeding, which may be prevented by first cauterizing the portion of the iris to be treated with argon laser energy. A 100- μ m spot size at 400–600 mW for 0.1-second exposure is used, applying enough energy and applications to see contraction of iris tissue in the area receiving Nd:YAG bursts. The Nd:YAG settings depend on the energy concentration of the particular machine but should be similar to those used for iridectomy and should be initiated with a single-shot burst.

If a small blood clot is obstructing the sclerostomy internally, pressure on the posterior lip of the sclerostomy incision may be used, either with a blunt spatula or muscle hook, or with digital pressure exerted through the lid margin while it is positioned just posterior to the scleral incision (see Fig. 36-19). This should reopen the sclerostomy and establish filtration. If the clot is quite small and the pressure not very high, waiting 2–3 days to see if the clot will lyse is an option. Argon or Nd:YAG laser can be used, as described above, to break up the clot if it is large. Argon laser is less likely to cause bleeding.

Vitreous in the sclerostomy is a more difficult problem, usually occurring after filtering surgery in an eye with prior cataract surgery (especially aphakia). Vitreous itself is not impermeable to aqueous but entrapped vitreous strands provide a scaffold for cicatrization of the filtering site. The Nd:YAG laser can be used to lyse small vitreal bands, but it is often tedious and of uncertain benefit. The best management is prevention by using great care not to rupture the hyaloid face during surgery or by performing a good anterior vitrectomy from the sclerostomy,^{121,123} but this is often unsuccessful. It is often best to wait until the eye quiets to re-evaluate the need for repeat surgery.

RETAINED VISCOELASTIC MATERIAL

Some surgeons routinely use viscoelastic material to re-form the anterior chamber at the end of a filtering procedure to retain the anterior chamber and reduce bleeding.¹²⁵ The viscosity of the material impedes aqueous egress from the anterior chamber.

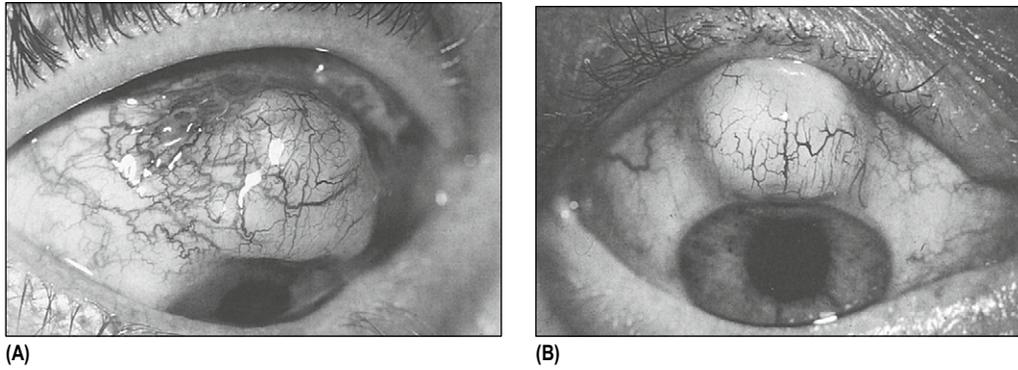


Fig. 36-20 Encysted blebs. **(A)** Two weeks after surgery, IOP was 24 mmHg in this eye. The patient was treated with timolol, and the bleb began to function. Ultimately, pressure was in the mid teens. **(B)** An eye 3 months postsurgery with a pressure of 26 mmHg. Bleb revision was required.

If aqueous production is high and the sclerostomy small, postoperative pressure elevation can be severe. Digital or direct pressure on the posterior lip of the scleral incision may widen the sclerostomy enough to allow aqueous and/or viscoelastic material to escape from the chamber. The viscous material may leave the chamber in a sudden bolus; thus the surgeon should be prepared to release the pressure quickly to prevent flattening the chamber. Most studies consistently find no essential differences among visco-dispersive agents – hydroxypropylmethylcellulose 2% (MethocelTM), sodium hyaluronate 3% with chondroitin sulfate 4% (ViscoatTM), or sodium hyaluronate 1% (HealonTM) or 1.4% (Healon – GV) in relation to endothelial cell protection, postoperative endothelial cell density, intraocular inflammation, or IOP elevation when used in cataract surgery.^{126–131} However, the visco-cohesive agent Healon-5TM can take several days before dissolving within the eye, causing prolonged IOP elevation.

TIGHT SCLERAL FLAP: RELEASABLE SUTURES AND LASER SUTURE LYSIS

Perhaps the most common cause of increased IOP during the first week after surgery is a scleral flap that is too tightly sutured. Digital pressure can reduce elevated IOP initially when secondary aqueous, wound edema, and surgical debris all contribute to reduce aqueous outflow. If digital pressure is still required after 4–7 days, or if it is unsuccessful initially, one or more of the scleral flap sutures should be loosened. This window of intervention may last many weeks if antimetabolites were used; one study suggests waiting 4 months postoperatively in mitomycin-treated eyes, thereby reducing the risk of hypotony.¹³² In our experience, however, the window is usually under 3–4 weeks.

If access to a laser is limited and releasable sutures were placed at the time of filtration surgery, their sequential release has proven useful in forestalling shallow chambers in the immediate postoperative period by allowing relatively tight flap closure for the first several days as well as later permitting IOP reduction simply by slit-lamp manipulation of the sutures.^{133,134} Experimental studies suggest the alternative method of suture adjustment to be more effective than either suture lysis or posterior lip manipulation of the filtering wound.¹¹⁵ A variety of suturing techniques have been described, including double-armed sutures and tamponade configurations.^{135–137} Adjustable sutures, tied with four-throw slip knots and manipulated postoperatively at the slit lamp, have also been described for incremental reduction of IOP.^{138,138b}

If an argon or diode laser is available, the nylon sutures routinely placed in the scleral flap are amenable to laser suture lysis. This

depends both on the visibility of the sutures through the bleb and on the extent of flap adherence to the scleral bed – a situation that can be modified by the use of intraoperative mitomycin-C or 5-FU under the flap. Multiple instruments have been described for this procedure: the standard Zeiss four-mirror gonioscopy lens, the specially designed Hoskins stalk lens, specially designed suture lysis contact lenses by Ritch, Mandelkorn, or Blumenthal, and even test tubes and micropipettes.^{139–144} The common feature among these devices is their ability to compress the conjunctiva and underlying hydrated Tenon's tissue to bring the nylon suture as close to the lens surface as possible for maximal laser effect. Argon laser settings typically are for 0.1-second duration at 400–600 mW with a 50- or 100- μ m spot size. Conjunctival perforation and its possible complications of leakage and hypotony may be minimized by using the larger spot size and incrementally increasing power. The diode laser has also been used, but it typically requires a high power density contact lens such as the Mandelkorn or Blumenthal lens.¹⁴⁵

Although the short-term effects of laser suture lysis are dramatic and obvious at lowering the IOP and improving bleb function in the short term, the long-term effects are less certain. When compared with eyes that did not undergo suture lysis and bleb manipulation, the IOP results at 2 years were the same.¹⁴⁶

INADEQUATE OPENING OF DESCMET'S MEMBRANE

In full-thickness surgery, and less often in guarded filtering procedures, there may be an inadequate opening of Descemet's membrane. This is suspected early in the postoperative period when the internal sclerostomy site is clear, yet the pressure is high and digital pressure is ineffective. In such cases, the Nd:YAG laser can be carefully focused at and slightly deep to the internal sclerostomy site and several bursts of moderately high energy delivered. If it is successful, digital pressure will open the wound and elevate the bleb.

ENCAPSULATED BLEB

An encapsulated or encysted filtering bleb (Fig. 36-20) is also referred to as exteriorization of the anterior chamber, walled-off bleb, Tenon's cyst, high-domed bleb, and localized cystic bleb.¹⁴⁷ This usually occurs during the second to fourth postoperative week, presenting as a dome-like elevation of the bleb that is walled off from the surrounding conjunctival tissue. The incidence may be as high as 9–15% after trabeculectomies.^{148–152}

A prospective study convincingly confirmed the superiority of medical aqueous suppressant therapy over bleb needling for the long-term success of such blebs as does a recent meta-analysis.^{153,154}

A comprehensive review of the literature bears out the relative superiority of topical pressure-lowering drops (e.g., timolol) over needling therapy for this condition.¹⁵⁴ Over the subsequent 4–8 weeks the pressure usually continues to fall, and the aqueous suppressants may be tapered or discontinued. Apparently the aqueous eventually modifies the bleb tissue in some manner, allowing it to become more permeable to aqueous and to function adequately as a filtering bleb. When evaluated over 3.5 years following surgery, filtration procedures complicated by encapsulated blebs, medically treated, fared as well as uncomplicated trabeculectomies, though the former required more medical therapy for IOP control.¹⁵⁵

The most convincing risk factor for the development of an encapsulated bleb is the use of a limbus-based conjunctival flap at the time of filtration surgery. Such bleb changes are less often seen with fornix-based conjunctival flaps, or in eyes never treated with topical β -blockers.^{155,156}

PROGRESSIVE SCARRING OF BLEB AND USE OF ANTIMETABOLITES

Progressive scarring of the filtering bleb may occur in the first months following filtering surgery as a continuation of the acute wound-healing process. The bleb remains vascular and gradually thickens, and the pressure starts to rise. Digital pressure three to four times daily, subconjunctival injections of 5-FU, topical application of mitomycin-C sponges,¹⁶² or laser suture lysis may salvage some of these operations.

Late scarring of the filtering bleb may be the result of an acute episode such as iritis or accidental or surgical trauma. More commonly it is a result of wound remodeling that closes the episcleral side of the sclerostomy. Usually the bleb is thick walled and diffuse, and the only apparent change is that it becomes less translucent and the pressure begins to rise. If the pressure is elevated and the bleb is thin walled and multiloculated, often a definite whitish membrane can be seen in the depths of the bleb (see Fig. 32-3). Disruption of this membrane with the Nd:YAG laser directed through the external surface of the bleb can be attempted. Late development of pigmented and non-pigmented membranes over the internal sclerostomy opening can also obstruct filtration. As in the acute situation, Nd:YAG and argon lasers can be used to disrupt these membranes and re-establish filtration.^{118,157}

The use of antimetabolites is the most important single advance in reducing the frequency of bleb scarification. Technically, perioperative corticosteroid eyedrops are antimetabolites that powerfully interrupt the normal inflammatory cascades¹⁵⁸ and whose use has proven to contribute to successful glaucoma filtration.¹⁵⁹ (The role of preoperative subconjunctival steroids and the use of the antimetabolites 5-FU and mitomycin-C are fully discussed in Ch. 34.)

REOPERATION AFTER FAILED FILTRATION

REVISION OF ENCYSTED BLEB

If a bleb continues to either scar or encapsulate so there is gradual loss of IOP control despite medical therapy, massage, or suture manipulation, reoperation becomes necessary if topical medical therapy proves ineffective. Needling of the bleb may be successful at the slit lamp or in a minor surgery setting. In a review of 81 consecutive needlings augmented with sub-conjunctival 5-FU

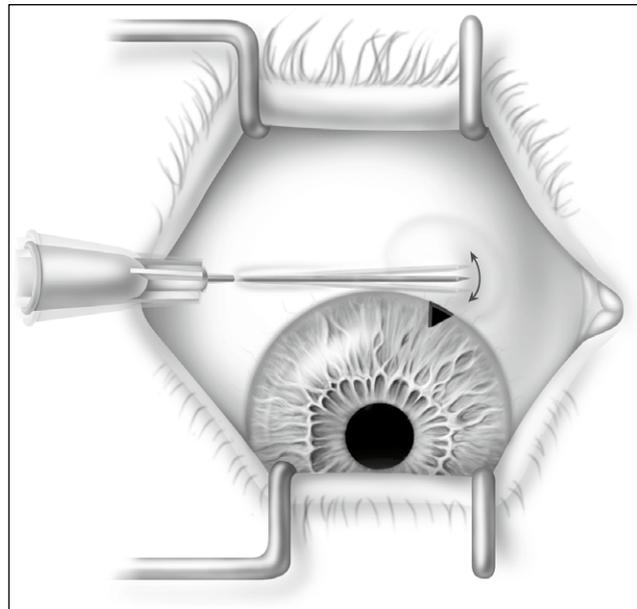


Fig. 36-21 Pederson needling. A 25-gauge needle is inserted approximately 8–10 mm from the failing bleb, and the subconjunctival tissue is ballooned with lidocaine 1%. After entry into the bleb, the episcleral fibrosis is lacerated with a sweeping motion using the sharp edge of the subconjunctival needle. Magnification by an operating microscope or loupe is advised to avoid unintentional perforation of the bleb.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

and followed for a mean of 3.4 years, favorable factors for success included immediate reduction to an IOP < 10mmHg, fewer repeat needlings, and on bleb morphology demonstrating elevation and the presence of microcysts.^{159b} Full surgical revision is sometimes required.¹⁶⁰

Needling of failed blebs Slit-lamp or minor surgery setting

The Pederson needling technique¹⁴⁸ was originally described for encapsulated blebs but has been found to be useful with failing blebs long after surgery, and even when nearly flat.¹⁶¹ If undertaken on one or two occasions and augmented with 5-FU injections or transconjunctival mitomycin-saturated cellulose sponges, full reoperation can often be avoided.^{162–164}

With the patient sitting at the slit lamp or supine under a microscope, the ocular area is cleansed with an iodine preparation and a wire lid speculum is placed using sterile technique. With the eye looking downward, the surgeon inserts a short three-quarter-inch 25-gauge needle attached to a 1-ml syringe with lidocaine 1% approximately 10mm away from and tangential to the limbus. While carefully monitoring the needle tip, the conjunctiva surrounding the bleb is ballooned. The surgeon continues to advance the needle up to one edge of the scarred capsule, at the bleb margin, and carefully penetrates the bleb. A gentle sweeping motion is used to engage and lyse fibrotic strands; small amounts of additional solution can be injected to further expand the bleb as it becomes more free (Fig. 36-21). In pseudophakic or aphakic eyes, the needle can even perforate into the anterior chamber at the site where the trabeculectomy stoma presumably is. After a bleb has been raised, the needle is withdrawn and the minute conjunctival entry wound

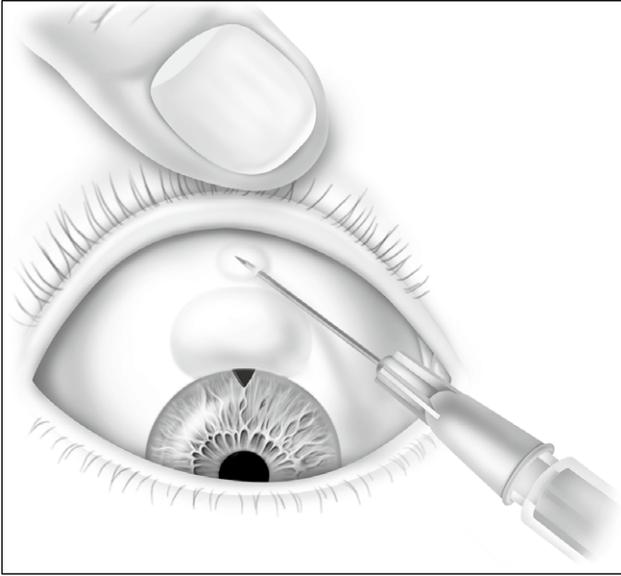


Fig. 36-22 5-Fluorouracil (5-FU) injection. After the successful lysing of the bleb scar, evidenced by an obvious reduction of IOP, an injection of 5-FU can be given. With a tuberculin syringe containing 0.2 ml of 5 mg/ml solution of 5-FU and a 30-gauge needle, a small bleb is raised with 0.15 ml (7.5 mg) injected above the true filtering site.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

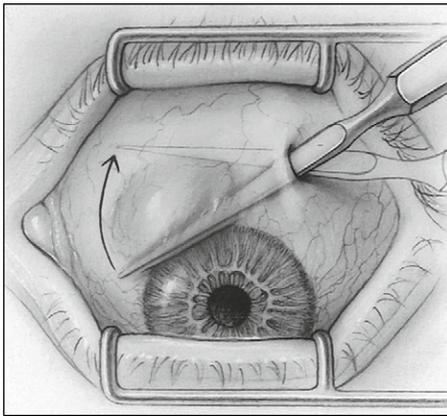


Fig. 36-23 Needling procedure. The Wheeler knife is used to lyse limiting walls of bleb. This technique is useful for blebs like the one depicted in Fig. 36-20B.

(Reprinted with permission from Cohen JS, and others: Arch Ophthalmol 95:1612, 1977, American Medical Association.)

can be closed either with a quick touch of a battery-powered cautery or with a 10-0 nylon purse-string suture. This can then be combined with the use of subconjunctival 5-FU injections¹⁶⁴ (Fig. 36-22) or mitomycin-C to enhance filtration.^{162,165}

Operating room setting

Following is the surgical technique performed in the operating room (Fig. 36-23). This technique is also useful when there is a pre-existing superior bleb that requires 'refreshing,' usually in conjunction with a temporally performed cataract/lens implantation. After local conjunctival anesthesia or retrobulbar block, the conjunctiva surrounding

the encysted bleb is elevated with Xylocaine 1% containing 1:100000 epinephrine (for hemostasis) injected through a 30-gauge needle introduced subconjunctivally at the limbus or 12–15 mm lateral to the bleb site. Either a short 25-gauge needle or a needle knife (e.g., Ziegler blade or Wheeler knife) is then introduced at the same location and passed through the fibrous capsule of the bleb. Since the eye will usually soften at this point, a preplaced paracentesis site is advised, or a Lewicke anterior chamber maintainer inserted. The knife should be passed across the bleb, incising the opposite wall and then the blade swept superiorly to open the bleb superiorly into the subconjunctival space. If the bleb wall is very dense, this upward sweep may not be possible and multiple stab incisions must suffice. The conjunctival entry point may be closed with 9-0 or 10-0 suture on a tapered needle if the wound leaks excessively.

An alternate method is to approach the bleb from the original limbal-based flap incision, carrying this forward until the thickened cystic wall is encountered. The wall is penetrated, and scissors are used to incise both lateral edges of the wall to the limbus. The conjunctiva is then closed. This allows free flow of aqueous peripheral to the cyst wall, which hopefully will not re-adhere to the episclera.

Excision of the cyst can be performed by approaching the bleb via the limbal incision, carefully dissecting conjunctiva away from the intact cyst until the conjunctiva is freed to the limbus. The cyst then can be excised in its entirety and the conjunctiva closed (Fig. 36-24).

In either of these latter two revisions, the sclerostomy opening can be modified if needed. In this situation, the sclerostomy usually is adequate as evidenced by a brisk flow of aqueous. Bleeding should be carefully controlled. Wound-modulating agents such as 5-FU or mitomycin-C may enhance success.

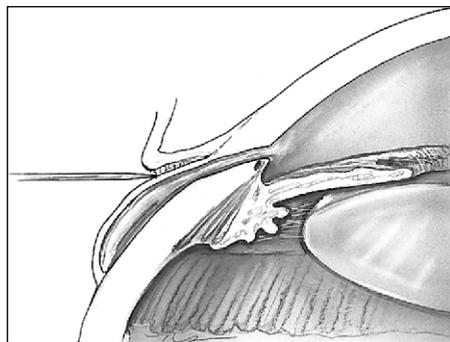
FAILED FILTRATION WITH NO BLEB

If there is no technical reason for failure of the first operation, it is important to discriminate what factors were involved: inadequate concentration or duration of subconjunctival antimetabolite; inadequate scheduling or compliance with postoperative steroids; untreated uveitis or blepharitis; inadvertent usage of former IOP-lowering drops postoperatively, etc. It may be wise to try a different filtering operation or to modify the original procedure in the hope of a more favorable response. For example, the thickness of the scleral flap in trabeculectomy may be reduced, or the flap may be sewn down more loosely in an effort to achieve better filtration. An antimetabolite, either of a different class if one was used the first time or in a higher concentration for a longer duration, may be used with re-operation.

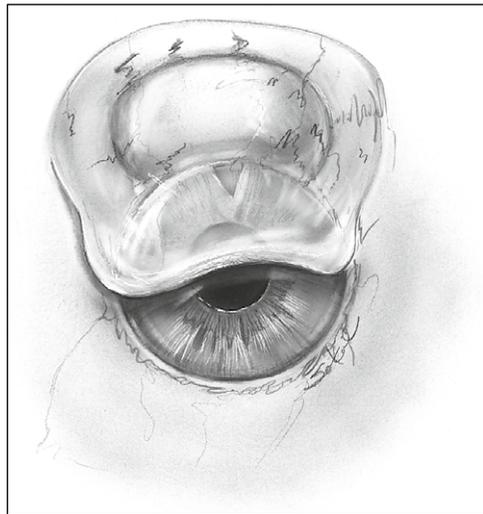
If one or more trabeculectomies have failed, either a full-thickness sclerostomy or glaucoma implant might be considered.¹⁶⁶ In the absence of antimetabolites, a reoperation with any of the external filtering procedures probably has at least a 50% chance of being successful. Such operations generally should be placed where there is unscarred conjunctiva and under the upper lid if possible. Blebs at the inferior limbus are prone to a significantly higher rate of infection, and should be avoided.^{90,100}

BLEB COMPLICATIONS AND MANAGEMENT

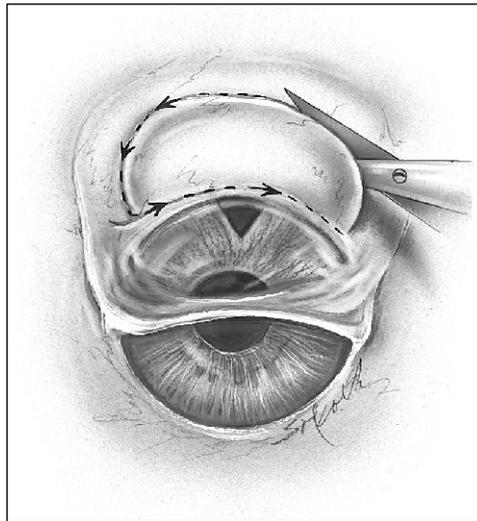
An established filtering bleb tends to be either localized or diffuse. Localized functioning blebs are thin walled and usually multiloculated, whereas diffuse blebs are shallower with thicker walls.



(A)



(B)



(C)

Fig. 36-24 Cyst revision. (A) Removal of Tenon's cyst may be accomplished by elevating the limbal flap and carefully dissecting the conjunctiva off the external surface of the cyst. (B) The conjunctiva is fully reflected forward. (C) The entire cyst can be excised. The cyst should not be perforated until the conjunctival dissection is complete because this complicates the dissection.

THIN-WALLED BLEBS

Thin-walled blebs (Fig. 36-25) are more common after full-thickness procedures and in guarded procedures augmented with antimetabolites. Such blebs are usually accompanied by lower IOP. Some surgeons believe thin-walled blebs last longer than do diffuse blebs. However, their thin walls make the eye more susceptible to infection, leaks and rupture.¹⁶⁷ A thin-walled bleb is usually more elevated than is a diffuse bleb, and patients may report discomfort. These blebs often function normally despite slow, microscopic aqueous weeping across the bleb surface, as demonstrated by a positive Seidel test. This seepage may cause tearing, especially at night, and 'microleaks' can be seen to sequentially appear and disappear, as though 'migrating,' especially in conjunction with surgical antimetabolite use.¹⁶⁸

A small hole may develop in the wall of a thin bleb, causing hypotony, increased tearing, and occasionally iritis. Infection is the danger in such an event. In the absence of antimetabolite usage, blebs with small holes often heal over time, responding simply to a regimen of aqueous suppression eyedrops, a soft bandage contact lens, and broad-spectrum antibiotics. The patient must be carefully instructed to recognize early signs of endophthalmitis, which is usually subjectively heralded by pain and uncharacteristic redness and irritation. Both the argon laser¹⁶⁹ and compression by a Simmons shell have been reported to occasionally be helpful in closing such leaks.^{26,27}

If a leak is too large or is unlikely to heal spontaneously because of prior 5-FU or mitomycin exposure, it may respond to the application of sterile cyanoacrylate 'tissue glue.'^{7,29} With the patient at a



Fig. 36-25 These thin-walled, multiloculated blebs are seen more commonly with full-thickness procedures. (From Campbell DC, Netland PN: Stereo atlas of glaucoma, St Louis, Mosby, 1998.)

slit lamp with a wire lid speculum keeping the lids open, the eye looks downward and the precise leaking area is identified with a fluorescein strip and the cobalt light. A small drop of the glue is placed either in a disposable pipette-like applicator or on the end of a wooden applicator; a variation of this technique uses a 'sandwich' of glue and a plastic 1-mm disc (Figs 36-26 through

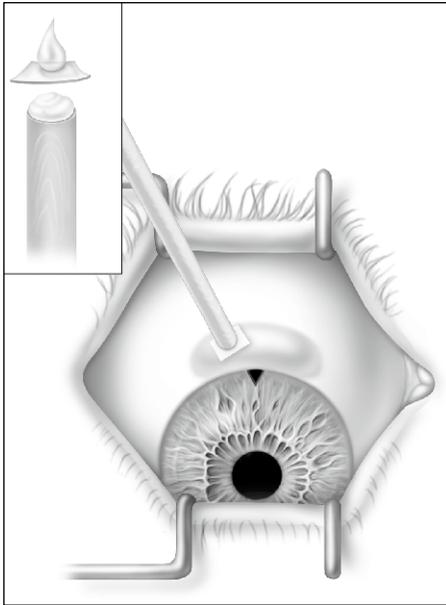


Fig. 36-26 Bleb gluing. After applying a topical anesthetic to the eye and positioning the patient supine under an operating microscope (or loupes), the surgeon prepares a 2–3-mm disc of sterile plastic cut from the drape material. This piece of sterile plastic is then applied to the end of a wooden applicator and secured by the use of any ophthalmic ointment between the wood and the plastic. Having initially dried the area carefully with a cellulose sponge, the surgeon applies a drop of cyanoacrylate glue to the upper surface of the plastic disc and then applies the entire 'sandwich' to the leaky bleb. After pressure is applied for 1 minute, the glue and plastic should adhere to the area of epithelial leak, and because of the ointment, the wooden applicator can easily be slid off the underlying plastic disc. A soft contact lens can then be applied to prevent the plastic itself from being dislodged by blinking.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

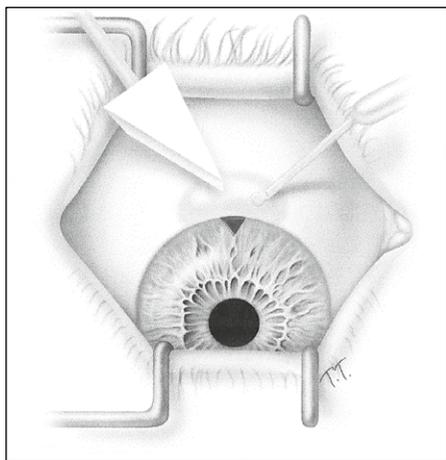


Fig. 36-27 Bleb gluing. After using a topical anesthetic on the eye and inserting a lid retractor to keep the lids apart while the patient is at the slit lamp, the surgeon meticulously dries the focus of the leaking bleb with a cellulose sponge. A very small drop of cyanoacrylate glue is then precisely applied to the dried bleb site using a pressure-activated micropipette. After 2 minutes, the glue is allowed to dry on the eye.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

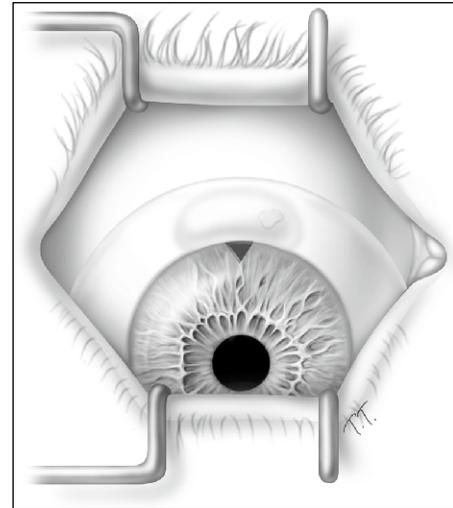


Fig. 36-28 Protecting the glue patch. Therapeutic soft contact lenses, ranging from 16 to 24 mm in diameter, are available to encompass the cornea and perilimbal areas. As illustrated here, such a large lens can amply cover the bleb and the dried site of glue so that the lid does not blink the glue patch loose before healing has occurred.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

36-28). A cellulose sponge dries the entire leaking site, and the glue is promptly applied and allowed to air dry for 1 minute. To minimize discomfort and dislocation of the glue patch by blinking, a special, large-diameter, soft contact lens is usually applied. The glue will spontaneously dislodge when there has been epithelialization and closure of the leak.

If a tear is too large or is resistant to conservative measures of closure (e.g., cyanoacrylate glue), surgical revision may be required. The use of a tapered needle with 10-0 nylon suture may be adequate for closing the leak; if the bleb has been treated with antimetabolites, however, the epithelial surface may be too friable to sustain suture repair. Another maneuver that may prove effective involves inserting of a piece of Tenon's capsule beneath the bleb (see Fig. 36-1). The Tenon's tissue is sutured directly into the undersurface of the fistula to plug the fistula.

If these strategies do not work, more extensive bleb revision is required. A sliding flap of conjunctiva is made accessible by either undermining the subconjunctival space toward the fornix with blunt-tipped scissors to mobilize available conjunctiva downward or by making a parallel vertical incision into the upper cul-de-sac and pulling it over the bleb area (Figs 36-29 through 36-34). If the bleb surface continues to leak or is necrotic, the bleb tissue is excised. If the scleral flap appears incontinent, the stoma can be tamponaded with a freehand partial-thickness autologous or donor scleral graft,¹⁷⁰ with a partial-thickness piece of host sclera, or with donor fascia lata.¹⁷¹ A groove incision is made in the superficial corneal tissue at the limbus. The flap is sutured into this groove and to adjacent conjunctiva with running 10-0 nylon. The flap must not be stretched too tautly or it will retract.

Although such extensive surgical disruption of the bleb can lead to unwanted scarring, the majority of refashioned blebs maintain adequate IOP control with or without medication.^{170,172,173} Nevertheless, as much adjacent limbal tissue as possible should be spared for future surgery if needed.

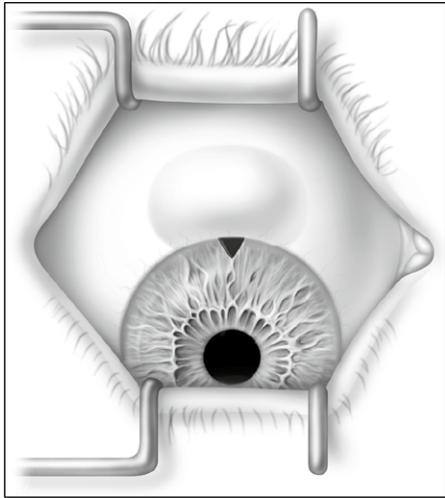


Fig. 36-29 Surgical bleb reduction. With retrobulbar administration of anesthesia in the operating room, the excessive bleb can be viewed at the operating microscope.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

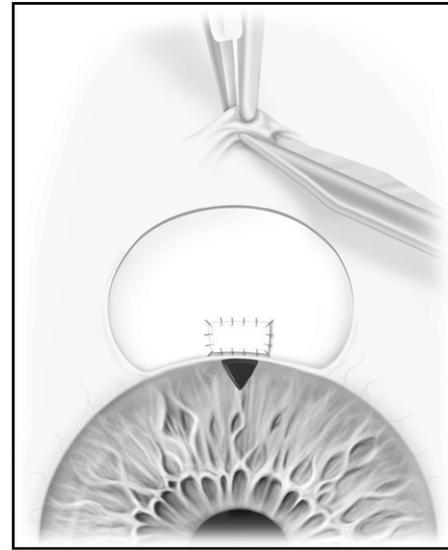


Fig. 36-32 Surgical bleb reduction. Once the scleral graft is secured above the trabeculotomy ostium, a relaxing incision can be made peripherally to mobilize the conjunctiva to be drawn toward the limbus.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

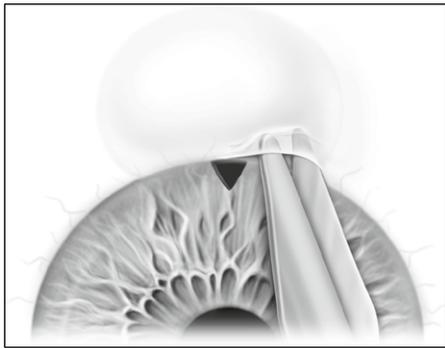


Fig. 36-30 Surgical bleb reduction. A fornix-based conjunctival flap is prepared at the base of the excessive bleb.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

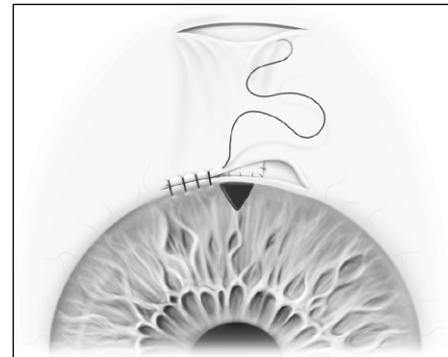


Fig. 36-33 Surgical bleb reduction. With the relaxation of the conjunctiva, a water-tight fornix flap can be closed (e.g., using 9-0 Vicryl suture) either by attachment to the apron of remaining conjunctiva, as illustrated here, or transconjunctally.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

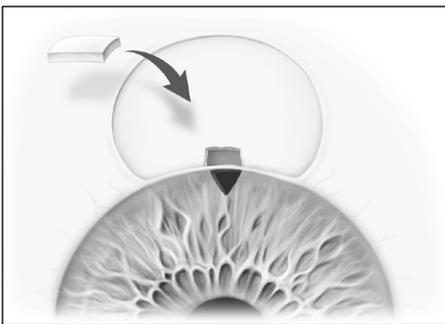


Fig. 36-31 Surgical bleb reduction. After removal of the offending bleb structure, the episclera is exposed and the stoma of the original trabeculotomy is evaluated. Sometimes, with the use of antimetabolites such as mitomycin, the scleral flap may have 'melted away' (as illustrated here), necessitating the use of a donor or host scleral patch graft that is hand cut and sutured as a secondary trabeculotomy flap.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

Because of the risk of perforating or infecting a thin-walled bleb, rigid contact lenses should be used carefully in such eyes⁷⁹; soft lenses may be used with similar precautions. Since even the value of prophylactic intraoperative antibiotics to prevent endophthalmitis after routine cataract surgery remains controversial,¹⁷⁴⁻¹⁷⁷ it is not surprising that there is even less evidence for prophylactic antibiotics in the presence of thin-walled blebs. Because of the risk of overgrowth of resistant species of bacteria and the irritating properties of the drops, many authorities prefer not to use them.^{167,178} Rather, patients are advised to return immediately if any symptom of conjunctivitis or discomfort occurs. Sometimes it is useful to give them a broad-spectrum antibiotic drop, which can be started immediately if such symptoms occur and while ophthalmologic attention is being sought.

BLEB MIGRATION ONTO CORNEA

Occasionally after a successful operation for external drainage, the conjunctival bleb dissects down into the cornea.¹⁷⁹ Here it forms a translucent white blister, which slowly extends toward the central cornea (Fig. 36-35). If the patient complains of foreign body sensation, the chronic intermittent use of topical lubricating drops or ointment or non-steroidal anti-inflammatory eyedrops (e.g., ketorolac 0.5% or diclofenac 0.1%) may bring relief.¹⁸⁰ If symptoms persist, the encroaching bleb can be removed by dissecting it off the cornea like a pterygium.¹⁸¹ Pathologically, this blister is largely acellular and filled with amorphous material. When the limbus is reached, the tissue can be excised without collapsing the filtering bleb. After several days of aqueous weeping, such 'amputated' blebs usually heal, especially if steroid drops are sparingly used.

DIFFUSE BLEBS

Thick-walled diffuse blebs are more cosmetically acceptable, comfortable, and less prone to infection or leakage than are thin-walled blebs. Diffuse blebs appear as pale and subtle conjunctival elevations, often with tiny, interepithelial microcysts on their surface. These microcysts are most abundant near the limbus and are best

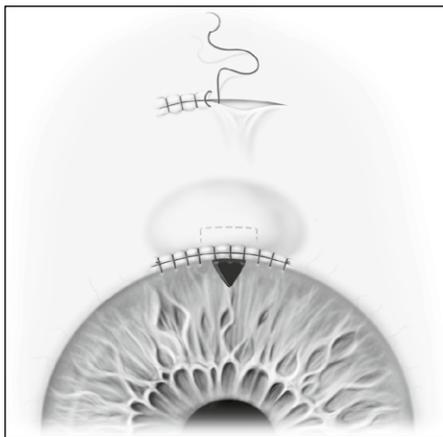


Fig. 36-34 Surgical bleb reduction. A Vicryl suture closure of the relaxing incision can be performed to ensure that the entire wound remains water tight. A bleb can be seen at the site of the revised bleb.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

seen with the slit lamp by directing the light to a spot adjacent to the viewing area (scleral scatter or retroillumination technique). Although rigid contact lenses appear to be safe with thick blebs, endophthalmitis has been reported.⁷⁹ There is little information about the long-term safety with thick blebs of soft contact lenses; but as with all patients who have undergone filtration surgery, awareness of the warning signs of infection is obligatory.

OVERFUNCTIONING BLEBS

A very large diffuse bleb can be an irritant to the patient and a source of hypotony. These blebs may appear more commonly with the use of antimetabolites, excessive suture lysis or manipulation, or aggressive digital massage. They sometimes appear to encircle the entire limbus ('gutter blebs'), causing boggy to all the bulbar conjunctiva (Fig. 36-36). More often they are limited to two quadrants. If the pressure is properly controlled, the patient often will accept the symptoms. As with blebs that have migrated onto the cornea, large blebs presumably interrupt the normal distribution of the tear film and hence cause discomfort. Relief may be obtained by using ocular lubricants, such as artificial tear drops or ointments, or by using topical non-steroidal anti-inflammatory eyedrops, such as ketorolac 0.5% or diclofenac 0.1%.¹⁸⁰

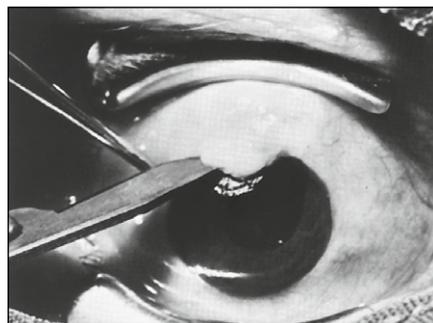
If hypotony exists in conjunction with an overfunctioning bleb, an attempt can be made to delimit the bleb without loss of its



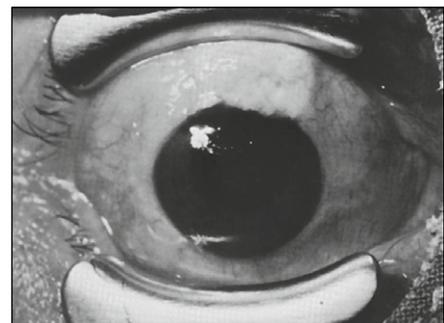
Fig. 36-36 A large diffuse bleb that nearly encircles the cornea but is most prominent nasally. Pressure was 12 mmHg. After 8 years the pressure had risen to 17 mmHg.



(A)



(B)



(C)

Fig. 36-35 (A) An extreme example of the bleb dissecting onto the corneal surface. (B) The bleb may be excised by sharp dissection from the cornea and excision at the limbus with scissors. (C) Postoperative appearance.

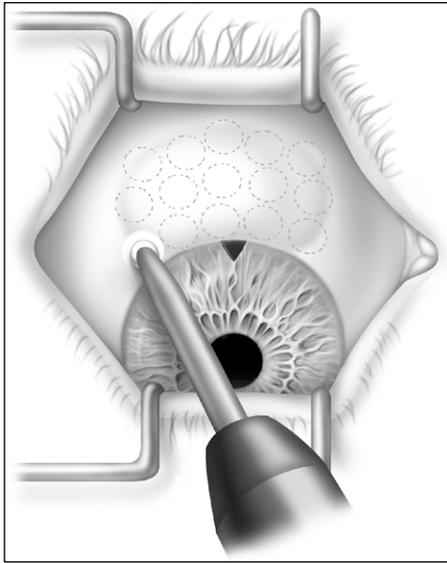


Fig. 36-37 Cryotherapy for bleb reduction. With the patient under topical anesthesia, a glaucoma probe can be applied on top of and surrounding the exuberant bleb, with a freeze allowed to enlarge approximately 2 mm on each side of the probe for approximately 5 seconds. Care should be taken for the iceball to thaw fully before the probe is removed so as not to disrupt the underlying bleb tissue.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications. Philadelphia, Lippincott-Raven, 1995.)

function. All of the techniques that have been described^{7,182} have in common the ability to induce inflammation: cryotherapy,¹⁸³ electric needle hyfrecation,¹⁸⁴ argon laser,¹⁸⁵ trichloroacetic acid applications,^{186,187} or transconjunctival obstruction sutures at the limbus with absorbable suture to delimit lateral guttering. As is common when there are many techniques available, each is unpredictable in its efficacy.

Cryotherapy can be controlled nicely, penetrates well into the episcleral region, and is widely available (Fig. 36-37). Three or four applications across the distal end of the bleb are used; if the bleb is not too elevated, applications across its surface can also be attempted. With the patient under topical anesthesia, the probe is pressed against the conjunctiva until a ring of ice approximately 4-mm wide encircles the probe. To avoid tearing the conjunctival surface, the probe should not be removed from the globe until the tip has thoroughly thawed. These applications are repeated as needed. It is better to do too little and add more after 1 or 2 weeks than to overdo it and close down the filtering bleb. This procedure can cause operative and postoperative pain.

The techniques of electrocautery (electric needle hyfrecation) and trichloroacetic acid application restrict treatment to the zone surrounding the bleb's extent. In the former technique, in which only topical anesthesia is used, a standard hyfrecator electrocautery at moderate settings applies mild burns in rows surrounding the exuberant bleb (Fig. 36-38). Applications should be made to barely blanch the conjunctiva, applying light pressure on the device to compress the conjunctiva and its underlying fluid down to the episcleral surface. The cautery is usually not applied to the bleb surface itself.

Using the chemical technique, a wooden applicator is dipped into a supersaturated solution of trichloroacetic acid. This is prepared fresh from a small spoonful of anhydrous crystals placed in

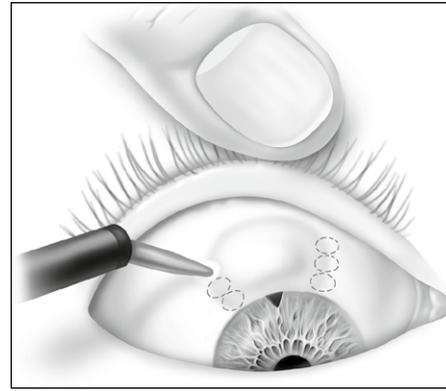


Fig. 36-38 Cautery bleb reduction. With the patient under topical anesthesia, a standard hyfrecator electrocautery applies mild burns in rows surrounding the exuberant bleb. Applications should be made to barely blanch the conjunctiva, applying light pressure on the device to compress the conjunctiva and its underlying fluid down to the episcleral surface. The cautery is usually not applied to the bleb surface itself.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications. Philadelphia, Lippincott-Raven, 1995.)



Fig. 36-39 Chemical bleb reduction. A wooden applicator is dipped into a supersaturated solution of trichloroacetic acid and carefully applied in several rows surrounding the exuberant bleb, with care taken to avoid leakage of the chemical onto the corneal surface. The bleb surface itself is usually avoided. Light chemical blanching and whitening is seen after a few seconds of application. This technique may be uncomfortable for the patient, and topical atropine and patching are often useful.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications. Philadelphia, Lippincott-Raven, 1995.)

10 ml of sterile water and stirred until all the crystals go into solution. A minimal drop on an applicator is carefully and repetitively applied in several rows surrounding the exuberant bleb, with care taken to avoid dripping the chemical onto the corneal surface (Fig. 36-39). The surface of the bleb is usually avoided. Light chemical blanching and whitening is seen after a few seconds of application. This technique may be uncomfortable for the patient, and topical atropine and patching may be useful. An untimely blink or tearing can wash the trichloroacetic acid onto the cornea causing epithelial burns and denudation. For this reason, this technique has been largely abandoned.

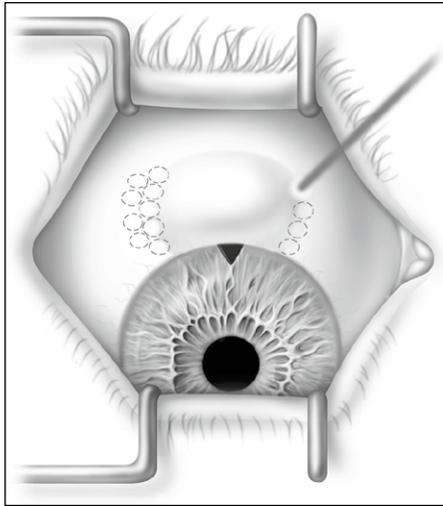


Fig. 36-40 Argon laser bleb treatment. With the patient under topical anesthesia, foci of bleb leakage (or the margins of large blebs, as illustrated here) can be lightly coagulated with an argon laser, using a large spot size and minimal energy. Topical dyes, such as fluorescein or rose bengal, may enhance the thermal absorption.
(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

Argon laser energy can be delivered to the surface of a conjunctival bleb that has been stained by swabbing it with methylthioninium chloride dye (Fig. 36-40). Laser settings of 400–700 mW with a 500- μ m spot size applied for 0.2–0.5 second will shrink the surface of the bleb. Because bleb perforation has occurred with this technique, it should be used with caution in blebs pretreated with antimetabolites, which may fail to heal spontaneously.

DELLEN

If a bleb is markedly elevated at the limbus, the lid cannot spread tears over the adjacent cornea, and dellen form (Fig. 36-41).¹⁸⁸ These dellen are almost always self-limited and may be palliated with ointment, frequent tear replacement eyedrop application, or non-steroidal anti-inflammatory drops. Steroid drops may be contraindicated because they retard corneal surface healing; vascularization of the base in fact precedes healing.¹⁸⁹ Cryotherapy over the bleb adjacent to the dellen has been effective.

HYPOTONOUS MACULOPATHY

One complication of hypotony may occur early or late, within hours or days, after the reduction of IOP. Although reported many decades ago during the advent of full-thickness filtering procedures,¹⁹⁰ hypotonous maculopathy was later described as a specific syndrome¹⁹¹ and is being appreciated as a serious cause of visual impairment, often reversible, following any IOP-lowering surgery. This situation has been extensively reported in filters augmented both with 5-FU^{192,193} and mitomycin-C.^{194–196} It is characterized by persistent hypotony (usually



Fig. 36-41 Dellen adjacent to a bleb. A large bleb after filtering surgery prevents the tear film from reaching that area of the cornea. Spontaneous healing is the rule.

defined as IOP less than 5 mmHg) for many weeks after surgery, with decreased visual acuity.¹⁹⁷ Funduscopy examination and OCT imaging¹⁹⁸ reveal no specific macular edema but rather choroidal wrinkling behind the macula leading to the appearance of choroidal folds – particularly well seen on red-free photography. Subsequent series have identified two risk factors associated with hypotonous maculopathy and loss of vision: high myopia and age younger than 50.^{199,200} These factors most likely relate to decreased scleral rigidity in the area of the posterior pole and tendency towards collapse in the presence of low IOP. Low pressure alone is not incompatible with good visual acuity.^{199,201}

Although it has been established that there is a slight decrease in the axial length of the eye after glaucoma shunt procedures or trabeculectomy without the use of antimetabolite (on the order of 0.27 mm),^{202,203} eyes with hypotonous visual loss often require vigorous intervention to reduce the apparent effect of a collapsed posterior pole.

By and large, non-surgical interventions (e.g., soft contact lenses, bleb size reduction by cryotherapy,¹⁹⁵ autologous blood injections (Fig. 36-42), with or without compression sutures,^{204–206} argon laser to the bleb²⁰⁷) are inconsistently effective. Returning to the operating room for tightly resuturing the scleral flap and elevating the IOP for the short term offers the most expeditious return of visual function and retention of IOP control,^{200,208–210} although a less complicated procedure has been described.^{210b} Occasionally more extensive surgery, such as vitrectomy with intraocular gas, is required.²¹¹ Avoidance of hypotony altogether with the primary surgery is, of course, the optimal procedure; surgical technique modifications with this goal in mind have been described.²¹²

When IOPs are consistently brought above the level of 6 mmHg, a return of visual function is seen in most eyes. It sometimes takes 8–24 months until restoration to within 1 or 2 Snellen lines of the preoperative acuity is achieved, albeit with some persistent metamorphopsia. Return of vision is faster with higher post-repair IOPs.

LATE HYPOTONY AFTER FILTERING SURGERY

Hypotony resulting from overfunctioning or perforation of a thin-walled filtering bleb has been described in an earlier section. Less frequently, delayed hypotony is encountered with ciliochoroidal

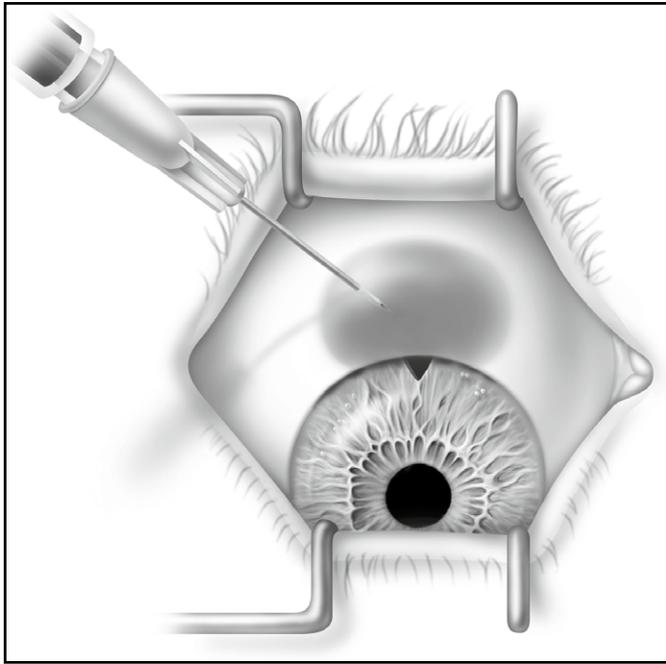


Fig. 36-42 Autologous blood injection. After a sterile extraction of approximately 1 ml of the patient's blood, a small 27-gauge needle is applied to the same syringe, and with the patient under topical anesthetic the autologous blood is injected into the bleb itself. Because of the high likelihood of blood entering the anterior chamber, this technique is sometimes varied to first fill the anterior chamber with sodium hyaluronate (Healon), which may produce a tamponade effect that minimizes the extent of the iatrogenic hyphema.

(From Lieberman MF: Complications of glaucoma surgery. In: Charlton J, Weinstein G, editors: Ophthalmic surgery complications, Philadelphia, Lippincott-Raven, 1995.)

detachment and no apparent filtering bleb. This occurs as a result of multiple separate mechanisms.^{23,213}

HYPOTONY WITH OCCULT FILTERING 'BLEB'

In rare cases after filtering or cataract surgery there may be an efficiently functioning limbal filtering site that cannot be recognized by routine clinical examination. There is no apparent evidence of a filtering bleb by either slit-lamp examination or gonioscopy. If other causes of hypotony cannot be found, injection of fluorescein into the anterior chamber can demonstrate whether such a filter exists by detection of accumulated fluorescein in a focal area of the perilimbal subconjunctival space. Such sites may be closed by one or two applications of cryotherapy sufficient to produce a 1–2-mm ice ring around the area of the fistula. If this fails, surgical exposure and direct suturing of the fistula with a trans-scleral absorbable suture almost always closes it. The pressure, however, may temporarily rise and respond only to miotics.

HYPOTONY WITH OCCULT CYCLODIALYSIS CLEFTS

A similar situation occurs with undetected cyclodialysis clefts, the size of which is unrelated to the extent of hypotony.²¹⁴ In the

presence of hypotony, gonioscopy may be difficult because of corneal folds; intracameral viscoelastic can be injected through a paracentesis at the slit lamp to permit visualization and, if needed, argon laser can be applied to the cleft.^{215,216} Visualization of such clefts is also possible with UBM imaging.²¹⁷ Sometimes the clefts are invisible or 'migratory,' appearing in different locations on different occasions as though the ciliary ring is fish-mouthing in different areas.²¹⁸

When not visualized, clefts can be surmised from the eye's response to atropine (elevation of pressure) or miotics (hypotony). Their occult location is often associated with the most recent surgical site, such as a filtration site, a recent phacoemulsification wound,²¹⁹ posterior lens suture site,²²⁰ or limbal incision made during an anterior chamber lens implant removal.²²²

The first line of therapy is full cycloplegia with atropine, with the possibility of an acute rise in IOP that may require prompt medical intervention. Multiple argon or diode²²³ laser applications to the cleft, cryotherapy, and trans-scleral suturing²²¹ through the cleft have all been successful treatments.

HYPOTONY WITH AQUEOUS SUPPRESSION THERAPY IN CONTRALATERAL EYE

Timolol in the fellow eye and oral acetazolamide therapy after previous failed trabeculectomy have been reported to cause profound hypotony with ciliochoroidal detachment in the operated eye.²²⁴ The postulated mechanism implies supersensitivity of the ciliary epithelium to the pharmacologic agent, which causes profound aqueous suppression. We have also seen one case resulting from topical epinephrine therapy. The hypotony usually disappears with cessation of the drug. Such supersensitivity may also appear as a crossover effect when the fellow eye is being treated with a β -blocker; the recently filtered eye may respond with hypotony but IOP may rise when drops are discontinued in the other eye.

HYPOTONY FROM RETINAL DETACHMENT

The sudden onset of hypotony in any eye should cause suspicion and examination of the eye for a retinal detachment.²²⁵ This is especially true after vitrectomy for eyes at risk for rhegmatogenous lesions (e.g., vitreoretinal proliferation in diabetes). If a detachment is found, retinal repair will resolve the hypotony.

HYPOTONY FROM IRITIS OR ISCHEMIA

Late hypotony resulting from iritis may occur after filtering surgery. Chronic uveitis and prior surgeries may also predispose to cyclitic membranes, which contract and detach the underlying ciliary body, with subsequent hypotony.²²⁶ Visualization of such membranes can be done with scleral depression and indirect ophthalmoscopy or by ultrasonic imaging; if found, surgical repair is necessary. A rare cause of chronic hypotony with inflammation is ischemia from vasculitis.²²⁷ If no other cause for the hypotony is evident in the presence of chronic flare and cell, treatment with topical cycloplegics and corticosteroids frequently will resolve the problem.¹⁸

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CHAPTER
37Pediatric and miscellaneous
proceduresSURGERY FOR INFANTILE AND
JUVENILE GLAUCOMA

GONIOTOMY

Perhaps the most satisfactory operations for treatment of primary congenital (infantile) glaucoma are goniotomy and trabeculotomy *ab externo* (see Ch. 19). Goniotomy is safe when performed under gonioscopic visualization by a trained surgeon, and usually can be performed without scarring the eye in ways that interfere with later procedures. Successful surgery improves aqueous outflow, probably by restoring outflow through Schlemm's canal, and can be maintained for long periods or even indefinitely.¹ However, recurrences of increased pressure in some of the children originally operated on 40 or more years ago make lifelong surveillance of these patients a necessity.

Preoperative considerations

The patient's family should be informed that an examination under anesthesia (EUA) will be undertaken to determine the extent of glaucoma and the patient's ocular health; all of the attendant risks of general anesthesia should be mentioned. If control of the glaucoma is uncertain, it is in the operating room at the conclusion of the EUA that decisions are made regarding whether to operate, which type of surgery to undertake, and whether to proceed on one or both eyes. All risks and benefits should be explained, and the long-term nature of the cooperative effort between doctor and family should be emphasized. All equipment for the EUA should be readily available, including gonioscopy lenses, microscopes, light sources, calipers, tonometers, pachymeter, ophthalmoscopes, and imaging devices such as a B-scan or fundus camera. A-scan measurements of axial length may be helpful in following progression or lack thereof in the first 2–3 years of life.²

If the intraocular pressure (IOP) is elevated and the cornea is hazy, preoperative medical therapy may clear the cornea and facilitate goniotomy. Many classes of effective topical medications, such as β -blockers, prostaglandins, and carbonic anhydrase inhibitors (topical or oral), may be given cautiously. The physician and family should remain alert to side effects of medications in children (see Ch. 22). Infants and children receiving topical β -blockers should be monitored for apneic spells or bronchospasm; the use of α -agonists in children under 6 years is *contraindicated*. To alleviate the risk of potential cardiopulmonary problems, the anesthesiologist should be made aware of any preoperative medications used by the patient.

If surgery is being considered, the pupil should not be preoperatively dilated for examination of the optic nerves because this increases the risk of lens injury during either goniotomy or trabeculotomy.

Often the discs can be satisfactorily viewed with a direct ophthalmoscope through a Koepe lens used at the time of gonioscopy; or ophthalmoscopy through a dilated pupil (e.g., for photographs) can be postponed until future examination. Often, a quite satisfactory view of the optic nerve can be obtained with the use of one drop of topical tropicamide 1%. If the pupil is not constricted at the conclusion of the EUA, miotic intracameral preparations (carbachol or acetylcholine) can be administered at the time of surgery.

Intraoperative procedures

If necessary for visualization of the angle, goniotomy can be preceded by application of topical anhydrous glycerin or removal of the cloudy corneal epithelium. The safety of goniotomy depends on good visibility, and epithelial haze may increase after diagnostic and surgical contact lenses have been used. If a great deal of edema is present, a sheet of epithelium comes off easily. Otherwise, considerable pressure on a curet or the side of a #15 Bard-Parker blade may be needed to remove the epithelial layer. Scrubbing the cornea with an applicator soaked in 70% ethyl alcohol loosens the epithelium and makes its removal much easier, but may increase postoperative discomfort.

If corneal edema is severe, only the junction point of the iris to the trabecular meshwork may be visible; this may be adequate for placement of the goniotomy incision. If extreme haziness is present, trabeculotomy is recommended.

Attention to detail is of utmost importance in goniotomy. A variety of classical surgical techniques are described here.

Two locking Elschmig forceps are used by the assistant to grasp the superior and inferior rectus muscles while the surgeon holds the lid out of the way with a muscle hook and turns the eye with forceps to expose the site of each tendon insertion. A speculum is not needed and would be in the way of the forceps throughout the procedure.

The patient's head is turned 30–45° away from the surgeon to prevent air bubbles from accumulating under the modified Hoskins-Barkan or Swan surgical contact lens (Fig. 37-1). The surgeon's left forefinger or an angled toothed forceps holds the contact lens against the eye. The Elschmig forceps under the surgeon's left hand must be rotated out of the way by the assistant. A drop of balanced salt solution (BSS) is placed under the contact lens. The lens is rotated away from the near limbus so that there will be ample room for the goniotomy knife to enter the cornea.

A high-powered binocular operating room microscope, as is used in phacoemulsification procedures, works well for this procedure; foot control for 'X-Y-Z' manipulation of the viewing system is extremely helpful. Tilting the head of the microscope to facilitate the view of the chamber angle may also be helpful. A paracentesis should first be made for the introduction of a miotic if needed and for

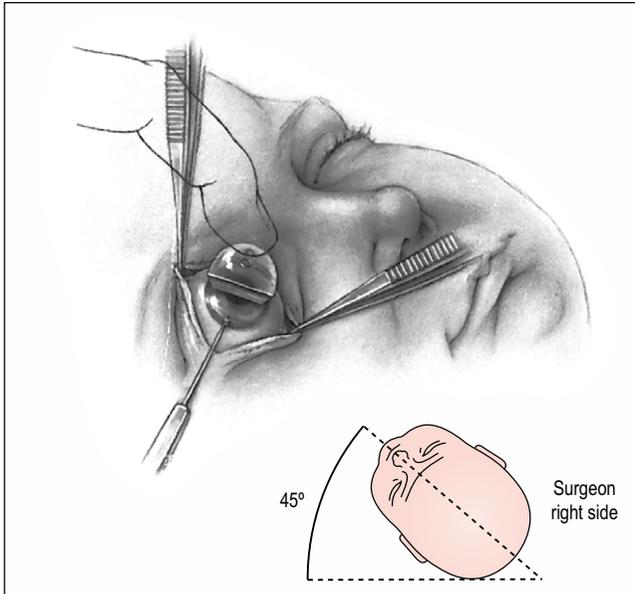


Fig. 37-1 Goniotomy, showing position of child's head turned away from surgeon at 45° away from vertical. The eye is fixated by two locking Elschnig forceps in the superior and inferior rectus muscles.

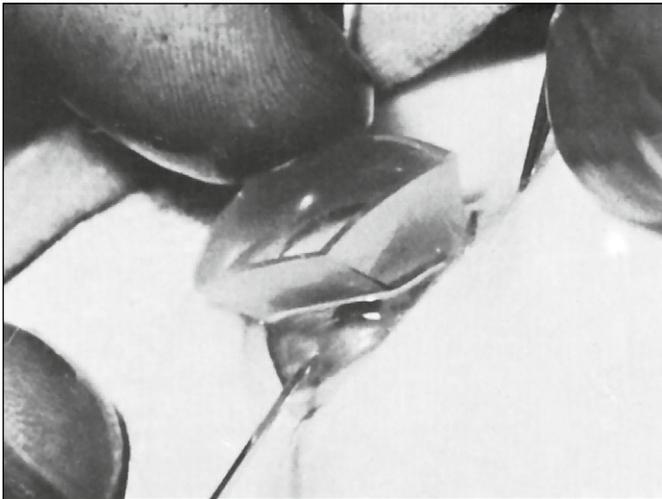


Fig. 37-2 Position of the surgical contact lens and goniotomy knife. With the patient's head turned 45° away from surgeon, air cannot get under the lens. (From Shaffer RN. Published with permission from the American Journal of Ophthalmology 47:90, 1959.)

inserting a viscoelastic to maintain and protect the anterior chamber. Entry of the knife into the anterior chamber should be done under low magnification. Higher power is used for the trabecular incision.

The assistant holds the eye so that the plane of the iris is parallel to the direction of the knife thrust. The eye should be lifted upward from the orbit to permit maximum exposure and should be rotated so that the incision can sweep for 4 or 5 clock hours of angle, allowing a second goniotomy to be performed on the opposite side if needed (see Fig. 19-22).

The contact lens is held against the cornea, several millimeters away from the lateral limbus (Fig. 37-2), to allow the goniotomy knife to enter the cornea 1–2mm inside the limbus. The assistant needs to

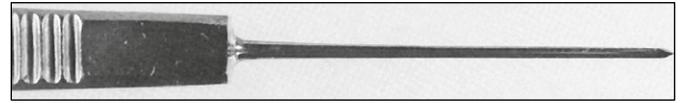
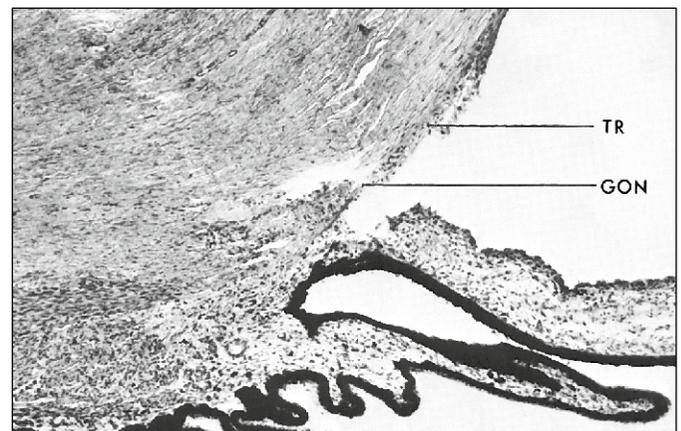


Fig. 37-3 Enlarged view of the Swan goniotomy knife showing the double-edged blade.



(A)



(B)

Fig. 37-4 (A) Isolated trabeculodysgenesis with an anterior iris insertion. **(B)** Opposite side of the same eye showing the goniotomy incision (GON). SC, Schlemm's canal; STR, scleral trabecular meshwork; UTR, uveal trabecular meshwork; TR, trabecular meshwork; AI, iris process. (Courtesy of L Christensen, MD, University of Oregon, Portland, Oregon.)

hold the eye against the pressure of the knife as it enters the cornea obliquely to minimize aqueous loss during and after the procedure. Care should be taken to penetrate the cornea neither too tangentially nor too perpendicularly.³ A Swan goniotomy knife (Fig. 37-3) with a thin, straight shaft helps maintain the chamber when the instrument is withdrawn. The blade is double sided so that the goniotomy incision can be made in opposite directions without rotating the knife. The blade is passed across and to the far side of the anterior chamber with a slight back-and-forth rotating motion around the long axis of the knife to facilitate its passage through the cornea.

The knife tip should engage the trabecular meshwork just below Schwalbe's line and barely enter the meshwork (Figs 37-4 and 37-5).

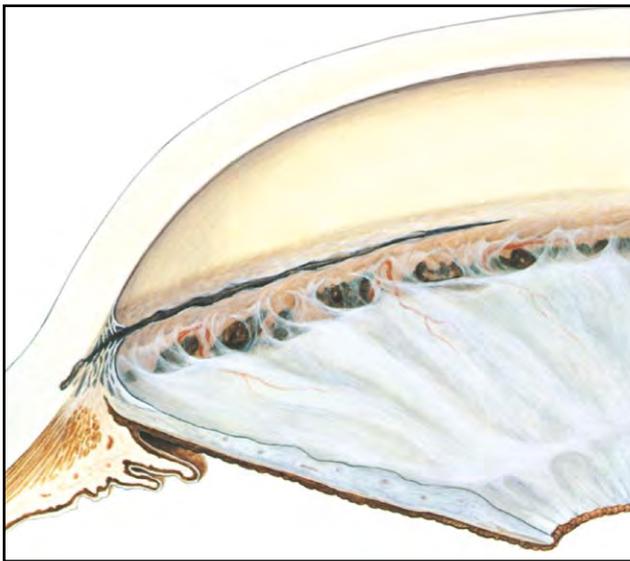
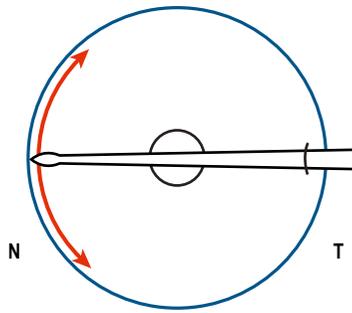


Fig. 37-5 Goniotomy. Through a temporal corneal incision (T), a goniotomy can be performed nasally (N). The illustrated gonioscopic cross-section shows the exact location of the incision in the abnormal trabecular meshwork.

Then with the use of the corneal entry site as the fulcrum, the surgeon can make a 100–110° incision in the meshwork in stages, pausing each 40–50° while the assistant rotates the eye to allow a new area of the meshwork to be incised. There should be no feeling of resistance in the tissue. If the blade is too deep and is cutting sclera, a grating sensation occurs (like cutting a lettuce core). If a cut of more than 50° is attempted in one direction, it may be difficult to maintain the chamber depth and keep the cornea free of folds and thereby more difficult to maintain accurate visual control of the knife tip. Visual control is essential to prevent misplacement of the incision. If the knife goes into the anterior ciliary body, severe and possibly disastrous bleeding may occur. If the knife strikes the lens, a cataract will form. If the incision extends anterior to Schwalbe's line, it is useless therapeutically. If it goes into the sclera, bleeding and fibrous proliferation are likely. The knife should be removed smoothly and quickly, with its handle kept parallel to the iris to avoid contact with the lens.

If an experienced assistant is not available, a modified goniotomy technique may be easier. A pediatric lid speculum (Wiener or Barraquer) is used. 4-0 silk sutures placed beneath the tendons of the superior and inferior rectus muscles will satisfactorily position the globe. The sutures are then clamped to the drapes to provide fixation of the globe. The Swan-Jacob goniolens (Fig. 37-6),

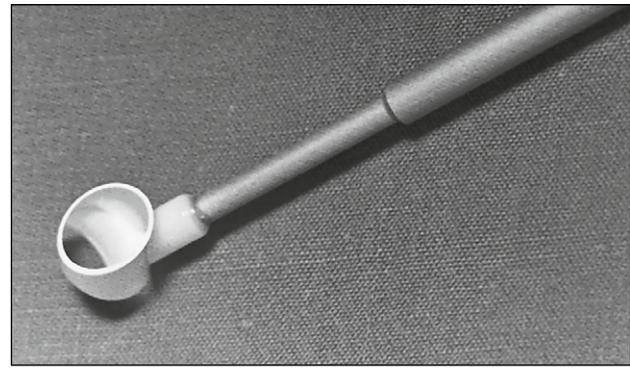


Fig. 37-6 Swan-Jacob goniolens.

which provides excellent angle visualization, requires no saline instillation under the lens. As with the previously described technique, the operating microscope is used for visualization of the angle throughout the operation. With the patient's head turned slightly away from the surgeon, the goniolens is applied to the cornea, and the microscope is adjusted to bring the angle into sharp focus. The lens is then removed from the cornea and held above the eye by the nurse so that it may be readily grasped by the surgeon and placed on the cornea.

Viscoelastic should be introduced to maintain a constant anterior chamber depth. The goniotomy can be performed with a needle-knife or 25–27-gauge needle attached to a hollow cannula. The cannula is connected to a syringe by means of plastic tubing and filled with BSS. The eye is grasped at the limbus with a toothed forceps, and the needle-knife (with the bevel down) is forced through the cornea just inside the limbus. It is then directed across the anterior chamber until the tip can be seen approaching the angle. If the chamber shallows, additional viscoelastic can be injected. Once the area of the angle is approached, the surgeon sets the toothed forceps aside, grasps the goniolens, and places it on the cornea, bringing the angle into focus. Viscoelastic injection is useful not only for maintaining the chamber depth but also for stretching the iris–trabecular meshwork attachment for easier and more bloodless surgery. The goniotomy incision is then performed as discussed previously. The chamber is deepened slightly, and the needle-knife is slowly withdrawn.

A third alternative is to use the Worst goniotomy lens, which is sutured to the limbus. Facing the surgeon, there is a hole in the flange of the lens through which the goniotomy knife enters the eye. The lens is used to stabilize the eye. This technique is also useful if no experienced assistant is available. Another approach, with limited validation in the literature, may be to use the Trabectome™ to perform trabecular ablation (see Ch. 38).

If ocular pressure and normal chamber depth can be maintained, bleeding is minimized. If necessary, BSS is instilled with a flat needle (Fig. 37-7) to irrigate blood from the anterior chamber and to deepen the chamber at the close of the procedure. Viscoelastic can be left in the eye; the surgeon may wish to use an aqueous suppressant for the first 12–24 hours postoperatively. After withdrawal of the goniotomy knife, the corneal wound may tend to leak. Either a 10-0 nylon suture closure or small-cannula injection of BSS into the corneal stroma at the edges of the entry site can be performed to seal the wound. An antibiotic ointment is instilled, and an aluminum shield is taped over the operated eye.

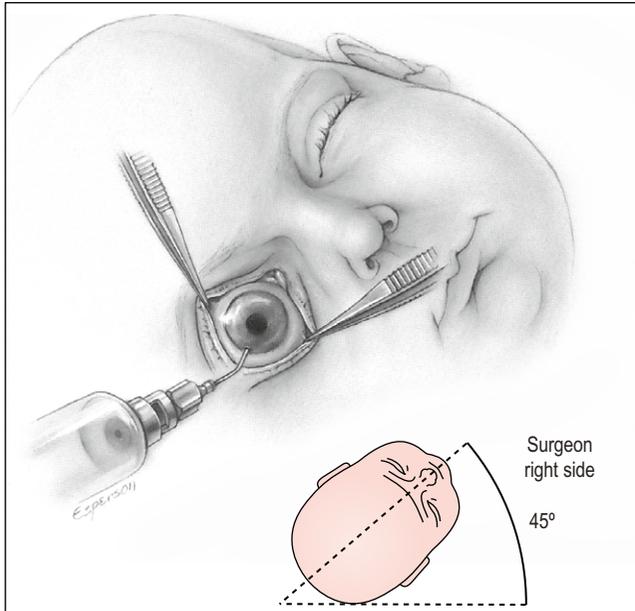


Fig. 37-7 The anterior chamber is re-formed with a flat-tipped irrigating needle. During the procedure, the patient's head is rotated, placing the goniotomy incision superiorly so that blood will drain away from the incision.

If no viscoelastic was used, the patient's head should be kept turned as much as possible toward the side of the puncture wound for the first hour after surgery to keep the goniotomy incision upward so that blood can flow away from it. Within 3 days, any blood present has usually disappeared from the anterior chamber.

The child should be seen routinely in the first few weeks after surgery to ascertain the absence of infection, the corneal health, and chamber depth; if possible, IOP measurement can be attempted (see Ch. 19). A follow-up EUA should be scheduled 4–6 weeks after the goniotomy, with preparations for additional surgery if the IOP is elevated or if the cornea and disc show deterioration. If symptoms and signs have not improved or are worsening, re-examination and reoperation may be performed after 3 weeks. Repeat surgery sooner than this may not allow enough time for the eye to stabilize and the first procedure to be effective. In one study, a higher preoperative IOP elevation was more predictive of surgical failure than if two simultaneous goniotomies were performed at the initial operation.⁴

If IOP is controlled, the child is re-examined in 2 months, then every 3–4 months for a year, twice in the next year, and annually thereafter. Intensive amblyopic management is essential to maximize visual potential.

If the pressure is still not normalized, or the disc cupping has failed to reverse in the first 4–6 weeks postoperatively, the technically more difficult temporal goniotomy, with the knife passed over the bridge of the nose, can be performed as the second operation. If two goniotomies fail, the third operation should be a trabeculotomy, which can be done temporally or superiorly. Large series of such cases were reported by Mandal and co-workers in India to respond well to combined trabeculotomy/trabeculectomy, or trabeculectomy with antimetabolite.^{5,6,6b}

Complications

Complications of goniotomy include those of general anesthesia in a neonate or infant, bleeding from the site of goniotomy, infection,



Fig. 37-8 Goniotomy incision in a cat's eye.

(From Shaffer RN. Published with permission from the American Journal of Ophthalmology 47:90, 1959.)

failure, and epithelial ingrowth.^{7,8} In cases of bilateral uncontrolled infantile glaucoma, the small risk of two general anesthetics within a few days of one another may nevertheless be greater than the small risk of performing *bilateral* goniotomies at one sitting. This possibility should be addressed with the parents in instances of bilateral disease. At the conclusion of the first procedure, completely fresh operative supplies – new IV bottles (ideally from separate manufacturing lots), gowns and gloves, sterile drapes and instruments, repeat sterile wash-ups by surgeons and nurses, etc. – should be used to eliminate the remote risk of bilateral intraocular infection: a risk thought to be less than the persistence of uncontrolled glaucoma and its possible unavoidable delay for quick surgical redress.

Practice goniotomy

The two essentials in performing skillful and safe goniotomies are thorough knowledge of the gonioscopic appearance of the infant angle and adequate practice of the technique under gonioscopic control. This is not a procedure that should be performed only occasionally. A good gonioscopist can quickly acquire knowledge of the infant angle by performing gonioscopy on babies who are under anesthesia for some other purpose, such as strabismus surgery. The surgical skill can be obtained by practice on animal eyes fastened (by toweling and thumbtacks) to a wooden block; the angle appearance of the cat eye is comparable to that of the human infant eye (Fig. 37-8).

Other *ab-interno* angle surgery

Another way to perform a goniotomy has recently been described. In this procedure, a probe is inserted into Schlemm's canal under gonioscopic control from across the anterior chamber and a radio frequency current is applied between the anterior chamber and the probe; this current ablates the trabecular meshwork and inner wall of Schlemm's canal, improving outflow. This operation is known as the Trabectome™ operation and is described in Chapter 38.^{9,10}

TRABECULOTOMY AB EXTERNO

External trabeculotomy (Figs 37-9 and 37-10) was recommended originally as surgical treatment for both primary infantile glaucoma

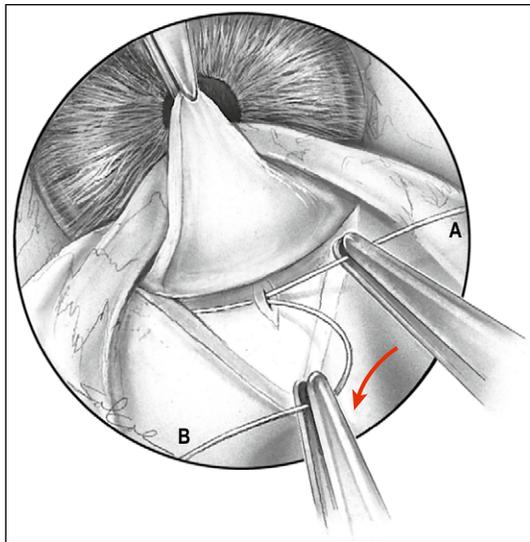


Fig. 37-9 A 5-0 nylon suture with a beveled tip is used to test the approach to Schlemm's canal. If Schlemm's canal has been correctly located, the leading end of the suture will not rotate to the anterior chamber when the suture is pulled posteriorly (arrow). Similarly, moving the suture in the opposite direction will not cause the suture to enter the choroidal space.

and primary open-angle glaucoma. In our practice, trabeculotomy, rather than goniotomy, is indicated for either primary infantile glaucoma when angle structures cannot be visualized through a cloudy cornea or after the failure of two goniotomies. However, reported results of trabeculotomy *ab externo* as the primary procedure for infantile glaucoma are essentially equivalent to those of goniotomy. It also has a role in managing juvenile open-angle glaucoma.

Long-term results are impressive in managing infantile glaucoma and open-angle glaucoma in younger adults. Because it is in part a procedure that uses variations of maneuvers familiar from trabeculectomy surgery, trabeculotomy may be easier to perform for some surgeons than is goniotomy. Some investigators prefer trabeculotomy *ab externo* as the initial surgical procedure in children,¹¹⁻¹³ whereas other investigators cite no superiority or preference between the two procedures.¹⁴ Trabeculotomy has a high success rate (80–90% in most studies¹⁵⁻¹⁷). It is less useful in older patients with chronic open-angle glaucoma unless there are angle changes compatible with juvenile anomalies (see Ch. 19).

The trabeculotomy procedure involves cannulation of Schlemm's canal with subsequent centripetal rupture through the trabecular meshwork into the anterior chamber. To locate Schlemm's canal, an operating microscope with high magnification is essential. The conjunctiva may be prepared in either a fornix-flap or limbus-flap configuration; the latter may be preferable if there is a possibility of

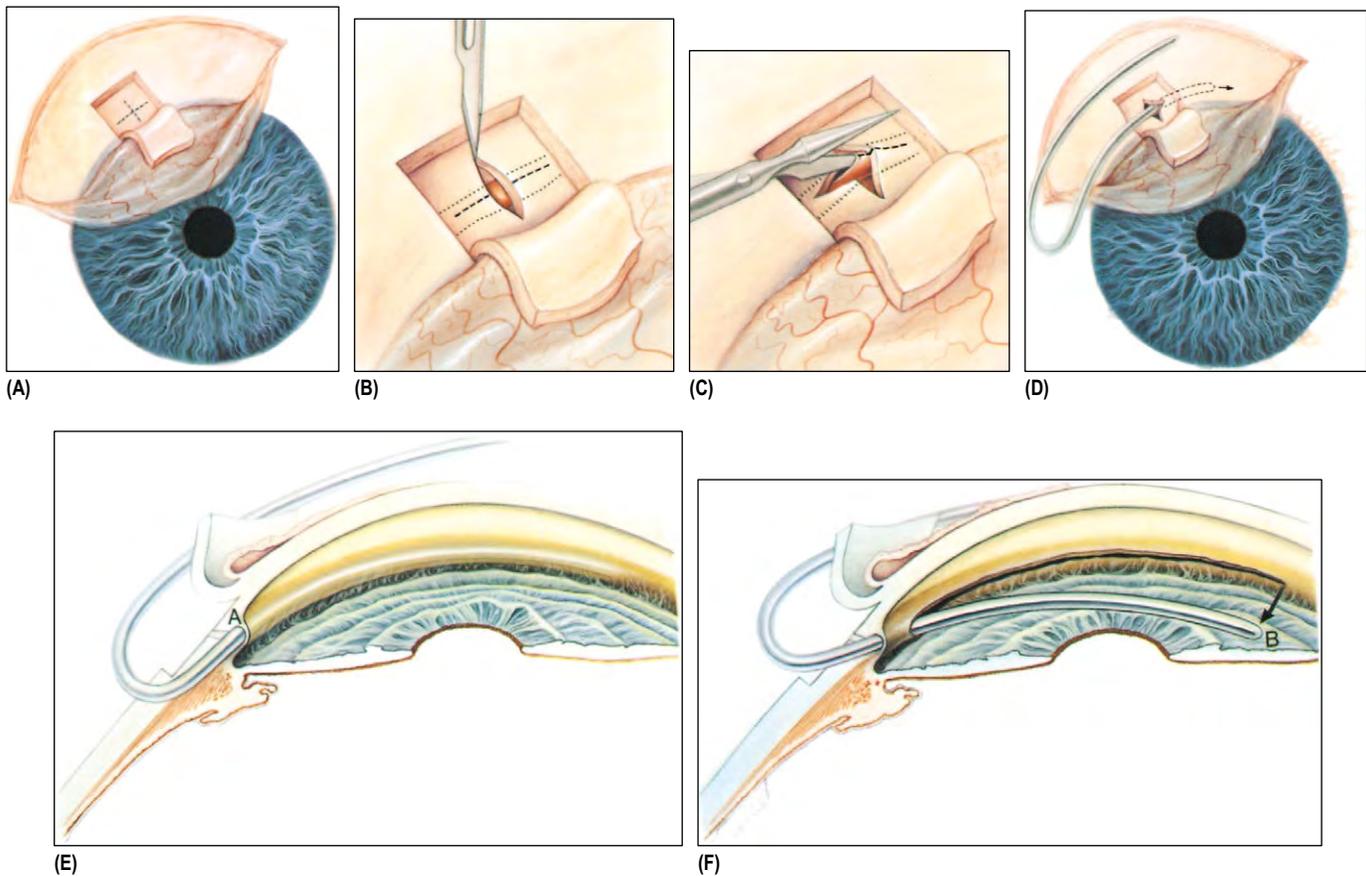


Fig. 37-10 Trabeculotomy. **(A)** The sclera is exposed by formation of a limbus-based conjunctival flap. A thick scleral flap can then be dissected forward so that it is hinged at the cornea. **(B)** Meticulous dissection of the remaining sclera over Schlemm's canal is performed under high magnification through a radial incision at the transitional white to blue-grey color change between the sclera and cornea. **(C)** Entrance to the canal is verified by inserting a 5-0 nylon suture and threading it a short distance. Probing is made easier if the canal is further exposed at the entry site with Vannas scissors. **(D)** The probe is gently passed along the canal with little resistance for 6–10 mm. **(E)** The probe is barely visible gonioscopically through the trabecular meshwork. **(F)** By rotating the probe internally, the trabeculum is ruptured and the probe appears in the anterior chamber with minimal bleeding.

combining the trabeculotomy with a trabeculectomy and antimetabolite. The scleral flap incision is similar to that used in trabeculectomy (either triangular or rectangular in shape), except that the scleral flap should be deeper to facilitate location of the canal. The scleral flap may extend into clear corneal tissue. This helps to define the anatomic landmarks and permits conversion of the operation into a trabeculectomy if the trabeculotomy procedure seems unsatisfactory. A paracentesis should be made in anticipation of filling the anterior chamber with viscoelastic.

The great challenge of the procedure is to correctly identify Schlemm's canal; intimate knowledge of the anatomy of the scleral-limbal junction is essential.¹⁸ The canal is found in the corneoscleral sulcus at the blue-grey/white transition between scleral and corneal tissue. Using high magnification (16× to 25×), a cellulose sponge can dry the junction and allow for the appreciation of droplets of clear aqueous beading precisely above the canal. A radial incision 2 mm in length is made at that point. If the surgeon is unsure of the landmarks, it is possible to extend and deepen the posterior end of the radial incision until choroid is seen. Carrying the incision anteriorly from that point allows the surgeon to see the scleral spur. The canal is just in front of the spur.

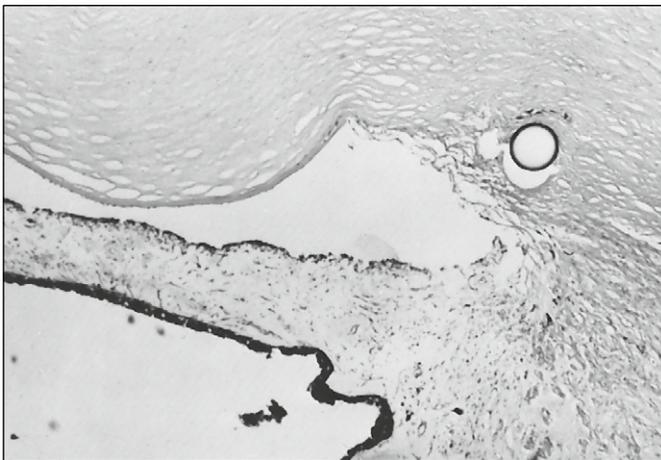


Fig. 37-11 Pathologic specimen showing the suture correctly placed in Schlemm's canal.



Fig. 37-12 An ICath (IScience, Menlo Park, CA) catheter with red LED light (arrow) can be seen through the sclera in Schlemm's canal.

Slow and meticulous dissection is performed by spreading tissues as this incision is deepened. As the canal is approached, there is a seeping of aqueous and often a tinge of blood as the outer wall of the canal is cut. To ensure the accuracy of the incision, 3 cm of 5-0 or 6-0 monofilament (e.g., Prolene or nylon) suture with a beveled tip is inserted for about 5 mm into the presumed opening of the canal (Figs 37-9 and 37-11). The suture should enter easily and slide into the eye following the course of the canal. If there is no false passage, it should not be possible to rotate the suture anteriorly into either the anterior chamber or posteriorly into the suprachoroidal space. The suture may be viewed gonioscopically to be sure of its proper positioning. Another approach is to use a specially designed catheter with an LED on the end which allows visualization of the catheter as it transits the 360° of Schlemm's canal (ICath, IScience, Menlo Park, CA) (Fig. 37-12) (see Ch. 38).

The suture is removed, and a Harms or McPherson trabeculotome is gently inserted along the course of the canal (Figs 37-10, 37-13 and 37-14A). When completely inserted, the probe is rotated toward the anterior chamber, breaking through the remaining trabecular tissue with virtually no resistance. Care must be taken to prevent the probe from moving anteriorly, which may tear Descemet's membrane (Fig. 37-14B). If the chamber collapses after the removal of the first trabeculotome, re-formation with viscoelastic is useful before using the second instrument. A similar insertion and rotation is done in the opposite direction using the corresponding probe. No iridotomy is performed. There is usually a moderate ooze of blood into the anterior chamber. The chamber is filled with viscoelastic or BSS.

If trabeculotomy alone is intended, at this point the scleral flap is closed with interrupted sutures and the conjunctiva closed. If the eye has had failed goniotomies or if a difficult management course is anticipated because of a complex childhood glaucoma a combined trabeculotomy/trabeculectomy can be performed. The insertion site of the trabeculotomes can be excised and enlarged to allow full filtration (trabeculectomy), iridectomy, and application of an antimetabolite after flap closure.^{5,6}

Another variation of this procedure in treating childhood glaucomas is the elaborate purse-string 360° trabeculotomy.¹⁹ After unroofing and identifying Schlemm's canal, a 6-0 Prolene suture is threaded 360° around and, after reappearing from the opposite direction at the initial surgical site, is drawn like a purse string, rupturing the entire canal in a centripetal fashion. In the event that the suture or catheter is stopped by an obstruction in Schlemm's canal, an additional scleral flap is prepared, the canal is unroofed at the site of obstruction, and the Prolene suture is rethreaded back on its

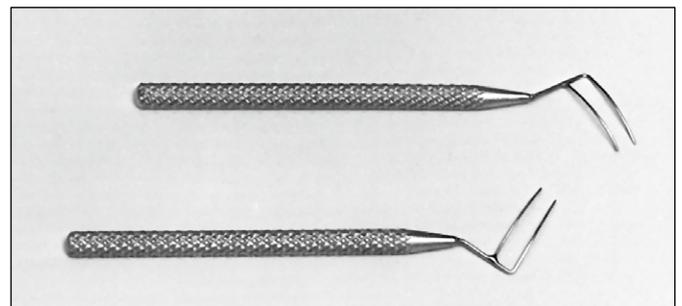


Fig. 37-13 McPherson probe. Hand-held curved right and left trabeculotomes approximately 0.2 mm in diameter and 10 mm long with a rounded tip designed to fit the configuration of Schlemm's canal.

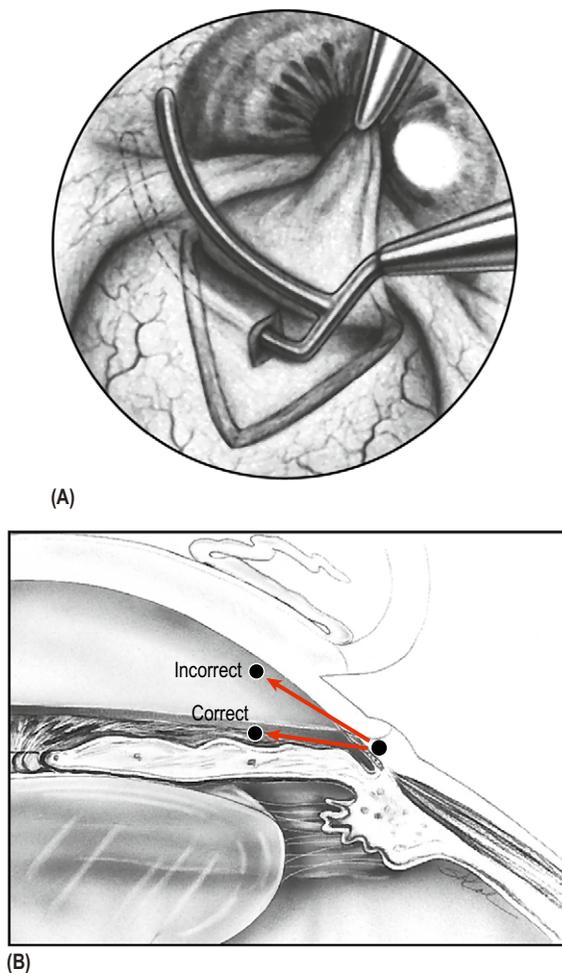


Fig. 37-14 (A) Trabeculotomy. A trabeculotome is gently inserted into the canal and, with gentle pressure against the scleral wall, is allowed to follow the course of the canal approximately 7–10 mm before rupturing the inner wall of the canal. **(B)** The Harms trabeculotome should be swept into the anterior chamber parallel to the plane of the iris. If it is allowed to dissect anteriorly, Descemet's membrane will be disinserted.

course. Gonioscopy can be performed intraoperatively to verify the location of the suture. One complication of this procedure is that the Prolene suture or the catheter can be misdirected into either the anterior chamber or, more ominously, into the suprachoroidal space.²⁰ The 360° suture technique has been reported to have an excellent 'success' rate for pressure control comparable to or better than goniotomy and trabeculotomy with metal trabeculotomes.²¹ This procedure can also be done with the ICath (IScience) by threading the catheter 360° and, once it has come out through the other end of the cut Schlemm's canal, it can be pulled like a noose until the trabecular meshwork has been torn around the entire circumference. Bleeding is minimized and insertion facilitated by injecting small amounts of viscoelastic through the catheter as it is threaded around.

Subconjunctival corticosteroid and antibiotic are administered postoperatively. Pilocarpine is recommended to put traction on the scleral spur and to rotate the trabecular flap downward out of the scleral sulcus. Complications of trabeculotomy include intraoperative hemorrhage, Descemet's detachment, iridodialysis, and iris prolapse.²²

EVALUATION OF GONIOTOMY AND TRABECULOTOMY

Goniotomy and trabeculotomy are highly successful in the control of primary congenital (infantile) glaucoma with isolated trabeculodysgenesis. The success rate, however, is dependent on the age of the patient at onset and the anatomic defect present. Only 26% of glaucomas that present at birth are controlled by one or two goniotomies.^{23,24} Newborn patients generally have more severe defects, usually with anomalous iris vessels. Similarly poor results are obtained when the diagnosis is made in patients older than 2 years of age. In contrast, one or two goniotomies control glaucoma in 90–94% of patients 1–24 months of age who present with isolated trabeculodysgenesis.^{23–25} Trabeculotomy achieves similar results, may be superior in the more severely anomalous cases, and may be more effective than goniotomy in older children.^{21,26} In one study, trabeculotomy achieved pressure control in 60% of congenital, 76% of juvenile, and 96% of infantile glaucoma eyes.²⁷ Trabeculotomy also seems to be particularly effective in the case of aniridia although Schlemm's canal may occasionally be absent in these eyes.²⁸ Dietlein and co-workers make the point that the results of any of the surgeries (goniotomy, trabeculotomy, or trabeculectomy) may depend more on the severity of the condition than on the nuances of the different techniques.²⁹

Most of the reports on goniotomy and trabeculotomy count success as keeping the IOP under a certain level. Long-term follow-up of patients with congenital or juvenile glaucoma suggest that either goniotomy or trabeculotomy are successful at controlling the pressure for 5–10 years but the visual results are definitely more sobering despite careful orthoptic treatment.³⁰ Many children have their pressures controlled but end up with amblyopia due to the high myopia and/or anisometropia. Less than 50% end up with a vision better than 0.5.²⁷ Care must be taken not to encourage the family too much even when it appears as if the operation was successful. These children require a lifetime of monitoring, and often require anti-glaucoma medication or additional surgery after several years even when the initial surgery normalized IOP.

Properly performed, goniotomy procedures should be free of complications. One series of 540 consecutive goniotomies performed by experienced surgeons resulted in only two serious complications of severe anterior chamber hemorrhages.³¹ There were, however, six instances of an abnormal cardiopulmonary event noted by the anesthesiologist. All of these infants survived, but the anesthesia-associated risk and the risk to the eye with delayed surgery are sufficiently great that bilateral goniotomies performed during the same anesthetic period should be considered rather than risking a second anesthetic. It is imperative that the second eye be approached as an entirely separate procedure. This advice applies with great caution to bilateral trabeculotomy, which is a more formidable intraocular operation with a greater chance for infection and other complications. Trabeculotomy in the eye with the cloudier cornea and goniotomy in the other eye can be performed in one surgery in children presenting with bilateral glaucoma.

COMBINED TRABECULOTOMY AND TRABECULECTOMY

Trabeculectomy with or without mitomycin-C may be combined with trabeculotomy in infants and children with satisfactory results although bleb complications may occur that would not have without the trabeculectomy portion.^{32,34} In complicated pediatric glaucomas,

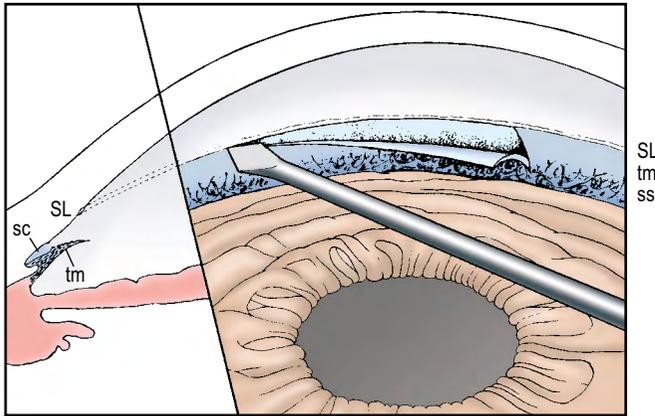


Fig. 37-15 Trabeculodialysis. With the spade-shaped goniotomy knife, the trabeculum is incised at Schwalbe's line (SL) and disinserted from the scleral sulcus. Vertical relaxing incisions at the extremes of the incision allow the trabecular flap to fall away from the scleral wall. sc, Schlemm's canal; tm, trabecular meshwork; ss, scleral spur.

the long-term outcome of mitomycin-C trabeculectomies was similar to that of Ahmed valve implants, but the complications were greater for the trabeculectomy group, whereas the Ahmed group was more likely to need subsequent medications to control the pressure.^{22,35}

TRABECULODIALYSIS

Glaucoma secondary to juvenile rheumatoid arthritis (Still's disease) responds relatively well to trabeculodialysis (Fig. 37-15).^{36,37} Frequently these eyes have been rendered aphakic in childhood. The appeal of this procedure is that nearly half of treated patients obtain pressure control,³⁸ which spares previously operated conjunctiva superiorly in the event that filtration or implant surgery is required later.

The procedure initially described by Haas resembles goniotomy.³⁶ Under the operating microscope, the anterior chamber is filled with viscoelastic and the globe is secured by the assistant. A superficial incision is made with a Barkan knife at the anterior portion of the trabeculum while viewed through a Barkan lens. Incised trabeculum is peeled downward away from the angle wall as a sheet, and the iris root moves posteriorly.

Complications with this procedure have been minimal. Like goniotomy, trabeculodialysis is relatively atraumatic, and failure does not jeopardize the success of other, more conventional procedures.

MISCELLANEOUS PROCEDURES

Goniosynechialysis

Goniosynechialysis has successfully reduced IOP in a small number of patients with chronic synechial angle closure.³⁹ It has been recommended for patients who have had extensive synechial angle closure for less than a year. Goniosynechialysis is similar to trabeculodialysis but can be performed with an irrigating cyclodialysis spatula with an attached bottle of irrigating solution. The spatula is introduced through a paracentesis incision 1–2 mm anterior to the limbus after the anterior chamber has been deepened by draining aqueous and replacing it with a viscoelastic substance. The spatula is used to push the synechiae down from the angle wall over an area of approximately one-half the angle circumference. If bleeding occurs, it can be instantly tamponaded by elevating the irrigation

bottle. The procedure is then repeated via a new paracentesis opposite the initial one to open the other half of the angle. The viscoelastic substance is replaced with BSS at the end of the procedure. If no peripheral iridotomy exists, a surgical iridectomy may be needed to prevent recurrence of angle closure.

Pressure has been controlled in some patients for at least a year after the procedure. Patient selection is critical if this is intended as the primary surgical intervention.⁴⁰ The most appropriate candidates are patients for whom a precise date for the beginning of progressive angle closure can be documented as being relatively recent. Such cases include an onset of an acute angle-closure attack or postoperative synechial closure documented after cataract or retinal surgery. In our hands, the technique is usually relegated to an ancillary maneuver during either filtration or cataract surgery in eyes with known peripheral anterior synechiae of recent onset.

Cyclocryotherapy

Trans-scleral cryoapplication to the underlying ciliary body may lower IOP by producing damage to the ciliary epithelium, thereby reducing aqueous secretion. Cyclocryotherapy is often painful and may induce a chronic, uncomfortable uveitis. We advise cyclocryotherapy use in patients with end-stage glaucoma who are unresponsive to other procedures, or in patients with minimal visual potential, when no laser is available. Cyclocryotherapy may be particularly useful in patients with chronic angle-closure glaucoma.^{41,42} Because of the greater comfort of trans-scleral laser techniques⁴³ and the precision of endolaser procedures,^{44,45} cyclocryotherapy should only be used in cases in which such lasers are not available (see Ch. 32).

Complete perioperative analgesia is imperative. We generally combine bupivacaine 0.5% with lidocaine 4% in a 2:1 mixture and wait 15–30 minutes or more before initiating treatment. The bupivacaine/lidocaine mixture produces a longer acting anesthetic agent, but the interval between injection and full anesthetic effect may be longer than with lidocaine alone. Subconjunctival anesthesia has also been reported to be effective in the majority of cases of cyclophotodestruction and precludes the possibility of subarachnoid injection of anesthetic which is advantageous especially in an outpatient setting.⁴⁶

A variety of cyclocryotherapy techniques exists. Usually, six equally spaced applications are made circumlimbally with the probe centered 2–3 mm from the limbus. Usually only 180° of the eye is treated at a time. Subsequent procedures can re-treat some areas and total 180°, but such treatments are not necessarily contiguous: one quadrant should remain untreated at all times. For example, the first session may freeze from the 12 to 6 o'clock positions; a second session from 3 to 9 o'clock positions; and a third session from 12 to 3 o'clock and 6 to 9 o'clock positions. In this example, the quadrant from the 9 to 12 o'clock positions remains untouched.

The larger 4-mm glaucoma probe (rather than the smaller cataract probe) attached to a liquid nitrogen supply is used. The tip is held against the conjunctiva with the probe's center approximately 3 mm from the limbus, and the temperature is lowered to 280°C for 60 seconds in adults and 30 seconds in children.⁴⁷ The extent of the freeze ball is approximately 10–12 mm and usually extends to the corneal limbus. The probe is allowed to warm until the iceball thaws, and then the probe is removed. Experimental studies indicate that greater tissue damage is produced by a freeze-thaw-freeze technique, and we do not advise its use.

In the immediate postoperative period, there is often a transient, marked elevation in IOP and moderate to severe pain that requires strong analgesics and maximal glaucoma therapy, including oral

carbonic anhydrase inhibitors. Some component of this pain and pressure rise appears to be associated with the volumetric change in the intraocular contents caused by the intravitreal iceball that occurs during the treatment.⁴⁸ Interestingly, there may be long-term pain relief in the absence of impressive pressure reduction when the procedure was performed for ocular comfort.⁴¹

Good pressure control has been maintained in some patients for several years postoperatively. There are patients whose eyes do not respond to repeated treatments, however; a significant number of eyes are lost over time, in part reflecting the end-stage disease being treated.

There are several situations in which cyclocryotherapy is useful, including neovascular glaucoma, absolute glaucoma, transient traumatic glaucoma, glaucoma in aphakic eyes, advanced developmental glaucoma, glaucoma associated with corneal transplant, chronic angle-closure glaucoma, and glaucomas for which intraocular surgery is contraindicated. Pain relief is often possible even when IOP is not normalized. Because it may cause loss of macular vision, possibly caused by persistent cystoid macular edema, cyclocryotherapy is a less desirable procedure in patients with relatively good acuity. As with all cyclodestructive procedures, phthisis bulbi is a persistent risk.^{41,49} Rare cases of sympathetic ophthalmia have been reported.^{50,51} Cyclodestructive procedures should thus be avoided when other surgical interventions may prove successful.

Retrobulbar alcohol injection

Retrobulbar alcohol injection may be used to relieve pain in severely damaged eyes in patients for whom enucleation is not an acceptable option. Ptosis and extraocular muscle paralysis frequently occur and may be prolonged, but this is rarely permanent. Initial pain and swelling subside quickly. The residual vision found in eyes being considered for this procedure is usually retained unless direct injection into the optic nerve occurs.⁵²

The technique is similar to that of preoperative retrobulbar injection. Either with or without local lid infiltration, lidocaine 4% (2 ml) is injected in the retrobulbar space via a retrobulbar needle on a syringe. While the needle is carefully held still behind the globe and stabilized at the lower lid entry site with a Kelly clamp, the syringe is twisted off and replaced with one containing 1.5 ml of a 70% alcohol solution, which is injected behind the globe. Again the needle is fixated with the Kelly clamp, the alcohol syringe removed, and the lidocaine 4% syringe replaced on the

needle so that 1–2 ml of anesthetic are injected while the needle is being withdrawn from the orbit. This prevents a track of alcohol from being brought into the anterior subconjunctival space, where it produces marked chemosis.

Severe swelling of the orbital tissues may occur, especially in children. An ice pack applied to the orbit for 1 hour immediately after the injection may reduce this swelling. The therapeutic effect generally lasts several months, with one study reporting a range of 2 weeks to 4 years.⁵³ Some have advocated using 1.5 ml of a 1:15 phenol solution instead of alcohol, citing similar therapeutic effects with much less pain at the time of injection.⁵⁴ In this series, the therapeutic effect lasted an average of 29 months (range 4–48 months). Retrobulbar chlorpromazine has also been used to good effect.⁵⁵

Earlier procedures

Before the widespread advent of filtration surgery with antimetabolites, glaucoma implants, and laser ciliodestructive procedures, a variety of surgical procedures had been described to reduce IOP when standard procedures had failed. Either their effectiveness has proven too limited or their complication profiles too intimidating to allow us to recommend their usage.

Goniotomy was basically a variation of the goniotomy procedure in which an ostium was made in the angle with the goniotomy knife, allowing aqueous egress to the subconjunctival space. Bleb failure was the rule rather than the exception, despite an internal approach that minimally disturbed the conjunctiva.

Cyclodialysis was once a mainstay in the management of aphakic glaucoma. Its principle was to mechanically disrupt the iris root at its scleral spur attachment so that a cleft was created between the anterior chamber and suprachoroidal space.⁵⁶ Significant hemorrhage was almost unavoidable, as was hypotony resulting from an overfunctioning cleft, which if spontaneously healed would lead to a precipitous rise in IOP. Other common complications included cataract and stripping of Descemet's membrane. With so many more physiologic options for surgical control of the IOP, this procedure is now of historical relevance only.

High-intensity focused therapeutic ultrasound of 4.6 MHz was reported to lower IOP in a variety of difficult glaucomas.^{57–59} However, the relative unavailability of this modality and the documented instances of marked post-treatment IOP spikes, cataract formation,⁶⁰ and staphyloma at the treatment site⁶¹ have caused it to be discarded.

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CHAPTER
38

New ideas in glaucoma surgery

INTRODUCTION

Over the last 100 or so years, many surgical approaches to glaucoma have been proposed and tried. Few have had the staying power of trabeculectomy or, more recently, the tube to posterior reservoir procedures. These are relatively easy to perform, generally have good success rates and have only rare disastrous consequences. On the other hand, the results are not always predictable; serious, if not disastrous, complications occur with alarming frequency and, with the advent of antifibrotic agents, serious late complications, such as failure, bleb leaks, blebitis, and even endophthalmitis, are occurring at increasing and disturbing rates. In addition, recent large-scale, prospective studies have shown the desirability of long-term, relatively tight pressure control in advanced glaucoma. Finally, as the problems of long-term medical therapy such as poor adherence, cost, side effects, and interference with the quality of life become more apparent, a simple, safe, and successful surgical procedure would be most welcome, especially for those patients with poor adherence for whatever reasons and in those parts of the world where the costs of chronic medical therapy are prohibitive.

We actually have several good operations for glaucoma including trabeculectomy with and without adjunctive antifibrotic agents, anterior chamber to posterior equatorial reservoir tube shunts, and cyclo-photocoagulation. However, in addition to unpredictability the long-term results are disappointing. For trabeculectomy, the complications of choroidal hemorrhage, hypotony, early and late bleb leaks, and early and late endophthalmitis can be daunting. For tube-shunt procedures, the need for supplemental antiglaucoma medications, late failure, and corneal decompensation are serious problems. Finally, for cyclophotocoagulation, the need for repeat procedures and the risks of uveitis, and phthisis bulbi are causes for concern.

Over the last decade or so, several new procedures have been described which seek to address some of the problems of these three general approaches. Procedures have been devised to bypass only the trabecular meshwork. These procedures shunt aqueous from the anterior chamber into Schlemm's canal. Other procedures have been devised to improve flow within the canal by dilating it; this type of operation is called viscocanalostomy. Another procedure bypasses the intrascleral channels by unroofing Schlemm's canal and creating an intrascleral reservoir. This latter procedure is called 'non-penetrating' deep sclerectomy. The Express shunt bypasses the entire drainage apparatus like a trabeculectomy into an anterior sub-Tenon's space using a stainless steel needle-like device with an internal flow restrictor. Finally, two devices are proposed for shunting aqueous from the anterior chamber into the suprachoroidal space. Each

of these will be discussed in turn with the known results, pros and cons. It is well to keep in mind that glaucoma is usually a lifetime disease and that, for each new procedure, long follow-up and randomized clinical trials will be necessary to determine the real place of each in the surgical armamentarium. Several procedures that seemed to make sense and had early successes did not stand the test of time.

NON-PENETRATING GLAUCOMA SURGERY

Back in the 1950s Epstein observed aqueous oozing from the site of thin sclera resulting from the deep removal of pterygia.¹ Krasnov actually described a procedure, called sinusotomy, to unroof Schlemm's canal over 180° allowing aqueous to drain sub-conjunctivally.² This early procedure was abandoned when it was found that the pressure-lowering effects were relatively short lived (and perhaps also because of the near simultaneous introduction of trabeculectomy).³ The concept was revived in the 1980s by Zimmerman and co-workers who described a procedure which was similar to sinusotomy but was performed under a scleral flap and which could be followed postoperatively, if necessary, with a yttrium-aluminum-garnet (YAG) laser goniotomy.⁴ The theoretical advantages of non-penetrating surgery include: less chance of both early and late infection; reduced risk of sudden and prolonged hypotony; less bleeding, and less chance of either serous or hemorrhagic choroidal detachment. As a general rule, these theoretical advantages have proven correct in practice.³ Whether adequate pressure control over the long haul is attained is still being debated.

The two main types of non-penetrating glaucoma surgery are the viscocanalostomy, where the primary focus is on dilating Schlemm's canal, and the deep sclerectomy, where the primary focus is on unroofing Schlemm's canal (and often the inner wall thereof) and creating an intrascleral reservoir with or without an intrascleral implant. Neither type of operation is as standardized as the trabeculectomy. There are overlapping features of both types of procedures and some surgical steps are used in both (Boxes 38-1 and 38-2).

VISCOCANALOSTOMY

Stegman contributed to the 'new' surgery trend with his description of a procedure in which Schlemm's canal was enlarged by viscoelastic material injected through a fine canula from an external dissection unroofing the canal. In addition, a window in Descemet's membrane was created to allow aqueous access to an intrascleral space.⁵ Theoretically, this procedure did not enter the anterior chamber but opened Schlemm's canal and, in addition,

Box 38-1 Advantages of non-penetrating glaucoma surgery (compared to trabeculectomy)

No sudden decompression of anterior chamber
 Suprachoroidal hemorrhage less likely
 Serous choroidal detachment less likely
 Reduced risk of prolonged hypotony
 Less likely to get filtering bleb
 Less chance of bleb leak – early or late
 Less chance of blebitis, endophthalmitis
 Contact lens wear less likely to be problematic
 Bleb dyesthesia rare
 Less intraocular inflammation
 Less chance of intraocular bleeding
 Fewer postoperative visits
 More rapid visual rehabilitation postoperatively

Box 38-2 Disadvantages of non-penetrating glaucoma surgery (compared to trabeculectomy)

Technically more difficult
 Takes longer in the operating room
 Requires some specialized instrumentation
 About 10% have actual perforation into anterior chamber requiring iridectomy
 Intraocular pressure less likely to be lowered sufficiently in advanced glaucoma
 Pressure lowering may not last as long

created an intrascleral reservoir (by removing an internal scleral block) from which the aqueous drained via intrascleral vascular channels. As noted above, operations unroofing Schlemm's canal without theoretically entering the anterior chamber had been previously described by Krasnov, Nesterov and Zimmerman⁶ in a limited number of patients but Stegman's procedure was presented with over 200 cases in black South Africans with reasonably long follow-up and impressive results. The success rate was over 80% defined as intraocular pressure (IOP) less than 22mmHg without need for supplemental antiglaucoma medications. The follow-up averaged almost 3 years.

Other groups had good results but not as good as Stegman. One group reported 36% success without medications and 73% with supplemental antiglaucoma medications at 1 year but with only a 2% complication rate.⁷ A few small randomized trials comparing primary viscocanalostomy against trabeculectomy, from Germany, England, Japan and Italy, showed lower IOPs with trabeculectomy and shorter duration of IOP lowering with viscocanalostomy but lower complication rates with viscocanalostomy.^{8–12} In one of these studies, complete success at 1 year (no medications) was found in 100% of the trabeculectomy patients but in only 64% of the eyes with viscocanalostomy.⁹ This same group found no serious complications over the follow-up period with either procedure in the 50 eyes. A randomized study of 50 eyes from Japan showed an average IOP at 1 year of 17mmHg in the eyes having viscocanalostomy and 12mmHg in eyes having trabeculectomy with mitomycin-C.¹³ The American Academy of Ophthalmology, through its technology assessment committee, found that of 100 citations in the literature, viscocanalostomy or deep sclerectomy succeeded in lowering IOP into the mid to upper teens most of the time with a low

complication rate, especially as it relates to overfiltration and hypotony.¹⁴ The committee also noted the need for more randomized, controlled trials. One 3-year prospective study of 67 eyes noted a complete success rate (target IOP without medications) of 60% at 3 years and a total success rate of 88% without any long-term complications.¹⁵ Yet another prospective study of 57 eyes followed for 5 years after viscocanalostomy found IOP less than 21mmHg without medications in 60% and with or without medications in 90% at 5 years.¹⁶ In this latter study, more than one-third of the eyes needed postoperative YAG laser goniopuncture to achieve adequate pressure lowering at an average time of 9 months after surgery. Intraocular pressure lowering after goniopuncture averaged 8mmHg.

Gimbel and co-workers described combining this procedure with cataract extraction and lens implant.¹⁷ Wishart and co-workers reported on a 2-year follow-up of viscocanalostomy and phacoviscocanalostomy in 101 eyes; 93% had IOPs less than 21mmHg at 2 years.¹⁸ Phacoemulsification combined with viscocanalostomy achieved lower IOPs than phacoemulsification alone, with a low complication rate in one non-randomized study.¹⁹ In a non-randomized trial, a group in Japan compared combined phacoemulsification and viscocanalostomy (phacoviscocanalostomy) with combined phacoemulsification and trabeculectomy in over 100 eyes with primary open-angle glaucoma; they found similar results in both groups.²⁰

The effectiveness of peeling of the juxtacanalicular tissue has been the subject of some debate; in one prospective study, it did not affect the long-term outcome but did reduce slightly the incidence of immediate postoperative pressure spikes.²¹ Johnson and Johnson attempted to determine the mechanism of action of viscocanalostomy and felt that it worked by making microperforations in the trabecular meshwork.²² Wild and co-workers were unable to show any perforations through trabecular meshwork in eye-bank eyes subjected to viscocanalostomy.²³ Furthermore, they demonstrated dilation of Schlemm's canal up to 6mm from the injection site and a small increment in the length of dilation using a more viscous viscoelastic. In an extensive study of primate and human eyes, Smit and Johnstone demonstrated disruption of the structure of Schlemm's canal, both inner and outer walls, as well as loss of bridging elements for as much as 16mm from the site of injection.²⁴ Furthermore, intrascleral channels were dilated. They concluded that viscocanalostomy may work by allowing direct access of aqueous from the juxtacanalicular tissue to the intrascleral collector channels. In Rhesus monkeys, viscocanalostomy appears to work by disrupting the inner wall of Schlemm's canal and opening the juxtacanalicular region to easier aqueous access.²⁵ A similar picture was obtained in two living human eyes using an endoscope during and after viscoelastic injection into Schlemm's canal.²⁶

The presence of the intrascleral chamber and the absence of a filtering bleb characterized the ultrasound biomicroscopic (UBM) appearance of postoperative eyes with successful viscocanalostomy.²⁷ In another study using the ultrasound biomicroscope in eyes following viscocanalostomy, perforation of the Descemet's window and the presence of the intrascleral 'lake' were correlated with successful surgery.²⁸ However, in yet another study, the intrascleral lake was not demonstrable on UBM in one-third of successful patients.²⁹ A concave appearing trabeculo-Descemet's membrane by gonioscopy or UBM heralded increased IOP in postoperative eyes with viscocanalostomy; the membrane became flat after Nd:YAG goniopuncture and the IOP was reduced.³⁰

Viscocanalostomy has also been shown to be effective in congenital glaucoma – at least as effective as trabeculectomy *ab externo* and perhaps more effective in more aggressive disease.³¹ The procedure

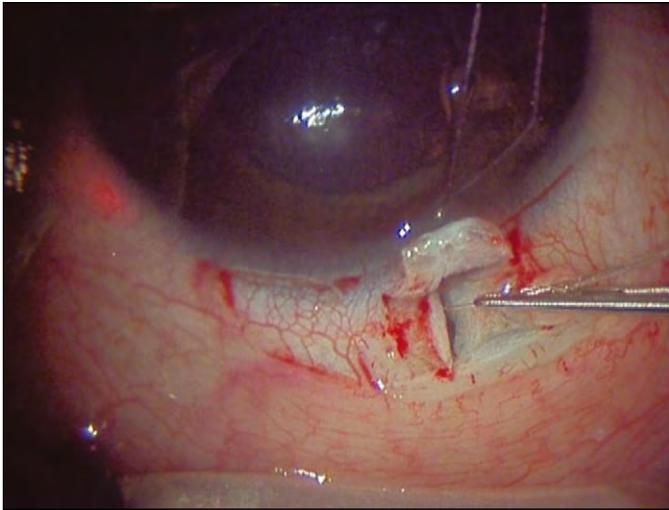


Fig. 38-1 The ITrack (IScience, Menlo Park, CA): a catheter which can inject viscoelastic into Schlemm's canal over 360° and which has a lighted tip to ensure positioning within the canal. Once threaded over the entire circumference, a suture can be attached to the tip, pulled back out, and tied to place tension on the circumference of the trabecular meshwork. The device can also be used as a method for 360° trabeculotomy.

also seems to have a high success rate (80%) in juvenile-onset glaucoma rivaling that reported for trabeculotomy.³² One small study suggests that viscocanalostomy may be a reasonable alternative to trabeculectomy in eyes with uveitic glaucoma.³³

Complications include failure to find Schlemm's canal and perforation or microperforations into the anterior chamber requiring an iridectomy and/or conversion to traditional trabeculectomy. Dietlein and co-workers examined 177 trabeculectomy specimens and found that older patients, in particular, had thin trabecular meshwork suggesting that perforation may be more likely in this group.³⁴ Hyphema and hypotony also can occur with consequent serous choroidal detachment, although less frequently than seen with trabeculectomy.⁵ Perforation of Descemet's membrane and hyphema each occurred at a rate of 10%. Detachment of Descemet's membrane requiring surgical repair may happen.³⁵ However, these may spontaneously recover without intervention and so should be watched for some time before surgical repair is attempted.³⁶ Injection of viscoelastic into the corneal stroma has also been reported as has one case of intracorneal hematoma.^{37,38} One case of delayed suprachoroidal hemorrhage has been published.³⁹

Several variations on the theme of viscocanalostomy have been proposed. Klink and colleagues reported the use of an erbium laser to assist in removing the inner scleral block.⁴⁰ Lewis presented experience with a Schlemm's canal catheter which can inject viscoelastic substance 360°; this same catheter can be used to thread a suture around the entire circumference of Schlemm's canal and can lower IOP by exerting a little tension on the suture so it expands trabecular meshwork into the anterior chamber (Fig. 38-1).⁴¹ Early studies with this technique by Stegman have been promising but long-term follow-up and larger numbers will be needed to determine if this variation on the technique will find a place in the surgical armamentarium.

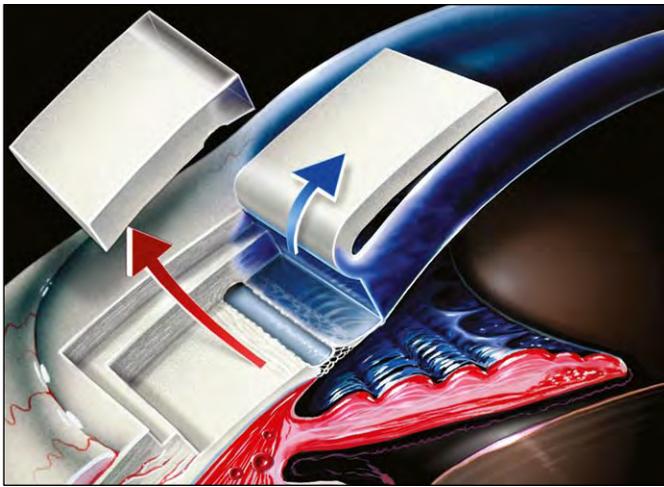
In summary, viscocanalostomy is a promising new surgical approach that effectively lowers IOP; compared to trabeculectomy, it lowers IOP less well, is more difficult to perform, and takes longer, but complications, especially those related to hypotony, are fewer and less severe.

BYPASS INTRASCLERAL CHANNELS (NON-PENETRATING DEEP SCLERECTOMY)

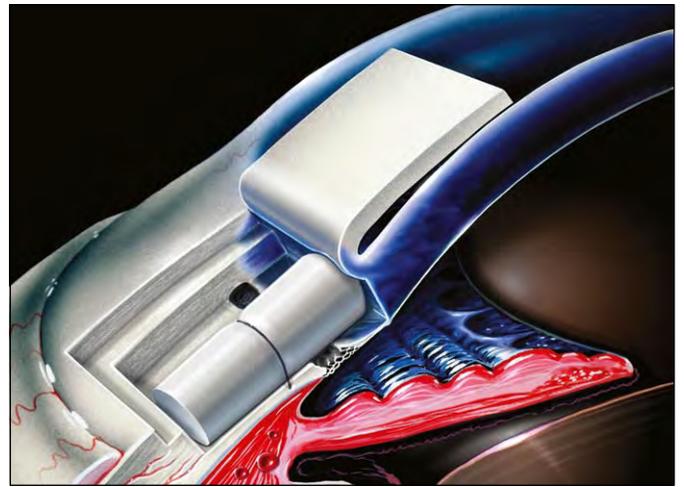
Building on the descriptions and experience of Krasnov, Zimmerman and Stegman with their procedure, others in Europe and Japan described a procedure in which an internal scleral block was removed under an outer scleral flap, Schlemm's canal was unroofed, and Descemet's membrane was exposed under the outer flap.^{42,43} Demailly and co-workers added a collagen implant to prolong the presence of the internal scleral reservoir.⁴² Transgonioscopic neodymium (Nd):YAG laser goniopuncture could be added at a later date if the pressure started to rise.⁴⁴ Mermoud and his group in Switzerland became fans of deep sclerectomy and were able to show that the collagen implant improved the outcome over deep sclerectomy without it.⁴⁵ Ultrasound biomicroscopy 1 month after the deep sclerectomy with collagen implant (DSCI) showed filtration around the scleral flap into the subconjunctival space and possibly some suprachoroidal filtration (Fig. 38-2).⁴⁶ Another proposed mechanism of action of this procedure is to increase the intrascleral vessels collecting aqueous from the intrascleral reservoir.⁴⁷ The collagen implant dissolved by about 9 months but the pressure-lowering activity continued (Fig. 38-3).⁴⁸

The results of DSCI have been reasonable with a reduction in IOP that is clinically significant and with a significant reduction in complications. Average IOP at 1 year has run about 12 mmHg and, in a matched, case control series, success as defined by IOP less than 21 mmHg without adjunctive medication was 69% as compared to that with trabeculectomy at 57%.⁴⁹ In this same group, complications with DSCI were fewer and less serious than those seen with trabeculectomy. In a series followed for up to 3 years, success using the above criterion was 44% and qualified success (controlled under 21 mmHg with topical medications) was 97%.⁵⁰ In a randomized, prospective trial of deep sclerectomy versus trabeculectomy from Saudi Arabia, deep sclerectomy produced an average IOP reduction at 1 year of 12 mmHg compared to 14 mmHg for trabeculectomy (not statistically significantly different).⁵¹ Success as defined by IOP equal to or less than 21 mmHg was 92% for deep sclerectomy versus 95% for trabeculectomy, but the rate of flat or shallow chambers was 7% for trabeculectomy and 0% for deep sclerectomy. In yet another study of intermediate-term results, DSCI lowered IOP from a preoperative level of 25 mmHg to 15 mmHg postoperatively with only about one-half requiring adjunctive topical medication (mostly betaxolol).⁵² Similar results were obtained with a reticulated hyaluronic acid implant although a higher per cent of these patients seem to have a visible filtering bleb.⁵³ Deep sclerectomy without implant lowers pressure less well than trabeculectomy in randomized, controlled trials, although complications do seem to be fewer than trabeculectomy with deep sclerectomy.⁵⁴ In a study where one eye was given a deep sclerectomy with implant and the other eye no implant, the eyes with the collagen implants had the lower IOPs and required fewer adjunctive topical antiglaucoma medications with no difference in complication rate.⁵⁵ In another randomized, prospective study by the same group, the collagen implant eyes had lower IOPs and a better success rate without medications than those with a deep sclerectomy and no implant.⁵⁶ It seems reasonable to conclude that the implants do enhance the success rate of deep sclerectomy.

Shaarawy and co-authors reported on 105 eyes in 105 patients followed for 5 years.⁵⁷ They found an average IOP of 11 mmHg with 95% of patients below 21 mmHg and 45% not requiring



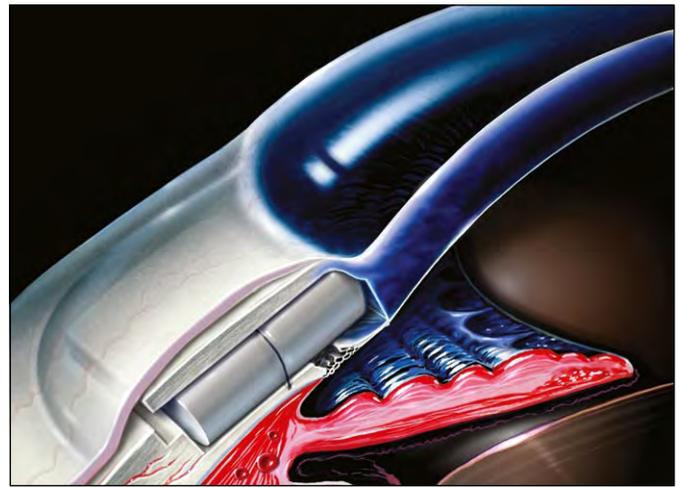
(A)



(C)

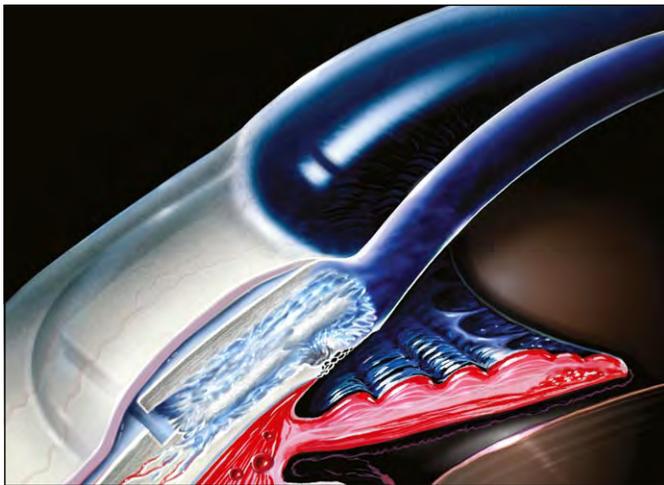


(B)



(D)

Fig. 38-2 (A) Deep sclerectomy: removal of internal scleral block. (B) Deep sclerectomy: removal of roof and inner wall of Schlemm's canal. (C) Sutured collagen implant. (D) Completed procedure. (Courtesy of Starr Surgical Inc.)



(A)



(B)

Fig. 38-3 (A) Collagen implant after 3 months. (B) Collagen implant after 3 months through ultrasound biomicroscope. (Courtesy of Starr Surgical Inc.)

adjunctive medication for control. In another study by the same group in which trabeculectomy was performed in one eye and deep sclerectomy with collagen implant in the other, the results were comparable although pressures were slightly lower for the eyes having trabeculectomy: 12.9mmHg at 2 years compared to 13.9mmHg for the DSCI eyes with equal overall success rates; however, the DSCI eyes had 50% less hyphema and serous choroidal detachments in the early postoperative period.⁵⁸ One almost 4-year study in patients with exfoliative glaucoma showed roughly half controlled at 19mmHg or below without medications and only one-third of patients with primary open-angle glaucoma controlled by the same criteria; the authors conclude that deep sclerectomy with implant works better in eyes with pseudoexfoliation than in eyes with primary open-angle glaucoma.⁵⁹ Over 2 years, deep sclerectomy without implants, mitomycin-C, or goniotomy works almost as well as trabeculectomy without mitomycin-C, but the trend of IOP suggests some loss of efficacy over time,⁶⁰ although results of DSCI may be maintained even up to 8 years of follow-up.^{61,62}

Postoperative Nd:YAG laser goniotomy is required to control pressure in anywhere from 3% to 80% with the average settling around 50% with long-term follow-up⁶¹⁻⁶⁴; intraoperative mitomycin-C application seems to reduce the need for this maneuver.⁶⁴ In one study, IOP fell from a pre-laser average level of 32mmHg to an immediate post-laser level of 17mmHg with maintenance of this level for at least 6 months.⁶⁵ Complications of Nd:YAG goniotomy have been limited to iris incarceration into the site with subsequent elevation of IOP.⁶⁷

Filtering blebs have been small or not observed; inflammation is reduced compared to trabeculectomy perhaps because no iridectomy is performed.⁶⁶

Despite the fact that this operation, theoretically at least, does not depend on filtration under the conjunctiva for success, the success rate appears enhanced with the use of intraoperative application of mitomycin-C to the operative site.^{67,68} However, in one randomized clinical trial in west African patients, the authors were unable to show any difference up to 18 months between those having deep sclerectomy with mitomycin-C and those not receiving mitomycin.⁶⁹ In this same study, while the results at 1 year were mildly encouraging with about 70+% having IOPs under 18mmHg, the results at 18 months were quite disappointing in both groups with success hovering only around 35%.

As with trabeculectomy, the operation seems to work better in eyes not previously treated with topical medications for glaucoma.⁷⁰ The procedure also seems to work in highly myopic eyes despite the thin sclera.⁷¹ Success in eyes with uveitic glaucoma has also been reported.⁷²

Deep sclerectomy with collagen implant can be successfully combined with phacoemulsification cataract surgery.⁷³ In one retrospective study of consecutive cases, there was no difference in pressure control or major complications between combined phacoemulsification with trabeculectomy and phacoemulsification with deep sclerectomy except a significantly higher risk of bleb leaks in the phacoemulsification with trabeculectomy group.⁷⁴

Complications include perforation of the trabecular meshwork with need to convert to trabeculectomy,^{45,75} scleral ectasia,⁷⁶ iris incarceration,^{51,77,78} hemorrhagic Descemet's detachment,⁷⁹ hypotony,^{80,81} and vitreous hemorrhage.⁸² Bleeding into the anterior chamber from the site of deep sclerectomy during gonioscopic examination can occur quite late in the postoperative period (Box 38-3).⁸² Having to convert to trabeculectomy because of

Box 38-3 Complications of deep sclerectomy

Conversion to trabeculectomy because of penetration through trabecular meshwork
Scleral ectasia
Iris incarceration, prolapse or peripheral anterior synechiae
Descemet's detachment
Hypotony
Hyphema
Serous choroidal detachment
Vitreous hemorrhage
Late anterior chamber bleeding during gonioscopy

perforation into the anterior chamber through Descemet's membrane or trabecular meshwork produces, as expected, ultimately a lower IOP than uncomplicated deep sclerectomy but increases the early postoperative complication rate and prolongs the time to recovery of best vision.⁸³

The operation is technically difficult and can be highly variable in the exact morphology of what is accomplished, even in the hands of experienced and capable surgeons.⁸⁴ Placing a trabeculotomy in Schlemm's canal before dissecting the internal scleral block seems to improve the accuracy.⁸⁵ Some have suggested that the internal scleral block can be more easily removed by erbium, excimer or CO₂ lasers.⁸⁶⁻⁸⁸

In summary, deep sclerectomy with or without an implant offers acceptable pressure levels, often with the need for adjunctive topical antiglaucoma medications, with a low rate of hypotony and bleb-related complications. Generally, this operation has been more accepted in Europe but, perhaps, because of its technical demands and its somewhat inferior pressure lowering, Americans by and large have stood on the sidelines waiting for more and longer term prospective, randomized trials.⁸⁹

SHUNTS INTO SCHLEMM'S CANAL

Another approach that seems to have potential as an effective operation in open-angle glaucoma is to bypass the obstructed trabecular meshwork by implanting a stent *ab interno* into Schlemm's canal, shunting aqueous from the anterior chamber directly into Schlemm's canal. The first such shunt was proposed by Rhea Brown. A slightly different version made from silicone tubing bent at a right angle was proposed by Spiegel and co-workers.⁹⁰ Early clinical trials suggest that this technique is feasible and both reduces IOP and the need for glaucoma medications.⁹¹ Using a variation of this technique in cultured human anterior segments, Bahler and co-workers showed that one shunt produced the largest IOP reduction and increase in facility of outflow but that each additional shunt in a different quadrant up to a total of four did, indeed, show increments of pressure reduction and outflow facility increase.⁹² Theoretical calculations by Zhou and Smedley suggest that a single shunt should be able to lower IOP into physiologic ranges.⁹³ A large-scale clinical trial of one such microshunt (iStent®, Glaukos Corp, Laguna Hills, CA) is under way. No long-term data are available at the time of this writing.

TRABECTOME®

An alternative approach to bypassing the trabecular meshwork is to ablate it. Goniotomy has been used for over 70 years in congenital glaucoma. However, it does not work in adult open-angle glaucoma possibly because the goniotomy knife causes damage to the outer wall of Schlemm's canal with resultant scarring and blockage of aqueous drainage beyond Schlemm's canal. Francis and colleagues set out to design an instrument that would ablate the trabecular meshwork without damaging the outer wall of Schlemm's canal.⁹⁴ The resulting instrument has a smooth but tiny tip that fits into Schlemm's canal by inserting it through the trabecular meshwork under gonioscopic control. A wire delivers a radiofrequency current that destroys the intervening trabecular meshwork between the wire and the tip-plate which protects the outer wall of Schlemm's canal from damage (Fig. 38-4). The concept was proven in eye-bank eyes as well as in rabbits.

A clinical trial in 37 adult eyes with open-angle glaucoma covering 3–13 months follow-up was recently reported.⁹⁵ Mean preoperative IOPs were about 28 mmHg with mean postoperative pressures ranging from about 18 mmHg on the first postoperative day to 17.5 mmHg at 6 months and 16.3 mmHg at 12 months. Numbers of medications decreased from 1.2 preoperatively to 0.4 at 6 months postoperatively. Vision returned to preoperative levels within 3 weeks in all but one patient who had trauma resulting in a hyphema. Blood reflux into the anterior chamber occurred in most patients but cleared by about 1 week. One patient had late hyphema following blunt trauma. No other complications occurred. The authors conclude that the operation may be useful as an alternative to goniotomy in infantile glaucoma and useful in adult open-angle glaucoma, somewhere between laser trabeculoplasty and filtering surgery. Larger trials with longer follow-up are awaited.

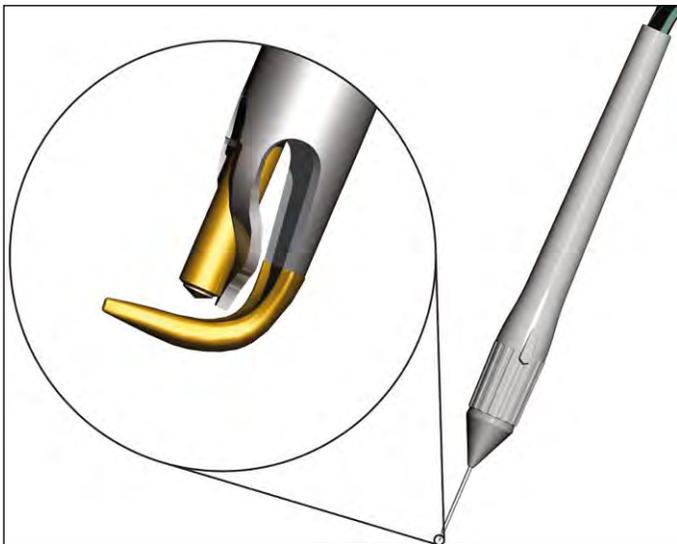


Fig. 38-4 Trabecular meshwork ablation instrument (Trabectome®). Gold tip fits into Schlemm's canal. Radiofrequency current ablates trabecular meshwork. Gold plate of tip protects outer wall of Schlemm's canal from damage.

(Courtesy of NeoMedix, Tustin, CA.)

SHUNTS INTO THE SUPRACHOROIDAL SPACE

The idea of shunting fluid from the anterior chamber into the suprachoroidal space is not new. The operation was cyclodialysis, in which a cut down was made through sclera onto the suprachoroidal space after which a special spatula was inserted anteriorly along the scleral wall into the anterior chamber to disrupt the ciliary body insertion into the sclera. This allowed aqueous direct access to the suprachoroidal space where the colloidal pressure is higher and the tissue pressure is lower.⁹⁶ Cyclodialysis was used as early as the 1930s by Otto Barkan among others.^{97,98} Cyclodialysis was used extensively in the 1950s and early 1960s especially in aphakic glaucoma and could be combined with intracapsular cataract extraction.^{99,100} Cyclodialysis seems to be effective at lowering the IOPs to normal in experimental rats made glaucomatous.¹⁰¹ Although still used by some in combination with modern cataract extraction techniques, it has been largely abandoned, in part because of the variability of pressure control, in part because of the complications of anterior chamber bleeding, stripping of Descemet's membrane, and hypotony, and in part because of the advent of the safer and more predictable trabeculectomy and tube-shunt procedures.^{102,103}

Adding a seton or stent to maintain patency of the cyclodialysis cleft was first described in the 1960s.¹⁰⁴ Nesterov used a scleral strip in the cleft in an attempt to keep it open longer.¹⁰⁵ This procedure seemed to increase outflow facility by about 25%.¹⁰⁶ In monkey eyes, this procedure resulted in a four-fold increase in uveoscleral outflow facility.¹⁰⁷ The late Michael Yablonski revived this idea and reported a series of cases successfully treated with a combination trabeculectomy and cyclodialysis augmented by two silicone tubes into the suprachoroidal space.¹⁰⁸ More recently, a similar procedure was described using a single silicone tube with successful results.¹⁰⁹ The Solx Company (Boston, MA) has begun making a thin gold wafer with microchannels that fits between the anterior chamber and the suprachoroidal space and drains fluid through the microchannels; some of the channels are not open and can be opened later by a titanium-sapphire laser (which also can be used for trabeculoplasty).¹¹⁰ Initial presentations show IOPs settling at about 17 mmHg at 6 months (Fig. 38-5). As of this writing, there

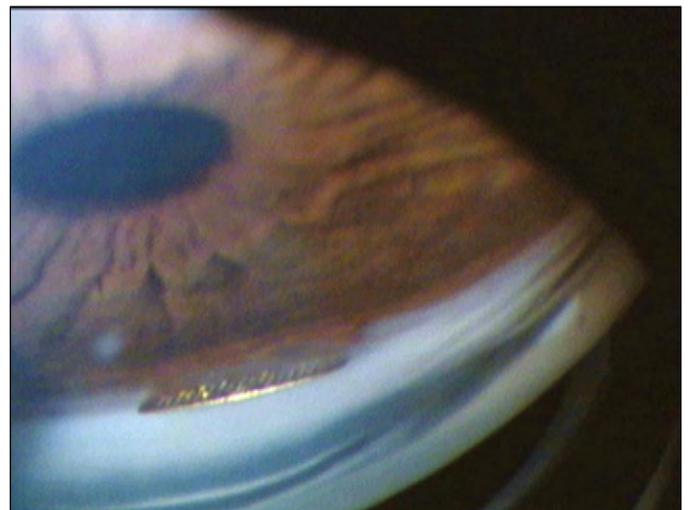


Fig. 38-5 Gold microshunt from anterior chamber to suprachoroidal space. (Courtesy of Solx Corp, Boston, Mass.)

are no published reports of clinical trials but the concept certainly shows promise; the idea of being able to modulate the flow in the postoperative period is very attractive.

SUMMARY

Several new approaches to glaucoma surgery have been described in the last few years. The ideas are novel and have theoretical attraction

although many are based on old concepts. Several have had good initial results. However, few have had a long follow-up, rigorous trials, and randomized, prospective studies to establish their place in the armamentarium. One would hope that one of these will become a standard of treatment like the trabeculectomy in its time.

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CHAPTER
39

Challenges for the new century

In the preceding chapters, we have tried to summarize the important information known about glaucoma, its classification, diagnosis, and management. It should be readily apparent to the thinking reader that there are many holes in our knowledge and understanding of this disease. No longer can we just say: “Glaucoma is elevated intraocular pressure and if you bring the pressure into the ‘normal’ range, the patient will retain vision.” Clearly, the glaucomas are optic neuropathies whose etiologies and pathophysiologies are still eluding us and represent a much more complex group of diseases than they have been given credit for in the past.

The decade since the last edition has seen some significant advances in pharmacologic and surgical management. Our understanding of the pathophysiology of plateau iris, pigmentary glaucoma, mechanisms of cell death, the genetics of juvenile glaucoma, epidemiology, the risk factors that presage future glaucoma in ocular hypertensives, and the efficacy of intraocular pressure lowering in preventing progression of the disease has been improved.¹

What follows is a wish list for the new millennium. Interestingly enough, despite some significant advances in our knowledge, the list does not differ terribly much from the one in the previous edition. So we may have come a long way but we still have a long way to go.

PATHOPHYSIOLOGY

It has been thought that in most cases of primary open-angle glaucoma (POAG), the primary site of outflow obstruction resides in the juxtacanalicular region of Schlemm’s canal. Work in the last two decades suggests that this obstruction is related to a change in the extracellular ground substance, perhaps associated with increased glycosaminoglycan moieties. Recent evidence points to mutations in the myocilin (TIGR) gene as driving changes similar to those seen in POAG. Yet a myocilin mutation is only present in a very small percent of patients with POAG. Does this mean that there are mutations in other genes that need to come into play, or some combination of environmental and genetic factors? The number of genetic mutations associated with glaucoma grows but our understanding of how these mutations cause glaucoma has not. We need to identify the triggers and environmental factors that allow the genetic predispositions to be actualized. Once we do that, then lifestyle modification may have some effectiveness in the prevention and treatment of glaucoma.

The loss of vision in glaucoma is due to death of ganglion cells, but our understanding of the mechanism(s) by which ganglion cells die is rudimentary. Most of what we know is inferred from empirical clinical observations. We still don’t know exactly how the axons of the ganglion cells are injured or die in glaucoma, or what the triggers are or even if only one mechanism is involved, multiple mechanisms

each working singly in different individuals, or different combinations in the same individual. Decreased optic nerve blood flow, mechanical deformation with blockage of axoplasmic transport, excitotoxicity from agents such as glutamate, autoimmune phenomena and apoptosis (programmed cell death) have all been indicted alone or in combination. As we learn more about each of these processes and develop the technology to measure and monitor them, we will probably find that all play some role – and to different degrees in different types of glaucoma and in different patients. Further studies in experimental models such as the lasered rat and mouse eyes, subhuman primate eyes and ‘knockout’ genetically altered small animals should better define the pathophysiological cascade that leads to ganglion cell death.

We are on the threshold of being able to assess blood flow to the optic nerve in humans. Although these tests are still primitive and only give us indirect measures of blood flow or direct measures of unknown circulations, new testing procedures should give us more and better insight into the role of blood flow in glaucomatous optic nerve damage. Further research should determine which of the noxious agents, ischemia, or axoplasmic blockage (or, again, some combination) serves as the trigger for apoptosis.

Of equally important promise in our comprehension of the dynamics of glaucomatous damage is the development of new technologies for measuring IOP in clinical and research settings. A revolutionary device would be a 24-hour IOP monitor with good ocular tolerability and capacity to assess weeks’ worth of momentary fluctuations, a phenomenon we can only crudely assess with our current technology. Such information could distinguish rates of disease progression, pharmacokinetics, and the precise effects of different glaucoma procedures on IOP control. Another technology of great value would be one that could sample the retro-bulbar pressures of the orbit, sub-arachnoid space, and CSF compartments.¹ The centrality of the lamina cribrosa region in the pathogenesis of glaucomatous disease (see Chapter 12) makes the understanding of trans-lamina pressure gradients a compelling new line of research.

The pathophysiologic mechanisms of many of the secondary glaucomas remain elusive. What causes exfoliative syndrome? Why is it manifest in only one eye or quite asymmetrically even when we know from postmortem studies that it is a bilateral (and systemic) disease? Why do only some people with exfoliative syndrome develop glaucoma? What causes iridocorneal endothelial syndrome? Is it a virus, or some other infectious agent? That might explain why this type of glaucoma is so overwhelmingly unilateral. What about pigmentary glaucoma? If the elegant hydrodynamic hypothesis of ‘reverse pupillary block’ is operating, why doesn’t iridotomy seem to reverse the process? Do we treat too late? If so, how do we identify the relatively small percentage of people with pigmentary dispersion who will go on to actually develop glaucoma so we can prophylactically treat them in the early stages?

CLASSIFICATION AND DIAGNOSIS

Already several different genes have been identified in which mutations can lead to glaucoma. The next decade or so should see some re-classification of glaucoma based on genetic abnormalities matched with phenotypic pictures. More exact definition of pathophysiological mechanisms should provide a more exact and scientific basis for our classification of the glaucomas.

It would of great value in our diagnosis and management of both the primary and secondary angle closure glaucomas were we to go beyond the enhanced visualization of angle structures and the retro-iris tissue made possible with ultrasonic biomicroscopy (UBM) and anterior segment optical coherent tomography (AS-OCT). These technologies have already led to an entirely new classification of the angle-closure glaucomas (see Ch. 15), and hopefully will evolve further into devices of greater scope and dynamic precision. Recognizing as we do in only fragmentary terms the normal pulsatile nature of aqueous flow both through the pupil and out through the trabecular meshwork, the ability to capture the entire anterior chamber angle and pupil in 3-D, live images (“video gonioscopy”) could profoundly impact our understanding of aqueous outflow in both the closed and open angle glaucomas.

We also need better methods of distinguishing pathologic from physiologic optic nerves. The current methods of imaging (e.g., the scanning laser ophthalmoscope, scanning laser polarimetry, and ocular coherence tomography) may provide better criteria for defining early glaucomatous optic nerve change and, by providing quantitative data, an earlier way of detecting progression. Already some evidence is emerging from the Ocular Hypertension Treatment Study (OHTS) that scanning laser ophthalmoscopy can predict which ocular hypertensives will progress to glaucoma.³ Newer Heidelberg retina tomography and optical coherence tomography methods will have higher resolution with the promise of earlier identification of changes and abnormalities. Perhaps the observations that cupping can improve in some patients with appropriately timed and judiciously applied treatment can be documented and, with new technology, give us an objective way of determining adequate therapy.

The advent of new technologies for measuring functional losses in glaucoma will allow earlier diagnosis and more appropriate treatment. The observation that short-wavelength automated perimetry (SWAP) identifies functional change from glaucoma before white-on-white threshold perimetry suggests that this goal is within reach. However, the specificity of the test needs to be improved. Already there is the promise that the Swedish Interactive Threshold Algorithm (SITA) version of SWAP will make the test less tedious, tiresome, and variable. Similarly, temporal contrast sensitivity, frequency-doubled technology, high-pass resolution perimetry, and motion perimetry all show promise for detecting glaucoma changes earlier than standard white-on-white threshold perimetry. The multifocal visual-evoked potential and electroretinogram offer the possibility that we may yet have an objective way of determining functional damage that will be useful in children, the elderly, and perhaps all patients as a way of reducing the variability due to inattention, anxiety, fatigue, and other factors. The exact way that glaucomatous damage first manifests itself functionally may vary from patient to patient; some may manifest changes in the short-wavelength perimetry, whereas others may show deficits in motion detection and still others in temporal contrast sensitivity.

SCREENING

Because only about one-half of the people in the United States who have glaucoma actually are aware that they have it, it is imperative that we do a better job of finding glaucoma before serious damage occurs. In the recent past, glaucoma screening has consisted of tonometry only. Since tonometry picks up only 50% of people with glaucoma and has a very high false-positive rate, there is a need for something more sensitive and specific.

Screening should include some estimation of risk factors, a fast, sensitive, and specific visual field assessment such as frequency-doubled perimetry, and an evaluation of the optic nerve. Because of the noise that accompanies most of our current technology, for the present, screening is most effective in high-risk populations such as the elderly and those of African or Hispanic ancestry. However, the educational value of screening programs cannot be underestimated. The reader can provide a great service in this regard. Patients in the presbyopic age group and who also have a cataract as well as those of African or Hispanic ancestry are at significant risk for open-angle glaucoma; those of Asian ancestry may have a higher risk of angle-closure or normal-pressure glaucoma. A high rate of suspicion, careful history taking, detailed optic nerve evaluation, and screening visual fields may allow earlier identification of those at greatest risk; monitoring with appropriate diagnostic modalities should help identify these patients earlier in the course of the disease and prevent serious visual loss. Recommendations to glaucoma patients that their immediate family members (parents, siblings, children) be examined periodically would be a great service. An increased public awareness of the seriousness of glaucoma, its insidious nature, and the need for periodic evaluations should help improve the rate of early detection of the disease.

TREATMENT

The last decade or so has seen the development of several new pharmacologic agents that have significantly improved our ability to lower intraocular pressure with a minimum of side effects. These new agents have almost completely replaced the ones recommended in the 6th edition of this textbook. Hopefully, several more agents will become available soon with different modes of action so that we can truly tailor the treatment for each patient according to the type of glaucoma, the amount of intraocular pressure lowering required, and the particular sensitivities of that patient.

One would hope that the new millennium will bring pharmacologic agents that can directly address the health of the nerve. Both neuroprotective and neurorestorative medications are needed. Perhaps the identification, isolation, and synthesis of nerve growth-promoting factors will help improve the health of the optic nerve, even in those whose ganglion cells have suffered widespread and severe damage.

As we uncover more of the genetic secrets of glaucoma, we can hope that repair of basic mutations will become possible. The injection of viral or other vectors carrying reparative genes that will prevent serious visual loss is one of the great hopes as we enter this new century. We can also hope for new surgical approaches that will allow a more controlled filtration, perhaps with a greater ability to titrate the exact amount of filtration to the needs of that particular patient. New surgical procedures may involve such radical approaches as enzymatic sclerostomy, better seton implants,

non-penetrating surgery, direct canalization of Schlemm's canal, and better antifibrosis agents with more controllable effects and toxicity.

Finally, as our society becomes more cost conscious about health care, we need to be able to factor cost-effectiveness into the other important aspects of our decision-making process.

CONCLUSION

Our goal is the elimination of unnecessary visual loss caused by glaucoma. Better understanding of the pathophysiologic mechanisms causing obstruction of aqueous outflow, optic nerve damage, ganglion cell loss, and visual dysfunction should point us in the right direction of better modalities of detection and management. Hopefully, the new millennium will see marked strides in the protection of the quality of life of our patients and the prevention of vision loss from glaucoma.

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World Glaucoma Association (WGA) Consensus Statements: 2004–2007

Robert N Weinreb

GLAUCOMA CONSENSUS

The Glaucoma Consensus Initiative of the World Glaucoma Association (formerly known as the Association of International Glaucoma Societies (AIGS)) is based on an assumption that groups make better decisions than even their smartest member. Assembling a sufficiently large and sufficiently diverse group of glaucoma specialists and scientists provides recommendations and insights that are likely to be superior to those of a single clinician. These recommendations and insights form the foundation for the Glaucoma Consensus Reports.

To prepare each of the consensus reports, there were several months of active discussion via the Internet by more than 100 expert members of the various consensus committees. The preliminary documents were circulated to each of the more than 70 member societies of the World Glaucoma Association, and additional comments were solicited. Participants were asked to meticulously review the international peer-reviewed literature, with special attention to the quality of available evidence. A consensus meeting attended by the experts and society representatives was then conducted. Consensus points were formulated and the report revised by the Consensus Panel following these discussions, with periodic modifications published on the Internet.

The skill, ingenuity and intelligence of numerous and diverse practitioners and scientists can be harnessed more efficiently and effectively than ever with the newest forms of interconnected global communication. We can learn from each other by sharing, adapting, and updating new information, and agreeing on the significance of the information. Linking networks of glaucoma specialists has tangible, ongoing important implications for glaucoma research, glaucoma clinical care, and glaucoma education on a global basis.

Consensus points from each of the four Consensus Reports are listed below. Updates as of 2007 are incorporated in each document. The complete reports are available from Kugler Publications, and all consensus points are posted on the Web sites of both the World Glaucoma Association (www.worldglaucoma.org), and the International Glaucoma Review (IGR) (www.e-IGR.com).

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Weinreb RN, Greve EL, editors: Glaucoma diagnosis – structure and function. Reports and consensus statements of the first global AIGS consensus meeting on structure and function in the management of glaucoma, The Hague, Kugler, 2004.

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GLAUCOMA DIAGNOSIS – STRUCTURE AND FUNCTION (2004)

ISBN-10: 90 6299 200 5; ISBN-13: 978-90-6299-200-3.

Hardbound, viii and 152 pages with 17 figures (of which 12 in full color) and 1 table.

CONSENSUS STATEMENTS

Structure*

1. A method for detecting abnormality and also documenting optic nerve structure should be part of routine clinical management of glaucoma.

Comment: It is known that documentation of optic nerve structure is often missing in routine ophthalmology practice.

2. According to limited evidence, available sensitivity and specificity of imaging instruments for detection of glaucoma are comparable to that of expert interpretation of stereo color photography and should be considered when such expert advice is not available.

Comment: Experts evaluating stereophotographs are those who have had specialized training and experience in this technique.

* At this time, evidence does not preferentially support any one of the above structural tests for diagnosing glaucoma.

3. Digital imaging is recommended as a clinical tool to enhance and facilitate the assessment of the optic disc and retinal nerve fibre layer in the management of glaucoma.

Comment: Digital imaging is available for scanning laser tomography, scanning laser polarimetry and optical coherence tomography. Digital imaging also is possible for photography, but assessment remains largely subjective.

4a. Automated analysis of results using appropriate databases is helpful for identifying abnormalities consistent with glaucoma.

Comment: The comparison of results of examination of individual patients with those of an appropriate database can delineate the likelihood of abnormality. Structural assessment should preferably include such a biostatistical analysis.

4b. Automated analysis of change using appropriate assessment of variability is helpful for identifying change consistent with glaucoma.

Comment: An eye can be changing and still be within the normal limits of a normative database.

5. Different imaging technologies may be complementary, and detect different abnormal features in the same patients.

Function

1. A method for detecting abnormality and documenting functional status should be part of routine clinical management of glaucoma.

2. It is unlikely that one functional test assesses the whole dynamic range.

3. Standard automated perimetry (SAP), as usually employed in clinical practice, is not optimal for early detection.

4. With an appropriate normative database, there is emerging evidence that short-wavelength automated perimetry (SWAP) and possibly also frequency-doubling technology (FDT) perimetry may accurately detect glaucoma earlier than SAP.

Comment: Earlier detection of glaucomatous damage with SWAP and FDT than with SAP has been consistent. SAP-SITA has similar sensitivity to detect visual field abnormalities as SWAP full threshold.

5. There is little evidence to support the use of a particular selective visual function test over another in clinical practice because there are few studies with adequate comparisons

Comment: FDT N30 may provide better sensitivity than SAP-SITA or SWAP full threshold. Evidence concerning the sensitivity of SWAP-SITA and FDT Matrix 2-2 is not yet available.

Function and structure[†]

1. Published literature often lags behind the introduction of new technology. Therefore literature based on previous versions of current technology should be viewed with caution.

2. In different cases, either structural examination or functional testing may provide more definitive evidence of glaucoma, so both are needed for detection and confirmation of the subtle early stages of the disease.

GLAUCOMA SURGERY – OPEN ANGLE GLAUCOMA (2005)

Hardbound, xiv and 140 pages with 9 tables and 2 figures, of which 1 in full color.

[†]Data from both functional and structural examinations always should be evaluated in relation to all other clinical data.

CONSENSUS STATEMENTS

Indications for glaucoma surgery

1. The decision for surgery should consider the risk/benefit ratio. Although a lower intraocular pressure (IOP) is generally considered beneficial to the eye, the risk of vision loss without surgery must outweigh the risk of vision loss with surgery.

2. Surgery for glaucoma is indicated when:

(a) Optimum medical therapy and/or laser surgery fail to sufficiently lower IOP.

(b) A patient does not have access to or cannot comply with medical therapy.

3. Clinicians should generally measure IOP more than once and preferably at different times of the day when establishing baseline IOP prior to surgery. When IOP is markedly elevated, a single determination may be sufficient.

4. Progression of glaucoma, considering both the structural and functional integrity of the optic nerve, is clearly a threat to vision and strongly influences the threshold for surgery.

5. Ongoing care of the patient with glaucoma requires careful periodic evaluation of structure and function.

6. Efforts should be directed at estimating the rate or risk of progression. A greater rate or risk of progression may lower the threshold for surgery but must be balanced against the risk and benefits of surgery and the life expectancy of the patient.

Comment: An elderly patient with slow progression may suffer no effect on quality of life during his/her lifetime. Advancing glaucomatous optic disc damage or retinal nerve fiber loss without detected visual loss is progression and can in certain circumstances be an indication for surgery.

7. Risk factors for progression of glaucoma are emerging from prospective studies. (Advanced Glaucoma Intervention Study (AGIS) – older age, lower education, male sex, diabetes; Collaborative Normal Tension Glaucoma Study (CNTGS) – female sex, migraine; Early Manifest Glaucoma Trial (EMGT) – high IOP, pseudoexfoliation, worsening visual fields during follow-up, disc hemorrhage, advanced stage of disease.) Presence of these risk factors may alter target IOP or lower the threshold to surgery.

Comment: Fellow eye vision loss from glaucoma may lower the threshold IOP for consideration of surgery. It is not clear that it is a risk factor for threat to vision. Family history of blindness from glaucoma is not a known risk factor for vision loss, but such patients warrant close observation.

8. Primary surgery may be indicated on the basis of socioeconomic or logistic constraints.

Comment: There is insufficient evidence to recommend primary surgery in all patients.

9. Patients who are unable or unwilling to use their medical therapy as prescribed represent failures of treatment efficacy and may need surgery to achieve consistent IOP reduction, even when isolated IOP measurements appear normal at office visits.

10. The extent and location of damage may alter the threshold for surgery. Patients with advanced damage or damage threatening central vision may require lower IOP than those with early disease.

Argon laser trabeculoplasty

1. Laser trabeculoplasty (LTP) with diode, or frequency-doubled Q-switched neodymium: yttrium-aluminum-garnet (Nd:YAG) are effective methods to lower IOP.

2. The principal indication for laser trabeculoplasty remains the failure of medical therapy to sustain acceptable IOP levels in adult eyes with POAG or intolerance of medical therapy. However, in appropriate cases, LTP may be used as a primary therapy.

3. Although IOP lowering after LTP tends to wane with time, it may produce clinically significant IOP reduction in phakic eyes for up to several years.

Comment: LTP often is effective in pseudophakic eyes for up to several years.

4. Postoperative monitoring of IOP and follow-up treatment of IOP spikes is appropriate.

Comment: IOP spikes tend to occur within the first few postoperative hours.

5. Uveitis, irido–corneal–endothelial (ICE) syndrome, congenital anomalies of the anterior chamber angle, and poor visualization of angle structures are contraindications for LTP, while age <40 years, angle recession, traumatic glaucoma, and high myopia are relative contraindications.

6. All commonly employed methods of LTP appear to be equivalent with respect to short-term side effects and IOP lowering.

7. There is longer follow-up data available for argon laser trabeculoplasty (ALT) than for selective laser trabeculoplasty (SLT). Randomized studies comparing these two modalities are not yet available.

8. Retreatment with ALT (applying additional laser spots to areas of the meshwork previously treated) is likely to be ineffective and perhaps detrimental. Although re-treatment with SLT has a theoretical advantage, studies to prove this have not yet been reported.

Wound healing

1. Excessive healing at the conjunctiva–Tenon’s fascia–episcleral interface is the major cause of inadequate long-term IOP lowering after trabeculectomy.

2. Risk factors for scarring should be evaluated and documented in all patients prior to undergoing glaucoma filtration surgery.

Comment: Conjunctival inflammation should be minimized prior to surgery.

3. The use of adjunctive antifibrosis agents should be considered in most patients undergoing trabeculectomy and should be titrated against the estimated risk of postoperative scar formation and estimated risk for postoperative complications.

Comment: Although some patients may have a successful result without adjunctive antifibrosis use, there is no systematic method for identifying these patients. Different antifibrotic agents may be associated with different risks and benefits: mitomycin-C may be a more effective adjunct than 5-fluorouracil (5-FU) but is associated with greater complications. A large antifibrotic treatment area is desirable to achieve diffuse non-cystic blebs with a lower risk of discomfort and leakage. Complications related to the use of antifibrosis agents are usually related to excessive inhibition of wound healing, which may result in or prolong early (wound leak, hypotony, shallow anterior chamber, choroidal detachment, etc.) and late (hypotony maculopathy, wound leak, and bleb-related ocular infection, etc.) complications.

4. Modern trabeculectomy techniques that include the use of lasered/releasable/adjustable sutures should be employed to minimize the complications of excessive filtration.

5. Early intervention (subconjunctival 5-FU and increased topical steroids) is recommended in eyes with evidence of active scar formation (conjunctival hyperemia and anterior chamber inflammation).

Comment: Use of subconjunctival 5-FU in eyes with a wound leak, corneal defect or ocular hypotony should be cautioned. Postoperative IOP elevation typically occurs after significant scarring has already taken place: as the scarring process might be slowed with additional measures, but not likely reversed, it is advised to intervene prior to an actual IOP rise, based on signs indicating the likelihood of an active scarring process.

6. Antifibrosis use is associated with enhanced bleb formation and lower IOP. However, they also have an increased long-term risk.

Comment: It is essential to inform patients about the signs and symptoms of ocular infection and advise them that they should seek ophthalmological advice urgently, should they occur. Long term follow up of these eyes is advisable.

Trabeculectomy

1. Incisional surgery for glaucoma is indicated when medical therapy and/or laser fail to sufficiently lower IOP or the patient does not have access to, or cannot comply with, other forms of therapy.

Comment: Primary surgery may also be indicated on the basis of socioeconomic or logistical constraints.

2. Trabeculectomy is the incisional procedure of choice in previously unoperated eyes.

3. Postoperative hypotony should be avoided and sequential IOP adjustment should be performed with suture modification.

4. Trabeculectomy provides better and more sustained IOP lowering than non-penetrating procedures.

5. Although adjunctive antifibrosis agents enhance the success of trabeculectomy, their risk/benefit ratio should be assessed for each individual patient prior to use. This applies to initial and repeat surgeries.

6. Preoperative conjunctival inflammation and postoperative conjunctival and intraocular inflammation should be suppressed vigorously with glucocorticoids.

7. Trabeculectomy success is highly dependent on postoperative care and management.

Comment: Early recognition of postoperative complications and timely, appropriate intervention enhance the success rate of surgery and minimize patient morbidity.

8. Patients that have had trabeculectomy should be warned of the signs and symptoms of late bleb-related ocular infection and should be counseled to seek immediate attention should these occur.

Combined cataract/trabeculectomy

1. A combined procedure is usually indicated when surgery for IOP lowering is appropriate and a visually significant cataract is also present.

Comment: Patients with glaucoma who are undergoing cataract do not necessarily require combined surgery. To avoid the complications associated with increased postoperative IOP, however, combined procedures should be considered in those patients on multiple medications or with advanced glaucomatous optic neuropathy.

2. The indication for combined surgery in an individual patient should take into account the level of desired IOP control after surgery, the severity of glaucoma, and the anticipated benefit in quality of vision after cataract extraction.

Comment: Visual rehabilitation may take longer following combined surgery compared to cataract surgery alone.

3. There is limited evidence to differentiate a one-site versus a two-site approach for combined surgery. Therefore, surgeon preference and experience will dictate the choice.

4. There is limited evidence to differentiate a limbal- versus a fornix-based conjunctival incision for combined surgery. Therefore, surgeon preference and experience will dictate the choice.

5. Mitomycin-C should be considered in all combined procedures to improve the chance of successful IOP control, unless there is a clear contraindication for its use.

Comment: Evidence for the use of adjunctive 5-FU data are limited and the bulk of the evidence suggests that it does not work well or at all.

6. Combined procedures are less successful for IOP reduction than trabeculectomy alone.

Comment: Subsequent cataract surgery may compromise the success of earlier trabeculectomy surgery.

7. In patients with cataract and stable glaucoma, a clear corneal approach is preferable in patients who may require subsequent trabeculectomy.

Aqueous shunting procedures with glaucoma drainage devices

1. Glaucoma drainage devices (GDD) are indicated when trabeculectomy is unlikely to be successful or because of socioeconomic or logistical issues.

Comment: In some patients, GDDs should be considered for socioeconomic or logistical issues relating to safety, follow-up care, etc.

2. The restriction of flow of aqueous humor from the eye is important in the prevention of immediate postoperative hypotony.

Comment: GDDs that do not have mechanisms to restrict aqueous flow require a suture ligature or internal stent or other flow-restricting mechanism.

3. In general, larger surface areas of the plate are associated with lower IOP.

4. Scar formation around the plate is the main cause of long-term device failure.

Comment: Antifibrotic agents have not been shown to improve long-term success when used intraoperatively or postoperatively.

5. Pars plana positioning of a GDD should be considered in a patient with a prior pars plana vitrectomy or in patient in whom a tube cannot be safely inserted into the anterior chamber.

6. The preponderance of evidence addresses GDDs that drain to a posterior reservoir.

Comment: Anterior drainage devices are under study. One should not extrapolate data from posterior drainage to anterior drainage devices.

Comparison of procedures: trabeculectomy versus aqueous shunting procedures with glaucoma drainage devices

1. Trabeculectomy with mitomycin-C is less expensive and requires less conjunctival dissection than aqueous shunting procedures.

Comment: Cost of GDDs varies significantly throughout the world.

2. With increased conjunctival scarring, the success of mitomycin-C trabeculectomy is reduced. Aqueous shunting procedures should be considered in patients with failed mitomycin-C trabeculectomy.

3. In general, lower IOP can be achieved with mitomycin-C trabeculectomy compared with aqueous shunting procedures, but good clinical studies are lacking.

Comment: There are currently limited data from prospective, randomized comparisons between mitomycin-C trabeculectomy and aqueous shunting procedures. To adequately compare mitomycin-C trabeculectomy with aqueous shunting procedures, comparable patient populations are required.

4. Bleb-related complications are less prevalent after aqueous shunting procedures. However, aqueous shunting procedures introduce a distinct set of complications including tube erosion or plate erosion, endothelial decompensation, and strabismus.

5. Aqueous shunting procedures should be considered in patients at high risk of mitomycin-C-related postoperative complications. These include severe lid margin disease, chronic contact lens wear, and a history of blebitis or bleb-related endophthalmitis.

Non-penetrating glaucoma drainage surgery

1. Non-penetrating glaucoma drainage surgery (NPGDS) provides an alternative surgical approach to trabeculectomy for moderate lowering of IOP in glaucoma patients.

2. Postoperative Nd:YAG laser goniopuncture may be an integral part of the procedure.

Comment: Laser goniopuncture is akin to flap suture manipulations following trabeculectomy.

3. Unlike viscocanalostomy, external filtration with deep sclerectomy may enhance the success of the procedure.

4. Deep sclerectomy may provide a lower IOP than viscocanalostomy, although the evidence for this is limited.

5. Failed NPGDS may compromise the success of subsequent trabeculectomy.

Comparison of trabeculectomy with non-penetrating drainage glaucoma surgery in open-angle glaucoma

1. Lower IOP can be achieved with trabeculectomy than with NPGDS.

2. Short-term complications associated with NPGDS may be fewer and less severe.

3. NPGDS is technically more challenging, with a longer operative time.

Comment: Both procedures may require postoperative intervention.

Cyclodestruction

1. Of the cyclodestructive procedures, laser diode cyclophotocoagulation with the G-probe is the procedure of choice for refractory glaucoma when trabeculectomy and drainage implants have a high probability for failure or have high risk of surgical complications.

2. Trans-scleral cyclophotocoagulation may be considered when maximal medical therapy, trabeculectomy, or drainage implant surgery is not possible due to resource limitations.

3. Prior to trans-scleral cyclophotocoagulation treatment, transillumination of the globe to reveal the location of the ciliary body may be useful, especially in morphologically abnormal eyes.

4. Postoperative treatment consisting of topical steroids and cycloplegics is suggested to minimize postoperative complications and discomfort.

Comment: The effectiveness of treatment should be assessed after 3–4 weeks, at which time re-treatment may be considered. Less intense laser therapy on a repeated basis rather than a single high dose treatment is suggested to minimize complications of treatment.

Comparison of cyclophotocoagulation and glaucoma drainage device implantation

1. Mechanism of action:

(a) GDDs increase aqueous humor outflow.

(b) Cyclodestructive procedures reduce aqueous production.

2. GDD implantation requires greater surgical training and is a more extensive procedure than cyclodestruction.

3. GDD implantation requires greater postoperative care than cyclodestruction.

4. GDD implantation should be performed in an operating room while cyclodestruction can be performed in the office, minor surgery area, or in the operating room.

5. The marginal cost of GDD implantation is more expensive than cyclodestruction. The initial cost of cyclodestruction related to the purchase of the device used for the procedure may be greater than that with GDD implantation.

6. Preoperative visual acuity may impact which of these two treatment modalities are preferred. All other things being equal, GDDs are more commonly used for patients with better visual acuity and/or visual potential relative to cyclodestructive procedures. Strong evidence in support of this practice is not currently available.

ANGLE CLOSURE AND ANGLE-CLOSURE GLAUCOMA (2006)

ISBN-10: 90 6299 210 2; ISBN-13: 978-90-6299-210-2.

Hardbound, xiv and 98 pages with 59 figures of which 3 in color, 1 table.

CONSENSUS STATEMENTS

Epidemiology, classification and mechanism Classification:

1. The proposed classification scheme can be used not only to classify the natural history of angle closure, but also to determine prognosis and describe an individual's need for treatment at different stages of the natural history of the disease.

2. Additional clinical sophistication can be gained describing sequelae of angle closure affecting the cornea, trabecular meshwork, iris, lens, optic disc, and retina. Specifically, the extent of peripheral anterior synechiae, level of presenting IOP (in asymptomatic cases), and presence of glaucomatous optic neuropathy should be noted.

3. Ascertaining the mechanism of angle closure (pupillary block, plateau, lens-related, retro-lenticular) is essential for management, and it should be used in conjunction with a classification of the stage of the disease.

*Comment: Further refinement of these systems (such as the inclusion of symptoms as a defining feature of angle closure) should be made on the basis of peer-reviewed evidence. Angle closure can be caused by one or a combination of abnormalities in the relative or absolute sizes or positions of anterior segment structures or abnormal forces in the posterior segment that may alter the anatomy of the anterior segment. Angle closure may be understood by regarding it as resulting from blockage of the trabecular meshwork caused by forces acting at four successive anatomic levels: the iris (pupillary block), the ciliary body (plateau iris), the lens (phacomorphic glaucoma), and vectors posterior to the lens (malignant glaucoma).**

4. Although the amount of pupillary block may vary among eyes with angle closure, all eyes with angle closure require treatment with iridotomy.

Gonioscopy:

1. Gonioscopy is indispensable to the diagnosis and management of all forms of glaucoma and is an integral part of the eye examination.

2. An essential component of gonioscopy is the determination that iridotrabecular contact is either present or absent. If present, the contact should be judged to be appositional or synechial (permanent).

Comment: The terms 'irido-trabecular contact' (stating the number of degrees) and 'primary angle-closure suspect' should be substituted for 'occludable,' as this is more accurate. The determination of synechial contact may require indentation of the cornea during gonioscopy, in which case a gonio-lens with a diameter smaller than the corneal diameter is preferred.

3. Access to a magnifying, Goldmann-style lens enhances the ability to identify important anatomical landmarks, and signs of pathology. Although the accuracy of indentation with this lens has not been validated, its use does complement that of a gonio-lens

with a diameter smaller than the corneal diameter. The ideal standard is access to both types of lens.

4. Anterior segment imaging devices may augment the evaluation of the anterior chamber angle, but their place in clinical practice still needs to be determined.

5. It is desirable to record gonioscopic findings in clear text. Describing the anatomical structures seen, the angle width, the iris contour, and the amount of pigmentation in the angle are all desirable.

Management of acute angle closure crisis

1. Laser iridotomy should be performed as soon as feasible in the affected eye(s), and should also be performed as soon as possible in the contralateral eye.

2. Medical management is the recommended first step in treating acute angle closure, but the results of studies comparing this to immediate laser surgery are not yet available.

3. Laser iridoplasty can be effective at breaking acute attacks and should be considered if an attack cannot be broken by other means.

4. Paracentesis should be reserved for cases where other approaches have failed.

5. Primary cataract extraction may be a treatment option, but data supporting its use are limited.

Surgical management of primary angle-closure glaucoma

1. Laser peripheral iridotomy (LPI) is recommended as the primary procedure in eyes with primary angle-closure glaucoma (PACG).

Comment: LPI can be performed easily on an outpatient basis and patients can then be monitored for response to treatment. This will allow time to undertake elective surgery in those with uncontrolled IOP, those with advanced disease, or with co-existing cataract. LPI also serves as prophylaxis against acute angle closure.

2. There is lack of evidence for recommending primary incisional surgery (without LPI) in eyes with PACG.

3. Trabeculectomy may be performed to lower IOP in eyes with chronic PAC(G) insufficiently responsive to laser or medical therapy.

4. There is insufficient evidence for deciding which cases with PACG should undergo cataract surgery alone (without trabeculectomy).

Comment: Cataract surgery alone may be considered in eyes with mild degree of angle closure (less than 180° of peripheral anterior synechiae), mild optic nerve/visual field damage or those that are not on maximal tolerated medical therapy.

5. There is lack of evidence for recommending lens extraction alone in eyes with more advanced PACG.

Comment: Published studies to date have been non-randomized with small sample sizes and short follow-up.

6. Combined cataract and glaucoma surgery in certain eyes may be useful to control IOP and restore vision.

Comment: There is limited published evidence about the effectiveness of combined cataract extraction and trabeculectomy in eyes with PACG. There is a need for studies comparing this form of surgery with separately staged cataract extraction and trabeculectomy.

7. There is limited evidence about the effectiveness of goniosynechialysis in the management of PACG.

Laser and medical treatment of primary angle-closure glaucoma

1. Laser iridotomy should be performed in all eyes with an acute episode of angle closure, the contralateral fellow of all such

*This tripartite scheme – distinguishing primary angle closure (PAC) suspect, closure and PAC glaucoma – is presented at length, in Ch. 15 – Primary Angle-Closure Glaucoma, where we have explained our reasons for relegating 'malignant glaucoma' to Ch. 16 – Secondary Angle-Closure Glaucoma.

eyes, and in eyes with established angle closure causing raised IOP and/or peripheral anterior synechiae. Eyes with anatomically narrow angles and typical symptoms of angle closure should also be treated. Consideration can be given to laser iridotomy in eyes with iridotrabeular apposition.

2. Iridoplasty can be considered in eyes with residual appositional closure provided a patent iridotomy is present.

3. Medical treatment should not be used as a substitute for laser iridotomy or surgical iridectomy in patients with PAC or PACG.

4. Iridoplasty is as effective as pressure-lowering medication in controlling IOP in people with an acute attack of angle closure.

5. Iridoplasty is successful in relieving appositional closure due to plateau iris configuration in asymptomatic cases.

Comment: Additional data in larger numbers of patients are needed. Iridoplasty may also have a role in managing cases of phacomorphic and pseudoplateau iris configuration caused by iris cysts.

Laser and medical treatment of primary angle-closure glaucoma

1. Medical treatment should not be used as a substitute for laser iridotomy or surgical iridectomy in patients with PAC or PACG.

2. Prostaglandin analogues appear to be the most effective medical agent in lowering IOP following laser iridotomy, regardless of the extent of synechial closure.

Detection of primary angle closure and angle-closure glaucoma

1. Angle closure case detection or opportunistic screening should be performed in all persons 40 years of age and older undergoing an eye examination.

2. Given the low specificity of the flashlight test, it is not recommended for use in population-based screening or in the clinic.

3. A shallow anterior chamber is strongly associated with angle closure. The use of anterior chamber depth for population-based screening is as yet unproven.

4. Many clinicians currently perform iridotomy as prophylaxis in the presence of any visible iridotrabeular contact.

Comment: Published evidence is lacking to justify this practice since it is unknown whether LPI is effective at preventing acute angle closure, PAC, and PACG from developing in individuals with gonioscopically detected iridotrabeular contact. Research is needed to determine racial/ethnic variations in response to iridotomy. Evidence is needed to evaluate the meaning of a shallow limbal anterior chamber depth in the presence of an 'open' angle on gonioscopy.

5. There is currently no evidence in the literature supporting the standard use of provocative tests for angle closure. A negative provocative test does not exclude angle closure.

INTRAOCULAR PRESSURE (2007)

Hardbound, xviii and 128 pages with 57 figures, of which 7 in full color, and 7 tables.

CONSENSUS STATEMENTS

Basic science of intraocular pressure

Aqueous flow:

1. IOP is determined by contributions from aqueous humor production (measured as aqueous flow), trabecular outflow, uveoscleral outflow, and episcleral venous pressure.

2. Aqueous flow has a distinctive circadian rhythm, being lower at night than during the day.

Comment: Aqueous flow is not affected by exfoliation syndrome, pigment dispersion syndrome, primary open-angle glaucoma, or ocular hypertension. Aqueous flow is reduced by diabetes mellitus and myotonic dystrophy.

3. The best technique to measure aqueous flow in humans is by fluorophotometry.

Comment: Limitations and assumptions associated with fluorophotometry include the following: (a) A rate of diffusion of fluorescein into the iris, limbal vessels, and tear film is assumed. (b) Fluorescein is distributed uniformly throughout the anterior chamber and cornea. (c) A lens-iris barrier is present to block the egress of the tracer into the posterior chamber. (d) Short-term fluctuations in aqueous flow of less than 30 minutes are not detectable.

Trabecular outflow:

1. The trabecular outflow pathway is comprised of the trabecular meshwork, the juxtacanalicular connective tissue (JCT), the endothelial lining of Schlemm's canal, the collecting channels, and aqueous veins.

Comment: Normal outflow resistance resides in the inner wall region of Schlemm's canal (SC), including JCT and inner endothelial lining of SC. Cells in trabecular meshwork influence the hydraulic conductivity of the inner wall region and outflow resistance by modulating extracellular matrix turnover and/or by actively changing cell shape. Trabecular outflow is under the influence of ciliary muscle tone.

2. Outflow facility in healthy human eyes is the range of 0.1–0.4 $\mu\text{l}/\text{min}/\text{mmHg}$.

Comment: Outflow facility is reduced in primary open-angle glaucoma, ocular hypertension, and exfoliation and pigment dispersion syndromes with accompanying ocular hypertension. In chronic open-angle glaucoma, there is an increase in extracellular material in the juxtacanalicular connective tissue and decrease in number of pores in Schlemm's canal endothelium.

3. Outflow facility can be measured with tonography and fluorophotometry. Both methods have inherent limitations associated with their use.

Uveoscleral outflow:

1. The uveoscleral outflow pathway is comprised of the ciliary muscle, supraciliary space, suprachoroidal space, sclera, and other less defined areas.

2. Uveoscleral outflow is 25–57% of total outflow in young healthy humans and uveoscleral outflow decreases with age.

Comment: Uveoscleral outflow is reduced in ocular hypertension with and without exfoliation syndrome, increased in uveitis, and unchanged in pigment dispersion syndrome with ocular hypertension.

3. In clinical studies, uveoscleral outflow is calculated from the modified Goldmann equation.

Comment: Inherent variability is great and reproducibility is fair. Invasive methods to measure uveoscleral outflow are: (a) The tracer collection method. (b) The indirect isotope method.

Episcleral venous pressure:

1. Episcleral venous pressure in healthy humans is 8–10 mmHg.

Comment: It is affected by body position, inhalation of O_2 , application of cold temperature, and treatment with vasoactive drugs. Episcleral venomanometry is used in clinical studies. This measurement is difficult to make and highly variable. Direct cannulation is used in animal studies. This is an accurate but invasive method.

Measurement of intraocular pressure

1. On average, greater central corneal thickness (CCT) results in overestimation of IOP as measured by Goldmann applanation tonometry (GAT).

Comment: The extent to which CCT contributes to the measurement error (in relation to other factors) in individual patients under various conditions has yet to be established.

2. Compared to GAT, CCT has a lesser effect on IOP measured by dynamic contour tonometry (DCT) and the ocular response analyzer (ORA) (corneal compensated IOP). CCT has a greater effect on IOP measured by non-contact and rebound tonometry.

3. Currently we have insufficient evidence comparing different tonometers in the same population. However, there are some data to suggest that Goldmann applanation tonometry is more precise (lowest measurement variability) compared to other methods.

4. Precision and agreement of tonometry devices should be reported in a standardized format:

- (a) Coefficient of repeatability (for intraobserver variation).
- (b) Mean difference (or difference trend over range) and 95% limits of agreement (for interobserver and interinstrument differences).

Comment: Under ideal circumstances for measurement, precision figures reported for GAT: (a) Intraobserver variability: 2.5 mmHg (two readings by the same observer will be within this figure for 95% of subjects). (b) Interobserver variability: ± 4 mmHg (95% confidence limits either side of mean difference between observers). (c) In clinical practice, these figures may be considerably higher. (d) Intra-class correlation coefficients are not clinically useful.

5. Currently there are no data to support a specific frequency of calibration verification for GAT.

Comment: The frequency for verification of GAT calibration of at least twice yearly is suggested. For clinical research, a verification error $> \pm 1$ mmHg should be the threshold to send the tonometer for recalibration; the threshold for clinical practice may be higher and requires a cost-benefit analysis.

6. Correction nomograms that adjust GAT IOP based solely on CCT are neither valid nor useful in individual patients.

Comment: A thick cornea gives rise to a greater probability of an IOP being overestimated (and a thin cornea of an IOP being underestimated), but the extent of measurement error in individual patients cannot be ascertained from the CCT alone.

7. Measurement of CCT is important in assessing risk for incident glaucoma among ocular hypertensives in the clinical setting, though the association between CCT and glaucoma risk may be less strong in the population at large.

8. The corneal modulus of elasticity likely has a greater effect on GAT IOP measurement error than CCT, especially with corneal pathology and after corneal surgery.

Comment: The corneal modulus of elasticity increases with age, thus generating artifactual increases in Goldmann tonometry with age. A higher modulus of elasticity is associated with greater stiffness.

9. Consideration of corneal viscoelasticity is essential for determining the ocular mechanical resistance to tonometry and hence improving the accuracy of IOP measurement.

Comment: Corneal aging affects the viscoelasticity of the tissue and adds another layer of complexity to determining the mechanical resistance of the cornea to tonometry.

10. Large amounts of corneal edema produce an underestimation of IOP when measured by applanation tonometry.

Comment: Small amounts of corneal edema (as induced by contact lens wear) probably cause an overestimation of IOP.

11. To obtain a GAT measurement, which is relatively unaffected by daytime changes in CCT, the patient should desirably have been awake with his/her eyes open for at least 2 hours prior to the measurement being made.

12. The wearing of contact lenses on the day when tonometry is performed may lead to an artifactually raised IOP as measured by GAT.

Comment: Contact lens wearing patients should have tonometry performed after having been awake, without contact lenses, for at least 2 hours for contact lens-induced and diurnal corneal edema to resolve.

13. There are changes in corneal biomechanics following many forms of keratorefractive surgery, associated with a mean fall in IOP as measured by applanation tonometry.

Comment: Although there is a mean fall across patients in measured IOP, there is a wide variability in response.

14. DCT and ORA (corneal-compensated IOP) may both be less sensitive to changes in corneal biomechanics following keratorefractive surgery and have less variance than standard applanation tonometry.

15. The use of a lid speculum, sedatives, and general anesthetics can significantly affect IOP measurement in children, and tonometers vary in their accuracy in pediatric eyes.

Comment: The clinician should adopt a consistent protocol for the measurement of IOP in children so that through experience the 'normal' range for their protocol can be determined.

Intraocular pressure as a risk factor for glaucoma development & progression

1. There is *strong evidence* to support higher mean IOP as a significant factor for the development of glaucoma.

2. There is *strong evidence* to support higher mean IOP as a significant risk factor for glaucoma progression.

3. IOP is more variable in glaucomatous than in healthy eyes, but both 24-hour IOP fluctuation and IOP variation over periods longer than 24 hours tend to be correlated with mean IOP.

4. There is currently *insufficient evidence* to support 24-hour IOP fluctuation as a risk factor for glaucoma development or progression.

Comment: 24-hour IOP measurements are comprised of daytime (diurnal) and night-time (nocturnal) periods. Diurnal IOP is generally highest after awakening and decreases during the daytime period. Posture is an important variable in the measurement of IOP; IOP in the sitting position is generally lower than in the supine position.

5. There is currently *insufficient evidence* to support IOP variation over periods longer than 24 hours as a risk factor for glaucoma development and progression.

6. Sufficiently low blood pressure, combined with sufficiently high IOP, generates low ocular perfusion pressure and is associated with increased open-angle glaucoma prevalence in cross-sectional studies.

Comment: Physiologic IOP variation occurs in regular rhythmic cycles. Regular IOP peaks and valleys are normal, and compensatory mechanisms are in place to preserve the integrity of the tissue and the organism. The peaks and troughs in circadian IOP and blood pressure do not necessarily occur simultaneously.

Epidemiology of intraocular pressure

1. Self-described race is a poor summary of human biodiversity.

Comment: Self-described race still contains important information that both correlates well with genetic measures of ancestry and disease risk on a populations basis.

2. Evidence for differences in IOP between blacks and whites is contradictory from available population-based studies.

3. Evidence for a relationship between IOP and age is contradictory from available population-based studies.

4. Evidence for a relationship between IOP and gender is contradictory from available population-based studies.

5. Studies with similar methodology comparing differences in IOP between multiple racial groups allowing direct comparisons generally have not been performed.

Comment: IOP appears lower in Asian populations than populations with European and African ancestry, however direct comparisons have not been made.

6. Variations in study designs and IOP measurement techniques limit comparison of mean IOPs across racial, ethnic, and regional strata.

Comment: Very few population-based surveys have included important biomarkers such as CCT that may effect the measured IOP. IOP is higher in eyes with shorter axial anterior chamber depth as a result of pathological angle closure. Corneal radius of curvature is a potential source of measurement error, and should be adjusted for when using an applanation tonometer.

7. There is a strong positive relationship between IOP and open-angle glaucoma, although prevalent and incident open-angle glaucoma cases occur commonly at IOP <22 mmHg.

Clinical trials and intraocular pressure

1. The type of clinical trial (i.e., phase II, III, or IV) influences the study design and subsequent considerations of treatment groups, recruitment criteria, and power.

2. An appropriately designed clinical trial for efficacy of IOP reduction should specify a clinically significant treatment effect (delta); probability of a type 1 error (alpha), usually set at 5%, and a desired power (conventionally at least 80%).

3. Clinical trials in related disease areas should strive to use similar designs and outcome measures to facilitate meta-analysis (i.e., a pooling of results of independent trials).

4. Clinical trials comparing IOP-lowering efficacy of different treatments should provide 95% confidence intervals for the difference in IOP reduction.

5. Efficacy trials should define *a priori* the clinically meaningful difference for that specific study.

Comment: In addition to IOP lowering, other factors such as safety and side effects must be considered in defining a clinically meaningful difference for that specific study.

6. Protocols should include at least two post-screening IOP measurements acquired on at least two different days for calculating baseline IOP, prior to randomization.

7. Protocol analyses also should include measurement of baseline IOP, central corneal thickness, and type of glaucoma to allow adjustment for these potentially confounding variables when comparing IOP-lowering interventions.

Target intraocular pressure in clinical practice

1. The target IOP is the IOP range at which the clinician judges that progressive disease is unlikely to affect the patient's quality of life.

Comment: The burdens and risks of therapy should be balanced against the risk of disease progression.

2. The determination of a target IOP is based upon consideration of the amount of glaucoma damage, the IOP at which the damage has occurred, and the life expectancy of the patient, and other factors including status of the fellow eye and family history of severe glaucoma.

Comment: At present, the target IOP is estimated and cannot be determined with any certainty in a particular patient. There is no validated algorithm for the determination of a target IOP. This does not, however, negate its use in clinical practice.

3. It is recommended that the target IOP be recorded so that it is accessible on subsequent patient visits.

4. The use of a target IOP in glaucoma requires periodic re-evaluation.

Comment: This entails examination of the optic nerve and assessment of visual function to detect glaucomatous progression, the effect of the therapy upon the patient's quality of life, and whether the patient has developed any new systemic or ocular conditions that might affect the risk/benefit ratio of therapy. During the re-evaluation, it is essential to determine whether the IOP target is appropriate and should not be changed, or that it needs to be lowered or raised.

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